Heteroatom Chemistry
Volume 16, Number 1, 2005

Synthesis of Some New Azole, Azepine, Pyridine, and Pyrimidine Derivatives Using 6-Hydroxy-4H-4-oxo[1]-benzopyran-3-carboxaldehyde as a Versatile Starting Material

A. H. Abdel-Rahman, M. A. A. Hammouda, and S. I. El-Desoky

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt

Received 2 February 2004

ABSTRACT: *Condensation of 3-formyl chromone* **1** *with hydroxylamine hydrochloride afforded the corresponding oxime* **2** *that was converted to nitrile* **3**. *Refluxing of oxime* **2** *and/or nitrile* **3** *with aceturic or hippuric acid gave* **16** *and* **17**. *Treatment of* **1** *with semicarbazide hydrochloride and thiosemicarbazide afforded the corresponding carbazones* **5–6** *that underwent cyclization with ethyl bromoacetate and/or chloroacetone yielding* **7–8**. *Also* **1** *reacted with acyclic active methylene reagents, e.g. malononitrile, ethyl cyanoacetate, and ethyl acetoacetate to form compounds* **11, 12**, *and* **13**. *Reaction of* **1** *with bifunctional reagents, e.g. benzil, o-phenylenediamine, o-aminophenol, and o-aminothiophenol yielding the corresponding imidazolyl bezopyranone and azepine derivatives* **14–20**. *Condensation of* **1** *with acyclic or heterocyclic compounds containing active methylene group, e.g. hippuric acid forming the condensed products* **21–27**. Heteroatom Chem 16:20–27, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20048

INTRODUCTION

It is well known that benzopyran derivatives are an important class of chemotherapeutic compounds [1,2] in addition to their widespread occurrence in plants. These compounds possess coronary vasodilating activity [3–5]. Recently, benzopyran derivatives are shown to possess desirable altering activity, for example, decreasing the atherogenic VLDL + LDL cholesterol fraction and elevating antiatherogenic HDL cholesterol fraction [6–11]. Also, benzopyran derivatives produced crosslinks in photoreaction with DNA [12]. Thus, the high pharmacological interest of the above derivatives prompted us to synthesize some new heterocyclic compounds of possible biological activity.

Correspondence to: A. H. Abdel-Rahman; e-mail: arahman@hotmail.com.

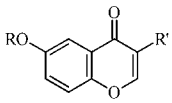
RESULTS AND DISCUSSION

The versatile starting compound, 6-hydroxy-4H-4-oxo[l]benzopyran-3-carboxaldehyde **(1)** [13] was obtained in good yield from Vilsmeier–Haack formylation of 2,5-dihydroxy acetophenone. Compound **1** was condensed with hydroxylamine hydrochloride in ethanol to give a quantitative yield of the corresponding oxime **2** that was refluxed in acetic anhydride to give 6-acetoxy-4H-4-oxo[1]-benzopyran-3-carbonitrile (**3**). The infrared spectrum of **3** showed clearly disappearance of the imino absorption band at υ 1630 cm^{-1} instead of new bands at υ = 2237 cm^{-1} for cyano group and 1759 cm^{-1} for acetoxy group.

Acid deformylation of **1** using concentrated sulfuric acid afforded 6-hydroxy-4H[1]benzopyran-4-one (**4**) that showed in its infrared spectrum the characteristic keto chromone group at υ = 1625 cm^{-1}

only, while the formyl peak at $\upsilon = 1697$ cm^{-1} was disappeared. Although refluxing of **1** with semicarbazide hydrochloride or thiosemicarbazide in alcohol, the corresponding carbazones **5** and **6** were obtained in good yield. The infrared spectra of **5** and **6** were in agreement with the assigned structures. Compound **5** revealed absorption bands at $\upsilon = 3345$, 3223, 3173 cm^{-1} for (OH, NH, and NH_2 groups), while the amide and chromone carbonyl groups were appeared at 1699 and 1626 cm^{-1} respectively.

The thiazole derivatives are well known as potent and selective human adenosine A_3 receptor antagonists [14,15], therefore the reaction of the thiosemicarbazone **6** with ethyl bromoacetate or chloroacetone in the presence of sodium acetate afforded the thiazole derivatives **7** and **8**. The mass spectra of the latter products gave molecular ion peaks [M^+] at $m/z = 303$ and 301 respectively which were in agreement with their molecular weights.



