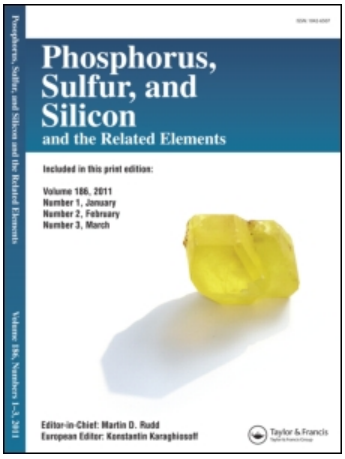

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Synthesis and Antimicrobial Activity of Some New Heterocyclic Schiff Bases Derived from 2-Amino-3-formylchromone

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Synthesis and Antimicrobial Activity of Some New Heterocyclic Schiff Bases Derived from 2-Amino-3-formylchromone

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*Some new hydrazone derivatives **3a–e** have been obtained from 2-amino-3-formylchromone (**1**). Heterocyclization of thiocarbohydrazone derivative **3e** via reaction with some electrophilic reagents afforded 1,2,4-triazoles **6–8** and 1,2,4-triazines **9–13**. Condensation reactions of aldehyde **1** with o-aminoaldehydes and/or ketones afforded some new isolated and condensed heterocyclic systems **17**, **19**, and **20**. The newly synthesized compounds were screened for their antimicrobial activity.*

Keywords Antimicrobial activity; chromone; Schiff bases; 1,2,4-triazines; 1,2,4-triazoles

INTRODUCTION

Chromone derivatives have received great attention for their applications. These compounds exhibit a wide spectrum of biological activities including antimicrobial,[1,2] antibacterial,[3,4] antitumor,[5] antifungal,[6–8] anti-allergic,[9] antiviral,[10] anti-inflammatory,[11] and anticancer activities.[12] Structural modification of the chromone by the introduction of heterocyclic substituents at 3-position has attracted considerable attention.[13,14] On the other hand, 1,2,4-triazole derivatives are found to be associated with various biological activities.[15–18] Moreover, various 1,2,4-triazine derivatives are known to possess an array of medicinal activities.[19] In view of these observations, the present work aimed to synthesize some new nitrogen heterocyclic systems combining chromone moiety and 1,2,4-triazole or 1,2,4-triazine in one molecular frame through an azomethine linkage to examine their antimicrobial activity.

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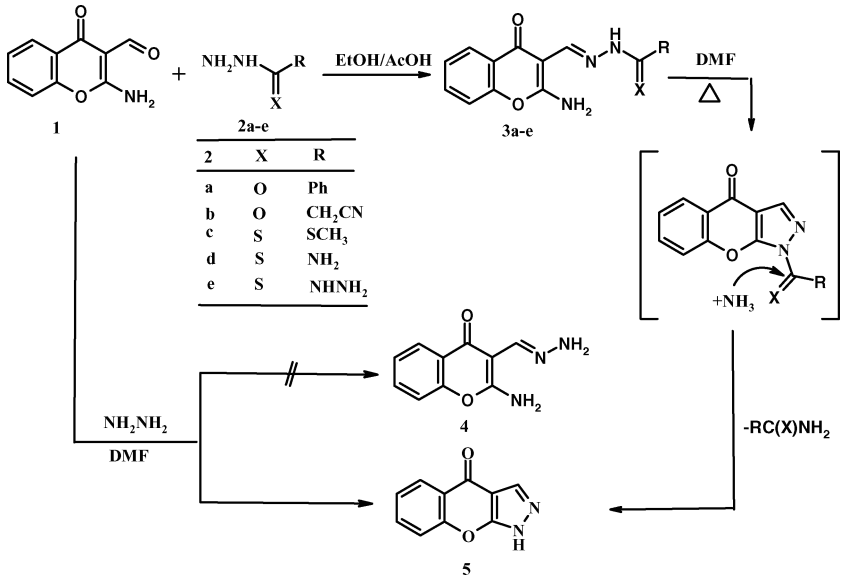
RESULTS AND DISCUSSION

