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DOI: 10.1039/C3MD00241A

ARTICLE TYPE

Novel benzofuran-chromone and –coumarin derivatives: synthesis and biological activity in K562 human leukemia cells

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Not widely distributed in nature, aurones, (*Z*)-2-benzylidene-benzofuran-3(*2H*)-ones, are one of the less common and lesser-known representatives of a flavonoid subclass. Nevertheless they exhibit a strong and broad variety of biological activities.

We have combined the benzofuranone part of a classical aurone with either a chromone or a coumarine scaffold which proved to feature interesting biological activities including antimicrobial, antiviral, anticancer, anti-inflammatory and antioxidant properties. Herein we present a series of 26 novel benzofuran derivatives with the first biological results in K562 human leukemia cells showing that compound **21b**, **29b** and **29c** are able to induce around 24% apoptosis.

Introduction

Flavonoids represent a large class of natural products in the plant kingdom, exhibiting multiple biological activities[1]. Not widely distributed in nature, aurones, (*Z*)-2-benzylidene-benzofuran-3(*2H*)-ones, are one of the less common and lesser-known representatives of a flavonoid subclass[2]. This is probably the reason why this class of compounds has received little attention in comparison to the structurally similar and widely investigated flavones and isoflavones[3, 4]. Nevertheless they exhibit a pronounced and broad variety of biological activities recently reviewed by us[5]. Aurones play an important role in the pigmentation of some flowers and fruits and contribute especially to the bright yellow colour of flowers[6]. Aureusidin, a common aurone (**1**), is an inhibitor of iodothyronine- deiodinase, an enzyme involved in hormone synthesis and regulation of the thyroid [7].

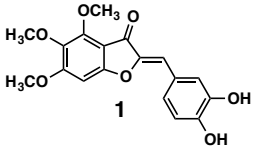


Fig. 1: Aureusidin, an example of a common aurone.

Some other aurones have been described as antiviral (influenza, hepatitis C)[8, 9], antiparasitic (malaria)[10] as well as antibacterial and antifungal agents[11, 12].

They are also known as inhibitors of tyrosinase[13] and as antioxidants[14].

Synthetic aurones bind to the nucleotide-binding domain of P-glycoprotein[15], inhibit cyclin-dependent kinases in connection with antiproliferative properties[16], and can act as anticancer agents[17].

In another study Bandgar *et al.* showed that certain aurones are able to inhibit the production of TNF-α and IL-6, two cytokines that are often involved in common diseases, such as autoimmune diseases, diabetes, arthrosclerosis and cancer[12].

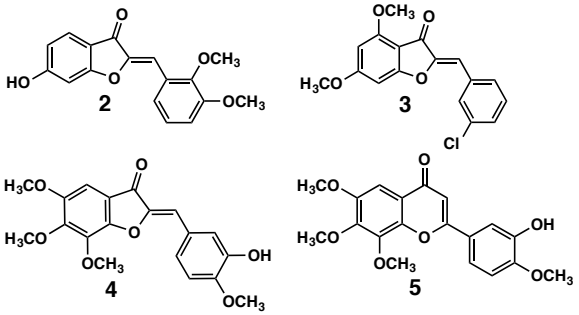


Fig. 2: Aurones (**2**-**4**) and the isomeric flavone (**5**) with postulated anticancer properties [3, 17, 18]

In recent literature[18, 17] several aurones such as **2** and **3** have been described with anti-cancer properties. Lawrence *et al.*[3] studied the aurones isolated from *Uvaria hamiltonii* for the total synthesis as well as for their anticancer properties in K562 cells. Among them compound **4** was the most active one with a growth inhibition IC_{50} value of 50 µM.

By reaction with potassium cyanide the aurone **4** converted into the flavone **5** providing a more active compound with an IC_{50} value of 40 µM.

Flavones as well as the aurones are belonging to the class of flavonoids and are known to possess anticancer activity, besides other biological activities like anti-oxidative or anti-inflammatory effects[19, 20]. They might also prevent cardiovascular diseases when they form part of a daily diet[21]. Besides other activities various chromones exhibit anticancer properties[22]. Their constitutional isomers, the coumarins, show similar biological activities, which have been recently reviewed [23].

Therefore our idea was to combine the benzofuran structure from aurones with the chromone motif or the isomeric coumarine motif, to obtain potential novel anticancer agents.

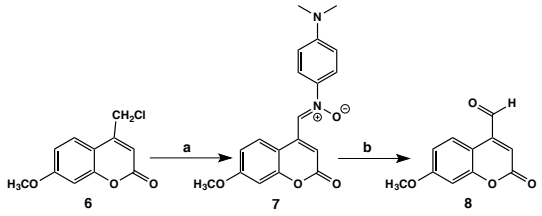
In this study we describe the preparation of 26 chromone- and coumarine-based benzofuran derivatives and their biological effects in K562 human leukemia cells when tested at 50 μM for 48 h. In particular, the effect of such new derivatives on the K562 cell cycle as well as induction of apoptosis (pre-G1 peak) have been determined.

Results and Discussion

Chemistry

Although the standard method to prepare coumarin-4-aldehyde **8** is reported using 4-methylcoumarine and SeO_2[24], we applied the Kröhnke oxidation[25] to the 4-chloromethylcoumarine **6** achieving the corresponding aldehyde **8** with an improved yield (90%). The reaction is carried out with *p*-nitrosodimethylaniline as oxidising agent at room temperature in basic conditions followed by an acidic hydrolysis of the intermediate **6** to yield the desired aldehyde **8** (Scheme 1).