1; R = H R' = CHO
2; = H = CH=NOH
3; = $COCH_3$ = CN
4; = H = H
5; = H = $CH=NNHCONH_2$
6; = H = $CH=NNHCSNH_2$

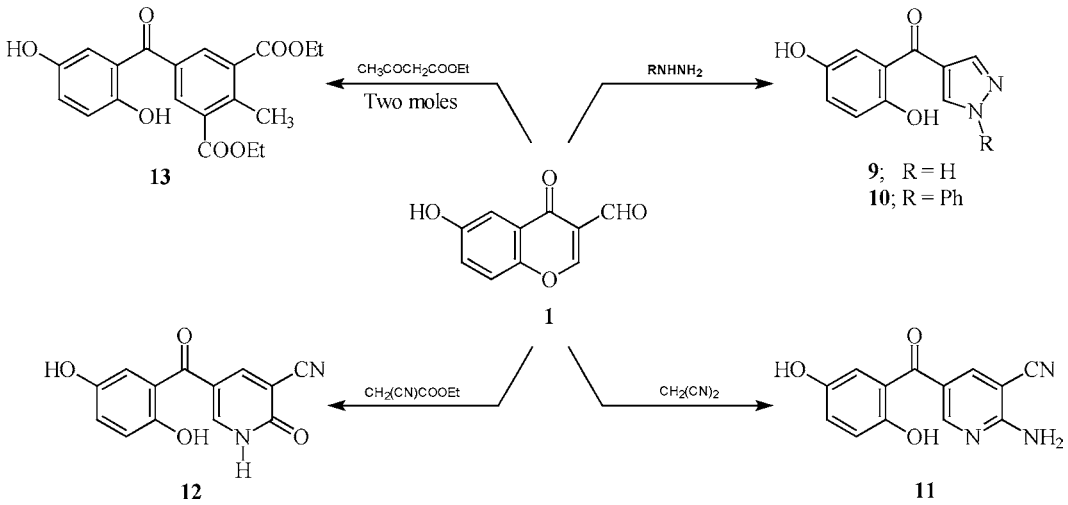
7; R = H R' = CH=NNH-

8; R = H R' = CH=NNH-

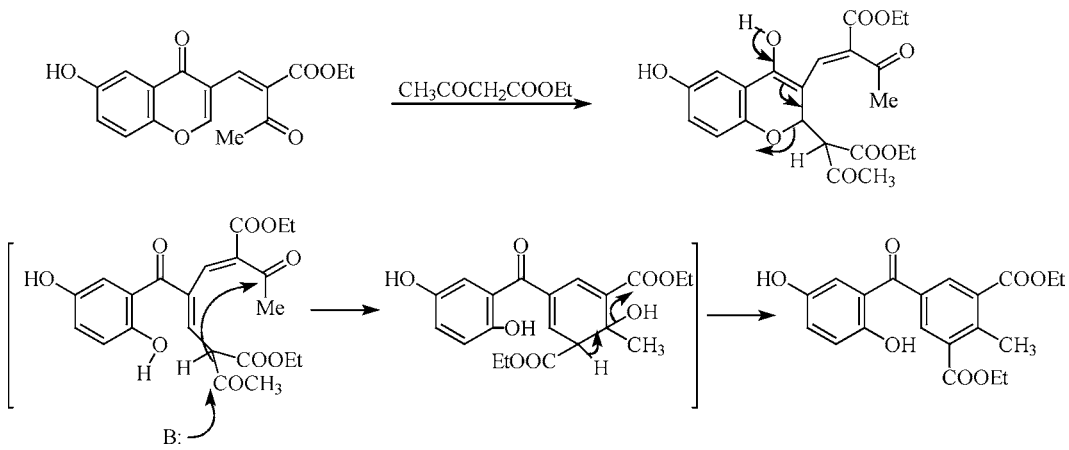
On treatment of **1** with hydrazine hydrate or phenylhydrazine (molar ratio 1:1) in ethanol, the corresponding pyrazole derivatives **9** and **10** were obtained in good yields. The reaction of aldehyde function of **1** with active nitriles to furnish the corresponding pyridine derivatives was reported by Ghosh et al. [16]. So the reaction of **1** with malononitrile or ethyl cyanoacetate in the presence of ammonium acetate afforded 2-amino-3-cyano-5-(2′,5′-dihydroxybenzoyl)pyridine (**11**) and 3-cyano-5-(2′,5′-dihydroxybenzoyl)-2-pyridone (**12**) respectively (Scheme 1). The assigned structures of **11** and **12** were confirmed by spectral data in addition to the correct elemental analysis; their infrared spectra revealed a characteristic absorption band at υ 2227 cm^{-1} for a cyano group in addition to the hydroxyl and amino absorption bands. ^{1}H NMR spectra of **11** and **12** showed the amino and hydroxyl signals at 7.8, 9.2, and 9.6 ppm in addition to the aromatic protons.

Also, a mixture of **1** with ethyl acetoacetate (two moles) in the presence of ammonium acetate was refluxed in ethanol, diethyl-2′,5′-dihydroxy-4-methylbenzophenone-3,5-dicarboxylate (**13**) was obtained. The reaction involved an initial condensation between aldehydic group and the active methylene group of ethyl acetoacetate to form the expected arylidene product followed by the Michael addition of another molecule of ethyl acetoacetate and subsequent opening of the γ-pyrone moiety then rearrangement to form the end product **13**, as outlined in Scheme 2.

Also, it was reported that the imidazole derivatives possessed high biological importance in the field of pharmaceutical chemistry as antimicrobials, antitumor, antiarrhythemic, anti-inflammatory, and antiulcer [17–19]. In light of these reports, compounds having a combination of benzopyranone and imidazole moieties can be expected to exhibit marked medicinal properties. Thus, refluxing of **1** with benzil or *o*-phenylenediamine in glacial



SCHEME 1



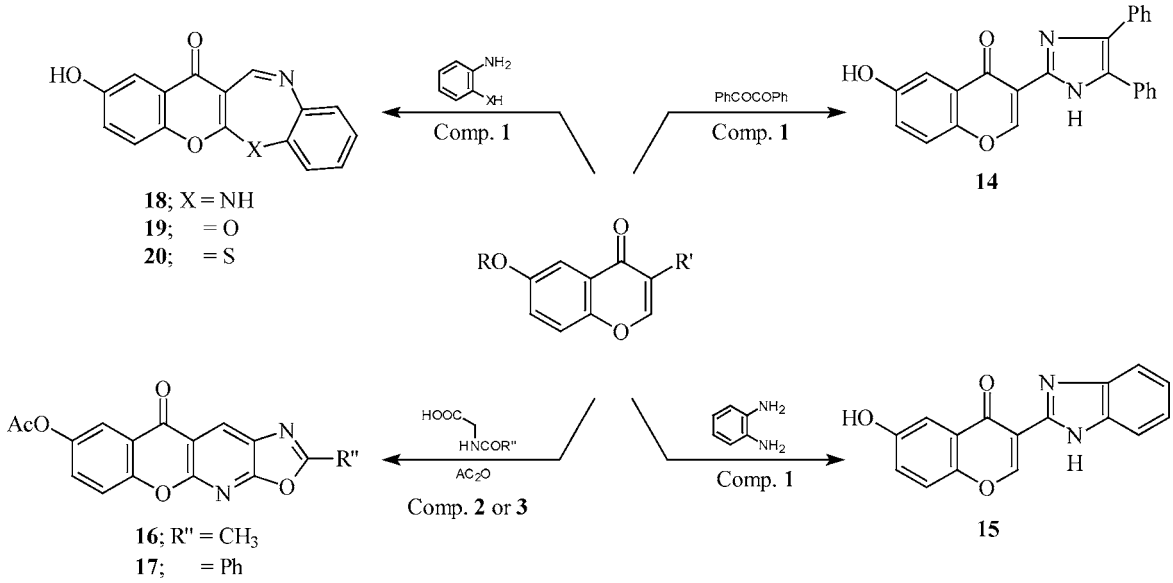
SCHEME 2

acetic acid and ammonium acetate, the corresponding imidazolyl benzopyranone derivatives **14** and **15** were obtained. Their structure assignment was based on the basis of the correct analytical and spectral data; compound **14** showed in its ^{1}H NMR spectrum besides the aromatic protons, two broad NH and OH signals at δ 9.5 and 11.5 ppm respectively (Scheme 3).

