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Original Article

Synthesis and cytotoxic evaluation of some quinazolinone- 5-(4-chlorophenyl) 1, 3, 4-oxadiazole conjugates

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Abstract

1, 3, 4- Oxadiazoles and quinazolinones are privileged structures with extensive biological activities. On account of reported anticancer activity of them, in this study, a multi-step reaction procedure has been developed for the synthesis of some quinazolinone-1, 3, 4-oxadiazole derivatives. Reaction of the synthesized 3-amino-4(3H) quinazolinone derivatives with chloroacetyl chloride in the presence of dichloromethane/triethylamine yielded 2-chloro -N-(4-oxo-2-quinazolin3 (3H)-yl) acetamide derivatives as intermediate. Treatment of the resultants with 5- (4-chlorophenyl) 1, 3, 4-oxadiazole-2-thiol in dry acetone and potassium carbonate gave coupled derivatives of quinazolinone-1, 3, 4-oxadiazole. The cytotoxic effect of final compounds was tested against MCF-7 and HeLa cell lines using MTT assay. Compound 2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylthio) N-(4-oxo-2-propylquinazolin)3(4H)acatamide **6a** exhibited remarkable cytotoxic activity at 10 and 100 µM against HeLa cell line. The alteration of substituents on C_2 of quinazolinone ring revealed that the introduction of propyl moeity improved cytotoxic activity against HeLa cell line.

Keywords: Cytotoxicity; Quinazolinone; Oxadiazole.

INTRODUCTION

Amongst heterocyclic compounds, oxadiazole is one of the attractive constructions for the development of new drugs. In drug discovery program, oxadiazole ring can be used as a main pharmacophore interfering with receptor, an aromatic linker, modulating molecular properties, and bioisosteres of amides and esters (1-5).

There are four known isomers of this five-membered ring including: 1,2,4-, 1,2,3-, 1,2,5-, and 1,3,4-oxadiazole. 2, 5 Disubstituted 1, 3, 4 oxadiazole isomer is associated with diverse pharmacological activities such as anticancer, antibacterial, antifungal, antitubercular, anticonvulsant, and anti-inflammatory effects (5-8). The proposed anticancer mechanisms for oxadiazoles include inhibition of tubulin polymerization and epidermal growth factor receptor (EGFR). Quinazolinone is another nitrogenated scaffold that was extensively used in drug development programs and its derivatives showed diverse biological activities as anticancer, antifungal, anti-inflammatory, and antimicrobial (9-15). Quinazolinone-based structures exert their anticancer activity through different mechanisms including inhibition of the DNA repair enzyme system, inhibition of EGFR (9), thymidylate enzyme inhibition, and inhibitory effects for tubulin polymerize (14). The efficacy of 1,3,4-oxadiazole and quinazolinone derivatives has been demonstrated in many literatures. Also quinazolinone-oxadiazole hybrid structures with antimicrobial, anti-inflammatory, antioxidant, anticancer, and analgesic effects have been reported (5,10,16-20).

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Because of the remarkable cytotoxic effects of 1, 3, 4-oxadiazole (6-8) and quinazolinone (9-13) derivatives, and in the hope of achieving synergistic response due to the presence of both quinazolinone and 1,3,4-oxadiazole moieties, in this study, some of new quinazoline derivatives containing the 1, 3, 4-oxadiazole were synthesized and evaluated for their cytotoxic activity.