The compounds **9-17**, **18b, 19** and **30** have been prepared by known literature methods. [2,3, 17, 18, 26-36]

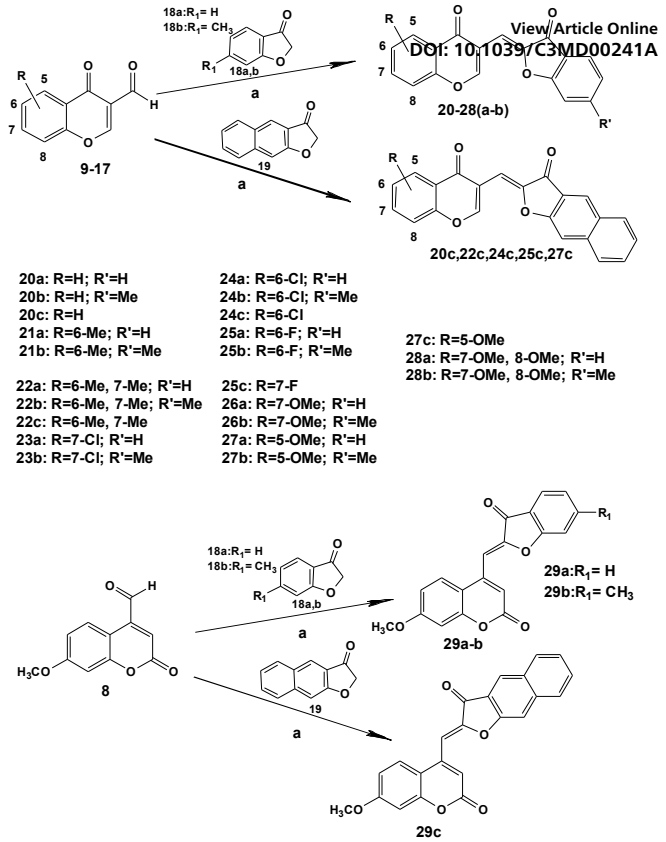


Scheme 1: Synthesis of coumarine-4-aldehyde **a** *p*-nitrosodimethylaniline, sodium ethanolate, ethanol, room temperature, 20 mins, 95%; **b** hydrolysis 5N H_2SO_4 room temperature, 30 mins, 95%

A common way to prepare aurones is based on the method of an aldol–like condensation of benzofuran-3(*2H*)-ones with benzaldehydes. These aldol reactions are usually carried out with catalytic amounts of acid (hydrochloric acid) or base (pyrrolidine) in ethanol or THF under reflux[2]. Firstly we used these conditions to synthesize the desired compounds in very low yields (about 5-10%). Then we decided to perform the aldolic condensation through the use of acidic Al_2O_3 (Brockmann I) [37]. The desired compounds were obtained at room temperature within 2 to 6 days in acceptable yields. No purification was necessary or in some cases recrystallization from ethanol was suffcient to obtain the pure compounds **20-29** (Scheme 2).

Although an unambiguous assignment of the isomeric structures of our series of compounds was not carried out, the values are consistent with those present in the literature for known (*Z*)-aurones[38, 39].

The synthetic yields, melting points, elemental analyses, ^1H and ^{13}C NMR spectra of all compounds are described in the experimental section.



Scheme 2: Synthetic route **a** acid Al_2O_3, anhydrous DCM, room temperature, 2-6 d

Biology

Effect of compounds 20-29 on cell cycle distribution and apoptosis induction in human K562 cells.

The described compounds **20-29** were tested at 50 μM for 48 h in K562 human leukemia cells to determine their effects on cell cycle and apoptosis induction (**Fig. 2 A** and **B**). The HDAC inhibitor SAHA was included as a positive control.

Analysing the results, we could observe that compound **21b** and, to a lesser extent, **22c**, **27c** and **29b** displayed slight cell cycle arrest in the G1 phase, whereas with some other derivatives (**20b**, **21a**, **23b**, **24b**, **25a and 25b**) a block in the S phase occurred. Only one among the new described compounds, **29c,** was able to arrest the cell cycle in G2 phase.

Taking in account the pre-G1 peak in **Fig. 2B** as an index of pro-apoptotic properties of the compounds, it results that **20a**, **20c**, **22c**, **24c**, **26a** and **27c** exhibit 17 to 22% of apoptosis induction in this assay, while **21b**, **29b** and **29c** showed the strongest effect with around 24%.

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DOI: 10.1039/C3MD00241A

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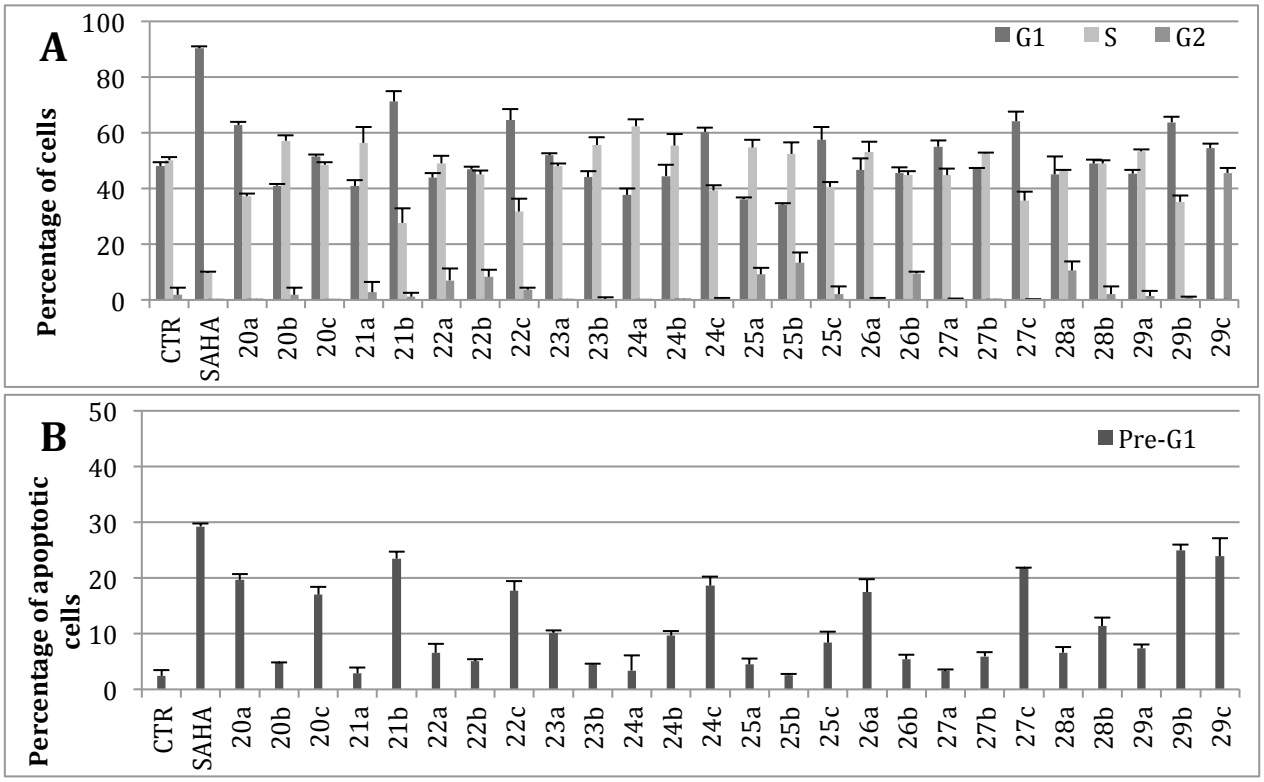
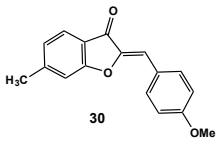


Fig. 2 (A) Cell-cycle phase distribution in K562 cells and **(B)** apoptosis induction in K562 cells treated with **20a -29c** at 50 μM for 48 h.

