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Synthesis and antitumor activities of novel bis-quinazolin-4(3*H*)-ones

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Abstract

With the aim of obtaining new antitumor agents, a series of bis-quinazolin-4(3*H*)-ones (**3a-3 f**) were designed and synthesized. These products contain 4-oxo-1,2,3,4-tetrahydro-quinazoline and 3*H*-quinazolin-4-one moieties linked together *via* a propyl chain. Cytotoxic activities of **3a-3 f** were evaluated against lung adenocarcinoma (A549), breast carcinoma (MCF-7) and ovarian cancer (SKOV3) cell lines using MTT method. Cisplatin was used as a positive control. Among the tested compounds **3a**, **3b**, and **3e** showed the best cytotoxic activities against all cancerous cell lines with IC_{50} values even less than cisplatin. Compounds **3d** and **3f** also showed desirable cytotoxic activities especially against A549 and MCF-7.

1 | INTRODUCTION

Quinazoline and its derivatives have emerged as an important class of nitrogen-containing heterocycles that have attracted significant synthetic interest because of their pharmacological and therapeutic properties such as antitumor,[1] antibacterial,[2] antifungal,[3] antihypertension,[4] antitubercular,[5] antioxidant,[6] anticonvulsant,[7] anticancer,[8] anti-inflammatory,[9] and antihyperlipidemic activities.[10] Some heterocyclic compounds containing quinazoline ring system also showed to be potent inhibitors of thymidylate synthase. Quinazoline derivatives with an amine substitution at position 4 have been demonstrated to be inhibitors of epidermal growth factor receptor (EGFR) which is a receptor tyrosine kinase regulating cell proliferation.[11] As cancer is continuing to be a major health problem and existing antineoplastic drugs have shown the various types of side effects, therefore many efforts have been made to prepare more efficient and novel antineoplastic drugs.[12,13]

In search for various chemical antitumor agents, quinazoline derivatives have been identified as a novel class of neoplastic chemotherapeutic agents that shows activity against different tumours.[13] Different representative synthetic methods including aza-reaction, microwave-assisted reaction, metal-catalyzed reaction, ultrasound-promoted reaction and phase-transfer catalysis were reported for quinazoline compounds.[14] A number of different strategies have been devised for condensation between aldehydes and *o*-aminobenzamides followed by oxidation of the aminal intermediate.[15] Notably, most of the reported synthetic routes require excess amounts of oxidants or bases and suitable ligands or microwave irradiation conditions are necessary in some cases. Hence, eco-friendly and practical methods to access valuable substituted quinazolines are highly desirable.

Bis-quinazoline derivatives as novel members of this family contain two quinazoline moieties and may afford unique biological activities. But only a few literature studies concern about the synthesis of bis-quinazoline derivatives. *In vitro* anticancer activity of some biquinazoline-2,2′-diones was also studied by Dou and co-workers.[16] To continue our previous researches[17–22] here we

decided to synthesize some bis-quinazolines and evaluate their cytotoxic properties against cancer. A549 as an invasive lung cancer cell line provide a useful tool for the study of biological properties of lung cancer *in vitro*.[23] MCF-7 is one of the most widely used breast cancer cell line which is hormone-dependent with a significant inherent metastatic ability.[24] SKOV3 contains cancer stem-like cells which are present in the human ovarian cancer cell line which is one of the leading causes of death among gynaecological malignancies.[25] These three cancerous cell lines were selected for cytotoxic evaluation of our products in comparing to cisplatin as a standard drug, using an *in vitro* cell proliferation MTT assay.

2 | RESULTS AND DISCUSSION

As a part of our continuing research on the synthesis of quinazoline derivatives, we have undertaken the facile and well-designed synthesis of novel bis-quinazoline derivatives **3a-3 f** (Table 1). Thus, bis-quinazolines were synthesized by the reaction of anthranilamide (**1**) with cyclohexanediones **2**. Six derivatives of bis-quinazolines were synthesized and characterized by different spectroscopic methods. In products **3**, two quinazoline rings are linked together *via* a propyl chain, which may contain two germinal methyl groups on its central carbon atom. Both quinazoline rings may also hold one or two bromine atoms.

