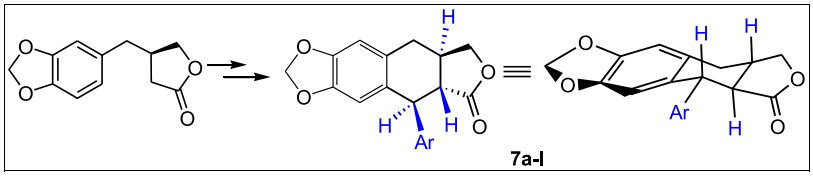
Babak Heidary Alizadeh,[a] Saeed Emami,[b] Gholamreza Dehghan,[c] Alireza Foroumadi,[d] and Abbas Shafiee[d]*

[a]Iranian Research Institute of Plant Protection (IRIPP), Shahid Chamran Avenue, Yaman St. No 1; P.O. Box: 1454, Tehran, Iran
[b]Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[c]Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran
[d]Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
*E-mail: shafieea@tums.ac.ir

Received October 31, 2015
DOI 10.1002/jhet.2618
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



A series of aryltetralin lignans **7a–l** were synthesized as cytotoxic isodeoxypodophyllotoxin analogs. The title compounds **7a–l** were synthesized from the reaction of (+)-(*R*)-4-[benzo(*d*)(1,3)dioxol-5-ylmethyl]-dihydrofuran-2-(3*H*)-one with different arylaldehydes to afford benzyl alcohol analogs and subsequent cyclization with trifluoroacetic acid in dichromethane. The preliminary screening of the compounds against viability of blood cancer human cell line K562 revealed that compounds **7d**, **7e**, and **7f** had higher inhibitory activity at 10 μg/mL concentration compared with etoposide as reference drug.

J. Heterocyclic Chem., **00,** 00 (2016).

INTRODUCTION

Cancer is a wide group of diseases which can be triggered by environmental pollutants and genetic mutations, involving unregulated cell growth and division [1]. There are over 200 different known cancers that affect most areas of the body in humans [2]. Cancers figure among the leading causes of human death, and the number of people living beyond a cancer diagnosis reached nearly 14.5 million in 2014 [3]. Chemotherapy is an important option for treatment of patients with cancer, but prolonged treatment with chemotherapeutic agents can result in multidrug resistance. Furthermore, almost all the chemotherapeutic agents have severe side effects on normal tissues [4]. To overcome drug resistance and toxicity, development of new anticancer agents with better selectivity is an urgent need in medicinal chemistry [5].

A number of nonalkaloid toxin lignins such as podophyllotoxin (**1**; Fig. 1) have been isolated from plants and used as a potential lead molecule to yield analogs endowed with higher potency, lower toxicity, and better physicochemical properties [6]. For example, several clinically valuable anticancer drugs, such as etoposide (**2**, VP-16), etoposide phosphate (**3**), and teniposide (**4**, VM-26) have been derived from podophyllotoxin (**1**) and are currently in clinical use for the treatment of small cell lung cancer, testicular carcinoma, non-Hodgkin's lymphoma, and Kaposi's sarcoma [7,8]. While podophyllotoxin inhibits tubulin polymerization through interaction with the protein at the colchicine binding site, the semi-synthetic analogs such as etoposide inhibit DNA topoisomerase II, leading to blockade in the late S stage of the cell cycle [9].

Subsequently, the substantial interest has been focused on the 4-deoxy analog of podophyllotoxin (**5**), which was isolated from the root of *Anthriscus sylvestris*. 4-Deoxypodophyllotoxin (**5**) exhibited potent anticancer activity against various cell lines [10,11]. Further studies indicated that 4-deoxypodophyllotoxin (**5**) inhibits tubulin polymerization and also induces cell cycle arrest at G2/M through activation of caspase-3 and caspase-7, and upregulation of p53 and Bax [12,13]. Moreover, it was reported that 4′-demethyl-4-deoxypodophyllotoxin (**6**) had a comparable *in vitro* potency respect to 4-deoxypodophyllotoxin (**5**). However, the antitumor activity of 4′-demethyl-4-deoxypodophyllotoxin (**6**) in the BDF1/3LL model was substantially less than that of 4-deoxypodophyllotoxin (**5**) [14].

The structure activity relationship studies of podophyllotoxin and its analogs demonstrated that the integrity of rings A, B, and D is necessary for maintaining the anticancer activity, while rings C and E are suitable portions of the molecules for structural modifications. The investigations on the stereochemistry of podophyllotoxin family revealed that the 5a,8a-*trans* configuration is important for high cytotoxic activity [15]. Interestingly, Zavala et al. have reported that isodeoxypodophyllotoxin (**7a**) with 5,5a-*trans*-5a,8a-*trans* configuration has equipotent inhibition against microtubule assembly in comparison to

