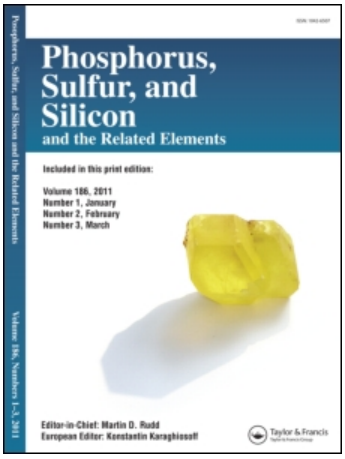

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Synthesis of Bioactive 4-Oxo-4*H*-Chromenes Bearing Heterocyclic Systems from Hydrazonecarbodithioic Acid and Thiocarbohydrazone

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Synthesis of Bioactive 4-Oxo-4*H*-Chromenes Bearing Heterocyclic Systems from Hydrazonecarbodithioic Acid and Thiocarbohydrazone

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*Condensation 4-oxo-4H-chromene-3-carboxaldehydes (**1a,b**) with acid hydrazinecarbodithioic acid and/or thiocarbohydrazide afforded hydrazonecarbodithioic acid **2,** monothiocarbohydrazone **3a,b** and bisthiocarbohydrazone **4**, respectively. Heterocyclization of **2–4** via reaction with oxygen, sulfur and/or halogen reagents in different media yielded pyridazinethione **5**; 1,3-thiazoles **7**; pyrazoles **9–12**; 1,2,4-thiadiazoles **8,13,14,** and **23**; 1,2,4-triazolethiones **15–17**; 1,2,4-triazinethiones **18–22**; imidazolethione **24** and pyrimidinethione **25** derivatives. Antifungal activity was screened for some the new synthesized compounds. Formulations of all products have been deduced by elemental analysis and spectral data (IR, ^{1}H NMR and Mass spectroscopy).*

Keywords Antifungal activity; chromone; heterocycles; hydrazonecarbodithioic acid; synthesis; thiocarbohydrazone

INTRODUCTION

A literature survey revealed that 4-oxo-4*H*-chromenes possess a broad spectrum of biological activity. They proved to be antimicrobial,[1,2] antifungal,[3,4] antiparasitic immunosuppresent agent,[5] and plant growth inhibitors.[6] On the other hand, some pyrazoles, pyrimidines, 1,2,4-triazoles, and 1,2,4-triazines are considered very interesting nitrogen heterocyclic rings systems because of their bioactivities including, antibacterial,[7,8] antifungal,[9,10] anti-inflammatory agents,[11] and antitumor.[12] It was also found that some 1,3-thiazoles and 1,2,4-thiadiazoles derivatives showed diverse biological activities as antifungal,[13] HIV[14] and herbicidal.[15,16] From all the forgoing facts and

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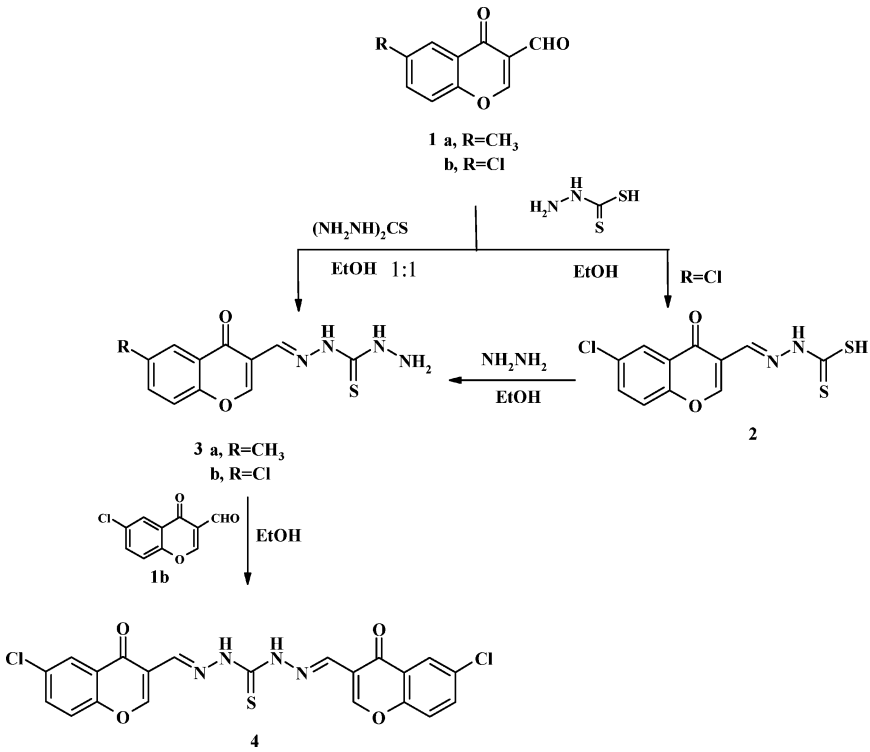
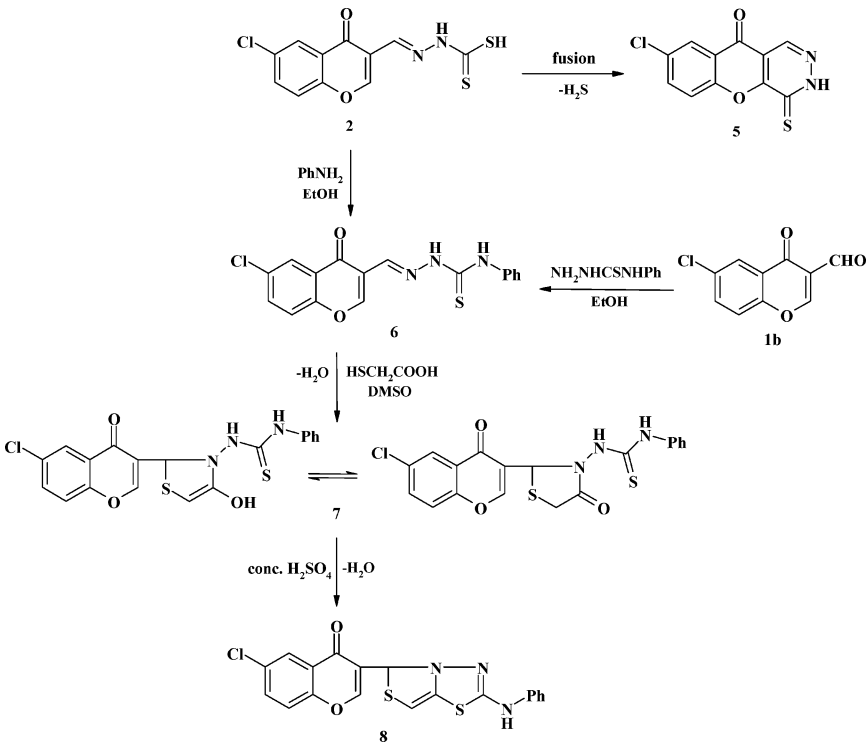


SCHEME 1

as a continuation of our interest in the synthesis of isolated heterocycles containing 4-oxo-4*H*-chromenes,[17,18] we report herein the synthesis of some new isolated chromone moiety bearing some nitrogen and/or sulfur heterocyclic systems which may have expected pharmacological activities via treatment of hydrazonecarbodithioic acid **2**, monothiocarbohydrazone **3a,b,** and bisthio-carbohydrazone **4** with oxygen, sulfur and/or halogen reagents.

