Synthesis of New Quinolone Derivatives Linked to Benzothiazole or Benzoxazole Moieties as Anticancer and Anti-Oxidant Agents

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Abstract

A new series of substituted quinolones linked to benzothiazole and/or benzoxazole moieties 5a-l was synthesized. 6-Benzoxazol-2-yl/benzothiazol-2-yl-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid ethyl esters 3a&b were reacted with hydrazine to give the hydrazide derivatives 4a&b and finally, 4a&b were reacted with different aromatic aldehydes giving the target compounds 5a-l. The benzylidenes derivatives 5a-l were screened for their cytotoxic activities against breast carcinoma cell lines (MCF-7) and anti-oxidant proprieties. All the tested compounds 5a-l showed from high to moderate activity as anticancer and anti-oxidant agents. Compounds 5h and 5i showed the highest cytotoxic activity against MCF-7 (IC50 0.058 and 0.052 µM, respectively) than 4-(benzothiazol-2-yl) aniline the reference drug (IC50 0.065 µM). Moreover, compounds 5e, 5g and 5h showed the highest anti-oxidant activity. The structure of the compounds 5a-l was confirmed using IR, 1H NMR, mass spectroscopy and elemental analysis.

Keywords: Quinolones; Benzothiazoles; Benzoxazoles; Anti-oxidant activity; Anticancer effect

Introduction

The cytotoxic activity of quinolone derivatives has become the source of new anticancer agents, which might also help addressing side-toxicity and resistance [1]. Moreover, the quinoline ring is considered an important structural unit in many anti-cancer agents [2]. New synthesized 4-arylcyclogenyl-7-chloroquinolines were screened in vitro for antioxidant activity by previous publication which demonstrated that compound presented a potent antioxidant effect [3].

Quinolones were used especially as radicals scavenger like quercetol (A) or coumestrol (B) and the copper or iron chelating molecules such as cloquinoic (C) [4,5]. Moreover, quinolone containing hydroxy group compounds exhibited antiradical activity against DPPH radical and anion superoxide tests activity [6].

On the other hand, benzothiazoles showed potent scavenging activities against DPPH radical and 2,2’-azino-bis-(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) (D) radicals had reducing power, and strong inhibitory capacity on lipid peroxidation. Also, benzothiazoles or benzoxazoles containing compounds were found to be cytotoxic against CNS cancer cell line SNB-75 [7]. Moreover, 4-(benzothiazol-2-yl) aniline (Eb) showed a promising cytotoxic activity against breast, ovarian, lung and renal cell lines [8-10]. Activity was partially retained in benzoxazole analogue Ea [8] (Figure 1). Compounds of thiol and aminothiol derived from benzothiazoles showed a promising anti-oxidant property [11].

Benzothiazoles and benzoxazoles containing compounds were showed anticancer activity against various cell lines [12,13]. New synthesized compounds containing benzothiazoles or benzoxazoles linked to quinolone showed anticancer and antimicrobial activities [14,15].

According to the aforementioned facts and as a continuation of our previous studies in the field of anticancer screening and anti-oxidant evaluation, [16-19] we attempt to design novel quinolone derivatives through:

- Substitution at quinolone nucleus with benzothiazole and benzoxazole rings (which have antioxidant or anticancer activity) at 6 position of quinolone.

- Maintain the main structure which responsible for receptor coupling of quinolone.

- Substitution of carboxyl group at 3-position by substituted phenylhydrazone to increase its lipophilicity.

- Over all incorporation of benzoxazole or benzothiazole and quinolone in one scaffold structure.

All the synthesized compounds were evaluated for their anticancer activity against human breast adenocarcinoma cell line (MCF-7) and antioxidant activity.

Materials and Methods

Chemistry

Melting points were determined on a Graffin apparatus and were uncorrected. Element analyses (C, H, and N) were carried out on Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA) at the Micro analytical unit of Cairo University, Egypt. All compounds were within ± 0.4% of the theoretical values. IR spectra were determined as KBr discs on Shimadzu IR 435 Spectrophotometer and values were represented in cm⁻¹. 1H NMR spectra were carried out on a Bruker 400.