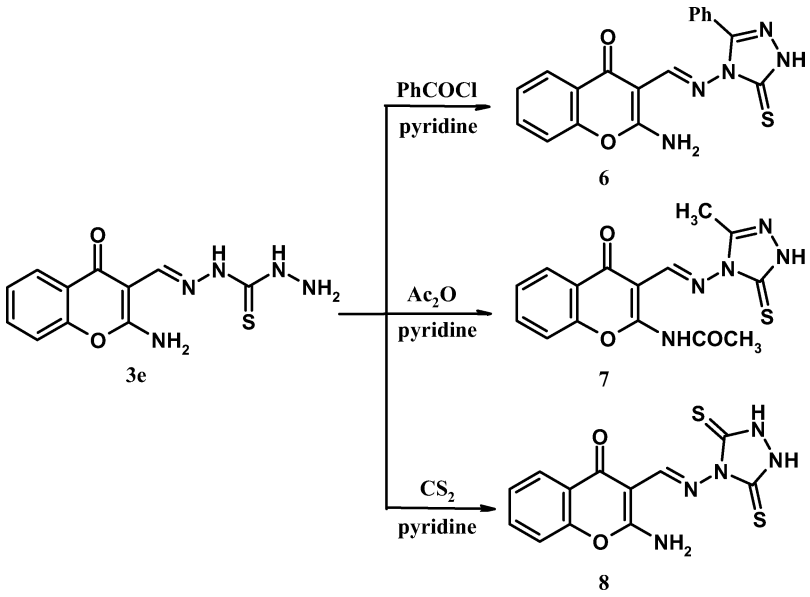
Condensation reaction of 2-amino-3-formylchromone (**1**) with some hydrazine derivatives **2a–e** in boiling absolute ethanol containing a catalytic amount of acetic acid gave the corresponding hydrazones **3a–e**. Refluxing of **3a–e** in DMF yielded the same product in all cases, which was identified as chromeno[2,3-c]pyrazol-4(1*H*)-one (**5**)[20] (Scheme 1). Alternatively, condensation of aldehyde **1** with hydrazine hydrate in boiling DMF produced compound **5** and not the hydrazone **4**, which was obtained previously by Ghosh et al.[21] Formation of **5** was explained via cyclization of hydrazones **3a–e** with loss of one molecule of ammonia, followed by cleavage of amido and thioamido groups[22] in high boiling solvents (Scheme 1). The IR spectrum of compound **5** revealed an absorption band at 3202 cm^{-1} assigned to a NH group. Moreover, in the mass fragmentation patterns of hydrazones **3a,b**, as examples, the fragment at m/z 186 (corresponding to chromenopyrazolone **5**) was observed while the fragment at m/z 203 (corresponding to hydrazone **4**) was not observed.[23–25] These results confirm cyclization with loss of ammonia at first, followed by cleavage of the –CXR group as amide or thioamide.

Thiocarbohydrazone **3e** was used as a starting material for building of some new isolated heterocyclic systems connected with the chromone



2	X	R
a	O	Ph
b	O	CH_2CN
c	S	SCH_3
d	S	NH_2
e	S	$NHNH_2$

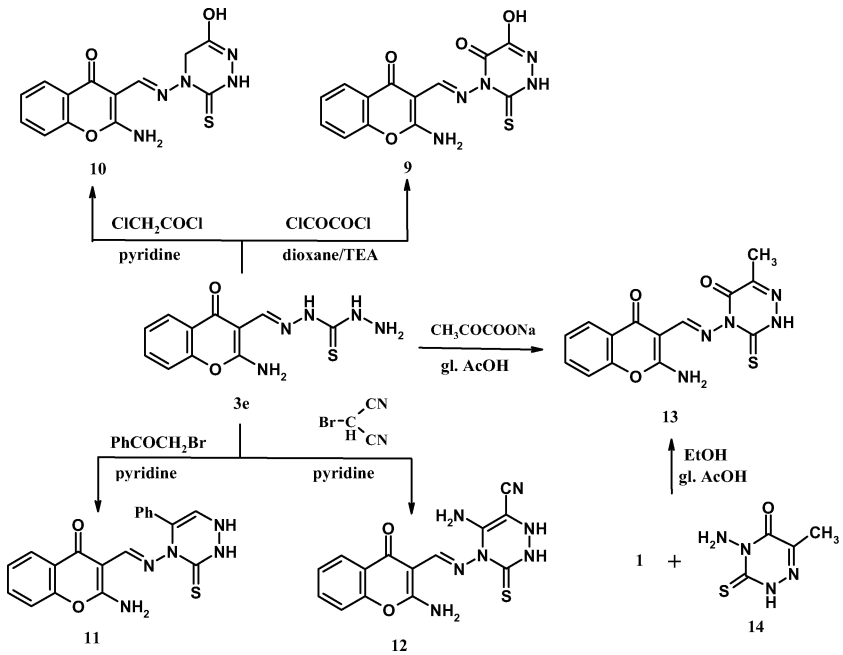
SCHEME 1



SCHEME 2

moiety at the position 3. Thus, heating thiocarbohydrazone **3e** under reflux with benzoyl chloride in pyridine gave 2-amino-3-{[(3-phenyl-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)imino] methyl}chromone (**6**), while boiling with acetic anhydride afforded N-(3-{[3-methyl-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]imino}methyl-4-oxo-4*H*-chromene-2-yl)acetamide (**7**). Also, reaction of **3e** with carbon disulfide in boiling pyridine afforded 2-amino-3-{[(3,5-dithioxo-1,2,4-triazolidin-4-yl)imino]methyl} chromone (**8**) (Scheme 2). The structures of **6–8** were confirmed by their elemental analysis and spectral data.

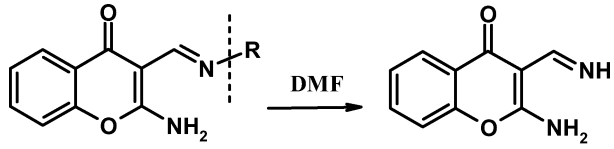
On the other hand, the starting compound **3e** was used for construction of some new Schiff bases bearing 1,2,4-triazine moiety through the reaction with 1,2-bifunctional electrophiles. Thus, heterocyclization of **3e** with oxalyl chloride, chloroacetyl chloride, phenacyl bromide, bromomalononitrile, and sodium pyruvate led to the formation of triazinyliminomethylchromones **9–13**, respectively (Scheme 3). Compound **13** was authentically obtained by condensation of aldehyde **1** with 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**14**) in boiling ethanol and few drops of acetic acid (Scheme 3). The IR and ^{1}H NMR spectra of compounds **9–13** confirmed cyclization of the side chain, –NHCSNHNH$_2$, in thiocarbohydrazone **3e** to 1,2,4-triazine derivatives **9–13**. Heating of the new synthesized compound **9–13** under