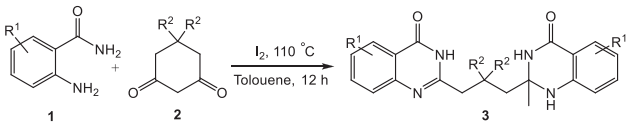
A mechanism for the formation of the structurally diversified products from the reactions of 2-aminobenzamides with 1,3-cyclohexanediones, similar to compounds **3** prepared in this work, is described.[1]

The cytotoxic activities of compounds **3a-3 f** were evaluated against lung adenocarcinoma (A549), breast carcinoma (MCF-7), and ovarian cancer (SKOV3) cell lines using MTT method (see Table 2). Cisplatin was used as a positive control. Among the tested compounds **3a**, **3b**, and **3e** showed the best cytotoxic activities against all cancerous cell lines with IC_{50} values even less than cisplatin. Compounds **3d** and **3f** also showed desirable cytotoxic activities especially against A549 and MCF-7. Comparing between **3b** and **3e** show that the presence of a bromo substituent in each quinazoline ring seems to be more critical for cytotoxic activity than *gem*-dimethyl group in the propyl chain. Compounds **3a** and **3d** lack the bromo substituents and showed moderate cytotoxic activities. Cytotoxic potencies of compounds **3c** and **3f** indicate that dibromo analogues of quinazoline ring showed less activities compared to the monobromo compounds **3b** and **3e**. Therefore, compounds **3a-3 f** collectively had IC_{50} comparable to or even less than cisplatin as a positive control. Compounds **3b** and **3e** as the most potent compounds, could be highly valuable as candidates for further *in vitro* and *in vivo* anticancer studies.

2.1 | Cell lines and cell culture

Three human cancer cell lines, A549 (lung carcinoma), MCF-7 (breast carcinoma) and SKOV3 (ovarian carcinoma), were purchased from the National Cell Bank of Pasteur Institute of Iran. Using aseptic techniques, the cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium (Biosera, France), containing 10% fetal bovine serum (FBS) (Biosera, France), 100 units penicillin, and 100 μg/mL streptomycin (Biosera, France), and incubated at 37°C in a humidified atmosphere with 5% CO_2. Following enough convergence, the cells were

TABLE 1 Synthesis of bis-quinazoline derivatives **3a-3 f**



Entry	R^1	R^2	Product	Mp (°C)	Yield (%)[a]
1	H	Me	**3a**	221-223	63
2	3-Br	Me	**3b**	253–255	57
3	3,5-diBr	Me	**3c**	300 (decomposed)	56
4	H	H	**3d**	210–212	70
5	3-Br	H	**3e**	230–232	62
6	3,5-diBr	H	**3f**	300 (decomposed)	79

[a]Yield = (Experimental amount) / (Theoretical amount).

TABLE 2 *In vitro* cytotoxicity effects of bis-quinazolines on different cancer cell lines

	$IC_{50}(\mu M)$		
Compounds	**A549**	**MCF-7**	**SKOV3**
3a	25.00 ± 0.85	22.83 ± 12.85	403.00 ± 17.68
3b	15.00 ± 1.77	10.70 ± 0.42	64.23 ± 12.12
3c	287.16 ± 7.65	>500	>500
3d	178.00 ± 7.07	46.58 ± 3.83	>500
3e	2.51 ± 0.18	4.48 ± 0.94	58.53 ± 13.58
3f	187.83 ± 28.87	171.57 ± 0.90	233.42 ± 3.55
Cisplatin	50.81 ± 3.10	61.56 ± 0.98	43.81 ± 3.79

treated with 25% trypsin–EDTA (Biosera, France) and sub-cultured. The cells were then washed, counted, and prepared for cytotoxic MTT assay as previously described.[26,27]

2.2 | Cytotoxic activities

The cytotoxic effects of six bis-quinazoline analogues **3a-3 f** were determines using a colorimetric MTT assay on A549, MCF-7, and SKOV3 cancer cell lines as *in vitro* models. The IC_{50} for each compound is displayed in Table 2. As shown in this table, compound **3e** showed cytotoxic activity against all investigated cell lines in lower concentration (IC_{50} for A549 = 2.51 ± 0.18, MCF-7 = 4.48 ± 0.94 SKOV3 = 58.83 ± 13.58, respectively). Our results indicated that among the other analogues, compounds **3a** and **3b** also showed desirable cytotoxic activities especially on A549 and MCF-7 (see Table 2). Compound **3d** and **3f** had moderate cytotoxic effects on A549 and MCF-7 cells while compound **3c** has the lowest effects.

