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ABSTRACT
The formation of isolated and fused benzo[f]chromene derivatives was achieved via reacting ethyl 3-amino-1-phenyl-1H-benzo[f]chromene-2-carboxylate (1) with some selected reagents under basic conditions. The new compound, ethyl 3-(dimethylaminomethyleneamino)-1-phenyl-1H-benzo[f]chromene-2-carboxylate (2) was prepared from compound 1 and N,N-dimethyl formamide in presence of phosphorus oxychloride under mild conditions in excellent yield using Vilsmeier reaction. Also, 10-amino-12-phenyl-9-sulfanyl-12H-benzo[f]chromen[2,3-d]pyrimidine-11(10H)-one (12), 10-aryl-14-phenyl-14H-benzo[f]chromen[2,3-d][1,3,4]thiazolido[3,2-e]pyrimidine-13-one (15), ethyl 3-(4-oxo-2-thioxothiazolidin-3-yl)-1-phenyl-1H-benzo[f]chromene-2-carboxylate (18), ethyl 3-(4-phenyl-2-thioxothiazol-3(2H)-yl)-1-phenyl-1H-benzo[f]chromene-2-carboxylate (20), ethyl 3-acetamido-1-phenyl-1H-benzo[f]chromene-2-carboxylate (21), and 10-amino-9-methyl-12-phenyl-12H-benzo[f]chromen[2,3-d]pyrimidine-11(10H)-one (23) were prepared. The structures of these compounds were established by elemental analysis, IR, MS and NMR spectral analysis.

1. Introduction
Chromene and fused chromene derivatives are an important class of compounds; they are widely distributed in nature [1]. Among chromene derivatives are biologically interesting compounds showing antimicrobial activities [2-4], inhibitors of influenza virus sildoses [5,6], compounds with antihypertensive [7] and anti-inflammatory activity [8] and hair growth stimulant properties [9]. Also, chromene derivatives were found useful as antiviral [10], antiproliferation agents [11], as sex pheromone [12], with antitumor [13], central nervous system activity [14] and as anti-HIV agent [15]. Some of their derivatives were utilized in the synthesis of macrocyclic ligands [16]. Due to these interesting properties of chromene derivatives and in continuation of our efforts directed to the synthesis of heterocyclic compounds [17-20] we wish to report here the results of our investigation on the reactivity of ethyl 3-amino-1-phenyl-1H-benzo[f]chromene-2-carboxylate (1) in the synthesis of new fused and isolated chromene compounds.

2. Experimental

2.1. Instrumentation
Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded from potassium bromide discs using a Bruker Vector 22 FT-IR spectrophotometer. 1H and 13C NMR spectra were obtained in deuterated dimethyl sulfoxide as solvent at 300 MHz and 75 MHz, respectively, on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV. Elemental analysis was carried out at the Micro analytical Center of Cairo University, Egypt.

2.2. Synthesis

2.2.1. Ethyl 3-(dimethylaminomethyleneamino)-1-phenyl-1H-benzo[f]chromene-2-carboxylate (2)
A sample of compound 1 (3.44 g, 0.1 mol) was dissolved in 10 mL of DMF, the reaction mixture was stirred and cooled to 0 ºC, and phosphorus oxychloride (0.1 mol, 4 mL) was added slowly. After the addition was complete, the mixture was stirred for one hour and then poured into stirred ice-water. A saturated solution of sodium hydroxide was added slowly. A solid product was precipitated, collected by filtration, washed with water and crystallized from ethanol (Scheme 1). Colorless crystals (DMF/H2O). Yield: 73 %, M.p.: 220-222 ºC. IR (KBr, νmax, cm⁻¹): 1698 (CO). 1H NMR (300 MHz, CDCl3, δ, ppm): 1.75 (t, 3H, CH3), 2.47 (s, 6H, 2CH3), 4.52 (q, 2H, CH2), 7.54 (s, 1H, N=CH), 7.57-7.95 (m, 12H, Ar-H + CH-phenyl). MS (m/z, [%]): 400 (M⁺, 25). Anal. calcd. for C25H24N2O3 (400.47): C, 74.98; H, 6.04; N, 7.00. Found: C, 75.08; H, 6.33; N, 7.15%.

