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RESEARCH ARTICLE

Synthesis and anti-cancer activity evaluation of new aurone derivatives

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Abstract

In this study, we have synthesized 2-[3- or 4-(2-aryl-2-oxoethoxy)arylidene]benzofuran-3-one derivatives (**D1–D38**) and evaluated their anti-cancer activities. The final compounds were obtained in multistep synthesis reactions using benzofuranon-3-one derivatives (**A1–A4, B**) as starting materials which were gained in various synthetic ways. Aurone derivatives (**C1–C10**) were acquired with the condensation reaction of these starting materials and 3-/4-hydroxybenzaldehyde which were then reacted with α-bromoacetophenones to get final compounds. The anti-cancer activity of the selected compounds was performed by National Cancer Institute (NCI), USA against 60 human tumor cell lines derived from nine neoplastic diseases. Compounds exhibited anti-cancer activity in varying ratios.

Keywords

Anti-cancer activity, aurone, benzofuranone, NCI, synthesis

History

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Introduction

Flavonoids are secondary metabolites of plants which exhibit various biological properties that are beneficial for human health via interacting with some cellular targets in the body. They can be classified into several subclasses and some of these subclasses are flavonols, flavones, isoflavones, flavanones, flavans, aurones and chalcones[1,2]. All classes of flavonoids exhibit variety of biological and pharmacological activities, but among them, the chalcones (Figure 1a) and their ring analogue flavones (Figure 1b) have been considerably explored. Various natural, semi-synthetic and synthetic derivatives of these structures have been investigated and reported with a wide range of biological applications[3,4].

Aurones, (*Z*)-2-benzylidenebenzofuran-3-(2*H*)-ones (Figure 1c), constitute a less studied subclass of flavonoids although they are isosteres of flavones[5,6]. However, they have attracted attention with promising biological potential such as anti-microbial[7], anti-cancer[8], anti-leishmanial[9–11], anti-histaminic[12], anti-inflammatory[13], antioxidant[14], insect anti-feedant[15], herbicidal[16], anti-HIV[17,18], anti-HCV (hepatis C virus)[19,20], anti-malarial[21,22], ChE inhibitory[23,24], MAO inhibitory[25] activities in the specified studies. The observed biological potential is thought to be due to the similarity of adenine of ATP and the flavonoids, consequently inhibition of the activity of ATP-dependent enzymes and proteins, which is essential for the function of enzymes and receptors. In particular, the aurones are estimated to mimic better the adenine because of the benzofuranone structure than the benzopyranone part of the corresponding flavones[26]. Some naturally occurring aurones maritimein, sulfuretin and aureusidin are also studied and among them sulfuretin (Figure 1d) has been known to have anti-inflammatory activity[27,28]. In recent years, flavonoids have been developed as anti-cancer agents and have interested medicinal chemists. In fact, some flavonoids have entered clinical trials such as flavopiridol which was identified as the first cyclindependent kinase inhibitor and entered phase II clinical trials[29,30]. Among them, aurones have been first reported in 2003 with high anti-cancer activity and they were determined to exhibite higher cytotoxic property than corresponding chalcone and flavon derivatives at same concentrations[31]. In subsequent years, many studies were performed about the anti-cancer activity of the aurones[32–39]. Along with the identified molecular mechanisms of flavonoids as carcinogen inactivation, anti-proliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance; α,β-unsaturated carbonyl structure has been evaluated inducing anti-cancer activity with acting as an alkylating agent[40–42].

Considering literature findings and as a continuation of our on-going studies[43], we synthesized new aurone derivatives and evaluated their anti-cancer activity.

Experimental section

Chemistry

All reagents and solvents were obtained from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO) and Merck KGaA (Darmstadt, Germany). Melting points were determined using a Electrothermal 9100 digital melting point apparatus (Essex, UK) and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Petroleum ether and ethyl acetate were used as mobile phase prepared in various ratios for TLC. Spectroscopic data were recorded as follows: IR spectra were IR Shimadzu 8400S FT-IR spectrometer (Tokyo, Japan), ^{1}H-NMR spectra on a Bruker 500 MHz spectrometer (Billerica, MA) in DMSO-d_6 with TMS as internal standard and mass

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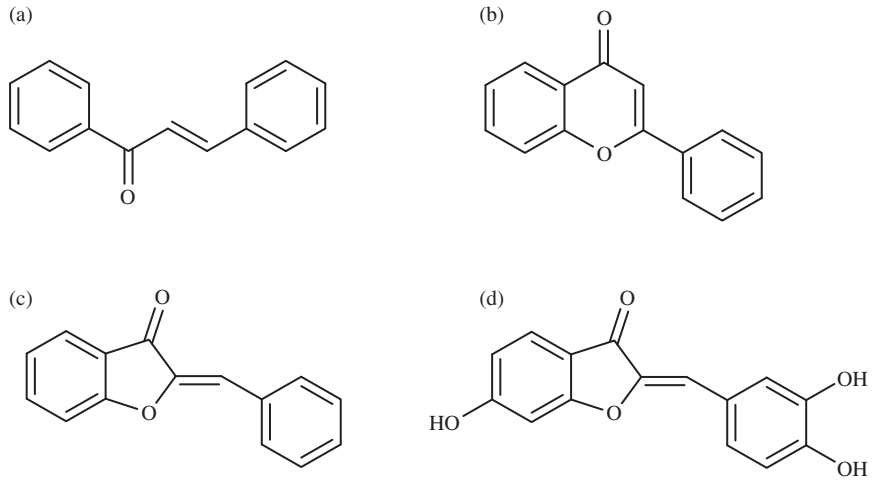


Figure 1. The chemical structures of (a) chalcone, (b) flavone, (c) aurone, (d) sulfuretin.

spectra using a Agilent 110 MSD spectrometer (Santa Clara, CA) instruments.

Benzofuran-3-one derivatives (A1–A4)

Phenole derivative (0.5 mol) (**R**: H, 5-methyl, 5-chloro, 6-methyl, 6-chloro) was first refluxed with acetic anhydride (0.6 mol) in pyridine for 30 min and then the reaction mixture was treated with water after cooling, the precipitated material was filtered or not solidified material was extracted with appropriate solvents. The obtained phenyl acetate derivative (**I**) (0.4 mol) was reacted with $AlCl_3$ (0.48 mol) in a flask placed in an oil bath kept under control at 160–170 °C. After exiting oil bath, viscous mixture was poured into ice water and dried up to get 2′-hydroxyacetophenone derivatives (**II**). Compound **II** (0.3 mol) was stirred with acetic anhydride (0.45 mol) at 50–100 °C for 3–4 h which was acetylated in order to prevent reaction ability of hydroxyl group. The obtained 2′-acetyloxyacetophenone derivatives (**III**) (0.25 mol) compound was brominated with Br_2 (0.3 mol) in ether or acetic acid to get 2′-acetyloxy-2-bromoacetophenone derivatives (**IV**) which was then hydrolized with 10% HCl acid (300 ml) to afford 2′-hydroxy-2-bromoacetophenone (**V**). Finally, compounds **A1, A2, A3** and **A4** (0.2 mol) were achieved from compound **V** and sodium acetate (0.6 mol) at reflux conditions in ethanol by a cyclization reaction. The intermediate products were gained by filtration from reaction medium which were then crystallized from petroleum ether. The obtained compounds and melting points indicated in the literature is given below.

Benzofuran-3-one (**A1**): 101–103 °C[44]. 5-Methlbenzofuran-3-one (**A2**): 83–85 °C[45].

5-Chlorobenzofuran-3-one (**A3**): 87–89 °C[45]. 6-Metilbenzofuran-3-one (**A4**): 83–85 °C[45].

6-Methoxybenzofuran-3-one (B)

Resorcinol was refluxed with dimethylsulfate and sodium hydroxide in acetone to give 1,3-dimethoxybenzene using standard procedures. The obtained compound was then reacted with chloroacetyl chloride and anhydrous aluminium chloride in carbon disulfide by Friedel-Crafts acetylation. The obtained 2′-hydroxy-4-methoxy-2-chloroacetophenone was reacted with sodium acetate in ethanol to give 6-methoxybenzofuran-3-one (**B**) m.p.120–122 °C[46].