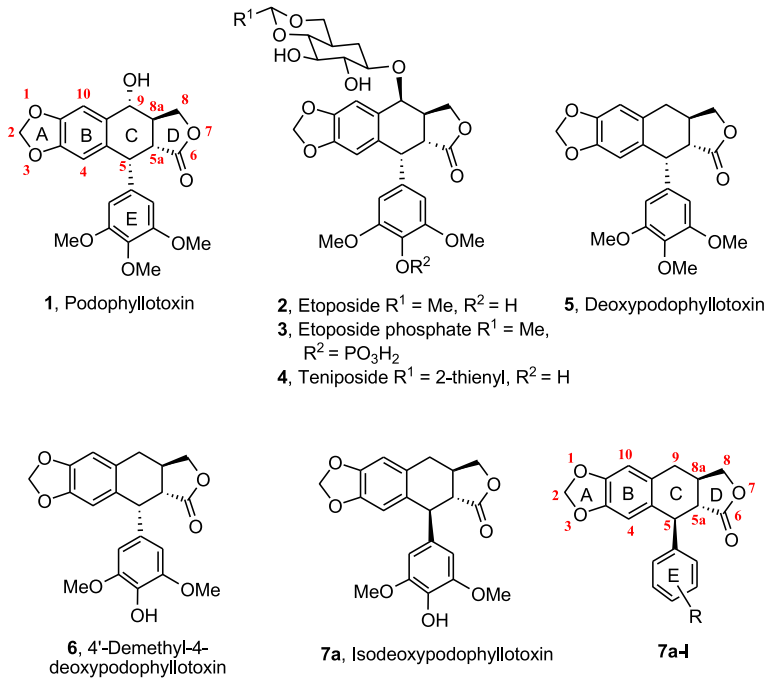
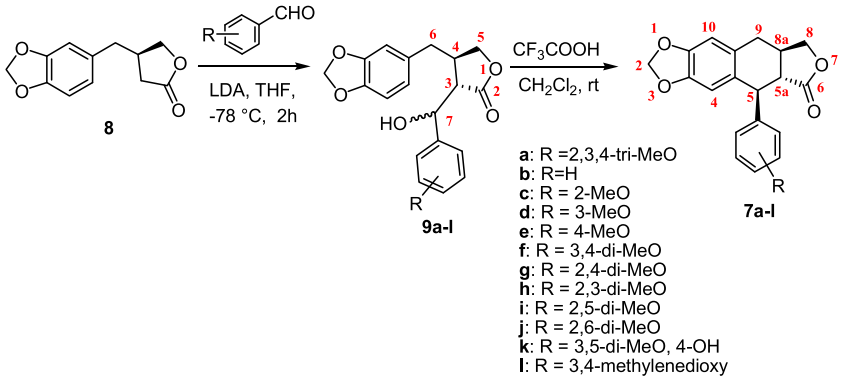


Figure 1. Structures of podophyllotoxins **1–4**, deoxypodophyllotoxins **5** and **6**, and isodeoxypodophyllotoxins **7a–l**. It should be noted that the atom numbering is based on the furo[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6-one structure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 1. Synthesis of isodeoxypodophyllotoxin analogs **7a–l**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



podophyllotoxin (bearing a 5,5a-*cis*-5a,8a-*trans* configuration) [16]. In continuation of our work on heterocyclic compounds [17–23], we describe here the synthesis and cytotoxic activity of isodeoxypodophyllotoxin derivatives with focusing on the modification of E ring (Fig. 1).

RESULTS AND DISCUSSIONS

Chemistry. Previously, Hanessian and Ninkovic have reported the synthesis of isodeoxypodophyllotoxin (**7a**), by using trimethylstannyl radical addition to a dienic system for the construction of the dibenzylbutyrolactone motif as well as the aryltetralin unit [24]. Furthermore, deoxypodophyllotoxin (**5**) was prepared from podophyllotoxin (**1**) by catalytic hydrogenolysis in the presence of 10% palladium/carbon [25]. In the present report, the synthesis of target compounds **7a–l** was performed according to the route illustrated in Scheme 1. The reaction of optically pure (*R*)-4-(3,4-methylenebenzyl) dihydrofuran-2(3*H*)-one (**8**) with various aromatic aldehydes in the presence of LDA at −78°C afforded benzyl alcohol analogs **9a-l**. The aldol products **9a–l** were mixture of two *syn*/*anti* diasteromers based on the *S* or *R* configuration of benzylic hydroxyl group [17]. Treatment of compounds **9a–l** with trifluoroacetic acid in dichromethane resulted in ring closure and formation of isodeoxypodophyllotoxin derivatives **7a–l**. The 5,5a-*trans*-

5a,8a-*trans* stereochemistry of compounds **7a–l** was confirmed by vicinal coupling of protons at the 5, 5a, and 8a positions. As illustrated in Figure 2, the H-5 protons of compounds **7a–l** appeared at 4.05–4.07 ppm as doublet with large coupling constants of 10.0–11.5 ppm. Also, the $J_{5a,8a}$ values of compounds **7a–l** were 13.0–13.8 ppm.

Cytotoxic activity. Primarily, the *in vitro* cytotoxic activity of the synthesized isodeoxypodophyllotoxin analogs **7a–l** were evaluated against blood cancer human cell line K562 at the concentrations of 10 and 50 µg/mL, in comparison to etoposide as reference drug. The growth inhibition values (%) of the compounds **7a–l** after 48 and 72 h incubation were listed in Table 1. As seen in Table 1, the percentages of inhibition for tested compounds at 10 µg/mL were in the range of 36–80% after maximum time of incubation 72 h. The obtained growth inhibition values at 10 µg/mL revealed that compounds **7d**, **7e**, and **7f** had higher inhibitory activity compared with etoposide. The maximum growth inhibition (87%) was observed with 4-methoxy analog **7e** at 50 µg/mL concentration, after 72 h incubation. The comparison of the growth inhibition values of unsubstituted compound **7b** and methoxy substituted derivatives **7c–e** demonstrated that the 3- or 4-methoxy substituent can improve the cytotxic activity. Furthermore, the 3,4-dimethoxy analog **7f** showed better inhibition compared with unsubstituted compound **7b**. Interestingly, the inhibitory activity of compounds **7d–f** was more than that of isodeoxypodophyllotoxin (**7a**). These finding showed that the 3,4,5-trimethoxy entity is not essential for activity. However, the presence of one or two methoxy groups at 3 and/or 4 positions can increase the activity. Other patterns of methoxy substituents were not favorable for activity, as observed with **7g–j** respect to the 3,4-dimethoxy analog **7f**.