RESULTS AND DISCUSSION

4-Oxo-4*H*-chromene-3-carboxaldehydes (**1a,b**) condensed with equimolar amount of hydrazinecarbodithioic acid and/or thiocarbohydrazide in ethanol to give the corresponding hydrazone derivatives **2** and **3a,b**, respectively (Scheme 1). Also, when compound **2** was allowed to react with hydrazine hydrate in ethanol produced **3b**. Condensation of **3b** with equimolar amount of **1b** in ethanol gave bisthiocarbohydrazone **4** (Scheme 1). The Structures of compounds **2–4** were confirmed by



SCHEME 2

elemental analysis and spectral data (Tables I and II). The IR spectra showed absorption bands for NH/NH_2, C=O pyrone and C=N groups at 3164–3265, 1636–1651 and 1584–1620 cm^{-1}, respectively. Also, ^1H NMR spectrum of **2** showed singlet signals at δ 11.97 and 12.19 ppm due to NH and SH protons beside signals at δ 7.60 and 8.85 ppm for H–9 and H–2 protons, while compound **3b** showed broad signals at δ 10.66 and 10.15 ppm due to NH and NH_2 protons and multiplet signal at δ 8.19 ppm for H–2 and H–9 protons. Also, their mass spectral data gave good accordance with the proposed formulas.

Fusion of hydrazonecarbodithioic acid **2**, above its melting point gave 8-chloro-4-thioxo-3,4-dihydro-10*H*-chromeno[2,3-d]pyridazin-10-one (**5**) (Scheme 2). IR spectrum of compound **5** showed broad absorption band at 3254 cm^{-1} for NH group, strong band at 1640 cm^{-1} for the carbonyl group of pyrone ring and strong band at 1605 cm^{-1} for C=N group. Also, ^1H NMR spectrum of compound **5** showed doublet signal for H–8 at δ 7.0 ppm, multiplet signals for aromatic protons at δ 7.31–7.94 ppm

TABLE I Physical Data and Mass Spectral Data of the Prepared Compounds 2–25

Compd. no.	Yield* %	M.p.°C	Cryst. solvent	Mol. formula** (Mol. wt.)	m/e (I%)
2	48	249–251	DMF	$C_{11}H_7ClN_2O_2S_2$ (298.78)	300 (M+1, 7.06%), 299 (M^+, 8.28), 298.5 (12.58), 208 (4.60), 207 (5.21), 155 (15.64), 126 (33.74), 98 (25.15), 65 (100), 53(33.44).
3a	78	193–194	Diluted DMF	$C_{12}H_{12}N_4O_2S$ (276.32)	279 (M+3, 1.94%), 278 (M+2, 18.81), 277(M+1, 91.12), 276 (M^+, 100), 246 (7.18), 117 (4.90), 115 (23.40), 91 (4.05), 90 (4.05), 87 (2.72), 65 (5.52).
3b	77[a] 74[b]	189–190	Diluted DMF	$C_{11}H_9ClN_4O_2S$ (296.74)	
4	51	222–223	Diluted DMF	$C_{21}H_{12}Cl_2N_4O_4S$ (487.32)	489 (M+2, 18.1%), 488(M+1, 24.0), 487 (M^+, 65.5), 486 (19.0), 485 (100), 279 (30.8), 233 (47.2), 207 (37.5), 206 (65.9), 180 (7.3), 155 (26.8), 154 (49.3), 53 (10.4).
5	66	>300	DMSO	$C_{11}H_5ClN_2O_2S$ (264.69)	267 (M+2, 2.56%), 266 (M+1, 21.7), 265 (M^+, 100), 236 (1.88), 222 (6.26), 221 (1.36), 205 (2.12), 194 (2.3), 51 (3.65).
6	75[a] 80[b]	230–232	DMF	$C_{17}H_{12}ClN_3O_2S$ (357.82)	358 (M^+, 1.94%), 356 (6.92), 299 (18.32), 298 (100), 265 (0.96), 223 (2.20), 155 (1.30), 92 (2.13), 77 (79.29).
7	61	202–203	Diluted DMF	$C_{19}H_{14}ClN_3O_3S_2$ (431.93)	433 (M+1, 11.22%), 355 (11.22), 339 (10.20), 295 (18.37), 253 (13.27), 236 (21.43), 179 (12.24), 154 (25.51), 152 (16.33), 111 (38.78), 87 (27.55), 57 (89.80), 55 (100).
8	55	>300	Diluted DMF	$C_{19}H_{12}ClN_3O_2S_2$ (413.91)	417 (M+3, 12.07%), 416 (M+2, 10.34), 415 (M+1, 10.34), 337 (8.62), 323 (20.69), 236 (14.66), 169 (19.83), 155 (26.72), 154 (62.07), 118 (16.38), 95 (100), 73 (50.86).
9	60	260–263	EtOH	$C_{14}H_{11}ClN_6O_2S$ (362.80)	335 (M–HCN, 17.06%), 154 (33.18), 127 (18.96), 69 (57.82), 67 (54.03), 55 (100), 54 (31.75), 52 (77.25).
10	42	152–153	MeOH	$C_{14}H_9ClN_4O_4S$ (364.77)	370 (M+5, 33.3%), 369 (M+4, 56.9), 336 (65.7), 265 (47.1), 224 (47.1), 223 (15.7), 222 (26.5), 206 (11.8), 155 (52.0), 154 (100), 72 (17.6), 55 (20.6).
11	37	220–222	Diluted EtOH	$C_{20}H_{15}ClN_4O_2S$ (410.89)	412 (M+1, 7.55%), 411 (M^+, 9.43), 234 (9.43), 154 (7.55), 147 (10.69), 78 (8.81), 69 (84.91), 55 (100).
12	78	95–96	Diluted EtOH	$C_{17}H_{15}ClN_4O_4$ (374.78)	374 (M–1, 13.6%), 245 (33.2), 222 (30.7), 206 (18.4), 205 (34.5), 169 (14.4), 168 (8.6), 155 (36.6), 154 (100), 96 (4.0), 82 (7.0), 80 (8.8), 73 (18.2), 66 (13.1).
13	45	140–141	MeOH	$C_{12}H_7ClN_4O_2S$ (306.73)	307 (M^+, 0.7%), 280 (3.4), 223 (8.0), 222 (32.4), 206 (0.6), 155 (13.2), 154 (100), 127 (3.6), 53 (5.8).

(Continued on next page)

TABLE I Physical Data and Mass Spectral Data of the Prepared Compounds 2–25 (*Continued*)

Compd. no.	Yield* %	M.p.°C	Cryst. solvent	Mol. formula** (Mol. wt.)	m/e (I%)
14	40	125–126	Diluted EtOH	$C_{18}H_{18}N_4O_5S$ (402.43)	402 (M^+, 28.7%), 401 (58.9), 359 (75.8), 317 (100), 316 (17.8), 274 (12.4), 244 (13.7), 202 (13.1), 186 (93.3), 135 (33.8), 134 (58.0), 115 (13.1), 85 (4.5).
15	56	220–222	MeOH	$C_{13}H_{10}N_4O_2S$ (286.32)	288 (M+2, 3.7%), 287 (M+1, 6.7), 286 (M^+, 32.9), 260 (7.2), 259 (44.2), 186 (12.8), 160 (1.9), 135 (15.3), 134 (100), 101 (2.6), 91 (1.9), 74 (1.3).
16	69	223–225	EtOH	$C_{14}H_{12}N_4O_2S$ (300.34)	301 (M+1, 0.23%), 300 (M^+, 0.44), 259 (0.30), 186 (40.20), 141 (0.45), 135 (12.00), 134 (17.91), 115 (100), 91 (13.7), 78 (23.07), 77 (30.13), 52 (32.17).
17	63	228–229	EtOH	$C_{12}H_7ClN_4O_2S_2$ (338.80)	340 (M+1, 3.14%), 339 (M^+, 2.35), 206 (52.29), 205 (26.54), 180 (6.01), 155 (37.65), 154 (100), 133 (5.10), 111 (17.65), 59 (20.92), 52 (28.89).
18	55	157–160	MeOH	$C_{14}H_{12}N_4O_3S$ (316.34)	319 (M+3, 0.5%), 318 (M+2, 3.6), 317 (M+1, 8.2), 316 (M^+, 45.5), 273 (10.7), 186 (8.2), 160 (2.1), 135 (38.5), 134 (100), 131 (1.8), 130 (1.1), 91 (2.0), 77(21.8).
19	32	230–231	MeOH	$C_{13}H_7ClN_4O_3S$ (334.74)	339 (M+4, 9.0%), 338 (M+3, 46.2), 279 (28.4), 222 (19.6), 206 (19.1), 180 (4.0), 155 (45.5), 154 (100), 128 (9.9), 101 (12.6), 69 (8.6), 59 (28.0), 53 (21.6).
20	28	242–244	EtOH	$C_{13}H_7ClN_4O_4S$ (350.74)	351 (M^+, 30.7%), 350 (21.9), 349 (72.6), 279 (21.2), 195 (18.6), 166 (23.4), 88 (100), 87 (23.7), 71 (20.1).
21	70	255–257	EtOH	$C_{19}H_{13}ClN_4O_2S$ (396.86)	367 ($M–N_2H_2$, 8.93%), 222 (3.84), 218 (4.32), 205 (8.92), 154 (4.96), 141 (4.39), 115 (8.77), 85 (35.91), 77 (8.25), 56 (27.52), 55 (100).
22	78	229–230	EtOH	$C_{15}H_{12}N_4O_3S$ (328.35)	330 (M+2, 5.6%), 329 (M+1, 20.9), 328 (M^+, 8.3), 186 (95.1), 160 (9.7), 143 (100), 134 (11.2), 115 (6.9), 102 (7.9), 91 (6.6), 84 (2.7), 52 (2.6).
23	59	242–244	DMF	$C_{23}H_{14}Cl_2N_4O_5S$ (529.36)	529 (M^+, 13.6%), 528 (24.6), 527 (13.6), 526 (31.6), 280 (17.1), 279 (81.3), 252 (4.2), 209 (3.3), 207 (7.7), 206 (19.1), 194 (5.9), 180 (5.2), 155 (55.5), 154 (100).
24	55	245–247	Diluted DMF	$C_{23}H_{12}Cl_2N_4O_5S$ (527.35)	530 (M+3, 12.3%), 529 (M+2, 10.9), 528 (M+1, 38.9), 527 (M^+, 17.9), 372 (19.4), 321 (5.7), 279 (84.2), 206 (19.8), 180 (2.1), 155 (48.4), 154 (100).
25	54	120–122	Diluted AcOH	$C_{24}H_{12}Cl_2N_4O_6S$ (555.36)	527 (M–CO, 10.4%), 321 (29.2), 279 (100), 206 (21.9), 180 (6.2), 155 (49.5), 154 (97.6), 115 (28.9), 101 (16.2).