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Received October 12, 2016; Accepted October 24, 2016; Published October 27, 2016

Citation: Abdelgawad MA, Lamie PF, Ahmed OM (2016) Synthesis of New Quinolone Derivatives Linked to Benzothiazole or Benzoxazole Moieties as Anticancer and Anti-Oxidant Agents. Med Chem (Los Angeles) 6: 652-657. doi:10.4172/2161-0444.1000410

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General procedure for the synthesis of (ZE)-6-(benzo[d] oxazol or thiazol-2-yl)-N'-substituted benzylidene-4-oxo-1,4-dihydroquinoline-3-carbohydrazide 4a&b

To a suspension of compounds 3a&b (0.01 mol) in absolute ethanol (30 mL), hydrazine hydrate 99% (5 g, 0.1 mol) was added. The mixture was heated under reflux for 20 h. The precipitated solid was filtered, dried and crystallized from DMF/ethanol.

6-(Benzo[d] oxazol-2-yl)-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (4a): Yield: 53%; yellow crystals; mp: 390-392°C; IR (cm\(^{-1}\)): 3645-3441 (2NH and NH\(_2\)); 3089 (CH aromatic), 1696, 1609 (2C=O); MS m/z: 320 [(M+H\(^+\)], 288 [(C\(_6\)H\(_9\)N\(_2\)O\(_4\))\(^+\)], 100%. Anal. Calcd. For C\(_{67}\)H\(_{64}\)N\(_8\)O\(_8\): C, 61.20; H, 3.13; N, 12.00. Found: C, 61.10; H, 3.15; N, 12.00.

6-(Benzo[d] thiazol-2-yl)-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (4b): Yield: 53%; yellow crystals; mp: 396-398°C; IR (cm\(^{-1}\)): 3422-3176 (2NH and NH\(_2\)); 3082 (CH aromatic), 1696, 1609 (2C=O); MS m/z: 336 [(M+H\(^+\)], 298 [(C\(_6\)H\(_9\)N\(_2\)O\(_4\))\(^+\)], 100%. Anal. Calcd. For C\(_{67}\)H\(_{64}\)N\(_8\)O\(_8\): C, 62.60; H, 3.20; N, 12.00. Found: C, 62.65; H, 3.20; N, 12.00.
1,4-dihydroquinoline-3-carbohydrazide (5f): Yield: 53%; brown solid; mp: 347-349°C; IR (cm⁻¹): 3434, 3141 (2NH), 3089 (CH aromatic), 1694, 1617 (C=O); 1H NMR (DMSO-d₆) δ ppm 7.54 (m, 4H, Ar-H), 7.76 (m, 2H, Ar-H), 8.13 (m, 3H, Ar-H), 8.82 (s, 2H, N=CH and CONH, D,O exchangeable), 8.87 (m, 3H, Ar-H), 11.19 (s, 1H, NH, D,O exchangeable); MS m/z: 454 [M+1]+, 365 [M]+, 448 [M-1]+, 184 [M-2H]+, 10% final concentration for 1 hour at 4°C. The plates were washed with dimethylsulfoxide (DMSO) and the prepared stock was stored at -20°C. Different concentrations of the compounds 0, 6.25, 12.5, 25, 50 and 100 µg/ml in culture medium were used.

Preparatory steps prior to cytotoxicity investigation

Maintenance of the breast carcinoma cell lines (MCF-7) in the laboratory, cryopreservation of cells, collection of cells by trypsinization and determination and counting of viable cells are performed according to the reported methods [20,21].