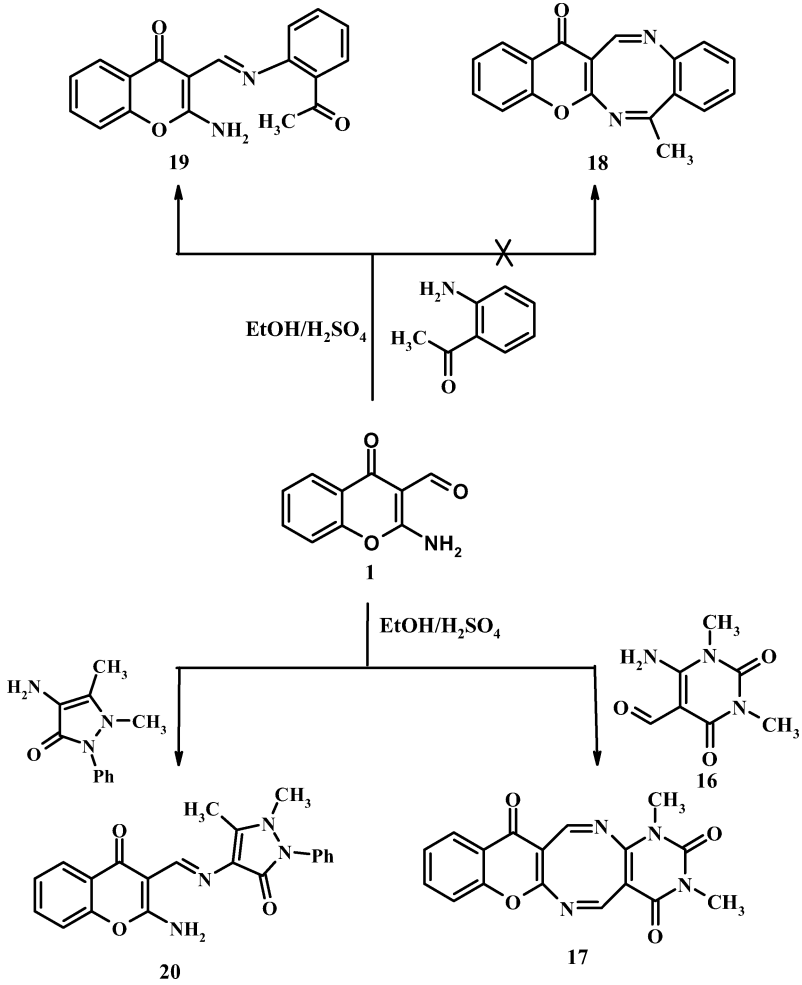
SCHEME 3

reflux in DMF afforded one product, which was identified as 2-amino-3-(iminomethyl)-4*H*-chromen-4-one (**15**). The formation of compound **15** is assumed to take place through cleavage of the N-N single bond in high boiling solvents (Scheme 4). The IR spectrum of compound **15** showed absorption bands at 3170, 1629, and 1605 cm^{-1} assigned to (NH_2, NH), (C=O pyrone), and (C=N), respectively. Its ^1H NMR spectrum exhibited signals at δ 8.76 (CH=N), 9.20, 10.32, and 10.53 ppm (NH, NH_2).

It is expected that combination of chromone moiety with other heterocycles may render the resulting compounds more biologically active.[26] Thus, cyclocondensation of aldehyde **1** with 6-amino-1,3-dimethyluracil-5-carboxaldehyde (**16**), in boiling ethanol containing catalytic amount of concentrated sulfuric acid, yielded the diazocine derivative **17**. Under the same conditions, condensation of aldehyde **1** with 2-aminoacetophenone did not give the expected diazocine derivative **18**, but furnished 3-{([(2-acetylphenyl)imino]methyl}-2-amino-4*H*-chromen-4-one (**19**). Similarly, pyrazolyliminomethylchromone **20** was obtained via reaction of aldehyde **1** with 4-aminoantipyrine under the same condition (Scheme 5).



SCHEME 4



SCHEME 5

TABLE I Antimicrobial Activity of the Newly Synthesized Compounds 3–21

Compound No.	Mean of zone diameter (mm)					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus (ATCC 25923)	*S. pyogenes* (ATCC 19615)	*P. phaseolicola* (GSPB 2828)	*P. fluorescens* (S 97)	*F. oxysporum*	*A. fumigatus*
3a	+	+	+	+	+	+
3b	+	+	+	+	+	+
3c	+	+	+	+	+	+
3d	+	+	+	+	+	+
3e	+	+	+	+	+	+
6	+	+	+	+	+	+
7	+	+	+	+	++	++
8	++	++	++	++	+++	+++
9	+	+	+	+	+++	+++
10	+	+	+	+	+	+
11	+	+	+	+	+	+
12	+	+	+	+	+	+
13	+	+	+	+	+++	+++
15	+	+	+	+	+++	+++
17	+	+	+	+	+	+
19	+	+	+	+	++	++
20	++	++	++	++	+++	+++
Control[#]	+++	+++	+++	+++	+++	+++

+Low activity = Mean of zone diameter $\leq$ 1/3 of mean zone diameter of control.

++Moderate activity = Mean of zone diameter $\leq$ 2/3 of mean zone diameter of control.

+++High activity = Mean of zone diameter $>$ 2/3 of mean zone diameter of control.