*C, H, N elemental analysis for all products gave satisfied results. **a,b indicated to the yields by methods A and B.

TABLE II IR and ^{1}H NMR Spectral Data for the Prepared Compounds 2–25

Compd. no.	IR (KBr), υ (cm^{-1})	^{1}H NMR (DMSO–d_6), δ (ppm)
2	3229 (br, NH), 3075 (CH_{arom}), 1643 ($C{=}O_{pyrone}$), 1584 (C=N).	7.60 (2H, m, H–8 and H–9), 7.95 (1H, dd, J = J = 5.34 and 2.0 Hz, H–7), 8.61 (1H, m, H–5), 8.85 (1H, s, H–2), 11.97, 12.19 (2H, ss, NH and SH)
3a	3193–3164 (br, NH, NH_2), 3002 (CH_{arom}), 2919 (CH_{aliph}), 1648 ($C{=}O_{pyrone}$), 1616 (C=N).	
3b	3265–3216 (br, NH, NH_2), 3049 (CH_{arom}), 2929 (CH_{aliph}), 1651 ($C{=}O_{pyrone}$), 1604 (C=N).	6.98 (1H, d, J = J = 6.1 Hz, H–8), 7.46 (1H, d,J = J = 6.1 Hz, H–7), 7.89 (1H, m, H–5), 8.19 (2H, m, H–2 and H–9), 10.15 (1H, br, NH), 10.66 (2H, br, NH_2).
4	3202 (br, NH), 3009 (CH_{arom}), 2919 (CH_{aliph}), 1636 ($C{=}O_{pyrone}$), 1620 (C=N).	
5	3254 (br, NH), 3063 (CH_{arom}), 1640 ($C{=}O_{pyrone}$), 1605 (C=N).	7.00 (1H, d, J = J = 12 Hz, H–8), 7.31–7.94 (3H, m, Ar–H), 10.43 (1H, s, NH).
6	3273, 3227 (NH), 3085, 3054, 3002 (CH_{arom}), 1636 ($C{=}O_{pyrone}$), 1596 (C=N).	7.20–7.58 (5H, m, Ph–H), 7.80 (1H, d, J = 12 Hz, H–8), 7.88–7.94 (1H, dd, J = 2.89, 12 Hz, H–7), 8.06 (1H, d, J = 2.89 Hz, H–5), 8.28 (1H, s, H–9), 9.38 (1H, s, H–2), 10.16 (1H, s, NH), 12.01 (1H, s, NH).
7	3258, 3148 (NH), 3070 (CH_{arom}), 2923 (CH_{aliph}), 1689 ($C{=}O_{thiazolidinone}$), 1626 ($C{=}O_{pyrone}$), 1602 (C=N).	3.91 (2H, s, $COCH_2$), 6.50 (1H, s, SCHN), 6.89–7.45 (9H, m, Ar–H, Ph–H and H–2), 10.70 (1H, s, NH), 11.6 (1H, s, NH).
8	3343 (NH), 3056 (CH_{arom}), 2920 (CH_{aliph}), 1659 ($C{=}O_{pyrone}$), 1595 (C=N).	
9	3455, 3358, 3226 (NH_2, NH), 3073 (CH_{arom}), 2926 (CH_{aliph}), 1637 ($C{=}O_{pyrone}$).	3.91 (2H, s, NH_2), 4.48 (2H, s, NH_2), 7.00–7.04, 7.51–7.55 (4H, m, Ar–H and $CH_{pyrazole}$), 8.52–8.69 (2H, m, H–2 and H–9), 10.45 (1H, s, NH).
10	3331 (br, NH), 3064 (CH_{arom}), 2925 (CH_{aliph}), 1761 (br, $C{=}O_{pyrazolinone}$), 1642 ($C{=}O_{pyrone}$), 1605 (C=N).	

(Continued on next page)

TABLE II IR and ^{1}H NMR Spectral Data for the Prepared Compounds 2–25 (*Continued*)

