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NEW QUINAZOLINONE DERIVATIVES: SYNTHESIS AND *IN VITRO* CYTOTOXIC ACTIVITY

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Abstract. The paper presents a simple synthesis of a series of new quinazolinone derivatives **13a-i**. First, the reaction of 5-hydroxyanthranilic acid (**11**) with acetic anhydride at 160–180^{o}C for 2 h gave the intermediate **12** in high yield. This intermediate was then reacted with amines in acetic acid at 180 ^{o}C for 14 h to afford new quinazolinone derivatives **13a-i** in 69–92%. Synthesized compounds were structurally confirmed using spectroscopic methods: ^{1}H, ^{13}CNMR and MS spectra. The bioassay result using three cancer cell lines including SKLU-1 (lung cancer), MCF-7 (breast cancer) and HepG-2 (liver cancer) showed that only compound **13e** exhibited significant cytotoxic effect against cancer cell lines tested with IC_{50} values of 9.48, 20.39 and 18.04 µg/ mL, respectively.

Keywords: 6-Hydroxy-4(3*H*) quinazolinone, cytotoxic, cancer.

Classification numbers: 1.2.4.

1. INTRODUCTION

Nowadays, one of the most important health-related problems in the developed and the developing countries is cancer. It is estimated that 9.6 million deaths occur in 2018 due to this disease. Globally, about 1 in 6 deaths is due to cancer. Additionally, statistics reported by the International Union Against Cancer (UICC) indicated that every year, more than 11 million new cases of cancer are diagnosed, among them more than 7 million people die of which maximum percentage is from low and middle-income countries [1]. One of the main reasons for this could be the drug resistance and adverse side effects of the chemotherapy [2]. In order to develop more effective and reliable anticancer agents that overcome these limitations, the search for novel antitumor agents is now urgent.

Over the past few years, there has been an increasing interest in the development and pharmacology of heteroaromatic organic compounds in which quinazolinone forms an important class of pharmacophores in medicinal chemistry due to their potential in H bonding and π–π stacking interactions with aromatic amino acid residues of receptors [3-6]. Therefore, a number of drug molecules and biologically active compounds often contain quinazolinone frames. In addition, the quinazolinone frames are common scaffolds found in many diverse biological

compounds, e.g. luotonin A (**1**), rutaecarpine (**2**), tryptanthrin (**3**), chloroqualone (**4**), and alloqualone (**5**) (Fig. 1) [7, 8].

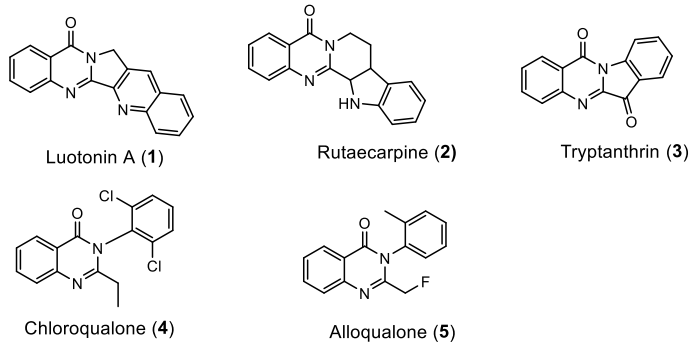


Figure 1. Some alkaloids containing quinazolinone moiety.

Indeed, several quinazolinone derivatives (**6-10**) (Fig. 2) have been reported to exhibit various types of pharmacological activities, including anticancer [9], antioxidant [10], antiviral [11], anticonvulsant [12], anti-inflammatory [13], antitubercular [14], anti-HIV [15], and so on. Furthermore, quinazolinone and their derivatives have been found to display several benefits over the agents that are clinically used [16] and closely connected to the anti-cancer therapies [17, 18]. Some quinazolinone derivatives (**6-10**) (Fig. 2) were proved substantial in treating human leukemia than the conventional agents, and showed the significant effect of quinazolinones derivatives against breast cancer cell lines [19-22].