[#]The antibiotic chloramphencol was used as the standard reference in the case of Gram-negative bacteria, cephalothin was used as the standard reference in the case of Gram-positive bacteria, and cycloheximide was used as the standard antifungal reference.

BIOLOGICAL ACTIVITY

The new synthesized compounds were screened in vitro for their antimicrobial activities, using the standardized disc–agar diffusion method,[27] against *Staphylococcus aureus* and *Streptococcus pyogenes* as Gram-positive bacteria, *Pseudomonas fluorescens* and *Pseudomonas phaseolicola* as Gram-negative bacteria, and the fungi *Fusarium oxysporum* and *Aspergillus fumigatus*. The antibiotic chloramphencol was used as the standard reference in the case of Gram-negative bacteria, cephalothin was used as the standard reference in the case of Gram-positive bacteria, and cycloheximide was used as the standard antifungal reference. The tested compounds were dissolved in DMF (where this solvent has no inhibition activity) to obtain concentrations of 100 μ/mL. Uniform size filter paper disks (3 disks per compound) were impregnated by an equal volume (10 μL) of dissolved tested compounds and carefully placed on the incubated agar surface. After incubation for 36 h at 27°C in the case of bacteria and for 48 h at 24°C in the case of fungi, inhibition of the organisms, which was evidenced by a clear zone surround each disk, was measured and used to calculate mean of inhibition zones.[27,28] From the results obtained, it is clear that compounds **8** and **20** showed moderate activity against the test bacteria and high activity against the tested fungi mainly due to the presence of dithioxo-1,2,4-triazole and antipyrine moieties. Compounds **9**, **13**, and **15** showed high activity toward the tested fungi, while compounds **7** and **19** showed moderate activity with respect to the references used (Table I).

CONCLUSION

In conclusion, we report herein a convenient route for the synthesis of some new Schiff bases containing 1,2,4-triazole or 1,2,4-triazine derivatives combined with chromone moiety via the reaction of thiocarbohydrazone **3e** with some electrophiles. Antimicrobial evaluation revealed moderate activity.

EXPERIMENTAL

Melting points are uncorrected and were recorded in open capillary tubes on a Stuart SMP3 melting point apparatus. Infrared spectra were recorded on a FT-IR Bruker Vector 22 spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were measured on a Gemini spectrometer 200 MHz using DMSO-d_6 as solvent and TMS (chemical shift in δ) as an internal standard. Mass spectra were obtained using a gas chromatography GCMS qp 1000 ex Shimadzu instrument mass

spectrometer (70eV). 2-Amino-3-formylchromone (**1**)[29] and 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**14**)[30] were prepared according to the literature.

Formation of Hydrazones 3a–e (General Procedure)

A mixture of aldehyde **1** (0.95 g, 5 mmol) and some hydrazine derivatives (5 mmol), namely benzoylhydrazine (**2a**, 0.68 g), cyanoacetohydrazide (**2b**, 0.50 g), *S*-methyl dithiocarbazate (**2c**, 0.61 g), thiosemicarbazide (**2d**, 0.46 g), and thiocarbohydrazide (**2e**, 0.53 g), in absolute ethanol (20 mL) containing a few drops of acetic acid, was refluxed for 15 min. The solid obtained after cooling was filtered off and crystallized from the proper solvent to give compounds **3a–e**, respectively.

N′-[(2-Amino-4-oxo-4H-chromen-3-yl)methylene] benzohydrazide (3a)

Crystallized from ethanol, yield (1.3 g, 84%), mp 297°C, IR (cm^{-1}, KBr): 3282, 3213 (NH_2, NH), 1666 (2 C=O), 1608 (C=N), 1318 (C=S). M/z (I.%): 307 (4), 187 (45), 186 (10), 174 (15), 121 (26), 120 (8), 93 (7), 77 (100), 65 (22). Anal. Calcd for $C_{17}H_{13}N_3O_3$ (307.31): C, 66.44; H, 4.26; N, 13.67. Found C, 66.43; H, 4.21; N, 13.54.

N′-[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]-2-cyanoacetohydrazide (3b)

Crystallized from dioxane, yield (1.1 g, 81%), mp 274–275°C, IR (cm^{-1}, KBr): 3285, 3197, 3114 (NH_2, NH), 2254 (C≡N), 1681 (2 C=O), 1604 (C=N), 1310 (C=S). M/z (I.%): 270 (15), 204 (9), 187 (95), 186 (37), 174 (38), 121 (100), 93 (30), 68 (71), 65 (51). Anal. Calcd for $C_{13}H_{10}N_4O_3$ (270.25): C, 57.78; H, 3.73; N, 20.73. Found C, 57.74; H, 3.71; N, 20.65.

Methyl 2-[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]-hydrazinecarbodithioate (3c)

Crystallized from ethanol, yield (1.15 g, 78%), mp 313°C, IR (cm^{-1}, KBr): 3297, 3168 (NH_2, NH), 1640 (C=O pyrone), 1605 (C=N), 1305 (C=S). Anal. Calcd for $C_{12}H_{11}N_3O_2S$ (293.37): C, 49.13; H, 3.78; N, 14.32; S, 21.86. Found C, 48.97; H, 3.67; N, 14.24; S, 21.81.

