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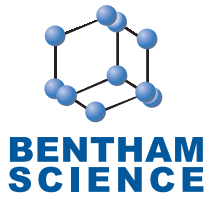
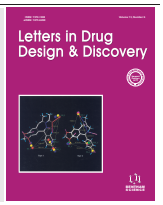
Letters in Drug Design & Discovery, 2016, *13*, 563-569



Synthesis and Antiproliferative Activity of 2-arylidene 6-(2-aryl-2-oxoethoxy)Benzofuran-3-one Derivatives



Seref Demirayak[a], Leyla Yurttas[b,*], Ahmet Cagri Karaburun[b], Nalan Gundogdu-Karaburun[b] and Ismail Kayagil[c]

[a]*Department of Pharmaceutical Chemistry, School of Pharmacy, Medipol University, 34083 Istanbul, Turkey;* [b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey;* [c]*Department of Chemistry, Faculty of Arts & Science, Mehmet Akif Ersoy University, 15030 Burdur, Turkey*

Leyla Yurttas

Abstract: The synthesis of 2-arylidene 6-(2-aryl-2-oxoethoxy)benzofuran-3-one derivatives was reported and selected compounds were determined for their anticancer activity evaluation in National Cancer Institute NCI, USA according to the drug screening protocol of the institute against approximately 60 tumor cell lines derived from nine cancer diseases. Compound **3r**, namely 2-(4-chlorobenzylidene)-6-[2-(4-methoxyphenyl)-2-oxoethoxy]benzofuran-3-one exhibited the highest antitumor activity against non-small lung cancer cell lines.

Keywords: Antitumor activity, aurone, benzofuranone, chalcone, cytotoxic activity.

Received: August 03, 2015 **Revised: September 22, 2015** **Accepted: October 29, 2015**

INTRODUCTION

Chalcones are molecular structures which consist of two benzene ring connected with α,β-unsaturated carbonyl group (Fig. **1**). Natural sourced flavonoids and isoflavonoids are chalcone including molecules which have known with broad spectrum of pharmacological activities such as anticancer, antileishmanial, anti-inflammatory, anti-HIV, antifungal, antiparasitic and antiprotozoal. Among them, cytotoxic activity profile of these compounds have attracted attention due to increasing number of encouraging research findings [1-4]. One of the most important finding is anticancer activity potential of naturally occurring bioactive chalcones xanthohumol and cardamonin (Fig. **1**) [5-7]. Another natural molecule sulfuretin (Fig. **1**) has been reported with promising anticancer activity alongside high antiinflammatory activity which is in aurone frame, a chalconic structure [8]. Aurones (Fig. **1**) are molecules which have 2-benzylidene benzofuran-3-(2*H*)-one scaffold in its molecular framework and they commonly found in flavonoids. During past decade numerous biological activities of aurones and their derivatives have been published such as the inhibition of platelet aggregation, analgesic, antiasthmatic, anti-inflammatory, antiallergic, antihyperlipidemic and coronary dilation effects [9-11]. Among these pharmacological diversity, cytotoxic activity of newly synthesized compounds were mostly studied [12-14]. The antiproliferative properties of these compouns against cancer cells were ascribed to binding P-glycoprotein inhibiting cyclin-dependent kinases (CDKs), blocking sphingosine kinase, interfering microtubule assembly, modulating ABCG2 (breast cancer resistance protein)-mediated multidrug resistance, exhibiting antioxidative activity and DNA strand scission activity [15, 16]. Additionally, the inhibitory activity of aurones was attributed to the structural mimicry between the benzofuranone ring of the aurone and the adenine of ATP (Adenosine triphosphate) [17]. In recent studies, especially hydroxylated aurones have come into prominence with higher anticancer activity [18-20].

In the view of above observations and as an extending study of our previous studies [21, 22], we have synthesized 2-arylidene 6-(2-aryl-2-oxoethoxy)benzofuran-3-one derivatives (**3a-3t**) using 6-hydroxyaurone as intermediate product and investigated their antiproliferative activity against varying tumour cell lines.

MATERIALS AND METHODS

Chemistry

The chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck KGaA (Darmstadt, Germany). Melting points were determined using a Electrothermal 9100 digital melting point apparatus (Essex, UK). Spectroscopic analyses were recorded with the following instruments : IR spectra were IR Shimadzu 8400S FT-IR spectrometer (Tokyo, Japan), ^{1}H-NMR spectra on a Bruker 500 MHz spectrometer (Billerica, MA, USA) in DMSO-d_6 with TMS as internal standard and mass spectra using a Agilent 110 MSD spectrometer (Santa Clara, CA, USA) instruments and elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyser (Perkin Elmer, Norwalk, CT, USA).

