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Synthesis of Some New 4-oxo-4H-Chromene Derivatives Bearing Nitrogen Heterocyclic Systems as Antifungal Agents

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Some new 4-oxo-4*H*-chromone derivatives bearing nitrogen heterocyclic systems were achieved by treatment of 3-[(4-aminophenylimino)methyl]-6-chloro-4-oxo-4*H*-chromene (**2**) with some aldehydes, cyclic oxygen, and halogen compounds, followed by heterocyclization. Significant antifungal activities were observed for some of the prepared compounds. Structures of all products were confirmed by elemental analysis, IR, ^{1}H-NMR, and mass spectra.

Key Words: Chromone, nitrogen heterocycles, antifungal activity.

Introduction

4-Oxo-4*H*-chromene derivatives have many applications in the biological field. A number of this class of compounds act as antimicrobial,[1,2] antiviral,[3]anti-inflammatory, and antitumor agents.[4,5] 4-Oxo-4*H*-chromene-3-carboxaldehydes and their Schiff bases derivatives have attracted considerable interest in human colon cancer[6] and as potential topoisomerase inhibitor anticancer agents.[7] The present work describes the preparation of 4-oxo-4*H*-chromene containing nitrogen heterocycles. Reactions of 3-[(4-aminophenylimino)methyl]-6-chloro-4-oxo-4*H*-chromene (**2**) with some aldehydes, cyclic oxygen, and halogen compounds, followed by heterocyclization, were achieved. Some of the new prepared compounds were tested for their antifungal activity against *Alternaria alternata*, *Aspergillus niger*, and *Aspergillus flavipes.*

Results and Discussion

Condensation reaction of 6-chloro-4-oxo-4*H*-chromene-3-carboxaldehyde (**1**) with *p*-phenylenediamine in dry benzene containing *p*-toluenesulfonic acid gave 3-[(4-aminophenylimino)methyl]-6-chloro-4-oxo-4*H*-chromene (**2**) (Scheme 1).