2-(3- or 4-Hydroxybenzylidene)benzofuran-3-one derivatives (C1–C10)

Benzofuranone derivative (20 mmol) (**A1–A4, B**) was refluxed with 3-/4-hydroxybenzaldehyde derivatives (22 mmol) in 70 mL *n*-butanol or isobutanol for 1 h using hydrochloric acid as a catalyst (1 ml). The precipate formed upon cooling was filtered and crytallized. The chemical properties of the obtained ten derivatives (**C1–C10**) were given in Table 1.

General procedure of the synthesis 2-[3- or 4-(2-aryl-2-oxoethoxy)arylidene]benzofuran-3-one derivatives (D1–D38)

2-(3- or 4-Hydroxybenzylidene)benzofuran-3-one derivatives (**C1–C10**) (3 mmol) were refluxed with brominated acetophenones (3 mmol) for 6 h in acetone with the presence of potassium carbonate (0.03 mmol). After TLC, the reaction solvent was evaporated and the obtained residue was washed with water and crystallized from ethanol to achieve 2-[3- or 4-(2-Aryl-2-oxoethoxy)arylidene]benzofuran-3-one compounds (**D1–D38**). The chemical properties of the obtained 10 derivatives (**D1–D38**) were given in Table 2.

*2-[3-(2-Phenyl-2-oxoethoxy)benzylidene]benzofuran-3-one **(D1)**.*

IR (KBr) ν_{max} (cm^{-1}): 3098, 3046 (Aromatic C–H), 2975, 2945, 2844 (Aliphatic C–H), 1704, 1669 (C = O), 1602–1477 (C = C), 1288, 1217 (C–O). ^{1}H-NMR δ (ppm): 5.69 (2H, s, OCH_2), 6.93 (1H, s, = CH−), 7.11 (1H, dd, J: 1.48 Hz, J: 8.25 Hz, Ar-H), 7.29–7.33 (2H, m, Ar-H), 7.42–7.45 (2H, m, Ar-H), 7.58–7.66 (4H, m, Ar-H), 7.72–7.83 (2H, m, Ar-H), 8.08 (2H, d, J: 8.10 Hz, Ar-H). MS $[M+1]^+$: *m/z* 357.1.

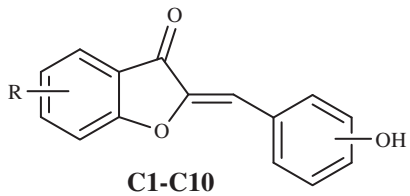
*2-[3-[2-(4-Methylphenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one **(D2)***

IR (KBr) ν_{max} (cm^{-1}): 3074, 3035 (Aromatic C–H), 2975, 2834 (Aliphatic C–H), 1699, 1669 (C = O), 1598–1475 (C = C), 1275, 1234 (C–O). ^{1}H-NMR δ (ppm): 2.45 (3H, s, CH_3), 5.66 (2H, s, OCH_2), 6.95 (1H, s, = CH−), 7.17 (1H, dd, J: 1.34 Hz, J: 8.22 Hz, Ar-H), 7.29–7.36 (2H, m, Ar-H), 7.43 (2H, d, J: 8.35 Hz, Ar-H), 7.47 (1H, s, Ar-H), 7.60–7.68 (2H, m, Ar-H), 7.78–7.83 (2H, m, Ar-H), 8.00 (2H, d, J: 8.12 Hz, Ar-H). MS $[M+1]^+$: *m/z* 371.

*2-[3-[2-(4-Methoxyphenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one **(D3)***

IR (KBr) ν_{max} (cm^{-1}): 3077, 3039 (Aromatic C–H), 2960, 2862 (Aliphatic C–H), 1705, 1681 (C = O), 1647–1464 (C = C), 1271, 1224 (C–O). ^{1}H-NMR δ (ppm): 3.90 (3H, s, OCH_3), 5.63 (2H, s, OCH_2), 6.95 (1H, s, = CH−), 7.10 (1H, dd, J: 1.32 Hz, J: 8.41 Hz, Ar-H), 7.12 (2H, d, J: 7.05 Hz, Ar-H), 7.34 (2H, d, J: 7.30 Hz, Ar-H), 7. 55 (1H, t, J: 8.20 Hz, Ar-H), 7.61–7.63 (2H, m, Ar-H),

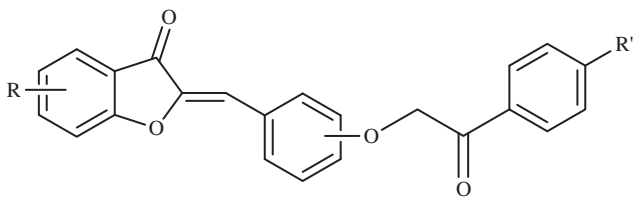
Table 1. Some characteristics of the compounds **(C1–C10)**.



C1-C10

C.	Chemical name	R	–OH	M.P. (°C)
C1	2-(3-Hydroxybenzylidene)benzofuran-3-one	H	3	195–196[51]
C2	2-(4-Hydroxybenzylidene)benzofuran-3-one	H	4	261–262[51]
C3	5-Methyl-2-(3-hydroxybenzylidene)benzofuran-3-one	5-CH_3	3	221–222
C4	5-Methyl-2-(4-hydroxybenzylidene)benzofuran-3-one	5-CH_3	4	263–264[52]
C5	6-Methyl-2-(3-hydroxybenzylidene)benzofuran-3-one	6-CH_3	3	195–197
C6	6-Methyl-2-(4-hydroxybenzylidene)benzofuran-3-one	6-CH_3	4	250–252
C7	6-Methoxy-2-(3-hydroxybenzylidene)benzofuran-3-one	6-OCH_3	3	220–222[53]
C8	6-Methoxy-2-(4-hydroxybenzylidene)benzofuran-3-one	6-OCH_3	4	219–220[53]
C9	5-Chloro-2-(3-hydroxybenzylidene)benzofuran-3-one	5-Cl	3	199–201
C10	5-Chloro-2-(4-hydroxybenzylidene)benzofuran-3-one	5-Cl	4	270–272

Table 2. Some characteristics of the compounds **(D1-D38)**.



D1-D38

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Compound	-R	$^{-}R'$	Position	M.P. (°C)	M.F.
D1	-H	-H	3	150–151	$C_{23}H_{16}O_4$
D2	-H	-CH_3	3	162–162	$C_{24}H_{18}O_4$
D3	-H	-OCH_3	3	135–136	$C_{24}H_{18}O_5$
D4	-H	-Cl	3	134–135	$C_{23}H_{15}ClO_4$
D5	-H	-NO_2	3	195–197	$C_{23}H_{15}NO_6$
D6	-H	-H	4	150–152	$C_{23}H_{16}O_4$
D7	-H	-CH_3	4	186–188	$C_{24}H_{18}O_4$
D8	-H	-OCH_3	4	180–181	$C_{24}H_{18}O_5$
D9	-H	-Cl	4	176–177	$C_{23}H_{15}ClO_4$
D10	-H	-NO_2	4	220–221	$C_{23}H_{15}NO_6$
D11	5-CH_3	-H	3	149–150	$C_{24}H_{18}O_4$
D12	5-CH_3	-OCH_3	3	173–174	$C_{25}H_{20}O_5$
D13	5-CH_3	-Cl	3	159–161	$C_{25}H_{17}ClO_4$
D14	5-CH_3	-H	4	203–204	$C_{24}H_{18}O_4$
D15	5-CH_3	-OCH_3	4	220–221	$C_{25}H_{20}O_5$
D16	5-CH_3	-Cl	4	226–227	$C_{25}H_{17}ClO_4$
D17	6-CH_3	-H	3	139–140	$C_{24}H_{18}O_4$
D18	6-CH_3	-OCH_3	3	130–132	$C_{25}H_{20}O_5$
D19	6-CH_3	-Cl	3	179–181	$C_{25}H_{17}ClO_4$
D20	6-CH_3	-H	4	175–176	$C_{24}H_{18}O_4$
D21	6-CH_3	-OCH_3	4	204–205	$C_{25}H_{20}O_5$
D22	6-CH_3	-Cl	4	209–210	$C_{25}H_{17}ClO_4$
D23	6-OCH_3	-H	3	136–137	$C_{24}H_{18}O_5$
D24	6-OCH_3	-CH_3	3	172–173	$C_{25}H_{20}O_5$
D25	6-OCH_3	-OCH_3	3	192–193	$C_{25}H_{20}O_6$
D26	6-OCH_3	-Cl	3	190–192	$C_{24}H_{17}ClO_5$
D27	6-OCH_3	-NO_2	3	212–214	$C_{24}H_{17}NO_7$
D28	6-OCH_3	-H	4	197–199	$C_{24}H_{18}O_5$
D29	6-OCH_3	-CH_3	4	185–187	$C_{25}H_{20}O_5$
D30	6-OCH_3	-OCH_3	4	178–179	$C_{25}H_{20}O_6$
D31	6-OCH_3	-Cl	4	202–203	$C_{24}H_{17}ClO_5$
D32	6-OCH_3	-NO_2	4	226–227	$C_{24}H_{17}NO_7$
D33	5-Cl	-H	3	158–160	$C_{23}H_{15}ClO_4$
D34	5-Cl	-OCH_3	3	205–207	$C_{24}H_{17}ClO_5$
D35	5-Cl	-Cl	3	199–200	$C_{23}H_{14}Cl_2O_4$
D36	5-Cl	-H	4	214–216	$C_{23}H_{15}ClO_4$
D37	5-Cl	-OCH_3	4	196–198	$C_{24}H_{17}ClO_5$
D38	5-Cl	-Cl	4	202–204	$C_{23}H_{14}Cl_2O_4$