Determination of potential cytotoxicity of drug on human cancer cell line

The cytotoxicity was carried out using Sulphorhodamine-B (SRB) assay following the reported method [22]. SRB is a bright pink aminothiolene dye with two sulfonic groups. It is a protein stain that binds to the amino groups of intracellular proteins under mildly acidic conditions to provide a sensitive index of cellular protein content. If the cells develop into a monolayer, the medium will be incubated for 72 h with various concentrations of drugs (0, 6.25, 12.5, 25, 50 and 100 µg/ml). Dulbecco's Modified Eagle Medium (DMEM), trypan blue, Fetal Bovine Serum, Penicillin/ Streptomycin antibiotic and Trypsin- EDTA Sigma Aldrich Chemical Co., St. Louis, Mo, USA. A trypan buffer was obtained from Applichem, Germany. All chemicals and reagents used in this study are of highest analytical grade.

Methods

Preparation of test compounds

The tested derivatives 5a-l were prepared by dissolving in dimethylsulfoxide (DMSO) and the prepared stock was stored at -20°C. Different concentrations of the compounds 0, 6.25, 12.5, 25, 50 and 100 µg/ml in culture medium were used.

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with 50 µl 0.4% SRB dissolved in 1% acetic acid for 30 minutes at room temperature in dark. The plates were washed with 1% acetic acid to remove unbound dye and air-dried (24 h). The dye was solubilized with 150 µl/well of 10 mMtris base (PH 7.4) for 5 min on a shaker at 1600 rpm. The optical density (OD) of each well will be measured spectrophotometrically at 490 nm with an ELISA microplate reader. The mean background absorbance was automatically subtracted and mean values of each derivative and 4-(benzothiazol-2-yl)-aniline (reference drug) concentration was calculated. The experiment was repeated three times. The percentage of cell survival was calculated by using formula, surviving percent=[OD (treated cells)/OD (control cells)] × 100. The IC₅₀ values (the concentrations of derivatives required to produce 50% inhibition of cell growth) were also calculated using linear trend linear equation.

Anti-oxidant assay

DPPH radical scavenging activity: The effect of the synthesized organic compounds on DPPH radical was estimated using the reported methods [23,24] with some modifications. A solution of 200 µmol DPPH in ethanol was prepared and 100 µl of this solution was mixed with 0.9 ml of varying concentrations of the synthesized derivatives (dissolved in ethanol) to reach a final concentration of 0.25, 0.5 and 1 mg/ml. The reaction mixture wasswirled and left in the dark for 30 min (room temperature). The color became light yellow from deep violet and the absorbance of the mixture was determined at 570 nm. The control was prepared by using adding 100 µl DPPH to 0.9 ml ethanol solution.

DPPH radical scavenging activity (%)\(=\frac{1}{2}[\text{A_{control}}-\text{A_{sample}}]/\text{A_{control}}\)×100

Where A_{control} is the absorbance of DPPH radical+ethanol and A_{sample} is the absorbance of DPPH radical+sample of derivative compound dissolved in ethanol.

Results and Discussion

Chemistry

In this work, the synthesis of different Schiff bases at C-3 of quinolone moiety was described. Biologically important benzoxazoles and benzothiazoles were merged with quinolone nucleus. 6-Benzoxazole/ benzothiazol-2-yl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl esters 3a&b were employed as the starting materials. They were synthesized following the precautions of their reported method [14]. Direct conversion of 3a&b into hydrazide derivatives 4a&b was achieved in good yield by the treatment of 3a&b with hydrazine hydrate 99%. Several solvents were carried out to prepare these intermediates 4a&b such as absolute ethanol, glacial acetic acid and dioxane. Absolute ethanol was the solvent of choice since it gave more pure products (using: TLC) as well as higher yields (Scheme 1). The structure of compounds 4a&b was established on the basis of IR, 

\[ ^1H \text{NMR} \]

