RESEARCH ARTICLE

Open Access

CrossMark

Synthesis and in vitro antitumor activity of (1*E*,4*E*)-1-aryl-5-(2-((quinazolin-4-yl)oxy) phenyl)-1,4-pentadien-3-one derivatives

Hui Luo[1,3,4*†], Shengjie Yang[2,3,4†], Da Hong[2], Wei Xue[3,4] and Pu Xie[1]

Abstract

Background: Cancer is one of the leading causes of death and only second to heart diseases. Recently, preclinical studies have demonstrated that curcumin had a number of anticancer properties. Thus, we planned to synthesize a series of curcumin analogs to assess their antiproliferation efficacy.

Results: A series of (1*E*,4*E*)-1-aryl-5-(2-((quinazolin-4-yl)oxy)phenyl)-1,4-pentadien-3-one derivatives (curcumin analogs) were synthesized and characterized by IR, NMR, and elemental analysis techniques. All of the prepared compounds were screened for antitumor activities against MGC-803, PC3, and Bcap-37 cancer cell lines. A significant inhibition for cancer cells were observed with compound **5f** and also less toxic on NIH3T3 normal cells. The mechanism of cell death induced by compound **5f** was further investigated by acridine orange/ethidium bromide staining, Hoechst 33,258 staining, TUNEL assay, and flow cytometry cytometry, which revealed that the compound can induce cell apoptosis in MGC-803 cells.

Conclusions: This study suggests that most of the derivatives could inhibit the growth of human cancer cell lines. In addition, compound **5f** could induce apoptosis of cancer cells, and it should be subjected to further investigation as a potential anticancer drug candidate.

Keywords: Synthesis, Asymmetric curcumin analogs, Quinazoline derivatives of curcumin, Antitumor activity, MGC-803, Apoptosis

Background

Cancer is one of the leading causes of death and only second to heart diseases [1, 2]. The efficacy of current chemotherapeutics is low and undesirable side effects are still unacceptably high [3–5]. Hence, the development of novel, and less toxic and anti-cancer agents remains an important and challenging goal of medicinal chemist worldwide, and much attention has recently been paid to the discovery and development of new, more selective anticancer agents [3, 6–8].

Natural products have become a leading category of compounds in improving the rational drug design for novel anti-cancer therapeutics [9, 10]. Curcumin is a natural phenolic compound originally isolated from turmeric, a rhizome used in India for centuries as a spice and medicinal agent [11]. A literature survey reveals that curcumin, and its derivatives (analogs) have various pharmacological activities and medicinal applications such as antioxidant [12, 13], anti-inflammatory [12, 14], anti-HIV [15, 16], anti-angiogenesis and so on [12]. Recently, preclinical studies have demonstrated that curcumin had a number of anticancer properties, such as growth inhibition and induction of apoptosis in a variety of cancer cell lines [17–19]. Its mechanisms of action include inhibition of transcriptional factor NF-jB, HSP90 and epigenetic modulation related to direct inhibition of the catalytic site of DNMT-1 [20]. Moreover, the latest research shows that curcumin can effectively suppress NF-kB activity and COX-2 expression, as well as cell proliferation/survival in

*Correspondence: luohui8732@126.com
†Hui Luo and Shengjie Yang contributed equally to this work
[4] Ctr for R&D of Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China
Full list of author information is available at the end of the article

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 2 of 10

the setting of NSCLC [21]. Consequently, analogues of curcumin with similar safety profiles but increased anticancer activity have been developed in recent years [22]. Chandru et al. synthesized four novel dienone cyclopropoxy curcumin analogs by nucleophilic substitution reaction with cyclopropyl bromide, and found that the tumor growth inhibitory effects of synthetic dienone cyclopropoxy curcumin analogs could be mediated by promoting apoptosis and inhibiting tumor angiogenesis [23]. New 1,5-diaryl-1,4-pentadien-3-one derivatives (curcumin analogs), which can effectively inhibit proliferation of cancer cells at very low concentrations, were synthesized [24, 25], and we also found that curcumin analogs exhibited promising ex vivo antiviral bioactivities against tobacco mosaic virus and cucumber mosaic virus [26].

In order to discover more potent and selective anticancer agents based on curcumin scafforld, we have synthesized a series of (1*E*,4*E*)-1-aryl-5-(2-((quinazolin-4-yl) oxy)phenyl)-1,4-pentadien-3-one derivatives (eleven novel compounds **5a**, **5b**, **5d**, **5f**–**5h**, and **5j**–**5n**) (Fig. 1). In our present study, all the target compounds were evaluated for their activity against MGC-803, PC3, and Bcap-37 cancer cell lines. Furthermore, the possible mechanism of MGC-803 cell growth inhibition by compound **5f** was also investigated in this paper.