General Procedure for the Synthesis of 2-arylidene 6-(2-aryl-2-oxoethoxy)benzofuran-3-one Derivatives (3a-3t)

The synthesized 2-arylidene-6-hydroxybenzofuranone derivatives (**2a-2d**) were reacted with appropriate 2'-

*Address correspondence to this author at the Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 26470 Eskisehir, Turkey; Tel: +90-222-3350580/3783; Fax: +90-222-3350750;
E-mail: lyurttas@anadolu.edu.tr

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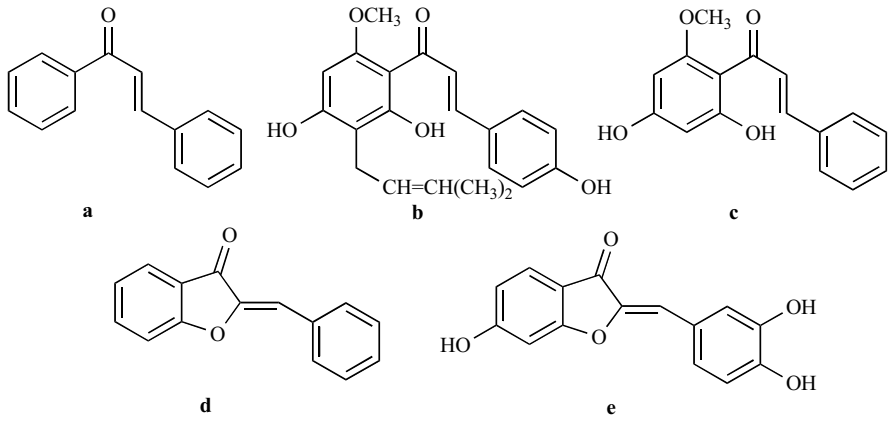


Fig. (1). The chemical structures of **a**) chalcone, **b**) xanthohumol, **c**) cardamomin, **d**) aurone **e**) sulfuretin.

bromoacetophenone derivatives in acetone at reflux conditions and in presence of potassium carbonate as a basic medium. At the end of the reaction, excess acetone was evaporated and the residue was washed with water. Then, it was filtered off to obtain crude product and the dried crude product was crystallized from ethanol.

2-Benzylidene-6-(2-phenyl-2-oxoethoxy)benzofuran-3-one (3a)

IR (KBr) ν_{max} (cm^{-1}): 3076, 3065 (Ar-H and =CH-), 2966, 2851 (Aliphatic-H), 1708, 1687 (C=O), 1638-1480 (C=C), 1276, 1222 (C-O). ^{1}H-NMR δ (ppm): 5.85 (2H, s, O-CH_2-), 6.85 (1H, s, =CH-), 6.95 (1H, dd, J: 2.06 Hz, J: 8.57 Hz, Ar-H), 7.27 (1H, d, J: 1.87 Hz, Ar-H), 7.41-7.49 (3H, m, Ar-H), 7.60 (2H, t, J: 7.61 Hz, Ar-H), 7.72 (2H, d, J: 8.62 Hz, Ar-H), 7.96 (2H, d, J: 7.60 Hz, Ar-H), 8.06 (2H, d, J: 7.45 Hz, Ar-H). For $C_{23}H_{16}O_4$ calculated (%) C 77.52, H 4.53, O 17.96; found (%) C 77.46, H 4.58, O 17.93. MS $[M+1]^+$: *m/z* 357.2.

2-Benzylidene-6-[2-(4-methylphenyl)-2-oxoethoxy]benzofuran-3-one (3b)

IR (KBr) ν_{max} (cm^{-1}): 3081, 3034 (Ar-H and =CH-), 2978, 2841 (Aliphatic-H), 1705, 1687 (C=O), 1638-1480 (C=C), 1276, 1223 (C-O). ^{1}H-NMR δ (ppm): 2.42 (3H, s, Ar-CH_3), 5.81 (2H, s, O-CH_2-), 6.86 (1H, s, =CH-), 6.94 (1H, dd, J: 1.25 Hz, J: 8.75 Hz, Ar-H), 7.25 (1H, brs, Ar-H), 7.40 (2H, d, J: 7.88 Hz, Ar-H), 7.44-7.50 (2H, m, Ar-H), 7.72 (2H, d, J: 8.55 Hz, Ar-H), 7.96-7.99 (4H, m, Ar-H). For $C_{24}H_{18}O_4$ calculated (%) C 77.82, H 4.90, O 17.28; found (%) C 77.76, H 4.71, O 17.25. MS $[M+1]^+$: *m/z* 371.4.

2-Benzylidene-6-[2-(4-methoxylphenyl)-2-oxoethoxy]benzofuran-3-one (3c)

IR (KBr) ν_{max} (cm^{-1}): 3078, 3036 (Ar-H and =CH-), 2981, 2854 (Aliphatic-H), 1703, 1688 (C=O), 1635-1476 (C=C), 1271, 1220 (C-O). ^{1}H-NMR δ (ppm): 3.93 (3H, s, Ar-O-CH_3), 5.83 (2H, s, O-CH_2-), 6.87 (1H, s, =CH-), 6.88 (1H, d, J: 8.70 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.28 (2H, d, J: 7.94 Hz, Ar-H), 7.50-7.56 (2H, m, Ar-H), 7.72-7.75 (3H, m, Ar-H), 7.96-8.01 (3H, m, Ar-H). For $C_{24}H_{18}O_5$ calculated (%) C 74.60, H 4.70, O 20.70; found (%) C 74.71, H 4.74, O 20.75. MS $[M+1]^+$: *m/z* 387.3.

