Synthesis of pyranochromene and pyranopyrimidine derivatives from substituted natural coumarin isolated from Ammi majus L. and their biological evaluation

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ORIGINAL RESEARCH

Anticancer activity of some newly synthesized pyrano [2,3-d][1,2,3]triazine derivatives using 1-(7-hydroxy-2, 2-dimethylchroman-6-yl)ethanone as synthon

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Abstract A series of the newly substituted pyrano[1,2,3]triazine derivatives **3**–**14** were synthesized using compounds **1** and **2** as starting materials. Compound **2** was methylated using methyl iodide to compound **3**, which was treated with aromatic aldehydes to give acryloyl derivatives **4a**–**c**. Compounds **4a**,**b** were reacted with ethyl cyano-acetate to give pyran-3-carboxylates **5a**,**b** which were reacted with ethyl glycinate hydrochloride to give **6a**,**b**. Treatment of **6a**,**b** with hydrazine hydrate gives acid hydrazides **7a**,**b**, which were reacted with 5,5-dimethyl-1,3-cyclohexanedione to give acetohydrazides **8a**,**b**. Cyclization of **8b** with 2-(4-nitrobenzylidene)malononitrile afforded hexahydroquinoline **9**. However, the acridindione **10** was synthesized by heating of **8b** with 2-(4-nitrobenzylidene)malononitrile in acetic acid containing few drops of triethylamine. Treatment of **7a**,**b** with phenyl isothiocyanate or 2,5-hexanedione or phthalic anhydride gave compounds **11a**,**b**, **13a**,**b** and **14a**,**b**, respectively. In the present work, all the selected pyrano[1,2,3]trizine derivatives were soluble in DMSO at concentrations high enough to allow cell experiments, and the in vitro biological activity of these compounds was evaluated by their growth inhibitory potency in liver HEPG2 cancer cell lines. The cytotoxic potency of compounds **3**–**14** was studied in comparison to the known anticancer drugs 5-fluorouracil and doxorubicin.

Keywords 1-(2,4-Dihydroxyphenyl)ethanone · Acryloyl derivatives · Pyrano[1,2,3]triazine · Anticancer and cytotoxic activities

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Introduction

A number of derivatives containing s-triazine nucleus have been reported as heterocyclic compounds (Smith *et al.,* 1980). They are applicable as reactive dyes and also are used as polymers and drugs (Chaudhari and Patel, 2010; Halverson and Hirt, 1951). Among the compound having good antimicrobial properties, s-triazine derivatives constitute an important class of compounds possessing diverse pharmacological activities including broadly active as herbicidal (Gamez *et al.,* 2003) and antimicrobial (Jain *et al.*, 2007). Some are also used for the treatment of HIV infection (Patel *et al.*, 2007). Several workers investigated the s-triazine nucleus in the scope of potential therapeutic agents for diseases due to bacteria (Srinivas *et al.,* 2006), cancer (Kaswala *et al.*, 2009), and antitumor (Shin-ichi *et al.*, 2006). As pyrimidine is basic nucleus in DNA and RNA, it has been found to associate with diverse pharmacological activities such as anticancer (Patel *et al.*, 2001), anti-inflammatory (Vanderhoek *et al.,* 1973), antiviral (Patel *et al.*, 2012), antibacterial (Karci *et al.,* 2009; Modha *et al.,* 2001), antioxidant (Sharma and Reddy, 1993),

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antiulcer (Laneri *et al.,* 1998), and anti-HIV/AIDS (Patel *et al.*, 2007) activities. Additionally, in our previous work, we reported the synthesis of substituted heterocyclic derivatives as anti-inflammatory (Amr *et al.*, 2005) and antitumor (Abo-Ghalia and Amr, 2004 and Hammam *et al.,* 2003) agents. On the other hand, pyrimidine and thiazolopyrimidine derivatives have promising biological and anticancer activities (Girgis and Ahmed-Farag, 2003 and Flefel *et al.*, 2007). Also, the newly substituted heterocyclic candidates exhibited antiandrogenic (Amr and Abdalla, 2006), analgesic, antiparkinsonian, anti-inflammatory (Amr and Abdalla, 2006; Ouf *et al.,* 2008 and Ouf and Amr, 2008), anticancer (Amr *et al.*, 2006a, 2006b), anticonvulsant (Nehad *et al.*, 2007), and antiarrhythmic (Ahmed *et al.*, 2007) activities. In view of these observations and in continuation of our previous work in heterocyclic chemistry, we synthesized some new pyrano[2,3-d][1,2,3]triazine derivatives and tested their anticancer activities with 5-fluorouracil (5-FU) and doxorubicin (DOX) as anticancer drugs.

Materials and methods

Chemistry

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analysis data were obtained from the microanalytical unit, Cairo University, Cairo, Egypt, and the results were in favorable agreements with the calculated values. The IR spectra (KBr) were recorded on a PYEUNICAM spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded at 300 MHz on a Perkin Elmer R12B Spectrometer using TMS as an internal standard. The mass spectra were performed using VG 2AB-3F spectrometer (70 eV). All reactions were followed by TLC (silica gel, aluminum sheets 60F_{254}, Merck). The starting materials **1** and **2** were prepared according to the reported procedures (Kumar *et al.*, 2011).

*1-(7-Methoxy-2,2-dimethylchroman-6-yl)ethanone (**3**)*

A mixture of compound **2** (2 g), methyl iodide (7 mL), and anhydrous potassium carbonate (7 g) in acetone (100 mL) was refluxed for 12 h and then filtered while hot. The filtrate solution was evaporated under reduced pressure to dryness, and the obtained residue was crystallized from ethanol to give compound **3** as yellow powder. Yield 75 %, m.p. 117 °C; IR (KBr, cm^{-1}): 1667 (C=O), 2995 (CH-Aliph.), 3080 (CH-Ar), 1223 (C–O ether); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.50 (d, 6*H*, 2CH_3), 2.00–2.42 (m, 4*H*, 2CH_2), 2.50 (s, 3*H*, $COCH_3$), 3.84 (s, 3*H*, OCH_3), 6.65, 7.58 (2 s, 2*H*, Ar–H); ^{1}H-NMR (DMSO-d_6, 67.5 MHz): δ = ^{13}C-NMR (DMSOd_6, ppm): δ = 27.45, 28.15 (3CH_3), 55.65 (OCH_3), 198.45 (C=O), 76.32 (C-1), 32.05 (C-2), 22.98 (C-3), 116.68 (C-4), 128.92 (C-5), 110.75 (C-6), 156.96 (C-7), 100.01 (C-8), 159.48 (C-9); MS (EI, 70 eV): *m*/*z* = 234 [M^{+}, 100]. Anal. calcd. for $C_{14}H_{18}O_3$ (234.29):C, 71.77; H, 7.74. Found: C, 71.74; H, 7.70.

*(E)-3-(Aryl)-1-(7-methoxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one **4a–c***

A mixture of compound **3** (0.01 mol) and aromatic aldehydes, namely, vanillin, benzaldehyde, or 3-anisaldehyde, in the presence of two drops of piperidine was heated under reflux for 2–4 h. The reaction mixture was cooled and triturated with ethanol then filtered off, dried, and then crystallized from propan-2-ol to give compounds (**4a–c**), respectively.

*(E)-3-(4-Hydroxy-3-methoxyphenyl)-1-(7-methoxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one (**4a**)*

Brown powder, yield 70 %, m.p. 197 °C; IR (KBr, cm^{-1}): 1667 (C=O), 3433 (OH); ^{1}H-NMR (DMSO-d_6, ppm): δ = 1.52 (d, 6*H*, 2CH_3), 1.98–2.38 (m, 4*H*, 2CH_2), 3.71, 4.03 (2 s, 6*H*, 2OCH_3), 5.36 (s, 1*H*, OH, exchangeable with D_2O), 6.84–7.39 (m, 7*H*, 5*H* Ar–H + CH=CH); ^{13}C-NMR (DMSOd_6, ppm): δ = 27.42 (2CH_3), 55.85, 56.02 (2OCH_3), 76.42 (C-1), 31.93 (C-2), 22.65 (C-3), 117.24 (C-4), 129.18 (C-5), 111.64 (C-6), 157.96 (C-7), 100.45 (C-8), 159.68 (C-9), 189.22 (C-10), 120.88 (C-11), 144.35 (C-12), 128.45 (C-13), 119.78 (C-14), 115.98 (C-15), 144.15 (C-16), 151.05 (C-17), 111.95 (C-18); MS (EI, 70 eV): *m*/*z* = 368 [M^{+}, 8] and at 178 (100, base peak). Anal. calcd. for $C_{22}H_{24}O_5$ (368.42): C, 71.72; H, 6.57. Found: C, 71.65; H, 6.52.