2-Amino-4-oxo-4H-chromene-3-carboxaldehyde thiosemicarbazone (3d)

Crystallized from acetic acid, yield (0.96 g, 73%), mp 315°C, IR (cm^{-1}, KBr): 3333, 3278, 3206 (NH_2, NH), 1644 (C=O pyrone), 1605 (C=N), 1332 (C=S). ^{1}H NMR (δ, DMSO-d_6): 7.40 (m, 2H, H_6 and H_8), 7.71 (d,

2H, NH_2), 7.87 (bs, 1H, NH), 8.00 (d, 2H, H_5 and H_7), 8.63 (bs, 3H, CH=N and NH_2). Anal. Calcd for $C_{11}H_{10}N_4O_2S$ (262.29): C, 50.37; H, 3.84; N, 21.36; S, 12.22. Found C, 50.35; H, 3.83; N, 21.14; S; 12.04.

N″-(2-Amino-4-oxo-4H-chromen-3-yl)methylene] thiocarbohydrazide (3e)

Crystallized from DMF/H_2O, yield (0.84 g, 60%), mp > 320°C, IR (cm^{-1}, KBr): 3269, 3209 ($2NH_2$, 2NH), 1642 (C=O pyrone), 1608 (C=N), 1315 (C=S). ^1H NMR (δ, DMSO-d_6): 5.04 (br, 2H, NH_2), 7.39 (m, 2H, H_6 and H_8), 7.68 (t, 1H, H_7), 8.00 (d, 1H, H_5), 8.64 (s, H, CH=N), 8.89 (bs, 1H, NH), 9.66 (d, 2H, NH_2), 11.06 (bs, 1H, NH). Anal. Calcd for $C_{11}H_{11}N_5O_2S$ (277.31): C, 47.64; H, 4.00; N, 25.25; S, 11.56. Found C, 47.51; H, 3.84; N, 24.94; S, 11.23.

Chromeno[2,3-c]pyrazol-4(1H)-one (5)

A solution of compounds **3a–e** (0.5 g) in DMF (15 mL) was refluxed for 2 h. The yellow crystals obtained during heating were filtered off to give compound **5**. Mp > 320°C, IR (cm^{-1}, KBr): 3202 (NH), 1658 (C=O pyrone), 1607 (C=N), 1290 (C=S). Anal. Calcd for $C_{10}H_6N_2O_2$ (186.17): C, 64.52; H, 3.25; N, 15.05. Found C, 64.32; H, 3.21; N, 14.95.

2-Amino-3-{[(3-phenyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)imino] methyl}chromone (6)

Benzoyl chloride (0.3 mL, 2.5 mmol) was added dropwise with continuous stirring to a solution of compound **3e** (0.69 g, 2.5 mmol) in dry pyridine (10 mL). The reaction mixture was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice/HCl. The solid obtained was filtered off, washed several times with water, and crystallized from acetic acid to give compound **6** as white crystals. Yield (0.65 g, 72%), mp > 320°C, IR (cm^{-1}, KBr): 3442, 3291 (NH_2, NH), 1635 (C=O pyrone), 1582 (C=N), 1325 (C=S). ^1H NMR (δ, DMSO-d_6): 7.45–7.78 (m, 7H, Ar-H), 7.89 (d, 1H, H_8), 8.06 (d, 1H, H_5), 8.78 (s, H, CH=N), 9.18 (d, 2H, NH_2), 13.69 (s, 1H, NH). Anal. Calcd for $C_{18}H_{13}N_5O_2S$ (363.40): C, 59.49; H, 3.61; N, 19.27; S, 8.82. Found C, 59.24; H, 3.54; N, 19.12; S, 8.69.

N-(3-{[3-Methyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl}imino]methyl-4-oxo-4H-chromen-2-yl)acetamide (7)

A mixture of compound **3e** (0.69 g, 2.5 mmol) and acetic anhydride (10 mL) was refluxed for 2 h. After cooling, the reaction mixture was poured

onto ice. The solid obtained was filtered off, washed several times with water, and crystallized from DMF to give acetamide **7** as pale brown crystals. Yield (0.42 g, 49%), mp 236–237°C, IR (cm^{-1}, KBr): 3423, 3212 (2NH), 1717 (C=O acetyl), 1666 (C=O pyrone), 1612 (C=N), 1302 (C=S). ^1H NMR (δ, DMSO-d_6): 2.29 (s, 3H, CH_3), 2.81 (s, 3H, $COCH_3$), 7.55 (d, 1H, H_8), 7.74 (t, 1H, H_7), 7.88 (t, 1H, H_6), 8.61 (d, 1H, H_5), 8.61 (s, 1H, CH=N), 9.15 (s, 1H, NH), 11.28 (s, 1H, NH). Anal. Calcd for $C_{15}H_{13}N_5O_3S$ (343.37): C, 52.47; H, 3.82; N, 20.40; S, 9.34. Found C, 52.26; H, 3.72; N, 20.49; S, 9.26.

2-Amino-3-{[(3,5-dithioxo-1,2,4-triazolidin-4-yl)imino} methyl]chromone (8)

A mixture of compound **3e** (0.69 g, 2.5 mmol) and carbon disulfide (0.19 g, 0.15 mL, 2.5 mmol) in dry pyridine (10 mL) was refluxed for 8 h or until evolution of H_2S ceased. After cooling, the reaction mixture was poured onto ice/HCl. The solid obtained was filtered off, washed several times with water, and crystallized from DMF/ethanol to give compound **8** as yellow crystals. Yield (0.45 g, 57%), mp > 320°C, IR (cm^{-1}, KBr): 3285, 3211 (NH_2, NH), 1642 (C=O), 1611 (C=N), 1317 (C=S). ^1H NMR (δ, DMSO-d_6): 7.43 (t, 2H, H_6 and H_8), 7.73 (t, 1H, H_7), 8.03 (d, 1H, H_5), 9.07 (s, 1H, CH=N), 9.31 (bs, 2H, NH_2) 9.73 (bs, 2H, 2NH). Anal. Calcd for $C_{12}H_9N_5O_2S_2$ (319.37): C, 45.13; H, 2.84; N, 21.93; S, 20.08. Found C, 44.95; H, 2.74; N, 21.75; S, 20.03.