2.2.2. 3-(Phenylaminomethyleneamino)-1-phenyl-1H-benzo[f]chromene-2-carboxylic acid (4)
A mixture of 2 (1 mmol), and aniline (1 mmol) in 20 mL of ethanol containing 0.1 mL of piperidine as catalyst was refluxed for 2 hours. The compound formed during reflux was collected by filtration and re-crystallized from dioxane/H2O to form compound 4 (Scheme 1). Colorless crystals (dioxane/H2O). Yield: 33 %, M.p.: 210-212 ºC. IR (KBr, νmax, cm⁻¹): 1698 (CO), 3119 (NH).
A mixture of 2 (1 mmol), and aniline (1 mmol) in 20 mL of pyridine was refluxed for 5 hours. The reaction mixture was concentrated under reduced pressure and the residue triturated with methanol, poured into acidified ice/water and the precipitate formed with washes with water thoroughly, dried and crystallized from methanol as buff powder (Scheme 1). Yield: 40 %. M.p.: 180-182 °C. IR (KBr, νmax, cm⁻¹): 1699 (CO). ¹H NMR (300 MHz, CDCl₃, δ, ppm): 7.45 (s, 1H, CH-pyrimidine), 7.75-7.97 (m, 17H, Ar-H + CH-pyran), MS (m/z (%)): 402 (M⁺, 15). Anal. calcld. for C₂₇H₁₈N₂O₂ (402.44): C, 80.58; H, 4.51; N, 12.91. Found: C, 80.64; H, 4.69; N, 12.10 %.

2.3. General procedure for synthesis of compounds (7a-b)

A mixture of 2 (1 mmol), and hydrazine hydrate (excess) in 20 mL of dioxane containing 0.1 mL of triethylamine as catalyst was refluxed for 3 hours. The compound formed during reflux was collected by filtration and re-crystallized from DMF/H₂O to afford compound 7b (Scheme 1).

10-Amino-12-phenyl-1H-benzo[j]chromene-2-carboxylate (11)

A mixture of 10 (1 mmol), and hydrazine hydrate (excess) in 20 mL of ethanol containing 0.1 mL of piperidine as catalyst was stirred at room temperature for 5 minutes. The compound formed was collected by filtration and crystallized from mixture of ethanol and water (3:1) to form compound 11 (Scheme 2). White powder (EtOH/H₂O). Yield: 70 %. M.p.: 240-242 °C. IR (KBr, νmax, cm⁻¹): 1200 (C=S), 1700 (CO), 3130 (NH), 3420 (NH₂).
A mixture of 10 (1 mmol) and hydrazine hydrate (excess) in 20 mL of ethanol containing 0.1 mL of piperidine as catalyst was refluxed for 8 hours. The reaction mixture was concentrated under reduced pressure and the residue triturated with methanol, the compound formed was collected by filtration and crystallized from ethanol to form compound 12 (Scheme 2). Colorless crystals (EtOH). Yield: 70 %. M.p.: 155-157 °C. IR (KBr, ν max, cm⁻¹): 1700 (CO), 2350 (SH), 3425 (N–H). ¹H NMR (300 MHz, CDCl₃, δ, ppm): 7.78-8.17 (m, 17H, Ar-H + CH-pyran). MS (m/z, %): 459 (M⁺, 15). Anal. calcd. for C₂₈H₁₇N₃O₂S (459.52): C, 73.23; H, 3.87; N, 9.35%. Found: C, 73.23; H, 3.87; N, 9.35%.

2.3.4. General procedure for synthesis of compounds (15a, b)

Compound 12 (1 mol) in 10 mL acetic acid and benzaldehyde (1.5 mol) was acidified to pH = 5 with dilute HCl, and the reaction mixture was stirred at 150 °C for 15 hours. The solution was allowed to stand overnight, then filtered and the resulting precipitate was washed with 5 % NaHCO₃ and water to neutrality and then dried, the resulting product was crystallized from ethanol. Analogously, compound 12 reacted with 4-chlorobenzaldehyde to afford compound 15b (Scheme 3).