3 | MATERIAL AND METHODS

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a VERTEX70 spectrometer, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded a BRUKER DRX-500 AVANCE instrument using DMSO-d_6 as deuterated solvent and TMS as internal standard at 500 and 125 MHz, respectively. Mass spectra were recorded on an Agilent 7890A-GC, Agilent 7000 Series Triple Quad-MS spectrometer.

The brominated aminobenzamide derivatives were prepared according to literature[28] from aminobenzamides using *N*-bromosuccinimide. In the second step, two aminobenzamides were joined by cyclohexanediones **2** in the presence of iodine.

General procedure for bromination of 2-aminobenzamide **1a.**

A solution of 2-aminobenzamide (**1a**, 0.27 g, 2 mmol) in acetonitrile (10 mL) was treated with *N*-bromosuccinimide (0.36 g, 2 mmol). The mixture was stirred at room temperature for 1 h and then quenched with ice-cold water. The resulting precipitate was filtered and the residue was recrystallized from MeCN to afford 2-amino-5-bromobenzamide (**1b**, 0.31 g, 72%) as a pale yellow solid, m.p. 186–187°C. This reaction was repeated with 2 equivalents of *N*-bromosuccinimide (0.85 g, 4.8 mmol) for 3 h to produce 2-amino-3,5-dibromobenzamide (**1c**, 0.41 g, 70%) as a colorless solid, m.p. 198–203°C.[28]

General procedure for synthesis of bis-quinazolin-4(3H)-ones **3a-3 f.**

A dry 50-mL flask was charged with iodine (0.026 g, 0.01 mmol), 1,3-cyclohexanediones (**2**, 1.0 mmol), 2-aminobenzamides (**1**, 2.1 mmol), toluene (10 mL), and stirred at reflux for 12 h. The progress of the reaction was monitored by TLC. After completion the reaction, toluene was removed under reduced pressure, EtOAc was added and the resulting precipitate was filtered. Then, the crude product was recrystallized from EtOAc to get the final bis-quinazoline compounds **3a-3 f**.

3.1 | 2-[2,2-Dimethyl-3-(2-methyl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-propyl]-3*H*-quinazolin-4-one (3a)

As this compound was introduced previously here we synthesized and checked its purity by melting point, IR spectroscopy, and mass spectrometry. Pale yellow solid; M.p.: 221–223°C; MS (EI, 70 eV): *m/z* (%) = 376 (M^+, 5), 361 (29), 225 (32), 201 (70), 161 (100).

3.2 | 6-Bromo-2-[3-(6-bromo-2-methyl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-2,2-dimethyl propyl]-3*H*-quinazolin-4-one (3b)

Pale yellow solid; yield 0.304 g (57%); M.p.: 253–255°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.08 (s, 3H, Me), 1.09 (s, 3H, Me), 1.40 (s, 3H, Me), 1.80 (AB-quartet, $\Delta\nu_{AB}$ = 30 Hz, $^2J_{AB}$ = 15.5 Hz, 2H, CH_2), 2.65 (AB-quartet, $\Delta\nu_{AB}$ = 55 Hz, $^2J_{AB}$ = 13.0 Hz, 2H, CH_2), 6.61 (d, *J* = 9.0 Hz, 1H, H–Ar), 7.05 (s, 1H, NH), 7.32 (d of d, *J* = 1.5, 7.0 Hz, 1H, H–Ar), 7.52 (d, *J* = 8.5 Hz, 1H, H–Ar), 7.61 (br s, 1H, H–Ar), 7.92 (d of d, *J* = 1.5, 7.0 Hz, 1H, H–Ar), 8.2 (br s, 1H, H–Ar), 8.40 (s, 1H, NH), 12.4 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ

28.1, 28.3, 30.5, 34.4, 45.4, 48.2, 69.3, 106.3, 114.3, 115.9, 117.9, 121.7, 127.2, 128.5, 128.6, 135.1, 136.6, 145.2, 146.7, 156.0, 160.0, 160.9 ppm; IR (KBr): = 3232 (N–H), 1676 (C=O), 1610 (C=N), 1249 (C–N) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 534 (M^+, 4), 279 (27), 239 (52), 198 (38), 161 (29), 77 (100).

3.3 | 6,8-Dibromo-2-[3-(6,8-dibromo-2-methyl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-2,2-dimethyl propyl]-3*H*-quinazolin-4-one (3c)

Pale yellow solid; Yield 0.387 g (56%); M.p.: 300°C (decomposed); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.03 (s, 3H, Me), 1.12 (s, 3H, Me), 1.53 (s, 3H, Me), 1.77 (AB-quartet, $\Delta\nu_{AB}$ = 55 Hz, $^2J_{AB}$ = 15.0 Hz, 2H, CH_2), 2.64 (AB-quartet, $\Delta\nu_{AB}$ = 34 Hz, $^2J_{AB}$ = 13.0 Hz, 2H, CH_2), 6.66 (s, 1H, N–H), 7.63 (s, 1H, H–Ar), 7.69 (s, 1H, H–Ar), 8.17 (s, 1H, H–Ar), 8.32 (s, 1H, H–N), 8.44 (s, 1H, H–Ar), 12.63 (s, 1H, H–N) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.7, 30.0, 32.0, 35,0, 44.7, 46.6, 71,0, 107.2, 108.6, 116.4, 118.8, 123.1, 123.9, 128.2, 129.5, 138.2, 140.1, 143.3, 145.5, 158.3, 160.6, 160.9 ppm; IR (KBr): = 3337 (N–H), 1646 (C=O), 1605 (C=N), 1241 (C–N) cm^{-1}.

3.4 | 2-[3-(2-Methyl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-propyl]-3*H*-quinazolin-4-one (3d)

Pale yellow solid; Yield 0.245 g (70%); M.p.: 210–212°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.36 (s, 3H, Me), 1.71–1.74 (m, 2H, CH_2), 1.84–1.90 (m, 2H, CH_2), 2.59–2.62 (m, 2H, CH_2), 6.58–6.61 (t, *J* = 7.5 Hz, 1H, H–Ar), 6.64 (s, 1H, NH), 6.66 (s, 1H. NH), 7.11–7.14 (m, 1H, H–Ar), 7.48 (t, *J* = 7.5 Hz, 1H, H–Ar), 7.57 (d, *J* = 8.0 Hz, 1H, H–Ar), 7.61 (d, *J* = 8.0 Hz, 1H, H–Ar), 7.79 (t, *J* = 7.5 Hz, 1H, H–Ar), 7.96 (s, 1H, NH), 8.10 (d, *J* = 7.5 Hz, 1H, H–Ar) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.2, 27.4, 33.3, 39.7, 68.5, 113.0, 113.5, 115.7, 120.0, 125.4, 125.9, 126.6, 127.6, 128.3, 132.7, 134.1, 146.6, 157.9, 160.8, 162.6 ppm; IR (KBr): = 3242 (N–H), 1680 (C=O), 1612 (C=N), 1277 (C–N) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 349 [$(M + 1)^+$, 3], 348 (M^+, 1), 331 (33), 247 (5), 173.1 (35), 161 (100), 128 (30),77 (19), 69 (58).