4-{[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]amino}-3-thioxo-1,2,4-triazin-5,6-dione (9)

Oxalyl chloride (0.22 mL, 0.01 mol) was added dropwise to a suspension of compound **3e** (0.69 g, 2.5 mmol) in dry dioxine (20 mL) and triethylamine (0.5 mL), and refluxed for 6 h. After cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off, washed several times with water, and crystallized from DMF/H_2O to give compound **9** as yellow crystals. Yield (0.41 g, 50%), mp 295–296°C. IR (cm^{-1}, KBr): 3267–3211 (NH_2, 2NH), 1724 (C=O), 1640 (C=O pyrone), 1608 (C=N), 1317 (C=S). ^1H NMR (δ, DMSO-d_6): 7.45 (d, 2H, H_6, H_8), 7.72 (t, 1H, H_7), 8.04 (d, 1H, H_5), 8.44 (bs, 1H, OH), 9.16 (d, 2H, NH_2), 9.59 (s, 1H, CH=N), 10.08 (s, 1H, NH). Anal. Calcd for $C_{13}H_9N_5O_4S$ (331.31): C, 47.13; H, 2.74; N, 21.14; S, 9.68. Found C, 46.87; H, 2.68; N, 21.06; S, 9.67.

4-{[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]amino}-3-thioxo-1,2,4-triazin-6-one (10)

A mixture of compound **3e** (0.69 g, 2.5 mmol) and chloroacetyl chloride (0.2 mL, 2.5 mmol) in dry pyridine (10 mL) was refluxed for 6 h. After cooling, the reaction mixture was poured onto ice/HCl. The solid obtained was filtered off and crystallized from DMF/H_2O to give compound **10** as yellow crystals. Yield (0.37 g, 47%), mp > 320°C. IR (cm^{-1}, KBr): 3384, 3265, 3163 (NH_2, NH, OH), 1622 (C=O pyrone). ^1H NMR (δ, DMSO-d_6): 2.77 (s, 2H, CH_2), 7.43 (t, 2H, H_6, H_8), 7.68 (t, 1H, H_7), 7.99 (d, 1H, H_5), 8.64 (s, 1H, CH=N), 9.43 (d, 2H, NH_2), 11.08 (s, 1H, NH), 11.61 (s, 1H, OH). Anal. Calcd for $C_{13}H_{11}N_5O_3S$ (317.33): C, 49.21; H, 3.49; N, 22.07; S, 10.10. Found C, 49.11; H, 3.36; N, 21.81; S, 10.05.

4-{[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]amino}-5-phenyl-3-thioxo-2,3-dihydro-1,2,4-triazin-6-one (11)

A mixture of compound **3e** (0.69 g, 2.5 mmol) and phenacyl bromide (0.5 g, 2.5 mmol) in dry pyridine (10 mL) was refluxed for 6 h. After cooling, the reaction mixture was poured onto ice/HCl. The solid obtained was filtered off and crystallized from DMF/H_2O to give compound **11** as yellow crystals. Yield (0.73 g, 78%), mp > 320°C. IR (cm^{-1}, KBr): 3350, 3193 (NH_2, 2NH), 1610 (C=N), ^1H NMR (δ, DMSO-d_6): 7.43–8.18 (m, 9H, Ar-H), 8.64 (s, 1H, CH triazine), 8.73 (s, 1H, CH=N), 9.06 (d, 2H, NH_2), 9.34 (s, 1H, NH), 9.77 (s, 1H, NH), Anal. Calcd for $C_{19}H_{15}N_5O_2S$ (377.43): C, 60.47; H, 4.01; N, 18.58; S, 8.50. Found C, 60.19; H, 3.96; N, 18.45; S, 8.42.

5-Amino-4-{[2-amino-4-oxo-4H-chromen-3-yl)methylene]amino}-3-thioxo-1,2,3,4-tetrahydro-1,2,4-triazine-6-carbonitrile (12)

A mixture of compound **3e** (0.69 g, 2.5 mmol) and bromomalononitrile (0.36 g, 2.5 mmol) in dry pyridine (10 mL) was refluxed for 6 h. After cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off, washed several times with water, and crystallized from DMF/H_2O to give compound **12** as yellow crystals. Yield (0.42 g, 45%), mp > 320°C, IR (cm^{-1}, KBr): 3374, 3244, 3146 ($2NH_2$, NH), 2210 (C≡N), 1671 (C=O pyrone), 1608 (C=N), 1335 (C=S). ^1H NMR (δ, DMSO-d_6): 6.95 (m, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 7.82 (s, 1H, CH=N), 8.86 (d, 2H, NH_2), 9.57 (s, 1H, NH), 10.43 (bs, 2H, NH_2), 13.34 (s, 1H, NH). Anal. Calcd for $C_{14}H_{11}N_7O_2S$ (341.35): C, 49.26; H, 3.25; N, 28.72; S, 9.39. Found C, 48.95; H, 3.12; N, 28.51; S, 9.18.

