Saudi Pharmaceutical Journal (2016) xxx, xxx–xxx

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Synthesis of chalcone incorporated quinazoline derivatives as anticancer agents

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Received 7 February 2016; accepted 19 June 2016

KEYWORDS

Gefitinib;
Erlotinib;
Resveratrol;
Chalcones;
Quinazolines;
Cytotoxicity

Abstract A series of ten novel chalcone incorporated quinazoline derivatives (**11a**–**11j**) were designed and synthesized. All the synthesized compounds were evaluated for their anticancer activities against four human cancer cell lines (A549, HT-29, MCF-7 and A375). Among them, four compounds, **11f**, **11g**, **11i** and **11j** showed more potent anticancer activity than the control drug, Combretastatin – A4.

1. Introduction

Quinazolines are nitrogen containing heterocyclic scaffolds and have showed a wide range biological activities, such as anticancer (Connell, 2004; Marvania et al., 2011), antitubercular (Jampilek et al., 2009), anti-inflammatory (Laddha and Bhatnagar, 2009), antimicrobial (McLaughlin and Evans, 2010), and anti-HIV (Selvam et al., 2010) activities. The quinazoline based molecules were found to inhibit the epidermal growth factor receptor (EGFR) tyrosine kinase (Kersemaekers et al., 1999; Maurizi et al., 1996). Some of the quinazoline based compounds are used as anticancer drugs, such as Gefitinib (**1**) (Murphy and Stordal, 2011; Sun et al., 2011) and Erlotinib (**2**) (Herbst, 2003). Both these compounds are first-generation EGFR-targeting 4-anilinoquinazoline chemotherapeutics and used to treat non-small cell lung cancer. Further, many quinazoline derivatives show antitumor activity through inhibition of several potential anticancer targets such as checkpoint H kinase 2 (Caldwell et al., 2011), non-receptor protein tyrosine kinase JAK2 (Yang et al., 2011), poly(ADP-ribose) polymerase (Hattori et al., 2004) and peptidylprolyl *cis*/*trans* isomerase Pin1 (Zhu et al., 2011).

Similarly, chalcones are well-known intermediates for synthesizing various heterocyclic compounds. Chalcones represent an important naturally occurring α,β-unsaturated ketones and showed a wide spectra of biological activities, such as antitumor (Modzelewska et al., 2006), antifungal (Lahtchev et al., 2008), antibacterial (Zangade et al., 2010), and anti-inflammatory (Won et al., 2005). The naturally occurring *E*-resveratrol (**3**) is a natural stilbene derivative that occurs in various edible plants such as grapes and nuts (Jang et al., 1997). It possesses multiple biological activities, those include anticancer (Fulda, 2010), antioxidant (Creasy and Coffee,

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2016.06.005

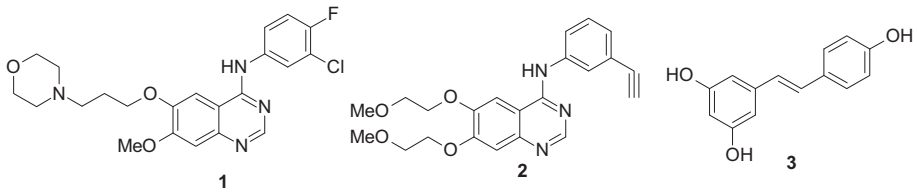


Figure 1 Structures of as Gefitinib (1), Erlotinib (2) and *E*-resveratrol (3).

1988), anti-inflammatory (Uenobe et al., 1997), and liver protecting (Virgili and Contestabile, 2000). The structures of anticancer drugs Gefitinib (**1**), Erlotinib (**2**) and *E*-resveratrol (**3**) are shown in Fig. 1.

In view of biological importunacy of quinazoline and chalcones, we have designed and synthesized a series of chalcone incorporated quinazoline derivatives (**11a–11j**). Further, these derivatives were evaluated for their anticancer activity. All the synthesized compounds were evaluated for their anticancer activities against four human cancer cell lines (A549, HT-29, MCF-7 and A375). Among them, four compounds, **11f**, **11g**, **11i** and **11j** showed more potent anticancer activity than the control drug, Combretastatin-A4.

2. Experimental

2.1. General

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity and Bruker UXNMR/XWIN-NMR (400 and 300 MHz) instrument. Chemical shifts (d) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus, and are uncorrected.