7.77–7.83 (2H, m, Ar-H), 8.07 (2H, d, J: 7.0 Hz, Ar-H). MS $[M+1]^+$: *m/z* 387.

2-[3-[2-(4-Chlorophenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one ***(D4)***

IR (KBr) ν_{max} (cm^{-1}): 3088, 3036 (Ar-H ve = CH−), 2965, 2844 (Alifatik–H), 1706, 1665 (C = O), 1602–1477 (C = C), 1288,1217 (C–O). ^{1}H-NMR δ (ppm): 5.79 (2H, s, OCH_2), 6.94 (1H, s, = CH−), 7.14 (1H, dd, J: 1.34 Hz, J: 8.22 Hz, Ar-H), 7.31–7.36 (2H, m, Ar-H), 7.58–7.63 (1H, m, Ar-H), 7.77–7.83 (2H, m, Ar-H), 7.72 (2H, d, J: 8.59 Hz, Ar-H), 7.83 (2H, d, J: 7.46 Hz, Ar-H), 8.10 (2H, d, J: 8.59 Hz, Ar-H). MS $[M+1]^+$: *m/z* 390.5.

2-[3-[2-(4-Nitrophenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one ***(D5)***

IR (KBr) ν_{max} (cm^{-1}): 3078, 3056 (Aromatic C–H), 2970, 2921, 2854 (Aliphatic C–H), 1697, 1649 (C = O), 1601–1478 (C = C, N = O), 1288,1217 (C–O). ^{1}H-NMR δ (ppm): 5.75 (2H, s, OCH_2), 6.94 (1H, s, = CH), 7.14 (1H, dd, J: 1.43 Hz, J: 8.26 Hz, Ar-H), 7. 34 (1H, t, J: 7.50 Hz, Ar-H), 7.44–7.48 (2H, m, Ar-H), 7.63–7.67 (2H, m, Ar-H), 7.81 (2H, d, J: 7.52 Hz, Ar-H), 8.29 (2H, d, J: 8.73 Hz, Ar-H), 8.42 (2H, d, J: 8.68 Hz, Ar-H). MS $[M+1]^+$: *m/z* 402.

2-[4-(2-Phenyl-2-oxoethoxy)benzylidene]benzofuran-3-one ***(D6)***

IR (KBr) ν_{max} (cm^{-1}): 3049, 3035 (Aromatic C–H), 2922, 2895 (Aliphatic C–H), 1709, 1693 (C = O), 1650–1479 (C = C), 1261,1230 (C–O). ^{1}H-NMR δ (ppm): 5.64 (2H, s, OCH_2), 6.99 (1H, s, = CH−), 7.21 (2H, d, J: 8.70 Hz, Ar-H), 7. 34 (1H, t, J: 7.50 Hz, Ar-H), 7.58 (2H, d, J: 8.84 Hz, Ar-H), 7.63 (2H, d, J: 7.65 Hz, Ar-H), 7.62–7.84 (2H, m, Ar-H), 8.0 (2H, d, J: 8.69 Hz, Ar-H), 8.07 (2H, d, J: 7.66 Hz, Ar-H). MS $[M+1]^+$: *m/z* 357.2.

2-[4-[2-(4-Methylphenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one ***(D7)***

IR (KBr) ν_{max} (cm^{-1}): 3084, 3025 (Aromatic C–H), 2972, 2832 (Aliphatic C–H), 1712, 1669 (C = O), 1622–1475 (C = C), 1275,1234 (C–O). ^{1}H-NMR δ (ppm): 2.43 (3H, s, Ar–CH_3), 5.68 (2H, s, O–CH_2), 6.98 (1H, s, = CH−), 7.14 (2H, d, J: 8.60 Hz, Ar-H), 7. 34 (1H, t, 7.43 Hz, Ar-H), 7.42 (2H, d, J: 7.93 Hz, Ar-H), 7.53 (1H, d, J: 8.61 Hz, Ar-H), 7.81–7.84 (2H, m, Ar-H), 7.97 (2H, d, J: 8.04 Hz, Ar-H), 8.0 (2H, d, J: 8.72 Hz, Ar-H). MS $[M+1]^+$: *m/z* 371.

2-[4-[2-(4-Methoxyphenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one ***(D8)***

IR (KBr) ν_{max} (cm^{-1}): 3070, 3032 (Aromatic C–H), 2965, 2844 (Aliphatic C–H), 1694, 1659 (C = O), 1598–1475 (C = C), 1275,1224 (C–O). ^{1}H-NMR δ (ppm): 3.89 (3H, s, OCH_3), 5.65 (2H, s, OCH_2), 6.98 (1H, s, = CH−), 7.12 (2H, d, J: 7.77 Hz, Ar-H), 7.14 (2H, d, J: 7.78 Hz, Ar-H), 7.14 (1H, t, 7.40 Hz, Ar-H), 7.58 (1H, d, J: 8.58 Hz, Ar-H), 7.80–7.84 (2H, m, Ar-H), 7.77 (2H, d, J: 8.82 Hz, Ar-H), 8.0 (2H, d, J: 8.83 Hz, Ar-H). MS $[M+1]^+$: *m/z* 387.

2-[4-[2-(4-Chlorophenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one ***(D9)***

IR (KBr) ν_{max} (cm^{-1}): 3085, 3020 (Aromatic C–H), 2975, 2832 (Aliphatic C–H), 1710, 1670 (C = O), 1622–1475 (C = C), 1271,1234 (C–O). ^{1}H-NMR δ (ppm): 5.66 (2H, s, OCH_2), 6.96 (1H, s, = CH−), 7.12 (2H, d, J: 7.90 Hz, Ar-H), 7. 14 (1H, t, 7.40 Hz, Ar-H), 7.58–7.62 (1H, m, Ar-H), 7.66 (2H, d, J: 8.59 Hz, Ar-H), 7.80–7.84 (2H, m, Ar-H), 7.94 (2H, d, J: 7.98 Hz, Ar-H), 8.10 (2H, d, J: 8.59 Hz, Ar-H). MS $[M+1]^+$: *m/z* 390.5.