4-{[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]amino}-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (13)

Method A

A mixture of compound **3e** (0.69 g, 2.5 mmol) and sodium pyruvate (0.28 g, 2.5 mmol) in glacial acetic acid (15 mL) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off, washed several times with water, and crystallized from acetic acid to give compound **13** as white crystals. Yield (0.47 g, 57%), mp 299–300°C.

Method B

A mixture of aldehyde **1** (0.95 g, 5 mmol) and 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (**14**)[28] (0.28 g, 5 mmol) in absolute ethanol containing few drops of acetic acid was refluxed for 30 min. The solid obtained during heating was filtered off and crystallized from acetic acid to give compound **13** as white crystals. Yield (0.75 g, 45%), mp 299–300°C, IR (cm^{-1}, KBr): 3256, 3137 (NH_2, NH), 1702 (C=O), 1655 (C=O pyrone), 1608 (C=N), 1292 (C=S). ^{1}H NMR (δ, DMSO-d_6): 2.19 (s, 3H, CH_3), 7.45 (t, 2H, H_7, H_8), 7.95 (t, 1H, H_7), 8.03 (d, 1H, H_5), 8.97 (s, 1H, CH=N), 9.63 (d, 2H, NH_2), 13.62 (s, 1H, NH), Anal. Calcd for $C_{14}H_{11}N_5O_3S$ (329.34): C, 51.06; H, 3.37; N, 4.26; S, 9.74. Found C, 51.00; H, 3.32; N, 4.15; S, 9.67.

2-Amino-3-(iminomethyl)-4H-chromen-4-one (15)

A solution of compounds **9–13** (0.82 g, 2.5 mmol) in DMF (15 mL) was refluxed for 4 h. The yellow crystals obtained after cooling were filtered off and recrystallized from DMF to give compound **15** as yellow crystals. Mp > 320°C. IR (cm^{-1}, KBr): 3170 (NH_2, NH), 1629 (C=O pyrone), 1605 (C=N). ^{1}H NMR (δ, DMSO-d_6): 7.43 (d, 1H, H_8), 7.56 (t, 1H, H_6), 7.95 (d, 1H, H_7), 8.03 (d, 1H, H_5), 8.76 (s, 1H, CH=N), 9.20 (s, 1H, NH), 10.32 (bs, 1H, NH), 10.53 (bs, 1H, NH). Anal. Calcd for $C_{10}H_8N_2O_2$ (188.19): C, 63.83; H, 4.28; N, 14.89. Found C, 63.16; H, 3.71; N, 14.72.

1,3-Dimethyl-2H-chromeno[2,3-b]pyrimido[4,5-f][1,5]diazocine-2,4,12-(1H,3H)-trione (17)

A mixture of aldehyde **1** (0.95 g, 5 mmol) and 6-amino-1,3-dimethyluracil-5-carboxaldehyde (**16**) (0.46 g, 5 mmol) in absolute ethanol (50 mL) and few drops of conc. H_2SO_4, was refluxed for 2 h. The solid obtained was filtered off and recrystallized from DMF to give diazocine **17** as yellow crystals. Yield (0.87 g, 52%), mp 301°C. IR

(cm^{-1}, KBr): 1743, 1718 (2 C=O), 1664 (C=O), 1607 (C=N). ^1H NMR (δ, DMSO-d_6): 3.59 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 7.55 (d, 1H, H_8), 7.77 (t, 1H, H_6), 7.93 (t, 1H, H_7), 8.18 (d, 1H, H_5), 8.92 (s, 2H, 2 CH=N). Anal. Calcd for $C_{17}H_{12}N_4O_4$ (336.31): C, 60.71; H, 3.60; N, 16.66. Found C, 60.63; H, 3.53; N, 16.62.

3-{[(2-Acetylphenyl)imino]methyl}-2-amino-4H-chromen-4-one (19)

A mixture of aldehyde **1** (0.95 g, 5 mmol) and 2-aminoacetophenone (0.68 g, 5 mmol) in absolute ethanol (50 mL) and few drops of conc. H_2SO_4, was refluxed for 4 h. The solid obtained after cooling was filtered off and recrystallized from dioxane to give compound **19** as yellow crystals. Yield (0.68 g, 44%), mp 223°C, IR (cm^{-1}, KBr): 3370, 3263 (NH_2), 1678 (C=O acetyl), 1653 (C=O pyrone), 1612 (C=N). ^1H NMR (δ, DMSO-d_6): 2.73 (s, 3H, CH_3), 6.77–8.12 (m, 7H, Ar-H), 8.35 (d, 1H, H_5), 9.07 (s, 1H, CH=N), 9.45 (d, 2H, NH_2). Anal. Calcd for $C_{18}H_{14}N_2O_3$ (306.32): C, 70.58; H, 4.61; N, 9.15, Found C, 70.51; H, 4.50; N, 9.03.