2-Benzylidene-6-[2-(4-chlorophenyl)-2-oxoethoxy]benzofuran-3-one (3d)

IR (KBr) ν_{max} (cm^{-1}): 3087, 3045 (Ar-H and =CH-), 2978, 2841 (Aliphatic-H), 1705, 1687 (C=O), 1638-1480 (C=C), 1276, 1222 (C-O). ^{1}H-NMR δ (ppm): 5.86 (2H, s, O-CH_2-), 6.86 (1H, s, =CH-), 6.95 (1H, dd, J: 1.97 Hz, J: 8.57 Hz, Ar-H), 7.11 (2H, d, J: 8.87 Hz, Ar-H), 7.26 (2H, brs, Ar-H), 7.40-7.49 (2H, m, Ar-H), 7.79-7.91 (3H, m, Ar-H), 8.06 (2H, d, J: 7.45 Hz, Ar-H). For $C_{23}H_{15}ClO_4$ calculated (%) C 70.69, H 3.87, O 16.37; found (%) C 70.75, H 3.92, O 16.34. MS $[M+1]^+$: *m/z* 391.4.

2-Benzylidene-6-[2-(4-nitrophenyl)-2-oxoethoxy]benzofuran-3-one (3e)

IR (KBr) ν_{max} (cm^{-1}): 3100, 3064 (Ar-H and =CH-), 2964, 2915, 2856 (Aliphatic-H), 1708, 1694 (C=O), 1651-1490 (C=C), 1274, 1220 (C-O). ^{1}H-NMR δ (ppm): 5.91 (2H, s, O-CH_2-), 6.85 (1H, s, =CH-), 6.98 (1H, dd, J: 2.01 Hz, J: 8.56 Hz, Ar-H), 7.28 (1H, d, J: 2.02 Hz, Ar-H), 7.53 (2H, d, J: 8.44 Hz, Ar-H), 7.74-7.85 (4H, m, Ar-H), 8.30 (2H, d, J: 8.81 Hz, Ar-H), 8.40 (2H, d, J: 8.83 Hz, Ar-H). For $C_{23}H_{15}NO_6$ calculated (%) C 68.83, H 3.77, O 23.92; found (%) C 68.78, H 3.82, O 23.96. MS $[M+1]^+$: *m/z* 402.2.

2-(4-Methylbenzylidene)-6-(2-phenyl-2-oxoethoxy)benzofuran-3-one (3f)

IR (KBr) ν_{max} (cm^{-1}): 3078, 3033 (Ar-H and =CH-), 2975, 2840 (Aliphatic-H), 1704, 1688 (C=O), 1639-1484 (C=C), 1273, 1221 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 5.82 (2H, s, O-CH_2-), 6.88 (1H, s, =CH-), 6.98 (1H, dd, J: 1.27 Hz, J: 8.76 Hz, Ar-H), 7.29 (1H, brs, Ar-H), 7.45 (2H, d, J: 7.86 Hz, Ar-H), 7.63-7.74 (4H, m, Ar-H), 7.85-7.92 (4H, m, Ar-H). For $C_{24}H_{18}O_4$ calculated (%) C 77.82, H 4.90, O 17.28; found (%) C 77.79, H 4.82, O 17.24. MS $[M+1]^+$: *m/z* 371.3.

2-(4-Methylbenzylidene)-6-[2-(4-methylphenyl)-2-oxoethoxy]benzofuran-3-one (3g)

IR (KBr) ν_{max} (cm^{-1}): 3095, 3068 (Ar-H and =CH-), 2966, 2838 (Aliphatic-H), 1708, 1693 (C=O), 1649-1487 (C=C), 1278, 1222 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 2.41 (3H, s, Ar-CH_3), 5.79 (2H, s, O-CH_2-), 6.81 (1H, s, =CH-), 6.93 (1H, dd, J: 1.86 Hz, J: 8.55 Hz, Ar-H), 7.24 (1H, d, J: 1.72 Hz, Ar-H), 7.29 (2H, d, J: 7.99 Hz, Ar-H), 7.40 (2H, d, J: 8.02 Hz, Ar-H), 7.70 (1H, d, J: 8.54 Hz, Ar-H), 7.85 (2H, d, J: 8.0 Hz, Ar-H), 7.96 (2H, d, J: 7.99 Hz, Ar-H). For $C_{25}H_{20}O_4$ calculated (%) C 78.11, H 5.24, O 16.65; found (%) C 78.16, H 5.28, O 16.70. MS $[M+1]^+$: *m/z* 385.1.

2-(4-Methylbenzylidene)-6-[2-(4-methoxyphenyl)-2-oxoethoxy]benzofuran-3-one (3h)

IR (KBr) ν_{max} (cm^{-1}): 3066, 3023 (Ar-H ve =CH-), 2966, 2851 (Aliphatic-H), 1708, 1687 (C=O), 1638-1480 (C=C), 1276, 1222 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 3.92 (3H, s, Ar-O-CH_3), 5.81 (2H, s, O-CH_2-), 6.80 (1H, s, =CH-), 6.92 (1H, dd, J: 2.05 Hz, J: 8.65 Hz, Ar-H), 7.11 (2H, d, J: 8.82 Hz, Ar-H), 7.23 (1H, d, J: 1.68 Hz, Ar-H), 7.29 (2H, d, J: 7.99 Hz, Ar-H), 7.71 (1H, d, J: 8.54 Hz, Ar-H), 7.85 (2H, d, J: 8.0 Hz, Ar-H), 8.06 (2H, d, J: 7.99 Hz, Ar-H). For $C_{25}H_{20}O_5$ calculated (%) C 74.99, H 5.03, O 19.98; found (%) C 75.06, H 5.08, O 19.92. MS $[M+1]^+$: *m/z* 401.1.

