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ORIGINAL ARTICLE

Synthesis of chalcone incorporated quinazoline derivatives as anticancer agents

Sapavat Madhavi, Reddymasu Sreenivasulu, Jyothsna Pragathi Yazala, Rudraraju Ramesh Raju *

Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar-522510, Andhra Pradesh, India

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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.
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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,

* Corresponding author.
E-mail address: rrraju1@gmail.com (R.R. Raju).
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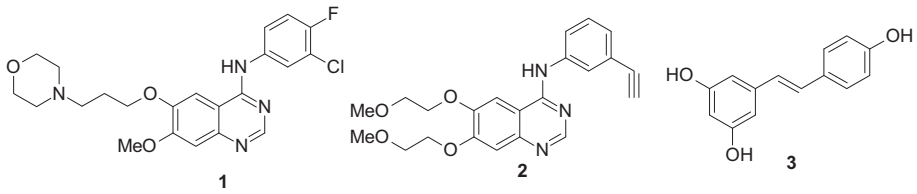

Figure 1 Structures of as Gefitinib (1), Erlotinib (2) and *E*-resveratrol (3).

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

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