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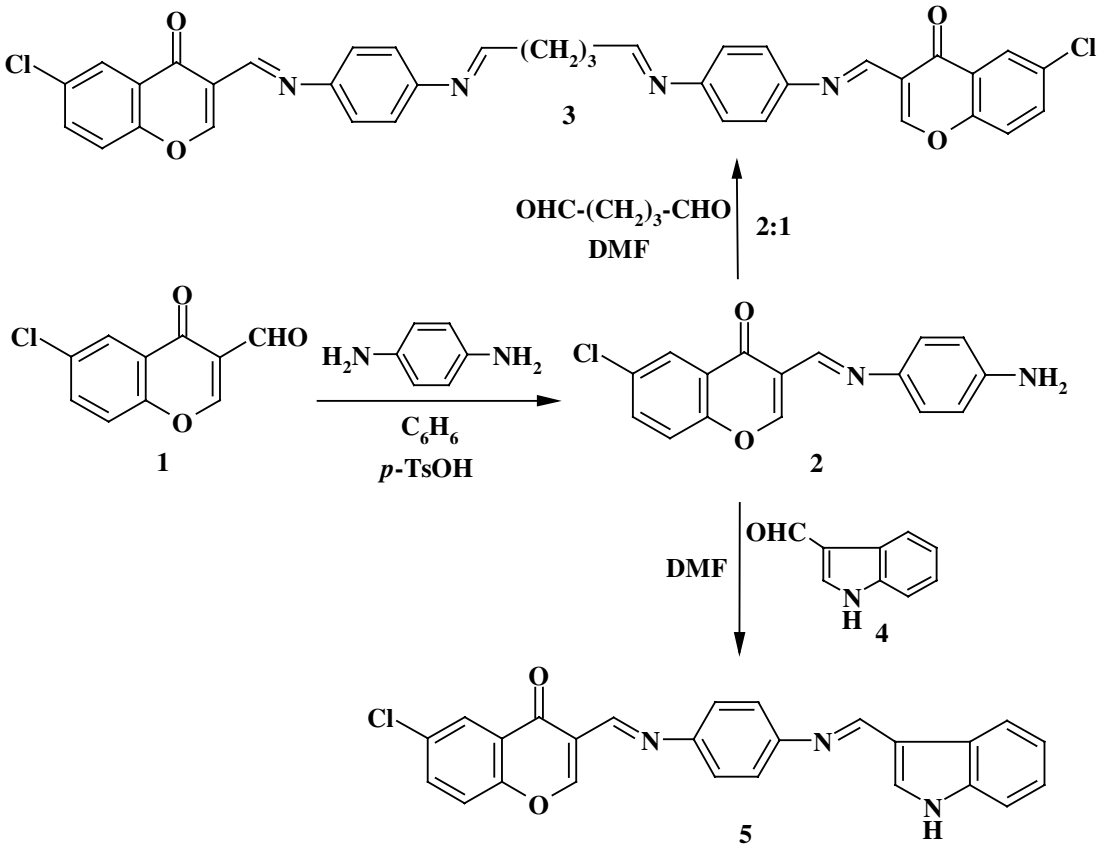
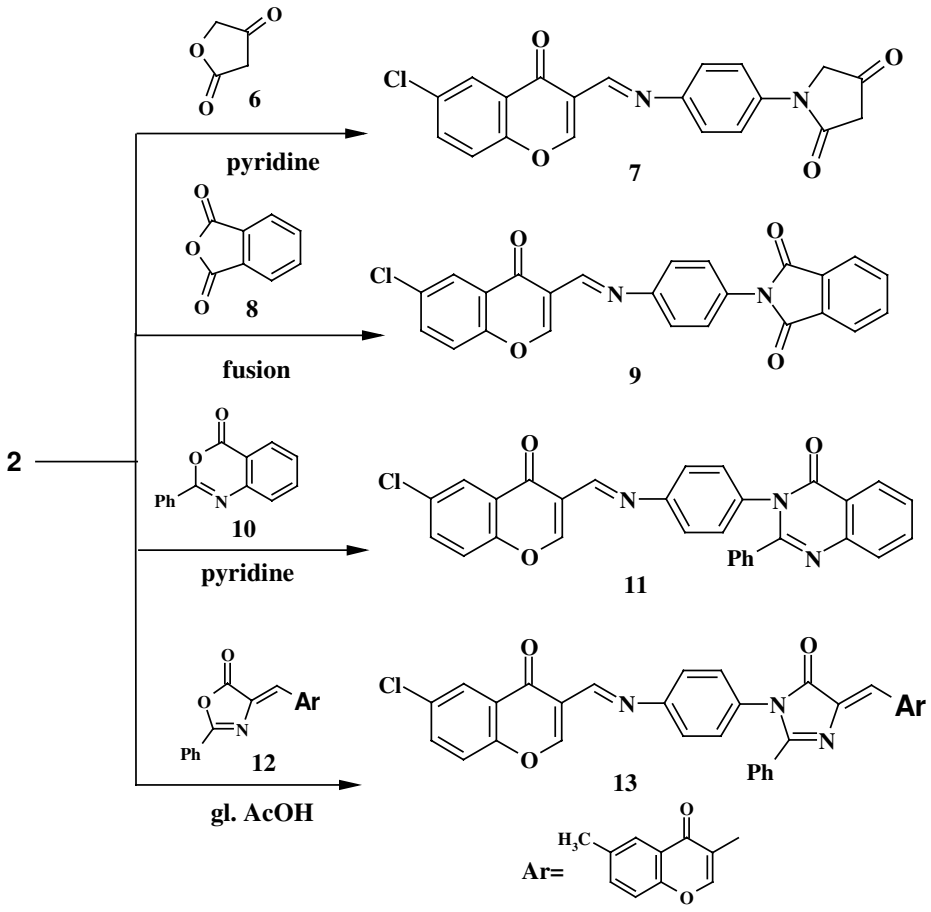


Scheme 1

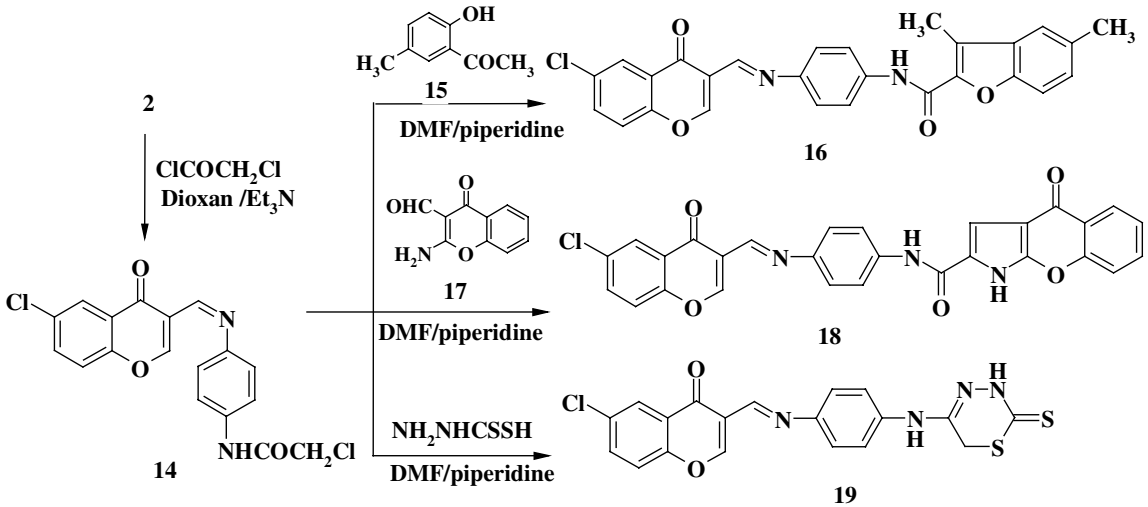
Treatment of amino compound **2** with glutaraldehyde in ratio 2:1 and/or 3-formylindole (**4**) in DMF afforded the condensation products **3** and **5**, respectively (Scheme 1).