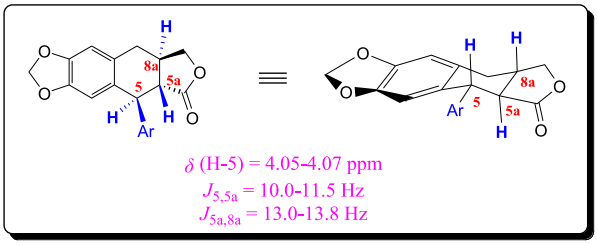


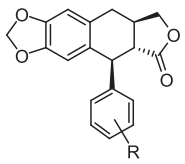
Figure 2. The 5,5a-*trans*-5a,8a-*trans* stereochemistry of compounds **7a–l**, confirmed by vicinal coupling of protons at the 5, 5a, and 8a positions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSIONS

We have synthesized a series of cytotoxic aryltetralin lignans, namely, isodeoxypodophyllotoxin analogs **7a–l**, starting from (+)-(*R*)-4-[benzo(*d*)(1,3)dioxol-5-ylmethyl]-dihydrofuran-2-(3*H*)-one. The reaction of the latter compound

Table 1

The percentages of growth inhibition of the compounds **7a–l** against human blood cancer cell line K562 at the concentrations of 10 and 50 µg/mL after 48 and 72 h incubation.



		48 h		72 h	
Compound	R	10 µg/mL	50 µg/mL	10 µg/mL	50 µg/mL
7a	3,4,5-tri-MeO	35 ± 2.7	43 ± 4.2	48 ± 3.5	46 ± 4.2
7b	H	22 ± 1.5	41 ± 3.7	48 ± 4.3	53 ± 4.3
7c	2-MeO	33 ± 3.4	39 ± 3.2	46 ± 3.6	56 ± 5.3
7d	3-MeO	64 ± 4.8	70 ± 5.7	80 ± 6.7	77 ± 8.2
7e	4-MeO	70 ± 5.9	57 ± 6.1	75 ± 6.6	87 ± 6.6
7f	3,4-di-MeO	74 ± 8.3	74 ± 5.7	72 ± 4.6	62 ± 4.6
7g	2,4-di-MeO	58 ± 4.8	28 ± 1.8	38 ± 3.1	41 ± 3.7
7h	2,3-di-MeO	42 ± 3.6	51 ± 6.3	66 ± 7.1	68 ± 5.8
7i	2,5-di-MeO	35 ± 3.2	36 ± 2.5	52 ± 4.8	43 ± 3.4
7j	2,6-di-MeO	36 ± 4.1	40 ± 2.8	36 ± 1.9	61 ± 4.9
7k	3,5-di-MeO, 4-OH	34 ± 4.1	69 ± 5.3	50 ± 4.5	46 ± 4.8
7l	3,4-O-CH_2-O	68 ± 5.3	47 ± 3.9	62 ± 4.8	58 ± 5.1
Etoposide		45.3 ± 6.7	ND[a]	68 ± 8.3	ND

[a]Not determined.

with different arylaldehydes afforded *syn*/*anti* diasteromers of (*3S*,*4R*)-4-[benzo(*d*)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(4-methoxyphenyl)methyl]-dihydrofuran-2(3*H*)-ones, which were treated with trifluoroacetic acid to give desired isodeoxypodophyllotoxin analogs **7a–l**. The cytotoxic activity of the compounds against blood cancer human cell line K562 demonstrated that 3-methoxy, 4-methoxy and 3,4-dimethoxy derivatives (compounds **7d**, **7e**, and **7f**, respectively) had higher inhibitons at 10 μg/mL concentration respect to the reference drug etoposide.

EXPERIMENTAL

Chemistry. The required chemicals and reagents were obtained from Merck and Sigma-Aldrich. The starting material (+)-(*R*)-4-[benzo(*d*)(1,3)dioxol-5-ylmethyl]-dihydrofuran-2-(3*H*)-one (**8**) was prepared according to the reported method [17]. The purity of all compounds was confirmed by thin-layer chromatography (TLC) using various solvents with different polarities. ^{1}H NMR spectra were recorded using a Bruker 500 spectrometer (Brucker, Rheinstetten, Germany), and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. The IR spectra were taken using Shimadzu IR prestige-21 spectrometer. Mass spectra were recorded on Agilent 6410 Triple Quad. LC/MS. The elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode, which were within ±0.4% of theoretical values for C, H, and N.

General procedure for the synthesis of (3S,4R)-4-[benzo(d)(1,3)dioxol-5-ylmethyl]-3-(hydroxy(aryl)methyl)-dihydrofuran-2(3H)-one derivatives 9a–l. A solution of compound **8** (70 mg, 0.3 mmol) in dry THF (0.5 mL) was added to a solution of LDA (0.4 mL, 0.6 mmol) in THF (3 mL) at −78°C and stirred for 30 min. To this, solution was added appropriate aldehyde (0.36 mmol) and HMPA (0.1 mL, 0.6 mmol) and the mixture was stirred for 2 h, then quenched with saturated aq. NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 × 20 mL). The extract was washed successively with water (3 mL), 10% HCl (2 mL), water, saturated aq. $NaHCO_3$ and NaCl. Organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a viscous oil. The residue was purified by TLC chromatography (silica gel, hexane/EtOAc, 5:1) to give compounds **9a–l** as mixture of diasteromers (*anti*/*syn*).

