

Synthesis of some novel dibromo-2-arylquinazolinone derivatives as cytotoxic agents

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Abstract

Recently the quinazoline derivatives have attracted much attention for their anticancer properties. In this study a series of new brominated quinazoline derivatives (**1a-1g**) were synthesized in two steps. In the first step we used N-bromosuccinimide to brominate the anthranilamid. Then in the second step we closed the quinazoline ring by different aromatic aldehydes. Our aldehydes contain different electron donating or electron withdrawing groups at different positions of the aromatic ring. The chemical structures of products were confirmed by spectroscopic methods such as IR, ¹HNMR, ¹³CNMR, and mass spectroscopy. The cytotoxic activities of the compounds were assessed on three cancerous cell lines including MCF-7, A549, and SKOV3 using colorimetric MTT cytotoxic assay in comparison with cisplatin as a standard drug. Our results collectively indicated that **1f** and **1g**, exhibited the best anti-proliferative activities on three investigated cancerous cell lines.

Keywords: Anticancer; Cytotoxicity; MTT; Quinazolinone.

INTRODUCTION

Cancer is commonly defined by irregular cellular proliferation. In cancerous cells, there is an abnormal response to the checkpoint mechanisms regulating cell division; hence, the cells remain to divide until they finally kill the host (1). Although current anti-cancer compounds make a significant contribution in cancer treatment there is a continuing search to improve anticancer pharmaceuticals (2). There are many reports about the incidence and prevalence of mortality from cancer (3). Quinazoline derivatives are an important class of compounds in medicinal chemistry with a wide variety of biological activities such as antimicrobial, antifungal, antiviral, antiinflammatory, anticonvulsant, analgesic, antitubercular, anti-HIV, and anticancer activities (13). Interests in quinazolines as anticancer agents have further increased since the discovery of raltitrexed. These compounds exert their antitumor activity through inhibition of the DNA repair enzyme system

(14). Quinazoline is a nitrogen-containing heterocyclic scaffold which is also known as 5,6-benzopyrimidine or benzo pyrimidine (5).

In this regard a vast number of quinazoline derivatives have been synthesized to provide synthetic drugs as more effective medicines (5). Amongst the different quinazolinone categories (Fig. 1), 2-substituted-4(3H)-quinazolinones is being studied extensively as an important pharmacophore which are the most prevalent pharmaceutical agents (7,8). The present study aimed to synthesize and evaluate the biological activity of some new quinazoline derivatives as potential cytotoxic agents. In continuation of our previous studies (15-17), here a new series of quinazoline compounds were synthesized and evaluated against three human cancer cell lines, MCF-7 (breast cancer), A549 (lung cancer), and SKOV3 (ovarian cancer) using the colorimetric MTT cytotoxic assay.

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Website: <http://rps.mui.ac.ir>

DOI: 10.4103/1735-5362.253358

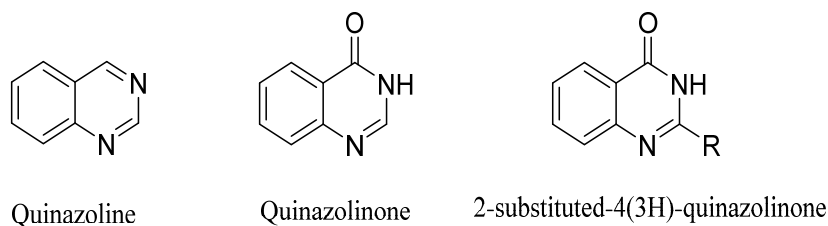


Fig. 1. Different quinazoline scaffolds

MATERIALS AND METHODS

All chemicals and solvents were purchased from Merck (Germany). Infrared (IR) spectra were run on a Shimadzu FTIR-8300 spectrophotometer (USA), proton nuclear magnetic resonance ($^1\text{H-NMR}$, 300 MHz), and carbon-13-NMR ($^{13}\text{C-NMR}$, 75 MHz) were run on a Bruker advanced DPX-250, FT-NMR spectrometer (Germany). Mass spectra were recorded on an Agilent 7890A-GC, Agilent 7000 Series Triple Quad-MS spectrometer (USA).

General procedure for the synthesis of dibromo anthranilamide

A mixture of 2-aminobenzamide and N-bromosuccinimide in chloroform was stirred at room temperature for 4 h. The solvent was removed by vacuum evaporation, and the crude product was purified by column chromatography over silica gel to provide dibromoanthranilamide (Scheme 1).