*(E)-1-(7-Methoxy-2,2-dimethylchroman-6-yl)-3-phenylprop-2-en-1-one (**4b**)*

Brown powder, yield 70 %, m.p. 220 °C; IR (KBr, cm^{-1}): 1680 (C=O), 2990 (CH-aliphatic), 3090 (CH aromatic),1220(C–O ether); ^{1}H-NMR (DMSO-d_6, ppm): δ = 1.48 (d, 6*H*, 2CH_3), 2.05–2.48 (m, 4*H*, 2CH_2), 3.92 (s, 3*H*, OCH_3), 7.33–8.06 (m, 9*H*, 7H Ar–H + CH=CH); ^{13}C-NMR (DMSOd_6, ppm): δ = 27.36 (2CH_3), 55.864 (OCH_3), 76.45 (C-1), 32.04 (C-2), 22.58 (C-3), 118.22 (C-4), 129.32 (C-5), 112.05 (C-6), 158.54 (C-7), 101.00 (C-8), 160.64 (C-9), 189.45 (C-10), 120.82 (C-11), 144.48 (C-12), 135.15 (C-13), 127.03 (C-14, C-18), 127.98 (C-15, C-17), 127.68 (C-16); MS (EI, 70 eV): *m*/*z* = 322 [M^{+}, 12] and at 132 (100, base peak). Anal. calcd. for $C_{21}H_{22}O_3$ (322.40): C, 78.23; H, 6.88. Found: C, 78.18; H, 6.82.

*(E)-1-(7-Methoxy-2,2-dimethylchroman-6-yl)-3-(3-methoxyphenyl)prop-2-en-1-one (**4c**)*

Crystallized from pale yellow powder, yield 80 %, m.p. 302 °C; IR (KBr, cm^{-1}): 1670 (C=O), 2992 (CH-aliphatic), 3090 (CH aromatic),1225 (C–O ether); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.48$ (d, 6*H*, $2CH_3$), 1.96–2.42 (m, 4*H*, $2CH_2$), 3.75, 3.92, (2 s, 6*H*, $2OCH_3$), 7.61–8.06 (m, 8*H*, 6*H* Ar–H + CH=CH); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 27.35$ ($2CH_3$), 55.76, 56.05 ($2OCH_3$), 76.45 (C-1), 31.92 (C-2), 22.54 (C-3), 117.32 (C-4), 130.02 (C-5), 111.72 (C-6), 158.65 (C-7), 100.32 (C-8), 160.38 (C-9), 188.99 (C-10), 121.18 (C-11), 144.65 (C-12), 136.01 (C-13), 118.02 (C-14), 129.06 (C-15), 113.12 (C-16), 160.22 (C-17), 110.08 (C-18); MS (EI, 70 eV): $m/z = 352$ [M^+, 18] and at 162 (100, base peak). Anal. calcd. for $C_{22}H_{24}O_4$ (352.44): C, 74.98; H, 6.86. Found: C, 74.95; H, 6.80.

*Ethyl 2-amino-4-(aryl)-6-(7-methoxy-2,2-dimethylchroman-6-yl)-4H-pyran-3-carboxylate (**5a**,**b**)*

A mixture of compound **4a** or **4b** (1 mmol) and ethyl cyanoacetate (1 mmol) in pyridine (50 mL) was refluxed for 12 h. The reaction mixture was poured into ice water and neutralized with hydrochloric acid, and the obtained precipitate was filtered off, washed with water, dried, and crystallized from propan-2-ol to give compounds **5a**,**b**, respectively.

*Ethyl 2-amino-4-(4-hydroxy-3-methoxyphenyl)-6-(7-methoxy-2,2-dimethylchroman-6-yl)-4H-pyran-3-carboxylate (**5a**)*

Pale yellow powder, yield 85 %, m.p. 106 °C; IR (KBr, cm^{-1}): 1735 (CO, ester), 3375 (OH), 3129, 3153 (NH_2); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.37$ (t, 3*H*, CH_3), 1.52 (d, 6*H*, $2CH_3$), 2.00–2.52 (m, 4*H*, $2CH_2$), 3.88, 3.98 (2 s, 6*H*, $2OCH_3$), 4.33 (q, 2*H*, CH_2), 4.46 (s, 1*H*, pyrane-CH), 5.72 (s, 1*H*, OH, exchangeable with D_2O), 6.98–7.85 (m, 6*H*, Ar–H + CH-pyrane), 8.14 (s, 2*H*, NH_2, exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 14.05$ (CH_3-ester), 27.05 ($2CH_3$), 56.10, 56.18 ($2OCH_3$), 61.45 (CH_2-ester), 166.86 (C=O, ester), 76.32 (C-1), 32.06 (C-2), 23.16 (C-3), 117.25 (C-4), 127.22 (C-5), 101.52 (C-6), 155.18 (C-7), 99.98 (C-8), 154.86 (C-9), 140.26 (C-10), 91.08 (C-11), 39.76 (C-12), 75.62 (C-13), 162.05 (C-14), 135.72 (C-15), 122.65 (C-16), 116.02 (C-17), 142.20 (C-18), 151.10 (C-19), 114.01 (C-20); MS (EI, 70 eV): $m/z = 481$ [M^+, 22] and at 246 (100, base peak). Anal. calcd. for $C_{27}H_{31}NO_7$ (481.53): C, 67.34; H, 6.49; N; 2.91. Found: C, 67.28; H, 6.40; N; 2.89.

*Ethyl 2-amino-6-(7-methoxy-2,2-dimethylchroman-6-yl)-4-phenyl-4H-pyran-3-carboxylate (**5b**)*

Pale yellow powder, yield 70 %, m.p. 113 °C; IR (KBr, cm^{-1}): 1732 (CO, ester), 3132, 3389 (NH_2). ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.26$ (t, 3*H*, CH_3), 1.50 (d, 6*H*, $2CH_3$), 1.98–2.40 (m, 4*H*, $2CH_2$), 3.83 (s, 3*H*, OCH_3), 4.23 (q, 2*H*, CH_2), 4.46 (s, 1*H*, CH-pyrane), 6.99–7.50 (m, 8*H*, Ar–H + CH-pyrane), 7.95 (s, 2*H*, NH_2, exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 14.07$ (CH_3-ester), 27.10 ($2CH_3$), 56.12 (OCH_3), 61.36 (CH_2-ester), 166.84 (C=O, ester), 76.38 (C-1), 32.10 (C-2), 23.15 (C-3), 117.36 (C-4), 127.18 (C-5), 101.48 (C-6), 155.16 (C-7), 99.99 (C-8), 154.82 (C-9), 140.24 (C-10), 91.00 (C-11), 39.75 (C-12), 75.60 (C-13), 162.08 (C-14), 142.01 (C-15), 122.65 (C-16), 116.02 (C-17), 142.20 (C-18), 151.10 (C-19), 114.01 (C-20); MS (EI, 70 eV): $m/z = 435$ [M^+, 24] and at 390 (100, base peak). Anal. calcd. for $C_{26}H_{29}NO_5$ (435.51): C, 71.70; H, 6.71; N; 3.22, Found: C, 71.65; H, 6.67; N; 3.15.

*Ethyl 2-(aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]-triazin-3(5H)-yl)acetate (**6a**,**b**)*

To a solution of ethyl carboxylate **5a** or **5b** (6 g, 0.039 mol) cooled solution of dilute hydrochloric acid, a solution of sodium nitrite (4.25 g) in water (10 ml) was added to form diazonium salt. A solution of ethyl glycinate hydrochloride (5.54 g, 0.039 mol) was added to the stirred solution of the diazonium salt with subsequent neutralization by sodium carbonate. After 1 h stirring, the obtained precipitate was separated by filtration, and the formed solid was washed with water, air-dried, and crystallized from absolute ethanol to give compounds **6a** or **6b.**

*Ethyl 2-(5-(4-hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetate (**6a**)*

Yield: 86 %, m.p. 226 °C; IR (KBr, cm^{-1}): 3380 (OH), 3050 (C–H Ar.), 2965 (C–H aliph.), 1739 (C=O, ester), 1680 (C=O, amidic), 1233 (C–O); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.36$ (t, 3*H*, CH_3), 1.54 (d, 6*H*, $2CH_3$), 2.02–2.46 (m, 4*H*, $2CH_2$), 3.80, 3.86 (2 s, 6*H*, OCH_3), 4.30 (q, 2*H*, CH_2), 4.38 (s, 1*H*, CH-pyrane), 4.68 (s, 2*H*, CH_2), 5.70 (s, 1*H*, OH exchangeable with D_2O), 6.86–7.72 (m, 6*H*, Ar–H + CH-pyrane); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 14.05$ (CH_3-ester), 27.48 ($2CH_3$), 56.15, 56.28 ($2OCH_3$), 61.45 (CH_2-ester), 168.65 (C=O, ester), 76.32 (C-1), 31.92 (C-2), 23.18 (C-3), 116.52 (C-4), 127.26 (C-5), 100.96 (C-6), 154.95 (C-7), 100.18 (C-8), 154.64 (C-9),

140.32 (C-10), 91.36 (C-11), 40.34 (C-12), 114.75 (C-13), 147.56 (C-14), 135.35 (C-15), 121.86 (C-16), 116.08 (C-17), 142.22 (C-18), 151.12 (C-19), 114.16 (C-20), 158.72 (C-21), 48.55 (C-22); MS (EI, 70 eV): $m/z = 550$ [M^+, 4] and at 192 (100, base peak). Anal. calcd. for $C_{29}H_{31}N_3O_8$ (549.57): C, 63.38; H, 5.69; N; 7.65. Found: C, 63.30; H, 5.65; N; 7.60.