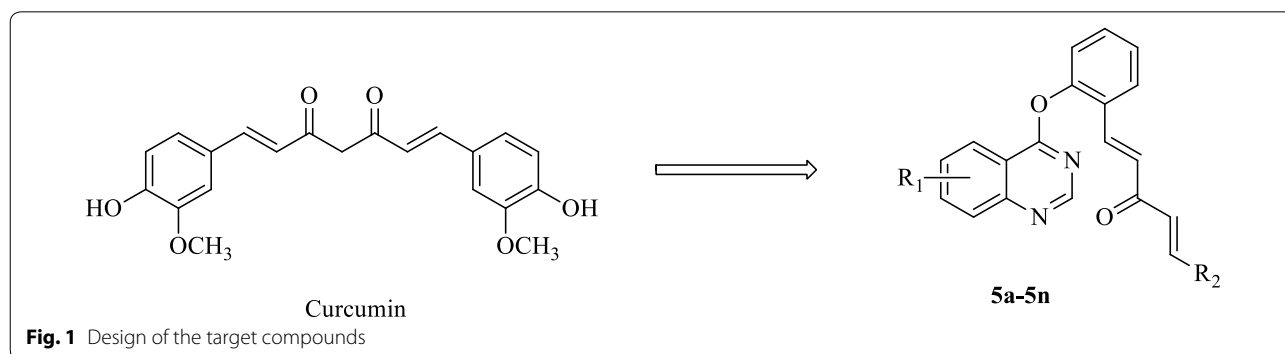## Results and discussion
Chemistry
Target compounds **5a**–**5n** were synthesized as shown in Scheme 1. The starting material 2-aminobenzoic acid was conveniently cyclized to intermediate **1** by heating it with formamide at 140–145 °C as described in the literature. Upon refluxing with freshly distilled phosphorus oxychloride and pentachlorophosphorane, intermediate **1** yielded the corresponding 4-chloro derivative **2**. Treatment of salicylaldehyde with acetone in the presence of sodium hydride at room temperature got intermediate **3**. The key intermediates **4** were synthesized by reacting intermediate **3** with substituted 4-chloroquiazoline **2** in the present of K_2CO_3 in CH_3CN at 30–50 °C for 6 h. And then, the target compounds **5a**–**5n** were synthesized
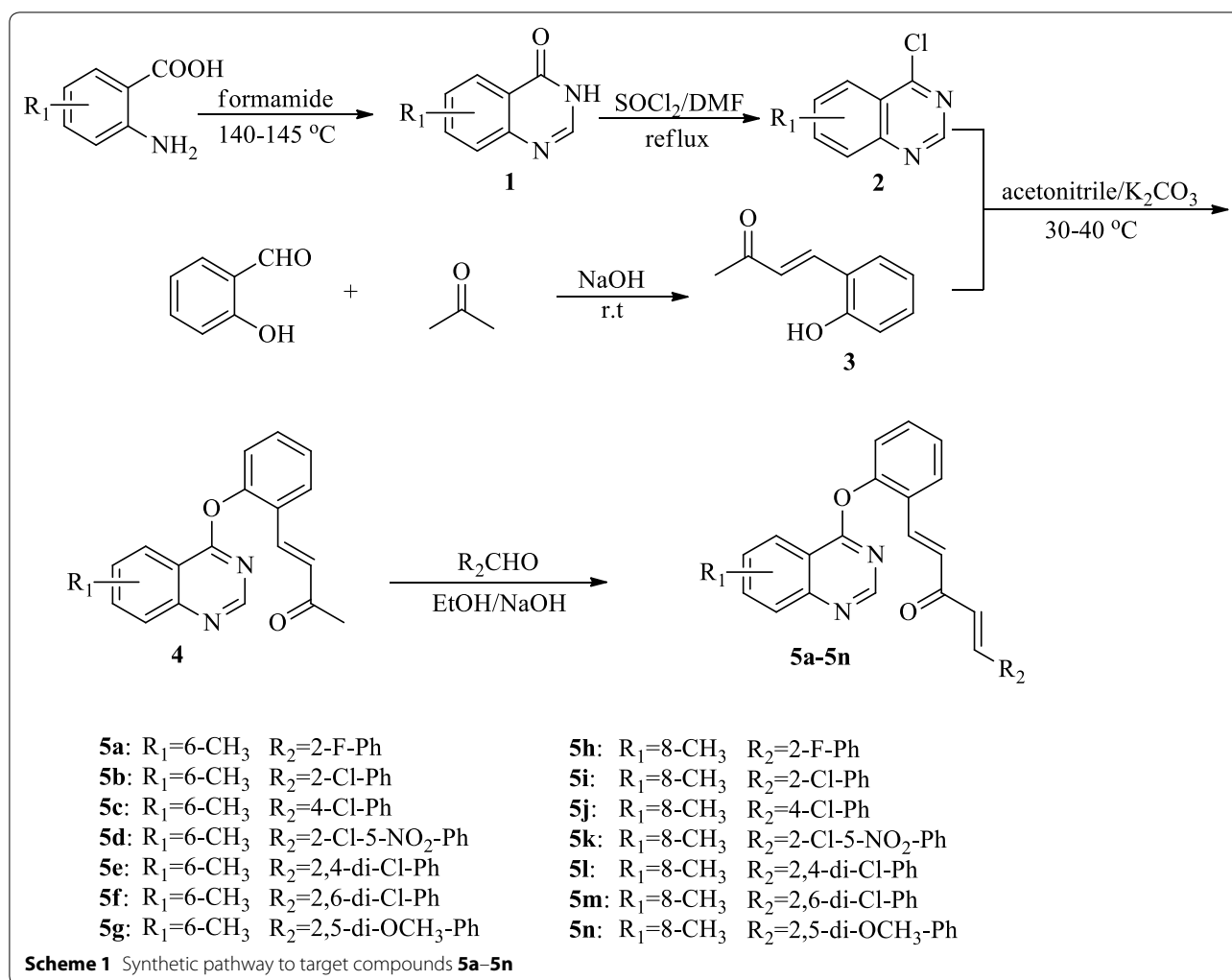
by reacting the substituted aldehydes with **4** in the present of anhydrous alcohol in acetone at room temperature. The structures of the final products were confirmed by their IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis techniques.