General procedure for the synthesis of dibromo-2-arylquinazolinone (1a-1g)

A mixture of 2-amino-3,5-dibromobenzamide and appropriate aromatic aldehyde in ethanol were refluxed for 3 h. Then CuCl_2 (3 eq) was added and refluxed for another 3 h at 70 °C. The progress of the reaction was checked by thin layer chromatography (TLC). After completion the reaction, the mixture was filtered, washed by cold ethanol and then recrystallized with hot ethanol to get the pure final compounds (Scheme 2).

Synthesis details and spectral data of products

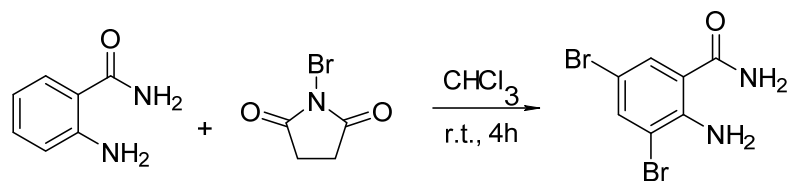
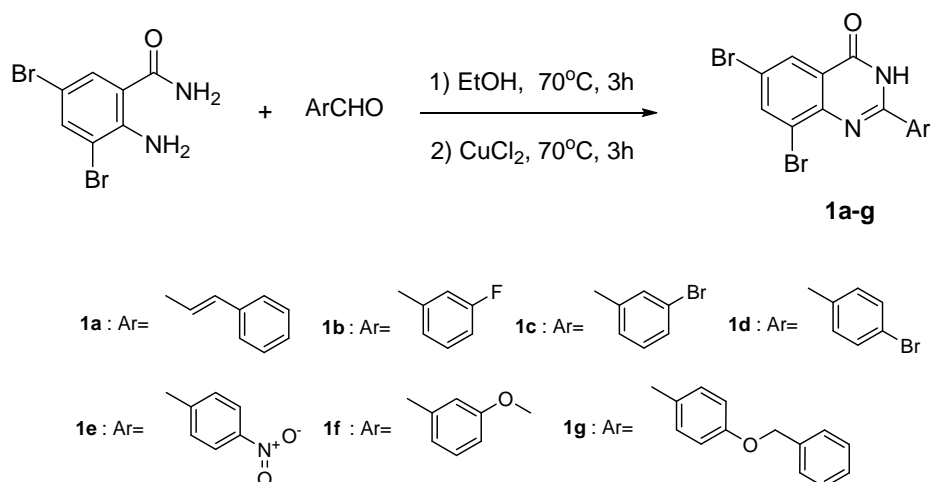
6,8-dibromo-2-styrylquinazolin-4(3H)-one (1a)

2-Amino-3,5 - dibromobenzamide (0.880 g)

was reacted with cinnamaldehyde (0.476 g). IR (KBr) ν (cm^{-1}): 3367 (N-H stretch), 3173-3074 (C-H stretch, aromatic), 2919 (C-H stretch, aliphatic), 1672 (C=O amid), 1581 (N-H bending), 691 (C-Br stretch). $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm): 12.81 (s, 1H, NH), 8.43 (d, 1H, $J = 1.8$ Hz, aromatic), 8.25 (d, 1H, $J = 1.8$ Hz, aromatic), 8.08 (d, 1H, $J = 12$ Hz, alkene), 7.75-7.77 (m, 2H, aromatic), 7.51-7.59 (m, 3H, aromatic), 7.08 (1H, d, $J = 12$ Hz, alkene). $^{13}\text{C-NMR}$ (75 MHz, DMSO- d_6): δ (ppm): 160.3, 152.5, 145.7, 139.8, 139.6, 134.6, 130.1, 129.2, 127.8, 126.7, 123.6, 123.2, 120.7, 118.2. MS m/z (%): 408 (40) [M^{+4}], 406 (80) [M^{+2}], 405.0 (100), 404.0 (37) [M^{+}], 276.9 (27), 122.5 (24), 103.0 (33), 77.1 (50).