*Ethyl 2-(7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetate (**6b**)*

Yield: 65 %, m.p. 205 °C; IR (KBr, cm^{-1}): 3050 (C–H Ar.), 2965 (C–H aliph.), 1739 (C=O, ester), 1680 (C=O, amidic), 1233 (C–O); ^{1}H-NMR (DMSO-d_6, ppm): δ 1.38 (t, 3*H*, CH_3), 1.48 (d, 6*H*, $2CH_3$), 1.98–2.42 (m, 4*H*, $2CH_2$), 3.92 (s, 3*H*, OCH_3), 4.32 (q, 2*H*, CH_2), 4.45 (s, 1*H*, CH-pyrane), 4.70 (s, 2*H*, CH_2), 6.82–7.76 (m, 8*H*, Ar–H + CH-pyrane); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 14.05$ (CH_3-ester), 27.48 ($2CH_3$), 56.15 (OCH_3), 61.45 (CH_2-ester), 168.65 (C=O, ester), 76.36 (C-1), 31.94 (C-2), 23.16 (C-3), 116.50 (C-4), 127.25 (C-5), 100.98 (C-6), 154.92 (C-7), 100.16 (C-8), 154.65 (C-9), 140.34 (C-10), 91.35 (C-11), 40.35 (C-12), 114.75 (C-13), 147.56 (C-14), 142.32 (C-15), 128.86 (C-16, C-20), 128.08 (C-17, C-19), 125.46 (C-18), 158.80 (C-21), 48.56 (C-22); MS (EI, 70 eV): $m/z = 504$ [M^+, 8] and at 191 (100, base peak). Anal. calcd. for $C_{28}H_{29}N_3O_6$ (503.54): C, 66.79; H, 5.80; N; 8.34. Found: C, 66.72; H, 5.74; N; 8.30.

*2-(5-(Aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-acetohydrazides (**7a**,**b**)*

A mixture of the ester **6a** or **6b** (0.05 mol) and hydrazine hydrate (2.5 g, 0.05 mol) in ethanol (20 ml) was stirred for 2 h at room temperature. Excess ethanol was evaporated under vacuum, and the obtained precipitate product was filtered off, dried, and crystallized from ethanol to give compounds **7a**,**b**.

*2-(5-(4-Hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetohydrazide (**7a**)*

Yield 77 %, m.p. 231 °C; IR (KBr, cm^{-1}): 3380 (OH), 3311–3300 (N–H str), 3070 (CH Ar.), 2957 (C–H aliph.), 1680, 1662 (C=O), 1577 (N–H bending scissoring). ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.46$ (d, 6*H*, $2CH_3$), 1.96–2.43 (m, 4*H*, $2CH_2$), 3.80, 3.92 (2s, 6*H*, $2OCH_3$), 4.32 (s, 2*H*, NH_2, exchangeable with D_2O), 4.45 (s, 1*H*, CH-pyrane), 4.86 (s, 2*H*, CH_2), 5.70 (s, 1*H*, OH exchangeable with D_2O), 6.88–7.72 (m, 6*H*, Ar–H + CH-pyrane), 10.30 (s, 1*H*, NH exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 27.12$ ($2CH_3$), 56.25, 56.42 ($2OCH_3$), 169.48 (C=O, hydrazide), 76.18 (C-1), 32.08 (C-2), 23.24 (C-3), 117.62 (C-4), 127.32 (C-5), 101.05 (C-6), 155.02 (C-7), 100.12 (C-8), 154.52 (C-9), 140.30 (C-10), 92.00 (C-11), 40.32 (C-12), 115.05 (C-13), 146.98 (C-14), 135.42 (C-15), 122.16 (C-16), 115.58 (C-17), 142.02 (C-18), 151.18 (C-19), 114.26 (C-20), 159.02 (C-21), 48.55 (C-22); MS (EI, 70 eV): $m/z = 536$ [M^+, 16] and at 314 (100, base peak). Anal. calcd. for $C_{27}H_{29}N_5O_7$ (535.54): C, 60.55; H, 5.46; N; 13.08. Found: C, 60.48; H, 5.40; N; 13.00.

*2-(7-(7-Methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl) acetohydrazide (**7b**)*

Yield: 80 %, m.p. 228 °C; IR (KBr, cm^{-1}): 3311–3300 (N–H str), 3070 (CH Ar.), 2957 (C–H aliph.), 1680, 1662 (C=O), 1577 (N–H bending scissoring); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.50$ (d, 6*H*, $2CH_3$), 2.00–2.44 (m, 4*H*, $2CH_2$), 3.90 (s, 3*H*, OCH_3), 4.36 (s, 2*H*, NH_2, exchangeable with D_2O), 4.45 (s, 1*H*, CH-pyrane), 4.78 (s, 2*H*, CH_2), 6.85–7.76 (m, 8*H*, Ar–H + CH-pyrane), 10.30 (s, 1*H*, NH exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 27.48$ ($2CH_3$), 56.15 (OCH_3), 169.64 (C=O, hydrazide), 76.42 (C-1), 31.95 (C-2), 23.15 (C-3), 116.52 (C-4), 127.22 (C-5), 106.00 (C-6), 154.95 (C-7), 100.18 (C-8), 154.63 (C-9), 140.33 (C-10), 92.12 (C-11), 40.32 (C-12), 114.78 (C-13), 147.56 (C-14), 142.35 (C-15), 129.08 (C-16, C-20), 128.34 (C-17, C-19), 125.52 (C-18), 169.80 (C-21), 52.56 (C-22); MS (EI, 70 eV): $m/z = 490$ [M^+, 12] and at 184 (100, base peak). Anal. calcd. for $C_{26}H_{27}N_5O_5$ (489.52): C, 63.79, H, 5.56; N; 14.31. Found: C, 63.74, H, 5.50; N; 14.24.

*2-(5-(Aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N′-(5,5-dimethyl-3-oxocyclohex-1-enyl)acetohydrazides (**8a**,**b**)*

A mixture of equimolar amounts of 5,5-dimethyl-l, 3-cyclohexadione (dimedone) and hydrazides **7a**,**b** (0.05 mol) in toluene (15 ml) was heated under reflux for 4 h. using Dean-Stark water separator. After cooling, the obtained crystalline product was filtered off, dried, and recrystallized from toluene to give compounds **8a**,**b**, respectively.

*2-(5-(4-Hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d]-[1,2,3]triazin-3(5H)-yl)-N′-(5,5-dimethyl-3-oxocyclohex-1-enyl)acetohydrazide (**8a**)*

Yield: 70 %, m.p. 248 °C; IR (KBr, cm^{-1}): 3380 (OH), 3197 (2N–H str), 3010 (CH-Ar), 2957 (C–H Aliph.), 1710,

1750, 1690 (C=O), 1583 (N–H bending scissoring); ^{1}H-NMR (DMSO-d_6, ppm): δ = 0.97, 1.02 (2s, 6*H*, $2CH_3$), 1.48 (d, 6*H*, $2CH_3$), 1.88–2.44 (m, 8*H*, $4CH_2$), 3.80, 4.10 (2s, 6*H*, $2OCH_3$), 4.42 (s, 1*H*, CH-pyrane), 5.84 (s, 1*H*, OH exchangeable with D_2O), 5.20 (s, 2*H*, N–CH_2), 5.42 (s, 1H, CH cyclohexene), 7.40–7.72 (m, 6*H*, Ar–H + CH-pyrane), 8.80 (s, 1*H*, NH exchangeable with D_2O), 10.30 (s, 1*H*, NH, NH exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): δ = 26.85 ($2CH_3$), 27.50 ($2CH_3$), 56.10, 56.15 ($2OCH_3$), 76.35 (C-1), 31.95 (C-2), 23.15 (C-3), 116.86 (C-4), 127.18 (C-5), 100.86 (C-6), 154.98 (C-7), 100.20 (C-8), 154.62 (C-9), 140.30 (C-10), 91.32 (C-11), 40.31 (C-12), 115.75 (C-13), 146.56 (C-14), 135.00 (C-15), 119.80 (C-16), 116.08 (C-17), 142.15 (C-18), 151.05 (C-19), 113.85 (C-20), 158.60 (C-21), 54.50 (C-22), 169.65 (C-23), 162.80 (C-24), 101.80 (C-25), 197.90 (C-26), 53.82 (C-27), 32.67 (C-28), 40.08 (C-29); MS (EI, 70 eV): *m*/*z* = 658 [M^+, 32] and at 286 (100, base peak). Anal. calcd. for $C_{35}H_{39}N_5O_8$ (657.71): C, 63.91; H, 5.98; N, 10.65. Found: C, 63.86; H, 5.92; N, 10.60.

*2-(7-(7-Methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N′-(5,5-dimethyl-3-oxocyclohex-1-enyl)acetohydrazide (**8b**)*

Yield: 75 %, m.p. 253 °C; IR (KBr, cm^{-1}): 3197 (2 N–H str), 3010 (CH-Ar), 2957 (C–H aliph.), 1710, 1750, 1690 (C=O), 1583 (N–H bending scissoring); ^{1}H-NMR (DMSO-d_6, ppm): δ = 0.97, 1.04 (2s, 6*H*, $2CH_3$), 1.55 (d, 6*H*, $2CH_3$), 1.95–2.50 (m, 8*H*, $4CH_2$), 3.90 (s, 3*H*, OCH_3), 4.46 (s, 1*H*, CH-pyrane), 5.18 (s, 2*H*, N-CH_2), 5.46 (s, 1*H*, CH cyclohexene), 7.40–7.72 (m, 8*H*, Ar–H + CH-pyrane), 8.80 (s, 1*H*, NH, exchangeable with D_2O), 10.30 (s, 1*H*, NH, exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): δ = 26.86 ($2CH_3$), 27.44 ($2CH_3$), 56.14 (OCH_3), 76.42 (C-1), 31.94 (C-2), 23.18 (C-3), 116.84 (C-4), 127.20 (C-5), 100.90 (C-6), 154.96 (C-7), 100.15 (C-8), 154.60 (C-9), 140.33 (C-10), 91.36 (C-11), 40.30 (C-12), 115.70 (C-13), 146.50 (C-14), 142.00 (C-15), 129.09 (C-16, C-20), 128.12 (C-17, C-19), 125.15 (C-18), 158.56 (C-21), 53.96 (C-22), 169.72 (C-23), 162.88 (C-24), 101.84 (C-25), 197.85 (C-26), 53.65 (C-27), 32.12 (C-28), 40.15 (C-29); MS (EI, 70 eV): *m*/*z* = 612 [M^+, 24] and at 181 (100, base peak). Anal. calcd. for $C_{34}H_{37}N_5O_6$ (611.68): C, 66.76; H, 6.10; N; 11.45. Found: C, 66.72; H, 6.05; N; 11.40.