Structure-activity relationship analysis highlighted that the different substitutions (halogen, methyl and methoxy) on the chromone (**20-28**) do not influence the potency of the compounds. Instead, exchanging the benzofuranone or methylbenzofuranone moiety with a napthofuranone seems to exert a more powerful effect toward apoptosis with the exception of **20a**, **21b** and **29b**.

The replacement of the chromone moiety (**20-28**) with the isomeric coumarin (**29**) afforded the only one compound able to block the cell cylce in G2 (**29c**).



30

To better ascertain the pro-apoptotic property of these oxobenzofuran-chromone and –coumarine derivatives, we selected **29b** as lead compound, and we tested it in K562 cells at doses ranging from 5 to 100 μM, in comparison with **8**, the comarin-4-aldheyde used for the synthesis of **29b**, and with the (*Z*)-2-(4-methoxybenzylidene)-6-methylbenzofuran-3(2*H*)-one (**30**), a compound showing a simple, classic aurone structure (**Fig. 3**). After 48 h as well as 72 h of treatment, **29b** showed at higher doses (50 and 100 μM) the strongest apoptosis induction, it being more efficient than **8** and **30**. These data suggest that combination of an aurone-like template with a chromome or coumarine scaffold can lead to new compounds endowed with interesting apoptotic effect in K562 leukemia cells.

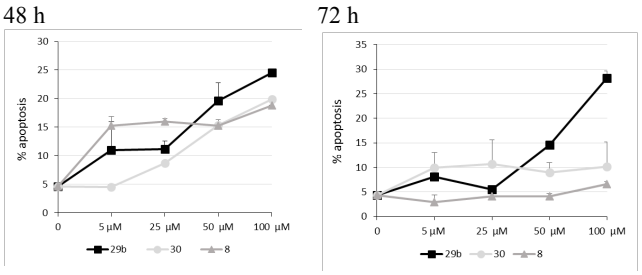


Fig. 3 Dose-dependent apoptosis induction in K562 cells treated with **29b**, **8** and **30** for 48 (**A**) and 72 (**B**) h.

Experimental

Chemistry

Melting points were determined with a Stuart SMP3 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 MHz spectrometer in $CDCl_3$ or DMSO. Chemical shifts are reported in δ (ppm) units relative to the internal standard

tetramethylsilane (Me_4Si). Mass spectra were recorded with a MicroTof-Q 98. All reactions were routinely monitored by TLC (Merck DC, Alufolien Kieselgel 60 F_{254}) with spots visualized by UV light. Column chromatography was performed on silica gel LC 60A (70-200 micron, SigmaAldrich). All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure of approx. 20 Torr. Organic solutions were dried over anhydrous magnesium sulfate. Elemental analysis has been used to determine purity of the described compounds, that is >95%. The solvents used were purchased from Carlo Erba (France) and the reactives from Sigma Aldrich (France) or Acros Organics (France).

General procedure for the synthesis of 3-formylchromones (9-17):

To a stirred solution of corresponding *o*-hydroxy-acetophenone (30 mmol) in dimethylformamide (40 mL), phosphorous oxychloride (60 mmol) was added dropwise at 0°C over 20-30 minutes. The mixture was stirred on ice for further 30 minutes and then continued at room temperature for 3-5 hrs. The mixture was treated with ice-cold water (100 mL). The resulting solid was filtered, washed with water and purified if necessary by recrystallization from ethanol. † The experimental data of these starting materials are provided in the supporting information.

Synthesis of 7-methoxy-coumarin-4-aldehyde (8)

*Synthesis of 7 (*E)-*N-[4-(dimethylamino)phenyl)-1-(7-methoxy-2-oxo-2*H-*chromen-4-yl]methanimine oxide*

A mixture of 7-methoxy-4(chloromethyl)coumarine (1 mmol) and *p*-nitrosodimethylaniline (3 mmol) in ethanol is added dropwise to sodium ethanolate (1 mmol) in ethanol at room temperature. An orange nitrone salt is almost immediately precipitating. After 20 minutes the solid was filtered and washed with an excess of ethanol. The product was used without further purification for the next step.

mp: 207-209; orange-red solid; yield: 95%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.06 (s, 6H, 2 $–CH_3$), 3.88 (s, 3H, $–OCH_3$), 6.67-6.70 (d, 2H, *J*=7.5 Hz,), 6.85–6.89 (m, 2H,), 7.53–7.56 (d, 1H, *J*=7.5 Hz,), 7.66–7.69 (d, 2H, *J*=15.0 Hz,), 8.26 (s, 1H,), 8.46 (s, 1H,), ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 40.28, 55.76, 101.62, 109.73, 110.40, 111.16, 111.35, 122.64, 123.34, 123.46, 138.62, 139.09, 151.96, 155.51, 162.22, 162.29 HRMS (ESI) [M+Na]+ $C_{19}H_{19}N_2O_4$ calculated: 339.1339, found 339.1338.