2.2. Synthesis of quinazolin-4-ol (*6*)

A mixture of anthranilic acid (**4**) (13 g, 94.7 mmol) was heated with formamide (**5**) (42 g, 94.7 mmol) in absolute ethanol at 65 °C for 4 h. Then it was cooled at room temperature. The mixture solidified. It was broken up and mixed with water and then filtered. The residue was crystallized from ethanol to afford pure compound **6,** 10.8 g in 78% in yield. Mp: 212–213°; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10–7.31 (m, 2H), 8.34–8.43 (s, 2H), 8.73 (s, 1H), 9.12 (bs, 1H); MS (FAB): 146 $[M]^+$.

2.3. Synthesis of 4-chloroquinazoline (*7*)

The quinazolin-4-ol **(6)** (9 g) was dissolved in 50 mL $POCl_3$ in a round bottom flask. The mixture was heated on an oil bath at 120 °C for 4 h by which time all the solid had dissolved and then for a further period of one hour. The volatile materials were removed under reduced pressure. The viscous oily mass was added continuously to ice-cold liquor ammonia. The precipitated materials were filtered and extracted with petroleum ether. The solid, thus obtained, was recrystallized from petroleum ether respectively to afford pure compound **7**, 8.2 g in 81% in yield. Mp: 97–98 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61–7.69 (m, 1H), 7.79–7.83 (m, 1H), 7.90–7.99 (m, 1H), 8.16–8.18 (m, 1H), 8.79 (s, 1H); MS (FAB): 164 $[M]^+$.

2.4. Synthesis of 4-(quinazolin-4-ylamino)benzaldehyde (*9*)

Compound 4-chloroquinazoline (**7**) (8 g, 48.7 mmol) was dissolved in 20 ml of N-methylpyrrolidine (NMP) and 4-aminobenzaldehyde (**8**) (5.9 g, 48.7 mmol) was added to this solution; reaction mixtures were heated at 60 °C and after that 4 drops of conc HCl were added and reaction mixtures were heated for 1 h. After heating the crystalline precipitate was separated by filtration and purified by recrystallization from ethanol to afford pure compound **9,** 9.4 g in 77% yield. Mp: 104–106 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (d, 2H, J = 7.89 Hz), 7.65–7.70 (m, 1H), 7.73–7.76 (m, 1H), 7.78–7.81 (m, 1H), 8.14–8.24 (m, 3H), 8.82 (s, 1H), 8.90 (s, 1H), 9.71 (s, 1H); MS (FAB): 249 $[M]^+$.

2.4.1. Synthesis of (E)-1-Phenyl-3-(4-(quinazolin-4-ylamino) phenyl)prop-2-en-1-one (*11a*)

The compound 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) was dissolved in 5 mL of ethanol, followed by addition of acetophenone (**10a)** (0.18 mL, 1.60 mmol) and 3 drops of piperidine. The reaction mixture was heated under reflux for 6 h. After cooling water (20 mL) was added slowly. The crystalline precipitate was separated by filtration and purified by recrystallization from ethanol to afford pure compound **11a,** 421 mg in 75% yield**.** Mp: 110–112 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25 (d, 1H, J = 15.6 Hz), 7.34–7.45 (m, 3H), 7.67–7.78 (m, 7H), 7.83 (t, 1H), 8.23 (d, 2H, J = 8.21 Hz), 8.47 (d, 1H, J = 7.23 Hz), 8.77 (s, 1H), 9.23 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 110.6, 118.5, 121.8, 122.4, 129.3, 130.4, 131.7, 132.8, 132.9, 134.5, 134.8, 139.6, 143.6, 145.4, 155.7, 160.2, 165.4, 181.6; MS (ESI): 352 $[M+H]^+$.

2.4.2. Synthesis of (E)-1-(3-Chlorophenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (*11b*)

The compound **11b** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 3-chloroacetophenone **(10b)** (0.2 mL, 1.60 mmol) to afford pure compound **11b**, 441 mg

in 71% yield. Mp: 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 (d, 1H, J = 15.8 Hz), 7.41 (t, 1H), 7.46 (d, 2H, J = 8.34 Hz), 7.54–7.59 (m, 3H), 7.78–7.85 (m, 3H), 7.90 (t, 1H), 7.94–7.98 (m, 2H), 8.47–8.50 (m, 1H), 8.83 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 111.2, 118.6, 122.4, 124.3, 130.3, 131.5, 133.8, 134.1, 134.6, 134.9, 135.3, 135.8, 136.4, 140.3, 143.5, 146.8, 155.4, 160.7, 164.7, 184.2; MS (ESI): 386 $[M+H]^+$.