Compounds **9a**, **9d**, and **9e** were reported in the literature [17], and physicochemical and spectroscopic data of remaining compounds were described here:

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(phenyl)methyl]-dihydrofuran-2(3H)-one (9b). Yield 74% as a mixture of diasteromers (*anti*/*syn*: 54/46); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.96 (dd, J = 4.8 Hz, J = 13.8 Hz, H-6), 2.09 (dd, J = 3.6 Hz, J = 13.8 Hz, H-6), 2.18 (dd, J = 6.4 Hz, J = 13.8 Hz, H-6), 2.30 (dd, J = 9.0 Hz, J = 13.8 Hz, H-6), 2.44 (m, –H4), 2.61 (t, J = 7.4 Hz, H-3), 2.65 (dd, J = 3.1 Hz, J = 7.4 Hz, H-3), 2.85 (m, H-4), 3.89 *anti* (t, J = 9.1 Hz, H-5), 3.93 *syn* (t, J = 8.6 Hz, H-5), 4.12 *anti* (t, J = 8.5 Hz, H-5), 4.89 *anti* (d, J = 8.3 Hz, H-7), 5.41 *syn* (s, J = 2.0 Hz, H-7), 5.92 and 5.96 (2 s, 2H, OCH_2O), 6.29–6.33 (m, 2H, Ar), 6.63 (m, 1 H, Ar), 7.30–7.45 (m, 5 H, Ph). FT-IR (film) ν_{max}: 3450, (OH), 1780 (C=O) cm^{-1}. ESI-Mass *m*/*z*: 349 $[M+Na]^+$. *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.76; H, 5.49.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(2-methoxyphenyl)methyl]-dihydrofuran-2(3H)-one (9c). Yield 75% as a mixture of diasteromers (*anti*/*syn*: 55/45); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.06 (dd, J = 4.9 Hz, J = 13.8 Hz, H-6), 2.18 (dd, J = 9.9 Hz, J = 13.8 Hz, H-6), 2.27 (dd, J = 6.9 Hz, J = 13.7 Hz, H-6), 2.38 (dd, J = 8.7 Hz, J = 13.7 Hz, H-6), 2.47 (m, H-4), 2.62 (dd, J = 8.3 Hz, J = 9.3 Hz, H-3), 2.66 (dd, J = 2.9 Hz, J = 6.8 Hz, H-3), 2.90 (m, H-4), 3.79 (s, –OMe), 3.88 (s, –OMe), 3.89 *anti* (m, H-5), 3.99 *syn* (m, J = 6.3Hz, J = 7.9 Hz, H-5), 4.14 *anti* (t, J = 6.9 Hz, H-5), 4.46 *syn* (t, J = 7.9 Hz, H-5), 4.85 *anti* (d, J = 11.2 Hz, H-7), 5.22 *syn* (s, J = 5.7 Hz, H-7), 5.90 and 5.91 (2 s, 2H, OCH_2O), 6.27–6.34 (m, 2H, Ar), 6.61 (d, J = 7.8 Hz, Ar), 6.66 (d, J = 8.4 Hz, Ar), 6.82–6.99 (m, Ph), 7.25–7.34 (m, Ph). FT-IR (film) ν_{max}: 3447 (OH), 1763 (lactone) cm^{-1}. ESI-Mass *m*/*z*: 379 $[M+Na]^+$. *Anal.* Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.65; H, 5.42.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(3,4-dimethoxyphenyl)methyl]-dihydrofuran-2(3H)-one (9f). FT-IR (film) ν_{max}: 3450, (OH), 1780 (C=O) cm^{-1}. ESI-Mass *m*/*z*: 409 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{22}O_7$: C, 67.41; H, 5.66. Found: C, 67.65; H, 5.42.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(2,4-dimethoxyphenyl)methyl]-dihydrofuran-2(3H)-one (9g). Yield 70% as a mixture of diasteromers (*anti*/*syn*: 54/46); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.06–2.38 (m, 2H, $–CH_2$), 2.54–2.82 (m, 2H, $–CH_2$), 2.01 (dd, J = 4.9 Hz, J = 13.8 Hz, H-6), 2.16 (dd, J = 9.9 Hz, J = 13.8 Hz, H-6), 2.22 (dd, J = 6.9 Hz, J = 13.7 Hz, H-6), 2.37 (dd, J = 8.7 Hz, J = 13.7 Hz, H-6), 2.47 (m, H-4), 2.92 (dd, J = 8.3 Hz, J = 9.3 Hz, H-3), 3.08 (dd, J = 5.0 Hz, J = 15.3 Hz, H-3), 3.17 (m, H-4), 3.74 (s, –OMe), 3.80 (s, –OMe), 3.91 (s, –OMe), 3.98 *anti* (m, J = 9.0 Hz, H-5), 4.13 *syn* (dd, J = 7.25Hz, J = 14.4 Hz, H-5), 4.46 *anti* (t, J = 8.0 Hz, H-5), 4.512 *syn* (m, H-7), 4.72 *anti* (d, J = 8.6 Hz, H-7), 5.09 *syn* (s, J = 5.6 Hz, H-7), 5.86 (s, 2H, OCH_2O), 6.27–6.68 (m, 3H, aromatic H), 7.33 (d, 1H, J = 5.7 Hz, aromatic). FT-IR (film) ν_{max}: 3460, (OH), 1770 (C=O) cm^{-1}. ESI-Mass *m*/*z*: 409 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{22}O_7$: C, 67.41; H, 5.66. Found: C, 67.55; H, 5.72.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(2,3-dimethoxyphenyl)methyl]-dihydrofuran-2(3H)-one (9h). Yield 65% as a mixture of diasteromers (*anti*/*syn*: 50/50); ^{1}H

