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Synthesis and in vitro cytotoxic effect of some novel 4*H*-furo [3,2–*c*]pyran-4-one derivatives

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Abstract: We report a series of novel 4*H*-furo[3,2–*c*]pyran-4-one derivatives. Structures of synthesized compounds were determined by the IR, NMR, elemental analysis and X-ray diffraction method. All the compounds were tested for genotoxicity in human lymphocytes cultures. Sister chromatid exchange (SCE), micronucleus (MN), mitotic index (MI) and replication index (RI) tests are used in toxicological screening for potential cytotoxic and genotoxic effects. According to the results of the genotoxic tests, the 4H-furo[3,2–c]pyran-4-one derivatives induce the frequencies of these parameters. The results showed that these compounds are potential genotoxic and cytotoxic compounds at high concentrations (especially 1 and 2 mg/mL).

Keywords: 2,3-furandione; pyran-2-one; 4*H*-furo[3,2–*c*]pyran-4-one; cyctoxic activity.

1. Introduction

4,5-Disubstituted-2,3-furandiones are important starting materials due to their high reactivity. Many different heterocyclic compounds can be obtained from these compounds. They are capable of undergoing thermolysis and nucleophilic addition reactions depending on the reaction conditions and structures of the nucleophiles [1-6].

α-Pyrone derivatives, also known as 2H-pyran-2-one, are heterocyclic compounds that exist in natural products and show biological activity. To illustrate, the experiments on animals revealed that Withaferin A isolated from *Withania somnifera* plant has antibiotic and antitumor activities [7,8]. Again Goniotriol isolated from a plant from Malaysia (*Goniothalamus giganteus*) is a 2*H*-pyran-2-one derivative with an antitumor activity [9]. Another herbal 2H-pyran-2-one derivative is Kava lactone compounds isolated from Kava Kava plant (*Piper methysticum*) and it is reported that it is used as a muscle relaxant and against epilepsy [10, 11].

Neo-tanshinlactone isolated from Tanshen, a traditional Chinese medicine, is a natural product with four membered cyclic compound like steroid. The preventive impact of Neo-tanshinlactone compound, a derivative of 6-phenyl-4*H*-furo[3,2–*c*]pyran-4-one, against the breast cancer is surveyed and positive results were obtained [12,13]. Inoscavin A and Niveulone are also natural products isolated from fungus. It is reported that these compounds show cytotoxic effect and act as radical scavenger agents [14-16].

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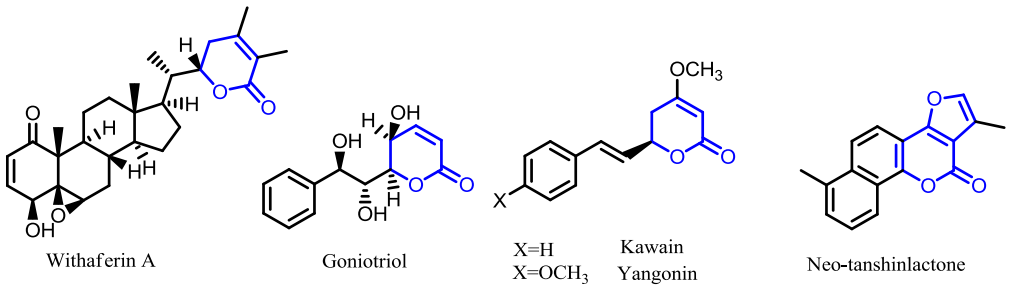


Figure 1. Some α-pyrone derivatives isolated from plants

In continuation to our previous efforts [17,18], novel 4*H*-furo[3,2–*c*]pyran-4-one derivatives were designed, and synthesized. The new compounds were screened for genotoxicity in human lymphocytes cultures by using sister chromatid exchange (SCE), micronucleus (MN), mitotic index (MI) and replication index (RI) tests.