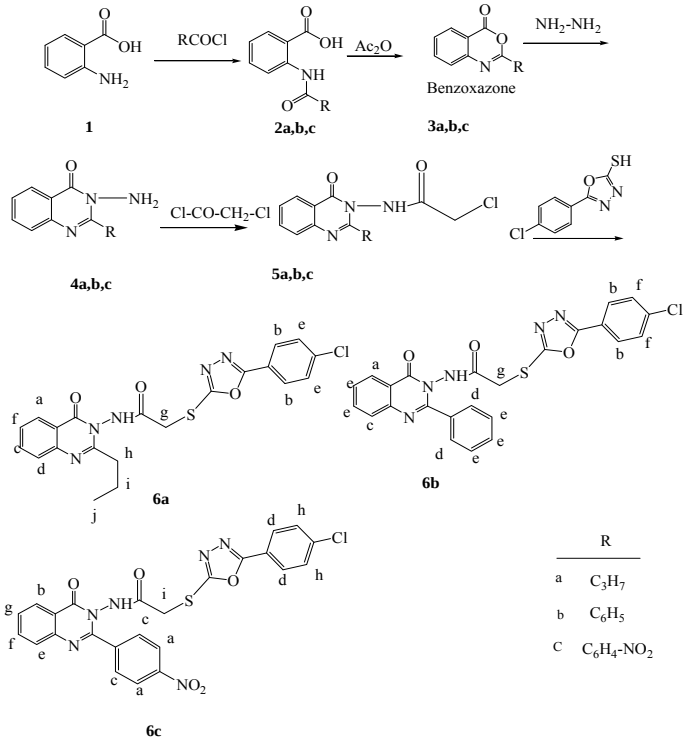
MATERIALS AND METHODS

Instrumentation

All starting materials, reagents, and solvents were purchased from commercial suppliers like Merck (Germany) and Aldrich (USA) companies. Merck silica gel 60 F_{254} plates (Germany) were applied for analytical thin layer chromatography (TLC). Proton nuclear magnetic resonance (HNMR) spectra were recorded using a Bruker 400 MHz spectrometer (Germany), and chemical shifts are expressed as ppm with tetramethylsilane (TMS) as internal standard. Infrared (IR) (KBr discs) was recorded with a WQF-510 fourier-transform IR (FT-IR) spectrophotometer (China). Melting points were determined using electrothermal 9200 melting point apparatus (United Kingdom) and are uncorrected.

General procedures for synthesis of compounds

2-Amido-benzoic acid derivatives (**2a-2c**) were prepared by reaction of anthranilic acid (**1**) with acylchloride derivatives. The reaction was followed by dehydrative cyclization of 2- amido-benzoic acid derivatives to form benzoxazinone intermediate (**3a-3c**). Reaction between benzoxazinone and hydrazine hydrate in ethanol under reflux condition produced 3-amino quinazolinone derivatives in high yield (**4a-4c**). Treatment of 3-amino quinazolinone with chloro acetylchloride in the presence of dichloromethane/triethylamine afforded 2-chloro -N-(4-oxo-2-quinazolin3 (3H)-yl) acetamide derivatives (**5a-5c**). Final compounds (**6a-6c**) obtained through the nucleophilic displacement of the chloride with thiol of 5-(4-chlorophenyl) 1, 3, 4-oxadiazole-2-thiol in dry acetone and potassium carbonate (Scheme 1) (21,22).



Scheme1. Synthesis of the target compounds (**6a-6c**).

Synthesis of 2- amido-benzoic acid derivatives (2a-2c)

To a magnetically stirred solution of anthranilic acid (**1**) (0.04 mol) in dimethyl formamide (35 mL) was added dropwise a solution of acylchloride (butyryl chloride, benzoyl chloride and 4-nitrobenzoyl chloride) (0.045 mol) over 15 min. The mixture was stirred at room temperature for 3 h until a solid product was formed. Then the mixture was poured into water and the precipitate was collected by filtration, washed with water, and dried under reduced pressure to achieve compounds **2a-2c** (Scheme 1) (23).

Synthesis of benzoxazone derivatives (3a-3c)

A solution of compounds **2a-2c** (0.01 mol) in acetic anhydride (30 mL) was heated for 1 h with vigorous stirring. After completion of the reaction which confirmed by TLC, the solvent was removed by distillation under reduced pressure to obtain derivatives **3a-3c** (Scheme 1)(23).

Synthesis of 3-aminoquinazolinone derivatives (4a-4c)

A mixture of related benzoxazone **3a-3c** (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol was refluxed for 3 h. After the reaction was completed, the mixture was cooled and the separated solid was collected by filtration and recrystallized from ethanol or isopropanol (21,22).