*N-(3-Amino-2-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxoquinolin-1(4H)-yl)-2-(7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetamide (**9**)*

A mixture of equimolar amounts of enaminones **8b** and 2-(4-nitrobenzylidene)malononitrile (0.00 l mol) in ethanol (15 ml) containing four drops of trimethylamine was heated under reflux for 12 h. The reaction mixture was cooled, and the separated solid product was filtered off, washed with water, and crystallized from ethanol to give compound **9**. Yield: 65 %, m.p. 278 °C; IR (KBr, cm^{-1}): 3446–3341 (NH_2, str), 3020 (C–H Ar.), 2958 (C–H Aliph.), 1750, 1690 (C=O), 1650 (C=C conj), 2184 (CN); ^{1}H-NMR (DMSO-d_6, ppm): δ = 0.80, 1.06 (2s, 6*H*, $2CH_3$), 1.52 (d, 6*H*, $2CH_3$), 2.02–2.45 (m, 8*H*, $4CH_2$), 3.90 (s, 3*H*, OCH_3), 4.48 (s, 1*H*, CH-pyrane), 4.56 (s, 1*H*, pyridine-H), 5.20 (s, 2*H*, N-CH_2), 6.63 (s, 2*H*, NH_2, exchangeable with D_2O), 6.78 (d, 1*H*, pyrane-H), 7.05–8.10 (m, 11*H*, Ar–H), 11.20 (s, 1*H*, NH, exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6, ppm): δ = 26.95 ($2CH_3$), 27.45 (2 CH_3), 56.18 (OCH_3), 115.04 (C≡N), 76.45 (C-1), 32.00 (C-2), 23.15 (C-3), 116.84 (C-4), 127.14 (C-5), 100.95 (C-6), 155.00 (C-7), 100.10 (C-8), 154.54 (C-9), 140.32 (C-10), 91.32 (C-11), 40.20 (C-12), 115.71 (C-13), 146.51 (C-14), 142.01 (C-15), 129.07 (C-16, C-16‘), 128.14 (C-17, C-17‘), 125.15 (C-18), 158.58 (C-19), 53.95 (C-20), 169.68 (C-21), 81.01 (C-22), 136.70 (C-23), 35.88 (C-24), 111.80 (C-25), 198.78 (C-26), 52.00 (C-27), 31.95 (C-28), 38.52 (C-29), 145.44 (C-30), 147.65 (C-31), 129.18 (C-32, C-32‘), 120.76 (C-33, C-33‘), 145.05 (C-34); MS (EI, 70 eV): *m*/*z* = 811 [M^+, 14] and at 458 (100, base peak). Anal. calcd. for $C_{44}H_{42}N_8O_8$ (810.85): C, 65.17; H, 5.22; N, 13.82. Found: C, 65.14; H, 5.18; N, 13.80.

*N-(1,2,3,4,5,6,7,8-Octahydro-3,3,6,6-tetramethyl-9-(4-nitrophenyl)-1,8-dioxoacridin-10(9H)-yl)-2-(7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetamide (**10**)*

A mixture of two molar amounts of enaminone **8b** and 2-(4-nitrobenzylidene) malononitrile (0.001 mol) was refluxed in glacial acetic acid (20 ml) for 3 h with few drops of trimethylamine. The reaction mixture was concentrated under vacuum, and the solid formed after cooling was collected by filtration, dried, and crystallized from aqueous ethanol to give compound **10**. Yield: 60 %, m.p. 288 °C; IR (KBr, cm^{-1}): 3020 (C–H Ar.), 2958 (C–H aliph), 1750, 1690 (C=O), 1650 (C=C conj). ^{1}H-NMR (DMSO-d_6, ppm): δ = 0.82, 1.06 (2s, 6*H*, $2CH_3$), 1.52 (d, 6*H*, $2CH_3$), 1.98–2.52 (m, 12*H*, $6CH_2$), 3.90 (s, 3*H*, OCH_3), 4.42 (s, 1*H*, CH-pyrane), 4.62 (s, 1*H*, pyridine-H), 5.16 (s, 2*H*, N–CH_2), 6.64 (d, 1*H*, pyrane-H), 7.15–8.04 (m, 11*H*, Ar–H), 11.20 (s, 1*H*, NH, exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6, ppm): δ = 26.88 ($2CH_3$), 27.42 ($4CH_3$), 56.34 (OCH_3), 76.44 (C-1), 32.01 (C-2), 23.16 (C-3), 116.85 (C-4), 127.13 (C-5), 100.90 (C-6), 155.02 (C-7), 100.13 (C-8), 154.55 (C-9), 140.34 (C-10), 91.32 (C-11), 40.24 (C-12), 115.70 (C-13), 146.50 (C-14), 142.04 (C-15), 129.08 (C-16, C-16‘), 128.15 (C-17, C-17‘), 125.18 (C-18),

158.60 (C-19), 53.92 (C-20), 169.64 (C-21), 145.52 (C-22, C-34), 38.74 (C-23, C-33), 31.65 (C-24, C-32), 51.32 (C-25, C-31), 198.82 (C-26, C-30), 111.45 (C-27, C-29), 41.02 (C-28), 148.13 (C-35), 129.76 (C-36, C-36‘), 120.65 (C-37, C-37‘), 145.30 (C-38); MS (EI, 70 eV): $m/z = 867$ [M^+, 10] and at 436 (100, base peak). Anal. calcd. for $C_{49}H_{50}N_6O_9$ (866.95): C, 67.88; H, 5.81; N; 9.69. Found: C, 67.82; H, 5.80; N; 9.64.

*1-(2-(5-(Aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetyl)-4-phenylthiosemicarbazide (**11a**,**b**)*

A mixture of compound **7a** or **7 b** (0.012 mol) and phenylisothiocyanate (0.012 mol, 1.62 g) in ethanol (15 ml) was refluxed for 1 h. After cooling, the obtained precipitate was filtered off, dried, and crystallized from ethanol to give compounds **11a** or **11b**.

*1-(2-(5-(4-Hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetyl)-4-phenylthiosemicarbazide (**11a**)*

Yield: 76 %, m.p. 261 °C; IR (KBr, cm^{-1}): 3380 (OH), 3331, 3227, 3219 (N–H str), 3050 (CH-Ar.), 2931 (C–H aliph), 1740, 1684 (C=O), 1570 (N–H bending scissoring), 1300 (C=S). ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.52$ (d, 6*H*, $2CH_3$), 1.94–2.45 (m, 4*H*, $2CH_2$), 3.80, 4.10 (2s, 6*H*, $2OCH_3$), 4.45 (s, 1*H*, CH-pyrane), 5.12 (s, 2*H*, N–CH_2), 5.70 (s, 1*H*, OH exchangeable with D_2O), 6.65 (d, 1*H*, CH-pyrane), 7.72–8.00 (m, 10*H*, Ar–H), 9.76, 10.01, 10.50 (3s, 3*H*, 3NH, exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 27.12$ ($2CH_3$), 56.25, 56.42 ($2OCH_3$), 179.48 (C=S), 76.18 (C-1), 32.10 (C-2), 23.24 (C-3), 117.63 (C-4), 127.30 (C-5), 101.08 (C-6), 155.00 (C-7), 100.12 (C-8), 154.50 (C-9), 140.30 (C-10), 92.00 (C-11), 40.32 (C-12), 115.07 (C-13), 146.94 (C-14), 135.43 (C-15), 121.96 (C-16), 116.08 (C-17), 142.12 (C-18), 151.18 (C-19), 114.26 (C-20), 159.02 (C-21), 48.55 (C-22), 169.10 (C-23), 136.96 (C-24), 126.36 (C-25, C-25′), 128.75 (C-26, C-26′), 124.10 (C-27); MS (EI, 70 eV): $m/z = 670$ [M^+, 26] and at 194 (100, base peak). Anal. calcd. for $C_{34}H_{34}N_6O_7S$ (670.73): C, 60.85; H, 5.11; N, 12.53, S, 4.78; Found: C, 60.80; H, 5.06; N, 12.48; S, 4.73.