2. Results and discussion

We reported the synthesis of eight 4*H*-furo[3,2–*c*]pyran-4-one derivatives earlier. Cytotoxic activity of two of them was investigated in human lymphocytes [17,18]. According to this study, investigated compounds may act as a proliferative and mitotic agent. So, different from earlier ones, we synthesized 4*H*-furo[3,2–c]pyran-4-one derivatives which are containing styryl and ester group. Our goal is to examine the behavior of the synthesized compounds in the presence of these groups.
The novel 4*H*-furo[3,2–*c*]pyran-4-one derivatives were obtained by reacting 2,3-furandiones [19,20] **1** with dialkyl acetylenedicarboxylates **2** and triphenyl phosphine in benzene under reflux condition **(Figure 2).**

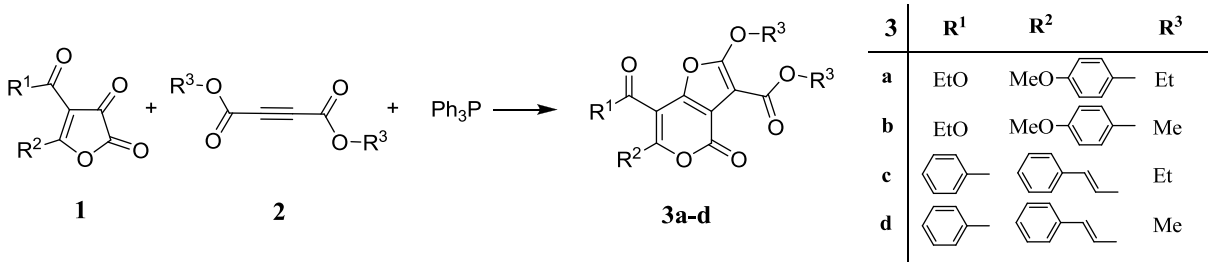


Figure 2. Synthesis of 4*H*-furo[3,2–*c*]pyran-4-one derivatives

The structures of the target compounds were identified using IR, ^{1}H NMR, ^{13}C NMR and XRD spectral data. Elemental analysis of these synthesized compounds was also in complete agreement with the proposed structures. The IR spectrum of 3a showed bands at 1766, 1717 and 1635 cm^{-1}, indicating three carbonyl stretching belong to the esters and lactone groups. ^{1}H NMR spectrum of **3a** in $CDCl_3$ showed three triplets at 1.51-1.20 ppm for methyl groups. And also three quartet signals arised at 4.57-4.27 ppm due to OCH_2 groups. Aromatic hydrogens are observed as a AA'BB' system (Fig. 3). The ^{13}C NMR spectrum of **3a** showed twenty signals in agreement with the proposed structure. The ^{1}H- and ^{13}C NMR spectra of **3b**– **3d** are similar to those for **3a**, except for the alkoxy groups and aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.
The structure of the product was further confirmed by an X-ray crystallographic study of **3a**. The ORTEP plot of **3a** is shown in Fig. 4. The compound crystallizes in the triclinic space group P-1(no:2) with 2 molecules in the unit cell. The bond lengths of carbonyl, C=O in the structure are in range of 1.177-1.190 Å. C2/C7 phenyl ring and 4*H*-furo[3,2–*c*]pyran bicycle are not co-planar. Dihedral angle formed by LSQ-planes is 47.3(1)°.
Figure 5 and **Figure 6** describe distribution of SCE and MN. When the SCE was analyzed after the treatment of the compounds with different concentrations of extracts, significant increases were

detected in the percentage of SCE for 1 (compound **3a**, **3b** and **3d**) and 2 mg/mL (compound **3c**) ($p < 0.01$) but not for other extract concentrations (0.05, 0.1 and 0.5 mg/mL) did not induce significant changes in SCE frequencies compared to the untreated group ($p = 0.01$).