NMR (500 MHz, $CDCl_3$) δ: 2.01 (dd, J = 3.9 Hz, J = 13.5 Hz, H-6), 2.08 (dd, J = 5.9 Hz, J = 13.5 Hz, H-6), 2.22 (dd, J = 9.5 Hz, J = 13.5 Hz, H-6), 2.58 (dd, J = 8.9 Hz, J = 13.5 Hz, H-6), 2.66 and 2.82 (m, H-3), 2.93 (dd, J = 8.5 Hz, 12.7 Hz, H-3), 3.86 (s, 6H, –OMe), 3.89 (s, 3H, –OMe), 3.98–4.22 (m, 2H, H-5), 4.81 *anti* (d, J = 8.2 Hz, H-7), 5.62 *syn* (s, J = 2.7 Hz, H-7), 5.91 (s, 2H, OCH_2O), 5.83–7.02 (m, aromatic H). FT-IR (film) ν_{max}: 3550, (OH), 1775 (C=O) cm^{-1}. ESI-Mass *m/z*: 409 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{22}O_7$: C, 67.41; H, 5.66. Found: C, 67.56; H, 5.65.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(2,5-dimethoxyphenyl)methyl]-dihydrofuran-2(3H)-one (9i). Yield 55% as a mixture of diasteromers (*anti*/*syn*: 46/54); ^1H NMR (500 MHz, $CDCl_3$) δ: 2.04–2.09 (m, H-6), 2.39 (m, H-6), 2.39 (dd, J = 8.9 Hz, J = 13.5 Hz, H-6), 2.76 and 2.97 (m, H-3), 3.79 and 3.87 (2 s, 6H, -OMe), 3.97–4.47 (m, 2H, H-5), 4.80 *anti* (d, J = 12.5 Hz, H-7), 5.15 *syn* (s, J = 6.5 Hz, H-7), 5.89 (s, 2H, OCH_2O), 5.83–7.02 (m, aromatic H). FT-IR (film) ν_{max}: 3450, (OH), 1780 (C=O) cm^{-1}. ESI-Mass *m/z*: 409 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{22}O_7$: C, 67.41; H, 5.66. Found: C, 67.55; H, 5.62.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(2,6-dimethoxyphenyl)methyl]-dihydrofuran-2(3H)-one (9j). Yield 57% as a mixture of diasteromers (*anti*/*syn*: 73/27); ^1H NMR (500 MHz, $CDCl_3$) δ: 2.15–2.36 (m, H-6), 2.22 (dd, J = 6.9 Hz, J = 13.7 Hz, H-6), 2.37 (dd, J = 8.7 Hz, J = 13.7 Hz, H-6), 2.50 (m, H-4), 2.77 (dd, J = 6.1 Hz, J = 14.1 Hz, H-3), 2.89 (m, H-3), 2.98 (m, H-4), 3.68 (s, –OMe), 3.83 (s, –OMe), 3.92 *anti* (t, J = 9.0 Hz, H-5), 3.94 *syn* (m, H-5), 4.13 *anti* (t, J = 9.0 Hz, H-5), 4.47 *syn* (t, J = 7.4 Hz, H-7), 4.81 *anti* (d, J = 12.1 Hz, H-7), 5.17 *syn* (s, J = 6.2 Hz, H-7), 5.91 and 5.92 (2 s, 2H, OCH_2O), 6.24 (s, Ar), 630 (s, Ph), 6.33 (m, Ar), 6.63 (d, J = 12.5 Hz, Ar), 6.85 (d, J = 12.5 Hz, Ar), FT-IR (film) ν_{max}: 3460, (OH), 1780 (C=O) cm^{-1}. ESI-Mass *m/z*: 409 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{22}O_7$: C, 67.41; H, 5.66. Found: C, 67.60; H, 5.26.

(3S,4R)-4-[Benzo(d)(1,3)dioxol-5-ylmethyl]-3-[hydroxy(4-hydroxy-3,5-dimethoxyphenyl) methyl]-dihydrofuran-2(3H)-one (9k). FT-IR (film) ν_{max}: 3430, (OH), 1720 (C=O) cm^{-1}. ESI-Mass *m/z*: 425 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.53; H, 5.36.

3-[Benzo(1,3)dioxol-5-yl-hydroxy-methyl]-4-benzo[1,3]dioxol-5-ylmethyl-dihydro-furan-2-one (9l). FT-IR (film) ν_{max}: 3450, (OH), 1750 (C=O) cm^{-1}. ESI-Mass *m/z*: 393 $[M+Na]^+$. *Anal.* Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.65; H, 4.96.

Typical procedure for the synthesis of compounds 7a–l: synthesis of compound 7f. To a solution of compound **9f** (30 mg, 0.077 mmol) in CH_2Cl_2 (0.5 mL), CF_3COOH (0.3 mL) was added, and the solution was stirred at room temperature overnight. After removing the excess of CF_3COOH by air flow under hood, the crude product was washed with saturated aq. $NaCO_3$ and extracted with CH_2Cl_2 and dried ($MgSO_4$). After evaporation of solvent, the resulting residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 3:1) to give compound **7f** (25 mg, yield 95%).

5-(3,4,5-Trimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7a). Yield 85%; mp 249–254°C; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.49 (dd, 1H, J = 10.9 Hz, J = 13.7 Hz , 5a-H), 2.62 (m, 1H, 8a-H), 2.96 (m, 2H, 9-H), 3.90 (m, 9H, –OMe), 3.98 (dd, 1H, ABX, J_{AB} = 8.5 Hz, J_{BX} = 10.5 Hz, 8-H), 4.06 (d, 1H, J = 10.6 Hz, 5-H), 4.52 (dd, 1H, ABX, J_{AB} = 6.5 Hz, J_{AX} = 8.5 Hz, 8-H), 5.90 (s, 2H, OCH_2O), 6.34 (s, 1H, 4-H), 6.60 (s, 1H, 10-H), 6.61 (s, 1H, aromatic H), 6.67 (s, 1H, aromatic H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 399 $[M+H]^+$, 422 $[M+Na]^+$. *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.45; H, 5.49.