Synthesis of 2-chloro -N-(4-oxo-2-quinazolin3 (3H)-yl) acetamide derivatives (5a-5c)

Chloroacetylchloride (0.01 mol) was added to a solution of 3-amino-quinazoline derivatives **4a-4c** (0.01 mol) in dry dichloromethane (20 mL) and triethylamine (0.01 mol), mixture was stirred at room temperature for 30 min. Then the reaction mixture was poured into ice water and extracted with dichloromethane and ethyl acetate. The extracted ethyl acetate was washed with sodium bicarbonate solution (3%) and dried over anhydrous magnesium sulfate, which upon evaporation afforded the products **5a-5c** (21,22).

Synthesis of quinazolinone-oxadiazole hybrid derivatives (6a-6c)

Title compounds **6a-6c** were synthesized by refluxing 2-chloro -N-(4-oxo-2-quinazolin3 (3H)-yl) acetamide derivatives **5a-5c** (0.01 mol) with 5-(4-chlorophenyl) 1, 3, 4-oxadazole-2-thiol in dry acetone (20 mL) and anhydrous potassium carbonate (0.01 mmol) for 6 h. The reaction mixture was filtered while hot. The organic solution was concentrated and purified by preparative TLC (21,22).

Cytotoxicity assay

Sample and culture media preparation

MCF-7 (breast cancer), and HeLa (cervical cancer) cells were purchased from pasture institute of Iran (Tehran, I.R. Iran) and maintained at 37 °C in a humidified atmosphere (90%) containing 5% CO2. Both cell lines were grown in RPMI 1640 completed with 5% v/v fetal bovine serum, 100 U/mL penicillin, and 100 mg/mL streptomycin. After 2-3 subcultures, 180 µL of the cell suspensions (5×10^4 cells/mL) were seeded in 96well plates and incubated for 24 h.

The stock solutions of compounds (10 mM, 1 mL) were prepared in minimum volume of dimethyl sulfoxide (DMSO) and diluted with the medium to obtain 10, 100, 1000 µM concentrations. After 24 h incubation, 20 µL of different concentrations of the derivatives were added\and the microplates were further incubated for 48 h. Paclitaxel was used as positive control. To evaluate cell survival, 20 µL of MTT solution (5 mg/mL in phosphate buffer solution) was added to each well and incubated for 4 h. Afterwards, the media in each well was gently replaced with 150 µL DMSO to dissolve formazan crystals. The absorbance of each well was measured at 540 nm using an ELISA plate reader. Each experiment was repeated three times. Analysis of variance (ANOVA) followed by Tukey test was used to determine the differences between various groups.

Cell viability calculated using the following equation:

$$Cell\ survival\ (\%) = \frac{Absorbance\ of\ treated\ well - absorbance\ of\ blank}{Absorbance\ of\ control\ well - absorbance\ of\ blank} \times 100$$

RESULTS

2-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-ylthio)N-(4-oxo-2-propylquinazolin)3(4H) acatamide (6a)

Yield: 31%, m.p.162.5-163 °C, IR ν_{max}, 3243(NH), 2931 (C-H), 1677 (C=O), 1611(C=N), cm^{-1}; ^{1}HNMR: (400 MHz; $CDCl_3$): δ 9.79 (b, NH), 8.07 (1H, dd, *J* = 8 Hz, *J* = 4 Hz, H^a), 7.87 (2H, d, *J* = 8 Hz, H^b), 7.66 (1H, m, H^c), 7.59 (1H, d, *J* = 8 Hz, H^d), 7.44(2H, d, *J* = 8 Hz, H^e), 7.34 (1H, t, *J* = 8 Hz, H^f), 4.17-4.21 (1H, d, *J* = 16 Hz, CH_2^g), 3.94-3.98 (1H, d, *J* = 16 Hz, CH_2^g), 2.64 (2H, t, *J* = 8 Hz, CH_2^h), 1.72 (2H, m, CH_2^i), 0.92 (3H, t, *J* = 8 *Hz*, CH_3 ^{J}).