*2.4.3. Synthesis of (E)-1-(4-Chlorophenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11c**)*

The compound **11c** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 4-chloroacetophenone **(10c)** (0.2 mL, 1.60 mmol) to afford pure compound **11c**, 462 mg in 75% yield. Mp: 120–122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 (d, 1H, J = 15.7 Hz), 7.38 (d, 2H, J = 8.23 Hz), 7.62 (d, 2H, J = 8.62 Hz), 7.89–7.98 (m, 5H), 8.45 (t, 1H), 8.78 (d, 2H, J = 8.62 Hz), 8.89 (d, 1H, J = 1.23 Hz), 8.96 (s, 1H), 9.36 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 111.8, 118.9, 122.7, 124.9, 130.4, 132.3, 133.7, 134.2, 134.6, 135.8, 138.3, 141.7, 143.8, 146.9, 156.4, 161.6, 165.8, 184.9; MS (ESI): 386 $[M+H]^+$.

*2.4.4. Synthesis of (E)-1-(4-Bromophenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11d**)*

The compound **11d** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 4-bromoacetophenone **(10d)** (318 mg, 1.60 mmol) to afford pure compound **11d**, 473 mg in 69% yield. Mp: 127–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37 (d, 1H, J = 15.4 Hz), 7.45 (d, 2H, J = 8.12 Hz), 7.49 (d, 2H, J = 8.12 Hz), 7.69–7.76 (m, 3H), 7.80–7.85 (m, 3H), 7.91 (d, 2H, J = 9.23 Hz), 8.49–8.53 (m, 1H), 8.76 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 112.4, 119.3, 123.5, 125.2, 130.8, 133.4, 134.7, 134.9, 135.6, 136.2, 136.8, 137.3, 143.2, 147.5, 154.3, 162.7, 166.7, 185.3; MS (ESI): 431 $[M+H]^+$.

*2.4.5. Synthesis of (E)-1-(3-Bromophenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11e**)*

The compound **11e** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 3-bromoacetophenone **(10e)** (0.21 mL, 1.60 mmol) to afford pure compound **11e**, 466 mg in 68% yield. Mp: 130–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (d, 1H, J = 15.3 Hz), 7.43 (t, 1H), 7.52 (d, 2H, J = 8.23 Hz), 7.64–7.78 (m, 6H), 7.83 (t, 1H), 8.44–8.49 (m, 2H), 8.56–8.59 (m, 1H), 8.79 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 112.7, 119.6, 122.5, 126.2, 131.4, 133.7, 134.5, 134.9, 135.4, 136.6, 136.9, 137.5, 143.7, 147.8, 154.6, 162.9, 165.8, 184.5; MS (ESI): 431 $[M+H]^+$.

*2.4.6. Synthesis of (E)-1-(2-Fluoro-4-(trifluoromethyl)phenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11f**)*

The compound **11f** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 1-(2-fluoro-4-(trifluoromethyl)phenyl)ethanone **(10f)** (0.32 mL, 1.60 mmol) to afford pure compound **11f**, 586 mg in 83% yield. Mp: 140–142 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (d, 1H, J = 15.7 Hz), 7.41 (d, 2H, J = 8.19 Hz), 7.58–7.67 (m, 6H), 7.76 (t, 1H), 7.86–7.95 (m, 1H), 8.35–8.37 (m, 1H), 8.45–8.49 (m, 1H), 8.88 (s, 1H), 9.29 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 120.8, 121.3, 121.9, 122.4, 124.4, 124.9, 125.4, 127.4, 131.3, 131.9, 132.4, 133.7, 135.6, 142.3, 143.6, 145.6, 156.8, 161.3, 163.7, 165.6, 180.5; MS (ESI): 438 $[M+H]^+$.

*2.4.7. Synthesis of (E)-1-(4-(Trifluoromethyl)phenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11g**)*

The compound **11g** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 1-(4-(trifluoromethyl)phenyl)ethanone **(10g)** (0.3 mL, 1.60 mmol) to afford pure compound **11g**, 512 mg in 76% yield. Mp: 134–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23 (d, 1H, J = 15.4 Hz), 7.35 (d, 2H, J = 8.21 Hz), 7.57–7.68 (m, 5H), 7.78 (t, 1H), 8.65–8.69 (m, 5H), 8.85 (s, 1H), 9.25 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 120.3, 121.4, 124.5, 124.8, 125.2, 125.9, 133.3, 133.6, 134.1, 134.5, 134.9, 135.3, 137.4, 142.4, 142.7, 147.5, 156.4, 160.7, 165.3, 182.5; MS (ESI): 420 $[M+H]^+$.