6,8-dibromo-2-(3-fluorophenyl)-quinazolin-4(3H)-one (1b)

2-Amino-3,5-dibromobenzamide (0.880 g) was reacted with 3-fluorobenzaldehyde (0.447 g). IR (KBr) ν (cm^{-1}): 3449 (N-H stretch), 3162-3094 (C-H stretch, aromatic), 1674 (C=O amid), 1574 (N-H bending). $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm): 13.04 (s, 1H, NH), 8.45 (s, 1H, aromatic), 8.28 (s, 1H, aromatic), 8.18 (d, $J = 6$ Hz, 1H, aromatic), 8.11 (d, $J = 7.8$ Hz, 1H, aromatic), 7.71 (q, $J = 5.7$, Hz, 1H, aromatic), 7.56 (t, $J = 6$ Hz, 1H, aromatic). $^{13}\text{C-NMR}$ (75 MHz, DMSO- d_6): δ (ppm): 163.3, 160.8, 152.0, 145.1, 139.7, 134.4, 130.9, 127.9, 124.2, 123.7, 119.0, 118.7, 114.8, 114.6. MS m/z (%): 400 (47) [M^{+4}], 398 (100) [M^{+2}], 396 (47) [M^{+}], 277 (100), 122.1 (53), 95.1 (67), 88.0 (32), 75.1 (30).


Scheme 1. Synthesis of dibromo anthranilamide.

Scheme 2. Synthesis of dibromo-2-arylquinazolinone (**1a-1g**).

6,8-dibromo-2-(4-bromophenyl) quinazolin-4(3H)-one (1c)

2-Amino-3,5-dibromobenzamide (0.880 g) was reacted with 4-bromobenzaldehyde (0.666 g). IR (KBr) ν (cm^{-1}): 3390 (N-H stretch), 3171-3072 (C-H stretch, aromatic), 1683 (C=O, amid), 1558 (N-H bending). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): δ (ppm): 8.97 (d, $J = 2.4$ Hz, 1H, NH), 7.89 (d, 1H, $J = 1.8$ Hz, aromatic), 7.76 (d, 1H, $J = 1.8$ Hz, aromatic), 7.65 (d, 2H, $J = 6.6$ Hz, aromatic), 7.42 (d, 2H, $J = 6.6$ Hz, aromatic). $^{13}\text{C-NMR}$ (75 MHz, $\text{DMSO-}d_6$): δ (ppm): 161.0, 143.2, 141.5, 137.9, 131.3, 130.0, 129.2, 128.2, 121.4, 117.8, 108.8, 108.0. MS m/z (%): 462 (15) [M^{+6}], 460 (20) [M^{+4}], 458 (10) [M^{+2}], 456 (5) [M^{+}], 305 (100), 278 (27), 76.0 (22), 44.2 (23).

6,8-dibromo-2-(3-bromophenyl) quinazolin-4(3H)-one (1d)

2-Amino-3,5-dibromobenzamide (0.880 g) was reacted with 3-bromobenzaldehyde (0.666 g). IR (KBr) ν (cm^{-1}): 3246 (N-H stretch), 3178 (C-H stretch, aromatic), 1685 (C=O, amid), 1559 (N-H bending). $^1\text{H-NMR}$

(300 MHz, $\text{DMSO-}d_6$): δ (ppm): 12.93-12.94 (m, 1H, NH), 8.17-8.44 (m, 3H, aromatic), 7.83 (m, 1H, aromatic), 7.51-7.74 (m, 2H, aromatic). $^{13}\text{C-NMR}$ (75 MHz, $\text{DMSO-}d_6$): δ (ppm): 161.0, 149.1, 144.1, 139.7, 137.5, 134.5, 130.8, 127.8, 127.0, 126.9, 124.9, 123.7, 121.9, 118.9. MS m/z (%): 462 (25) [M^{+6}], 460 (70) [M^{+4}], 458 (65) [M^{+2}], 456 (25) [M^{+}], 380.0 (90), 277(100), 199.0 (99), 170 (30), 155.0 (42), 102.1 (35), 88.0 (42), 75.1 (72), 63.2 (31), 50.1 (25).