2-(4-Methylbenzylidene)-6-[2-(4-chlorophenyl)-2-oxoethoxy]benzofuran-3-one (3i)

IR (KBr) ν_{max} (cm^{-1}): 3071, 3042 (Ar-H and =CH-), 2978, 2841 (Aliphatic-H), 1705, 1687 (C=O), 1638-1480 (C=C), 1276, 1222 (C-O). ^{1}H-NMR δ (ppm): 2.41 (3H, s, Ar-CH_3), 5.80 (2H, s, O-CH_2-), 6.78 (1H, s, =CH-), 6.91 (1H, dd, J: 1.77 Hz, J: 8.68 Hz, Ar-H), 7.23 (1H, d, J: 1.55 Hz, Ar-H), 7.29 (2H, d, J: 7.99 Hz, Ar-H), 7.71 (1H, d, J: 8.54 Hz, Ar-H), 7.85 (2H, d, J: 8.0 Hz, Ar-H), 8.29 (2H, d, J: 8.79 Hz, Ar-H), 8.41 (2H, d, J: 8.78 Hz, Ar-H). For $C_{24}H_{17}ClO_4$ calculated (%) C 71.20, H 4.23, O 15.81; found (%) C 71.24, H 4.29, O 15.90. MS $[M+1]^+$: *m/z* 405.5.

2-(4-Methylbenzylidene)-6-[2-(4-nitrophenyl)-2-oxoethoxy]benzofuran-3-one (3j)

IR (KBr) ν_{max} (cm^{-1}): 3101, 3073 (Ar-H and =CH-), 2962, 2912, 2863 (Aliphatic-H), 1704, 1695 (C=O), 1644-1483 (C=C), 1273, 1221 (C-O). ^{1}H-NMR δ (ppm): 2.40 (3H, s, Ar-CH_3), 5.92 (2H, s, O-CH_2-), 6.89 (1H, s, =CH-), 6.97 (1H, dd, J: 2.02 Hz, J: 8.46 Hz, Ar-H), 7.30 (1H, d, J: 2.05 Hz, Ar-H), 7.53 (2H, d, J: 8.57 Hz, Ar-H), 7.72 (1H, d, J: 8.54 Hz, Ar-H), 7.99 (2H, d, J: 8.82 Hz, Ar-H), 8.32 (2H, d, J: 8.81 Hz, Ar-H), 8.54 (2H, d, J: 8.72 Hz, Ar-H). For $C_{24}H_{17}NO_6$ calculated (%) C 69.39, H 4.13, O 23.11; found (%) C 69.43, H 4.16, O 23.15. MS $[M+1]^+$: *m/z* 416.1.

2-(4-Methoxybenzylidene)-6-(2-phenyl-2-oxoethoxy)benzofuran-3-one (3k)

IR (KBr) ν_{max} (cm^{-1}): 3075, 3028 (Ar-H and =CH-), 2974, 2840 (Aliphatic-H), 1705, 1682 (C=O), 1636-1478 (C=C), 1259, 1226 (C-O). ^{1}H-NMR δ (ppm): 3.87 (3H, s, Ar-O-CH_3), 5.82 (2H, s, O-CH_2-), 6.87 (1H, s, =CH-), 6.96 (1H, dd, J: 1.32 Hz, J: 8.70 Hz, Ar-H), 7.33 (1H, brs, Ar-H), 7.40 (2H, d, J: 7.64 Hz, Ar-H), 7.48-7.52 (2H, m, Ar-H), 7.79 (2H, d, J: 8.48 Hz, Ar-H), 7.95-7.97 (4H, d, Ar-H). For $C_{24}H_{18}O_5$ calculated (%) C 74.60, H 4.70, O 20.70; found (%) C 74.68, H 4.72, O 20.73. MS $[M+1]^+$: *m/z* 387.3.

2-(4-Methoxybenzylidene)-6-[2-(4-methylphenyl)-2-oxoethoxy]benzofuran-3-one (3l)

IR (KBr) ν_{max} (cm^{-1}): 3060, 3025 (Ar-H and =CH-), 2960, 2850 (Aliphatic-H), 1704, 1684 (C=O), 1630-1467 (C=C), 1270, 1227 (C-O). ^{1}H-NMR δ (ppm): 2.35 (3H, s, Ar-CH_3), 3.91 (3H, s, Ar-O-CH_3), 5.82 (2H, s, O-CH_2-), 6.80 (1H, s, =CH-), 6.94 (1H, dd, J: 2.01 Hz, J: 8.60 Hz, Ar-H), 7.12 (2H, d, J: 8.56 Hz, Ar-H), 7.23 (1H, d, J: 1.56 Hz, Ar-H), 7.29 (2H, d, J: 7.83 Hz, Ar-H), 7.70 (1H, d, J: 8.53 Hz, Ar-H), 7.80 (2H, d, J: 8.21 Hz, Ar-H), 8.05 (2H, d, J: 7.84 Hz, Ar-H). For $C_{25}H_{20}O_5$ calculated (%) C 74.99, H 5.03, O 19.98; found (%) C 75.02, H 5.04, O 19.93. MS $[M+1]^+$: *m/z* 401.1.