Moreover, refluxing amino compound **2** with tetrahydrofuran-2,4-dione (**6**) in pyridine yielded 1-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}pyrrolidine-2,4-dione (**7**), while its fusion with phthalic anhydride (**8**) afforded the isoindole derivative **9** (Scheme 2). Similarly, 3-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-2-phenyl-3*H*-quinazolin-4-one (**11**) and 5-(6-methyl-4-oxo-4*H*-chromen-3-ylmethylene)-3-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene) amino]phenyl}-2-phenyl-3,5-dihydroimidazol-4-one (**13**) were obtained from refluxing amino compound **2** with 2-phenyl-4-oxo-1,3-benzoxazine (**10**) in pyridine and/or oxazolone derivative **12** in boiling glacial acetic acid, respectively (Scheme 2).

Reactions of α-halocarbonyl derivatives with oxygen, nitrogen, and sulfur nucleophiles provide several heterocycles via cyclocondensation reactions.[8] Thus, the reaction of amino compound **2** with chloroacetyl chloride in dioxane containing a few drops of triethylamine gave N-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene) amino]phenyl}-2-chloro-acetamide (**14**) (Scheme 3). Therefore, cyclocondensation reactions of α-chlorocarbonyl derivative **14** with 5-methyl-2-hydroxyacetophenone (**15**) and/or 2-amino-3-formylchromone (**17**) in boiling DMF containing a few drops of piperidine gave N-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-3,5-dimethylbenzofuran-2-carboxamide (**16**) and N-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-1,4-dihydro-chromono[2,3-b]pyrrole-2-carboxamide (**18**), respectively (Scheme 3). Formation of compounds **16** and **18** may occur via nucleophilic attack of the OH or NH_2 group of compounds **15** and **17**,respectively, at the CH_2–Cl group of compound **14**, followed by cyclocondensation on elimination of the water molecule by the effect of piperidine.