6,8-dibromo-2-(4-nitrophenyl) quinazolin-4(3H)-one (1e)

2-Amino-3,5-dibromobenzamide (0.880 g) was reacted with 4-nitrobenzaldehyde (0.544 g). IR (KBr) ν (cm^{-1}): 3155 (N-H stretch), 3074-3011 (C-H stretch, aromatic), 1681 (C=O, amid), 1585 (N-H bending), 1519, 1354 (NO_2 stretch). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): δ (ppm): 13.23 (s, 1H, NH), 8.46-8.50 (m, 5H, aromatic), 8.30-8.32 (m, 1H, aromatic). $^{13}\text{C-NMR}$ (75 MHz, $\text{DMSO-}d_6$): δ (ppm): 160.8, 151.9, 149.2, 145.1, 139.8, 138.1, 137.6, 129.5, 129.4,

128.0, 127.3, 123.7, 123.6, 119.5. MS m/z (%): 427 (55) [M^{+4}], 425 (100) [M^{+2}], 423 (50) [M^{+}], 395 (21), 345.1 (60), 305.0 (61), 277 (67), 192.0 (35), 170.0 (32), 119.0 (20), 103.2 (44), 88.0 (45), 76.2 (68), 63.1 (28), 50.1 (25).

6,8-dibromo-2-(3-methoxyphenyl) quinazolin-4(3H)-one (1f)

2-Amino-3,5-dibromobenzamide (0.880 g) was reacted with 3-methoxybenzaldehyde (0.490 g). IR (KBr) ν (cm^{-1}): 3446 (N-H stretch), 3194-3093 (C-H stretch, aromatic), 2837 (C-H stretch aliphatic), 1672 (C=O, amid), 1571 (N-H bending), 1237 (C-O stretch). 1H -NMR: δ (ppm): 13.01 (s, 1H, NH), 8.47 (d, 1H, $J = 1.8$ Hz, aromatic), 8.30 (d, 1H, $J = 1.8$ Hz, aromatic), 7.96 (d, 1H, $J = 6$ Hz, aromatic), 7.91-7.92 (m, 1H, aromatic), 7.59 (t, 1H, $J = 6$ Hz, aromatic), 7.29 (dd, 1H, $J = 6, 1.8$ Hz, aromatic), 3.95 (s, 3H, OCH₃). ^{13}C -NMR (75 MHz, DMSO- d_6): δ : 160.9, 159.3, 153.0, 145.3, 139.7, 133.4, 129.9, 127.8, 123.7, 123.6, 120.3, 118.7, 117.9, 112.9, 55.4. MS m/z (%): 412 (3) [M^{+4}], 410 (5) [M^{+2}], 408 (2) [M^{+}], 171.1 (11), 91.0 (10), 77.1 (10), 40.1 (100).

6,8-dibromo-2-(4-benzyloxyphenyl) quinazolin-4(3H)-one (1g)

2-Amino-3,5-dibromobenzamide (0.880 g) was reacted with 4-benzyloxybenzaldehyde (0.764 g). IR (KBr) ν (cm^{-1}): 3327 (N-H Stretch), 3194-3032 (C-H stretch, aromatic), 2942 (C-H stretch aliphatic), 1666 (C=O, amid), 1563 (N-H bending), 1237 (C-O stretch). 1H -NMR: δ (ppm): 12.85 (s, 1H, NH), 8.40 (d, 1H, $J = 1.8$ Hz, aromatic), 8.32 (d, 2H, $J = 6.9$ Hz, aromatic), 8.24 (d, 1H, $J = 1.8$ Hz, aromatic), 7.54-7.56 (m, 2H, aromatic), 7.48 (t, 2H, $J = 5.7$ Hz, aromatic), 7.42-7.44 (m, 1H, aromatic), 7.27 (d, 2H, $J = 6.9$ Hz, aromatic), 5.29 (s, 2H, CH₂-benzyl). ^{13}C NMR (75 MHz, DMSO- d_6): δ (ppm): 161.4, 160.9, 152.8, 145.5, 139.6, 136.5, 129.8, 128.5, 128.0, 127.8, 127.7, 124.3, 123.4, 123.2, 118.0, 114.9, 69.5. MS m/z (%): 484.1 (1) [M^{+}], 337.0 (25), 169.0 (47), 151.0 (60), 124.0 (93), 94.0 (100), 44.1 (97).