Elemental Analysis: calculated: C: 67.44%; H: 5.36%; N: 8.28%; O: 18.91% found: C: 67.22%; H: 5.49%

Compound **7** is added slowly into vigorously stirring diluted sulfuric acid (5M). After 30 minutes of stirring the reaction is quenched with water and extracted with DCM. The organic phased is washed with diluted HCl (2M), dried with magnesium sulfate and the evaporated giving pure 7-methoxycoumarine-4-aldehyde.

mp: 194-196; yellow solid; yield: 95%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.89 (s, 3H, $–OCH_3$), 6.72 (s, 1H, -CHCOO-), 6.88–6.95 (m, 2H, aromatic protons) 7.48-7.52 (d, 1H, *J*=10.0 Hz, aromatic proton), 10.08 (s, 1H -CHO) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 55.81, 110.10, 108.17, 113.27, 122.17, 127.37, 143.75, 156.51, 160.75, 163.35, 191.75 [24]

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Synthesis of the benzofuran-chromone and –coumarin derivatives:

A mixture of the chromone-3 aldehydes or coumarine-4-aldehydes (5 mmol) and different benzofuranone derivatives (5 mmol) were stirred at room temperature in dichloromethane (5 mL) with acidic Al_2O_3 (Beckmann I, 1g) for 2 to 6 days. The suspension was filtered through celite and washed with dichloromethane/THF to remove all traces of aluminium oxide. After distillation of the solvent in vacuo the obtained solid was recrystallized from ethanol.

20a) (*Z*)-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl)]-chromone

mp: 233-234; yellow solid; yield: 36%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.23-7.33 (d, 2H, *J*= 10.0 Hz, aromatic protons), 7.38 (s, 1H =C-C*H*=C), 7.44–7.54 (m, 2H, aromatic protons), 7.64–7.77 (m, 2H, aromatic protons), 7.81–7.84 (d, 1H, *J*= 7.5 Hz, aromatic proton), 8.29-8.33 (d, 1H, *J*=10.0 Hz, aromatic proton), 9.09 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 102.25, 112.75, 118.13, 118.27, 121.75, 123.62, 123.83, 124.87, 125.84, 126.53, 134.15, 136.92, 147.15, 155.90, 158.77, 165.58, 175.13, 183.57 HRMS (ESI) [M+H]+ $C_{18}H_{11}O_4$ calculated: 291.0652 found: 291.0663.

Elemental Analysis: calculated: C: 74.48%; H: 3.47%; O: 22.05% found: C: 74.48%; H: 3.47%

20b) (*Z*)-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]-chromone

mp: 210-212; yellow solid; yield: 66%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, $–CH_3$), 7.04-7.08 (d, 1H, *J*= 10.0 Hz, aromatic proton), 7.11 (s, 1H, aromatic proton), 7.33 (s, 1H =C-C*H*=C), 7.43–7.54 (m, 2H, aromatic protons), 7.68–7.76 (m, 2H, aromatic protons), 8.29-8.33 (d, 1H, *J*= 10.0 Hz, aromatic proton), 9.06 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.66, 101.70, 112.91, 118.18, 118.27, 119.39, 123.60, 124.50, 125.17, 125.80, 126.51, 134.12, 147.62, 149.13, 155.89, 158.61, 166.14, 175.17, 183.17 HRMS (ESI) [M+H]+ $C_{19}H_{13}O_4$ calculated: 305.0808 found: 305.0811.

Elemental Analysis: calculated: C: 74.99%; H: 3.97%; O: 21.03% found: C: 74.42 H: 4.22

20c) (*Z*)-2-[(chromon-3-yl)methylene]naphtho[2,3-*b*]furan-3(2*H*)-one

mp: 243-245; yellow solid; yield: 21%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.37 (s, 1H =C-C*H*=C), 7.43-7.55 (m, 3H, aromatic proton), 7.59–7.65 (m, 2H, aromatic protons), 7.70–7.76 (t, 1H, *J*=7.5 Hz, aromatic proton), 7.87–7.90 (d, 1H, *J*=7.5 Hz, aromatic proton), 7.98–8.01 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.30–8.33 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.40 (s, 1H, aromatic proton), 9.16 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 101.07, 107.74, 118.29, 121.75, 123.61, 125.53, 126.54, 126.64, 127.84, 129.69, 130.05, 130.73, 130.90, 134.12, 138.26, 147.84, 155.92, 158.58, 159.44, 175.19, 183.95 HRMS (ESI) [M+H]+ $C_{22}H_{13}O_4$ calculated: 341.0808 found: 341.0803.

Elemental Analysis: calculated: C: 77.64%; H: 3.55%; O: 18.80% found: C: 77,78%; H: 3.11%

21a) (*Z*)-6-methyl-3-[3-oxobenzofuran-2((3*H*)-ylidene)methyl]-chromone

mp: 218-220; pale yellow solid; yield: 37%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.48 (s, 3H, –CH_3), 7.21-7.28 (m, 1H, aromatic proton), 7.32 (s, 1H =C-C*H*=C), 7.37 (s, 1H, aromatic proton), 7.33–7.34 (d, 1H, *J*= 10.0 Hz, aromatic proton), 7.50–7.54 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.63–7.70 (t, 1H, *J*=7.5 Hz, aromatic proton), 7.80–7.83 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.07 (s, 1H, aromatic proton), 9.06 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 20.98, 102.54, 112.75, 117.87, 118.03, 121.77, 123.25, 123.78, 124.84, 125.81, 135.97, 136.88, 147.02, 154.18, 158.74, 165.55, 175.21, 183.59 HRMS (ESI) [M+H]+ $C_{19}H_{13}O_4$ calculated: 305.0808, found: 305.0820.

Elemental Analysis: calculated: C: 74.99%; H: 3.97%; O: 21.03% found: C: 75.24%; H: 4.03%

21b) (*Z*)-6-methyl-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]-chromone

mp: 255-257; pale orange solid; yield: 37%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.48 (s, 3H, –CH_3), 2.50 (s, 3H, –CH_3), 7.03-7.06 (d, 1H, *J*= 7.5 Hz, aromatic proton), 7.10 (s, 1H, aromatic proton), 7.33 (s, 1H =C-C*H*=C), 7.39–7.43 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.50–7.53 (d, 1H, J=7.5 Hz, aromatic proton), 7.67–7.70 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.08 (s, 1H, aromatic proton), 9.03 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 20.98, 22.64, 101.99, 112.89, 117.95, 118.01, 119.44, 123.31, 124.48, 125.13, 125.82, 135.33, 135.90, 147.51, 149.05, 154.18, 158.57, 166.22, 175.31, 183.32 HRMS (ESI) [M+H]+ $C_{20}H_{15}O_4$ calculated: 319.0965, found: 319.0961.