2-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-ylthio)N-(4-oxo-2-phenylquinazolin)3(4H) acatamide (6b)

Yield: 30%, m.p.150-151 °C, IR ν_{max}, 3216 (NH), 1696 (C=O) cm^{-1}; ^{1}HNMR δ: (400 MHz; $CDCl_3$), 8.73 (1H, s, NH), 8.23 (1H, d, *J* = 8 Hz, H^a), 7.72-7. 78 (3H, m, $H^{b,c}$), 7.57(2H, d, *J* = 8 Hz, H^d), 7.38-7.50(7H, m, $H^{e,f}$), 4.08-4.12(1H, d, *J* = 16 Hz,CH_2^g),3.87-3.91(1H, d, *J* = 16Hz, CH_2^g).

2-(5-(4-Chlorophenyl)-1,3 ,4 - oxadiazol – 2 - ylthio)N(2-4nitrophenyl)4-oxoquinazolin) 3(4H)acatamide(6C)

Yield: 33%, m.p.177 °C (decomposed), IR ν_{max}, 3313 (NH), 1696 (C=O), 1596, 1349 NO_2 cm^{-1}; ^{1}HNMR δ: (400 MHz; $CDCl_3$), 8.74 (1H, s, NH), 8.24-8.28 (3H, m, $H^{a,b}$), 7.73-7.83 (5H, m, $H^{c,d,e}$), 7.53 (1H, t, *J* = 8 Hz, H^f), 7.1-7.24 (3H, m, $H^{g,h}$), 4.12-4.16 (1H, d, *J* = 16 Hz,CH_2^i), 3.91 -3.95 (1H, d, *J* = 16 Hz, CH_2^i).

Cytotoxic effects of the derivatives (6a-6c)

The cytotoxicity of compounds were evaluated against HeLa and MCF-7 cell lines at different concentrations (1, 10, and 100 µM) using MTT assay. Results are shown in Fig. 1A, 1B, and Table 1.

Compound **6a** exhibited remarkable cytotoxic effect at all tested concentrations (1, 10, and 100 µM) on HeLa cell line and cell viability reduced to about 61%, 37% and 24% respectively. Compounds **6b** and **6c** indicated similar effects in the same concentrations on HeLa cell line. These two compounds reduced cell viability to about 42% at 100 µM.

Remarkable differences were not observed between the cytotoxicity of these compounds on MCF-7 cell line. These compounds displayed the highest cytotoxic activities against MCF-7 cells at 100 µM that cell viability reduced to about 50%.

These compounds exhibited significant differences in viability compared to the negative control on both cell lines which presented in Fig. 1A and 1B.

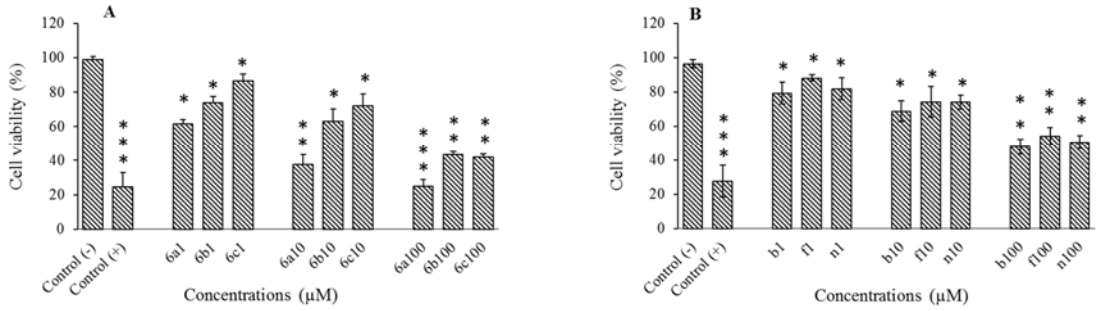


Fig. 1. Cytotoxic effect of compounds **6a-6c** on (A) HeLa and (B) MCF-7 cells following exposure to different concentrations (1, 10, and 100 µM). Data are presented as mean ± SD, n = 3. **P* < 0.05, ***P* < 0.01, and *** *P* < 0.001 Shows significant differences in comparison with negative control group, Paclitaxel was used as positive control.