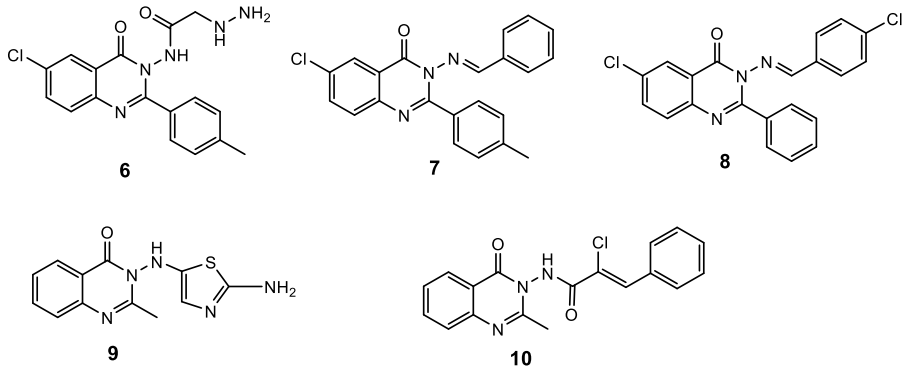


Figure 2. Several reported quinazolinone derivatives as anticancer agents.

Accordingly, in our continuous program for the search of novel anti-cancer agents, we continue to focus on the synthesis of new quinazolinone derivatives, and evaluate the cytotoxic effects on some cancer cell lines. The paper presents the result of this study.

2. MATERIALS AND METHODS

Chemistry: All products were examined by thin-layer chromatography (TLC), performed on Whatman® 250 μm Silica Gel GF Uniplates and visualized under UV light at 254 nm. Melting points were determined in open capillaries on Electrothermal IA 9200 Shimadzu apparatus and uncorrected. Purification was done by crystallization and the open flash silica gel column chromatography using Merck silica gel 60 (240 to 400 mesh). Nuclear magnetic

resonance spectra (^{1}H and ^{13}C NMR) were recorded using tetramethylsilane (TMS) as an internal standard on a Bruker 500 MHz spectrometer with CD_3OD, $CDCl_3$ and DMSO-*d*6 as solvents. Chemical shifts are reported in parts per million (ppm) downfield from TMS as internal standard, and coupling constants (*J*) are expressed in hertz (Hz). Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet). Reagents and solvents were purchased from Aldrich or Fluka Chemical Corp. (Milwaukee, WI, USA) or Merck unless noted otherwise. Solvents were distilled and dried before use.

Bioassay: All media, sera and other reagents used for cell culture were obtained from a GIBCO Co. Ltd. (Grand Island, New York, USA) and three human cancer cell lines for testing including HepG-2 (liver cancer), MCF-7 (breast cancer), and SKLU-1 (lung cancer) were provided by Institute of Biotechnology, Vietnam Academy of Science and Technology. The cytotoxic effect of the synthesized compounds was determined by a method of the American National Cancer Institute (NCI) as described in literature. Briefly, these cancer cell lines were grown as monolayers in 2 mM of L-glutamine, 10 mM of HEPES, 1.0 mM of sodium pyruvate, and supplemented with 10 % fetal bovine serum – FBS (GIBCO). Cells were cultured for 3–5 days after the transfer, and maintained at 37 ^oC in a humidified atmosphere containing 5 % CO_2. Assay samples were initially dissolved in DMSO and serially diluted to appropriate concentrations with a culture medium right before the assay. Then the cells in each well, incubated for 24 hours as described above, were treated with 20 µL of samples at 20 µg/mL; 4 µg/mL; 0.8 µg/mL; 0.16 µg/mL. The plates were further incubated for 48 h. The medium was removed and the cells were fixed by 10 % solution of trifluoroacetic acid. The fixed cells were stained for 30 minutes by a staining solution (MTT). Protein-bound dye was dissolved in a 10 mM tris-base solution and the ODs were measured at 510 nm using an Elisa reader. The IC_{50} values were then calculated using Probits method. Ellipticin (Sigma) was used as a positive control and the values reported for the compounds are presented as averages of three determinations.

*Synthesis of 6-hydroxy-2methyl-4H-benzo[d][1,3]oxazin-4-one (**12**)*

A mixture of 5-hydroxy anthranilic acid (**11**) (5.0 g, 32.67 mmol) in acetic anhydride (15 ml) was refluxed at 150 ^oC for 2 h. The mixture was then poured in ice-water. The resulting precipitates were filtered, washed with distilled water and dried in vacuum to afford **12** (5.03 g, 87 %) which was used for next step.

*General procedure for the synthesis of **13a-i***

A mixture of **12** (1.0 g, 5.64 mmol) and primary amines (3 eq) in acetic acid (10 mL) was refluxed at 120 ^oC for 14 h. The reaction was monitored by TLC (*n*-hexane : ethyl acetate = 1 : 1). The reaction mixture was then neutralized with 50 % $NaHCO_3$ to pH = 7, and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was separated, dried on anhydrous Na_2SO_4 and evaporated in reduced vacuum to obtain the corresponding residues which was subjected to column chromatography on silica gel using *n*-hexane/ethyl acetate as eluting systems to give desired **13a-i**.