Evaluation of anti-tumor bioactivity of synthetic compounds
The in vitro antitumor activity of the newly synthesized compounds **5a**–**5n** were evaluated against a panel of three human cancer cell lines, including human gastric cancer cell line MGC-803, human prostate cancer cell line PC3, and human breast cancer cell line Bcap-37, and one normal cell line NIH3T3 (mouse embryo fibroblast cell line) by MTT method. Adriamycin (ADM) was chosen as a reference drug due to its availability and widespread use. Each experiment was repeated at least three times. The results are presented in Table 1.

As depicted in Table 1, the title compounds suppressed proliferation of the above three cancer cell lines in different extents (IC_{50} values of 0.85–15.64 μM), and exhibited broad spectrum antitumor activity. Among these studied compounds, the inhibitory ratios of **5d**–**5g**, and **5m** against MGC-803 cells at 10 μM were 87.5, 87.0, 90.7, 85.9, and 81.1%, respectively, and their IC_{50} values were 1.72, 1.89, 0.85, 2.02, and 2.05 μM, respectively, similar to that of ADM (0.74 μM). Compounds **5d**, **5f**, **5g**, and **5m** displayed higher inhibitory activities against PC3 cells at 10 μM than that of the rest compounds, with inhibitory ratios of 86.3, 93.0, 83.1, and 81.2%, respectively, which were similar to or higher than that of ADM (91.2%). The inhibitory ratios of **5f** and **5g** against Bcap-37 cells at 10 μM, were 76.5 and 74.9% (IC_{50} values of 4.98 and 5.61 μM), respectively, which were higher than that of the rest compounds. Also noteworthy is that the potency of the compounds was generally more pronounced against the MGC-803 cells than against PC3 and Bcap-37 cells. Moreover, the antiproliferation activities of the title compounds against NIH3T3 normal cell line were also evaluated. Most of the title compounds showed stronger antiproliferative activities against the cancer cell lines

Fig. 1 Design of the target compounds

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 3 of 10

Scheme 1 Synthetic pathway to target compounds **5a–5n**

5a: R_1=6-CH$_3$ R_2=2-F-Ph
5b: R_1=6-CH$_3$ R_2=2-Cl-Ph
5c: R_1=6-CH$_3$ R_2=4-Cl-Ph
5d: R_1=6-CH$_3$ R_2=2-Cl-5-NO$_2$-Ph
5e: R_1=6-CH$_3$ R_2=2,4-di-Cl-Ph
5f: R_1=6-CH$_3$ R_2=2,6-di-Cl-Ph
5g: R_1=6-CH$_3$ R_2=2,5-di-OCH$_3$-Ph

5h: R_1=8-CH$_3$ R_2=2-F-Ph
5i: R_1=8-CH$_3$ R_2=2-Cl-Ph
5j: R_1=8-CH$_3$ R_2=4-Cl-Ph
5k: R_1=8-CH$_3$ R_2=2-Cl-5-NO$_2$-Ph
5l: R_1=8-CH$_3$ R_2=2,4-di-Cl-Ph
5m: R_1=8-CH$_3$ R_2=2,6-di-Cl-Ph
5n: R_1=8-CH$_3$ R_2=2,5-di-OCH$_3$-Ph

than NIH3T3 lines. Compound **5f**, which showed excellent levels of inhibition against MGC-803, PC3, and Bcap-37 cancer cells, have no significant activity against NIH3T3 cells, with inhibitory ratio of 21.5% at 10 μM. That is to say that the compound was less toxic on normal fibroblasts than on the investigated cancer cell lines and more selective to cancer cells.

Subsequently structure–activity relationships (SAR) studies were performed to determine how the substituents affected the anticancer activity. To examine SAR, different substituent groups were introduced into R_1 and R_2 in the quiazoline ring. Based on the activity values indicated in Table 1, the relationships of the activities with different R_1 and R_2 (type, position, and number of substituents) were deduced. Two main conclusions were drawn. On the one hand, compared with the same substituents on quiazoline, the corresponding molecules containing a 6-methyl group always had higher inhibitory rates than the compound containing a 8-methyl group.

For example, the IC$_{50}$ values of **5f** (R_1: 6-methyl, R_2: 2,6-dichlorophenyl) and **5m** (R_1: 8-methyl, R_2: 2,6-dichlorophenyl) on MGC-803 cells were 0.85 and 2.05 μM, respectively. By contrast, the inhibition rates of **5c** (R_1: 6-methyl, R_2: *p*-chlorophenyl) and **5j** (R_1: 8-methyl, R_2: *p*-chlorophenyl) at 10 μM were 79.2 and 76.3% on MGC-803 cells, 76.5 and 71.9% on PC3 cells, and 54.2 and 45.4% on Bcap-37 cells, respectively. On the other hand, when R_2 was *o*-flurophenyl-fixed, the compounds always showed weak activity. For example, the inhibition rates of **5a** (R_1: 6-methyl, R_2: *o*-flurophenyl) at 10 μM were 71.9, 68.5, and 44.1% on the three cancer cells, respectively, which suggested the weaker activity than that of the rest compounds.