Table 1. The IC_{50} of tested compounds against MCF-7 and HeLa cell lines.

Target compounds	R	IC_{50} (µM) MCF-7	IC_{50} (µM) HeLa
6a	Propyl	82.18 ± 3	7.52 ± 0.6
6b	Phenyl	97.17 ± 4	79.74 ± 3
6c	Nitro phenyl	101.47 ± 4	79.32 ± 3

DISCUSSION

1, 3, 4-Oxadiazole heterocycle as good bioisosteres of amides and esters, can improve pharmacological activity via hydrogen bonding interactions with the receptors (6,24). Literature survey revealed that little changes in the structure of substituted 1, 3, 4-oxadiazole can lead to quantitative and qualitative alterations in their biological activities (3).

A series of 2, 5-disubstituted-1, 3, 4-oxadiazoles has been reported as tubulin polymerization inhibitors (8,25). Moreover, 1, 3, 4-oxadiazole derivatives possessing 1,4-benzodioxan moiety have been introduced as potential anticancer agents (8,26). Besides, quinazolinone is a heterocyclic scaffold with extensive biological effects, in particular, anticancer activity. Derivatives of substituted quinazolinone at 2, 3 or 2, 4 positions have been reported as anticancer agents (22,27-29). Literature surveys have shown many reports on cytotoxic activities of quinqzolinone (9,22,27) and oxadiazoles (1,2,6,8).

Hybrid structures of quinazolinone-oxadiazole have presented anticancer (5,14,19) and antimicrobial (14,16,20) activities. Some of the 4-alkoxyquinazoline derivatives containing the 1, 3, 4-oxadiazole scaffold showed potent inhibitory activity against HeLa and MCF-7 cell lines (19).

We reported the synthesis of a novel series of quinazolin-4(3H)-one derivatives bearing oxadiazole, in the 3-position of the quinazolinone nucleus in a multiple-step reaction procedure. Amongst tested compounds, **6a** showed the highest cytotoxic activity against HeLa cell line at all tested concentrations while compounds **6b** and **6c** indicated mild cytotoxic effects against HeLa cell line at highest tested concentration. Three compounds displayed the highest cytotoxic activities against MCF-7 cells at 100 µM concentration.

According to the results shown in Table 1, compounds **6b** and **6c** bearing aromatic substituents on C_2 of the quinazolinone ring showed lowest cytotoxic activities on both cell lines, while compound **6a** containing aliphatic substituent on C_2 was more active on HeLa cell line with IC_{50} value 7.52 µM.

Khodarahmi *et al.* reported the synthesis and cytotoxic evaluation of quinazolinone-benzimidazole hybrid derivatives against MCF-7 and HeLa cell lines. Cytotoxicity results revealed that compounds with phenyl and nitrophenyl substitutes on C_2 of the quinazolinone ring had the lowest cytotoxic activity against both cell lines and compounds with aliphatic substituents in this position had the highest potency (30). Other hybrids of quinazolinone-triazole were recently reported by Jafari *et al*. Cytotoxicity results exhibited that the presence of electron donating substituents on C_2 of the quinazolinone ring could be in favor of the activity for these compounds (22). Collectively it could be assumed that the presence of electron-donating groups such as propyl substitution on C2 of quinazolinon ring could improve activity for these compounds while electron withdrawing groups such as phenyl and nitrophenyl substitutes have opposite effects.

CONCLUSION

In the present study, some of the conjugated oxadiazole-quinazolinone derivatives with amide linker were synthesized and evaluated for their cytotoxicity against HeLa and MCF-7 cell lines. Compound **6a** showed the highest cytotoxic activities with the IC_{50} value of 7.52 µM against HeLa cell line. Substitution of propyl group at 2 position of quinazolinone improved the cytotoxic activity against HeLa possibly due to electronic effects.

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