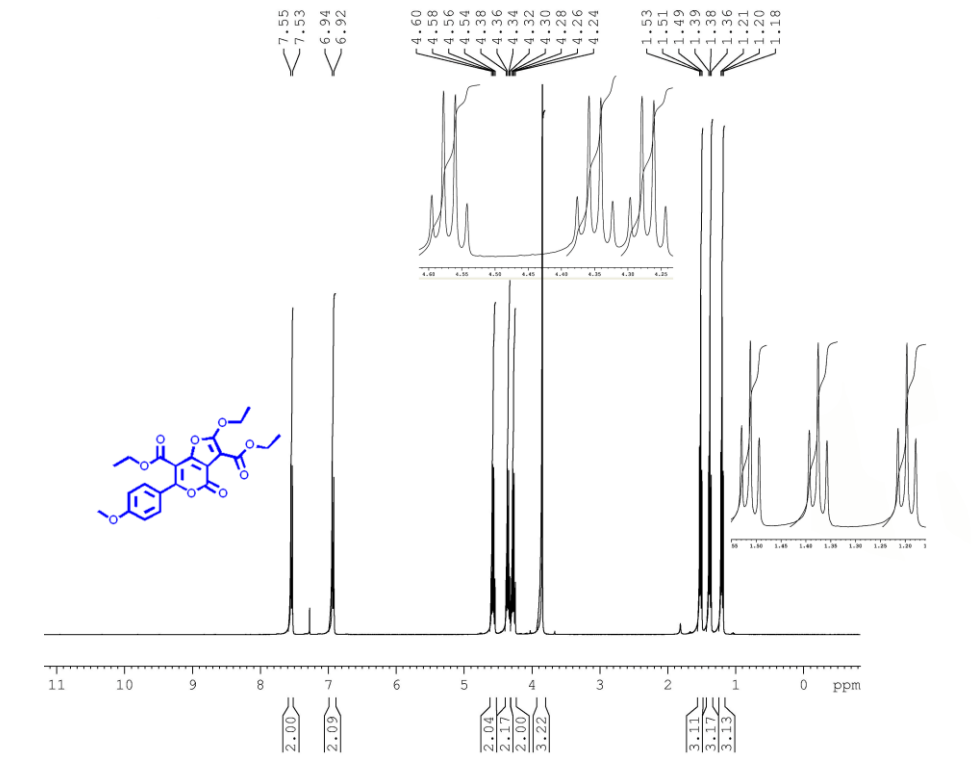


Figure 3. ^{1}H NMR spectra of compound **3a**

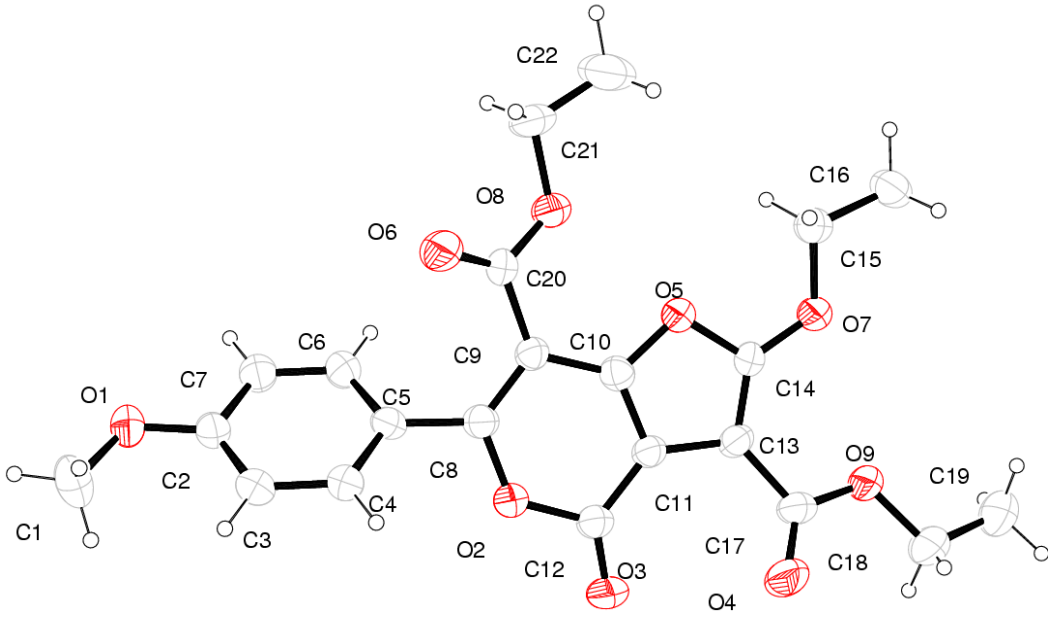
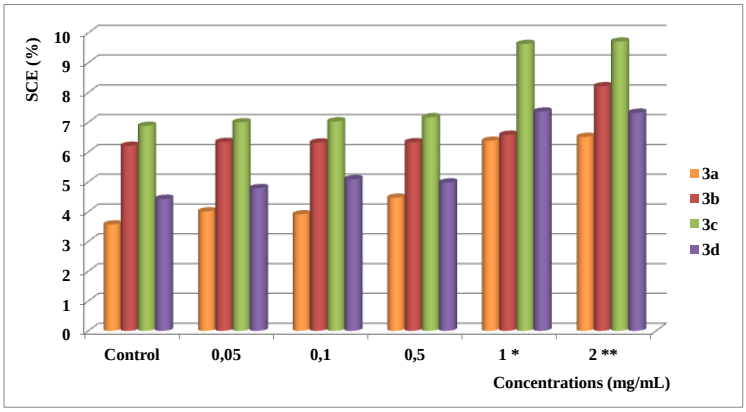
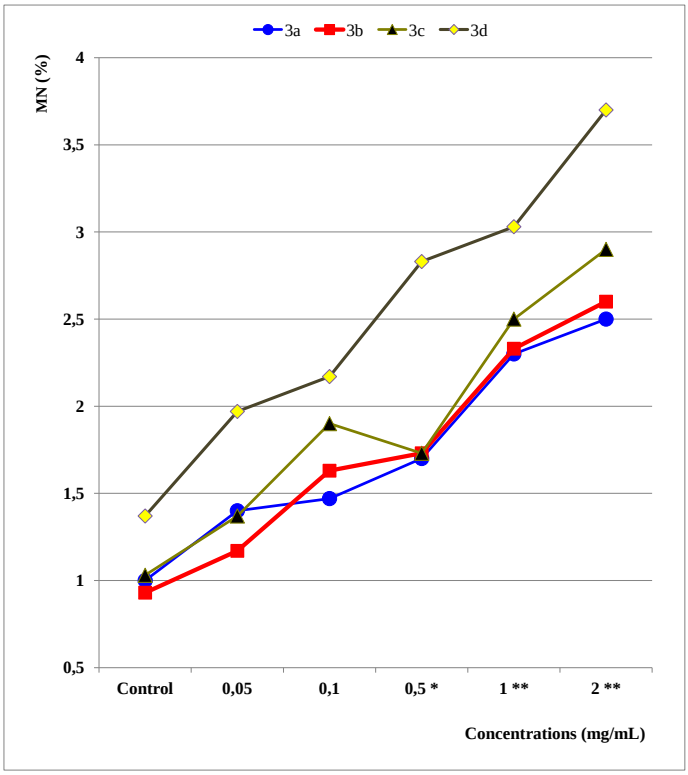


Figure 4. *ORTEP* drawing of the molecule **3a**. Thermal ellipsoids are shown at 40% probability level



ANOVA: * $p < 0.01$ (**3a**, **3b** and **3d**), ** $p < 0.01$ (**3c**)

Figure 5. Sister chromatid exchange rates of the compounds



ANOVA: * $p < 0.01$ (**3d**), ** $p < 0.01$ (**3a**, **3b** and **3c**)

Figure 6. Micronucleus frequencies of the compounds

When the potential genotoxicity of the extracts of the compounds in lymphocyte cultures were analyzed through MN evaluation, the significant increases were found for 3d (0.5, 1 and 2 mg/mL). Other compounds were increased the MN frequencies at the concentrations of 1 and 2 mg/mL ($p < 0.01$) too.

Table 1 and **Table 2** show the dose-response properties of the cultures for MI and RI, respectively. A dose-dependent increase was detected in the rates of MI and RI. When compared with the untreated group, a significant difference was found at 1 and 2 mg/mL concentrations of all compounds for MI rates, respectively ($p < 0.01$). RI results showed similarities with the results of MI except for some minor differences. While 2 mg/mL concentration of the all compounds significantly was increasing the RI rates, 1 mg/mL concentration of the compound **3a** and **3c** was affected the RI rates ($p < 0.01$).

Table 1. Mitotic index (%) (mean ± SDs) in human lymphocyte cultures exposed to different concentrations of compounds.