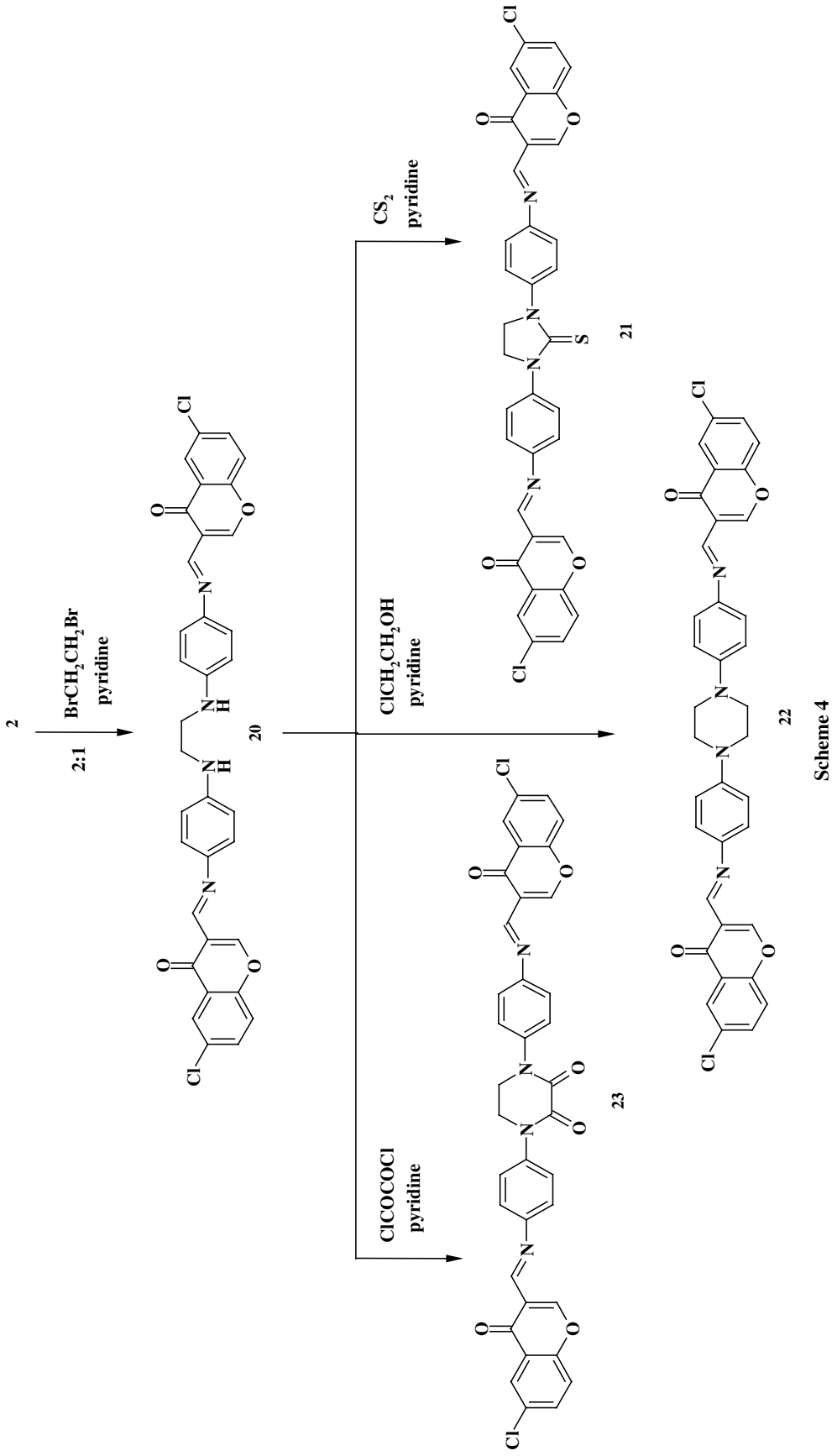


Scheme 2



Scheme 3

On the other hand, refluxing compound **14** with hydrazinecarbodithioic acid in DMF led directly to the formation of 6-chloro-3-{[4-(2-thioxo-3,6-dihydro-2*H*-1,3,4-thiadiazin-5-ylamino)phenylimino]methyl}-4-oxo-4*H*-chromene (**19**) (Scheme 3).


2
2:1
BrCH2CH2Br
pyridine
20
CS2
pyridine
21
ClCH2CH2OH
pyridine
22
ClCOCOCl
pyridine
23

Scheme 4

Alkylation of amino compound **2** with 1,2-dibromoethane in ratio 2:1 in pyridine gave N,N'-bis{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}ethylene- diamine (**20**) (Scheme 4).

Imidazole and piperazine derivatives represent 2 of the most biologically active classes of compounds, possessing a wide spectrum of biological activities.[9,10] Thus, treatment of ethylenediamine derivative **20** with carbon disulfide in boiling pyridine yielded 1,3-bis{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino] phenyl}-2-thioxoimidazolidine (**21**) (Scheme 4). Therefore, the piperazine derivatives **22** and **23** were obtained from refluxing ethylenediamine derivative **20** with 2-chloroethanol and/or oxalyl chloride, respectively, in pyridine (Scheme 4).

Antifungal Activities

Some of the newly synthesized compounds were screened for their antifungal activities against 3 species of fungi, *Alternaria alternata, Aspergillus niger*, and *Aspergillus flavipes*, using disk diffusion method.[11,12] Activity of each compound was compared with that of flucanazole as the standard. The investigation of fungicidal screening data revealed that all the tested compounds showed variable activities towards the 3 species of fungi used, which showed that these compounds are biologically active due to the presence of different heterocycles and functional groups (Table). Compounds **2, 3, 16**, and **22** showed very high activities against the 3 species of fungi, while compound **18** showed high activity against them. On the other hand, compounds **5** and **13** showed lower activities against *Alternaria alternata* and *Aspergillus niger*, while compound **11** showed high activity against *Alternaria alternata* and moderate activity against *Aspergillus niger* and *Aspergillus flavipes.*

Table. Antifungal activities of some compounds.

Compd.	Diameter of inhibition zone (mm)		
No.	*Alternaria alternata*	Aspergillus niger	*Aspergillus flavipes*
2	++++	++++	++++
3	++++	++++	++++
5	+	++	++
11	+++	++	++
13	+	+	++
16	+++	++++	++++
18	+++	+++	+++
22	++++	++++	++++
flucanazole	++++	++++	++++

Very high active = ++++ (inhibition zone > 30 mm)
High active = +++ (inhibition zone 21-30 mm)
Moderately active = ++ (inhibition zone 11-20 mm)
Lower active = + (inhibition zone 1-10 mm)

Experimental

All melting points were determined on a digital Stuart SMP3 and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 293 spectrophotometer (in cm^{-1}), using KBr disks. ^{1}H-NMR spectra were measured on a Gemini-200 spectrometer (200 MHz), using DMSO-d_6 as a solvent and TMS (δ, 0.0 ppm) as internal standard. The mass spectra were measured on gas chromatographic GCMSqp 1000-ex Shimadzu instrument or HP–MS 5988 mass spectrometer by direct inlet operating at 70 eV. Elemental microanalyses were performed in the microanalysis center at Cairo University. 6-Chloro-4-oxo-4*H*-chromene-3-carboxaldehyde (**1**),[13] hydrazinecarbodithioic acid,[14] 2-phenyl-4-oxo-1,3-benzoxazine (**10**),[15] oxazolone derivative **12**,[16]and 2-amino-3-formylchromone (**17**)[17,18]were prepared by published methods.