5-(Phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7b). Yield 60%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.53 (dd, 1H, J = 11.5 Hz, J = 13.5 Hz, 5a-H), 2.78 (m, 1H, 8a-H), 2.97 (m, 2H, 9-H), 3.98 (dd, 1H, ABX, J_{AB} = 8.4 Hz, J_{BX} = 10.5 Hz, 8-H), 4.06 (d, 1H, J = 11.5 Hz, 5-H), 4.52 (dd, 1H, ABX, J_{AB} = 6.5 Hz, J_{AX} = 8.4 Hz, 8-H), 5.87 (2 s, 2H, OCH_2O), 6.32 (s, 1H, 4-H), 6.60 (s, 1H, 10-H), 6.66-7.52 (m, 5H, Ph). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 331 $[M+Na]^+$. *Anal.* Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.25; H, 5.09.

5-(2-Methoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7c). Yield 65%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.57 (dd, 1H, J = 10.5 Hz, J = 13.5 Hz, 5a-H), 2.69 (m, 1H, 8a-H), 2.98 (m, 2H, 9-H), 3.85 (s, 3H, –OMe), 3.94 (dd, 1H, ABX, J_{AB} = 7.0 Hz, J_{BX} = 9.5 Hz, 8-H), 4.07 (d, 1H, J = 10.5 Hz, 5-H), 4.46 (dd, 1H, ABX, J_{AB} = 6.0 Hz, J_{AX} = 7.0 Hz, 8-H), 5.84 (2 s, 2H, OCH_2O), 6.29 (s, 1H, 4-H), 6.58 (s, 1H, 10-H), 6.69-7.17 (m, 4H, aromatic H). FT-IR (film) ν_{max}: 1790 (lactone) cm^{-1}. ESI-Mass *m/z*: 361 $[M+Na]^+$. *Anal.* Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.05; H, 5.59.

5-(3-Methoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7d). Yield 55%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.38 (dd, 1H, J = 10.0 Hz, J = 13.8 Hz, 5a-H), 2.48 (m, 1H, 8a-H), 2.89 (m, 2H, 9-H), 3.80 (s, 3H, –OMe), 3.97 (dd, 1H, ABX, J_{AB} = 8.6 Hz, J_{BX} = 11.8 Hz, 8-H), 4.06 (d, 1H, J = 10.0 Hz, 5-H), 4.36 (dd, 1H, ABX, J_{AB} = 6.3 Hz, J_{AX} = 8.7 Hz, 8-H), 5.88 (s, 2H, OCH_2O), 6.25 (s, 1H, 4-H), 6.66 (s, 1H, 8-H), 6.73–7.36 (m, 3H, aromatic H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 361 $[M+Na]^+$. *Anal.* Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 70.75; H, 5.21.

5-(4-Methoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7e). Yield 90%; mp 228–232°C; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.51 (dd, 1H, J = 11.0 Hz, J = 13.5 Hz, 5a-H), 2.60 (m, 1H, 8a-H), 2.96 (m, 2H, 9-H), 3.80 (s, 3H, –OMe), 3.97 (dd, 1H, ABX,

J_{AB} = 8.5 Hz, J_{BX} = 10.5 Hz, 8-H), 4.07 (d, 1H, J = 11.0 Hz, 5-H), 4.51 (dd, 1H, ABX, J_{AB} = 7.0 Hz, J_{AX} = 8.5 Hz, 8-H), 5.87 (2 s, 2H, OCH_2O), 6.29 (s, 1H, 4-H), 6.59 (s, 1H, 10-H), 6.87 (d, 2H, J = 9.0 Hz, aromatic H), 7.12 (d, 2H, J = 9.0 Hz, aromatic H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 361 $[M+Na]^+$. *Anal.* Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 70.85; H, 5.59.

5-(3,4-Dimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7f). Yield 95%; mp 220–225°C; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.50 (dd, 1H, J = 11.2 Hz, J = 13.6 Hz, 5a-H), 2.61 (m, 1H, 8a-H), 2.95 (m, 2H, 9-H), 3.85 and 3.88 (2 s, 6H. –OMe), 3.98 (dd, 1H, ABX, J_{AB} = 8.9 Hz, J_{BX} = 10.5 Hz, 8-H), 4.06 (d, 1H, J = 11.1 Hz, 5-H), 4.52 (dd, 1H, ABX, J_{AB} = 6.8Hz, J_{AX} = 8.4 Hz, 8-H), 5.89 (2 s, 2H, OCH_2O), 6.34 (s, 1H, 4-H), 6.60 (s, 1H, 10-H), 6.78 (s, 1H, Ph-H), 6.81 (d, 1H, J = 8.2 Hz, Ph-H), 6.85 (d, 1H, J = 8.2 Hz, Ph-H). FT-IR (film) ν_{max}: 1790 (lactone) cm^{-1}. ESI-Mass *m/z*: 391 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.32; H, 5.59.

5-(2,4-Dimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7g). Yield 70%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.53 (dd, 1H, J = 11.0 Hz, J = 13.5 Hz, 5a-H), 2.68 (m, 1H, 8a-H), 2.96 (m, 2H, 9-H), 3.81 (s, 6H, –OMe), 3.95 (dd, 1H, ABX, J_{AB} = 8.9 Hz, J_{BX} = 10.5 Hz, 8-H), 4.06 (d, 1H, J = 11.0 Hz, 5-H), 4.50 (dd, 1H, ABX, J_{AB} = 6.5Hz, J_{AX} = 8.9 Hz, 8-H), 5.85 (2 s, 2H, OCH_2O), 6.25 (s, 1H, 4-H), 6.29 (dd, 1H, J = 2.5 Hz, J = 8.5 Hz, Ph-H), 6.47 (d, 1H, J = 2.5 Hz, Ph-H), 6.57 (s, 1H, 10-H), 6.60 (d, 1H, J = 8.2 Hz, Ph-H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 391 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.52; H, 5.29.