2-(4-Methoxybenzylidene)-6-[2-(4-methoxyphenyl)-2-oxoethoxy]benzofuran-3-one (3m)

IR (KBr) ν_{max} (cm^{-1}): 3087, 3042 (Ar-H and =CH-), 2956, 2921, 2863 (Aliphatic-H), 1703, 1687 (C=O), 1600-1489 (C=C), 1276, 1220 (C-O). ^{1}H-NMR δ (ppm): 3.87 (3H, s, Ar-O-CH_3), 3.98 (3H, s, Ar-O-CH_3), 5.78 (2H, s, O-CH_2-), 6.84 (1H, s, =CH-), 6.90 (1H, dd, J: 2.07 Hz, J: 8.65 Hz, Ar-H), 7.06 (2H, d, J: 8.12 Hz, Ar-H), 7.11 (2H, d, J: 7.79 Hz, Ar-H), 7.23 (1H, d, J: 1.68 Hz, Ar-H), 7.29 (2H, d, J: 7.99 Hz, Ar-H), 7.71 (1H, d, J: 8.54 Hz, Ar-H), 7.98 (2H, d, J: 7.97 Hz, Ar-H). For $C_{25}H_{20}O_6$ calculated (%) C 72.11, H 4.84, O 23.05; found (%) C 72.15, H 4.75, O 23.09. MS $[M+1]^+$: *m/z* 417.2.

2-(4-Methoxybenzylidene)-6-[2-(4-chlorophenyl)-2-oxoethoxy]benzofuran-3-one (3n)

IR (KBr) ν_{max} (cm^{-1}): 3083, 3040 (Ar-H and =CH-), 2950, 2928, 2869 (Aliphatic-H), 1706, 1690 (C=O), 1612-1494 (C=C), 1278, 1223 (C-O). ^{1}H-NMR δ (ppm): 3.88 (3H, s, Ar-O-CH_3), 5.79 (2H, s, O-CH_2-), 6.86 (1H, s, =CH-), 6.92 (1H, dd, J: 2.05 Hz, J: 8.61 Hz, Ar-H), 7.08 (2H, d, J: 8.06 Hz, Ar-H), 7.12 (2H, d, J: 7.64 Hz, Ar-H), 7.27 (1H, d, J: 1.74 Hz, Ar-H), 7.30 (2H, d, J: 7.80 Hz, Ar-H), 7.80 (1H, d, J: 8.52 Hz, Ar-H), 7.95 (2H, d, J: 7.98 Hz, Ar-H). For $C_{24}H_{17}ClO_5$ calculated (%) C 68.50, H 4.07, O 19.01; found (%) C 68.45, H 4.10, O 19.08. MS $[M+1]^+$: *m/z* 421.4.

2-(4-Methoxybenzylidene)-6-[2-(4-nitrophenyl)-2-oxoethoxy]benzofuran-3-one (3o)

IR (KBr) ν_{max} (cm^{-1}): 3102, 3062 (Ar-H and =CH-), 2956, 2913, 2846 (Aliphatic-H), 1708, 1687 (C=O), 1646-1484 (C=C), 1270, 1224 (C-O). ^{1}H-NMR δ (ppm): 3.88 (3H, s, Ar-O-CH_3), 5.84 (2H, s, O-CH_2-), 6.88 (1H, s, =CH-), 6.95 (1H, dd, J: 2.03 Hz, J: 8.60 Hz, Ar-H), 7.31 (1H, d, J: 2.11 Hz, Ar-H), 7.63 (2H, d, J: 8.54 Hz, Ar-H), 7.76 (2H, d, J: 8.64 Hz, Ar-H), 7.91 (2H, d, J: 8.92 Hz, Ar-H), 8.25-8.29

(1H, m, Ar-H), 8.40 (2H, d, J: 8.73 Hz, Ar-H). For $C_{24}H_{17}NO_7$ calculated (%) C 66.82, H 3.97, O 25.96; found (%) C 66.78, H 3.95, O 25.94. MS $[M+1]^+$: *m/z* 432.2.

2-(4-Chlorobenzylidene)-6-(2-phenyl-2-oxoethoxy)benzofuran-3-one (3p)

IR (KBr) ν_{max} (cm^{-1}): 3077, 3045 (Ar-H and =CH-), 2978, 2841 (Aliphatic-H), 1705, 1687 (C=O), 1638-1480 (C=C), 1276, 1222 (C-O). ^{1}H-NMR δ (ppm): 5.87 (2H, s, O-CH_2-), 6.88 (1H, s, =CH-), 6.96 (1H, dd, J: 1.67 Hz, J: 8.60 Hz, Ar-H), 7.25 (1H, brs, Ar-H), 7.55 (2H, d, J: 8.44 Hz, Ar-H), 7.61 (2H, t, J: 7.50 Hz, Ar-H), 7.73 (2H, d, J: 8.49 Hz, Ar-H), 7.97 (2H, d, J: 8.41 Hz, Ar-H), 8.06 (2H, d, J: 8.15 Hz, Ar-H). For $C_{23}H_{15}ClO_4$ calculated (%) C 70.69, H 3.87, O 16.37; found (%) C 70.75, H 3.92, O 16.34. MS $[M+1]^+$: *m/z* 391.4.