3-Ethyl-6-hydroxy-2-methylquinazolin-4(3H)-one (13a)

White solid; Yield: 85 %; Mp: 224-225 ^oC; R_f = 0.51 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, CD_3OD, δ (ppm)): 7.50-7.48 (overlap, 2H, H-5, H-8), 7.29 (dd, *J* = 3.0 Hz, 9.0

Hz, H-7), 2.66 (s, 3H, CH_3), 4.22 (q, *J* = 7.50 Hz, 2H, H-1′), 1.36 (t, *J* = 7.0 Hz, 3H, CH_3, H-2′). ^{13}C NMR (125 MHz, CD_3OD, δ (ppm)): 163.3 (C-4), 157.7 (C-6), 153.6 (C-2), 141.80 (C-9), 128.6 (C-8), 125.3 (C-7), 122.4 (C-10), 110.2 (C-5), 40.8 (C-1′), 22.6 ($\underline{C}H_3$), 13.8 (C-2′). ESI-MS m/z: 205.3 $[M+H]^+$.

6-Hydroxy-2-methyl-3-propylquinazolin-4(3H)-one (13b)

White solid; Yield: 91%; Mp: 260-261°C; R_f = 0.53 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, DMSO-d6, δ (ppm)): 9.96 (s, 1H, OH), 7.44 (d, *J* = 8.50 Hz, 1H, H-8), 7.38 (d, *J* = 2.50 Hz, 1H, H-5), 7.22 (dd, *J* = 2.50 Hz, 8.50 Hz, 1H, H-7), 3.95 (t, *J* = 6.50 Hz, 2H, H-1′), 2.54 (s, 3H, CH_3), 1.66-1.62 (m, 2H, H-2′), 0.92 (t, *J* = 7.50 Hz, 3H, CH_3, H-3′). ^{13}C NMR (125 MHz, DMSO-d6, δ (ppm)): 160.9 (C-4), 155.6 (C-6), 151.4 (C-2), 140.4 (C-9), 128.1 (C-8), 123.7 (C-7), 120.9 (C-10), 108.8 (C-5), 45.3 (C-1′), 22.4 (CH_3), 21.3 (C-2′), 11.1 (C-3′). ESI-MS m/z: 219.5 $[M+H]^+$.

3-Butyl-6-hydroxy-2-methylquinazolin-4(3H)-one (13c)

Bright yellow solid; Yield: 92 %; Mp: 140-141 °C; R_f = 0.57 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)): 7.85 (d, *J* = 3.0 Hz, H-5), 7.54 (d, *J* = 9.0 Hz, H-8), 7.31 (dd, *J* = 3.0 Hz, 9,0 Hz, 1H, H-7), 7.63 (brs, 1H, OH), 4.09 (t, *J* = 3.0 Hz, 2H, H-1′), 2.64 (s, 3H, CH_3), 1.74-1.70 (m, 2H, H-2′), 1.50-1.46 (m, 2H, H-3′), 1.0 (t, *J* = 2.5 Hz, 3H, CH_3, H-4′). ^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 162.2 (C-4), 155.2 (C-6), 152.4 (C-2), 141.4 (C-9), 128.3 (C-8), 124.2 (C-7), 121.2 (C-10), 110.1 (C-5), 44.7 (C-1′), 30.7 (C-2′), 22.8 (CH_3), 20.3 (C-3′), 13,7 (C-4′). ESI-MS m/z: 233.3 $[M+H]^+$.

3-(sec-Butyl)-6-hydroxy-2-methylquinazolin-4(3H)-one (13d). Oil; Yield: 88 %; R_f = 0.57 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, CD_3OD, δ (ppm)): 7.49 (d, *J* = 8.50 Hz, 1H, H-8), 7.46 (d, *J* = 3.0 Hz, 1H, H-5), 7.28 (dd, *J* = 3.0 Hz, 8.50 Hz, 1H, H-7), 3.79 (m, 1H, H-1′), 1.94 (s, 3H, CH_3), 1.47 (m, 2H, H-2′), 1.12 (d, *J* = 6.50 Hz, 3H, CH_3, H-5′), 0.91 (t, *J* = 7.50 Hz, 3H, CH_3, H-4′). ^{13}C NMR (125 MHz, CD_3OD, δ (ppm)): 172.5 (C-4), 157.7 (C-6), 154.2 (C-2), 141.5 (C-9), 128.4 (C-8), 125.2 (C-7), 109.9 (C-10), 54.8 (C-1′), 23.9 (CH_3), 22.6 (C-2′), 20.4 (C-4′), 10.8 (C-3′). ESI-MS m/z: 233.3 $[M+H]^+$.