5-(2,3-Dimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7h). Yield 64%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.55 (dd, 1H, J = 10.4 Hz, J = 13.5 Hz, 5a-H), 2.60 (m, 1H, 8a-H), 3.06 (m, 2H, 9-H), 3.77 (2 s, 6H, –OMe), 3.98 (dd, 1H, ABX, J_{AB} = 8.5 Hz, J_{BX} = 10.5 Hz, 8-H), 4.05 (d, 1H, J = 10.4 Hz, 5-H), 4.55 (dd, 1H, ABX, J_{AB} = 6.0 Hz, J_{AX} = 8.5 Hz, 8-H), 5.82 (2 s, 2H, OCH_2O), 6.23 (s, 1H, 4-H), 6.45 (s, 1H, 10-H), 6.51–6.90 (m, 3H, aromatic H). FT-IR (film) ν_{max}: 1796 (lactone) cm^{-1}. ESI-Mass *m/z*: 391 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.32; H, 5.59.

5-(2,5-Dimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7i). Yield 61%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.55 (dd, 1H, J = 11.0 Hz, J = 13.0 Hz, 5a-H), 2.72 (m, 1H, 8a-H), 2.97 (m, 2H, 9-H), 3.68 (s, 6H, –OMe), 3.95 (dd, 1H, ABX, J_{AB} = 8.4 Hz, J_{BX} = 11.5 Hz, 8-H), 4.06 (d, 1H, J = 11.0 Hz, 5-H), 4.50 (dd, 1H, ABX, J_{AB} = 7.0Hz, J_{AX} = 8.4 Hz, 8-H), 5.85 (2 s, 2H, OCH_2O), 6.24 (s, 1H, 4-H), 6.29 (s, 1H, aromatic H), 6.57 (s, 1H, 10-H), 6.61 (dd, 1H, J = 7.5 Hz, Ph-H), 6.86 (d, 1H, J = 7.5 Hz, aromatic H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 391 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.52; H, 5.29.

5-(2,6-Dimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7j). Yield 54%; viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.55 (dd, 1H, J = 11.5 Hz, J = 13.0 Hz, 5a-H), 2.61 (m, 1H, 8a-H), 2.91 (m, 2H, 9-H), 3.77 (2 s, 6H, –OMe), 3.97 (dd, 1H, ABX, J_{AB} = 8.5 Hz, J_{BX} = 11.5 Hz, 8-H), 4.05 (d, 1H, J = 11.5 Hz, 5-H), 4.54 (dd, 1H, ABX, J_{AB} = 7.0 Hz, J_{AX} = 8.5 Hz, 8-H), 5.85 (2 s, 2H, OCH_2O), 6.42 (s, 1H, 4-H), 6.51–6.92 (m, 3H, aromatic H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 391 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.52; H, 5.34.

5-(4-Hydroxy-3,5-dimethoxy-phenyl)-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7k). Yield 80%; mp 240–246°C; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.49 (dd, 1H, J = 11.1 Hz, J = 13.8 Hz, 5a-H), 2.62 (m, 1H, 8a-H), 2.96 (m, 2H, 9-H), 3.99 (m, 6H, –OMe), 4.02 (dd, 1H, ABX, J_{AB} = 8.6 Hz, J_{BX} = 11.1 Hz, 8-H), 4.05 (d, 1H, J = 11.1 Hz, 5-H), 4.52 (dd, 1H, ABX, J_{AB} = 6.6 Hz, J_{AX} = 8.6 Hz, 8-H), 5.88 (2 s, 2H, OCH_2O), 6.35 (s, 1H, 4-H), 6.63 (s, 2H, aromatic H), 6.66 (s, 1H, 10-H). FT-IR (film) ν_{max}: 1790 (lactone) cm^{-1}. ESI-Mass *m/z*: 407 $[M+Na]^+$. *Anal.* Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.40; H, 5.39.

5-[Benzo(1,3)dioxol-5-yl]-5,8,8a,9-tetrahydro-5aH-furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6-one (7l). Yield 89%; mp 250–256°C; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.50 (dd, 1H, J = 11.1 Hz, J = 13.6 Hz, 5a-H), 2.60 (m, 1H, 8a-H), 2.95 (m, 2H, 9H), 3.98 (dd, 1H, ABX, J_{AB} = 8.9 Hz, J_{BX} = 10.5 Hz, 8-H), 4.06 (d, 1H, J = 11.1 Hz, 5-H), 4.52 (dd, 1H, ABX, J_{AB} = 6.8 Hz, J_{AX} = 8.4 Hz, 8-H), 5.89 (s, 2H, OCH_2O), 5.95 (s, 2H, OCH_2O), 6.30 (s, 1H, 4-H), 6.60 (s, 2H, 10-H), 6.78 (s, 2H, aromatic H). FT-IR (film) ν_{max}: 1795 (lactone) cm^{-1}. ESI-Mass *m/z*: 375 $[M+Na]^+$. *Anal.* Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.32; H, 4.50.

Biology. ***Reagents and chemicals.*** RPMI 1640 and fetal bovine serum (FBS) were purchased from Gibco BRL (Grand Island, NY). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), trypsin–EDTA solution and dimethyl sulphoxide (DMSO) were obtained from Sigma (Saint Louis, MO, USA). Penicillin/streptomycin was purchased from Invitrogen (San Diego, CA, USA).

Cell lines and cell culture. Human blood cancer cell line K562 was obtained from the National Cell Bank of Iran, Pasteur Institute, Tehran, Iran, and cultured at a density of $3–5 \times 10^4$/mL RPMI 1640 medium supplemented with FBS (10%, v/v), streptomycin (100 µg/mL), and penicillin (100 U/mL) and kept at 37°C in a 5% CO_2 humidified atmosphere. Drug treatments were usually performed 24 h after seeding the cells.