Synthesis of fused benzopyranopyridine derivatives that were used as potential antiarthritic agents was reported in the literature [20].

Therefore, oxime **2** or nitrile **3** was reacted with aceturic or hippuric acid in acetic anhydride, 7-acetoxy-2-methyl (or 2-phenyl)-4H[1]benzopyrano-[3,2-e]-oxazolo[5,4-b]pyridin-5-one **16** and **17** were obtained, respectively (Scheme 3). The elemental analyses of **16** and **17** in addition to their spectral data were compatible with the proposed structures. Their infrared spectra revealed disappearance of the cyano absorption band, whereas the signals at υ = 1752 and 1655 cm^{-1} attributable to CH_3COO and C=O (chromone) appeared. Also, ^{1}H NMR spectrum of compound **16** showed two singlet peaks at δ = 1.8 and 2.2 ppm for two methyl groups in addition to multiplet aromatic protons at δ = 7.6–7.8 ppm.

Compounds containing diazepine moiety are recently used as NNRTI-resistant HIV [21]. 3-Formyl (or cyano) benzopyran-4-one contains three potential sites of nucleophilic attack: C-2, C-4, and 3-formyl (or cyano) group, thus condensation of a suitable reactant at two of these sites afforded new ring system. Aniline having a nucleophilic function H—X



SCHEME 3

(X = NH, O, S) at its ortho position reacts easily with **1** to give the corresponding azepine derivatives **18–20**. The ^{1}H NMR spectrum of **18** showed signals at $\delta = 6.7–7.4$ (m, 7H, Ar-H), 8.5 (br, s, 1H, NH), 8.6 (s, 1H, 12-H), and 14.3 ppm (s, 1H, OH).

The Knoevenagel reaction of 3-formyl chromones with heterocyclic compounds containing active methylene group has been reported as a synthetic route for the preparation of a wide variety of heterocycles [22]. The reaction of **1** with acyclic or heterocyclic compounds such as hippuric acid, 1-phenyl-3-methyl-5-pyrazolone, ethyl-2-cyano-2-(3-phenyl-5-oxo-1,3-thiazolan-2-ylidene)acetate, *N*-phenyl rhodanine, 4-aminoantipyrine, barbituric acid, and thiobarbituric acid formed the corresponding arylidene compounds **21–27**. The structures of the latter products could be directly deduced from the good elemental analyses as well as their spectral data (Scheme 4).

CONCLUSION

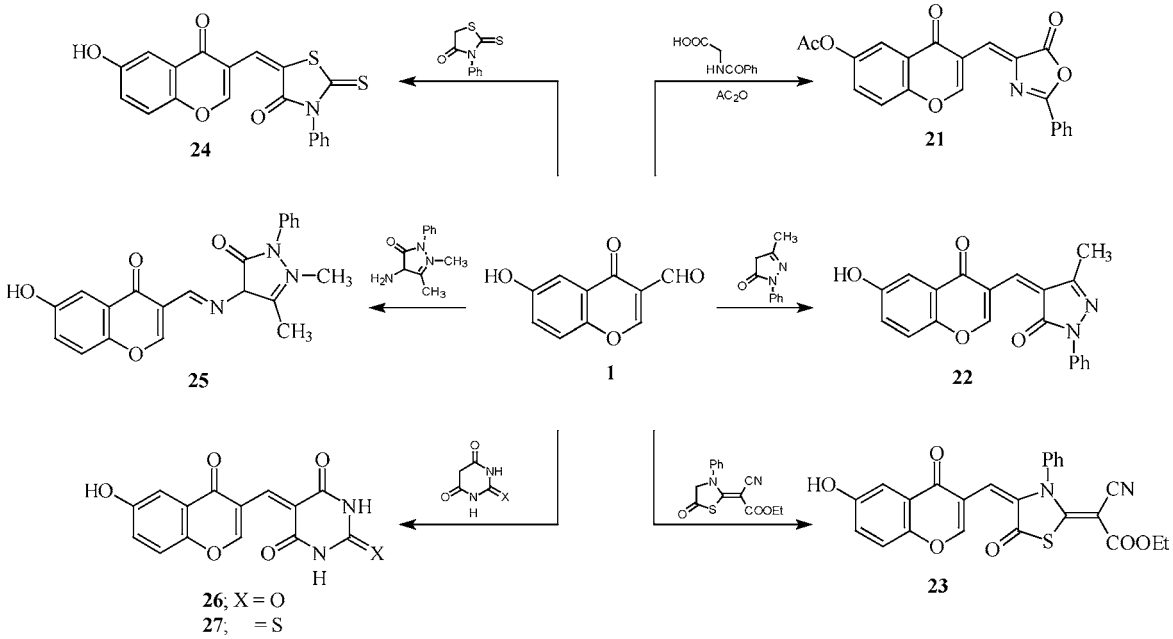
Hydrazines and active nitriles reacted with 6-hydroxy-3-formyl chromone **1** through addition followed by pyran ring opening affording dihydroxybenzoyl derivatives **9–12**. Compound **1** was used as a starting material to synthesize new chromone derivatives containing heterocyclic rings fused onto a chromone moiety. Compound **1** was reacted with *N*-substituted glycine and *o*-aniline derivatives to produce the corresponding benzopyranoxazolopyridines **16–17** and benzopyranoazepines **18–20** respectively. Compound **1** was also condensed with several nitrogen acyclic and cyclic compounds, e.g. hippuric acid, 1-phenyl-3-methyl-5-pyrazolone, ethyl-2-cyano-2-(3-phenyl-5-oxo1,3-thiazolan-2-ylidene)acetate, *N*-phenyl rhodanine, 4-aminoantipyrine, barbituric acid, and thiobarbituric acid to form compounds **21–27** with expected high biological activity.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and uncorrected. Elemental analysis was carried out in the Microanalytical Unit, National Research Centre, Dokki, Giza, Cairo. Infrared spectra were recorded on Matheson 5000 FTIR spectrometer using KBr wafer technique. ^{1}H NMR spectra were determined on Varian-Gemini 200 MHz and Jeol-Ex-270 MHz NMR spectrometer using TMS as an internal standard with (chemical shift $\delta = 0$ ppm). Mass spectra were determined on AGC-MS. QP-1000 Ex. Schimadzu (Japan). The purity of the synthesized compounds was tested by thin-layer chromatography (TLC).