mass spectral data and elemental analysis. IR spectra of 4a&b revealed the appearance of new absorption bands at 3465-3176 cm\(^{-1}\). The structure of the compounds 4a&b was confirmed by \[ ^1H \text{NMR} \] which was performed in DMSO as a solvent, appearance of D\(_2\)O exchangeable singlet signal at δ 4.51 and 4.65 ppm indicated NH protons, beside the appearance of another exchangeable singlet signal corresponding to CONH proton at δ 10.63 and 10.84 ppm, respectively. Moreover, mass spectra of 4a&b showed molecular ion peaks at m/z 320 and 336, sequentially. Heating compounds 4a&b for 8-10 hours with different aromatic aldehydes in absolute ethanol containing catalytic amount of glacial acetic acid led to the formation of 5a-l. The formation of the target Schiff bases 5a-l was substantiated on basis of spectral data and elemental analysis (see Experimental Section).

\[ ^1H \text{NMR} \] spectra of compounds 5a-l showed disappearance of D\(_2\)O exchangeable singlet signal of NH protons of the parent hydrazide derivatives 4a&b and the appearance of new singlet signal due to azomethine proton (N=C(=H)) at δ 8.82-9.08 ppm in benzoxazole derivatives 5a-l for at δ 8.80-9.60 ppm for benzothiazole derivatives 5g-l.

Additionally, the mass spectrum of compound 5d revealed molecular ion peaks at m/z 443 and 445 corresponding to (M\(^{+}\)and (M+2)\(^{+}\), respectively in ratio of 3:1 (CI pattern). The reactivity of the applied aromatic aldehydes was appeared in parallel manner with the yield of the resulting targets 5a-l, which ranged between 45% up to 79% starting from benzaldehyde to 4-nitrobenzaldehyde in both benzoxazole and benzothiazole derivatives.

Anticancer activity

The data showing the anti-proliferative effects of the tested derivatives on breast carcinoma cell lines (MCF-7) are illustrated in Figures 1 and 2. All derivatives from 5a to 5l produced a marked gradual decrease in the survival percent of MCF-7 as the dose of derivatives increased from 0 to 100 µg/ml. Based on the values of IC₅₀, the derivatives are arranged according to their tumor cytotoxic potencies in the following order: derivatives 5f, 5h, 5g, 5k, 5e, 5a, 5i, 5d, 5j, 5c and 5a recording IC₅₀ of 40.783, 45.461, 48.953, 50.627, 52.138, 53.665, 54.163, 55.344, 57.462, 58.452, 69.214 and 82.300 µg/ml, respectively Scheme 2. Thus, derivative 5l produced the most potent tumor cytotoxic efficacy, while derivative 5a followed by derivative 5c are the least potent (Figure 2 and Table 1).

Anti-oxidant activity

The antioxidant capacity was evaluated by detection of DPPH radical scavenging activity. Different concentrations of derivatives were tested. All tested derivatives had marked antioxidant activity. At
2-yl)-N'-((2-hydroxybenzylidene)-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5h) seemed to have the most potent antitumor action (IC\textsubscript{50}: 0.052 µM and 0.058 µM, respectively), in addition to five new compounds 5e, 5f, 5g, 5i and 5k showed good activity with IC\textsubscript{50} between 0.072 µM and 0.099 µM. On the other hand, (ZE)-6-(benzo[d]oxazol-2-yl)-N'-(4-(dimethylamino)benzylidene)-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5e), (ZE)-6-(benzo[d]thiazol-2-yl)-N'-benzylidene-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5g) and (ZE)-6-(benzo[d]thiazol-2-yl)-N'-(2-hydroxybenzothiazole)-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5h) have the most efficient antioxidant activity as indicated by the results of DPPH radical scavenging capacity. Finally, it was found that compound 5h bearing 4-hydroxyphenyl moiety and benzothiazole nucleus has dual anticancer and anti-oxidant activity and need further investigations.

Conflict of Interest

The authors declared that there is no conflict of interest.