Apoptosis is one of the major pathways that lead to the process of cell death [27]. Most cancer cells retain their sensitivity to some apoptotic stimuli from chemotherapeutic agent [28]. In the present study, compound **5f** was selected and its mechanism of growth inhibition

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 4 of 10

Table 1 Effect of title compounds against cell viability of different cell lines

Compds	Inhibition rates against different cells (%)[a]				IC$_{50}$ (µM)[b]		
	MGC-803	PC3	Bcap-37	NIH3T3	MGC-803	PC3	Bcap-37
5a	71.9 ± 0.9	68.5 ± 2.3	44.1 ± 2.6	65.7 ± 1.3	7.69 ± 0.37	9.24 ± 0.46	11.71 ± 0.39
5b	83.5 ± 1.5	78.7 ± 2.4	57.3 ± 2.0	15.4 ± 1.5	5.20 ± 0.51	8.12 ± 0.46	10.05 ± 0.67
5c	79.2 ± 2.8	76.5 ± 1.7	54.2 ± 1.1	16.1 ± 2.7	5.44 ± 0.45	7.85 ± 0.32	9.34 ± 0.52
5d	87.5 ± 0.2	86.3 ± 0.8	58.5 ± 1.3	71.9 ± 1.4	1.72 ± 0.22	2.68 ± 0.43	7.52 ± 0.36
5e	87.0 ± 1.0	75.2 ± 7.8	67.3 ± 3.9	53.8 ± 1.8	1.89 ± 0.26	4.71 ± 0.36	9.6 ± 0.42
5f	90.7 ± 0.6	93.0 ± 1.8	76.5 ± 1.9	21.5 ± 2.7	0.85 ± 0.43	1.37 ± 0.22	4.98 ± 0.39
5g	85.9 ± 1.2	83.1 ± 2.8	74.9 ± 2.0	74.3 ± 0.9	2.02 ± 0.37	2.18 ± 0.31	5.61 ± 0.50
5h	62.3 ± 1.4	43.7 ± 12.1	36.6 ± 2.7	13.4 ± 2.2	9.06 ± 0.40	11.68 ± 0.48	15.64 ± 0.51
5i	79.4 ± 2.4	65.1 ± 2.6	47.1 ± 2.6	14.4 ± 2.6	7.78 ± 0.48	9.36 ± 0.52	10.73 ± 0.62
5j	76.3 ± 0.8	71.9 ± 3.1	45.4 ± 2.2	41.0 ± 2.1	6.42 ± 0.44	8.64 ± 0.47	12.11 ± 0.31
5k	82.1 ± 3.0	76.3 ± 2.5	60.2 ± 1.4	3.0 ± 2.3	2.94 ± 0.32	8.12 ± 0.46	8.92 ± 0.58
5l	61.2 ± 1.3	55.7 ± 1.5	54.6 ± 1.0	0.8 ± 1.6	4.33 ± 0.35	9.08 ± 0.52	9.83 ± 0.46
5m	81.1 ± 1.7	81.2 ± 2.8	66.4 ± 1.5	12.4 ± 2.5	2.05 ± 0.39	3.79 ± 0.47	7.82 ± 0.39
5n	78.7 ± 2.7	69.0 ± 1.7	55.8 ± 1.1	29.6 ± 2.4	3.33 ± 0.42	4.16 ± 0.43	8.70 ± 0.54
ADM[c]	97.5 ± 1.2	91.2 ± 0.4	94.5 ± 0.9	100.0 ± 0.7	0.74 ± 0.24	1.01 ± 0.20	1.90 ± 0.25

[a] Inhibitory percentages of cells treated with 10 µM concentration of each compound for 72 h

[b] Agent concentration (µM) that inhibited cell growth by 50% at 72 h after treatment

[c] Adriamycin, positive control

of MGC-803 cells was evaluated. To determine whether antiproliferation and cell death are associated with apoptosis, MGC-803 cells were stained with acridine orange (AO)/ethidium bromide (EB) staining and Hoechst 33,258 staining after exposure to compound **5f** and observed under fluorescence microscopy.

It is well known that AO can pass through cell membranes, but EB cannot. Under the fluorescence microscope, living cells appear green. Necrotic cells stain red but have a nuclear morphology resembling that of viable cells. Apoptotic cells appear green, and morphological changes such as cell blebbing and formation of apoptotic bodies will be observed [29].

Representative images of the cells treated with 10 µM of HCPT (used as positive control) and 1, 5, 10 µM of compound **5f** for 12 h are shown in Fig. 2a. While treatment of cells with HCPT and compound **5f**, the apoptotic cells with typical apoptotic features, such as staining brightly, condense chromatin and fragment nuclei were observed. These results suggested that the proliferative inhibition and the death of target cells upon treatment with compound **5f** were consequent to the induction of apoptosis.

Membrane-permeable Hoechst 33,258 was a blue fluorescent dye and stained the cell nucleus. When cells were treated with Hoechst 33,258, live cells with uniformly
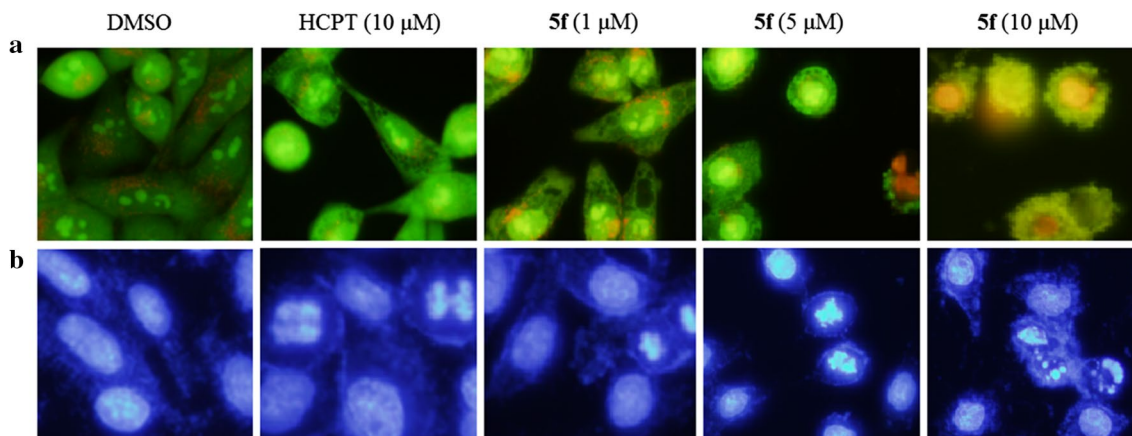
Fig. 2 Apoptosis induction studies of compound **5f**. **a** AO\EB staining. **b** Hoechst 33,258 staining