2-(4-Chlorobenzylidene)-6-[2-(4-methylphenyl)-2-oxoethoxy]benzofuran-3-one (3q)

IR (KBr) ν_{max} (cm^{-1}): 3077, 3045 (Ar-H and =CH-), 2978, 2841 (Aliphatic-H), 1705, 1687 (C=O), 1638-1480 (C=C), 1276, 1222 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 5.88 (2H, s, O-CH_2-), 6.89 (1H, s, =CH-), 6.97 (1H, dd, J: 1.72 Hz, J: 8.59 Hz, Ar-H), 7.23 (1H, brs, Ar-H), 7.56 (2H, d, J: 8.40 Hz, Ar-H), 7.62 (2H, t, J: 7.62 Hz, Ar-H), 7.70 (2H, d, J: 8.41 Hz, Ar-H), 7.94 (2H, d, J: 8.40 Hz, Ar-H), 8.11 (1H, d, J: 8.08 Hz, Ar-H). For $C_{24}H_{17}ClO_4$ calculated (%) C 71.20, H 4.23, O 15.81; found (%) C 71.24, H 4.27, O 15.72. MS $[M+1]^+$: *m/z* 405.4.

2-(4-Chlorobenzylidene)-6-[2-(4-methoxyphenyl)-2-oxoethoxy]benzofuran-3-one (3r)

IR (KBr) ν_{max} (cm^{-1}): 3074, 3040 (Ar-H and =CH-), 2972, 2840 (Aliphatic-H), 1702, 1683 (C=O), 1635-1475 (C=C), 1272, 1220 (C-O). ^{1}H-NMR δ (ppm): 3.88 (3H, s, Ar-O-CH_3), 5.88 (2H, s, O-CH_2-), 6.89 (1H, s, =CH-), 6.97 (1H, dd, J: 1.58 Hz, J: 8.56 Hz, Ar-H), 7.32 (1H, brs, Ar-H), 7.61 (2H, d, J: 8.55 Hz, Ar-H), 7.71 (2H, t, J: 7.62 Hz, Ar-H), 7.77 (2H, d, J: 8.42 Hz, Ar-H), 7.99 (2H, d, J: 8.38 Hz, Ar-H), 8.07 (1H, d, J: 8.18 Hz, Ar-H). For $C_{24}H_{17}ClO_5$ calculated (%) C 68.50, H 4.07, O 19.01; found (%) C 68.47, H 4.12, O 19.09. MS $[M+1]^+$: *m/z* 421.4.

2-(4-Chlorobenzylidene)-6-[2-(4-chlorophenyl)-2-oxoethoxy]benzofuran-3-one (3s)

IR (KBr) ν_{max} (cm^{-1}): 3112, 3065 (Ar-H and =CH-), 2978, 2841 (Aliphatic-H), 1704, 1687 (C=O), 1638-1480 (C=C), 1276, 1227 (C-O). ^{1}H-NMR δ (ppm): 5.85 (2H, s, O-CH_2-), 6.89 (1H, s, =CH-), 6.96 (1H, dd, J: 1.96 Hz, J: 8.65 Hz, Ar-H), 7.27 (1H, d, J: 1.85 Hz, Ar-H), 7.56 (2H, d, J: 8.49 Hz, Ar-H), 7.69 (2H, d, J: 8.51 Hz, Ar-H), 7.73 (1H, d, J: 8.6 Hz, Ar-H), 7.98 (2H, d, J: 8.51 Hz, Ar-H), 8.07 (2H, d, J: 8.49 Hz, Ar-H). For $C_{23}H_{14}Cl_2O_4$ calculated (%) C 64.96, H 3.32, O 15.05; found (%) C 64.91, H 3.42, O 15.12. MS $[M+1]^+$: *m/z* 426.2.

2-(4-Chlorobenzylidene)-6-[2-(4-nitrophenyl)-2-oxoethoxy]benzofuran-3-one (3t)