*Synthesis of 6-Hydroxy-4H-4-oxo[1]benzopyran-3-carboxaldehyde (**1**)*

To a stirred solution of 2,5-dihydroxyacetophenone (1.52 g, 10 mmol) in dimethyl-formamide (20 mL),



SCHEME 4

phosphorous oxychloride (10 mL) was added dropwise at −5°C during about 10 min. The mixture was stirred at room temperature for 13 h and decomposed by ice water. The resulting precipitate was collected by filteration, washed with water, and recrystallized from ethyl acetate to afford **1** as orange crystals, mp 234–236°C; yield (61%). IR (υ/cm^{-1}) = 3450–3200 (br, OH bonded), 3370 (free OH), 1697 (CHO), 1630 (CO chromone), and 1593 cm^{-1} (Ar.). Anal. Calcd for $C_{10}H_6O_4$ (190.15): C, 63.16; H, 3.18. Found: C, 62.95; H, 3.00%.

*Synthesis of 6-Hydroxy-3-hydroxyiminomethyl-4H-4-oxo[1]benzopyran (**2**)*

To a well-stirred solution of compound **1** (0.68 g, 4 mmol) in ethanol (30 mL), hydroxylamine hydrochloride (0.139 g, 4 mmol) was added. The solution was stirred vigorously for 1 h. The solid obtained was filtered off, washed with water, dried, and recrystallized from ethanol to give **2** as beige crystals, mp 225°C, yield (95%). IR (υ/cm^{-1}) = 3450–3000 (br, OH), 3203 (=N—OH free), 1630 (CO), and 1597 cm^{-1} (Ar.). Anal. Calcd for $C_{10}H_7NO_4$ (205.17): C, 58.54; H, 3.44; N, 6.83. Found: C, 57.99; H, 2.97; N, 6.45%.

*Synthesis of 6-Hydroxy-4H-4-oxo[1]benzopyran-3-carbonitrile (**3**)*

A solution of compound **2** (0.41 g, 2 mmol) in acetic anhydride (10 mL) was heated at 100°C for 2 h. The precipitate formed after cooling was filtered off, washed with hot water, dried, and recrystallized from ethyl acetate to give compound **3** as brown crystals, mp 164–165°C; yield (95%). IR (υ/cm^{-1}) = 2237 (CN), 1759 (CH_3COO), 1665 (C=O), and 1616 cm^{-1} (Ar.). ^{1}H NMR (DMSO): δ = 2.2 (s, 3H, CH_3), 7.5–7.7 (m, 3H, Ar-H), 8.5 ppm (s, 1H, 2-H). Anal. Calcd for $C_{12}H_7NO_4$ (223.41): C, 62.89; H, 3.08; N, 6,11. Found: C, 62.39; H, 2.50; N, 5.75%.

*Synthesis of 6-Hydroxy-4H-4-oxo[1]benzopyran (**4**)*

A suspension of compound **1** (0.34 g, 2 mmol) in sulfuric acid (3N 10 mL) was refluxed for 2 h. The reaction mixture was allowed to cool and extracted with ethyl acetate (4 × 50 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ followed by water several times, dried ($MgSO_4$), and evaporated. The resulting residue was digested with petroleum ether and recrystallized from ethanol to give **4** as faint yellowish brown crystals, mp 182°C; yield (60%). IR (υ/cm^{-1}) = 3500–2950 (OH), 1625 (CO chromone), and 1571 cm^{-1} (Ar.). ^{1}H NMR (DMSO): δ = 6.3 (d, 1H, 3-H), 7.2–7.6 (m, 3H, Ar-H), 7.8 (d, 1H, 2-H), and 11.8 ppm (s, 1H, OH). Anal. Calcd for $C_9H_6O_3$ (162.14): C, 66.67; H, 3.73. Found: C, 66.46; H, 3.50%.

Condensation of 6-Hydroxy-3-formylchromone with Semicarbazide Hydrochloride and Thiosemicarbazide. Synthesis of Compounds **5** *and* **6**

General Method: A mixture of compound **1** (0.38 g, 2 mmol) and semicarbazide hydrochloride (0.22 g, 2 mmol) or (thiosemicarbazide) (0.18 g, 2 mmol) in ethanol (15 mL) was refluxed for 1 h. The precipitate that was formed filtered off, dried, and recrystallized from acetone to give **5** and **6**.

Compound **5** was obtained as faint brown crystals, mp 260–262°C; yield (87%). IR (υ/cm^{-1}) = 3600–3100 (bonded OH), 3445, 3223-3173 (OH free, NH and NH_2), 1690 ($CONH_2$), and 1626 cm^{-1} (CO). ^{1}H NMR (DMSO): δ = 6.7–7.6 (m, 5H, Ar-H and NH_2), 7.9 (s, 1H, olefinic CH), 8.5 (s, 1H, 2-H), 9.0 (s, 1H,NH), and 14.2 ppm (s, 1H, OH). Anal. Calcd for $C_{11}H_9N_3O_4$ (247.21): C, 53.45; H, 3.67; N, 16.99. Found: C, 53.40; H, 3.60; N, 17.15%.

Compound **6** was obtained as brown crystals, mp 256–258°C; yield (90%). IR (υ/cm^{-1}) = 3460, 3200–2120, 3100 (OH, NH_2, NH) and l646 cm^{-1} (CO). ^{1}H NMR (DMSO): δ = 6.6–7.6 (m, 5H, Ar-H and NH_2), 7.8 (s, 1H, olefinic CH), 8.4 (s, 1H, 2-H), 8.8 (s, 1H, NH), and 14.1 ppm (s, 1H, OH). Anal. Calcd for $C_{11}H_9N_3O_3S$ (263.27): C, 50.18; H, 3.45; N, 15.96. Found: C, 50.59; H, 3.86; N, 16.01%.