*2.4.8. Synthesis of (E)-1-(3-fluorophenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11h**)*

The compound **11h** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 1-(3-fluorophenyl)ethanone **(10h)** (0.2 mL, 1.60 mmol) to afford pure compound **11h**, 472 mg in 80% yield. Mp: 139–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (d, 1H, J = 15.8 Hz), 7.37 (d, 2H, J = 8.45 Hz), 7.54–7.76 (m, 7H), 7.79 (t, 1H), 7.85–7.87 (m, 1H), 8.38 (m, 1H), 8.76 (s, 1H), 9.30 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 119.4, 120.5, 121.6, 124.5, 126.7, 129.5, 130.3, 133.2, 133.7, 134.3, 134.6, 134.9, 135.6, 139.4, 142.4, 146.4, 155.7, 160.3, 162.4, 164.3, 180.4; MS (ESI): 370 $[M+H]^+$.

*2.4.9. Synthesis of (E)-1-(3,4-Dimethoxyphenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11i**)*

The compound **11i** was prepared following the method described for the preparation of the compound **11a**, employing 4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 1-(3,4-dimethoxyphenyl)ethanone **(10i)** (288 mg, 1.60 mmol) to afford pure compound **11i,** 511 mg in 77% yield. Mp: 149–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H), 3.83 (s, 3H), 7.45 (d, 1H, J = 15.5 Hz), 7.49 (d, 1H, J = 1.22 Hz), 7.54 (d, 2H, J = 8.93 Hz), 7.62–7.66 (m, 2H), 7.70–7.76 (m, 5H), 7.81–7.84 (t, 1H), 7.91–7.94 (m, 1H), 8.79 (s, 1H), 9.23 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 56.8, 57.3, 118.5, 121.4, 124.8, 128.4, 128.9, 129.5, 131.6, 131.9, 132.3, 132.8, 134.5, 143.6, 147.4, 149.3, 151.8, 155.6, 160.3, 165.6, 179.9; MS (ESI): 412 $[M+H]^+$.

*2.4.10. Synthesis of (E)-1-(4-Methoxyphenyl)-3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one (**11j**)*

The compound **11j** was prepared following the method described for the preparation of the compound **11a**, employing

4-(quinazolin-4-ylamino)benzaldehyde **(3)** (400 mg, 1.60 mmol) and 1-(4-methoxyphenyl)ethanone (**10j)** (240 mg, 1.60 mmol) to afford pure compound **11j**, 492 mg in 80% yield. Mp: 146–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 7.39 (m, 3H), 7.46 (d, 2H, J = 8.26 Hz), 7.49 (d, 2H, J = 8.26 Hz), 7.63–7.70 (m, 3H), 7.75 (t, 1H); 7.85 (d, 2H, J = 9.12 Hz), 8.36 (m, 1H), 8.83 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 56.7, 110.4, 120.6, 122.4, 124.5, 125.4, 130.3, 131.8, 132.5, 132.8, 134.7, 142.5, 143.7, 151.3, 160.2, 163.5, 164.7, 180.6; MS (ESI): 382 $[M+H]^+$.

2.5. Cytotoxicity – MTT assay

The cytotoxic activity of the compounds was determined using MTT assay (Kamal et al., 2012). 1×10^4 cells/well were seeded in 200 µl DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37 °C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 µl MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/ml) was added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 µl of DMSO and absorbance at 540 nm wavelength was recorded.