Elemental Analysis: C: 75.46%; H: 4.43%; O: 20.10% found: C: 75.64% H: 4.50%

22a) (*Z*)-6,7-dimethyl-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 238-240; pale yellow solid; yield: 42%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.38-2.41 (d, 6H, *J*=7.5 Hz, 2 –CH_3), 7.21-7.29 (m, 2H, aromatic protons), 7.31 (s, 1H =C-C*H*=C), 7.38 (s, 1H, aromatic proton), 7.63–7.69 (t, 1H, *J*=7.5 Hz, aromatic proton), 7.79–7.82 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.01 (s, 1H, aromatic proton), 9.02 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 19.34, 20.46, 102.77, 112.73, 117.80, 118.35, 121.42, 121.81, 123.73, 124.81, 126.06, 135.26, 136.81, 144.78, 146.94, 154.45, 158.61, 165.53, 175.04, 183.57 HRMS (ESI) [M+H]+ $C_{20}H_{15}O_4$ calculated: 319.0965 found: 319.0977.

Elemental Analysis: calculated: C: 75.46%; H: 4.43%; O: 20.10% found: C: 75.40%; H: 4.40%

22b) (*Z*)-6,7-dimethyl-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 286-288; pale yellow solid; yield: 44%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.37-2.40 (d, 6H, *J*=7.5 Hz, 2 –CH_3), 2.50 (s, 3H, –CH_3), 7.03-7.06 (d, 1H, *J*= 7.5 Hz, aromatic proton), 7.10 (s, 1H, aromatic proton), 7.28 (s, 1H =C-C*H*=C), 7.33 (s, 1H, aromatic proton), 7.67–7.70 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.02 (s, 1H, aromatic proton), 8.99 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 19.34, 20.45, 22.63, 102.20, 112.88, 117.87, 118.34, 119.47, 121.43, 124.44, 125.07, 126.05, 135.20, 144.71, 147.42, 148.97, 154.45, 158.43, 166.09, 175.07, 183.16 HRMS (ESI) [M+H]+ $C_{21}H_{17}O_4$ calculated: 333.1121 found: 333.1120.

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Elemental Analysis: calculated: C: 75.89%; H: 4.85%; O: 19.26% found C: 75.80%; H: 4.74%

22c) (*Z*)-2-[(6,7-dimethylchromon-3-yl)methylene]naphtho[2,3-*b*]furan-3(2*H*)-one

mp: 207-209; yellow solid; yield: 41%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.38-2.42 (d, 6H, J=10.0 Hz, 2 –CH_3), 7.30 (s, 1H =C-C*H*=C), 7.39 (s, 1H, aromatic proton), 7.45–7.51 (m, 1H, aromatic proton), 7.59–7.63 (m, 2H, aromatic protons), 7.87–7.90 (d, 1H, *J*=7.5 Hz, aromatic proton) 7.98–8.04 (m, 2H, aromatic protons), 8.41 (s, 1H, aromatic proton), 9.12 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 18.82, 19.15, 113.96, 114.03, 115.58, 119.52, 120.88, 124.53, 124.95, 126.07, 129.03, 129.29, 129.34, 130.71, 130.90, 131.55, 133.46, 149.02, 149.37, 151.05, 153.39, 154.13, 177.51, 182.66 HRMS (ESI) [M+Na]+ $C_{24}H_{17}O_4$ calculated: 369.1121, found 369.1117.

Elemental Analysis: calculated: C: 78.25%; H: 4.38%; O: 17.37% found: C: 78.34%; H: 4.36%;

23a) (*Z*)-7-chloro-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl] chromone

mp: 253-255; pale yellow solid; yield: 45%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.23 (s, 1H =C-C*H*=C), 7.29–7.33 (m, 2H, aromatic proton), 7.40-7.45 (d, 1H, *J*=12.5Hz, aromatic protons), 7.65–7.72(m, 2H, aromatic protons), 7.80–7.84 (d, 1H, *J*=10.5 Hz, aromatic proton) 8.22-8.26 (d, 1H, *J*=10.0 Hz, aromatic proton), 9.06 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 101.57, 112.76, 118.36, 118.50, 121.65, 122.08, 123.95, 124.93, 126.72, 127.91, 137.05, 140.35, 147.33, 155.94, 158.59, 165.59, 174.36, 183.54 HRMS (ESI) [M+H]+ $C_{18}H_{10}ClO_4$ calculated: 325.0262 found: 325.0286.

Elemental Analysis: calculated: C: 66.58%; H: 2.79%; Cl: 10.92%; O: 19.71% found: C: 66.65%, H: 2.83%

23b) (*Z*)-7-chloro-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 267-269; pale yellow solid; yield: 55%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, –CH_3), 7.04 (s, 1H =C-C*H*=C), 7.07-7.11 (d, 1H, *J*=10.0 Hz, aromatic protons), 7.40–7.44 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.54 (s, 1H, aromatic proton), 7.68–7.70 (d, 1H, *J*=5.0Hz, aromatic proton) 8.21-8.25 (d, 1H, *J*=10.0 Hz, aromatic proton), 9.01 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.68, 101.01, 112.92, 118.34, 118.57, 119.31, 122.09, 124.55, 125.28, 126.66, 127.90, 140.28, 147.82, 149.28, 155.94, 158.41, 166.15, 174.38, 183.10 HRMS (ESI) [M+H]+ $C_{19}H_{12}ClO_4$ calculated: 339.0419 found: 339.0428.

Elemental Analysis: calculated: C: 67.37%; H: 3.27%; Cl: 10.47%; O: 18.89% found: C: 67.55%, H: 3.26%

24a) (*Z*)-6-chloro-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl] chromone

mp: 250-252; pale yellow solid; yield: 42%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.23 (s, 1H =C-C*H*=C), 7.29–7.32 (d, 2H, *J*=7.5 Hz, aromatic proton), 7.47-7.51 (d, 1H, *J*=10.0Hz, aromatic protons), 7.64–7.71 (m, 2H, aromatic protons), 7.80–7.83 (d, 1H, J=7.5 Hz,

aromatic proton) 8.26-8.27 (d, 1H, *J*=2.5 Hz, aromatic proton), 9.07 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 101.60, 112.75, 118.21, 120.03, 121.64, 123.95, 124.46, 124.93, 125.90, 131.88, 134.39, 137.04, 147.29, 154.20, 158.66, 165.59, 174.06, 183.52 HRMS (ESI) [M+Na]+ $C_{18}H_9ClNaO_4$ calculated: 347.0082 found: 347.0092.