2-[4-[2-(4-Nitrophenyl)-2-oxoethoxy]benzylidene] benzofuran-3-one ***(D10)***

IR (KBr) ν_{max} (cm^{-1}): 3074, 3035 (Aromatic C–H), 2975, 2834 (Aliphatic C–H), 1699, 1669 (C = O), 1598–1475 (C = C, N = O), 1275,1234 (C–O). ^{1}H-NMR δ (ppm): 5.76 (2H, s, OCH_2), 6.94 (1H, s, = CH–), 7.12 (2H, d, J: 7.90 Hz, Ar-H), 7. 32–7.34 (1H, m, Ar-H), 7.44–7.48 (2H, m, Ar-H), 7.63–7.67 (1H, m, Ar-H), 7.80–7.84 (2H, m, Ar-H), 8.31 (2H, d, J: 8.82 Hz, Ar-H), 8.43 (2H, d, J: 8.84 Hz, Ar-H). MS $[M+1]^+$: *m/z* 402.

2-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-5-methylbenzofuran-3-one ***(D11)***

IR (KBr) ν_{max} (cm^{-1}): 3088, 3056 (Aromatic C–H), 2975, 2921, 2854 (Aliphatic C–H), 1702, 1664 (C = O), 1601–1477 (C = C), 1288,1217 (C–O). ^{1}H-NMR δ (ppm): 2.35 (3H, s, CH_3), 5.68 (2H, s, OCH_2), 6.87 (1H, s, = CH−), 7.09 (1H, dd, J: 2.50 Hz, J: 8.23 Hz, Ar-H), 7.14 (1H, d, J: 8.91 Hz, Ar-H), 7.42 (2H, t, J: 8.0 Hz, Ar-H), 7.55–7.63 (5H, m, Ar-H), 7.74 (1H, t, J: 7.4 Hz, Ar-H), 8.08 (2H, d, J: 7.24 Hz, Ar-H). MS $[M+1]^+$: *m/z* 371.

2-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-5-methyl-benzofuran-3-one ***(D12)***

IR (KBr) ν_{max} (cm^{-1}): 3053, 3012 (Aromatic C–H), 2918, 2841 (Aliphatic C–H), 1685, 1655 (C = O), 1601–1487 (C = C), 1275,1238 (C–O). ^{1}H-NMR δ (ppm): 2.36 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 5.58 (2H, s, OCH_2), 6.86 (1H, s, = CH−), 7.08 (1H, m, Ar-H), 7.11 (2H, d, J: 8.91 Hz, Ar-H), 7.16 (2H, d, J: 8.0 Hz, Ar-H), 7.41 (1H, t, J: 8.10 Hz, Ar-H), 7.54–7.56 (3H, m, Ar-H), 8.08 (2H, d, J: 7.24 Hz, Ar-H). MS $[M+1]^+$: *m/z* 401.

2-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-5-methylbenzofuran-3-one ***(D13)***

IR (KBr) ν_{max} (cm^{-1}): 3077, 3029 (Aromatic C–H), 2987, 2860 (Aliphatic C–H), 1702, 1681 (C = O), 1621–1476 (C = C), 1274, 1223 (C–O). ^{1}H-NMR δ (ppm): 5.66 (2H, s, OCH_2), 6.86 (1H, s, = CH−), 7.10 (1H, dd, J: 2.30 Hz, J: 8.12 Hz, Ar-H), 7.22 (1H, d, J: 8.86 Hz, Ar-H), 7.42 (1H, t, J: 7.40 Hz, Ar-H), 7.54–7.62 (4H, m, Ar-H), 7.68 (2H, d, J: 8.54 Hz, Ar-H), 8.08 (2H, d, J: 8.54 Hz, Ar-H). MS $[M+1]^+$: *m/z* 404.5.

2-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-5-methylbenzofuran-3-one ***(D14)***

IR (KBr) ν_{max} (cm^{-1}): 3079, 3057 (Aromatic C–H), 2981, 2932, 2867 (Aliphatic C–H), 1703, 1666 (C = O), 1601–1477 (C = C), 1288, 1217 (C–O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, CH_3), 5.70 (2H, s, OCH_2), 6.89 (1H, s, = CH−), 7.04 (2H, d, J: 8.15 Hz, Ar-H), 7.44–7.46 (3H, m, Ar-H), 7.48 (1H, s, Ar-H), 7.57–7.65 (2H, m, Ar-H), 7.72 (2H, d, J: 8.20 Hz, Ar-H), 8.05 (2H, d, J: 7.40 Hz, Ar-H). MS $[M+1]^+$: *m/z* 371.

2-[4-(2 -(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-5-methylbenzofuran-3-one ***(D15)***

IR (KBr) ν_{max} (cm^{-1}): 3058, 3010 (Aromatic C–H), 2915, 2853 (Aliphatic C–H), 1687, 1656 (C = O), 1610–1482 (C = C), 1258,1224 (C–O). ^{1}H-NMR δ (ppm): 2.35 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 5.59 (2H, s, OCH_2), 6.87 (1H, s, = CH−), 7.10–7.16 (3H, m, Ar-H), 7.24 (2H, d, J: 8.50 Hz, Ar-H), 7.48 (2H, d, J: 8.0 Hz, Ar-H), 7.58–7.62 (2H, m, Ar-H), 8.09 (2H, d, J: 7.32 Hz, Ar-H). MS $[M+1]^+$: *m/z* 401.

2-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-5-methylbenzofuran-3-one ***(D16)***

IR (KBr) ν_{max} (cm^{-1}): 3063, 3025 (Aromatic C–H), 2981, 2864 (Aliphatic C–H), 1704, 1685 (C = O), 1642–1481 (C = C), 1256, 1258 (C–O). ^{1}H-NMR δ (ppm): 5.68 (2H, s, OCH_2), 6.88 (1H, s, = CH–), 7.11–7.17 (3H, m, Ar-H), 7.34 (2H, d, J: 8.64 Hz, Ar-H), 7.48 (2H, d, J: 7.54 Hz, Ar-H), 7.63–7.67 (2H, m, Ar-H), 8.08 (2H, d, J: 8.32 Hz, Ar-H). MS $[M+1]^+$: *m/z* 404.5.

2-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-6-methylbenzofuran-3-one ***(D17)***

IR (KBr) ν_{max} (cm^{-1}): 3052, 3037 (Aromatic C–H), 2944, 2876 (Aliphatic C–H), 1696, 1667 (C = O), 1587–1469 (C = C), 1288, 1224 (C–O). ^{1}H-NMR δ (ppm): 2.44 (3H, s, CH_3), 5.67 (2H, s, OCH_2), 6.88 (1H, s, = CH–), 7.12–7.15 (3H, m, Ar-H), 7.34 (2H, d, J: 7.85 Hz, Ar-H), 7.68 (2H, d, J: 7.88 Hz, Ar-H), 7.93–7.95 (3H, m, Ar-H), 8.08 (2H, d, J: 8.74 Hz, Ar-H). MS $[M+1]^+$: *m/z* 371.

2-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-methylbenzofuran-3-one ***(D18)***

IR (KBr) ν_{max} (cm^{-1}): 3084, 3051 (Aromatic C–H), 2975, 2827 (Aliphatic C–H), 1694, 1661 (C = O), 1618–1478 (C = C), 1292,1219 (C–O). ^{1}H-NMR δ (ppm): 2.44 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 5.65 (2H, s, OCH_2), 6.89 (1H, s, = CH–), 6.91 (1H, d, J: 8.42 Hz, Ar-H), 7.13–7.17 (3H, m, Ar-H), 7.35 (1H, s, Ar-H), 7.62–7.65 (2H, m, Ar-H), 7.75 (1H, t, J: 7.48 Hz, Ar-H), 7.94 (1H, d, J: 8.84 Hz, Ar-H), 8.07 (2H, d, J: 7.29 Hz, Ar-H). MS $[M+1]^+$: *m/z* 401.

2-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-methylbenzofuran-3-one ***(D19)***

IR (KBr) ν_{max} (cm^{-1}): 3077, 3029 (Aromatic C–H), 2987, 2860 (Aliphatic C–H), 1705, 1681 (C = O), 1621–1476 (C = C), 1271, 1223 (C–O). ^{1}H-NMR δ (ppm): 2.46 (3H, s, CH_3), 5.68 (2H, s, OCH_2), 6.89 (1H, s, = CH–), 7.12–7.14 (3H, d, J: 8.85 Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.65–7.80 (3H, m, Ar-H), 7.94 (2H, d, J: 8.74 Hz, Ar-H), 8.05 (2H, d, J: 8.47 Hz, Ar-H). MS $[M+1]^+$: *m/z* 404.5.