3-[(4-Aminophenylimino)methyl]-6-chloro-4-oxo-4*H*-chromene (2)

A mixture of 6-chloro-4-oxo-4*H*-chromene-3-carboxaldehydes (**1**) (0.005 mol) and 1,4-phenylenediamine (0.005 mol) in dry benzene (50 mL) containing 4-toluenesulfonic acid (0.01 g) was refluxed for 5 h. The obtained solid was filtered off and crystallized to give **2**. Yield 61%, mp 203-205 °C (Dioxane). IR (KBr), /cm^{-1}: 3378 (NH_2), 1641.5 ($C{=}O_{pyrone}$), 1604 (C=N). ^{1}H-NMR (DMSO), δ: 6.60 (1H, d, J=6.7 Hz, H–8), 6.92–7.28 (7H, m, Ar–H and CH=N), 7.76 (1H, s, H–2), 12.08–12.15 (2H, br, NH_2). Anal. Calcd for $C_{16}H_{11}ClN_2O_2$ (298.72): C, 64.33; H, 3.71; N, 9.38 Found: C, 64.38; H, 3.54; N, 9.12.

1,3-Bis{(4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenylimino)methyl}propane(3)

A mixture of 3-[(4-aminophenylimino)methyl]-6-chloro-4-oxo-4*H*-chromene (**2**) (0.01 mol) and glutaraldehyde (0.005 mol) in DMF (50 mL) was refluxed for 6 h. The mixture was cooled and poured into ice. The obtained solid was filtered off and crystallized to give **3**. Yield 67%, mp 295-297 °C (Benzene). IR (KBr), /cm^{-1}: 3070 (CH_{arom}), 2979, 2849 (CH_{aliph}), 1641 ($C{=}O_{pyrone}$), 1594 (C=N). ^{1}H-NMR (DMSO), δ: 2.73–3.02 (6H, m, CH_2), 6.82–8.00 (18H, m, Ar–H, and 4 CH=N), 8.34 (2H, s, H–2). MS (m/z, %): 661 (M^+, 72.22%), 595 (88.89), 557 (66.67), 456 (66.67), 422 (61.11), 276 (55.56), 263 (83.33), 262 (83.33), 179 (61.11), 161 (61.11), 147 (55.56), 69 (100), 68 (88.89), Anal. Calcd for $C_{37}H_{26}Cl_2N_4O_4$ (661.53): C, 67.18; H, 3.96; N, 8.47 Found: C, 66.84; H, 3.74; N, 8.11.

6-Chloro-3-({4-[(1*H*-indol-3-ylmethylene)amino]phenylimino}methyl)-4-oxo-4H-chromene (5)

A mixture of **2** (0.005 mol) and 3-formylindole (**4**) (0.005 mol) in DMF (50 mL) was refluxed for 6 h. The mixture was cooled and poured into ice. The obtained solid was filtered off and crystallized to give **5**. Yield 50%, mp > 300 °C (THF). IR (KBr), /cm^{-1}: 3351, 3221 (NH), 3064 (CH_{arom}), 2925 (CH_{aliph}), 1632 ($C{=}O_{pyrone}$). ^{1}H-NMR (DMSO), δ: 7.10–7.94 (14H, m, Ar–H, 2 CH=N and H–2), 12.13 (1H, br, NH). MS (m/z, %): 424 (M–2, 6.0%), 379 (100), 309 (7.3), 246 (9.3), 220 (12.3), 206 (6.5), 205 (26.2), 180 (20.8), 155 (35.1), 154 (19.6), 143 (5.2), 117 (5.0), 111 (13.3), 91 (8.5), 77 (34.5). Anal. Calcd for $C_{25}H_{16}ClN_3O_2$ (425.86): C, 70.51; H, 3.79; N, 9.87, Found: C, 70.23; H, 3.63; N, 9.59.

General procedure for the preparation of compounds 7 and 11

A mixture of **2** (0.005 mol) and tetrahydrofuran-2,4-dione (**6**) or 2-phenyl-4-oxo-1,3-benzoxazine (**10**) (0.005 mol) in pyridine (50 mL) was refluxed for 12 h. The mixture was cooled and poured into ice–HCl. The obtained solid was filtered off and crystallized to give **7** and **11**, respectively.

1-{4-[(6-Chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-pyrrolidine-2,4-dione (7): Yield 51%, mp > 300 °C (DMF/H_2O). IR (KBr), /cm^{-1}: 3372 (br, OH), 3066 (CH_{arom}), 2956, 2859 (CH_{aliph}), 1722 ($C{=}O_{pyrrolidinedione}$), 1630 ($C{=}O_{pyrone}$). ^{1}H-NMR (DMSO), δ: 2.72–2.88 (2H, m, NCH_2CO), 4.12–4.13 (2H, m, $COCH_2CO$), 7.06–7.94 (9H, m, Ar–H, CH=N and H–2). MS (m/z, %): 380 (M–1, 11.8%), 206 (10.5), 155 (12.5), 154 (42.1), 149 (100), 135 (30.9), 127 (13.8), 126 (17.1), 107 (15.8), 93 (26.3), 84 (11.2), 77 (27.0), 66 (14.5), 56 (11.51), 55 (28.9), 52 (15.8). Anal. Calcd for $C_{20}H_{13}ClN_2O_4$ (380.78): C, 63.08; H, 3.44; N, 7.36, Found: C, 63.41; H, 3.40; N, 7.09.