3-Benzyl-6-hydroxy-2-methylquinazolin-4(3H)-one (13e)

White solid; Yield: 79 %; Mp: 64-65 °C; R_f = 0.50 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, DMSO, δ (ppm)): 8.31 (brs, 1H, OH), 7.50 (d, *J* = 9.0 Hz, 1H, H-8), 7.45 (d, *J* = 3.0 Hz, 1H, H-5), 7.36-7.28 (m, 3H, H-7, H-4′, H-6′), 7.26-7.21 (m, 2H, H-3′, H-7′), 7.17 (d, *J* = 7.50 Hz, 1H, H-5′), 5.35 (s, 2H, H-1′), 1.87 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d6, δ (ppm)): 169.2 (C-4), 161.3 (C-6), 155.9 (C-2), 139.6 (C-9), 136.7 (C-2′), 128.8 (C-8), 128.3 (C-4′, C-6′), 127.2 (C-5′), 126.7 (C-7), 126.2 (C-10), 109.1 (C-5), 46.3 (C-1′), 22.5 (CH_3). ESI-MS m/z: 267.2 $[M+H]^+$.

6-Hydroxy-2-methyl-3-(4-methylbenzyl)quinazolin-4(3H)-one (13f)

White solid; Yield: 69 %; Mp: 246-247 °C; R_f = 0.55 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, DMSO-d6, δ (ppm)): 10.05 (s, 1H, OH), 7.49 (d, *J* = 8.80 Hz, 1H, H-8), 7.43 (d, *J* = 2.80 Hz, 1H, H-5), 7.28 (dd, *J* = 3.20 Hz, 8.80 Hz, 1H, H-7), 7.15 (d, *J* = 8.80 Hz, 2H, H-4′, H-6′), 7.04 (d, *J* = 8.80 Hz, 2H, H-3′, H-7′), 5.30 (s, 2H, H-1′), 2.42 (s, 3H, CH_3), 2.08 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d6, δ (ppm)): 169.5 (C-4), 161.8 (C-6), 156.4 (C-2), 152.1 (C-9), 140.9 (C-5′), 134.1 (C-2′), 129.8 (C-8), 128.8 (C-4′, C-6′), 128.2 (C-3′, C-7′), 124.6 (C-2′), 121.3 (C-7, C-10), 109.6 (C-5), 46.5 (C-1′), 23.1 (CH_3), 21.2 (CH_3). ESI-MS m/z: 281.5 $[M+H]^+$.

6-Hydroxy-3-(4-methoxybenzyl)-2-methylquinazolin-4(3H)-one (13g)

White solid; Yield: 79 %; R_f = 0.49 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, DMSO-d6, δ (ppm)): 10.03 (s, 1H, OH), 7.48 (d, *J* = 8.50 Hz, 1H, H-8), 7.44 (d, *J* = 2.50 Hz, 1H, H-5), 7.26 (dd, *J* = 2.50 Hz, 8.50 Hz, 1H, H-7), 7.13 (d, *J* = 8.50 Hz, 2H, H-3′, H-7′), 6.90 (d, *J* = 8.50 Hz, 2H, H-4′, H-6′), 5.27(s, 2H, H-1′), 3.71 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d6, δ (ppm)): 161.3 (C-4), 158.4 (C-5′), 155.8 (C-6′), 151.6 (C-2), 140.4 (C-9), 128.6 (C-3′, C-7′), 128.2 (C-2′), 127.8 (C-8), 123.9 (C-7), 120.8 (C-10), 114.1 (C-4′, C-6′), 109.1 (C-5), 55.0 (OCH_3), 45.7 (C-1′), 22.6 (CH_3). ESI-MS m/z: 297.2 $[M+H]^+$.