Compd. no.	IR (KBr), υ (cm^{-1})	^{1}H NMR (DMSO–d_6), δ (ppm)
11	3424 (br, NH), 3059 (CH_{arom}), 2926 (CH_{aliph}), 1625 ($C{=}O_{pyrone}$), 1597 (C=N).	1.90 (2H, s, $CH_{2pyrazoline}$), 2.89 (1H, s, $CH_{pyrazoline}$), 7.02 (1H, dd, J = 12.6, 3.9 Hz, H–7), 7.51–7.55, 8.14–8.31 (9H, m, Ph–H, Ar–H, N = $CH_{pyrazoline}$ and H–9), 8.93 (1H, s, H–2), 10.45 (1H, s, NH).
12	3198 (br, NH), 3071 (CH_{arom}), 2983 (CH_{aliph}), 1709 ($C{=}O_{ester}$), 1627 ($C{=}O_{pyrone}$), 1596 (C=N).	1.09 (3H, t, J = 9.47 Hz, CH_3), 3.37 (3H, s, Ar–CH_3), 4.10 (2H, q, J = 9.47 Hz, CH_2), 7.02 (1H, d, J = 8.23 Hz, H–8), 7.43–7.47 (2H, m, H–5 and H–7), 8.08 (1H, s, H–9), 8.62 (1H, s, H–2), 10.68 (1H, s, NH), 13.56 (1H, s, NH).
13	3274, 3126 (br, NH), 1628 ($C{=}O_{pyrone}$), 1581 (C=N).	7.01 (1H, d, J = 8.64 Hz, H–8), 7.39–7.52 (2H, m, H–5 and H–7), 8.12–8.36 (3H, m, $CH_{thiadizole}$, H–9 and H–2), 9.01, 9.52 (1H, ss, NH).
14	3262 (br, NH), 3071, 3016 (CH_{arom}), 2928 (CH_{aliph}), 1715 (br, $C{=}O_{acetyl}$), 1646 ($C{=}O_{pyrone}$), 1620 (C=N).	2.05 (6H, s, CH_3), 2.11 (3H, s, CH_3), 2.45 (3H, s, Ar–CH_3), 6.77 (1H, s, $CH_{thidiazole}$), 7.59–7.72 (2H, m, H–7 and H–8), 7.88 (1H, d, J = 1.16 Hz, H–5), 8.92 (1H, s, H–2), 11.02 (1H, s, NH).
15	3112 (NH), 2927 (CH_{aliph}), 1625 ($C{=}O_{pyrone}$), 1598 (C=N).	2.29 (3H, s, CH_3), 6.93 (1H, d, J = 11.23 Hz, H–8), 7.32 (1H, d, J = 11.23 Hz, H–7), 7.50 (1H, s, H–5), 8.38 (1H, s, H–9), 9.03 (1H, s, H–2,), 9.52 (1H, s, $CH_{triazole}$), 10.65 (1H, s, NH).
16	3109 (NH), 3067 (CH_{arom}), 2938 (CH_{aliph}), 1651 ($C{=}O_{pyrone}$), 1619 (C=N), 1601 (C = C).	2.46 (3H, s, Ar–CH_3), 2.50 (3H, s, Ar–CH_3), 7.48–7.66 (2H, m, H–7 and H–8), 7.93 (1H, s, H–5), 8.20 (1H, br, H–9), 8.71 (1H, br, H–2), 11.03 (1H, s, SH).
17	3219 (br, NH), 3028 (CH_{arom}), 1639 ($C{=}O_{pyrone}$), 1613 (C=N).	6.98–7.52 (1H, m, H–8), 7.79–8.29 (2H, m, H–5 and H–7), 8.87 (1H, m, H–9), 9.32–9.35 (1H, m, H–2), 10.51, 10.64 (2H, ss, NH), 12.01, 12.37 (2H, ss, SH).
18	3258, 3149 (NH), 3070 (CH_{arom}), 2924 (CH_{aliph}), 1689 ($C{=}O_{triazinone}$), 1650 ($C{=}O_{pyrone}$), 1626 (C=N).	3.77 (2H, s, CH_2), 6.90 (1H, d, J = 11.12 Hz, H–8), 7.27–7.38 (2H, m, H–5 and H–7), 8.22 (1H, s, H–9), 8.60 (1H, s, H–2), 10.60 (1H, s, NH), 11.49 (1H, s, NH).

(Continued on next page)

TABLE II IR and ^{1}H NMR Spectral Data for the Prepared Compounds 2–25 (*Continued*)

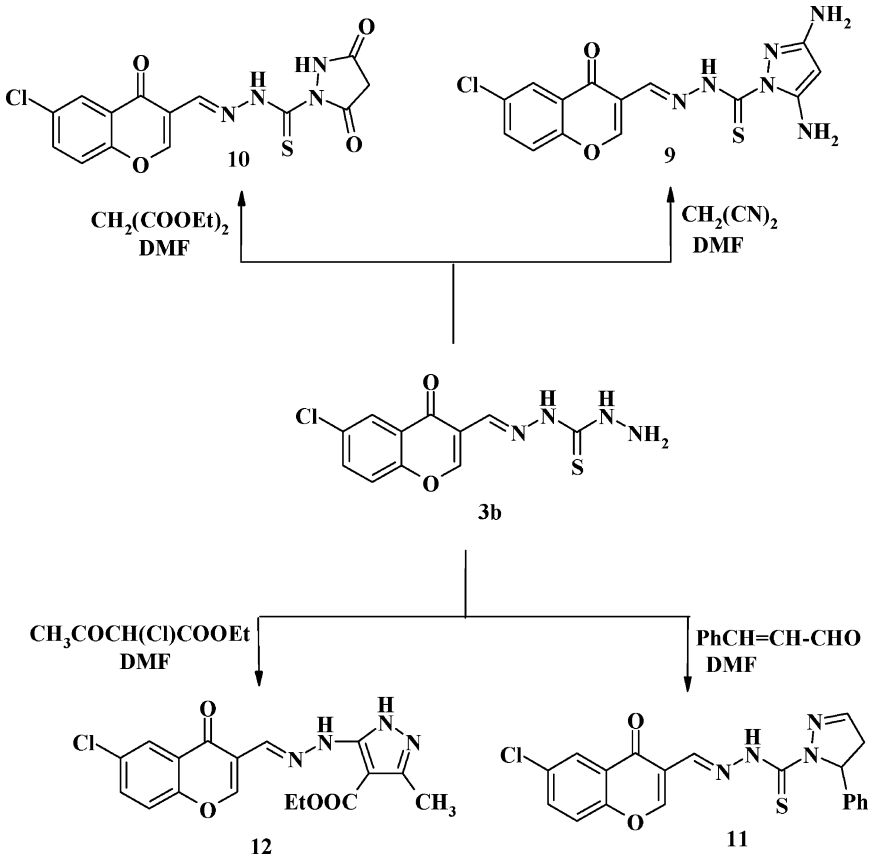
Compd. no.	IR (KBr), υ (cm^{-1})	^{1}H NMR (DMSO–d_6), δ (ppm)
19	3112 (NH), 1702 ($C{=}O_{triazinone}$), 1626 ($C{=}O_{pyrone}$), 1599 (C=N).	7.44–8.32 (4H, m, Ar–H and H–9), 8.93 (1H, s, H–2), 9.48 (1H, s, $CH_{triazinone}$), 10.50 (1H, br, NH).
20	3425 (br, NH, enolic OH), 3066 (CH_{arom}), 1647 (br, $C{=}O_{triazinedione}$), 1619 ($C{=}O_{pyrone}$).	
21	3111 (br, NH), 2928 (CH_{aliph}), 1624 ($C{=}O_{pyrone}$), 1598 (C=N).	7.03 (1H, d, J = 12.5 Hz, H–8), 7.49–7.53 (3H, m, H–5, H–7 and $CH_{triazinone}$), 8.41 (1H, s, H–9), 9.06 (1H, s, H–2), 10.70 (1H, s, NH).
22	3173 (NH), 3085 (CH_{arom}), 2958 (CH_{aliph}), 1701 ($C{=}O_{triazine}$), 1641 ($C{=}O_{pyrone}$).	2.20 (3H, s, Ar–CH_3), 2.47 (3H, s, Ar–CH_3), 7.64–7.75 (2H, m, H–7 and H–8), 7.93 (1H, s, H–5), 8.76 (1H, s, H–9), 9.14 (1H, s, H–2), 13.66 (1H, s, SH).
23	3066 (br, NH), 2960 (CH_{aliph}), 1724 ($C{=}O_{acetyl}$), 1651 (br, $C{=}O_{pyrone}$), 1605 (C=N).	2.89 (3H, s, CH_3), 6.38 (1H, d, J = 6.3 Hz, H–8), 7.00–7.03, 7.42–7.51 (7H, m, Ar–H, H–9 and $CH_{thiadiazole}$), 8.42, 8.49 (2H, ss, H–2 and H–2′), 11.23 (1H, s, NH).
24	3082 (CH_{arom}), 2924 (CH_{aliph}), 1695 ($C{=}O_{imidazolinone}$), 1654 ($C{=}O_{pyrone}$), 1615 (C=N).	3.59–3.63 (2H, m, CH_2), 7.06 (2H, d, J = 9.15 Hz, H–8 and H–8′), 7.42–7.51 (4H, m, H–7, H–7′, H–5 and H–5′), 8.11 (1H, s, $=CH_{imidazole}$), 8.40 (2H, s, H–9 and H–9′), 9.05 (2H, s, H–2 and H–2′), 12.20 (1H, br, enolic OH).
25	3125 (br, enolic OH), 2933 (CH_{aliph}), 1710 ($C{=}O_{pyrimidinedione}$), 1630 ($C{=}O_{pyrone}$), 1602 (C=N).	

and singlet signal for NH proton at δ 10.43 ppm (Table II). Moreover, its mass spectrum recorded a molecular ion peak at m/e = 265 (M^+, 100%).