3-{4-[(6-Chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-2-phenyl-3*H*-quinazolin-4-one (11): Yield 53%, mp 160-162 °C (EtOH). IR (KBr), /cm^{-1}: 3064 (CH_{arom}), 2926 (CH_{aliph}), 1760 ($C{=}O_{quinazolinone}$), 1643 ($C{=}O_{pyrone}$), 1604 (C=N). ^{1}H-NMR (DMSO), δ: 7.02–8.02 (17H, m, A–H and CH=N), 8.12 (1H, s, H–2). MS (m/z, %): 488 (M–O, 18.2%), 298 (100), 207 (13.0), 206 (18.2), 155 (9.5), 154 (8.8), 131 (16.1), 127 (10.2), 110 (8.1), 105 (24.6), 102 (11.2), 77 (48.8), 76 (9.8), 52 (21.4). Anal. Calcd for $C_{30}H_{18}ClN_3O_3$(503.93): C, 71.50; H, 3.60; N, 8.34, Found: C, 71.32; H, 3.41; N, 8.12.

2-{4-[(6-Chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-isoindole-1,3-dione (9)

Equimolar amounts of compound **2** (0.005 mol) and phthalic anhydride (**8**) (0.005 mol) were fused at 250 °C for 15 min. After cooling, the mixture was treated with methanol. The obtained solid was filtered off and crystallized to give **9**. Yield 71%, mp 283-286 °C (Dioxane). IR (KBr), /cm^{-1}: 3065 (CH_{arom}), 2960 (CH_{aliph}), 1723 ($C{=}O_{isoindoledione}$), 1650 ($C{=}O_{pyrone}$), 1605 (C=N). ^{1}H-NMR (DMSO), δ: 7.01–8.01 (12H, m, A–H and CH=N), 8.09 (1H, s, H–2). MS (m/z, %): 428 (M–1, 4.51%), 368 (100), 325 (3.26), 298 (1.97), 222 (3.52), 206 (2.27), 179 (4.43), 155 (7.63), 154 (7.38), 132 (3.10), 111 (1.78), 104 (51.82), 76 (98.23), Anal. Calcd for $C_{24}H_{13}ClN_2O_4$ (428.82): C, 67.22; H, 3.06; N, 6.53, Found: C, 66.98; H, 3.13; N, 6.39.

5-(6-Methyl-4-oxo-4*H*-chromen-3-ylmethylene)-3-{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-2-phenyl-3,5-dihydroimidazol-4-one (13)

A mixture of **2** (0.005 mol) and oxazolone derivative **12** (0.005 mol) in glacial acetic acid (50 mL) was refluxed for 10 h. The mixture was cooled and poured into ice. The obtained solid was filtered off and crystallized to give **13**. Yield 55%, mp 295-296 °C (EtOH). IR (KBr), /cm^{-1}: 3036 (CH_{arom}), 2925 (CH_{aliph}), 1798 ($C{=}O_{imidazolinone}$), 1719 ($C{=}O_{pyrone}$), 1651 ($C{=}O_{pyrone'}$), 1602 (C=N). ^{1}H-NMR (DMSO), δ: 2.15 (3H, s, CH_3), 6.81 (1H, s, CH=C exo-imidazole), 7.52–7.66, 7.97–8.00 (16H, m, Ar–H and CH=N), 8.66 (2H, s, H–2). MS (m/z, %): 612 (M^+, 62.50%), 539 (68.75), 573 (75.00), 525 (62.50), 420 (62.50), 410 (100), 403 (62.50), 395 (62.50), 299 (75.00), 250 (81.25), 213 (75.00), 180 (75.00), 155 (68.75), 144 (68.75) 133 (75.00), 105 (75.00), 56 (75.00). Anal. Calcd for $C_{36}H_{22}ClN_3O_5$ (612.02): C, 70.65; H, 3.62; N, 6.87, Found: C, 70.22; H, 3.44; N, 6.49.