Cell lines and cell culture

Three human cell lines (MCF-7, A549, SKOV3) were obtained from the National Cell Bank of Iran (NCBI, Pasteur Institute, Tehran,

I.R. Iran) and were cultured under aseptic conditions in the complete culture media containing Roswell Park Memorial Institute (RPMI) 1640 medium (Biosera, France), 10% fetal bovine serum (FBS; Gibco, USA), and 1% penicillin/streptomycin (Biosera, France) at 37 °C in a humidified CO₂ incubator. Following 70-80 confluency, the cells were trypsinized using 25% trypsin-EDTA solution (Biosera, France), were counted and then seeded in 96-well cell culture microplate in a density of 10×10^3 cells per well in 100 μ L complete culture medium for MTT assay.

Cytotoxicity assay

The cytotoxic effects of the synthesized 2-aryldibromoquinazolinones on these cell lines were evaluated using the 3-(4,5-dimethylthiazolyl) - 2,5 - diphenyltetrazolium bromide (MTT) standard assay as previously described. Briefly, following 24 h incubation to recover and reattach, the seeded cells were treated with different concentrations of each compound in triplicate manner. The compounds were first solved in high-grade DMSO and then diluted in culture medium to make different concentrations (31.25-1000 μ M).

To prevent bystander cytotoxic effect, the final concentration of DMSO was kept less than 0.1%. cisplatin with different concentrations was also used as positive control. Three wells were left without treatment as cell-based negative controls, and three wells of cell culture medium alone were also considered as blanks. Following 72 h incubation at 37 °C in a humidified CO₂ incubator, the media were completely removed and 100 μ L of RPMI-1640 containing 0.5 mg/mL MTT solution were added to the wells including controls, incubated for more 3 h at room temperature, and checked periodically for the appearance of purple formazan precipitates. The media containing MTT were then completely discarded and 100 μ L DMSO was added to each well to dissolve the formazan crystals. Following 30 min incubation at 37 °C in the dark, the absorbance of each well was measured at 495 nm with a microplate ELISA reader.

Data analysis

Excel 2013 and CurveExpert 1.4. were used to calculate and analyze the data. The inhibitory concentration (IC) for each compound was calculated and reported using following equation:

$$\text{Inhibitory concentration (\%)} = 100 - \left(\frac{\text{OD test} - \text{OD blank}}{\text{OD negative}} \times 100 \right)$$

where, OD is optical density. In this equation the differences between the OD of the tested samples and blank were divided by those of the negative controls (untreated wells) and multiplied by 100 to obtain the percentage of viable cells. Then this value was subtracted from 100 to calculate the IC.

A plot of the IC vs concentration was depicted for each compound using Curve Expert 1.4 and an IC₅₀, indicating the 50% growth inhibition of the cells was obtained for each compound. Data are presented as mean ± SD.

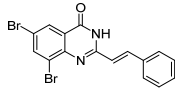
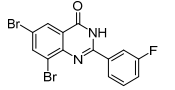
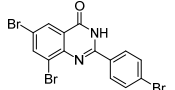
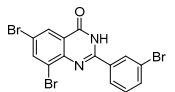
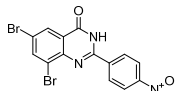
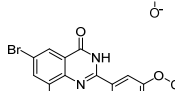
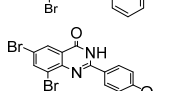
RESULTS**Chemistry**

Seven derivatives of 2-aryldibromoquinazolinones were prepared with desirable yields. The identity of the final products was checked by melting points and different spectroscopic methods. The characteristic of the synthesized compounds are shown in Table 1.

Cytotoxic effects of quinazolinone derivatives

The cytotoxic effects of the synthesized 2-aryldibromoquinazolinone derivatives were evaluated on three cancerous cell lines of MCF-7, A549, and SKOV3. Amongst tested compounds, **1f** and **1g** were considered most active compounds of this series as they exhibited higher toxicities against all examined cancer cell lines with IC₅₀ of 101.37 ± 12.20, 124.5 ± 20.51, and 125 ± 7.07 for MCF-7, A549, and SKOV3, respectively. Amongst other compounds, **1b** and **1c** showed cytotoxicity only on MCF-7 cell line whilst the others showed no cytotoxic effects against examined cell lines (Table 2).