*Synthesis of 2-{2-[-1-(6-Hydroxy-4-oxo-4H-3-chromenyl)methylidene]-hydrazono}-1,3-thiazolan-4-one (**7**)*

A solution of compound **6** (0.52 g, 2 mmol), ethyl bromoacetate (0.41 g, 2.5 mmol), and anhydrous sodium acetate (0.5 g) in ethanol (50 mL) was refluxed for 1 h. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from ethanol/DMSO (2: 1) to give compound **7** as red crystals, mp 270–272°C; yield (85%). IR (υ/cm^{-1}) = 3600–3400 (OH bonded), 3443 (OH free), 3140 (NH), 1702 (CONH), 1628 (CO), and 1610 cm^{-1} (C=N). ^{1}H NMR (DMSO): δ = 4.1 (s, 2H, CH_2), 6.7–7.8 (m, 4H, Ar-H, and NH), 8.0 (s, 1H, olefinic CH), 8.4 (s, 1H, 2-H), and 9.5 ppm (s, 1H, OH). MS: m/z = 303 (M^+, 56%), 261 (27%), 188 (100%), 136 (45%), 92 (12%), 52 (37%). Anal. Calcd for $C_{13}H_9N_3O_4S$ (303.29): C, 51.48; H, 2.99; N, 13.85. Found: C, 51.01; H, 3.87; N, 13.27%.

*Synthesis of 2-{2-[1-(6-Hydroxy-4-oxo-4H-3-chromenyl)methylidene]hydrazono}-4-methyl-1,3-thiazolane (**8**)*

A mixture of compound **6** (0.52 g, 2 mmol), chloroacetone (0.3 g, 2 mmol), and sodium acetate (0.5 g) in ethanol (20 mL) was refluxed for 1 h. The precipitate that was formed filtered off, washed with water, dried, and recrystallized from ethanol/acetone (1:1) to give compound **8** as pale yellow crystals, mp 250–252°C; yield (90%). IR (υ/cm^{-1}) = 3450–3150 (OH), 3283 (NH), 1639 (CO), and 1624 cm^{-1} (C=N). ^1H NMR (DMSO): $\delta = 2.4$ (s, 3H, CH_3), 6.5 (s, 1H, C-5 thiazole-H), 6.8–7.6 (m, 4H, Ar-H, and NH), 8.1 (s, 1H, olefinic CH), 8.4 (s, 1H, 2-H), and 10.2 ppm (s, 1H, OH). MS: $m/z = 301$ (M^+, 55%), 188 (18%), 166 (100%), 136 (40%), 114 (20%), 71 (14%). Anal. Calcd for $C_{14}H_{11}N_3SO_3$ (301.32): C, 55.80; H, 3.68; N, 13.95. Found: C, 55.88; H, 3.40; N, 13.59%.

*Synthesis of 4-(2′,5′-Dihydroxybenzoyl)pyrazole and 2-Phenyl-4-(2′,5′-dihydroxybenzoyl)-pyrazole (**9** and **10**)*

General Method: A mixture of compound **1** (0.38 g, 2 mmol) and hydrazine hydrate (0.09 mL, 2 mmol) or phenylhydrazine (0.22 g, 2 mmol) in absolute ethanol (30 mL) was refluxed for 3 h. The solvent was concentrated to 10 mL, diluted with water, and left to cool. The solid that was formed filtered off, dried, and recrystallized from light petroleum ether/diethyl ether (1:3) to give (**9** and **10**).

Compound **9** was obtained as beige crystals, mp above 300°C; yield (70%). IR (υ/cm^{-1}) = 3400–3200 (OH), 3119 (NH), and 1628 cm^{-1} (CO). ^1H NMR (DMSO): $\delta = 7.0$–7.4 (m, 5H, Ar-H), 8.1 (s, 1H, OH), 8.4 (s, 1H, OH), and 9.3 ppm (s, 1H, NH). Anal. Calcd for $C_{10}H_8N_2O_3$ (204.18): C, 58.82; H, 3.95; N, 13.72. Found: C, 58.50; H, 3.85; N, 13.40%.

Compound **10** was obtained as yellow needles, mp 188–190°C; yield (65%). IR (υ/cm^{-1}) = 3362, 3300 (OH), and 1630 cm^{-1} (CO). ^1H NMR($CDCl_3$): $\delta = 7.0$–7.10 (m, 10H, Ar-H), 8.2 (s, 1H, OH), and 8.5 ppm (s, 1H, OH). Anal. Calcd for $C_{16}H_{12}N_2O_3$ (280.28): C, 68.56; H, 4.32; N, 9.90. Found: C, 68.09; H, 4.88; N, 9.33%.

*Synthesis of 2-Amino-3-cyano-5-[2′,5′-dihydroxy benzoyl]pyridine (**11**)*

A mixture of compound **1** (0.38 g, 2 mmol), malononitrile (0.13 g, 2 mmol), and ammonium acetate (1.5 g) was refluxed in either glacial acetic acid (15 mL) or ethanol (15 mL) for 8 h. After cooling, the reaction mixture poured on crushed ice and the solid was separated, filtered off, dried, and recrystallized from ethanol to give (**11**) as red crystals, mp 238–240°C; yield (50%). IR (υ/cm^{-1}) = 3450–3100 (br, OH), 3380, 3332 (NH_2), 2227 (CN), 1679 (CO), and 1639 cm^{-1} (C=N). ^1H NMR (DMSO): $\delta = 6.8$–7.0 (m, 3H, 3′,4′, 6′-H), 7.8 (s, 2H, NH_2), 8.2 (d, 1H, C-4 pyridine-H), 8.5 (d, 1H, C-6 pyridine-H), 9.2 (s, 1H, OH), and 9.6 ppm (s, 1H, OH). Anal. Calcd for $C_{13}H_9N_3O_3$ (255.23): C, 61.18; H, 3.55; N, 16.46. Found: C, 61.51; H, 3.37; N, 15.83%.