2.3.5. Ethyl 3-(4-oxo-2-thioxothiazolidin-3-yl)-1-phenyl-1H-benzof[1,3]chromene-2-carboxylate (18)

To a vigorously stirred solution of 1 (3.44 g, 0.02 mol) in dimethyl formamide (10 mL) at room temperature, carbon disulfide (1.98 g, 0.02 mol) and aqueous potassium hydroxide (1.2 mL, 10 mol solution) were added simultaneously over 30 min. then the mixture was allowed to stir for additional 30 min. Chloroacetic acid (0.02 mol) was added drop wise to the reaction mixture with stirring at 5-10 °C, and the mixture was further stirred for 2 hours and poured into ice-water. The solid so obtained was filtered off, dried and crystallized from dioxane/H₂O (Scheme 4). Yellow crystals (dioxane/H₂O). Yield: 55 %. M.p.: >300 °C. IR (KBr, ν max, cm⁻¹): 1520 (C=O), 1700 (CO).
2.3.6. Ethyl 3-(4-phenyl-2-thioxothiazol-3(2H)-yl)-1-phenyl-1H-benzo[f]chromene-2-carboxylate (20)

To a vigorously stirred solution of 1 (3.44 g, 0.02 mol) in dimethyl formamide (10 mL) at room temperature, carbon disulfide (1.98 g, 0.02 mol) and aqueous potassium hydroxide (1.2 mL, 10 M solution) were added simultaneously over 30 min, then the mixture was allowed to stir for additional 30 min. Phenacyl bromide (0.02 mol) was added drop wise to the reaction mixture with stirring at 5-10 °C. The mixture was further stirred for 2 hours and poured into ice-water. The solid so obtained was filtered off, dried and crystalized from dioxane/H2O (Scheme 4). Greenish yellow crystals (dioxane/H2O). Yield: 50 %. M.p.: >300 °C IR (KBr, νmax cm⁻¹): 3120 (NH), 1325 (C=S), 1690 (CO). 1H NMR (300 MHz, CDCl₃, δ, ppm): 1.54 (t, 3H, CH₃), 4.35 (s, CH₂), 4.44 (q, 2H, CH₂), 7.78-8.23 (m, 12H, Ar-H + CH-pyran). MS (m/z, (%)): 508 (M⁺, 30), 510 (M⁺+2, 9). Anal. calcd. for C₂₂H₂₀NO₃S₂ (508.63): C, 70.82; H, 4.64; N, 2.76. Found: C, 70.99; H, 4.46; N, 2.91%.

2.3.7. Ethyl 3-acetamido-1-phenyl-1H-benzo[f]chromene-2-carboxylate (21)

A mixture of 1 (0.004 mol), acetic anhydride (0.012 mol) and zinc dust (0.28 g) was refluxed on water bath for 4 hours with stirring and filtered hot. The resulting clear solution was cooled to room temperature and the solid so obtained was filtered off (Scheme 5). Colorless crystals (dioxane/H2O). Yield: 70 %. M.p.: 120-122 °C IR (KBr, νmax cm⁻¹): 1695 (CO), 3120 (NH). 1H NMR (300 MHz, CDCl₃, δ, ppm): 1.54 (t, 3H, CH₂), 2.43 (s, 3H, COCH₃), 4.39 (q, 2H, CH₂), 7.78-8.23 (m, 12H, Ar-H + CH-pyran), 10.23 (s, 1H, NH). MS (m/z, (%)): 387 (M⁺, 30). Anal. calcd. for C₂₃H₂₂NO₃ (387.43): C, 74.40; H, 5.36; N, 3.62. Found: C, 74.53; H, 5.36; N, 3.76 %.
2.3.8. 10-Amino-9-methyl-12-phenyl-12H-benzo[\(f\)]chromeno[2,3-\(d\)]pyrimidine-11(10H)-one (23)

To a solution of 21 (0.014 mol) in absolute ethanol (10 mL) hydrazine hydrate (80 %, 0.14 mol) was added and the reaction mixture was heated for 3 hours on a water bath. The reaction mixture was cooled to room temperature and the solid so obtained was filtered off as colorless crystals, (dioxane/H\(_2\)O) (Scheme 5). Yield: 60 %. M.p.: 165-167 \(^\circ\)C (KBr, vs, cm\(^{-1}\)); 1695 (CO), 3420 (NH\(_2\)). \(^{1}H\) NMR (300 MHz, CDCl\(_3\), \(\delta\), ppm): 1.60 (s, 3H, \(CH_3\)).

Yield: 60 %.

M.p.: 165–167 \(^\circ\)C.