3.5 | 6-Bromo-2-[3-(6-bromo-2-methyl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-propyl]-3*H*-quinazolin-4-one (3e)

Pale yellow solid; Yield 0.313 g (62%); M.p.: 230–232°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.35 (s, 3H, Me), 1.70–1.72 (m, 2H, CH_2), 1.78–1.81 (m, 2H, CH_2), 2.57–2.61 (m, 2H, CH_2), 6.60 (d, *J* = 8.5 Hz, 1H, H–Ar), 6.91 (s, 1H, NH), 7.31 (d of d, *J* = 2.0, 9.0 Hz, 1H, H–Ar), 7.54 (d, *J* = 8.5 Hz, 1H, H–Ar), 7.59 (d, *J* = 2.0 Hz, 1H, H–Ar), 7.93 (d of d, *J* = 2.0, 9.0 Hz, 1H, H–Ar), 8.12 (s, 1H, NH), 8.15 (d, *J* = 2.0 Hz, 1H. H-Ar), 12.3 (br s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9, 27.3, 33.3, 39.6, 68.5, 106.4, 114.6, 115.9, 118.2, 121.7, 124.7, 127.4, 128.3, 128.6, 135.1, 136.8, 145.5, 158.3, 159.8, 161.2 ppm; IR (KBr): = 3317 (N–H), 1672 (C=O), 1607 (C=N), 1254 (C–N) cm^{-1}.

3.6 | 6,8-Dibromo-2-[3-(6,8-dibromo-2-methyl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-propyl]-3*H*-quinazolin-4-one (3f)

Pale yellow solid; Yield 0.526 g (79%); M.p.: 300°C (decomposed); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.45 (s, 3H, Me), 1.75–1.77 (m, 2H, CH_2), 1.89–1.94 (m, 2H, CH_2), 2.58–2.60 (m, 2H, CH_2), 6.23 (s, 1H, NH), 7.65 (d of d, *J* = 2.0, 8.0 Hz, 2H, H–Ar), 8.12 (d, *J* = 2.5 Hz, 1H, H–Ar), 8.26 (d, *J* = 2.5 Hz,1H, H–Ar), 8.37 (br s, 1H, NH), 12.57 (br s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.7, 27.2, 33.8, 39.5, 69.2, 106.5, 107.6, 116.2, 117.4, 122.4, 122.9, 127.1, 128.5, 137.1, 138.8, 142.8, 144.9, 158.3, 159.8, 160.2 ppm; IR (KBr): = 3397 (N–H), 1678 (C=O), 1614 (C=N), 1261 (C–N) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 665 [$(M + 1)^+$, 4], 664 (M^+, 1), 331 (25.6), 319 (100), 277 (26), 238 (16).

3.7 | MTT assay

The cytotoxic effects of bis-quinazoline compounds were investigated using a standard MTT assay. Briefly the cells were plated at the 8×10^3 cells concentration for A549 and 10×10^3 cells concentration for SKOV3 and MCF-7 in 100 mm^3 complete culture media per well. Then, the cells were incubated for 24 h to reattach. After attachment the cells were treated with different concentrations of each compound (1–500 μM). All compound were prepared in DMSO (Sigma, Germany) as 400 μM as stock solution. The desired concentrations were then obtained by serial dilution of stocks in culture media. The final concentration of DMSO was kept to less than 10% to avoid solvent cytotoxic effect. Three wells were left without treatment as cell-based negative controls, and three wells containing cell culture medium alone were considered as blanks. After 72 hours incubation, the culture media were completely removed and 100 μL of MTT solution with 0.5 mg/mL concentration were added to the wells including controls. The plate was incubated for 3–4 h at 37°C and checked periodically for the appearance of purple precipitate. Then, after

complete removing of MTT solution, 150 μL of DMSO was added to the wells and leaved in the 37°C incubator for more 30 min. The absorbance of all wells including the blanks, were measured at 492 nm. Each experiment was separately repeated at least three times.

3.8 | Data analysis

Excel 2013 software package was used for calculation. The average values from triplicate readings were determined and subtracted the average value for the blank. The inhibitory concentration (IC) of each compound was calculated and reported using following formula:

$$IC = 100 - [(OD_{test} - OD_{blank}) / (OD_{negative}) \times 100].$$

For each chemical a plot of the IC versus concentration was depicted using Curve Expert 1.4 software and an Inhibition Concentration 50 (IC_{50}), indicating the 50% growth inhibition of the cells was obtained for each compound. P values less than 0.05 (two-tailed) were considered statistically significant.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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