Table 1. Synthesized 2-aryldibromoquinazolinones derivatives and their chemical properties

ID Code	Chemical structures	Chemical formula and names	MW (g/mol)	MP (°C)	Yield (%)
1a		C ₁₆ H ₁₀ Br ₂ N ₂ O 6,8-dibromo-2-styrylquinazolin-4(3H)-one	404	331-334	85
1b		C ₁₄ H ₇ Br ₂ FN ₂ O 6,8-dibromo-2-(3-fluorophenyl)quinazolin-4(3H)-one	396	332-334	90
1c		C ₁₄ H ₇ Br ₃ N ₂ O 6,8-dibromo-2-(3-bromophenyl)quinazolin-4(3H)-one	456	346-349	85
1d		C ₁₄ H ₇ Br ₃ N ₂ O 6,8-dibromo-2-(4-bromophenyl)quinazolin-4(3H)-one	456	382-385	87
1e		C ₁₄ H ₇ Br ₂ N ₃ O ₃ 6,8-dibromo-2-(4-nitrophenyl)quinazolin-4(3H)-one	423	345-349	85
1f		C ₁₅ H ₁₀ Br ₂ N ₂ O ₂ 6,8-dibromo-2-(3-methoxyphenyl)quinazolin-4(3H)-one	408	302-304	86
1g		C ₂₁ H ₁₄ Br ₂ N ₂ O ₂ 2-(4-(benzyloxy)phenyl)-6,8-dibromoquinazolin-4(3H)-one	484	256-259	80

MW, molecular weight; MP, melting point.

Table 2. *In vitro* cytotoxic activity of 2-aryldibromoquinazolinones against cancer cell lines Data are presented as mean \pm SD.

ID Code	IC ₅₀ (μ M)		
	MCF-7	A549	SKOV3
1a	> 1000	> 1000	> 1000
1b	201.5 \pm 26.2	> 1000	> 1000
1c	599.5 \pm 136.5	> 1000	> 1000
1d	> 1000	> 1000	> 1000
1e	> 1000	> 1000	> 1000
1f	101.4 \pm 12.20	124.5 \pm 20.51	125 \pm 7.07
1g	156 \pm 22.63	290 \pm 14.14	909 \pm 187
Cisplatin	61.56 \pm 0.98	50.81 \pm 3.10	43.81 \pm 3.79

DISCUSSION

Quinazoline derivatives exhibits a class of compounds with diverse spectrum of therapeutic potential (18, 19). A vast number of quinazoline derivatives have been recently synthesized to design more effective medicaments. Various aromatic groups with electron-withdrawing and electron-donating substituents at various positions of the quinazoline ring were also considered (20). Chandrika *et al.* synthesized some quinazoline derivatives with iodine substitution on the quinazoline ring exhibiting desirable anticancer activity on U937 leukemia cell line (9). Some brominated derivatives of quinazoline were also synthesized by DiMauro *et al.* to bind to lymphocyte-specific kinase (Lck) as anti-inflammatory agents (4). In addition, several reports for synthesis of 4-chloroquinazoline and 6-bromoquinazoline as anticancer and antimicrobial agents have been reported (21-23). Here we reported the synthesis of some 2-aryldibromoquinazolinone derivatives. The cytotoxic activities of these derivatives were also assessed against three cancerous cell lines. The results collectively illustrated that **1f** and **1g** had satisfactory anti-tumor activities especially on breast (MCF-7) and lung (A549) carcinoma cell lines. Based on MTT results and chemical features, the activity can be related to the chemical structure of the compounds. As it is observed in Table 1, both **1f** and **1g** contain alkoxy groups (methoxyphenyl in **1f** and benzyloxyphenyl in **1g**) in their structures. These alkoxy groups at 2 position of the quinazoline ring increased the cytotoxic activities. According to our results compounds having electron-withdrawing groups such as

halogens or nitro group at para position of the benzene ring displayed no cytotoxic effect while, compounds having halogen groups at meta position of the benzene ring, (**1b** and **1c**) exhibited some cytotoxic activities.

CONCLUSION

It could be concluded that the presence of electron-donating groups such as methoxy or benzyloxy substitutions remarkably increases the cytotoxic activity of the **1f** and **1g**. Further evaluation of these compounds revealed that substitution of a methoxy group at position 3 of the aromatic ring of aldehyde, could improve the cytotoxic activity than a benzyloxy group at position 4 of this ring. Compound **1f** with the highest potency could be introduced as a candidate for further *in vitro* and *in vivo* anticancer studies.

ACKNOWLEDGEMENTS

Financial support of Shiraz University of Medical Sciences (Shiraz, I.R. Iran) through the Grant No. 95-01-36-11687 is highly appreciated.

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