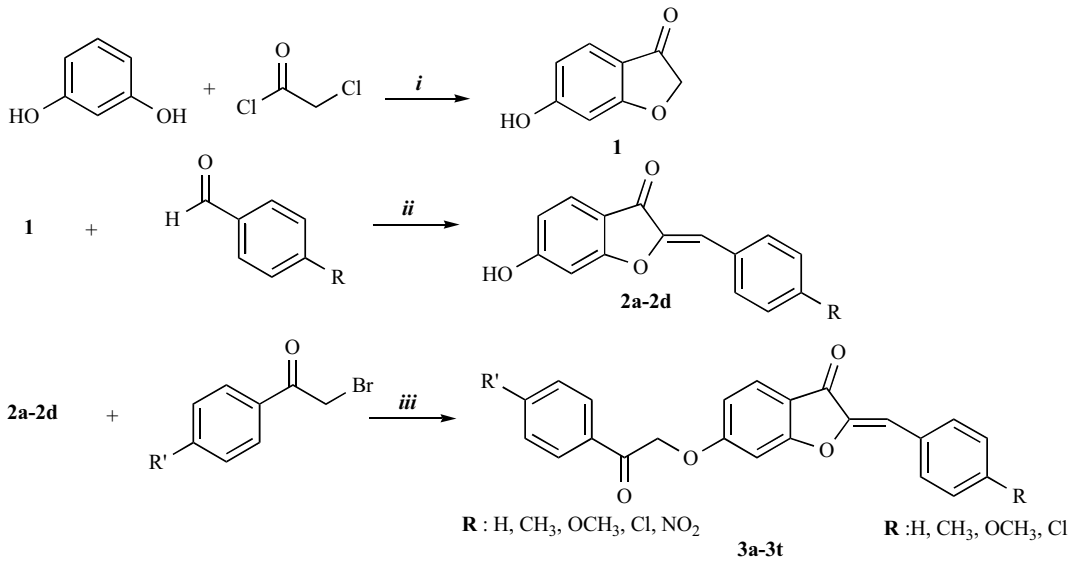
IR (KBr) ν_{max} (cm^{-1}): 3105, 3068 (Ar-H and =CH-), 2960, 2918, 2851 (Aliphatic-H), 1708, 1693 (C=O), 1649-1487 (C=C), 1278, 1222 (C-O). ^{1}H-NMR δ (ppm): 5.90 (2H, s, O-CH_2-), 6.87 (1H, s, =CH-), 6.97 (1H, dd, J: 2.05 Hz, J: 8.57 Hz, Ar-H), 7.32 (1H, d, J: 2.03 Hz, Ar-H), 7.54 (2H, d, J: 8.56 Hz, Ar-H), 7.72 (1H, d, J: 8.56 Hz, Ar-H), 7.96 (2H, d, J: 8.85 Hz, Ar-H), 8.29 (2H, d, J: 8.79 Hz, Ar-H), 8.41 (2H, d, J: 8.78 Hz, Ar-H). For $C_{23}H_{14}ClNO_6$ calculated (%) C 63.39, H 3.24, O 22.03; found (%) C 63.45, H 3.31, O 22.12. MS $[M+1]^+$: *m/z* 436.3.

Table 1. Some characteristics of 2-arylidene 6-(2-aryl-2-oxoethoxy)benzofuran-3-one derivatives.

Compound	-R	-R'	M.P. (°C)	Molecular Formula
3a	-H	-H	191	$C_{23}H_{16}O_4$
3b	-H	-CH_3	193	$C_{24}H_{18}O_4$
3c	-H	-OCH_3	194	$C_{24}H_{18}O_5$
3d	-H	-Cl	201	$C_{23}H_{15}ClO_4$
3e	-H	-NO_2	232	$C_{23}H_{15}NO_6$
3f	-CH_3	-H	184	$C_{24}H_{18}O_4$
3g	-CH_3	-CH_3	188	$C_{25}H_{20}O_4$
3h	-CH_3	-OCH_3	181	$C_{25}H_{20}O_5$
3i	-CH_3	-Cl	223	$C_{24}H_{17}ClO_4$
3j	-CH_3	-NO_2	208	$C_{24}H_{17}NO_6$
3k	-OCH_3	-H	186	$C_{24}H_{18}O_5$
3l	-OCH_3	-CH_3	201	$C_{25}H_{20}O_5$
3m	-OCH_3	-OCH_3	171	$C_{25}H_{20}O_6$
3n	-OCH_3	-Cl	217	$C_{24}H_{17}ClO_5$
3o	-OCH_3	-NO_2	215	$C_{24}H_{17}NO_7$
3p	-Cl	-H	202	$C_{23}H_{15}ClO_4$
3q	-Cl	-CH_3	203	$C_{24}H_{17}ClO_4$
3r	-Cl	-OCH_3	178	$C_{24}H_{17}ClO_5$
3s	-Cl	-Cl	212	$C_{23}H_{14}Cl_2O_4$
3t	-Cl	-NO_2	237	$C_{23}H_{14}ClNO_4$

Anticancer Activity

The effects of the benzofuranone compounds on the percentage growth were investigated in sixty human tumour cell lines comprising 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



Scheme (1). The synthesis of the compounds (**3a-3t**). Reactants and reaction conditions; ***i*** $AlCl_3$, Nitrotoluene, 2h, 50-60 ^oC ; ***ii*** : *n*-butanol/isobutanol, HCl, reflux, 1h ; ***iii*** : K_2CO_3, Acetone, reflux, 3h.

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 anticancer activity was performed at the National Cancer Institute (NCI) of Bethesda, USA, according to *in vitro* screening program at 10^{-5} mol/l [25, 26].