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 5 of 10

light blue nuclei were observed under fluorescence microscope, while apoptotic cells exhibited bright blue because of karyopyknosis and chromatin condensation, and the nuclei of dead cells could not be stained [30]. MGC-803 cells treated with compound **5f** at concentrations of 1, 5, and 10 µM for 12 h were stained with Hoechst 33,258, with HCPT as positive control at 10 µM for 12 h. The results are illustrated in Fig. 2b.

Figure 2b shows that MGC-803 cells treated with the negative control DMSO were normally blue. Compared with the negative control, a part of cells with smaller nuclei and condensed staining appeared in the positive control group. After treated with compound **5f**, the cells exhibited strong blue fluorescence and revealed typical apoptotic morphology. These findings demonstrate that compound **5f** induced apoptosis against MGC-803 cell lines, consistent with the results for AO/EB double staining.

To further verify AO/EB and Hoechst 33,258 staining results, TUNEL assay was also carried out. TUNEL (Terminal deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling) is a very popular assay for identifying apoptotic cells. The assay identifies apoptotic cells in situ by using terminal deoxynucleotidyl transferase (TdT) to transfer biotin-dUTP to these strand breaks of cleaved DNA. The biotin-labeled cleavage sites are then detected by reaction with HRP conjugated streptavidin and visualized by DAB showing brown color [24]. MGC-803 cells treated with compound **5f** at 5 µM for 6, 12, and 18 h were stained with TUNEL, with HCPT as positive control at 5 µM for 18 h. As shown in Fig. 3, cells in control group (DMSO treatment) did not appear as brown precipitates. However, the cells treated with compound

5f and HCPT appeared as brown precipitate. We further concluded that compound **5f** induced apoptosis against MGC-803.
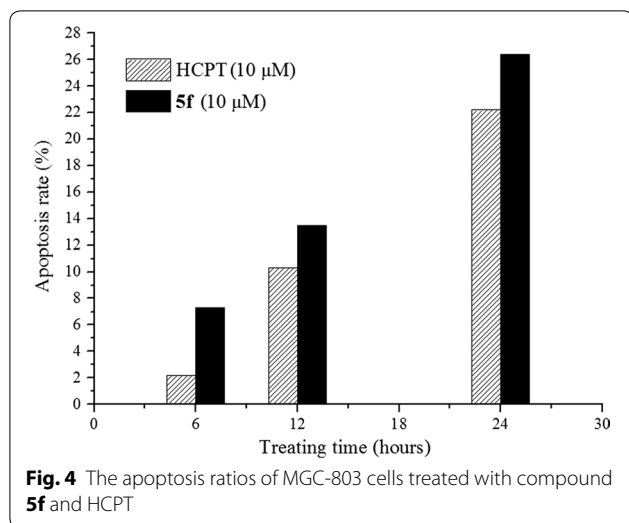
In addition, the apoptosis ratios induced by compound **5f** in MGC-803 cells were determined by flow cytometry, using Annexin V/PI double staining. Flow cytometry was performed on the total cell population (including both adherent and detached cells) and apoptosis detection was carried out as mentioned above. This double staining procedure discriminated necrotic cells (Q1, Annexin^{-}/PI^{+}), late apoptotic cells (Q2, Annexin^{+}/PI^{+}), intact cells (Q3, Annexin^{-}/PI^{-}) and early apoptotic cells (Q4, Annexin^{+}/PI^{-}) [31, 32]. As shown in Fig. 4, compound **5f** could induce apoptosis of MGC-803 cells, and the highest apoptosis ratio (26.4%) was obtained after 24 h of treatment at a concentration of 10 µM. For the positive control HCPT, the apoptosis ratio was only 22.3% after 24 h of treatment at a concentration of 10 µM. In addition, as shown in Fig. 5, the apoptosis of MGC-803 cells treated with compound **5f** gradually increased in a time-dependent manner.