Compound	Concentrations (mg/mL)	Total counted cells	Total number: dividing cells	Mean ± SDs (%)
3a	Control	6000	85	1.41 ± 0.45
	0.05	6000	103	1.71 ± 0.37
	0.1	6000	116	1.93 ± 0.34
	0.5	6000	119	1.98 ± 0.41
	1	6000	145	2.41 ± 0.63 *
	2	6000	152	2.53 ± 0.44 *
3b	Control	6000	81	1.35 ± 0.37
	0.05	6000	100	1.66 ± 0.33
	0.1	6000	115	1.91 ± 0.55
	0.5	6000	119	1.98 ± 0.41
	1	6000	143	2.38 ± 0.48 *
	2	6000	156	2.60 ± 0.63 *
3c	Control	6000	79	1.31 ± 0.31
	0.05	6000	93	1.55 ± 0.45
	0.1	6000	101	1.68 ± 0.16
	0.5	6000	126	2.10 ± 0.52
	1	6000	150	2.50 ± 0.46 *
	2	6000	166	2.76 ± 0.48 *
3d	Control	6000	86	1.43 ± 0.40
	0.05	6000	100	1.66 ± 0.54
	0.1	6000	120	2.00 ± 0.19
	0.5	6000	133	2.21 ± 0.36
	1	6000	168	2.80 ± 0.46 *
	2	6000	183	3.05 ± 0.46 *

ANOVA: * $p < 0.01$ (significantly different from control)

SCE, MN, MI and RI assays are used in toxicological screening for potential cytotoxic and genotoxic compounds. According to **Figure 5, 6** and **Table 1, 2**, the *4H*-furo[3,2–*c*]pyran-4-one derivatives are induced the frequencies of these parameters. The results showed that these compounds are potential toxic compounds at high concentrations (especially 1 and 2 mg/mL).

Table 2. Replication index (mean ± SDs) in human lymphocyte cultures exposed to different concentrations of compounds.

Concentrations (mg/mL)	Compound 3a	Compound 3b	Compound 3c	Compound 3d
Control	1.111 ± 0.041	1.142 ± 0.045	1.114 ± 0.047	1.126 ± 0.107
0.05	1.128 ± 0.050	1.159 ± 0.036	1.127 ± 0.057	1.133 ± 0.103
0.1	1.172 ± 0.043	1.191 ± 0.039	1.154 ± 0.062	1.198 ± 0.124
0.5	1.190 ± 0.056	1.212 ± 0.035	1.219 ± 0.049	1.306 ± 0.168
1	1.251 ± 0.060 *	1.211 ± 0.026	1.248 ± 0.051 *	1.358 ± 0.160
2	1.271 ± 0.055 *	1.295 ± 0.034 *	1.306 ± 0.040 *	1.420 ± 0.130 *

ANOVA: * $p < 0.01$ (significantly different from control)

3. Conclusion

In this study, we have synthesized a series of furo[3,2-*c*]pyran-4-one compounds by multicomponent reaction and characterized by spectroscopic technique as well as microanalysis. Many of chemical compounds are tested by potential safety concerns including cytotoxic, genotoxic, teratogenic, carcinogenic and antiproliferative activities. The genotoxic and cytotoxic effects of 4*H*-furo[3,2–*c*]pyran-4-one derivatives were evaluated. The cytotoxic and genotoxic effects were mainly

observed in cultures treated with the compounds. An increase in the parameters for the evaluation of genotoxicity and cytotoxicity such as SCE, MN, MI and RI was determined when comparing 4*H*-furo[3,2–*c*]pyran-4-one derivatives treatment with respect to the untreated cultures. The cytotoxic effects were concentration-dependent. Taken as a whole, these results suggest that all compounds had a significantly cytotoxic and genotoxic effects at the tested concentrations (1 and 2 mg/mL) for human peripheral lymphocyte cultures.

4. Experimental Section

4.1. Chemistry: Melting points are uncorrected and recorded on Electrothermal 9200 digital melting point apparatus. Leco-932 CHNS-O Elemental Analyser was used for elemental analyses. IR spectra were obtained with Perkin Elmer Spectrum Two Model FT-IR Spectrophotometer using ATR method. The ^{1}H and ^{13}C NMR spectra were measured with Bruker Avance III 400 MHz spectrometer using $CDCl_3$ solvent. The reactions were monitored by TLC (Silica gel, aluminium sheets 60 F254, Merck). Solvents were dried by refluxing with the appropriate drying agents and distilled before use.