Cytotoxicity assay. The *in vitro* cytotoxic activity of all synthesized compounds was determined against human blood cancer cell line K562 using MTT colorimetric assay [26]. Exponentially growing cells (4×10^4 cells/well) were seeded in 96 well plates in RPMI with 10% FBS and incubated for 24 h. After treatment of cells with different concentrations of test compounds for 48 and 72 h at 37°C, the medium was removed and phenol red-free medium with FBS was added to cells. Then, MTT solution was added to each well (2 mg/mL) and incubated for 4 h. The viable cell number is directly proportional to the formation of formazan. After that, the formed formazan dye in each well was dissolved in isopropyl alcohol and the absorbance was measured using a microplate reader at 492 nm. In each plate, there were control wells (cells without test compounds) and blank wells (the medium with 0.1% DMSO). The percentage of cell viability versus control was assessed by the formula $[1 - (\text{absorbance of treated cells/absorbance of control cells})] \times 100$.

Acknowledgment. This work was supported by grants from the Iran National Science Foundation and Research Council of Tehran University of Medical Sciences.

REFERENCES AND NOTES

[1] Ducasse, H.; Arnal, A.; Vittecoq, M.; Daoust, S. P.; Ujvari, B.; Jacqueline, C.; Tissot, T.; Ewald, P.; Gatenby, R. A.; King, K. C.; Bonhomme, F.; Brodeur, J.; Renaud, F.; Solary, E.; Roche, B.; Thomas, F. Evol Appl 2015, 8, 527.

[2] Hasima, N.; Aggarwal, B. B. Int J Biochem Mol Biol 2012, 3, 328.

[3] National Cancer Institute. http://www.cancer.gov/about-cancer/what-is-cancer/statistics.

[4] Kunjachan, S.; Rychlik, B.; Storm, G.; Kiessling, F.; Lammers, T. Adv Drug Deliv Rev 2013, 65, 1852.

[5] Emami, S.; Dadashpour, S. Eur J Med Chem 2015, 102, 611.

[6] Wang, C. Y.; Bai, X. Y.; Wang, C. H. Am J Chin Med 2014, 42, 543.

[7] Kamal, A.; Ali Hussaini, S. M.; Rahim, A.; Riyaz, S. Expert Opin Ther Pat 2015, 25, 1025.

[8] You, Y. Curr Pharm Des 2005, 11, 1695.

[9] Gordaliza, M. Clin Transl Oncol 2007, 9, 767.

[10] Khaled, M.; Jiang, Z. Z.; Zhang, L. Y. J Ethnopharmacol 2013, 149, 24.

[11] Muto, N.; Tomokuni, T.; Haramoto, M.; Tatemoto, H.; Nakanishi, T.; Inatomi, Y.; Murata, H.; Inada, A. Biosci Biotechnol Biochem 2008, 72, 477.

[12] Shin, S. Y.; Yong, Y.; Kim, C. G.; Lee, Y. H.; Lim, Y. Cancer Lett 2010, 287, 231.

[13] Yong, Y.; Shin, S. Y.; Lee, Y. H.; Lim, Y. Bioorg Med Chem Lett 2009, 19, 4367.

[14] Terada, T.; Fujimoto, K.; Nomura, M.; Yamashita, J.; Kobunai, T.; Takeda, S.; Wierzba, K.; Yamada, Y.; Yamaguchi, H. Chem Pharm Bull 1992, 40, 2720.

[15] Gordaliza, M.; MaMiguel del Corral, J.; Castro, M. A.; López-Vázquez, M.; García, P. A.; San Feliciano, A.; García-Grávalos, M. Bioorg Med Chem Lett 1995, 5, 2465.

[16] Zavala, F.; Guenard, D.; Robin, J. P.; Brown, E. J Med Chem 1980, 23, 546.

[17] Heidary Alizadeh, B.; Foroumadi, A.; Emami, S.; Khoobi, M.; Panah, F.; Ardestani, S. K.; Shafiee, A. Eur J Med Chem 2010, 45, 5979.

[18] Heidary Alizadeh, B.; Foroumadi, A.; Kobarfard, F.; Saeedi, M.; Shafiee, A. J Heterocyclic Chem 2015, 52, 1693.

[19] Mohammadhosseini, N.; Moradi, S.; Khoobi, M.; Shafiee, A. J Heterocyclic Chem 2015. DOI:10.1002/jhet.2470.

[20] Rahmani-Nezhad, S.; Safavi, M.; Pordeli, M.; Kabudanian Ardestani, S.; Khosravani, L.; Pourshojaei, Y.; Mahdavi, M.; Emami, S.; Foroumadi, A.; Shafiee, A. Eur J Med Chem 2014, 86, 562.

[21] Mahdavi, M.; Pedrood, K.; Safavi; Saeedi, M.; Pordeli, M.; Kabudanian Ardestani, S.; Emami, S.; Adib, M.; Foroumadi, A.; Shafiee, A. Eur J Med Chem 2015, 95, 492.

[22] Ramazani, A.; Khoobi, M.; Torkaman, A.; Zeinali Nasrabadi, F.; Forootanfar, H.; Shakibaie, M.; Jafari, M.; Ameri, A.; Emami, S.; Faramarzi, M. A.; Foroumadi, A.; Shafiee, A. Eur J Med Chem 2014, 78, 151.

[23] Molaverdi, F.; Khoobi, M.; Emami, S.; Alipour, M.; Firuzi, O.; Foroumadi, A.; Dehghan, G.; Miri, R.; Shaki, F.; Jafarpour, F.; Shafiee, A. Eur J Med Chem 2013, 68, 103.

[24] Hanessian, S.; Ninkovic, S. Can J Chem 1996, 74, 1880.

[25] Xu, H.; Wang, J. J Bioorg Med Chem Lett 2010, 20, 2500.

[26] Mosmann, T. J Immunol Methods 1983, 65, 55.