Conclusions

As a development of our previous studies, we have synthesized and evaluated in vitro a series of (1*E*,4*E*)-1-aryl-5-(2-((quinazolin-4-yl)oxy)phenyl)-1,4-pentadien-3-one derivatives as potential antitumor agents. Most of the derivatives exhibited equivalent inhibitory activities against MGC-803, PC3, and Bcap-37 cancer cells. Compound **5f** appeared to be more effective than other compounds against the three cells, with IC$_{50}$ values of 0.85, 1.37, and 4.98 µM, respectively. And compounds **5f** was found to exhibit a good degree of selectivity towards
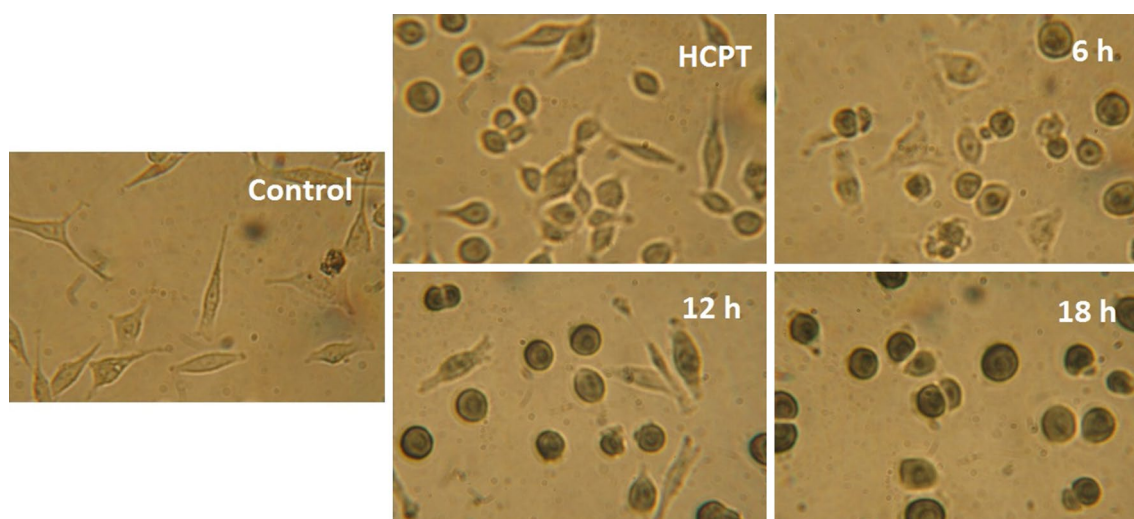
Fig. 3 Apoptosis was assayed with TUNEL after treatment of MGC-803 cells with 5 µM **5f**, and observed under light microscopy

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 6 of 10

Fig. 4 The apoptosis ratios of MGC-803 cells treated with compound **5f** and HCPT

cancer cells than normal cells. In addition, the apoptosis-inducing activity of compound **5f** in MGC-803 cells was investigated by AO/EB staining, Hoechst 33,258 staining, TUNEL assay, and flow cytometry. The results revealed that the compound may inhibit cell growth by inducing apoptosis, with apoptosis ratio of 26.4% at 10 μM for 24 h, which was higher than that of HCPT (22.3% at 10 μM for 24 h). Further studies on the specific mechanisms of compound **5f** in MGC-803 cells are currently underway.

Experimental

Reagents and chemicals

Melting points were determined by using an XT-4 binocular microscope (Beijing Tech Instrument Co., China) without correction. IR spectra were recorded on a Bruker VECTOR 22 spectrometer. NMR spectra were recorded in a CDCl₃ solvent using a JEOL-ECX 500 NMR spectrometer operating at 500 MHz for ^{1}H, and at 125 MHz for ^{13}C by using TMS as internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Silica gel (200–300 mesh) and TLC plates

(Qingdao Marine Chemistry Co., Qingdao, China) were used for chromatography. All solvents (Yuda Chemistry Co., Guiyang, China) were analytical grade, and used without further purification unless otherwise noted.
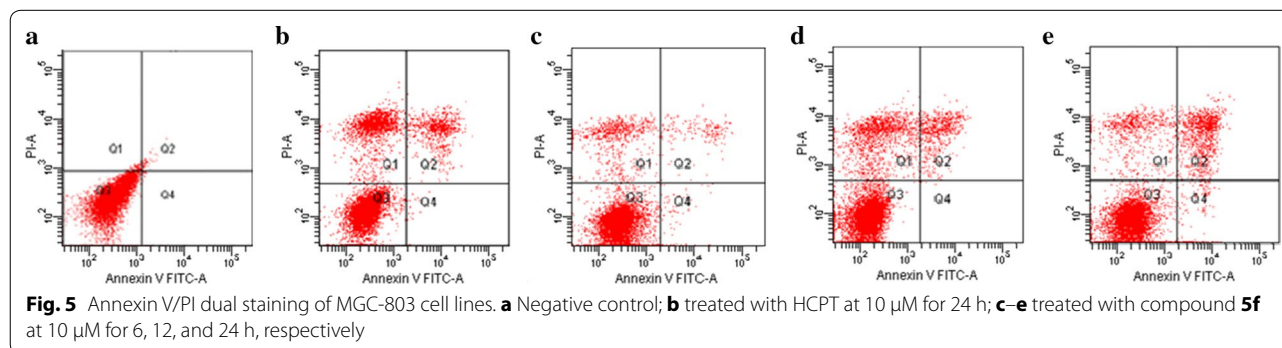
Synthetic procedures

6-methyl-quinazolin-4(3*H*)-one, 8-methyl-quinazolin-4(3*H*)-one, 6-methyl-4-chloroquiazoline, and 8-methyl-4-chloroquiazoline were prepared according to a previously described method [33]. Intermediate (*E*)-4-(2-hydroxyphenyl)-3-butylene-2-one was prepared according to a previously reported [34].

General synthetic procedures for the preparation of compounds 5a–5n

Compounds **2** (10 mmol), **3** (10 mmol) and K₂CO₃ (70 mmol) in 20 mL of acetonitrile was stirred at 30–40 °C for 3.5 h. The reaction mixture was concentrated and allowed to cool. The solid product obtained was filtered, and recrystallized with ethanol to afford the desired solid compound **4a** or **4b**, respectively. To the mixture of compound 4a or 4b (0.5 mmol) and sodium hydroxide (1%) in 20 mL of 75 vol% ethanol/water solution was added substituted aldehydes (0.5 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and suspended in water (20 mL), adjusted with 5% HCl to pH 7, and filtered. Recrystallization with ethanol afforded the desired solid compounds **5a–5n**.