N-{4-[(6-Chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-2-chloroacetamide (14)

A mixture of **2** (0.005 mol) and chloroacetyl chloride (0.005 mol) in dioxane (50 mL) containing a few drops of triethylamine was refluxed for 3 h. The obtained solid was filtered off and crystallized to give **14**. Yield 59%, mp 255-256 °C (MeOH). IR (KBr), /cm^{-1}: 3216 (NH), 3050 (CH_{arom}), 2929 (CH_{aliph}), 1651 ($C{=}O_{amide}$), 1618 ($C{=}O_{pyrone}$), 1604 (C=N). ^{1}H-NMR (DMSO), δ: 4.22 (2H, s, CH_2), 7.10–7.90 (9H, m, Ar–H, CH=N and H–2), 10.26 (1H, s, NH). MS (m/z, %): 374 (M–1, 45.83%), 340 (41.67), 304 (45.83), 299

(41.67), 282 (41.67), 262 (100), 206 (45.83), 184 (100), 159 (70.83), 133 (45.83), 108 (70.83), 107 (87.50), 77 (62.50). Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_3$ (375.20): C, 57.62; H, 3.22; N, 7.47, Found: C, 57.45; H, 3.03; N, 7.11.

General procedure for the preparation of compounds 16, 18, and 19

A mixture of **14** (0.005 mol) and 5-methyl-2-hydroxyacetophenone (**15**), 2-amino-3-formylchromone (**17**) or hydrazinecarbodithioic acid (0.005 mol) in DMF (50 mL) containing a few drops of piperidine was refluxed for 10 h. The mixture was cooled and poured into ice. The obtained solid was filtered off and crystallized to give **16**, **18**, and **19**, respectively.

N-{4-[(6-Chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-3,5-dimethyl-benzofuran-2-carboxamide (16): Yield 30%, mp 203-205 °C (DMF/H_2O). IR (KBr), /cm^{-1}: 3167 (NH), 2984 (br, CH_{aliph}), 1716 (C=O_{amide}), 1657 (C=O_{pyrone}), 1617 (C=N). ^{1}H-NMR (DMSO), δ: 2.16 (3H, s, CH_3), 2.94 (3H, s, CH_3), 6.49–7.25 (11H, m, Ar–H and CH=N), 7.95 (1H, s, H–2), 9.10 (1H, s, NH). MS (m/z, %): 471 (M^+, 30.30%), 248 (33.33), 206 (84.85), 161 (100), 155 (63.64), 154 (30.30), 129 (51.52), 111 (57.58), 105 (48.48), 83 (72.73), 57 (42.42). Anal. Calcd for $C_{27}H_{19}ClN_2O_4$ (470.90): C, 68.87; H, 4.07; N, 5.95, Found: C, 68.58; H, 3.87; N, 5.69.

N-{4-[(6-Chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-1,4-dihydro-chromono [2,3-b]pyrrole-2-carboxamide (18): Yield 40%, mp 168-169 °C (EtOH). IR (KBr), /cm^{-1}: 3400 (br, NH), 3066 (CH_{arom}), 2926 (CH_{aliph}), 1741 (C=O_{amide}), 1668 (C=O_{pyrone}), 1599 (C=N). ^{1}H-NMR (DMSO), δ: 7.12–7.93 (13H, m, A–H, C_4–$H_{pyrrole}$ and CH=N), 8.10 (1H, s, H–2), 9.41 (br, 1H, NH exchanged with D_2O), 10.83 (br, 1H, NH exchanged with D_2O). MS (m/z, %): 510 (M^+, 52.63%), 476 (52.63), 450 (52.63), 315 (52.63), 156 (84.21), 125 (63.16), 92 (100), 65 (63.16). Anal. Calcd for $C_{28}H_{16}ClN_3O_5$ (509.89): C, 65.95; H, 3.16; N, 8.24, Found: C, 65.63; H, 3.01; N, 8.51.

6-Chloro-3-{[4-(2-thioxo-3,6-dihydro-2*H*-1,3,4-thiadiazin-5-ylamino)phenylimino] methyl}-4-oxo-4*H*-chromene (19): Yield 45%, mp 197-200 °C (EtOH). IR (KBr), /cm^{-1}: 3256 (br, NH), 3070 (CH_{arom}), 2925 (CH_{aliph}), 1659 (C=O_{pyrone}), 1610 (C=N). ^{1}H-NMR (DMSO), δ: 4.41–4.17 (2H, m, CH_2), 6.99–7.81 (8H, m, Ar–H and CH=N), 8.54 (1H, s, H–2), 10.40 (1H, s, NH), 10.80 (1H, s, NH). MS (m/z, %): 429 (M+1, 24.32%), 382 (24.32), 311 (32.43), 270 (32.43), 237 (24.32), 208 (27.03), 177 (24.32), 135 (32.43), 116 (43.24), 108 (37.84), 93 (48.65), 91 (37.84), 85 (51.35), 70 (56.76), 58 (56.70), 57 (100). Anal. Calcd for $C_{19}H_{13}ClN_4O_2S_2$ (428.91): C, 53.20; H, 3.05; N, 13.06, Found: C, 53.43; H, 2.94; N, 12.89.