The IR spectrum of compound 10 showed the disappearance of absorption bands characterized for amino function and showed the presence of absorption bands at \(\nu\) 1320 cm\(^{-1}\) due to C=S and 3120 cm\(^{-1}\) due to the NH function. The \(^{1}H\) NMR spectrum of compound 10 showed a singlet at \(\delta\) 4.74 ppm due to \(CH_3\) protons. However, compound 10 containing several reactive functions represented a good intermediate for further reactions when treated with hydrazine hydrate. So, compound 10 when reacted with hydrazine hydrate in ethanol with stirring at room temperature yielded the open chain thiosemicarbazide derivative 11 via elimination of methylsulfane, while, under reflux in ethanol for 8 hours, it yielded the expected benzo[\(f\)]chromeno[2,3-\(d\)]pyrimidine 12 via elimination of methylsulfane and ethanol. Boiling the thiosemicarbazide 11 in ethanol in presence of triethylamine yielded the same compound 12. The IR spectrum of 11 showed the presence of absorption bands at \(\nu\) 1200 cm\(^{-1}\) due to C=S, 1700 cm\(^{-1}\) due to C=O, 3130 cm\(^{-1}\) due to NH and 3420 cm\(^{-1}\) due to the NH\(_2\) function. The \(^{1}H\) NMR spectrum of compound 11 showed a singlet at \(\delta\) 2.56 ppm due to the NH\(_2\) protons. The MS of 11 showed a peak at \(m/z\) 420 ([M+\(^{+}\)]\(^{+}\), 16 %). The IR spectrum of 12 showed the presence of absorption bands at \(\nu\) 1700 cm\(^{-1}\) due to C=O, 2350 cm\(^{-1}\) due to SH and 3425 cm\(^{-1}\) due to the NH\(_2\) function. However, the \(^{1}H\) NMR spectrum of compound 12 showed the disappearance of absorption signals characteristic for ester protons and two singlets at 6.4.47 ppm and at 10.23 ppm due to NH and \(CH_3\) protons, respectively. The MS of 12 showed a peak at \(m/z\) 373 (M\(^+\), 20 %).

Aimed at the preparation of some new derivatives of \(\beta\)-lactones and/or thiazolidinone, compound 12 was allowed to react with benzaldehyde and/or 4-chlorobenzaldehyde to give the corresponding expected Schiff’s base 13. However, the isolated compounds proved to be the new and unexpected compounds 15a,b formed via simultaneous nucleophilic attack of the sulfur atom on the hydrazine carbon with cyclization to the new thiadiazole derivatives 15a,b, as shown in Scheme 3.

Furthermore compound 1, when treated with carbon disulfide and potassium hydroxide solution, yielded the soluble potassium salt of dithiocarbamic acid 16 which was further treated in situ with chloroacetic acid and phenacyl bromide, respectively, to afford ethyl 3-(4-oxo-2-thioxothiazolidin-3-yl)-1-phenyl-1H-benzo[\(f\)]chromene-2-carboxylate (18) and ethyl 1-phenyl-3-(4-phenyl-2-thioxothiazolidin-3(2H)-yl)-1H-benzo[\(f\)] chromene-2-carboxylate (20) via release of water from the two corresponding intermediates 17 and 19, respectively (Scheme 4). The structures of compounds 18 and 20 were confirmed by IR, \(^1\)H NMR, mass spectroscopy and elemental analysis (see experimental section).

Finally, compound 1 was acylated with acetic anhydride yielding the acetyl derivative 21 which easily reacted with hydrazine hydrate to afford the new substituted 10-amino-9-methyl-12-phenyl-12H-benzo[\(f\)]chromeno[2,3-\(d\)]pyrimidine-
11(10H)-one (23) via intermediate 22 which formed from 21 by displacement of ethanol rather than water as shown in Scheme 5. The IR spectrum of 23 showed the presence of absorption band at ν 1710 cm⁻¹ due to C=O and 3420 cm⁻¹ due to NH₂ function. The 1H NMR spectrum of compound 23 showed two singlets at δ 1.53 and 2.57 ppm due to CH₃ and NH₂ protons, respectively, with disappearance of absorption pattern of ester protons confirming the proposed rationale of losing ethanol. The MS of 23 showed m/z at 355 (M⁺, 15 %).

References