4.1.1. General procedure for the synthesis of compound 3: 2,3-Furandione compounds **1** (1 mmol) and dialkyl acetylenedicarboxylates **2** (1 mmol) were solved in benzene (20 mL). To this solution, Ph_3P (1 mmol) in benzene (5 mL) was added dropwise, and the mixture was stirred at r.t. for 10 min. Then, the mixture was refluxed for 15 min. The solvent was removed by rotary evaporator. The obtained residue was treated with 2-propanol to give the corresponding products **3**, which were filtered off, recrystallized from the methyl or ethyl alcohol and dried on P_2O_5.

4.1.1.1. Diethyl 2-ethoxy-4-oxo-6-phenyl-4H-furo[3,2-c]pyran-3,7-dicarboxylate 3a: Yield 0.23 g (53%), yellow crystals, mp: 133 ^{o}C. IR (ATR) : 1766, 1709, 1607 (C=O), 1248 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 6.92 (AA'BB', 4H, Ar-H); 4.57 (q, 2H, *J*=8.0, OCH_2); 4.35 (q, 2H, *J*=8.0, OCH_2); 4,27 (q, 2H, *J*=8.0, OCH_2); 3.82 (s, 3H, OCH_3); 1.51 (t, 3H, *J*=8.0, CH_3); 1.38 (t, 3H, *J*=8.0, CH_3); 1.20 (t, 3H, *J*=8.0, CH_3) ppm. ^{13}C NMR ($CDCl_3$): 162.8, 161.9 (C=O, ester), 155.1 (C=O, lactone); 161.4, 161.3 (2×C), 150.8, 130.4, 123.8, 113.7, 107.3, 101.8, 90.0 (C=C); 69.8, 61.9, 60.9 (OCH_2); 55.4 (OCH_3); 14.9, 14.2, 13.9 (CH_3) ppm. Anal. calcd for $C_{22}H_{22}O_9$ (430.40): C, 61.39; H, 5.15. Found: C, 61.16; H, 4.96.

4.1.1.2. 7-ethyl 3-methyl 2-methoxy-4-oxo-6-phenyl-4H-furo[3,2-c]pyran-3,7-dicarboxylate 3b: Yield 0.18 g (45%), yellow crystals, mp: 162 ^{o}C. IR (ATR) : 1770, 1714, 1605 (C=O), 1259 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 6.95 (AA'BB', 4H, Ar-H); 4.30 (q, 2H, *J*=8.0, OCH_2); 4.26, 3.92, 3.87 (3×s, 9H, OCH_3); 1.22 (t, 3H, *J*=8.0, CH_3) ppm. ^{13}C NMR ($CDCl_3$): 163.2, 162.7 (C=O, ester), 155.0 (C=O, lactone); 161.9, 161.6, 161.5, 150.7, 130.4, 123.8, 113.7, 107.4, 101.7, 88.9 (C=C); 61.9 (OCH_2); 59.3, 55.4, 51.9 (OCH_3); 13.8 (CH_3) ppm. Anal. calcd for $C_{22}H_{22}O_9$ (402.35): C, 59.70; H, 4.51. Found: C, 59.88; H, 4.74.

4.1.1.3. Ethyl 7-benzoyl-2-ethoxy-4-oxo-6-styryl-4H-furo[3,2-c]pyran-3-carboxylate 3c: Yield 0.18 g (39%), yellow crystals, mp: 115 ^{o}C. IR (ATR) : 1766, 1714, 1658 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 6.91 (m, 10H, Ar-H); 7.74 (d, 1H, *J*=16.0, CH=CH-Ph), 6.94 (d, 1H, *J*=16.0, CH=CH-Ph), 4.38 (q, 2H, *J*=8.0, OCH_2); 4.15 (q, 2H, $_{J=}$8.0, OCH_2); 1.41 (t, 3H, $_{J=}$8.0, CH_3); 1.26 (t, 3H, *J*=8.0, CH_3) ppm. ^{13}C NMR ($CDCl_3$): 189.4 (Ph-C=O), 157.6 (C=O, ester), 154.7 (C=O, lactone), 162.8, 161.2, 150.6, 138.1, 138.0, 135.2, 134.1, 129.8, 129.5, 128.9, 128.9, 127.8, 116.4, 108.2, 107.9, 89.9 (C=C), 69.5, 60.9 (OCH_2); 14.6, 14.2 (CH_3) ppm. Anal. calcd for $C_{27}H_{22}O_7$ (458.46): C, 70.73; H, 4.84. Found: C, 70.77; H, 4.82.