RESULTS AND DISCUSSION

Chemistry

The synthesis of the target compounds **3a-3t** were prepared in three steps as shown in Scheme (**1**). Initially, resorcinol (1,3-dihydroxybenzene) was reacted with aluminium chloride and chloro acetylchloride in nitrotoluene. First, chloro acetyl residue was bonded to aromatic ring (ortho position) according to Friedel-Crafts reaction, then ring closure reaction was occurred with phenolic hydroxyl group and chloro acetyl group. The obtained product, 6-hydroxybenzofuran-3-one (**1**), was reacted with four different benzaldehyde derivatives according to Claisen-Schmidt condensation. The synthesized 2-arylidene-6-hydroxybenzofuranone derivatives (**2a-2d**) and 2'-bromoacetophenone derivatives were reacted to achieve 2-arylidene 6-(2-aryl-2-oxoethoxy)benzofuran-3-one (**3a-3t**). The structures of the final compounds were elucidated by using IR, ^{1}H-NMR, MS spectral data and elemental analyses results. In the IR spectra of the compounds, characteristic stretching bands were observed at 1708-1682, 1651-1467 and 1278-1220 cm^{-1} due to C=O, C=C and C-O bonds. In double bond region, two carbonyl function was detected that belongs to C=O bonds 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 5.92-5.78 ppm. The methylene protons, –C=CH-, were resonated as singlets at about 6.89-6.78 ppm. All other aliphatic and aromatic protons were observed at expected regions. The aromatic protons were seen at 8.54-6.88 ppm. Due to *E* and *Z* isomerism of the arylidene structure, it is possible to see peaks at two different places of the spectrum. The presence of isomeric forms was confirmed by thin layer chromatography, but in the NMR spectra this situation was not observed that one of the isomers may have been lost in the synthesis steps or during purification. All compounds gave satisfactory elemental analyses results within +0.4 %. In the MS spectra, the electron spraying technique with positive polarity mode was applied and M+1 peaks were detected as base peak in agreement with the molecular weights.

Anticancer Activity

All final compounds **(3a-3t)** were offered to National Cancer Institute, USA (NCI) for testing their anticancer activity. The cytotoxic activities of selected compounds were evaluated according to Developmental Therapeutics Program (DTP) drug screening protocols of the institute. *In vitro* single dose (10^5 M) anticancer 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 tested compounds (Table **2**). According to mean values, only compound **3r** exhibited antitumor activity with a percentage growth under 100 %. The other percentage growth values belongs to the other selected compounds (**3c, 3i, 3o**) were found over this number. The percentage growth values represent growth percentage of tumor cells treated with test compounds. Therefore smaller values means higher activity. When we evaluate antitumor activity according to subpanels, compound **3r** showed the highest activity to non-small cell lung cancer and breast cancer with growth percentages 64.52 and 79.82 %, respectively. Compound **3o** affected renal cancer cell lines with a

Table 2. 60 human tumor cell lines' anticancer 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
3c	104.05	107.2	97.18	108.12	100.66	95.44	93.41	247.18	105.31	109.62
3i	101.49	98.73	105.07	96.89	127.70	104.50	86.88	269.91	107.34	108.54
3o	98.02	107.71	102.03	108.74	141.30	79.26	92.76	113.45	113.57	107.13
3r	64.52	94.93	79.82	95.73	132.28	92.76	105.03	100.68	92.09	97.38

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.

mean percentage growth of 79.26 %. Prostate cancer cell lines were determined as the most resistant cell lines against to compounds **3c** and **3i** which they had percentage growth values over 200 %. If we examine results at cellular level, it is not possible to interpret, clearly that it varies. Compound **3c** exhibited significantly cytotoxic activty with a percentage growth of 5.59 % against UO-31 which is a renal cancer cell line. Compound 3i showed noticeble activity to SK-MEL-28 cell line with a percentage growth of 48.37 % (melanoma). As stated above, PC-3 cell line (prostate cancer) was found as the most resistant cell against to compound **3c** and **3i** (percentage growth : ≥389.44 %). Compound **3o** and **3r** exhibited observable antitumor activity against SK-MEL-2 (41.43%) and RXF 393 (49.98 %) which are melanoma and renal cancer cell lines, respectively. Compound **3r** also showed respectable activity against ovarian cancer cell lines IGROV1 and OVCAR-8 with the values of 52.16 and 61.25 %. A clear inference could not be made based on these results. But we can comment that methoxy and chloro substituents contributed to antitumor activity referring to compound **3r** which possesses both of the substituents [23,24]. This study is thought to be develop with new anticancer activity tests and newly synthesized compounds in further studies.

CONCLUSION

In this work, twenty new 2-arylidene 6-(2-aryl-2-oxoethoxy)benzofuran-3-one derivatives (**3a-3t**) were synthesized by Friedel-Crafts and Claisen-Schmidt condensation reactions in good yields. The structures of the compounds were elucidated with IR, ^{1}H-NMR, MS spectroscopic data and elemental analysis results. Their anticancer activity were evaluated against 60 tumor cell lines derived from nine cancer disease. Compound **3r** possessing 4-chloro and 4-methoxy substituents showed the highest antitumor activity among tested four compounds (**3c, 3i, 3o**).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The study was financially supported by Anadolu University, Turkey (BAP Project No: 050301). The authors present their thanks to NCI (USA) and Anadolu University BIBAM (Türkiye) for anticancer test results and NMR spectra, respectively.

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