Elemental Analysis: calculated: C: 66.58%; H: 2.79%; Cl: 10.92%; O: 19.71% found: C: 66.78%; H: 2.80%

24b) (*Z*)-6-chloro-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 253-255; pale yellow solid; yield: 37%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, –CH_3), 7.04–7.07 (d, 2H, *J*=7.5 Hz, aromatic proton), 7.13 (s, 1H =C-C*H*=C), 7.26 (s, 1H, aromatic proton), 7.47-7.50 (d, 1H, *J*=7.5Hz, aromatic protons), 7.63–7.64 (d, 1H, *J*=2.5 Hz, aromatic proton), 7.67–7.70 (m, 1H, aromatic proton) 8.25-8.26 (d, 1H, *J*=2.5 Hz, aromatic proton), 9.03 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.76, 101.04, 112.91, 118.28, 119.31, 120.01, 124.47, 124.55, 125.28, 125.89, 131.34, 134.34, 147.78, 149.27, 154.20, 158.49, 166.51, 174.08, 183.08 HRMS (ESI) [M+H]+ $C_{19}H_{12}ClO_4$ calculated: 339.0419 found: 339.0422.

Elemental Analysis: calculated: C: 67.37%; H: 3.27%; Cl: 10.47%; O: 18.89% found: C: 67.37%; H: 3.29%

24c) (*Z*)-2-[(6-chloro-chromon-3-yl)methylene]naphtho[2,3-*b*]furan-3(2*H*)-one

mp: 310-312; yellow solid; yield: 25%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.32 (s, 1H =C-C*H*=C), 7.46–7.52 (m, 2H, aromatic protons), 7.60–7.71 (m, 3H, aromatic protons), 7.87–7.90 (d, 1H, *J*=7.5 Hz, aromatic proton) 7.99–8.03 (d, 1H, *J*=10.0 Hz, aromatic proton), 8.29 (s, 1H, aromatic proton), 8.42 (s, 1H, aromatic proton), 9.15 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 100.41, 107.76, 118.39, 120.03, 124.48, 125.61, 125.92, 126.75, 127.85, 129.78, 130.09, 130.93, 131.83, 134.34, 138.28, 148.02, 154.26, 157.99, 158.45, 159.40, 174.21, 183.81 HRMS (ESI) [M+H]+ $C_{22}H_{12}ClO_4$ calculated: 375.0419 found: 375.0426.

Elemental Analysis: calculated: C: 74.48%; H: 3.47%; O: 22.05% found: C: 74.53%; H: 3.56%

25a) (*Z*)-6-fluoro-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl] chromone

mp: 249-251; pale yellow solid; yield: 44%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.23 (s, 1H =C-C*H*=C), 7.29 (s, 1H, aromatic proton), 7.32 (s, 1H, aromatic proton), 7.41-7.48 (m, 1H, aromatic proton), 7.52–7.58 (m, 1H, aromatic proton), 7.65–7.71 (t, 1H, *J*=7.5 Hz, aromatic proton), 7.81–7.84 (d, 1H, *J*=7.5 Hz, aromatic proton), 7.92-7.95 (d, 1H, *J*=7.5 Hz, aromatic proton), 9.09 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.66, 101.76, 111.23, 111.61, 112.75, 117.53, 120.41, 120.54, 121.68, 122.62, 123.92, 124.92, 136.65, 147.30, 158.72, 165.59, 174.47, 183.52 HRMS (ESI) [M+H]+ $C_{18}H_{12}FO_4$ calculated: 309.0558 found: 309.0557.

Elemental Analysis: calculated: C: 70.13%; H: 2.94%; F: 6.16%; O: 20.76% found: C: 70.39%; H: 2.76%

25b) (*Z*)-6-fluoro-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 230-232; pale yellow solid; yield: 38%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, –CH_3), 7.05–7.11 (t, 2H, *J*=7.5 Hz, aromatic proton), 7.28 (s, 1H =C-C*H*=C), 7.44-7.48 (m, 1H, aromatic proton), 7.52–7.57 (m, 1H, aromatic proton), 7.68–7.71 (d, 1H, *J*=7.5 Hz, aromatic proton) 7.92-7.95 (d, 1H, *J*=7.5 Hz, aromatic proton), 9.05 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.66, 101.20, 111.60, 112.90, 117.62, 119.35, 120.38, 124.47, 124.55, 124.55, 124.83, 125.25, 147.79, 149.22, 152.13, 157.86, 166.15, 174.50, 183.09 HRMS (ESI) [M+H]+ $C_{19}H_{12}FO_4$ calculated: 323.0714 found: 323.0715.

Elemental Analysis: calculated: C: 70.81%; H: 3.44%; F: 5.89%; O: 19.86% found: C: 69.81%; H: 3.44%

25c) (*Z*)-2-[(6-fluoro-chromon-3-yl)methylene]naphtho[2,3-*b*]furan-3(2*H*)-one

mp: 303-305; yellow solid; yield: 38%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.32 (s, 1H =C-C*H*=C), 7.41–7.67 (m, 5H, aromatic protons), 7.87–8.01 (m, 3H, aromatic protons), 8.41 (s, 1H, aromatic proton), 9.16 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 100.60, 107.77, 120.43, 120.56, 121.66, 122.61, 125.61, 126.75, 127.85, 129.78, 130.08, 130.94, 131.83, 134.34, 138.28, 142.61, 148.01, 157.99, 158.56, 159.43, 174.26, 184.89HRMS (ESI) [M+H]+ $C_{22}H_{12}FO_4$ calculated: 359.0714 found: 359.0710.

Elemental Analysis: calculated: C: 73.74%; H: 3.09%; F: 5.30%; O: 17.86% found: C: 73.75%, H: 3.14%

26a) (*Z*)-7-methoxy-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 233-235; pale yellow solid; yield: 45%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.93 (s, 3H, –OCH_3), 6.88 (s, 1H, aromatic proton), 6.98–7.03 (d, 1H, *J*=12.5 Hz, aromatic proton), 7.21-7.32 (m, 2H, aromatic protons), 7.37 (s, 1H =C-C*H*=C), 7.54 (s, 1H, aromatic proton), 7.63-7.67 (m, 1H, aromatic protons), 7.80–7.83 (d, 1H, J=7.5Hz, aromatic proton), 8.18-8.22 (d, 1H, *J*=10.0 Hz, aromatic proton), 9.00 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 55.92, 100.57, 102.49, 112.74, 114.98, 117.43, 117.97, 121.78, 123.78, 124.84, 127.94, 136.86, 147.08, 157.64, 158.43, 164.44, 165.54, 174.42, 183.56 HRMS (ESI) [M+H]+ $C_{19}H_{13}O_5$ calculated: 321.0757 found: 321.0764.