Table 1: IC\textsubscript{50} of the test compounds (5a-l) against breast cancer (MCF-7).

| Compound No. | IC\textsubscript{50} (µM) |
|--------------|--------------------------|
| 5a           | 0.2                      |
| 5b           | 0.117                    |
| 5c           | 0.15                     |
| 5d           | 0.106                    |
| 5e           | 0.078                    |
| 5f           | 0.085                    |
| 5g           | 0.072                    |
| 5h           | 0.058                    |
| 5i           | 0.099                    |
| 5j           | 0.104                    |
| 5k           | 0.074                    |
| 5l           | 0.052                    |

Table 2: DPPH radical scavenging activity (%) of derivative compounds (5a-l) at various concentrations.

| Derivatives | 0.25 mg/ml | 0.5 mg/ml | 1 mg/ml |
|-------------|------------|-----------|---------|
| 5a          | 26.33      | 12.16     | 13.50   |
| 5b          | 15.58      | 10.75     | 11.50   |
| 5c          | 10.25      | 20.00     | 0.00    |
| 5d          | 15.75      | 13.75     | 18.33   |
| 5e          | 21.58      | 31.84     | 39.75   |
| 5f          | 3.58       | 2.5       | 9.83    |
| 5g          | 12.97      | 25.52     | 40.83   |
| 5h          | 12.97      | 25.52     | 40.82   |
| 5i          | 13.64      | 19.39     | 31.65   |
| 5j          | 8.92       | 6.58      | 11.75   |
| 5k          | 11.59      | 20.63     | 27.28   |
| 5l          | 12.33      | 14.83     | 15.92   |

Conclusion

The synthesized derivatives exhibited various degrees of cytotoxic effects on breast carcinoma cell line (MCF-7) in vitro. Comparing the new compounds with 4-(benzothiazol-2-yl)aniline – known with its cytotoxic activity- which has IC\textsubscript{50} 0.065µM, we observed that: (ZE)-6-(benzo[d]thiazol-2-yl)-N'-((4-nitrobenzylidene)-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5l) was the most efficient compound IC\textsubscript{50}: 0.052 µM and 0.058 µM, respectively), in addition to five new compounds 5e, 5f, 5g, 5i and 5k showed good activity with IC\textsubscript{50} between 0.072 µM and 0.099 µM. On the other hand, (ZE)-6-(benzo[d]oxazol-2-yl)-N'-(4-(dimethylamino)benzylidene)-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5e), (ZE)-6-(benzo[d]thiazol-2-yl)-N'-benzylidene-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5g) and (ZE)-6-(benzo[d]thiazol-2-yl)-N'-(2-hydroxybenzothiazole)-4-oxo-1,4-dihydroquinoline-3-carboxhydrazide (5h) have the most efficient antioxidant activity as indicated by the results of DPPH radical scavenging capacity. Finally, it was found that compound 5h bearing 4-hydroxyphenyl moiety and benzothiazole nucleus has dual anticancer and anti-oxidant activity and need further investigations.

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| 5d           | 0.106                    |
| 5e           | 0.078                    |
| 5f           | 0.085                    |
| 5g           | 0.072                    |
| 5h           | 0.058                    |
| 5i           | 0.099                    |
| 5j           | 0.104                    |
| 5k           | 0.074                    |
| 5l           | 0.052                    |

Table 2: DPPH radical scavenging activity (%) of derivative compounds (5a-l) at various concentrations.

| Derivatives | 0.25 mg/ml | 0.5 mg/ml | 1 mg/ml |
|-------------|------------|-----------|---------|
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| 5e          | 21.58      | 31.84     | 39.75   |
| 5f          | 3.58       | 2.5       | 9.83    |
| 5g          | 12.97      | 25.52     | 40.83   |
| 5h          | 12.97      | 25.52     | 40.82   |
| 5i          | 13.64      | 19.39     | 31.65   |
| 5j          | 8.92       | 6.58      | 11.75   |
| 5k          | 11.59      | 20.63     | 27.28   |
| 5l          | 12.33      | 14.83     | 15.92   |
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