*Synthesis of 3-Cyano-5-[2′,5′-dihydroxybenzoyl]-2-pyridone (**12**)*

A mixture of **1** (0.38 g, 2 mmol), ethyl cyanoacetate (0.23 g, 2 mmol), and ammonium acetate (1.5 g) was refluxed in glacial acetic acid (15 mL) for 5 h. After cooling, the reaction mixture was poured on crushed ice, the solid that separated was filtered off, dried and recrystallized from acetone to give compound (**12**) as yellow crystals, mp 220–222°C; yield (48%). IR (υ/cm^{-1}) = 3450–3100 (br OH), 2227 (CN), 1692 (CO), and 1666 cm^{-1} (CO). ^1H NMR (DMSO): $\delta =$ 6.7–7.0 (m, 3H, 3′,4′, 6′-H), 8.1 (d, 1H, C-4 pyridine-H), 8.4 (d, 1H, C-6 pyridine-H), 9.2 (s, 1H, OH), and 9.6 ppm (s, 1H, OH). Anal. Calcd for $C_{13}H_7N_2O_4$ (255.21): C, 61.18; H, 2.76; N, 10.98. Found: C, 60.93; H, 2.40; N, 11.01%.

*Synthesis of Diethyl-2′,5′-dihydroxy-4-methyl benzophenone-3,5-dicarboxylate (**13**)*

A mixture of compound **1** (0.38 g, 2 mmol), ethyl acetoacetate (0.51 g, 4 mmol), and ammonium acetate (2 g) was refluxed in ethanol (20 mL) for 4 h. After cooling, the reaction mixture was poured on crushed ice. The solid that was formed filtered off, dried, and recrystallized from acetone to give compound **13** as colorless crystals, mp 140–142°C; yield (40%). IR (υ/cm^{-1}) = 3500–3250 (br OH), 1722 (CO ester), 1694 (CO), and 1600 cm^{-1} (Ar). ^1H NMR($CDCl_3$): $\delta = 1.20$ and 1.40 (2t, 6H, $2CH_3$), 2.88 (s, 3H, CH_3), 3.9 and 4.5 (2q, 4H, $2CH_2$), 6.1 (s, 2H, 2,6-H), 6.8–7.0 (m, 3H, 3′,4′, 6′-H), 7.8 (s, 1H, OH), and 8.2 ppm (s, 1H, OH). Anal. Calcd for $C_{20}H_{20}O_7$ (372.37): C, 64.51; H, 5.41. Found: C, 64.13; H, 5.50%.

*Synthesis of 6-Hydroxy-3-[4′,5′-diphenyl-2′-imidazolyl]-4H[l]benzopyran-4-one (**14**)*

A mixture of 3-formyl derivative **1** (0.34 g, 2 mmol), benzil (0.42 g, 2 mmol), and ammonium acetate (1 g) was refluxed in glacial acetic acid (15 mL) for 2 h. The precipitate that was formed filtered off, washed several times with water, dried, and recrystallized from

ethanol to give **14** as yellow crystals, mp 220–222°C; yield (75%). IR (υ/cm^{-1}) = 3500–3100 (OH), 3075 (NH), 1630 (CO), and 1593 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): $\delta = 7.0–7.4$ (m, 13H, Ar-H), 8.8 (s, 1H, 2-H), 9.5 (br, s, 1H, NH), and 11.5 ppm (s, 1H, OH). Anal. Calcd for $C_{24}H_{16}N_2O_3$ (380.40): C, 75.78; H, 4.24; N, 7.36. Found: C, 75.58; H, 3.84; N, 7.06%.

*Synthesis of 6-Hydroxy-3-[2′-benzimidazolyl]-4H[1]benzopyran-4-one (***15***)*

A mixture of compound **1** (0.34 g, 2 mmol) and *o*-phenylenediamine (0.22 g, 2 mmol) was refluxed in glacial acetic acid (15 mL) for 2 h. Dilution of the reaction mixture with crushed ice gave a precipitate that was formed, filtered off, washed with water, dried, and recrystallized from ethanol to give **15** as colorless crystals, mp above 300°C; yield (70%). IR (υ/cm^{-1}) = 3400–3200 (OH), 3147 (NH), 1639 (CO), and 1610 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): $\delta = 6.9–7.3$ (m, 7H, Ar-H), 8.6 (s, 1H, 2-H), 9.0 (br, s, 1H, NH), and 11.4 ppm (s, 1H, OH). Anal. Calcd for $C_{16}H_{10}N_2O_3$ (278.26): C, 69.06; H, 3.62; N, 10.06. Found: C, 68.70; H, 3.22; N, 9.86%.

*Synthesis of 7-Acetoxy-2-methyl (or 2-phenyl)-4H[l]benzopyran[3,2-e]oxazolo-[5,4-b]-pyridin-5-one (***16** *and* **17***)*

General Method: A mixture of compound **3** (0.37 g, 2 mmol) was refluxed with *N*-acetyl glycine (0.23 g, 2 mmol) or *N*-benzoyl glycine (0.36 g, 2 mmol) in the presence of anhydrous sodium acetate (0.5 g) in acetic anhydride (15 mL) for 2 h. The precipitate was formed, filtered off, washed with water then hot water–ethanol, dried, and recrystallized from ethanol-DMSO (2: 1) to give **16** and **17**.

Compound **16** was obtained as beige crystals, mp above 300°C; yield (75%). IR (υ/cm^{-1}) = 1753 (CO ester), 1659 (CO), 1630 (C=N), and 1592 cm^{-1} (Ar.). ^1H NMR (DMSO): $\delta = 1.8$ (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 7.6–7.8 (m, 3H, Ar-H), and 8.8 ppm (s, 1H, 4-H). Anal. Calcd for $C_{16}H_{10}N_2O_5$ (311.26): C, 61.94; H, 3.25; N, 9.03. Found: C, 61.57; H, 2.90; N, 8.55%.

Compound **17** was obtained as red crystals, mp above 300°C; yield (80%). IR (υ/cm^{-1}) = 1752 (CO ester), 1655 (CO), and 1633 (C=N) cm^{-1}. MS: m/z = 329 (M^+-acetyl, 20%), 286 (32%), 244 (100%). Anal. Calcd for $C_{21}H_{12}N_2O_5$ (372.33): C, 67.74; H, 3.25; N, 7.52. Found: C, 67.45; H, 3.19; N, 8.03%.