Elemental Analysis: calculated: C: 71.25%; H: 3.78%; O: 24.98% found: C: 71.13% H: 3.83%

26b) (*Z*)-7-methoxy-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone

mp: 222-224; pale yellow solid; yield: 41%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.50 (s, 3H, –CH_3), 3.93 (s, 3H, –OCH_3), 6.88 (s, 1H, aromatic proton), 6.97-7.09 (m, 3H, aromatic protons), 7.32 (s, 1H =C-C*H*=C), 7.40–7.44 (d, 1H, *J*= 10.0 Hz, aromatic proton), 7.54 (s, 1H, aromatic proton), 7.66–7.69 (d, 1H, *J*= 7.5Hz, aromatic proton), 8.17-8.21 (d, 1H, *J*=10.0 Hz, aromatic proton), 8.97 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.64, 55.90, 100.54, 101.90, 112.89, 114.93, 117.43, 118.03, 119.43, 124.45, 125.11, 127.91, 147.54, 149.04, 157.62, 158.24, 164.40, 166.09, 174.44, 183.13 HRMS (ESI) [M+H]+ $C_{20}H_{15}O_5$ calculated: 335.0914 found: 335.0924.

Elemental Analysis: C: 71.85%; H: 4.22%; O: 23.93% found: C:

71.60%; H: 4.31%

27a) (*Z*)-5-methoxy-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone
mp: 236-238; pale yellow solid; yield: 33%; ^{1}H NMR (250 MHz, $CDCl_3$) d) 4.01 (s, 3H, –OC*H*$_3$), 6.84–6.88 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.04–7.08 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.21-7.31 (m, 3H, aromatic protons), 7.37 (s, 1H =C-C*H*=C), 7.54 (s, 1H, aromatic proton), 7.56–7.69 (m, 2H, aromatic protons), 7.80-7.83 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.90 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 56.53, 102.66, 107.05, 110.16, 112.71, 114.24, 119.13, 121.84, 123.72, 124.82, 134.28, 136.80, 147.10, 157.10, 157.80, 160.28, 165.48, 174.41, 183.55 HRMS (ESI) [M+H]+ $C_{19}H_{13}O_5$ calculated: 321.0757 found: 321.0762.
Elemental Analysis: calculated: C: 71.25%; H: 3.78%; O: 24.98% found: C: 71.03%; H: 3.78%

27b) (*Z*)-5-methoxy-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone
mp: 260-262; pale yellow solid; yield: 43%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, –C*H*$_3$), 4.00 (s, 3H, –OC*H*$_3$), 6.83–6.87 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.02-7.08 (m, 3H, aromatic protons), 7.32 (s, 1H =C-C*H*=C), 7.40–7.44 (d, 1H, *J*=10.0 Hz, aromatic proton), 7.54 (s, 1H, aromatic proton), 7.55–7.62 (m, 1H, aromatic proton), 7.66-7.69 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.90 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.64, 56.52, 102.08, 106.99, 110.15, 112.86, 114.24, 119.20, 119.49, 124.43, 125.06, 134.22, 147.57, 148.94, 156.90, 157.80, 160.27, 166.03, 174.44, 183.12 HRMS (ESI) [M+H]+ $C_{20}H_{15}O_5$ calculated: 335.0914 found: 335.0914.
Elemental Analysis: C: 71.85%; H: 4.22%; O: 23.93% found: C: 71.60%; H: 4,26%

27c) (*Z*)-2-[(5-methoxy-chromon-3-yl)methylene]naphtho[2,3-*b*]furan-3(2*H*)-one
mp: 286-288; yellow solid; yield: 37%; ^{1}H NMR (250 MHz, $CDCl_3$) d 4.02 (s, 3H, –OC*H*$_3$), 6.85-6.88 (m, 1H, aromatic proton), 7.07-7.10 (m, 1H, aromatic proton), 7.37 (s, 1H =C-CH=C), 7.45–7.49 (m, 1H, aromatic proton), 7.54–7.67 (m, 3H, aromatic protons), 7.83–7.92 (m, 1H, aromatic proton), 7.95–8.03 (m, 1H, aromatic proton), 8.40 (s, 1H, aromatic proton), 9.02 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 56.52, 101.47, 107.00, 107.66, 110.18, 114.25, 119.30, 121.88, 125.44, 126.51, 127.81, 129.59, 130.02, 130.86, 134.23, 138.22, 147.79, 156.90, 157.83, 159.40, 160.29, 174.46, 183.89 HRMS (ESI) [M+H]+ $C_{23}H_{15}O_5$ calculated: 371.0914 found: 371.0920.
Elemental Analysis: calculated: C: 74.59%; H: 3.81%; O: 21.60% found: C: 74.19%; H: 3.44%

28a) (*Z*)-7,8-dimethoxy-3-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone
mp: 250-252; pale yellow solid; yield: 40%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, –C*H*$_3$), 4.03 (s, 6H, 2 –OC*H*$_3$), 7.07–7.10 (d, 1H, *J*= 7.5Hz, aromatic proton), 7.22-7.31 (m, 2H, aromatic protons), 7.36 (s, 1H =C-C*H*=C), 7.61-7.64 (m, 1H, aromatic proton), 7.81–7.84 (d, 1H, *J*= 7.5Hz, aromatic proton), 8.02-8.06 (d, 1H, *J*=10.0 Hz, aromatic proton), 9.11 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 56.49, 61.73, 102.31, 110.51, 112.74, 117.58, 118.20, 121.76, 121.98, 123.81, 124.86, 147.17, 150.23, 156.92, 158.55, 165.55, 174.61, 183.51 HRMS (ESI) [M+H]+ $C_{20}H_{15}O_6$ calculated: 351.0863 found: 351.0853.
Elemental Analysis: calculated: C: 68.57%; H: 4.03%; O: 27.40% found: C: 68.90%; H: 4.14%