3. Results and discussion

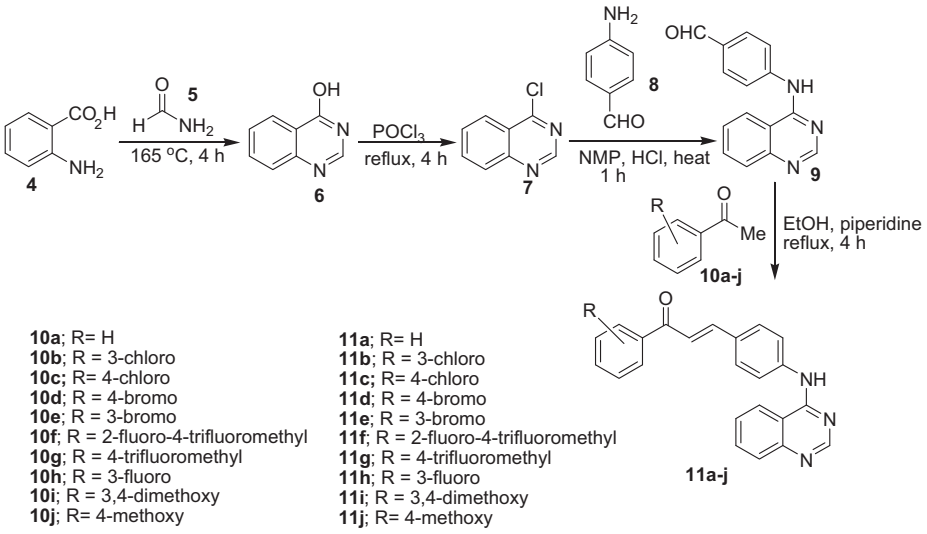
3.1. Chemistry

Synthesis of these new chalcone incorporated quinazoline derivatives (**11a–11j**) was shown in Scheme 1. The anthranilic acid (**4**) was heated with formamide (**5**) in absolute ethanol at 165 °C for 4 h, to afford compound **6** with good yield. The intermediate **6** was dissolved in 60 mL $POCl_3$ and reflux for 4 h, to afford pure 4-chloroquinazoline (**7**), which was coupled with 4-aminobenzaldehyde (**8**) in NMP, catalytic amount of hydrochloric acid and heated for 1 h to afford pure 4-(quinazolin-4-ylamino)benzaldehyde (**9**). This aldehyde intermediate (**9**) undergone aldol condensation with substituted acetophenones (**10a–10j**) in the presence of ethanol and catalytic amount of piperidine at reflux for 4 h to afford pure chalcone derivatives of quinazolines (**11a–11j**).

4. Biological evaluation

4.1. *In vitro* cytotoxic activity

The *in vitro* anticancer activities of all the synthesized target molecules (**11a**–**11j**) were evaluated by MTT assay, wherein selected four human cancer cell lines such as A549 (Human alveolar adenocarcinoma cell line), MCF-7 (Human breast adenocarcinoma cell line), HT-29 (Human Colorectal Adenocarcinoma Cell Line) and A375 (Melanoma cancer cell line). The IC_{50} was calculated for these tested compounds in µM. IC_{50} may be defined as the drug concentration that produced 50% inhibition of the cells. Combretastatin-A4 (CA-4) was chosen as reference molecule. The cytotoxicities were expressed as IC_{50} values presented in Table 1. Among the synthesized compounds, 11 g exhibits most potent activity towards HT-29, MCF 7 and A 549 cancer cell lines with IC_{50} values 0.13 µM, 0.17 µM and 0.10 µM than the control drug Combretastatin-A4. While the compound 11f showed good cytotoxicity with IC_{50} value 0.18 µM towards Human Colorectal Adenocarcinoma Cell Line than the control drug, the compound 11i exhibited maximum cytotoxic effect on A549, MCF 7 and A375 with IC_{50} values 0.10 µM, 0.14 µM and 0.19 µM than the positive control. Compound 11j exhibited better anti-cancer activity with IC_{50} value 0.16 µM on MCF 7 cell line than the standard drug. The remaining compounds 11a, 11b, 11c, 11d, 11e and 11h also show significant anti-cancer activities towards A549, HT-29, MCF 7 and A375 cell lines. The anti-cancer activity results of all the synthesized compounds are shown in Table 1.



Scheme 1 Synthesis of Chalcone incorporated Quinazoline derivatives.

Table 1 Anticancer activity (IC_{50}) data of chalcone-quinazoline compounds (**11a–11j**).

Compound	A549	HT-29	MCF-7	A375
11a	2.67	4.67	3.78	–
11b	–	12.6	–	5.87
11c	1.34	–	2.01	2.23
11d	3.67	2.11	–	2.30
11e	7.45	2.33	–	–
11f	2.90	0.18	–	1.89
11g	0.10	0.13	0.17	1.34
11h	2.55	–	–	9.34
11i	0.10	1.56	0.14	0.19
11j	2.10	2.89	0.16	1.37
Combretastatin-A4	0.11	0.93	0.18	0.21

"–" indicate not active.
A549 – Human alveolar adenocarcinoma cell line.
HT-29 – Human Colorectal Adenocarcinoma Cell Line.
MCF-7 – Human breast adenocarcinoma cell line.
A375 – Melanoma cancer cell line.

5. Conclusion

In conclusion, we have synthesized a new chalcone incorporated quinazoline derivatives (**11a–11j**) and evaluated for their anticancer activity against four human cancer cell lines (A549, MCF-7, HT-29 and A375). Among them, the compounds **11f**, **11g**, **11i** and **11j** were showed more potent activity than positive control of combretastatin-A4. The concentrations of the compounds which produce 50% inhibition of cell growth (IC_{50}) were compared with those of the standard drug, that is, combretastatin-A4.

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Please cite this article in press as: Madhavi, S. et al., Synthesis of chalcone incorporated quinazoline derivatives as anticancer agents. Saudi Pharmaceutical Journal (2016), http://dx.doi.org/10.1016/j.jsps.2016.06.005