N.B. The compounds (**16** and **17**) were prepared by applying the above procedure when the oxime **2** (0.41 g, 2 mmol) was used instead of the nitrile **3**.

*Synthesis of 9-Hydroxy-11H-11-oxo[1]benzopyrano[2,3-b][1,5]benzo-diazepine, Oxazepine and Thiazepine (***18–20***)*

General Method: A mixture of compound **1** (0.34 g, 2 mmol) and *o*-phenylenediamine (0.22 g, 2 mmol,) or *o*-aminophenol, (0.22 g, 2 mmol) or *o*-aminothiophenol (0.25 g, 2 mmol) was refluxed in absolute ethanol (30 mL) for 3 h. The precipitate that was formed filtered off, dried, and recrystallized from the suitable solvent to give **18–20**.

Compound **18** was obtained as pale yellow crystals, mp 280–282°C (DMSO); yield (80%). IR (υ/cm^{-1}) = 3600–3100 (br, OH, and NH), 1655 (CO), 1620 (C=N), and 1567 cm^{-1} (Ar.). ^1H NMR(DMSO): $\delta = 6.7–7.4$ (m, 7H, Ar-H), 8.5 (s, 1H, NH), 8.6 (s, 1H, 12-H), and 14.3 ppm (s, 1H, OH). Anal. Calcd for $C_{16}H_{10}N_2O_3$ (278.26): C, 69.06; H, 3.62; N, 10.07. Found: C, 68.80; H, 3.32; N, 9,88%.

Compound **19** was obtained as orange crystals, mp above 300°C (THF); yield (77%). IR (υ/cm^{-1}) = 3500–3150 (br, OH), 1642 (CO), 1602 (C=N), and 1580 cm^{-1} (Ar). ^1H NMR (DMSO): $\delta = 6.8–7.5$ (m, 7H, Ar-H), 8.8 (s, 1H, 12-H), and 14.5 ppm (s, 1H, OH). Anal. Calcd for $C_{16}H_9NO_4$ (279.25): C, 68.82; H, 3.25; N, 5.02. Found: C, 68.52; H, 3.00; N, 4.78%.

Compound **20** was obtained as yellow crystals, mp 280–282°C (ethyl acetate); yield (73%). IR (υ/cm^{-1}) = 3500–3200 (OH), 1625 (CO), and 1589. cm^{-1} (C=N). ^1H NMR (DMSO): $\delta = 6.6–7.3$ (m, 7H, Ar-H), 8.6 (s, 1H, 12-H), and 14.0 ppm (s, 1H, OH). Anal. Calcd for $C_{16}H_9NO_3S$ (295.31): C, 65.07; H, 3.07; N, 4.74. Found: C, 64.70; H, 2.85; N, 4.30%.

Condensation of **1** *with Hippuric Acid, 1-Phenyl-3-methyl-5-pyrazolone, Ethyl 2-cyano-2-[5-oxo-3-phenyl-1.3-thiazolan-2-ylidene]acetate, N-phenyl rhodanine, 4-Amino-antipyrine, Barbituric and Thiobarbituric Acids: Syntheses of Compounds* **21–27**

General Method: A mixture of 3-formy1 chromone derivative **1** (0.38 g, 2 mmol), the appropriate active methylene derivative (2 mmol), and anhydrous sodium acetate (0.2 g) in glacial acetic acid (15 mL) was refluxed for 2 h. The precipitate that was formed, filtered off, washed with hot water several times, dried, and recrystallized from the suitable solvent to give **21–27**.

Compound **21** as yellow crystals, mp 268–270°C (ethanol); yield (90%). IR (υ/cm^{-1}) = 1796 (CO ester), 1763 (CO oxazolone), 1650 (CO chromone), and 1601 cm^{-1} (C=C). ^1H NMR (DMSO): $\delta = 2.3$ (s, 3H, CH_3), 7.4–8.3 (m, 9H, Ar-H, and C-2 pyranone-H),

and 9.8 ppm (s, 1H, olefinic C-H). Anal. Calcd for $C_{21}H_{13}NO_6$ (375.33): C, 67.20; H, 3.49; N, 3.73. Found: C, 67.44; H, 3.54; N, 3.53%.

Compound **22** as reddish yellow crystals, mp above 320°C (ethyl acetate); yield (95%). IR (υ/cm^{-1}) = 3550–3200 (OH), 1682 (CONPh), and 1628 cm^{-1} (CO). ^{1}H NMR (DMSO): $\delta = 2.3$ (s, 3H, CH_3), 7.1–7.9 (m, 9H, Ar-H, and C-2 pyranone-H), 10.3 (s,1H ,olefinic C—H), and 10.5 ppm (s, 1H, OH). MS: m/z = 346 (M^+, 100%), 318 (49%), 301 (33%), 289 (28%), 182 (24%), 77 (16%). Anal. Calcd for $C_{20}H_{14}N_2O_4$ (346.34): C, 69.36; H, 4.07; N, 8.09. Found: C, 69.00; H, 3.67; N, 7.88%.

Compound **23** as yellow crystals, mp above 300°C (ethanol); yield (95%). IR (υ/cm^{-1}) = 3500, 3150 (br OH), 2212 (CN), 1728 (CO ester), 1692 (CO thiazole), 1626 (CO chromone), and 1596 cm^{-1} (Ar.). ^{1}H NMR (DMSO): $\delta = 1.3$ (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.5–9.00 (m, 10H, Ar-H), and 10.3 ppm. (s, 1H, OH). Anal. Calcd for $C_{24}H_{16}NO_6S$ (446.45): C, 64.57; H, 3.61; N, 3.14. Found: C, 64.27; H, 3.20; N, 3.00%.

Compound **24** as yellow crystals, mp 320°C (ethanol); yield (95%). IR (υ/cm^{-1}) = 3500–3200 (OH), 1704 (CONPh), 1628 (CO), and 1586 cm^{-1} (Ar). ^{1}H NMR (DMSO): $\delta = 7.0$–7.9 (m, 9H, Ar-H, and C-2 pyranone-H), 9.5 (s, 1H, olefinic C—H), and 10. 1 ppm (s, 1H, OH). Anal. Calcd for $C_{19}H_{11}NO_4S_2$ (381.42): C, 59.83; H, 2.91; N, 3.67. Found: C, 59.63; H, 2.69; N, 3.37%.