28b) (*Z*)-7,8-dimethoxy-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]chromone
mp: 214-216; pale yellow solid; yield: 34%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.51 (s, 3H, –C*H*$_3$), 4.03 (s, 6H, 2 –OC*H*$_3$), 7.04-7.10 (m, 3H, aromatic protons), 7.31 (s, 1H =C-C*H*=C), 7.68–7.71 (d, 1H, *J*= 7.5Hz, aromatic proton), 8.02-8.05 (d, 1H, *J*=7.5 Hz, aromatic proton), 9.07 (s, 1H –O-C*H*=C-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.66, 56.48, 61.72, 101.75, 110.46, 112.87, 117.65, 118.23, 119.43, 121.98, 124.49, 125.16, 136.77, 147.65, 149.11, 150.23, 156.87, 158.36, 166.12, 174.64, 183.16 HRMS (ESI) [M+H]+ $C_{21}H_{17}O_6$ calculated: 365.1020 found: 365.1006.
Elemental Analysis: C: 69.23%; H: 4.43%; O: 26.35% found: C: 69.47%, H: 4,49%

29a) (*Z*)-7-methoxy-4-[(3-oxobenzofuran-2(3*H*)-ylidene)methyl]-2*H*-coumarine
mp: 225-227; yellow solid; yield: 36%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.91 (s, 3H, –OC*H*$_3$), 6.88-6.95 (m, 2H, aromatic protons), 7.03 (s, 1H, =C*H*COO–), 7.17 (s, 1H, =C-C*H*=C), 7.33–7.38 (m, 2H, aromatic protons), 7.71–7.76 (m, 2H, aromatic protons), 7.82–7.85 (d, 1H, *J*=7.5 Hz, aromatic proton) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 55.84, 101.46, 102.00, 111.72, 112.64, 113.28, 114.73, 120.67, 124.54, 125.15, 125.18, 138.18, 143.68, 151.00, 155.64, 161.29, 162.95, 166.66, 184.19 HRMS (ESI) [M+Na]+ $C_{19}H_{12}NaO_5$ calculated: 343.057 found: 343.059.
Elemental Analysis: calculated: C: 71.25%; H: 3.78%; O: 24.98% found: C: 70.96%; H: 3.90%

29b) (*Z*)-7-methoxy-4-[(6-methyl-3-oxobenzofuran-2(3*H*)-ylidene)methyl]-2*H*-coumarine
mp: 238-240; yellow solid; yield: 40%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.53 (s, 3H, –C*H*$_3$), 3.88 (s, 3H, –OC*H*$_3$), 6.87-6.95 (m, 2H, aromatic protons), 6.97 (s, 1H, =C*H*COO–), 7.09–7.15 (m, 3H, aromatic protons,=C-C*H*=C), 7.69–7.76 (t, 2H, *J*=9.5 Hz, aromatic protons) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 22.84 55.83, 101.43, 101.52, 111.77, 112.60, 113.41, 114.53, 118.34, 124.82, 125.18, 125.86, 143.83, 150.75,151.57, 155.62, 161.34, 162.90, 167.11, 183.65 HRMS (ESI) [M+Na]+ $C_{20}H_{14}NaO_5$ calculated: 357.0733, found: 357.0742.
Elemental Analysis: calculated: C: 71.85%; H: 4.22%; O: 23.93% found: C: 71.67%; H: 4.32%

29c) (*Z*)-2-[(7-methoxycoumarin-yl)methylene]naphtho[2,3-*b*]furan-3(2*H*)-one
mp: 291-293; orange solid; yield: 38%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.91 (s, 3H, –OC*H*$_3$), 6.89-6.96 (m, 2H, aromatic protons), 7.01 (s, 1H, =C*H*COO–), 7.26 (s, 1H, =C-C*H*=C), 7.49–7.54 (m, 1H, aromatic proton), 7.64–7.70 (m, 2H, aromatic protons), 7.76–7.80 (d, 1H, *J*=10.0 Hz, aromatic proton) ppm, 7.90–7.94 (d, 1H, *J*=10.0 Hz, aromatic proton) ppm, 8.00–8.03 (d, 1H, *J*=7.5 Hz, aromatic proton) ppm, 8.45 (s, 1H, aromatic

proton); ^{13}C NMR (62.5 MHz, $CDCl_3$) d 55.83, 100.65, 101.45, 108.47, 111.78, 112.60, 114.43, 120.48, 125.13, 126.03, 127.47, 128.23, 130.27, 130.40, 131.07, 138.70, 143.83, 151.93, 155.65, 159.79, 161.42, 162.90, 184.53 HRMS (ESI) [M+Na]+ $C_{23}H_{14}NaO_5$ calculated: 393.074 found: 393.074.
Elemental Analysis: calculated: C: 74.59%; H: 3.81%; O: 21.60% found: C: 74.63%; H: 3.82%

Biology:

Cell culture :
K562 (chronic myeloid leukemia) cells were cultured in RPMI (Invitrogen) with 10% fetal calf serum (Hyclone), 100 U/mL penicillin.

Cell Cycle Analysis on K562 Cells
2.5×10^5 treated (containing the tested compound and 0. 1% DMSO) and untreated (containing 0.1% DMSO) cells were collected, fixed and resuspended in 500 µL of a hypotonic buffer (0.1% Triton X-100, 0.1% sodium citrate, 50 µg/mL propidium iodide (PI), RNAse A). Cells were incubated in the dark for 30 min. Samples were acquired on a FACS-Calibur flow cytometer using the Cell Quest software (Becton Dickinson) and analysed with standard procedures using the Cell Quest software (Becton Dickinson) and the ModFit LT version 3 Software (Verity) as previously reported[40]. All the experiments were performed in triplicates.

Conclusions

In summary, new benzofuran-chromone and –coumarine derivatives have been synthesized and evaluated against K562 human leukeima cells. Both these chemical structures displayed anticancer acitivity because they are able to block the K562 cell cycle in G1 (**21b** 72%), S (**24a** 63%) or G2 (**29c** 46%) phase, and to induce high (around 24%) apoptosis (**21b**, **29b** and **29c)**. These new compounds seem to provide a promising scaffold for medicinal chemistry bearing in mind the possibility to access heterocyclic analogues of benzofurans. Complementary investigations must be launched into the discovery of other biological properties as well as their molecular mechanism of action.

Acknowledgments

The research leading to these results has received funding from the [European Community's] Seventh Framework Program ([FP7/2007-2013] under grant agreements n° 215009, n° 28251 (Blueprint) and Italian Association for Cancer Reserarch (AIRC, n° 11812).

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DOI: 10.1039/C3MD00241A

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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