4-{[(2-Amino-4-oxo-4H-chromen-3-yl)methylene]amino}-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (20)

A mixture of compound **1** (0.95 g, 5 mmol) and 4-aminoantipyrine (0.51 g, 5 mmol) in absolute ethanol (50 mL) and few drops of conc. H_2SO_4 was refluxed for 6 h. After cooling, the product was poured onto ice. The solid obtained was filtered off and recrystallized from acetic acid to give pyrazolone **20** as yellow crystals. Yield (0.65 g, 35%), mp 167°C, IR (cm^{-1}, KBr): 3440, 3289 (NH_2), 1635 (C=O), 1610 (C=N). ^1H NMR (δ, DMSO-d_6): 3.75 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 7.32–8.35 (m, 9H, Ar-H), 9.13 (d, 2H, NH_2), 9.51 (s, 1H, CH=N). Anal. Calcd for $C_{21}H_{18}N_4O_3$ (374.40): C, 67.37; H, 4.85; N, 14.96. Found C, 67.25; H, 4.74; N, 14.75.

REFERENCES

[1] H. Goker, D. W. Boykin, and S. Yildiz, *Bioorg. Med. Chem.*, **13,** 1707 (2005).
[2] M. J. Nawort, E. Nawrot, and J. Graczyk, *Eur. J. Med. Chem.*, **41,** 1301 (2006).
[3] J. B. Harborne and C. A. Williams, *Photochemistry*, **55,** 481 (2000).
[4] N. R. Guz, F. R. Stermitz, J. B. Johnson, T. D. Beeson, S. Willen, J. F. Hstang, and K. Lewis, *J. Med. Chem.*, **44,** 261 (2001).
[5] E. A. Yakout, *Egypt. J. Chem.*, **45,** 1029 (2003).
[6] T. E. Ali, S. Abdel-Ghfaar, H. M. El-Shaaer, F. I. Hanafy, and A. Z. El-Fauomy, *Turk. J. Chem.*, **32,** 365 (2008).
[7] T. E. Ali, *Phosphorus, Sulfur, and Silicon*, **182,** 1717 (2007).
[8] M. Uher, V. Konecny, and O. Rajniakova, *Chem. Pap.*, **48,** 282 (1994).

[9] M. Ohata, K. Watanabe, K. Kumata, K. Hisamichi, S. Suzuki, and H. Ito, *Annu. Rep. Tohoku Coll. Pharm.*, **38,** 35 (1991); *Chem. Abstr.*, **118**, 168937 (1993).
[10] N. Desideri, P. Mastromarino, and C. Conti, *Antiviral Chem. & Chemotherapy*, 195 (2003); *Chem. Abstr.*, **140**, 192203 (2003).
[11] K. Jerzy and Z. Teodor, *Acta Pot. Pharm.*, **52,** 133 (1995); *Chem. Abstr.*, **123,** 339629 (1995).
[12] L. Denis, M. S. Morton, and K. Griffith, *Eur. Urol.*, **35,** 377 (1999).
[13] W. Huang, D. Teng, Z. Zhou, and G. Yang, *Acta Cryst.*, **61,** 2510 (2005).
[14] T. E. Ali, S. Abdel-Ghfaar, H. M. El-Shaaer, F. I. Hanafy, and A. Z. El-Fauomy, *Phosphorus, Sulfur, and Silicon*, **183,** 2139 (2008).
[15] D. H. Chung, S. C. Kumarapperuma, Y. Sun, Q. Li, Y. K. Chu, J. B. Arterburn, W. B. Parker, J. Smith, K. Spik, H. N. Ramanathan, C. S. Schmaljohn, and C. B. Jonsson, *Antiviral Res.*, **79,** 19 (2008).
[16] Z. A. Kaplancikli, G. T. Zitouni, A. Ozdemir, and G. Revial, *Eur. J. Med. Chem.*, **43,** 155 (2008).
[17] O. Bekircan, B. Kahveci, and O. B. Ozgumus, *Chinese J. Chem.*, **25,** 1871 (2007).
[18] J. Chen, X. Y. Sun, K. Y. Chai, J. S. Lee, M. S. Song, and Z. S. Quan, *Bioorg. Med. Chem.* **15,** 6775 (2007).
[19] F. Li, Y. Feng, Q. Meng, W. Li, Q. Wang, and F. Tao, *ARKIVOC*, **i,** 40 (2007).
[20] G. Singh, R. Singh, N. K. Girdhar, and M. P. S. Ishar, *Tetrahedron*, **58,** 2471 (2002).
[21] C. K. Ghosh, N. Tewari, and C. Bandyopadhyay, *Indian J. Chem.*, **22B,** 1200 (1983).
[22] D. L. M. Coutinho and P. S. Fernandes, *Indian J. Chem.*, **31B,** 573 (1992).
[23] L. Cao, L. Zhang, and J. J. Liu, *Chem. Heterocycl. Compd.*, **40,** 214 (2004).
[24] L. Cao and W. Wang, *Chem. Heterocycl. Compd.*, **39,** 1072 (2003).
[25] L. Tsao, L. Chzhan, and Ts. Lyu, *Chem. Heterocycl. Compd.*, **37,** 311 (2001).
[26] A. Dandia, R. Singh, and S. Khaturia, *Bioorg. Med. Chem.*, **14,** 1303 (2006).
[27] A. W. Bauer, W. W. M. Kirby, J. C. Sherris, and M. Turck, *Am. J. Clin. Pathol.*, **45,** 493 (1966).
[28] D. C. Gross and S. E. De Vay, *Physiol. Plant Pathol.*, **11,** 13 (1977).
[29] U. Petersen and H. Heitzer, *Liebigs Ann. Chem.*, 1659 (1976).
[30] A. Dornow and M. P. Menzel, *Chem. Ber.*, **97,** 2173 (1964).