2-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-6-methylbenzofuran-3-one ***(D20)***

IR (KBr) ν_{max} (cm^{-1}): 3066, 3032 (Aromatic C–H), 2975, 2844 (Aliphatic C–H), 1698, 1659 (C = O), 1598–1475 (C = C), 1285, 1234 (C–O). ^{1}H-NMR δ (ppm): 2.43 (3H, s, CH_3), 5.69 (2H, s, OCH_2), 6.86 (1H, s, = CH–), 7.09–7.13 (5H, m, Ar-H), 7.31 (1H, s, Ar-H), 7.65 (2H, d, J: 7.81 Hz, Ar-H), 7.93 (2H, d, J: 7.93 Hz, Ar-H), 8.02 (2H, d, J: 8.88 Hz, Ar-H). MS $[M+1]^+$: *m/z* 371.

2-[4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-methylbenzofuran-3-one ***(D21)***

IR (KBr) ν_{max} (cm^{-1}): 3098, 3045 (Aromatic C–H), 2976, 2834 (Aliphatic C–H), 1698, 1659 (C = O), 1611–1477 (C = C), 1288,1217 (C–O). ^{1}H-NMR δ (ppm): 2.45 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 5.64 (2H, s, OCH_2), 6.88 (1H, s, = CH–), 7.03 (1H, d, J: 8.02 Hz, Ar-H), 7.12 (2H, d, J: 8.85 Hz, Ar-H), 7.31 (1H, s, Ar-H), 7.57–7.60 (2H, m, Ar-H), 7.71 (1H, t, J: 7.45 Hz, Ar-H), 7.92 (2H, d, J: 8.84 Hz, Ar-H), 8.08 (2H, d, J: 7.28 Hz, Ar-H). MS $[M+1]^+$: *m/z* 401.

2-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-methylbenzofuran-3-one ***(D22)***

IR (KBr) ν_{max} (cm^{-1}): 3077, 3029 (Aromatic C–H), 2987, 2860 (Aliphatic C–H), 1705, 1681 (C = O), 1621–1476 (C = C), 1271, 1223 (C–O). ^{1}H-NMR δ (ppm): 2.46 (3H, s, Ar–CH_3), 5.68 (2H, s, OCH_2), 6.89 (1H, s, = CH–), 7.12–7.14 (3H, d, J: 8.85 Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.65–7.80 (3H, m, Ar-H), 7.94 (2H, d, J: 8.74 Hz, Ar-H), 8.05 (2H, d, J: 8.47 Hz, Ar-H). MS $[M+1]^+$: *m/z* 404.5.

2-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D23)***

(KBr) ν_{max} (cm^{-1}): 3074, 3056 (Aromatic C–H), 2968, 2845 (Aliphatic C–H), 1696, 1661 (C = O), 1605–1475 (C = C), 1269,1224 (C–O). ^{1}H-NMR δ (ppm): 3.90 (3H, s, OCH_3), 5.66 (2H, s, OCH_2), 6.80 (1H, s, = CH–), 6.85–6.89 (2H, m, Ar-H), 7.07–7.15 (2H, m, Ar-H), 7.35 (1H, t, J: 7.74 Hz, Ar-H), 7.42 (2H, d, J: 8.05 Hz, Ar-H), 7.58–7.64 (2H, m, Ar-H), 7.67–7.71 (1H, m, Ar-H), 8.05 (2H, d, J: 8.04 Hz, Ar-H). MS $[M+1]^+$: *m/z* 387.

2-[3-(2-(4-Methylphenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D24)***

(KBr) ν_{max} (cm^{-1}): 3085, 3034 (Aromatic C–H), 2967, 2879 (Aliphatic C–H), 1701, 1669 (C = O), 1597–1473 (C = C), 1267, 1234 (C–O). ^{1}H-NMR δ (ppm): 2.47 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 5.77 (2H, s, OCH_2), 6.84 (1H, s, = CH–), 6.88 (1H, d, J:7.85 Hz, Ar-H), 6.95–7.02 (2H, m, Ar-H), 7.21 (2H, d, J: 7.86 Hz, Ar-H), 7.48–7.52 (2H, m, Ar-H), 7.91 (2H, d, J: 8.14 Hz, Ar-H), 8.15 (2H, d, J: 8.69 Hz, Ar-H). MS $[M+1]^+$: *m/z* 401.

2-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D25)***

(KBr) ν_{max} (cm^{-1}): 3095, 3030 (Aromatic C–H), 2961, 2857 (Aliphatic C–H), 1702, 1668 (C = O), 1585–1484 (C = C), 1274,1232 (C–O). ^{1}H-NMR δ (ppm): 3.89 (3H, s, OCH_3), 5.76 (2H, s, OCH_2), 6.83 (1H, s, = CH–), 6.86 (1H, dd, J: 2.02 ve 1.95 Hz, J: 8.55 Hz, Ar-H), 6.77–6.98 (1H, m, Ar-H), 7.15–7.21 (3H, m, Ar-H), 7.45 (1H, t, J: 8.05 ve 8.24 Hz, Ar-H), 7.59–7.61 (2H, m, Ar-H), 7.88–8.01 (2H, m, Ar-H), 8.22 (2H, d, J: 8.68 Hz, Ar-H). MS $[M+1]^+$: m/z 417.1.

2-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D26)***

(KBr) ν_{max} (cm^{-1}): 3074, 3038 (Aromatic C–H), 2954, 2887 (Aliphatic C–H), 1702, 1667 (C = O), 1585–1454 (C = C), 1268, 1252 (C–O). ^{1}H–NMR δ (ppm): 3.91 (3H, s, OCH_3), 5.78 (2H, s, OCH_2), 6.85 (1H, s, = CH–), 6.94–7.05 (2H, m, Ar-H), 7.12–7.18 (3H, m, Ar-H), 7.45 (2H, d, J: 7.85 Hz, Ar-H), 7.88 (2H, d, J: 8.22 Hz, Ar-H), 8.13 (2H, d, J: 8.53 Hz, Ar-H). MS $[M+1]^+$: *m/z* 420.6.

2-[3-(2-(4-Nitrophenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D27)***

(KBr) ν_{max} (cm^{-1}): 3088, 3055 (Aromatic C–H), 2972, 2831 (Aliphatic C–H), 1697, 1659 (C = O), 1612–1477 (C = C, N = O), 1288,1217 (C–O). ^{1}H-NMR δ (ppm): 3.89 (3H, s, OCH_3), 5.64 (2H, s, OCH_2), 6.81 (1H, s, = CH–), 6.85–6.89 (2H, d, J: 8.85 Hz, Ar-H), 7.07 (1H, dd, J: 1.37 Hz, J: 8.23 Hz, Ar-H), 7.32 (1H, t, J: 7.67, Hz, Ar-H), 7.38–7.43 (2H, m, Ar-H), 7.52–7.53 (2H, m, Ar-H), 7.67–7.71 (1H, m, Ar-H), 7.98 (2H, d, J: 8.03 Hz, Ar-H). MS $[M+1]^+$: *m/z* 432.1.

2-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D28)***

(KBr) ν_{max} (cm^{-1}): 3048, 3063 (Aromatic C–H), 2948, 2838 (Aliphatic C–H), 1697, 1663 (C = O), 1606–1454 (C = C), 1252,1228 (C–O). ^{1}H-NMR δ (ppm): 3.91 (3H, s, OCH_3), 5.67 (2H, s, OCH_2), 6.81 (1H, s, = CH−), 6.94–7.02 (3H, m, Ar-H), 7.35 (2H, d, J: 7.78 Hz, Ar-H), 7.51 (2H, d, J: 8.05 Hz, Ar-H), 7.62–7.67 (2H, m, Ar-H), 7.67 (1H, s, Ar-H), 8.08 (2H, d, J: 8.06 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 387.