*1-(2-(7-(7-Methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)acetyl)-4-phenylthiosemicarbazide (**11b**)*

Yield: 70 %, m.p. 266 °C; IR (KBr, cm^{-1}): 3331, 3227, 3219 (N–H str), 3050 (CH-Ar.), 2931 (C–H Aliph.), 1740, 1684 (C=O), 1570 (N–H bending scissoring), 1300 (C=S); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.50$ (d, 6*H*, $2CH_3$), 2.02–2.48 (m, 4*H*, $2CH_2$), 3.86 (s, 1*H*, OCH_3), 4.44 (s, 1*H*, CH-pyrane), 5.12 (s, 2*H*, N–CH_2), 6.74 (s, 1*H*, CH-pyrane), 7.25–8.05 (m, 12*H*, Ar–H), 9.80, 10.05, 10.45 (3s, 3*H*, 3NH, exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 27.48$ ($2CH_3$), 56.15 (OCH_3), 179.45 (C=S), 76.36 (C-1), 31.98 (C-2), 23.16 (C-3), 116.54 (C-4), 127.26 (C-5), 106.05 (C-6), 154.92 (C-7), 100.13 (C-8), 154.65 (C-9), 140.35 (C-10), 92.13 (C-11), 40.34 (C-12), 114.76 (C-13), 147.58 (C-14), 142.31 (C-15), 129.01 (C-16, C-20), 128.31 (C-17, C-19), 125.51 (C-18), 169.81 (C-21), 52.51 (C-22), 169.00 (C-23), 136.92 (C-24), 126.37 (C-25, C-25‘), 128.76 (C-26, C-26‘), 124.12 (C-27); MS (EI, 70 eV): $m/z = 624$ [M^+, 18] and at 194 (100, base peak). Anal. calcd. for $C_{33}H_{32}N_6O_5S$ (624.70): C, 63.45; H, 5.16; N, 13.45; S, 5.13. Found: C, 63.40; H, 5.10; N, 13.40; S, 5.90.

*(30Z)-2-(5-(Aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N′-(3,4-diphenylthiazol-2(3H)-ylidene)acetohydrazides (**12a**,**b**)*

A mixture of compound **11a** or **11b** (0.001 mol), phenacylbromide (0.233 g, 0.001 mol), and fused sodium acetate (0.238 g, 0.004 mol) in absolute ethanol (10 ml) was heated under reflux for 10 h with stirring. The reaction mixture was cooled and diluted with water, and the separated product was filtered off, dried, and crystallized from ethanol to give compounds **12a** or **12b**.

*(30Z)-2-(5-(4-Hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano [2,3-d][1,2,3]triazin-3(5H)-yl)-N′-(3,4-diphenylthiazol-2(3H)-ylidene)acetohydrazide (**12a**)*

Yield: 72 %, m.p. 283 °C; IR (KBr, cm^{-1}): 3380 (OH), 3242 (N–H str), 1715, 1750, 1680 (C=O), 3050 (CH Ar.); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.54$ (d, 6*H*, $2CH_3$), 1.96–2.44 (m, 4*H*, $2CH_2$), 3.78, 4.08 (s, 6*H*, $2OCH_3$), 4.46 (s, 1*H*, CH-pyrane), 5.13 (s, 2*H*, N–CH_2), 5.76 (s, 1*H*, OH exchangeable with D_2O), 6.52 (s, l*H*, CH thiazole), 6.72–7.55 (m, 16*H,* Ar–H + CH-pyrane), 10.50 (s, l*H*, NH exchangeable with D_2O); ^{13}C-NMR ($DMSOd_6$, ppm): $\delta = 27.24$ ($2CH_3$), 56.18, 56.28 ($2OCH_3$), 76.34 (C-1), 31.93 (C-2), 23.22 (C-3), 116.54 (C-4), 127.28 (C-5), 101.06 (C-6), 155.08 (C-7), 99.98 (C-8), 154.60 (C-9), 140.30 (C-10), 91.44 (C-11), 40.42 (C-12), 114.74 (C-13), 147.56 (C-14), 135.36 (C-15), 121.86 (C-16), 116.12 (C-17), 142.24 (C-18), 151.16 (C-19), 114.24 (C-20), 158.75 (C-21), 48.56 (C-22), 168.68 (C-23), 156.70 (C-24), 148.05 (C-25), 106.65 (C-26), 141.60 (C-27), 116.02 (C-28, C-28‘), 129.52 (C-29, C-29‘), 118.95 (C-30), 135.01

(C-31), 126.68 (C-32, C-32‘), 128.78 (C-33, C-33‘), 127.82 (C-34); MS (EI, 70 eV): $m/z = 771$ [M^+, 22] and at 266 (100, base peak). Anal. calcd. for $C_{42}H_{38}N_6O_7S$ (770.85): C, 65.44; H, 4.97; N, 10.90; S, 4.16. Found: C, 65.40; H, 4.92; N, 10.86; S, 4.12.

*(30Z)-2-(7-(7-Methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N′-(3,4-diphenylthiazol-2(3H)-ylidene)acetohydrazide (**12b**)*

Yield: 75 %, m.p. 270 °C; IR (KBr, cm^{-1}): 3242 (N–H str), 1715, 1750, 1680 (C=O), 3050 (CH Ar); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.49$ (d, 6*H*, $2CH_3$), 2.04–2.46 (m, 4*H*, $2CH_2$), 3.86 (s, 3*H*, OCH_3), 4.48 (s, 1*H*, CH-pyrane), 5.16 (s, 2*H*, N–CH_2), 6.45 (s, l*H*, CH thiazole), 6.78–7.58 (m, 18*H,* Ar–H + CH-pyrane), 10.46 (s, l*H*, NH, exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): $\delta = 27.52$ ($2CH_3$), 56.18 (OCH_3), 76.38 (C-1), 31.94 (C-2), 23.18 (C-3), 116.50 (C-4), 127.25 (C-5), 100.96 (C-6), 154.92 (C-7), 100.16 (C-8), 154.65 (C-9), 140.30 (C-10), 91.33 (C-11), 40.35 (C-12), 114.75 (C-13), 147.56 (C-14), 142.32 (C-15), 128.86 (C-16, C-20), 128.05 (C-17, C-19), 125.42 (C-18), 158.82 (C-21), 48.54 (C-22), 168.65 (C-23), 156.68 (C-24), 148.00 (C-25), 106.60 (C-26), 141.55 (C-27), 116.00 (C-28, C-28‘), 129.50 (C-29, C-29‘), 118.92 (C-30), 135.00 (C-31), 126.64 (C-32, C-32‘), 128.75 (C-33, C-33‘), 127.85 (C-34); MS (EI, 70 eV): $m/z = 725$ [M^+, 28] and at 268 (100, base peak). Anal. calcd. for $C_{41}H_{36}N_6O_5S$ (724.82): C, 67.90; H, 5.05; N, 11.59; S, 4.42. Found: C, 67.85; H, 5.00; N, 11.54; S, 4.38.

*2-(5-(Aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N-(2,5-dimethyl-1H-pyrrol-1-yl)acetamide (**13a**,**b**)*

A mixture of hydrazide **7a** or **7b** (0.002 mol) and 2,5-hexanedione (0.25 ml, 0.002 mol) in glacial acetic acid (5 ml) was stirred at room temperature overnight. The reaction mixture was poured onto water, and the separated solid was filtered off, dried, and crystallized from ethanol to give compounds **13a**,**b**, respectively.

*2-(5-(4-Hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N-(2,5-dimethyl-1H-pyrrol-1-yl)acetamide (**13a**)*

Yield: 82 %, m.p. 268 °C; IR (KBr, cm^{-1}): 3380 (OH), 3284 (N–H str), 3067 (C–H Ar), 2978 (C–H aliph.), 1750, 1681 (C=O), 1582 (N–H bending scissoring); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.48$ (d, 6*H*, $2CH_3$), 1.95 (s, 6*H*, $2CH_3$), 2.08–2.42 (m, 4*H*, $2CH_2$), 3.80, 4.10 (2s, 6*H*, $2OCH_3$), 4.42 (s, 1*H*, CH-pyrane), 5.18 (s, 2*H*, N–CH_2), 5.74 (s, 1*H*, OH exchangeable with D_2O), 6.56 (d, 2*H*, 2CH pyrole), 6.68–7.72 (m, 6*H*, Ar–H + CH-pyrane), 11.14 (s, 1*H*, NH exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): $\delta = 12.54$ ($2CH_3$), 27.32 ($2CH_3$), 56.13, 56.16 ($2OCH_3$), 76.42 (C-1), 31.90 (C-2), 23.12 (C-3), 116.82 (C-4), 127.19 (C-5), 100.85 (C-6), 154.95 (C-7), 100.23 (C-8), 154.63 (C-9), 140.29 (C-10), 91.35 (C-11), 40.34 (C-12), 115.71 (C-13), 146.51 (C-14), 135.01 (C-15), 119.81 (C-16), 116.08 (C-17), 142.15 (C-18), 151.06 (C-19), 113.86 (C-20), 158.62 (C-21), 54.51 (C-22), 170.65 (C-23), 132.80 (C-24, C-24‘), 105.80 (C-25, C-25‘); MS (EI, 70 eV): $m/z = 614$ [M^+, 12] and at 138 (100, base peak). Anal. calcd. for $C_{33}H_{35}N_5O_7$ (613.66): C, 64.59, H, 5.75; N, 11.41. Found: C, 64.56; H, 5.71; N, 11.36.