3-(4-Fluorobenzyl)-6-hydroxy-2-methylquinazolin-4(3H)-one (13h)

White solid; Yield: 81 %; Mp: 96-97 ^{o}C; R_f = 0.52 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, DMSO-d6, δ (ppm)): 10.04 (s, 1H, OH), 7.49 (d, *J* = 9.0 Hz, 1H, H-8), 7.43 (d, *J* = 3.0 Hz, 1H, H-5), 7.28-7.25 (dd, *J* = 3.0 Hz, 9.0 Hz, 1H, H-7), 7.24-7.22 (d, *J* = 8.50 Hz, 2H, H-3′, H-7′), 7.18-7.16 (d, *J* = 8.50 Hz, 2H, H-4′, H-6′), 5.32 (s, 2H, H-1′), 2.50 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d6, δ (ppm)): 162.3 (C-4), 161.3 (C-5′), 160.3 (C-6), 155.9 (C-2), 140.4 (C-9), 132.9 (C-2′), 128.5 (C-8), 128.4 (C-3′, C-7′), 128.3 (C-7), 124.9 (C-10), 115.6 (C-4′, C-6′), 109.1 (C-5), 45.7(C-1′), 22.6 (CH_3). ESI-MS m/z: 285.2 $[M+H]^+$.

3-(4-Chlorobenzyl)-6-hydroxy-2-methylquinazolin-4(3H)-one (13i)

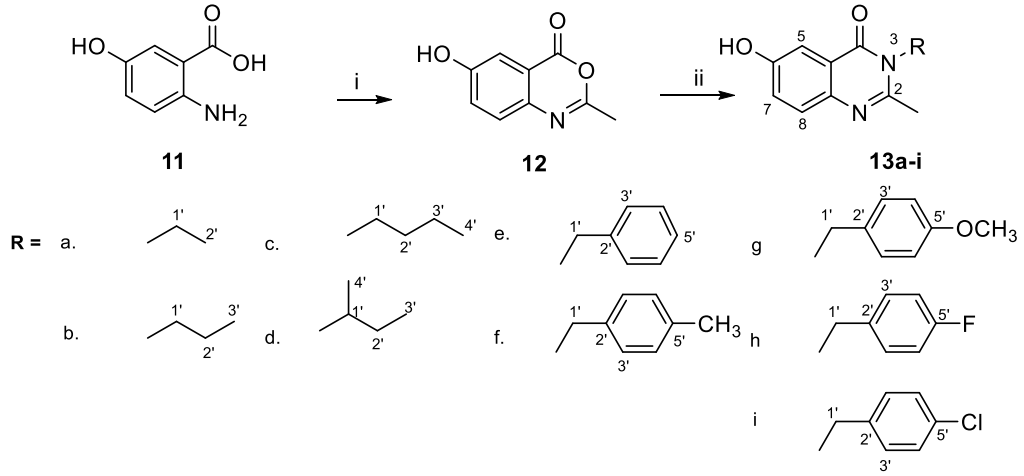
White solid; Yield: 82 %; Mp: 113-114 ^{o}C; R_f = 0.53 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR (500 MHz, DMSO-d6, δ (ppm)): 10.07 (s, 1H, OH), 7.49 (d, *J* = 9.0 Hz, 1H, H-8), 7.43 (d, *J* = 3.0 Hz, 1H, H-5), 7.04-7.38 (d, *J* = 8.50 Hz, 2H, H-3′, H-7′), 7.28 (dd, *J* = 3.0 Hz, 9.0 Hz, 1H, H-7), 7.21 (d, *J* = 8.50 Hz, 2H, H-4′, H-6′), 5.33 (s, 2H, H-1′), 2.42 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d6, δ (ppm)): 161.3 (C-4), 155.9 (C-6), 151.4 (C-2), 140.4 (C-9), 135.7 (C-5′), 131.8 (C-2′), 128.7 (C-3′, C-7′), 128.3 (C-8), 124.0 (C-4′, C-6′), 120.8 (C-7, C-10), 109.1 (C-5), 45.8 (C-1′), 22.6 (CH_3). ESI-MS m/z: 301.1 $[M+H]^+$.