2-[4-(2 -(4-Methylphenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D29)***

(KBr) ν_{max} (cm^{-1}): 3072, 3045 (Aromatic C–H), 2977, 2885 (Aliphatic C–H), 1702, 1668 (C = O), 1585–1456 (C = C), 1255, 1241 (C–O). ^{1}H-NMR δ (ppm): 2.48 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 5.76 (2H, s, OCH_2), 6.85 (1H, s, = CH−), 6.98–7.05 (2H, m, Ar-H), 7.24 (2H, d, J: 7.86 Hz, Ar-H), 7.49–7.53 (3H, m, Ar-H), 7.94 (2H, d, J: 8.24 Hz, Ar-H), 8.16 (2H, d, J: 8.28 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 401.

2-[4-(2 -(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D30)***

(KBr) ν_{max} (cm^{-1}): 3098, 3032 (Aromatic C–H), 2965, 2844 (Aliphatic C–H), 1704, 1665 (C = O), 1598–1475 (C = C), 1285,1227 (C–O). ^{1}H-NMR δ (ppm): 3.91 (3H, s, OCH_3), 5.75 (2H, s, OCH_2), 6.82 (1H, s, = CH−), 6.86 (1H, dd, J: 2.02, J: 8.55 Hz, Ar-H), 6.95–6.97 (1H, m, Ar-H), 7.11–7.14 (1H, m, Ar-H), 7.43 (1H, t, J: 8.05 ve 8.24 Hz, Ar-H), 7.59–7.61 (2H, m, Ar-H), 7.69 (1H, d, J: 8.56, Hz, Ar-H), 8.30 (2H, d, J: 8.73 Hz, Ar-H), 8.41 (2H, d, J: 8.68 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 417.1.

2-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D31)***

(KBr) ν_{max} (cm^{-1}): 3041, 3027 (Aromatic C–H), 2932, 2873 (Aliphatic C–H), 1701, 1668 (C = O), 1580–1451 (C = C), 1253, 1242 (C–O). ^{1}H-NMR δ (ppm): 3.90 (3H, s, OCH_3), 5.77 (2H, s, OCH_2), 6.86 (1H, s, = CH−), 6.94 (1H, d, J:7.85 Hz, Ar-H), 7.14 (1H, d, J:7.89 Hz, Ar-H), 7.19–7.24 (2H, m, Ar-H), 7.45 (2H, d, J: 7.85 Hz, Ar-H), 7.54 (1H, d, J: 8.02 Hz, Ar-H), 7.88 (2H, d, J: 8.22 Hz, Ar-H), 8.13 (2H, d, J: 8.53 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 420.6.

2-[4-(2-(4-Nitrophenyl)-2-oxoethoxy)benzylidene]-6-methoxybenzofuran-3-one ***(D32)***

(KBr) ν_{max} (cm^{-1}): 3084, 3057 (Aromatic C–H), 2952, 2868 (Aliphatic C–H), 1698, 1658 (C = O), 1603–1474 (C = C, N = O), 1275,1226 (C–O). ^{1}H-NMR δ (ppm): 3.89 (3H, s, OCH_3), 5.64 (2H, s, OCH_2), 6.81 (1H, s, = CH−), 7.10–7.16 (2H, m, Ar-H), 7.38 (2H, d, J: 8.23 Hz, Ar-H), 7.77 (2H, d, J: 7.68, Ar-H), 7.85–7.89 (2H, m, Ar-H), 7.94–7.96 (1H, m, Ar-H), 8.31 (1H, d, J: 8.03 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 432.1.

2-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-5-chlorobenzofuran-3-one ***(D33)***

IR (KBr) ν_{max} (cm^{-1}): 3071, 3063 (Aromatic C–H), 2982, 2943, 2832 (Aliphatic C–H), 1701, 1665 (C = O), 1605–1458 (C = C), 1254,1285 (C–O). ^{1}H-NMR δ (ppm): 5.67 (2H, s, OCH_2), 6.88 (1H, s, = CH−), 7.14 (1H, d, J: 8.18 Hz, Ar-H), 7.29 (1H, d, J: 8.75 Hz, Ar-H), 7.46 (2H, t, J: 8.10 Hz, Ar-H), 7.58–7.65 (3H, m, Ar-H), 7.74 (1H, t, J: 7.40 Hz, Ar-H), 7.89 (2H, d, J: 8.15 Hz, Ar-H), 8.12 (2H, d, J: 7.59 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 390.5.

2-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-5-chlorobenzofuran-3-one ***(D34)***

IR (KBr) ν_{max} (cm^{-1}): 3072, 3035 (Aromatic C–H), 2953, 2839 (Aliphatic C–H), 1686, 1657 (C = O), 1623–1475 (C = C), 1284,1242 (C–O). ^{1}H-NMR δ (ppm): 3.93 (3H, s, OCH_3), 5.62 (2H, s, OCH_2), 6.90 (1H, s, = CH−), 7.14 (2H, d, J: 8.42 Hz, Ar-H), 7.16 (2H, d, J: 8.51 Hz, Ar-H), 7.35 (2H, d, J: 8.19 Hz, Ar-H), 7.45 (1H, t, J: 8.24 Hz, Ar-H), 7.58–7.62 (2H, m, Ar-H), 8.14 (2H, d, J: 7.18 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 420.5.

2-[3-(2 -(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-5-chlorobenzofuran-3-one ***(D35)***

IR (KBr) ν_{max} (cm^{-1}): 3039, 3028 (Aromatic C–H), 2976, 2884 (Aliphatic C–H), 1701, 1683 (C = O), 1634–1482 (C = C), 1252, 1225 (C–O). ^{1}H-NMR δ (ppm): 5.67 (2H, s, OCH_2), 6.87 (1H, s, = CH−), 7.25 (1H, d, J: 8.14 Hz, Ar-H), 7.35 (2H, d, J: 8.74 Hz, Ar-H), 7.63 (1H, t, J: 7.46 Hz, Ar-H), 7.64–7.68 (3H, m, Ar-H), 7.76 (2H, d, J: 8.23 Hz, Ar-H), 8.24 (2H, d, J: 8.56 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 425.

2-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-5-chlorobenzofuran-3-one ***(D36)***

IR (KBr) ν_{max} (cm^{-1}): 3055, 3027 (Aromatic C–H), 2977, 2951, 2846 (Aliphatic C–H), 1702, 1667 (C = O), 1606–1463 (C = C), 1265, 1294 (C–O). ^{1}H-NMR δ (ppm): 5.68 (2H, s, OCH_2), 6.89 (1H, s, = CH−), 7.15 (1H, d, J: 8.20 Hz, Ar-H), 7.33 (1H, d, J: 8.84 Hz, Ar-H), 7.52 (2H, t, J: 8.24 Hz, Ar-H), 7.67–7.76 (3H, m, Ar-H), 7.86 (1H, t, J: 7.85 Hz, Ar-H), 7.94 (2H, d, J: 8.21 Hz, Ar-H), 8.11 (2H, d, J: 7.63 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 390.5.

2-[4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-5-chlorobenzofuran-3-one ***(D37)***

IR (KBr) ν_{max} (cm^{-1}): 3072, 3035 (Aromatic C–H), 2953, 2839 (Aliphatic C–H), 1686, 1657 (C = O), 1623–1475 (C = C), 1284,1242 (C–O). ^{1}H–NMR δ (ppm): 3.93 (3H, s, OCH_3), 5.62 (2H, s, OCH_2), 6.90 (1H, s, = CH–), 7.14 (2H, d, J: 8.42 Hz, Ar-H), 7.16 (2H, d, J: 8.51 Hz, Ar-H), 7.35 (2H, d, J: 8.19 Hz, Ar-H), 7.45 (1H, t, J: 8.24 Hz, Ar-H), 7.58–7.62 (2H, m, Ar-H), 8.14 (2H, d, J: 7.18 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 420.5.