Treatment of hydrazonecarbodithioic acid **2** with aniline in ethanol yielded N-(6-chloro-4-oxo-4*H*-chromene-3-carbaldehyde)phenylthiose micarbazone (**6**), which also was obtained in high yield from condensation of 6-chloro-4-oxo-4*H*-chromene-3-carboxaldehyde (**1b**) with 4-phenylthiosemicarbazide in ethanol (melting point and mixed melting point gave no depression) (Scheme 2). IR spectrum of **6** showed strong bands at 3273, 3227 cm^{-1} for NH groups, strong band at 1636 cm^{-1} for C=O pyrone group and strong band at 1596 cm^{-1} for C=N group. Also, ^{1}H NMR spectrum of **6** recorded two singlet signals at δ 8.28 and 9.38 ppm for H–9 and H–2 protons, respectively and the other two singlet signals at δ 10.16 and 12.01 ppm for NH protons, while its mass spectrum recorded a molecular ion peak at m/e = 358 (M^+, 1.94%) (Tables I and II).

The addition–condensation reaction of thioglycolic acid to thiosemicarbazone **6** in boiling DMSO furnished, 1-[2-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenylthiourea (**7**), which on cyclization with concentrated sulfuric acid afforded 3-(2-anilino-1, 3-thiazolo[4,3-b][1,3,4]thiadiazol-5-yl)-6-chloro-4*H*-chromen-4-one (**8**) (Scheme 2). The reaction pathway is assumed to proceed *via* intramolecular nucleophilic attack by the thionic S of the thiourea moiety to cyclic electrophilic C=O of thiazolidinone moiety followed by elimination of water molecule.[15] IR spectrum of compound **7** revealed broad bands at 3258, 3148 cm^{-1} for NH groups, strong bands at 1689, 1626, and 1602 cm^{-1} for C=O thiazolidinone, C=O pyrone, and C=N groups, respectively, while that of compound **8** showed absence of carbonyl group of thiazolidinone and the presence of strong band at 1659 cm^{-1} for carbonyl group of pyrone is agreement with the postulated structure. Also, ^{1}H NMR spectrum of compound **7** recorded singlet signal at δ 3.91 ppm for CH_2 of thiazolidinone, signal at δ 6.50 ppm due to H–2 of thiazolidinone proton, multiplet signals at δ 6.89–7.45 ppm due to aromatic protons and two singlet signals at δ 10.70, 11.60 ppm for NH protons (Table II). Mass spectral data of compounds **7** and **8** gave a good accordance with the formed structures (Table I).

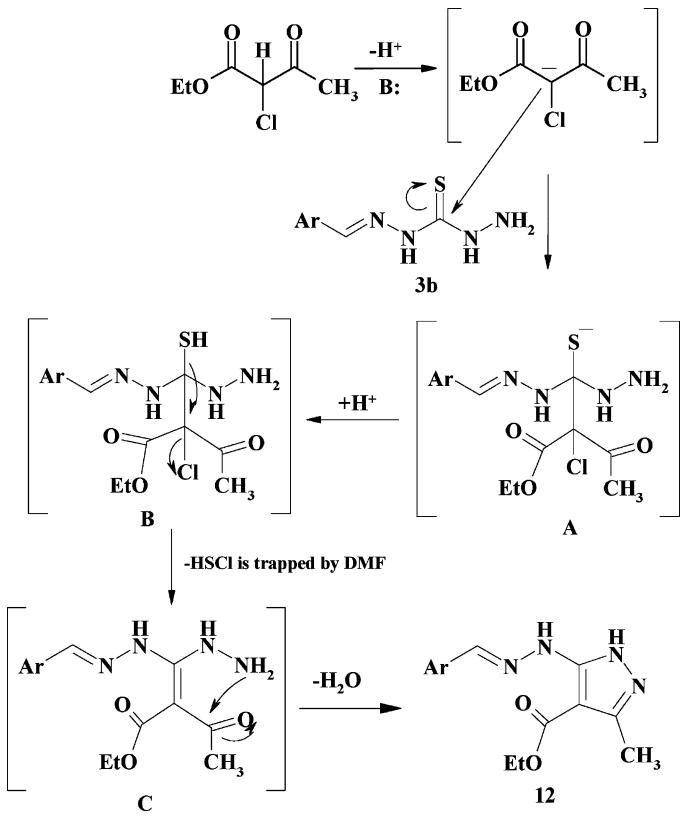
On treating monothiocarbohydrazone **3b** with malononitrile, diethyl malonate and/or cinnamaldehyde in DMF and few drops of piperidine afforded the pyrazoles derivatives **9**–**11**, respectively (Scheme 3). Assignment of the products **9** and **10** was based on their elemental analysis, IR, ^{1}H NMR, and MS spectral data (Tables I and II). Their IR spectra revealed absorption bands for NH_2 and NH groups and strong bands for carbonyl groups of pyrone. The ^{1}H NMR spectrum of compound **9** showed two singlet signals at δ 3.91, 4.48 ppm for NH_2 protons, multiplet signals at δ 8.52–8.69 ppm for H–2, H–9 protons and singlet signal



SCHEME 3

at δ 10.45 ppm for NH proton. Mass spectra of compounds **9** and **10** exhibited a molecular ion peaks at m/e = 335 (M–HCN, 17.06%) and m/e = 370 (M+5, 33.3%), respectively. On the other hand, IR spectrum of **11** revealed the presence of NH group at 3424 cm^{-1}, C=O pyrone group at 1625 cm^{-1} and strong band at 1597 cm^{-1} due to C=N group. The ^{1}H NMR spectrum of compound **11** exhibited signals due to CH_2 and CH–N of pyrazole moiety at δ 1.90 and 2.89 ppm respectively, singlet signal at δ 8.93 ppm for H–2 proton and singlet signal at δ 10.45 ppm for NH proton (Table II).

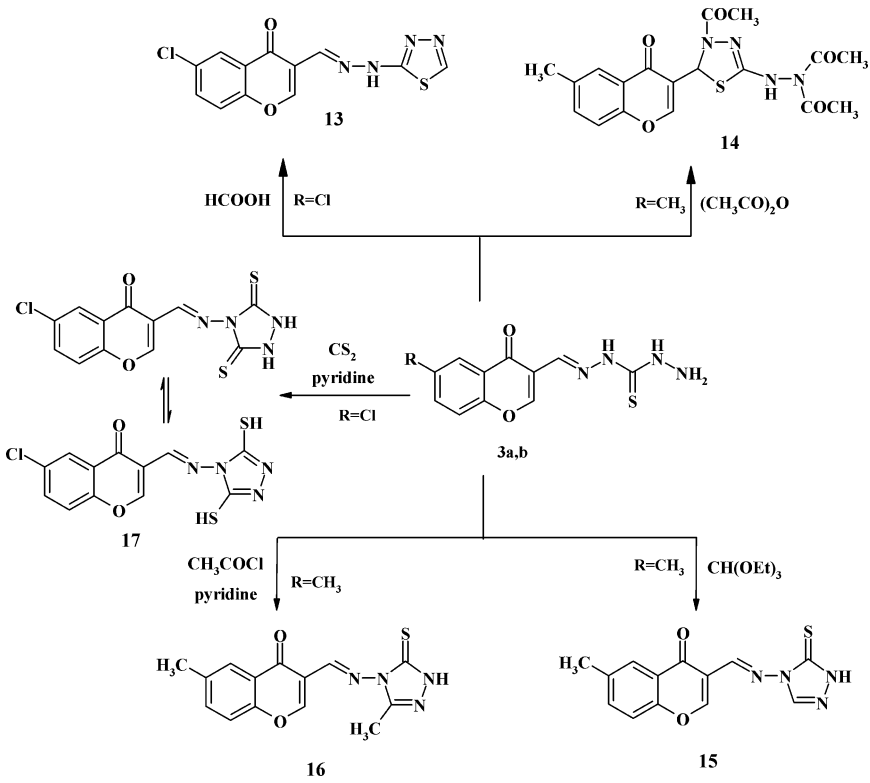
Also, treatment of **3b** with ethyl 2-chloro-acetoacetate in DMF[19,20] yielded unexpected product ethyl 5-[2-(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)hydrazino]-3-methyl-1*H*-pyrazole-4-carboxylate (**12**) (Scheme 3). Formation of compound **12** may be occurred by carbanion attack of ethyl 2-chloroacetoacetate at C=S group of compound **3b**



SCHEME 4

to form intermediate **A** which accept proton to form intermediate **B** followed by elimination of HSCl molecule to give intermediate **C**. Cyclocondensation reaction of intermediate **C** gave compound **12** (Scheme 4). Sulfur test and spectral data of compound **12** emphasized that sulfur atom was removed through the reaction. IR spectrum of compound **12** showed broad band at 3198 cm^{-1} for NH groups and strong bands at 1709, 1627, and 1596 cm^{-1} for C=O ester, C=O pyrone and C=N group, respectively, while its ^1H NMR spectrum recorded signals at δ 1.09, 4.10 ppm due to ethoxy protons, singlet signals at δ 8.08, 8.62, 10.68, and 13.56 ppm for H–9, H–2, and NH protons, respectively (Table II).