3. RESULTS AND DISCUSSION

3.1. Chemistry

Novel quinazolinone derivatives **13a-i** were synthesized as outlined in Scheme 1. 6-hydroxyanthranilic acid (**11**) was first condensed with the excess of acetic anhydride at 160 ^{o}C for 2 h to afford the desired benzoxazinone **12** in 87 % yields. The purification of compound **12** was simply carried out by pouring the reaction mixture into the ice-water. The resulting precipitates was filtered, washed with distilled water, and dried in vacuum. Compound **12** was next coupled to alkyl amines, benzylamines to give target compounds **13a–i** in good to excellent yields. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and MS spectra. Due to the structural similarity of target compounds, compound **13h** was used as an example to elucidate the structure of synthesized compounds. In the ^{1}H NMR spectrum, the chemical shift at the lowest field at 10.04 ppm is attributed to OH group. The characteristic splitting pattern of 3 protons H-5, H-7 and H-8 as ABC system of quinazolinone skeleton was easily observed. The proton H-5 resonates as a doublet at 7.43 ppm (*J* = 3.0 Hz) resulting from long coupling with H-7. The proton H-8 resonates as a doublet at δ 7.49 (*J* = 9.0 Hz) due to near coupling with H-7. The proton H-7 was observed as a doublet of doublet at δ 7.26 (d, *J* = 3.0 Hz, 9.0 Hz) due to coupling with H-8 and H-7. Besides, four protons of aromatic ring were observed as two doublets at 7.24-7.22 ppm (*J* = 8.50 Hz, 2H, H-3′, H-7′), and 7.18-7.16 ppm (d, *J* = 8.50 Hz, 2H, H-4′, H-6′), and the strong singlet signal at 5.32 ppm is assigned to CH_2-benzyl. CH_3 group connecting to quinazolinone moiety resonates at 2.50 ppm. The ^{13}C NMR spectrum showed the presence of 14 carbons in the molecule, in which the carbonyl signal was observed at

δ 162.3 ppm. The signal at δ 161.3 ppm is attributed to C-5′ due to connecting to F and signal at 155.9 ppm belongs to C-2. In addition, two couples of four equivalent carbons resonate at δ 127.8 and 115.6 ppm.



Scheme 1. Reagents and conditions: (i) $(CH_3CO)_2O$, 160–180 ^oC, 2 h; (ii) acetic acid, amines, 180 ^oC, 14 h, 69–92 %.

*Table 1***.** In vitro cytotoxic activity of quinazolinone derivatives 13a-i.

No	Compounds	R	IC_{50} (μg/mL)		
			SK-LU-1	**MCF-7**	**HepG-2**
1	**13a**	Ethyl	>100	>100	>100
2	**13b**	*n*-Propyl	>100	>100	>100
3	**13c**	*n*-Butyl	>100	>100	>100
4	**13d**	*sec*-Butyl	>100	>100	>100
5	**13e**	Benzyl	**9.48**	**20.39**	**18.04**
6	**13f**	4-Methylbenzyl	>100	>100	>100
7	**13g**	4-Methoxybenzyl	>100	>100	>100
8	**13h**	4-Fluorobenzyl	>100	>100	>100
9	**13i**	4-Chlorobenzyl	>100	>100	>100
	Ellipticine		**0.43**	**0.43**	**0.40**

[a]Concentration (μg/mL) that produces a 50 % reduction in cell growth or enzyme activity, the numbers represent the averaged results from triplicate experiments with deviation of less than 10 %. [b]Cell lines: HepG2, liver cancer; MCF-7, breast cancer; SKLU-1, lung cancer.

All target compounds **13a-i** were evaluated for their *in vitro* cytotoxicity. Three human cancer cell lines including SKLU-1, MCF-7 and HepG-2 were chosen for screening their inhibition effect using MTT method [23]. All compounds were initially screened at a fixed concentration of 100 μg/mL. If the compounds are active, they will be further screened at smaller concentrations (e.g., 20 μg/mL, 4 μg/mL, 0.8 μg/mL and 0.16 μg/mL), and IC_{50} values for each compound were calculated (Table 1). In this assay, ellipticine was used as a positive control.

However, as shown in Table 1, most of quiniazolinone derivatives were inactive against three cancer cell lines tested except compound **13e** showing cytotoxic effect with IC_{50} values of 9.48, 20.39 and 18.04 µg/mL, respectively.

4. CONCLUSIONS

We have reported a series of new quinazolinone derivatives **13a-i** via a simple synthetic procedure. The structure of all synthesized compounds has been confirmed based on ^{1}H, ^{13}C NMR and MS spectra. Although the bioassay results showed that most of target compounds exhibited no cytotoxic effect in terms of cytotoxicity in comparison with ellipticine, compound **13e** displayed cytotoxic effect with IC_{50} values of 9.48, 20.39 and 18.04 µg/mL, respectively, suggesting that it could be served as basis for further design of antitumor agents in the future.

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