(1E,4E)-1-(2-fluorophenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one *(***5a***)* Yield: 52.6%; yellow powder; mp: 121–123 °C; IR (KBr, cm^{-1}) *v*: 3442, 1657, 1622, 1596, 1465, 1398, 1356, 1221, 983; ^{1}H NMR (CDCl₃, 500 MHz) *δ:* 8.70 (s, 1H, Qu-2-H), 8.23 (d, *J* = 12.00 Hz, 1H, F–Ar–CH=), 7.93 (d, *J* = 8.6 Hz, 1H, Ar–CH=), 7.78–7.85 (m, 3H, Qu-5,7,8-H), 7.47–7.50 (m, 3H, F–Ar-4,6-H, Ar-3-H), 7.30–7.39 (m, 5H, F–Ar-3,5-H, Ar-4,5-H, F–Ar–C=CH), 7.10 (d, *J* = 16.0 Hz, 1H, Ar–C=CH), 6.81 (d, *J* = 14.8 Hz, 1H, Ar-6-H), 2.61 (s, 3H, CH₃); ^{13}C NMR (CDCl₃, 125 MHz) *δ*: 188.8, 166.4, 153.4,

Fig. 5 Annexin V/PI dual staining of MGC-803 cell lines. **a** Negative control; **b** treated with HCPT at 10 μM for 24 h; **c–e** treated with compound **5f** at 10 μM for 6, 12, and 24 h, respectively

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 7 of 10

153.4, 151.7, 150.4, 136.9, 136.7, 136.5, 131.7, 129.4, 128.2, 127.9, 127.7, 127.2, 127.1, 126.6, 126.5, 123.6, 123.5, 122.3, 116.4, 21.9; Anal. Calcd for $C_{25}H_{19}FN_2O_2$: C 76.08; H 4.67; N 6.83; Found: C 76.42; H 4.78; N 6.80.

(1E,4E)-1-(2-chlorophenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5b)** Yield: 46.3%; yellow powder; mp: 152–154 °C; IR (KBr, cm^{-1}) *v*: 3445, 1653, 1618, 1584, 1481, 1400, 1359, 1223, 986; ^{1}H NMR (CDCl$_3$, 500 MHz) *δ*: 8.69 (s, 1H, Qu-2-H), 8.22 (d, *J* = 8.0 Hz, 1H, Cl–Ar–CH=), 7.76–7.95 (m, 4H, Ar–CH=, Qu-5,7,8-H), 7.38–7.53 (m, 3H, Cl–Ar-3,6-H, Ar-3-H), 7.23–7.31 (m, 5H, Cl–Ar-4,5-H, Ar-5-H, Ar–C=CH, Cl–Ar–C=CH), 7.21 (m, 1H, Ar-4-H), 6.82 (d, *J* = 14.8 Hz, 1H, Ar-6-H), 2.62 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) *δ*: 188.6, 167.1, 154.3, 153.1, 151.0, 142.6, 142.1, 136.5, 134.5, 133.3, 132.6, 130.0, 129.6, 129.4, 127.4, 125.8, 125.6, 122.9, 122.7, 121.2, 116.3, 17.7; Anal. Calcd for $C_{26}H_{19}ClN_2O_2$: C 73.2; H 4.50; N 6.56; Found: C 73.27; H 4.56; N 6.42.

(1E,4E)-1-(4-chlorophenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5c)** Yield: 55.8%; yellow powder; mp: 173–176 °C; IR (KBr, cm^{-1}) *v*: 3445, 1653, 1622, 1558, 1489, 1373, 1229, 986; ^{1}H NMR (CDCl$_3$, 500 MHz) *δ*: 8.70 (s, 1H, Qu-2-H), 8.23 (d, *J* = 12.0 Hz, 1H, Cl–Ar–CH=), 7.93 (d, *J* = 8.6 Hz, 1H, Ar–CH=), 7.78–7.85 (m, 3H, Qu-5,7,8-H), 7.47–7.50 (m, 3H, Cl–Ar-2,6-H, Ar-3-H), 7.30–7.39 (m, 5H, Cl–Ar-3,5-H, Ar-4,5-H, Cl–Ar–C=CH), 7.10 (d, *J* = 16.0 Hz, 1H, Ar–C=CH), 6.81 (d, *J* = 14.8 Hz, 1H, Ar-6-H), 2.61 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) *δ*: 185.7, 167.4, 154.3, 153.1, 148.1, 147.4, 134.5, 134.1, 133.5, 132.3, 131.3, 130.0, 129.8, 129.2, 128.9, 127.3, 127.1, 122.8, 122.6, 121.1, 116.3, 17.8; Anal. Calcd for $C_{26}H_{19}ClN_2O_2$: C 73.15; H 4.49; N 6.56; Found: C 72.43; H 4.12; N 6.79.

(1E,4E)-1-(2-chloro-5-nitrophenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5d)** Yield: 58.2%; yellow powder; mp: 176–178 °C; IR (KBr, cm^{-1}) *v*: 3445, 1653, 1622, 1576, 1522, 1458, 1348, 1277, 1221, 983; ^{1}H NMR (CDCl$_3$, 500 MHz) *δ*: 8.68 (s, 1H, Qu-2-H), 8.40 (s, 1H, Cl–Ar-6-H), 8.21 (d, *J* = 15.0 Hz, 1H, Cl–Ar-4-H), 8.10–8.12 (d, *J* = 10.0 Hz, 1H, Qu-8-H), 7.73–7.92 (m, 5H, Cl–Ar–CH=, Qu-5,7-H, Cl–Ar-3-H, Ar–CH=), 7.54–7.57 (m, 2H, Cl–Ar–C=CH, Ar-3-H), 6.91–7.41 (m, 4H, Ar-4,5,6-H, Ar–C=CH), 2.61 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) *δ*: 187.8, 179.6, 158.5, 153.3, 151.9, 146.8, 138.1, 136.7, 136.4, 134.6, 132.1, 131.3, 130.7, 130.2, 128.4, 127.8, 126.7, 125.1, 123.6, 122.9, 122.5, 122.2, 116.7, 21.9; Anal. Calcd for $C_{26}H_{18}N_3O_4$: C 66.18; H 3.84; N 8.90; Found: C 65.81; H 3.66; N 9.30.