2-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-5-chlorobenzofuran-3-one ***(D38)***

IR (KBr) ν_{max} (cm^{-1}): 3056, 3038 (Aromatic C–H), 2984, 2897 (Aliphatic C–H), 1702, 1685 (C = O), 1635–1474 (C = C), 1236, 1227 (C–O). ^{1}H-NMR δ (ppm): 5.68 (2H, s, OCH_2), 6.88 (1H, s, = CH−), 7.29 (2H, d, J: 8.20 Hz, Ar-H), 7.55–7.64 (3H, m, Ar-H), 7.75 (2H, d, J: 8.12 Hz, Ar-H), 7.86 (2H, d, J: 8.12 Hz, Ar-H), 8.18 (2H, d, J: 8.27 Hz, Ar-H). MS $[M + 1]^+$: *m/z* 425.

Anti-cancer activity

The cytotoxic and/or growth inhibitory effects of the compounds were evaluated *in vitro* against approximately sixty human tumor cell lines derived from nine neoplastic diseases namely; leukemia (L, 4 or 6 cell lines), non-small cell lung cancer (NSCLC, 9 cell lines), colon cancer (CC, 7 cell lines), central nervous system cancer (CNSC, 6 cell lines), melanoma (M, 8 or 9 cell lines), ovarian cancer (OC, 6 or 7 cell lines), renal cancer (RC, 8 cell lines), prostate cancer (PC, 2 cell lines), breast cancer (BC, 6 or 8 cell lines). The evaluation of anti-cancer activity was performed at the National Cancer Institute (NCI) of Bethesda, USA, following the *in vitro* screening program at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. The percentage growth was evaluated spectrophotometrically versus controls not

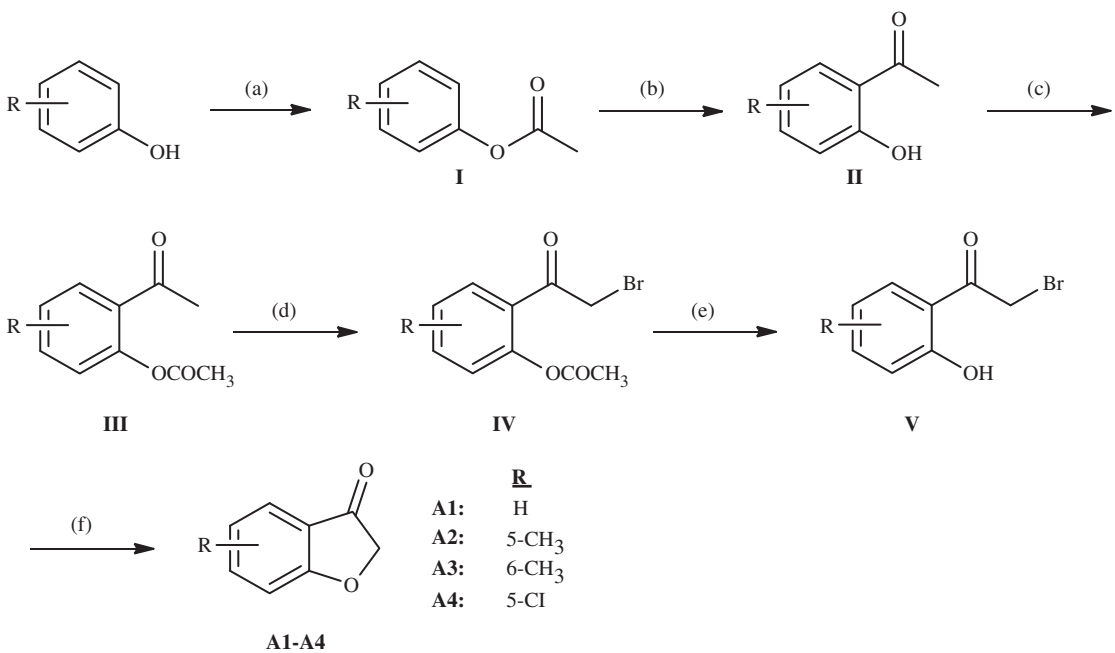
treated with test agents. A 48 h continuous drug exposure protocol was followed and a sulforhodamine B (SRB) protein assay was used to estimate cell viability of growth. Three dose response parameters (GI_{50}, TGI and LC_{50}) were calculated for each experimental agent[47,48].

Results and discussion

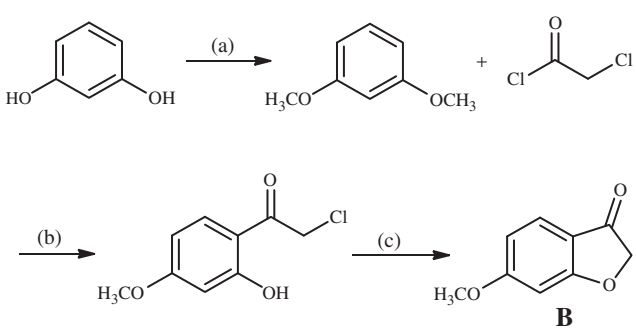
Chemistry

New aurone derivatives (**D1–D38**) were synthesized by an extensive synthetic procedure. Synthetic way for the compounds was outlined inSchemes 1,2 and3. Aurone synthesis is usually carried out with condensation reaction of benzofuranones and benzaldehydes and cyclization of various 2′-hydroxy aryl compounds[49]. In this study, we also used condensation reaction and obtained 10 different aurone derivatives (**C1–C10**) from five benzofuranone derivatives (**A1–A4, B**) and final 38 compounds were gathered from these aurones derivatives. Benzofuranone derivatives (**A1–A4, B**) were synthesized in two different ways. Compounds **A1–A4** were acquired at the end of an extended and laborious synthetic procedure (Scheme 1). Initially, 2′-hydroxyacetophenone derivative was obtained and used as starting material. For this, phenole derivative was primarily acetylated with acetic anhydride or acetyl chloride in pyridine, then the obtained acetyloxyphenol (**I**) derivative was heated at 160–170 °C in Fries conditions to get 2′-hydroxyacetophenone (**II**). This compound (**II**) was acetylated to protect phenolic hydroxyl group. Bromination of the obtained acetyloxyacetophenone (**III**) compound in acetic acid gave 2′-acetyloxy-2-bromoacetophenone (**IV**), which was then hydrolized with 10% HCl acid to afford 2′-hydroxy-2-bromoacetophenone (**V**). Eventually 5/6-substituted benzofuranone derivatives (**A1–A4**) were reached with the reaction of compound **V** and sodium acetate in ethanol via Williamson ether synthesis reaction.

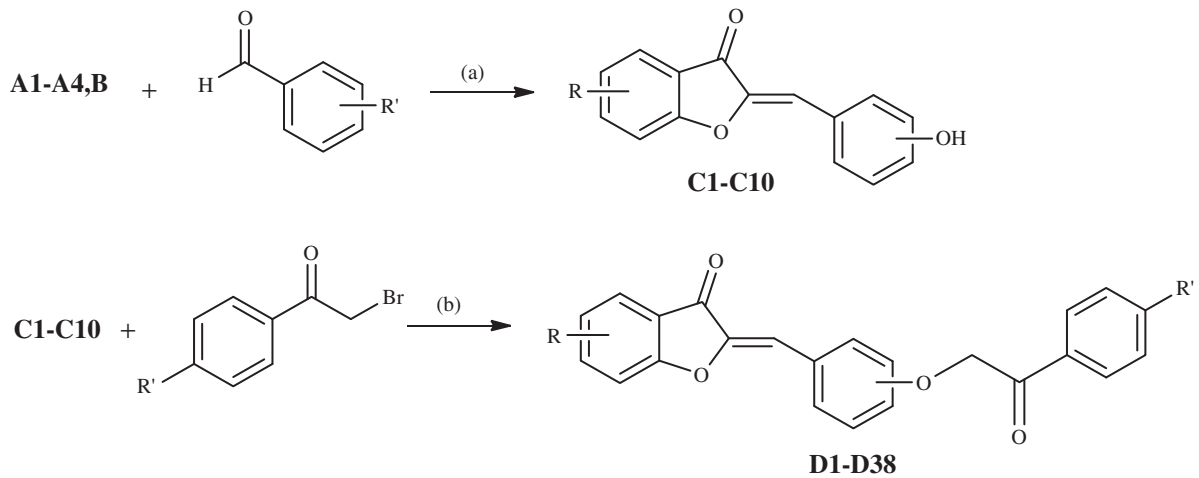
As for 6-methoxybenzofuranone (**B**) compound, it was obtained by a three step reaction using resorcinol as a starting material (Scheme 2). In first step, 1,3-dihydroxybenzene was methylated with dimethylsulfate in basic medium to get 1,3-dimethoxybenzene. Second, according to Friedel–Crafts reaction, chloro acetyl group was linked to the aromatic ring when methoxy group on the *ortho* position of the carbonyl group including carbon loss of methyl radical with the effect of aluminium chloride and turn into phenolic hydroxyl. 6-Methoxybenzofuranone was gained from the obtained