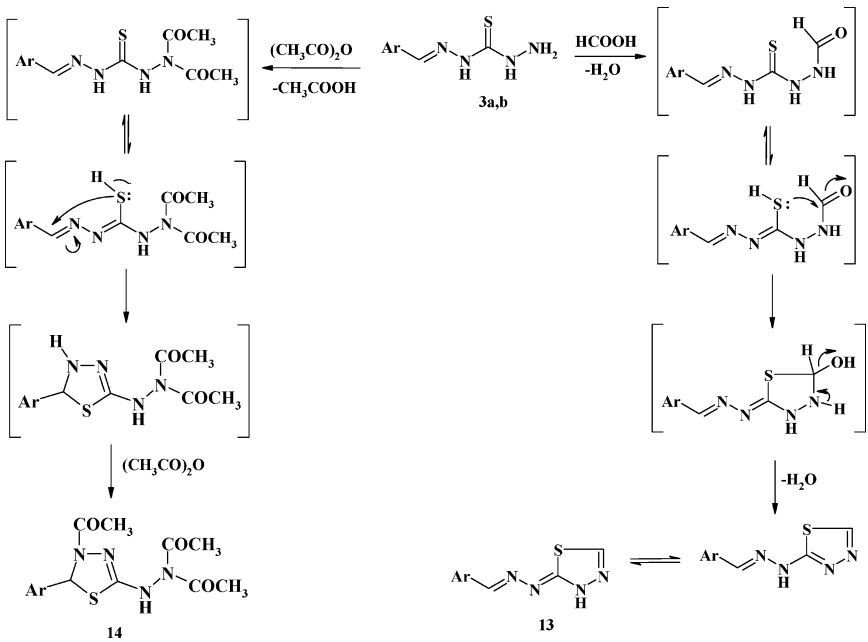
On the other hand, refluxing of compound **3b** with excess formic acid at 95°C yielded 6-chloro-3-(1,3,4-thiadiazol-2-yl-hydrazonomethyl)-4*H*-chromen-4-one (**13**) (Scheme 5). Structure of compound **13** was deduced from IR spectrum which showed broad band at 3274, 3126 cm^{-1} for NH



SCHEME 5

group and broad bands at 1628 and 1581 cm^{-1} for C=O pyrone and C=N groups, respectively, while its ^1H NMR spectrum recorded multiplet signals at δ 7.01–8.36 ppm for aromatic protons and singlet signals at δ 9.01, 9.52 ppm for NH proton (Table II). Moreover, its mass spectrum recorded a molecular ion peak at m/e = 307 (M^+, 5.7%) (Table I).

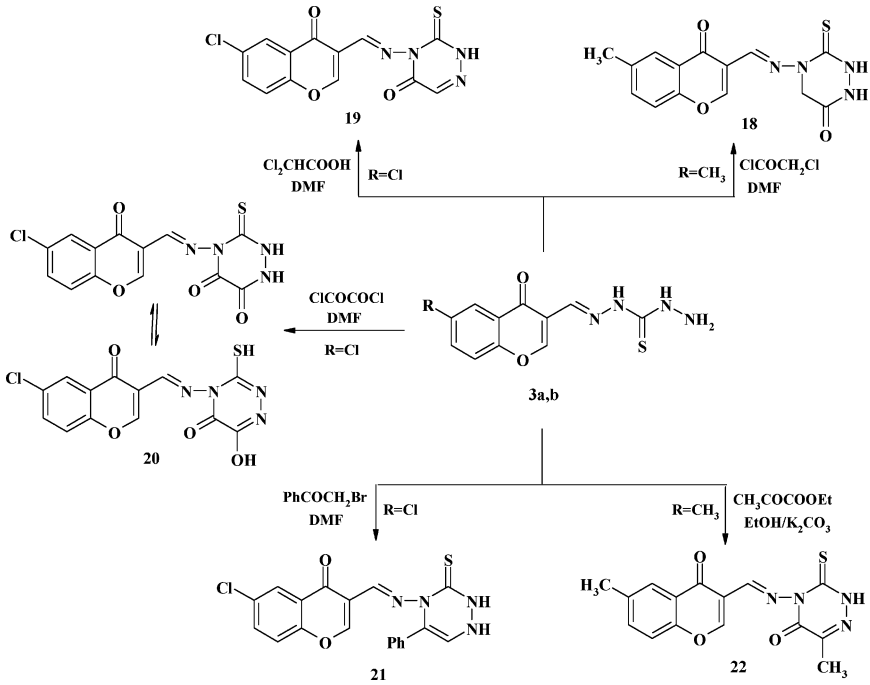
Also, refluxing of compound **3a** with acetic anhydride gave N-acetyl-N′-[4-acetyl-5-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1, 3,4-thiadiazol-2-yl]acetohydrazide (**14**), (Scheme 5). IR spectrum of compound **14** showed broad bands at 3262, 1715 and 1646 cm^{-1} for NH, C=O acetyl groups and C=O pyrone, respectively. Also, its ^1H NMR spectrum showed singlet signals at δ 2.05, 2.45, and 2.51 ppm for four groups of methyl protons, singlet signal at δ 8.92 ppm for H–2 proton and singlet signal at δ 11.02 ppm for NH proton (Table II). Formation of compound **13** took place by formylation of amino group of compound **3b** with formic acid instead of reduction of C=N and then cyclization of the formyl derivative (Scheme 6), while Formation compound **14** may be occurred



SCHEME 6

via acetylation of amino group followed by cycloaddition reaction of thiol form of monothiocarbohydrazone **3a** in acidic medium to form an intermediate which on acetylation gave compound **14** (Scheme 6).[21]

A facile route to synthesize 6-methyl-3-[3-thioxo-1,5-dihydro-1,2,4-triazol-4-yliminomethyl]-4*H*-chromen-4-one (**15**) and 6-methyl-3-[5-methyl-3-thioxo-1,5-dihydro-1,2,4-triazol-4-yliminomethyl]-4*H*-chromen-4-one (**16**) have been achieved by refluxing of monothiocarbohydrazone **3a** with triethylorthoformate and/or acetyl chloride in pyridine, respectively (Scheme 5). In addition, refluxing **3b** with carbon disulfide in pyridine gave 1,2,4-triazole-3,5-dithione derivative **17** (Scheme 5). Formation of compound **17** may be occurred *via* addition reaction of NH_2 group to carbon disulfide followed by cyclocondensation reaction with elimination of one molecule of H_2S. The spectral data of **15–17** were consistent with their structures (Tables I and II). IR spectra showed broad bands at 3219–3109 cm^{-1} for NH groups and also strong bands at 1625–1639 and 1598–1619 cm^{-1} for C=O pyrone and C=N groups, respectively. The ^1H NMR spectrum of compounds **15** and **16** showed characteristic signals for NH triazole at δ 10.65 and 11.03 ppm, respectively, while ^1H NMR spectrum of compound **17** recorded multiplet signals at δ 6.98–9.35 ppm for aromatic protons, two singlet signals at δ 10.51, 10.64 ppm for NH protons and the other two singlet signals at



SCHEME 7

δ 12.01, 12.37 ppm for SH protons which support that compound **17** exists in tautomeric forms. Mass spectra of compounds **15–17** recorded molecular ion peaks at m/e = 286 (M^+, 32.9%), and 300 (M^+, 0.44%) and 339 (M^+, 2.35%), respectively.