*2-(7-(7-Methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N-(2,5-dimethyl-1H-pyrrol-1-yl)acetamide (**13b**)*

Yield: 80 %, m.p. 263 °C; IR (KBr, cm^{-1}): 3284 (N–H str), 3067 (C–H Ar), 2978 (C–H aliph.), 1750, 1681 (C=O), 1582 (N–H bending scissoring); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.50$ (d, 6*H*, $2CH_3$), 1.94 (s, 6*H*, $2CH_3$), 2.05–2.46 (m, 4*H*, $2CH_2$), 3.86 (s, 3*H*, OCH_3), 4.48 (s, 1*H*, CH-pyrane), 5.10 (s, 2*H*, N-CH_2), 6.58 (d, 2*H*, 2CH pyrole), 6.64–7.78 (m, 8*H*, Ar–H + CH-pyrane), 10.50 (s, 1*H*, NH exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): $\delta = 13.08$ ($2CH_3$), 27.44 ($2CH_3$), 56.14 (OCH_3), 76.44 (C-1), 31.95 (C-2), 23.19 (C-3), 116.84 (C-4), 127.20 (C-5), 100.90 (C-6), 154.96 (C-7), 99.96 (C-8), 154.61 (C-9), 140.33 (C-10), 91.35 (C-11), 40.31 (C-12), 115.71 (C-13), 146.51 (C-14), 142.01 (C-15), 129.05 (C-16, C-20), 128.15 (C-17, C-19), 125.17 (C-18), 158.59 (C-21), 53.93 (C-22), 170.68 (C-23), 132.77 (C-24, C-24‘), 106.09 (C-25, C-25‘); MS (EI, 70 eV): $m/z = 568$ [M^+, 16] and at 137 (100, base peak). Anal. calcd. for $C_{32}H_{33}N_5O_5$ (567.63): C, 67.71, H, 5.86; N, 12.34. Found: C, 67.65; H, 5.82; N; 12.28.

*2-(5-(Aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N-(1,3-dioxoisoindolin-2-yl)acetamide (**14a**,**b**)*

A mixture of hydrazides **7a**,**b** (0.002 mol) and phthalic anhydride (0.296 g, 0.002 mol) in absolute ethanol (10 ml) with a few drops of glacial acetic acid was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure, and the obtained solid was filtered off, dried, and crystallized from ethanol to give compounds **14a**,**b**, respectively.

*2-(5-(4-Hydroxy-3-methoxyphenyl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N-(1,3-dioxoisoindolin-2-yl)acetamide (**14a**)*

Yield: 75 %, m.p. 297 °C; IR (KBr, cm^{-1}): 3380 (OH), 3197 (N–H str), 3093 (C–H Ar), 1750, 1727, 1694, 1672 (C=O), 1574 (N–H bending scissoring); ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.54$ (d, 6*H*, $2CH_3$), 1.99–2.42 (m, 4*H*, $2CH_2$), 3.80, 4.10 (2s, 6*H*, $2OCH_3$), 4.45 (s, 1*H*, CH-pyrane), 5.20 (s, 2*H*, N–CH_2), 5.72 (s, 1*H*, OH exchangeable with D_2O), 6.64 (d, 1*H*, CH-pyrane), 7.05–8.30 (m, 9*H*, Ar–H), 11.20 (s, 1*H*, NH exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): $\delta = 27.34$ ($2CH_3$), 56.28, 56.30 ($2OCH_3$), 76.35 (C-1), 31.95 (C-2), 23.23 (C-3), 116.54 (C-4), 127.25 (C-5), 101.08 (C-6), 155.04 (C-7), 99.92 (C-8), 154.61 (C-9), 140.31 (C-10), 91.46 (C-11), 40.40 (C-12), 114.73 (C-13), 147.59 (C-14), 135.39 (C-15), 121.85 (C-16), 116.13 (C-17), 142.22 (C-18), 151.15 (C-19), 114.26 (C-20), 158.76 (C-21), 48.55 (C-22), 168.65 (C-23), 164.56 (C-24, C-24‘), 131.75 (C-25, C-25‘), 127.56 (C-26, C-26‘), 123.12 (C-27, C-27′); MS (EI, 70 eV): $m/z = 666$ [M^+, 36] and at 190 (100, base peak). Anal. calcd. for $C_{35}H_{31}N_5O_9$ (665.64): C, 63.15; H, 4.69; N, 10.52. Found: C, 63.10; H, 4.65; N, 10.46.

*2-(7-(7-Methoxy-2,2-dimethylchroman-6-yl)-4-oxo-5-phenyl-4H-pyrano[2,3-d][1,2,3]triazin-3(5H)-yl)-N-(1,3-dioxoisoindolin-2-yl)acetamide (**14b**)*

Yield: 78 %, m.p. 307 °C; IR (KBr, cm^{-1}): 3197 (N–H str), 3093 (C–H Ar), 1750, 1727, 1694, 1672 (C=O), 1574 (N–H bending scissoring). ^{1}H-NMR (DMSO-d_6, ppm): $\delta = 1.54$ (d, 6*H*, $2CH_3$), 2.00–2.48 (m, 4*H*, $2CH_2$), 3.90 (s, 3*H*, OCH_3), 4.42 (s, 1*H*, CH-pyrane), 5.14 (s, 2*H*, N-CH_2), 6.68 (d, 1*H*, CH-pyrane), 7.15–8.32 (m, 11*H*, Ar–H), 11.18 (s, 1*H*, NH exchangeable with D_2O); ^{13}C-NMR (DMSOd_6, ppm): $\delta = 27.48$ (2 CH_3), 56.18 (OCH_3), 76.40 (C-1), 31.95 (C-2), 23.18 (C-3), 116.50 (C-4), 127.25 (C-5), 100.96 (C-6), 154.92 (C-7), 100.18 (C-8), 154.65 (C-9), 140.36 (C-10), 91.33 (C-11), 40.36 (C-12), 114.75 (C-13), 147.56 (C-14), 142.30 (C-15), 128.85 (C-16, C-20), 128.06 (C-17, C-19), 125.45 (C-18), 158.81 (C-21), 48.55 (C-22), 168.61 (C-23), 164.55 (C-24, C-24‘), 131.72 (C-25, C-25‘), 127.50 (C-26, C-26‘), 123.12 (C-27, C-27‘); MS (EI, 70 eV): $m/z = 620$ [M^+, 24] and at 190 (100, base peak). Anal. calcd. for $C_{34}H_{29}N_5O_7$ (619.62): C, 65.91; H, 4.72; N, 11.30. Found: C, 65.88; H, 4.70; N, 11.26.

Anticancer activity

Measurement of cytotoxicity by sulforhodamine B (SRB) assay

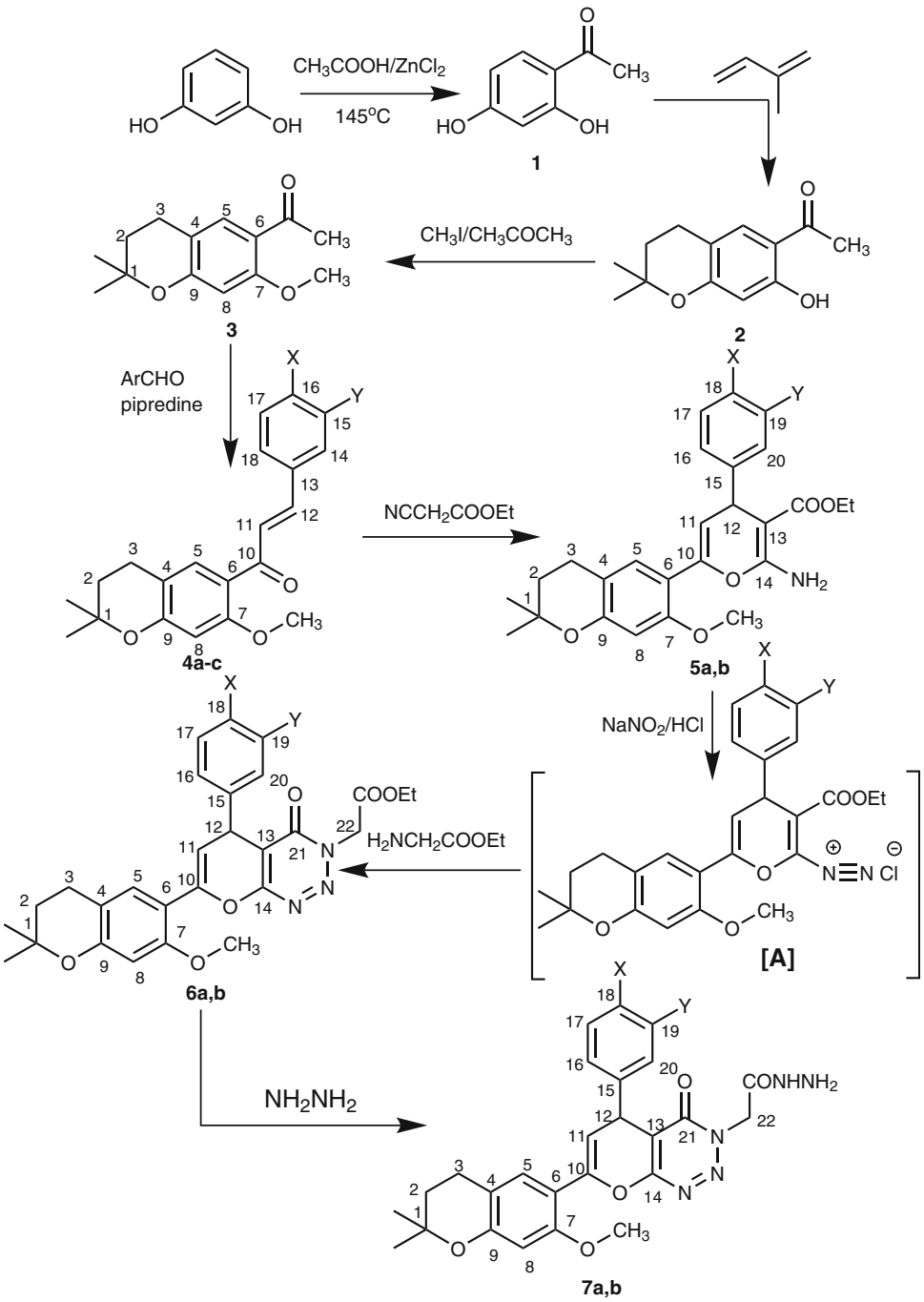
Compounds were subjected to a screening system for evaluation of their antitumor activity against liver HEPG2 cancer cell lines in comparison to the known anticancer drugs: 5-FU and DOX. Potential cytotoxicity of the selected derivatives was tested using the method of Skehan *et al.* (1990) as follows: Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compound(s) to allow attachment of cells to the wall of the plate. Different concentrations of the compounds under test (0, 1, 2.5, 5, 10 μg/mL) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 h at 37 °C and in an atmosphere of 5 % CO_2. Cultures were then fixed with trichloroacetic acid and stained for 30 min with 0.4 % (w/v) sulforhodamine B (SRB) dissolved in 1 % acetic acid. Unbound dye was removed by four washes with 1 % acetic acid, and protein-bound dye was extracted with 10 mM-unbuffered Tris base [tris(hydroxymethyl)amino-methane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The SRB assay results were linear with the number of cells and with values for cellular protein measured by both the Lowry and Bradford assays at densities ranging from sparse subconfluence to multilayered supraconfluence. The signal-to-noise ratio at 564 nm was approximately 1.5 with 1,000 cells/well. The relation between surviving fraction and drug concentration was plotted to get the survival curve of both cancer cell lines after the specified compound.