4.1.1.4. Methyl 7-benzoyl-2-methoxy-4-oxo-6-styryl-4H-furo[3,2-c]pyran-3-carboxylate 3d: Yield 0.19 g (44%), yellow crystals, mp: 120 ^{o}C. IR (ATR) : 1728, 1698, 1660 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 6.91 (m, 10H, Ar-H); 7.74 (d, 1H, *J*=16.0, CH=CH-Ph), 6.93 (d, 1H, *J*=16.0, CH=CH-Ph), 3.92, 3.84 (2×s, 6H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$): 189.3 (Ph-C=O), 157.7 (C=O, ester), 154.6 (C=O, lactone), 163.1, 161.5, 150.6, 138.1, 138.0, 135.2, 134.1, 129.9, 129.5, 129.0,

128.9, 128.9, 127.9, 116.2, 108.2, 107.8, 89.2 (C=C), 58.9, 52.0 (OCH_3) ppm. Anal. calcd for $C_{25}H_{18}O_7$ (430.40): C, 69.76; H, 4.22. Found: C, 70.09; H, 4.36.

4.2. Crystallography: For the crystal structure determination, the single crystal of the compound **3a** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) and oscillation scans technique with Δ*w*= 5° for each image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software [22]. The structures were solved by direct methods using SHELXS-97 [23] and refined by a full-matrix least-squares procedure using the program SHELXL-97 [23]. H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for compound 3a:* $C_{14}H_{12}N_4O$, crystal system, space group: triclinic, P-1; (no:2); unit cell dimensions: a =8.2328(6), b = 10.8622(4), c = 12.0145(6) Å, α=82.047(2) β = 84.306(2) γ =78.650(2)°; volume: 1040.40(5) $Å^3$; Z = 2; calculated density: 1.37 g/cm3; absorption coefficient: 0.108 mm^{-1}; F(000): 452; θ-range for data collection 2.4-26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 4264/285; goodness-of-fit on F^2: 1.005; final R indices [$I > 2\sigma(I)$]: R_1 = 0.089, wR_2 = 0.144; largest diff. peak and hole: 0.219 and -0.231 e $Å^3$; Crystallographic data were deposited in CSD under CCDC-919120 registration number. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

4.3. The peripheral lymphocyte cultures for the cytogenetic analyses: Blood samples of the six healthy subjects with the permission of Local Ethic Committee were also taken into heparinized tubes. The blood samples were cultured at 37 °C for 72 h in peripheral blood karyotyping medium (Biological Industries, Israel) supplemented with phytohemagglutinin, L-glutamine, fetal calf serum and antibiotic. Then, the compounds were added to obtain five final concentrations (0.05, 0.1, 0.5, 1 and 2 mg/mL). The colchicine (Sigma, Germany) in a final concentration of 0.2 µg/mL was added 60 min prior to the harvesting. The SCE assay was done according to the literature [21]. Chromatid differentiation in lymphocyte cultures was initiated by adding of 5-Bromo-2-deoxyuridine (BrdU) (Sigma, USA) in final concentration of 10 µg/mL. The MN assay was done according to the literature [18]. Cytochalasin-B (Sigma, Germany) in final concentration of 6 µg/mL was added after 44 h of incubation.

50 metaphase, 500 consecutive metaphase, 1000 nuclei and 500 cells were analyzed from each treatment for SCE rate, RI, MI and MN frequency, respectively. The statistical package system SPSS 10.0 was used to analyze the data. The statistical significance of the effects of the compounds on the SCE, RI, MI and MN rates was assessed using repeated measures of the analysis of variance (ANOVA). The differences between groups were determined by the Tukey test with $p < 0.01$ were considered significant.

Acknowledgments

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