Cyclocondensation reaction of monothiocarbohydrazone **3a,b** with chloroacetyl chloride, dichloroacetic acid, and/or oxalyl chloride in DMF and few drops of piperidine as catalyst led direct to the formation of 1,2,4-triazine-3-thione derivatives **18–20**, respectively (Scheme 7). Assignment of the products **18–20** was based on their elemental analysis, IR, ^{1}H NMR and MS spectral data (Tables I and II). The IR spectra revealed characteristic absorption broad bands at 3112–3425 cm^{-1} for NH groups, strong bands at 1647–1702 cm^{-1} for C=O triazinone groups and strong bands at 1619–1650 cm^{-1} for C=O pyrone groups. The ^{1}H NMR spectrum of compound **18** recorded singlet signal at δ 3.77 (CH_2), 10.60 (NH triazine) and 11.49 ppm (NH triazine). Also, ^{1}H NMR spectrum of **19** showed singlet signal at δ 9.48 ppm (C_6—H triazinone) and broad signal at δ 10.50 ppm for NH triazinone. Mass spectral data of compounds **18–20** showed gave a good accordance with the formed structures.

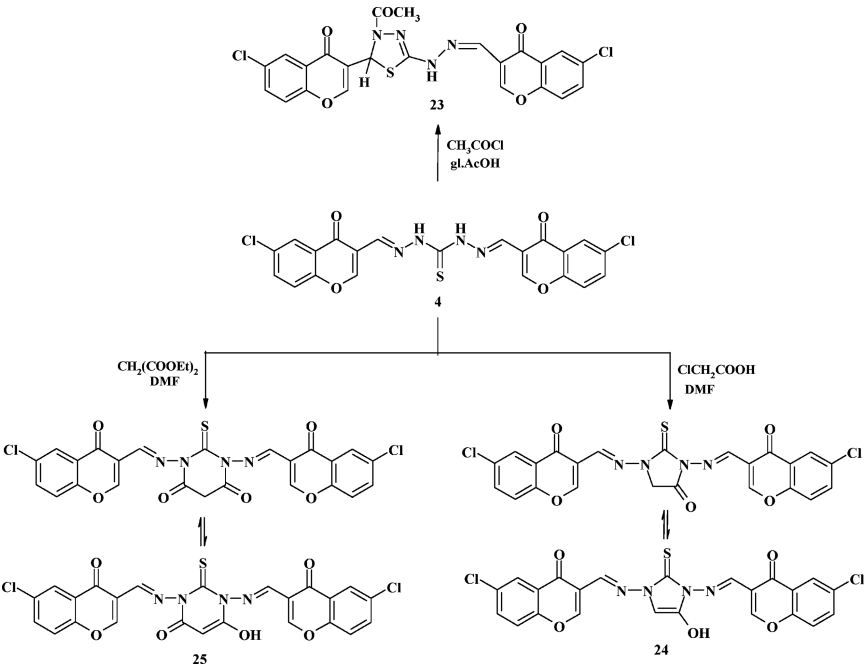
The interaction between compound **3b** and phenacyl bromide in DMF containing few drops of piperidine gave 4-([6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]-5-phenyl-3-thioxo-2,3-dihydro-1,2,4-triazine (**21)** and while cyclocondensation reaction of monothiocarbohydrazone **3a** with ethyl pyruvate in ethanol and presence of potassium carbonate yielded 6-methyl-4-[(6-methyl-4-oxo-4*H*-chromen-3-ylmethylene)amino]-3-thioxo-3,4-dihydro-1,2,4 -triazin-5(2*H*)-one (**22**) (Scheme 7). IR spectra of compounds **21** and **22** showed characteristic absorption broad band at 3111, 3173 cm^{-1} for NH groups and strong bands at 1624 and 1641 cm^{-1} for C=O pyrone groups, respectively. Also, the ^1H NMR spectra of compounds **21** and **22** recorded singlet signals at δ 10.70 and 13.66 ppm for NH protons, respectively (Table II); while their mass spectra recorded a molecular ion peaks at m/e 367 ($M\text{-}N_2H_2$, 8.93%) and 328 (M^+, 8.30%), respectively (Table I).

Cycloaddition of bisthiocarbohydrazone **4** with acetyl chloride in glacial acetic acid[21,22] afforded 6-chloro-4-oxo-4*H*-chromene-3-carbaldehyde[4-acetyl-5-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro -1,3,4-thiadiazol-2-yl]hydrazone (**23**) (Scheme 8). IR spectrum of compound **23** showed a broad band at 3066 cm^{-1} for NH group and strong bands at 1724, 1651 and 1605 cm^{-1} for C=O acetyl, C=O pyrone and C=N groups respectively. The ^1H NMR spectrum of compound **23** recorded singlet signal at δ 2.89 ppm for acetyl protons, doublet signal at δ 6.38 ppm for H–8 proton, multiplet signals at δ 7.00–7.51 ppm for aromatic protons and three singlet signals at δ 8.42, 8.49, and 11.23 ppm for H–2, H–2′ and NH protons, respectively (Table II).

Finally, 2-thioxoimidazolidin-4-one **24** and 2-thioxodihydropyrimidine-4,6(1*H*, 5*H*)-dione **25** derivatives were obtained from treatment bisthiocarbohydrazone **4** with chloroacetic acid and/or diethyl malonate, respectively in DMF containing few drops of piperidine (Scheme 8).[23] IR spectra of **24** and **25** showed the disappearance of NH groups and appearance of a new strong bands at 1695 cm^{-1} for C=O imidazolinone and 1710 cm^{-1} for C=O pyrimidinedione, respectively. The ^1H NMR spectrum of **24** confirmed appearance new multiplet signal at δ 3.59–3.63 ppm for CH_2 of imidazolinone and broad singlet signal at δ 12.20 ppm for enolic OH group of imidazole (Table II). Mass spectral data of **24** and **25** gave accordance with the suggested formulas (Table I).

Antifungal Activity

Some new synthesized compounds were screened for their antifungal activities against three species of fungi, *Alternaria alternata,*



SCHEME 8

Aspergillus niger, and *Aspergillus flavipes* using disc diffusion method.[24,25] The tested compounds were dissolved in DMF, which was used as a control to get 1 mg/ml solution. The inhibition zones of microbial growth surrounding the filter paper disc (2.5 mm) were measured in millimeters at the end of an incubation period at 30°C for 3 days. Activity of each compound was compared with that of flucanazole as the standard. The investigation of fungicidal screening data (Table III) revealed compound **4** and **8** showed high activity against the three species of fungi. Also, Compound **6** showed high activities against *Aspergillus flavipes* and moderate activities against *Alternaria alternata* and *Aspergillus niger,* while compound **10** showed moderate activities against *Alternaria alternata* and *Aspergillus flavipes* and lower activity against *Aspergillus nig*er. Moreover, compounds **19** and **12** showed moderate activities against the three species of fungi, while compounds **17** and **25** showed moderate activities against *Aspergillus niger* and *Aspergillus flavipes*, while Compound **13** showed lower activities against *Alternaria alternata* and *Aspergillus niger*.

TABLE III Antifungal Activities Data of Some the Prepared Compounds

	Diameter of inhibition zone (mm)		
Compd. no.	*Alternaria alternata*	*Aspergillus niger*	*Aspergillus flavipes*
4	+++	+++	++++
6	++	++	+++
8	+++	+++	+++
10	++	+	++
12	++	++	++
13	+	+	++
17	+	++	++
19	++	++	++
25	+	++	++
flucanazole	++++	++++	++++

+ (Inhibition zone 1–10 mm) = lower active; ++ (inhibition zone 11–20 mm) = moderately active; +++ (inhibition zone 21–30 mm) = high active. and ++++ (inhibition zone >30 mm) = very high active.