Result and discussion

Chemistry

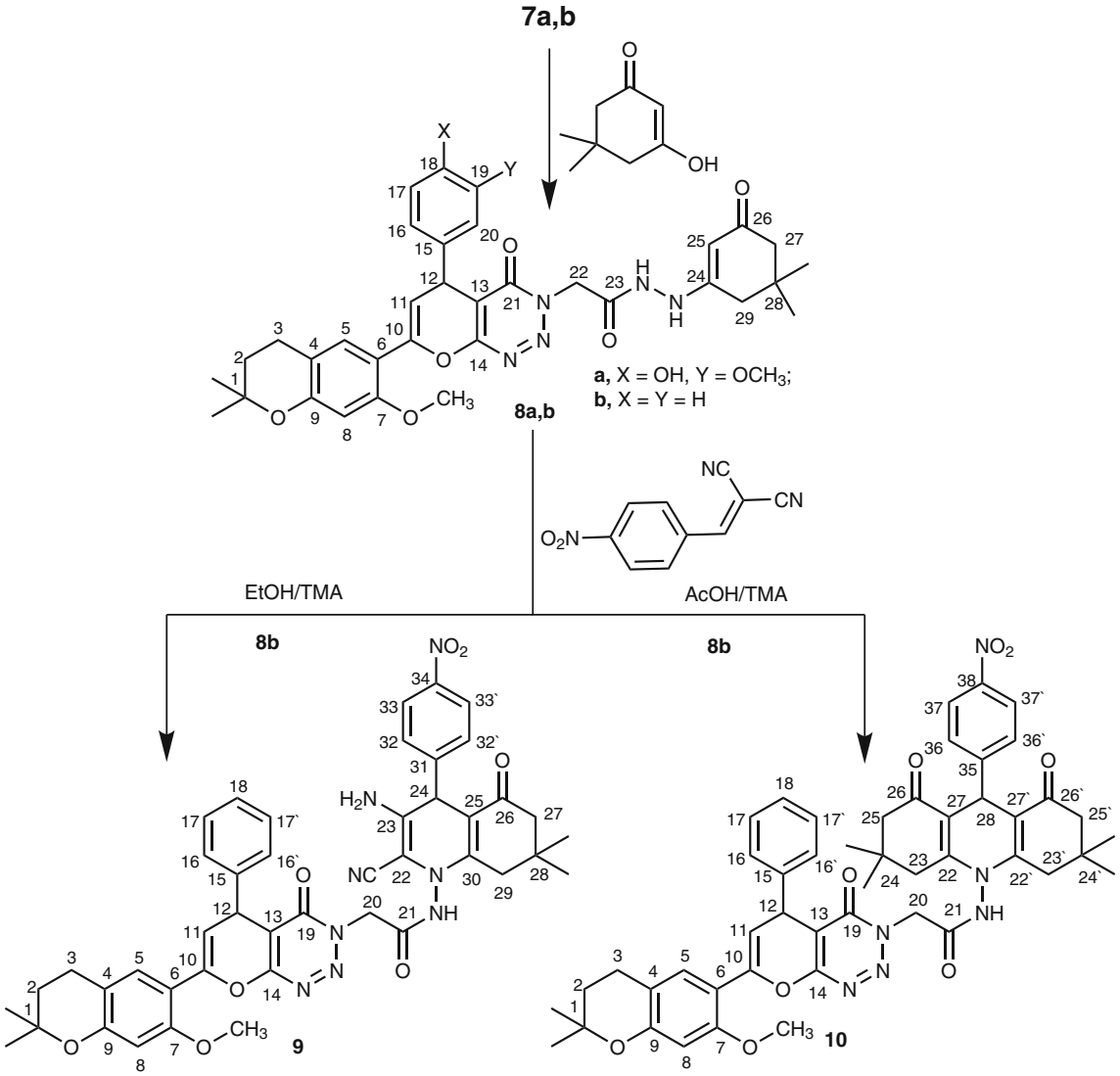
The newly substituted pyrano[1,2,3]triazine derivatives were synthesized by using 1-(2,4-dihydroxyphenyl) ethanone **1** and 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone **2** as starting materials, which were synthesized by reported method (Kumar *et al.*, 2011). The derivative **2** was methylated using methyl iodide in acetone to give 1-(7-methoxy-2,2-dimethylchroman-6-yl)ethanone (**3**), which was treated with aromatic aldehydes in the presence of piperidine to give the corresponding acryloyl derivatives (**4a**–**c**). Compounds **4a**,**b** were reacted with ethyl cyanoacetate in pyridine and

Scheme 1 Synthetic route to compounds **3**–**7**



gave the corresponding ethyl 2-amino-4-(aryl)-6-(7-methoxy-2,2-dimethylchroman-6-yl)-4*H*-pyran-3-carboxylates (**5a**,**b**). The diazotization of compounds **5a**,**b** with sodium nitrite and hydrochloric acid gives unseparated intermediate [**A**], which was converted to the corresponding esters **6a**,**b** by reacting with ethyl glycinate hydrochloride. Treatment of ester derivatives **6a**,**b** with hydrazine hydrate gives the corresponding acid hydrazide derivatives **7a**,**b** (Scheme 1).

The reaction of compounds **7a**,**b** with 5,5-dimethyl-1,3-cyclohexanedione afforded the corresponding pyrano[2,3-d]1,2,3]triazin-3(5*H*)-yl)-N'-(5,5-dimethyl-3-oxocyclohex-1-enyl)acetohydrazide derivatives **8a**,**b**, respectively. Cyclization of **8b** with 2-(4-nitrobenzylidene)malononitrile (Yao *et al.*, 2008) in ethanol in the presence of few drops of TMA afforded hexahydroquinoline derivative **9**. However, the acridindione **10** was synthesized by heating