Scheme 1. The synthesis of the benzofuran-3-one derivatives (A1–A4). Reactants/reagents and reaction conditions. a: $(CH_3CO)_2O$, reflux, 30 min; b: $AlCl_3$, 160–170 °C; c: $(CH_3CO)_2O$, 50–100 °C, 3–4 h; d: Br_2, HBr, diethyl ether or acetic acid; e: 10% HCl, reflux; f: CH_3COONa, EtOH, reflux.



Scheme 2. The synthesis of 6-methoxybenzofuranone (B). Reactants/reagents and reaction conditions. a: $(CH_3)_2SO_4$, NaOH, acetone, reflux, 4 h; b: $AlCl_3$, CS_2, dichloromethane, reflux, 30 min; c: CH_3COONa, EtOH, reflux.



Scheme 3. The synthesis of the final compounds (D1–D38). Reactants/reagents and reaction conditions. a: *n*-butanol/isobutanol, catalytic HCl, reflux, 1 h; b: acetone, K_2CO_3, reflux, 6 h.

Table 3. Sixty human tumor cell lines' anti-cancer screening data at single dose assay as percent cell growth promotion of selected compounds.

Com	NSCLC	CC	BC	OC	L	RC	M	PC	CNSC	Mean
D-2	94.50	108.37	124.84	105.53	81.24	83.22	115.04	111.98	107.64	102.25
D-3	95.50	112.32	92.64	98.69	77.72	93.86	106.45	109.78	93.22	97.16
D-5	88.83	103.21	82.68	100.07	74.30	100.28	99.02	98.90	109.49	94.76
D-8	91.01	103.28	91.17	100.10	91.10	85.04	96.47	108.69	108.71	95.76
D-9	102.86	103.02	101.92	103.84	95.51	101.78	103.90	108.37	135.51	105.83
D-10	102.20	124.04	116.29	129.25	101.45	100.06	102.47	109.20	114.76	113.99
D-14	87.21	101.61	94.51	97.39	113.88	98.59	92.88	107.45	96.06	97.28
D-17	91.82	98.69	91.41	104.45	72.27	97.85	90.17	230.58	97.49	97.76
D-23	90.93	87.06	80.34	101.09	72.06	95.71	103.25	110.97	113.84	95.03
D-27	93.94	96.15	93.85	94.13	92.49	96.67	99.96	97.86	84.96	94.47
D-28	99.40	113.57	135.62	105.58	86.41	96.76	113.30	107.18	116.13	108.32
D-30	99.58	111.34	100.96	95.91	82.68	112.45	103.37	113.69	101.56	102.09
D-32	98.87	106.82	104.76	100.76	89.24	98.86	103.19	122.53	99.78	101.21
D-37	86.58	89.17	85.26	85.01	49.47	101.78	89.21	107.41	94.49	86.23

NSCLC, non-small cell lung cancer; CC, colon cancer; BC, breast cancer; OC, ovarian cancer; L, leukemia; RC, renal cancer; M, melanoma; PC, prostate cancer; CNSC, central nervous system cancer.

2′-hydroxy-4'-methoxy-2-chloroacetophenone compound with ring closure reaction in Williamson ether synthesis conditions in third step.

2-(3- or 4-Hydroxybenzylidene)benzofuran-3-one derivatives (**C1–C10**) were formed with the reaction of ketone compounds (**A1–A4, B**) and 3-/4-hydroxybenzaldehydes according to Claisen-Schmidt condensation. Finally, final 2-[3- or 4-(2-aryl-2-oxoethoxy)arylidene]benzofuran-3-one compounds (**D1–D38**) were achieved with the reaction of brominated acetophenones and 2-(3- or 4-hydroxybenzylidene)benzofuran-3-one derivatives (**C1–C10**) according to S_N2 nucleophilic substitution reaction (Scheme 3).

The melting points were determined and uncorrected for all new compounds. The reactions were carried out in 55–75% yield. The structures of the final compounds (**D1–D38**) were elucidated by using IR, ^{1}H-NMR and MS spectral data. In the IR spectra of the compounds, characteristic stretching bands were observed at 1649–1712, 1456–1647 and 1217–1288 cm^{-1} due to C = O, C = C and C–O bonds. In double bond region, two bands were seen belonging to two carbonyl group which are on third position of benzofuranone ring and on benzoyl moiety. In the ^{1}H-NMR spectra, protons of acetyl residue were observed at about 5.62–5.79 ppm. The azomethine protons, −N = CH−, were resonated as singlets at about 6.81–6.99 ppm. All other aliphatic and aromatic protons were observed at expected regions. The aromatic protons were seen at 6.85–8.43 ppm. The aurone derivatives are expected to be found mostly in both of *E* and *Z* isomerism and β-hydrogen atoms resonated ranged from 6.7 to 7.1 ppm. According to reported values for ^{1}H chemical shifts for (*Z*)-aurones (ca. 6.7 ppm) and (*E*)-aurones (ca. 7.2 ppm)[50], therefore the obtained final compounds are thought to be in (*Z*) isomerism. ES–MS spectra of the compounds gave confirmative molecular peaks.

All final compounds (**D1–D38**) were offered to NCI, USA for testing their anti-cancer activity according to drug screening protocol of the institute. Compounds **D2, D3, D5, D8, D9, D10, D14, D17, D23, D27, D28, D30, D32** and **D37** were selected by NCI for 60 human tumor cell lines' anti-cancer screening test at single dose assay. *In vitro* single dose anti-cancer assay was performed in full NCI 60 cell panel representing leukemia (L), non-small cell lung cancer (NSCLC), colon cancer (CC), central nervous system cancer (CNSC), melanoma (M), ovarian cancer (OC), renal cancer (RC), prostate cancer (PC), and breast cancer (BC). Results were given as percentage growth of the cancer diseases which were treated with selected compounds (Table 3, Supplementary material). As can be seen from Table 3, according to mean values, most of the compounds have affected primarily leukemia cell lines and compound **D37** exhibited the highest anti-tumor activity on leukemia cancer type with the growth percentage of 49.47%. Same compound showed the lowest mean growth

percentage among all tested compounds and it can be claimed as the most effective compound. HOP-92 (NSCLC) with 48.94%, HCT-116 (CC) with 23.58%, MCF7 (BC) with 47.13%, IGROV-1 (OC) with 32.85%, MOLT-4 (L) with −17.79% and SR (L) with −22.38% growth percentages were determined as the most susceptible cell lines against compound **D37**. Among all tumor cell lines, UO-31 which is renal cancer cell, has detected as the most sensitive one with growth percentages −37.07% against **D2**, −44.36% against **D8**, −29.24% against **D28**. Compound **D17** has also caused −34.25% growth percentage against MOLT-4 which is a leukemia cell line.

Conclusion

In this work, the synthesis of 2-[3- or 4-(2-aryl-2-oxoethoxy)arylidene]benzofuran-3-one derivatives (**D1–D38**) and anti-cancer activity of the selected compounds were investigated. The final compounds were obtained in a multistep synthetic procedure and the structures of the final compounds were proved using IR, ^{1}H-NMR and MS spectral data. According to anti-cancer activity results, compound **D8** exhibited the highest activity causing a growth percentage −44.36% on UO-31 cell line.

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Declaration of interest

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Supplementary material available online
Supplementary data