Compound **25** as beige powder, mp 310–312°C (ethanol); yield (95%). IR (υ/cm^{-1}) = 3500–2950 (OH), 1720 (CONPh), and 1642 cm^{-l} (CO). ^{1}H NMR (DMSO): $\delta = 2.5$ (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 7.1–7.9 (m, 9H, Ar-H, and C-2 pyranone-H), 8.1 (s, 1H, CH=N) and 10.5 ppm (s, 1H, OH). Anal. Calcd for $C_{21}H_{18}N_3O_4$ (376.39): C, 67,01; H, 4.82; N, 11.16. Found: C, 66.83; H, 4.50; N, 11.00%.

Compound **26** as yellow crystals, mp above 300°C (ethanol); yield (95%). IR (υ/cm^{-1}) = 3346, 3202, 3073 (OH, 2NH), 1700 (CON), and 1675 cm^{-1} (CO chromone). ^{1}H NMR (DMSO): $\delta = 7.0$–7.8 (m, 4H, Ar-H, and C-2 pyranone-H), 9.2 (s, 1H, olefinic C-H), 9.8–10.0 (br, s, 2H, 2NH), and 10.5 ppm (s, 1H, OH). Anal. Calcd for $C_{14}H_8N_2O_6$ (300.22): C, 56.01; H, 2.69; N, 9.33. Found: C, 56.40; H, 2.80; N, 9.50%.

Compound **27** as faint green crystals, mp 280–282°C (ethanol); yield (90%). IR (υ/cm^{-1}) = 3351, 3133, 3061 (OH, 2NH) and 1685, 1646 cm^{-1} (CO). ^{1}H NMR (DMSO): $\delta = 7.2$–7.8 (m, 4H, Ar-H, and C-2 pyranone-H), 9.5 (s, 1H, olefinic C—H), 9.5 (s, H, NH), 10.5 (s, 1H, OH), and 11.4 ppm (s, 1H, NH). Anal. Calcd for $C_{14}H_8N_2O_5S$ (316.29): C, 53.16; H, 2.55; N, 8.86. Found: C, 52.90; H, 2.13; N, 8.53%.

REFERENCES

[1] Degen, S. J.; Mueller, K. L.; Shen, H. C.; Mulder, J. A.; Golding, G. M.; Wei, L. L., Zificsak, C. A.; Neeno-Eckwall, A.; Hsung, R. P. Bioorg Med Chem Lett 1999, 9, 973.

[2] Fawzy, N. M.; Swelam, S. A.; Batran, S. A. Bol Chim Farm 2004, 143, 24.

[3] Kandil, A.; Baraka, Y.M.; Bekemeier, H. J Drug Res 1977, 9, 195.

[4] Oguro, K.; Hashimoto, K. Jpn J Pharmacol 1974, 24, 227.

[5] Oguro, K.; Kubota, K.; Kimura, T.; Hashimoto, K. Jpn J Pharmacol 1973, 23, 459.

[6] (a) Stevens, T. J.; Schurr, P. E.; Gammill, R. B.; Day, C. E. Atherosclerosis 1985, 56, 313; (b) Stevens, T. J. Chem Abstr 1986, 104, 534.

[7] Stevens, T. J.; Jones, B. W.; Vidmar, T. J.; Moran, J. J.; Manni, D. S.; Day, C. E. Arzneim-Forsch 1985, 35(8), 1257.

[8] (a) Stevens, T. J.; Vidmar, T. J.; Day, C. E. Atherosclerosis 1985, 56, 301; (b) Stevens, T. J. Chem Abstr 1986, 104, 533.

[9] Yamashita, A.; Toy, A.; Scahill, T. A. J Org Chem 1989, 54, 3625.

[10] El-Naser, H.; Abdel-Ghaffar, E.; Mahmoud, S. S. Arzeneim-Forsch 1992, 42, 140.

[11] Gammill, R. B.; Hyde, R. H. J Org Chem 1983, 48, 3863.

[12] (a) Martelli, P.; Bovalini, L.; Ferri, S.; Franchi, G. G.; Bari, M. FEBS Lett 1985, 189, 255; (b) Martelli, P. Chem Abstr 1985, 103, 174715.

[13] El-Shaaer, H. M. Chem Pap 1996, 50(6), 349.

[14] Jung, K.-Y.; Kim, S.-K.; Gao, Z.-G.; Gross, A. S; Melman, N.; Jacoloson, K. A.; Kim, Y.-C. Bioorg Med Chem 2004, 12, 613.

[15] Phiel, C. J.; Wilson, C. A; Lee, V. M. and Klein, P. S. Nature 2003, 423, 435.

[16] Ghosh, C. K.; Ray, A.; Patra, A. J Heterocycl Chem 2001, 38, 1459.

[17] Varoli, L.; Burnelli, S.; Garuti, L.; Guarnieri, A.; Rossi, M. Pharmazie 1997, 52, 578.

[18] Wang, Y.; Stevens, M. F. G. J Org Chem 1997, 62, 7288.

[19] He, H.; Yang, J.; Wu, B.; Robinson, D.; Sprankle, K.; Kung, P.-P.; Lowery, K.; Mohan, V.; Hofstadler, S.; Swayze, E.; Giffery, R. Bioorg Med Chem Lett 2004, 14, 695.

[20] Kubo, K.; Ukawa, K.; Kuzuna, S.; Nohara, A. Chem Pharm Bull 1986, 34, 1108.

[21] Yoakim, C.; Bonneau, P. R.; Ziel, R. D.; Doyon, L.; Duan, J.; Guse, I.; Landry, S.; Malenfant, E.; Naud, J.; Ogilvie, W. W; Meara, J. A. O.; Plante, R.; Simoneau, B.; Thavonekham, B.; Bos, M.; Cordingley, M. G. Bioorg Med Chem Lett 2004, 14, 739.

[22] Lacova, M.; Gasparova, R.; Loos, D.; Liptay, T.; Pronayova, N. Molecules 2000, 5 , 167.