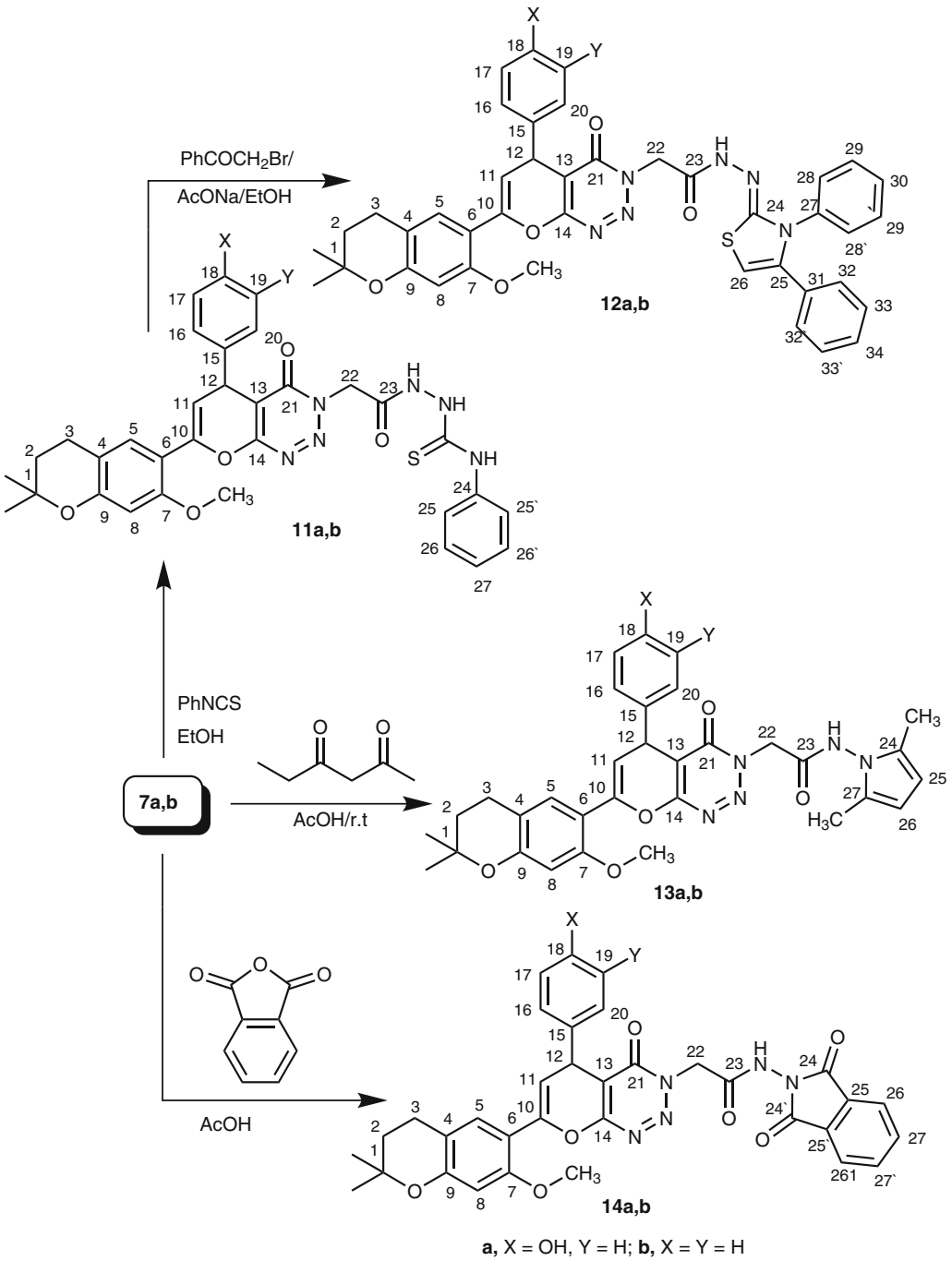
Scheme 2 Synthetic route to compounds **8**–**10**

of **8b** with 2-(4-nitrobenzylidene)malono-nitrile in acetic acid containing few drops of TMA (Scheme 2).

Treatment of compounds **7a**,**b** with phenyl isothiocyanate in ethanol gave the corresponding thiosemicarbazide derivatives **11a**,**b**, respectively, which were cyclized with phenacyl bromide in the present of sodium acetate to give the corresponding 1,3-thiazole derivatives **12a**,**b**, respectively. Cyclization of compounds **7a**,**b** with 2,5-hexanedione in acetic acid affords 2-(5-(aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4*H*-pyrano[2,3-d][1,2,3]triazin-3(5*H*)-yl)-N-(2,5-dimethyl-1*H*-pyrrol-1-yl)acetamide **13a**,**b**. Also, the reaction of compounds **7a**,**b** with phthalic anhydride in acetic acid gave 2-(5-(aryl)-7-(7-methoxy-2,2-dimethylchroman-6-yl)-4-oxo-4*H*-pyrano[2,3-d][1,2,3]triazin-3(5*H*)-yl)-N-(1,3-dioxoisoindolin-2-yl)acetamide **14a,b** (Scheme 3).

Anticancer activity

The selected compounds showed reasonable antitumor activity in comparison to 5-FU and DOX. Cytotoxic drugs remain the main stay of cancer chemotherapy and are being administered with novel ways of therapy such as inhibitors of signals (Guilbaud *et al.*, 2001). It is therefore important to discover novel cytotoxic agents with spectra of activity and toxicity that differ from those current agents (El-Nakkady *et al.*, 2012). It is well known that chemotherapy aims to destroy the cancer cells with various types of chemicals (Pautus *et al.*, 2006). The substances used are supposed to target mainly the cancer cells and doses are calculated to minimize the collateral damage to surrounding tissues, which nevertheless occurs (Hayakawa *et al.*, 2004).



Scheme 3 Synthetic route to compounds **11**–**14**

This kind of treatment increases the entropy of the organism, suppresses the immune system, and forms a toxic cell environment which may destroy surrounding healthy cells. It is important to use minimum effective doses in a hope to minimize the side effects of chemotherapeutic drugs.

Preliminary screening of the selected derivatives showed that compounds exhibited a moderate to strong growth inhibition activity on the tested cell line between 1 and 10 μg/mL concentrations in comparison to the known anticancer drugs: 5-FU and DOX. The results in Table 1 indicated the cytotoxic activity of the newly synthesized derivatives (compounds **3**, **4a**, **4b**, **4c**, **5**, **6**, **7**, **8a**,**b**, **9**, **10** **11**, **12**, **13**, **14a**,**b**) on liver HEPG2 cancer cell lines in comparison to the traditional anticancer drugs: 5-FU and DOX. It can be deduced from the results that compounds

Table 1 Cytotoxicity of the prepared compounds against liver HEPG2 cancer cell lines

Comp. no.	IC_{50} [μM]
5-Fluorouracil	0.0380
Doxorubicin	0.00620
3	0.0365
4a	0.0060
4b	0.0075
4c	0.0068
5a	0.0105
5b	0.0112
6a	0.0122
6b	0.0135
7a	0.0272
7b	0.0280
8a	0.0252
8b	0.0270
9	0.0178
10	0.0239
11a	0.0182
11b	0.0195
12a	0.0285
12b	0.0295
13a	0.0442
13b	0.0480
14a	0.0297
14b	0.0350

4a–c, **5a**,**b**, **6a**,**b**, **9**, and **11a**,**b** were the most active and induced a reasonable growth inhibition, in a dose-dependent manner against HEPG2 when compared to 5-FU and DOX (IC_{50} equals 0.0060, 0.0075, 0.0068, 0.0105, 0.0112, 0.0122, 0.0135, 0.0178, 0.0182, and 0.0195 μM, while for 5-FU and DOX were 0.0380 and 0.00620 μM). Also compounds **11b**, **8a**,**b**, **7a**,**b**, **12a**,**b**, **14a**,**b**, and **3** were the moderately active and induced a moderate growth inhibition, in a dose-dependent manner against HEPG2 when compared to 5-FU and DOX (IC_{50} equals 0.0239, 0.0252, 0.0270, 0.0272, 0.0280, 0.0285, 0.0295, 0.0297, 0.0350, and 0.0365 μM, while for 5-FU and DOX were 0.0380 and 0.00620 μM). Also compounds **13a**,**b** were the weakly active and induced a little growth inhibition, in a dose-dependent manner against HEPG2 when compared to 5-FU and DOX (IC_{50} equals 0.0442 and 0.0480 μM, while for 5-FU and DOX were 0.0380 and 0.00620 μM). From these results, it appeared that compounds **4a–c** >**5a**,**b** > **6a**,**b** > **9** > **11a**,**b** have a strong anticancer activity. Also, compounds **10** > **8a**,**b** > **7a**,**b** > **12a**,**b** > **14a**,**b** > **3** have a moderate anticancer activity, whereas **13a**,**b** has weak anticancer activity. Novel derivatives of pyrano[1,2,3]trizine possessing a broader spectrum of antitumor activity and fewer toxic side effects than 5-FU and DOX have been sought. The antitumor activities of such compounds were assessed against HEPG2 cancer cell line in comparison to the traditional anticancer drugs: 5-FU and DOX.

Structure–activity relationship (SAR)

It appeared from analysis of the structure of the most strongly active anticancer compounds that compounds **4a–c** have a strong anticancer activities due to the conjugation of enone with aromatic moities; **4a** is the most active due to the presence of OH in para-position (it may be anti-oxidant) then **4c** due to the presence of OCH_3 group. Compounds **5a**,**b** are active due to the presence of ester (COOEt) and amino (NH_2) groups, and compounds **6a**,**b** are active due to the presence of ester group, the activity of **9** due to the presence of amino group and **11b** has C=S and NH-groups. Compound **10** is less active than **9** due to the cyclization of the CN and NH_2 group in **9** and compound **7** is less reactive than **6** due to the changing of the ester group to aceto-hydrazide. Also compound **12** is less active than **11** due to the formation of thiazole ring. And also compound **13** is weak due to the formation of pyrrole ring. Additionally, the difference in activities between the compounds which were due to the indicated substituents in the molecule.

Conclusion

A series of the newly substituted pyrano[1,2,3]triazine derivatives **3–14** were synthesized using compounds **1** and **2** as starting materials. Some of the synthesized compounds were screened as anticancer agents. All the selected pyrano[1,2,3]trizine derivatives were soluble in DMSO at concentrations high enough to allow cell experiments, and the in vitro biological activity of these compounds was evaluated by their growth inhibitory potency in liver HEPG2 cancer cell lines. The cytotoxic potency of compounds **3–14** was studied in comparison to the known anticancer drugs 5-FU and DOX. The derivatives **4a–c**, **5a**,**b**, **6a**,**b**, **9**, and **11a**,**b** have a strong cytotoxic activity. Also, compounds **10**, **8a**,**b**, **7a**,**b**, **12a**,**b**, **14a**,**b** > **3** have a moderate cytotoxic activity, whereas compounds **13a**,**b** have weak cytotoxic activity.

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