EXPERIMENTAL

Melting points were determined on a digital Stuart SMP3 and are uncorrected. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer (γ in cm^{-1}), using KBr disks. ^1H NMR spectra were measured on 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 on Perkin Elmer CHN–2400 analyzer or C, H, N manual in microanalysis center at Cairo University. 4-Oxo-4*H*-chromene-3-carboxaldehydes (**1a,b**),[26] hydrazinecarbodithioic acid,[27] and thiocarbohydrazide[27] were prepared by published methods.

2-[(6-Chloro-4-oxo-4*H*-chromen-3-yl) methylene]hydrazinecarbodithioic acid (2)

A mixture of **1b** (2.08 g, 10 mmol) and hydrazinecarbodithioic acid (1.08 g, 10 mmol) in absolute ethanol (50 ml) was refluxed for 2 h. The obtained solid was filtered off and crystallized from the proper solvent to give **2** (Table I).

N′-[(6-Substituted-4-oxo-4*H*-chromen-3-yl) methylene]thiocarbohydrazide (3a,b)

Method A

Equimolar amounts of **1a,b** (10 mmol) and thiocarbohydrazide (1.06 g, 10 mmol) in absolute ethanol (50 ml) was refluxed for 2 h. The obtained solid was filtered off and crystallized from the proper solvent to give **3a,b** (Table I).

Method B

A mixture of **2** (2.98 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in ethanol (50 ml) was refluxed for 3 h. The obtained solid was filtered off and crystallized from the proper solvent to give **3b** (Table I).

1,5-Bis[(6-chloro-4-oxo-4*H*-chromen-3-yl) methylene]thiocarbohydrazide(4)

A mixture of **3b** (2.96 g, 10 mmol) and 6-chloro-3-formylchromone (**1b**) (2.08 g, 10 mmol) in absolute ethanol (50 ml) was refluxed for 5 h. The obtained solid was filtered off and crystallized from the proper solvent to give **4** (Table I).

8-Chloro-4-thioxo-3,4-dihydro-10*H*-chromeno[2,3-d] pyridazin-10-one (5)

N′-(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)hydrazinecarbothioic acid (**2b**) (1 g) was fused above its melting point for 15 min. The product was treated with methanol then filtered off and crystallized from the proper solvent to give **5** (Table I).

N-(6-Chloro-4-oxo-4*H*-chromene-3-carbaldehyde) phenylthiosemicarbazone (6)

Method A

A mixture of **2** (2.98 g, 10 mmol) and aniline (0.93 g, 10 mmol) in ethanol (50 ml) was refluxed for 5 h. The obtained solid was filtered off and crystallized from the proper solvent to give **6** (Table I).

Method B

A mixture of **1b** (2.08 g, 10 mmol) and 4-phenylthiosemicarbazide (1.67 g, 10 mmol) in ethanol (50 ml) was refluxed for 1 h. The obtained

solid was filtered off and crystallized from the proper solvent to give **6** (Table I).

1-[2-(6-Chloro-4-oxo-4*H*-chromen-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenyl-thiourea (7)

A mixture of **6** (3.57 g, 10 mmol) and thioglycolic acid (0.92 g, 10 mmol) in DMSO (50 ml) was refluxed for 6 h. The solution was cooled and poured onto ice–water. The solid obtained was filtered off and crystallized from the proper solvent to give **7** (Table I).

3-(2-Anilino[1,3]thiazolo[4,3-b][1,3,4]thiadiazol-5-yl)-6-chloro-4*H*-chromen-4-one (8)

A mixture of **7** (4.31 g, 10 mmol) and concentrated sulfuric acid (20 ml) was stirred for 1 h at 0–5°C and poured onto ice. The obtained solid was filtered off and crystallized from the proper solvent to give **8** (Table I).

The 1H-pyrazole-1-thiocarbohydrazide Derivatives (9–11)—General Method

A mixture of **3b** (2.96 g, 10 mmol) and malononitrile, diethyl malonate or cinnamaldehyde (10 mmol) in DMF (50 ml) containing few drops of piperidine was refluxed for 10 h. The mixture was cooled and poured onto ice–water. The solid obtained was filtered off and crystallized from the proper solvent to give **9–11,** respectively (Table I).

Ethyl 5-{[2-(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene) hydrazino]}-3-methyl-1*H*-pyrazole-4-carboxylate (12)

A mixture of **3b** (2.96 g, 10 mmol) and ethyl 2-chloroacetoacetate (1.64 g, 10 mmol) in DMF (50 ml) was refluxed for 6 h. The mixture was cooled and poured onto ice–water. The solid obtained was filtered off and crystallized from the proper solvent to give **12** (Table I).

6-Chloro-3-(1,3,4-thiadiazol-2-ylhydrazonomethyl)-4*H*-chromen-4-one (13) and N-Acetyl-N′-[4-acetyl-5-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]acetohydrazide (14)

A mixture of **3a** or **3b** (10 mmol) and formic acid or acetic anhydride (40 ml) was refluxed for 6 h. The mixture was cooled and neutralized with sodium carbonate solution (10%). The solid obtained was filtered off

and crystallized from the proper solvent to give **13** and **14,** respectively (Table I).

6-Methyl-3-[(3-thioxo-1,5-dihydro-1,2,4-triazol-4-ylimino) methyl]-4*H*-chromen-4-one (15)

A mixture of **3a** (2.76 g, 10 mmol) and triethylorthoformate (30 ml) was refluxed for 4 h. The obtained mixture was concentrated to half volume then cold water (20 ml) was added. The obtained solid was filtered off and crystallized from the proper solvent to give **15** (Table I).

6-Methyl-3-[(5-methyl-3-thioxo-1,5-dihydro-1,2,4-triazol-4-ylimino)methyl]-4*H*-chromen-4-one (16) and 6-chloro-3-{[(3,5-dithioxo-1,2,4-triazolidin-4-ylimino) methyl]}–4*H*-chromen-4-one (17)

A mixture of **3a** or **3b** (10 mmol) and acetyl chloride or carbon disulfide (10 mmol) in pyridine (50 ml) was refluxed for 6 h. The mixture was cooled and poured onto ice–HCl. The solid obtained was filtered off and crystallized from the proper solvent to give **16** and **17**, respectively (Table I).

The 3-thioxo–1,2,4-triazine derivatives (18–21)—General Method

A mixture of **3a** or **3b** (10 mmol) and chloroacetyl chloride, dichloroacetic acid, oxalyl chloride or phenacyl bromide (10 mmol) in DMF (50 ml) containing few drops of piperidine was refluxed for 4 h. The mixture was cooled and poured onto ice–water. The solid obtained was filtered off and crystallized from the proper solvent to give **18–21** respectively (Table I).

6-Methyl-4-[(6-methyl-4-oxo-4*H*-chromen-3-ylmethylene)amino]-3-thioxo-1,2,4-triazin-5(2*H*)-one (22)

A mixture of **3a** (2.76 g, 10 mmol) and ethyl pyruvate (1.10 g, 10 mmol) in ethanol (50 ml) and potassium carbonate solution (10%, 20 ml) was refluxed for 8 h. The mixture was cooled and poured onto ice–water. The solid obtained was filtered off and crystallized from the proper solvent to give **22** (Table I).

6-Chloro-4-oxo-4*H*-chromen-3-carbaldehyde[4-acetyl-5-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]hydrazone (23)

A mixture of **4** (2.43 g, 5 mmol) and acetyl chloride (0.39 g, 5 mmol) in glacial acetic acid (50 ml) was refluxed for 6 h. The mixture was cooled and neutralized with sodium carbonate (10%). The solid obtained was filtered off and crystallized from the proper solvent to give **23** (Table I).

1,3-Bis[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]-2-thioxoimidazolidin-4-one (24) and 1,3-Bis[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]-2-thioxodihydro-pyrimidine-4,6(1*H*,5*H*)-dione (25)

A mixture of **4** (2.43 g, 5 mmol) and chloroacetic acid or diethyl malonate (5 mmol) in DMF (50 ml) containing few drops of piperidine was refluxed for 10 h. The mixture was cooled and poured onto ice–water. The solid obtained was filtered off and crystallized from the proper solvent to give **24** and **25**, respectively (Table I).

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