N,N'-Bis{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}ethylenediamine (20)

A mixture of **2** (0.005 mol) and 1,2-dibromoethane (0.005 mol) in pyridine (50 mL) was refluxed for 5 h. The mixture was cooled and poured into ice–HCl. The obtained solid was filtered off and crystallized to give **20**. Yield 73%, mp 240-242 °C (DMF/H_2O). IR (KBr), /cm^{-1}: 3356, 3213 (NH), 3056 (CH_{arom}), 2925 (CH_{aliph}), 1635 (C=O_{pyrone}), 1605 (C=N). ^{1}H-NMR (DMSO), δ: 2.07 (4H, m, CH_2CH_2), 4.16–4.19 (2H, br, NH), 6.37–8.48 (18H, m, Ar–H, 2 CH=N and H–2). MS (m/z, %): 623 (M^+, 94.12%), 410 (58.82), 358 (100), 327 (58.82), 308 (76.47), 292 (64.71), 270 (58.82), 104 (64.71). Anal. Calcd for $C_{34}H_{24}Cl_2N_4O_4$ (623.48): C, 65.50; H, 3.88; N, 8.99, Found: C, 65.33; H, 4.10; N, 8.71.

General procedure for the preparation of compounds 21, 22, and 23

A mixture of **20** (0.005 mol) and carbon disulfide, 2-chloroethanol, or oxalyl chloride (0.005 mol) in pyridine (50 mL) was refluxed for 10 h. The mixture was cooled and poured into ice–HCl. The obtained solid was filtered off and crystallized to give **21**,**22**, and **23**, respectively.

1,3-Bis{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}-2-thioxo-imidazolidine (21): Yield 67%, mp 200-203 °C (DMF/MeOH). IR (KBr), /cm^{-1}: 3072 (CH$_{arom}$), 2925 (CH$_{aliph}$), 1631 (C=O$_{pyrone}$), 1606 (C=N). ^{1}H-NMR (DMSO), δ: 2.07 (4H, m, CH$_2$–CH$_2$), 7.06–7.75 (16H, m, Ar–H and 2 CH=N), 8.32 (2H, s, H–2). MS (m/z, %): 666 (M$^+$, 22.86%), 367 (25.71), 327 (28.57), 308 (22.86), 299 (34.29), 283 (22.86), 155 (28.57), 130 (31.43), 129 (25.71), 112 (28.57), 105 (28.57), 86 (25.71), 77 (28.57), 57 (100). Anal Cald for $C_{35}H_{22}Cl_2N_4O_4S$ (665.54): C, 63.16; H, 3.33; N, 8.42; S, 4.82 Found: C, 62.89; H, 3.53; N, 8.09; S, 4.45.

1,4-Bis{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}piperazine (22): Yield 42%, mp > 300 °C (DMF/H$_2$O). IR (KBr), /cm^{-1}: 3058 (CH$_{arom}$), 2923 (CH$_{aliph}$), 1631 (C=O$_{pyrone}$), 1604 (C=N). ^{1}H-NMR (DMSO), δ: 2.00–2.11 (8H, m, CH$_{2piperazine}$), 7.00–7.69 (16H, m, Ar–H and 2 CH=N), 8.21 (2H, s. H–2). MS (m/z, %): 651 (M+1, 39.39%), 368 (30.30), 283 (33.33), 206 (45.45), 153 (51.52), 120 (36.36), 92 (36.36), 63 (66.67), 55 (54.55), 54 (100), 53 (78.79). Anal. Calcd for $C_{36}H_{26}Cl_2N_4O_4$ (649.52): C, 66.57; H, 4.03; N, 8.63, Found: C, 66.23; H, 3.78; N, 8.49.

1,4-Bis{4-[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]phenyl}piperazine-2,3-dione (23): Yield 65%, mp > 300 °C (MeOH). IR (KBr), /cm^{-1}: 3034 (CH$_{arom}$), 2956, 2924, 2854 (CH$_{aliph}$), 1718 (C=O$_{\text{piperazinedione}}$), 1632 (C=O$_{\text{pyrone}}$), 1604 (C=N).^{1}H-NMR (DMSO), δ: 2.28–2.33 (4H, m, CH$_{2piperazinedione}$), 7.07–8.09 (16H, m, Ar–H and 2 CH=N), 8.11 (2H, s, H–2). MS (m/z, %): 677.5 (M$^+$, 24.32%), 471 (27.03), 381 (40.54), 323 (21.62), 318 (27.03), 294 (37.84), 265 (8.11), 238 (27.03), 219 (24.32), 206 (29.73), 182 (24.32), 156 (29.73), 144 (21.26), 117 (32.43), 115 (37.84), 99 (35.14), 93 (40.54), 86 (54.04), 77 (51.35), 63 (100), 58 (27.03). Anal. Calcd for $C_{36}H_{22}Cl_2N_4O_6$ (677.48): C, 63.82; H, 3.27; N, 8.27, Found: C, 63.61; H, 3.43; N, 7.99.

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