(1E,4E)-1-(2,4-dichlorophenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5e)** Yield: 60.5%; yellow powder; mp: 211–214 °C; IR (KBr, cm^{-1}) *v*: 3443, 1655, 1618, 1582, 1499, 1371, 1225, 986; ^{1}H NMR (CDCl$_3$, 500 MHz) *δ*: 8.68 (s, 1H, Qu-2-H), 8.21 (s, 1H, Qu-5-H), 7.60–7.93 (m, 4H, Qu-7,8-H, Cl–Ar–CH=, Ar–CH=), 7.38–7.43 (m, 4H, Cl–Ar-3-H, Ar-3-H, Cl–Ar-5,6-H), 7.26–7.31 (m, 3H, Ar-4,5-H, Cl–Ar–C=CH), 7.12 (d, *J* = 16.5 Hz, 1H, Ar–C=CH), 6.80 (d, *J* = 16.1 Hz, 1H, Ar-6-H), 2.61 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) *δ*: 188.5, 167.1, 153.4, 153.1, 151.4, 142.7, 137.9, 136.6, 136.5, 134.5, 132.3, 131.6, 130.2, 130.1, 128.7, 128.3, 127.6, 127.4, 125.0, 122.7, 121.2, 116.2, 17.7; Anal. Calcd for $C_{26}H_{18}Cl_2N_2O_2$: C 67.69; H 3.93; N 6.07; N 7.07; Found: C 67.56; H 3.45; N 5.65.

(1E,4E)-1-(2,6-dichlorophenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5f)** Yield: 55.2%; yellow powder; mp: 187–189 °C; IR (KBr, cm^{-1}) *v*: 3443, 1655, 1618, 1582, 1499, 1333, 1225, 986; ^{1}H NMR (CDCl$_3$, 500 MHz) *δ*: 8.68 (s, 1H, Qu-2-H), 8.20 (s, 1H, Qu-5-H), 7.89 (d, *J* = 8.5 Hz, 1H, Qu-8-H), 7.80–7.85 (m, 2H, Ar–CH=, Cl–Ar–CH=), 7.73 (d, *J* = 8.8 Hz, 1H, Qu-7-H), 7.52–7.61 (m, 2H, Cl–Ar-3,5-H), 7.39 (m, 1H, Cl–Ar-4-H), 7.24–7.30 (m, 3H, Ar-3,5-H, Ar–C=CH), 7.15 (m, 1H, Ar-4-H), 7.06 (d, *J* = 16.0 Hz, 1H, Cl–Ar–C=CH), 7.00 (d, *J* = 16.5 Hz, 1H, Ar-6-H), 2.60 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) *δ*: 188.9, 166.4, 153.4, 151.7, 150.4, 138.4, 137.5, 136.7, 136.5, 135.2, 132.9, 132.3, 131.8, 129.9, 128.9, 128.2, 128.0, 127.9, 127.5, 126.7, 123.6, 122.2, 116.0, 21.9; Anal. Calcd for $C_{26}H_{18}Cl_2N_2O_2$: C 67.69; H 3.93; N 6.07; Found: C 68.06; H 4.14; N 6.11.

1E,4E)-1-(2,5-dimethoxyphenyl)-5-(2-((6-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5g)** Yield: 49.6%; yellow powder; mp: 122–123 °C; IR (KBr, cm^{-1}) *v*: 3443, 1653, 1618, 1576, 1497, 1458, 1360, 1223, 1114, 1045; ^{1}H NMR (CDCl$_3$, 500 MHz) *δ*: 8.68 (s, 1H, Qu-2-H), 8.22 (s, 1H, Qu-5-H), 7.81–7.92 (m, 5H, Qu-7,8-H, Ar–CH=, CH$_3$O–Ar–CH=, Ar-3-H), 7.75 (d, *J* = 8.6 Hz, 1H, CH$_3$O–Ar–C=CH), 7.51 (m, 1H, Ar-5-H), 7.38 (m, 1H, Ar-4-H), 7.17 (d, *J* = 16.0 Hz, 1H, Ar–C=CH), 6.99 (d, *J* = 2.8 Hz, 1H, Ar-6-H), 6.89–6.94 (m, 2H, CH$_3$O–Ar-3,6-H), 6.81 (d, *J* = 2.8 Hz, 1H, CH$_3$O–Ar-4-H), 3.76 (s, 6H, 2-OCH$_3$), 2.57 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) *δ*: 189.3, 166.5, 153.5, 153.4, 153.2, 151.6, 150.4, 138.8, 138.4, 136.6, 136.2, 131.5, 128.4, 128.1, 127.8, 127.1, 126.7, 126.6, 123.5, 122.4, 117.6, 113.2, 112.5, 56.1, 55.8, 21.9; Anal. Calcd for $C_{28}H_{24}N_2O_4$: C 74.3; H 5.35; N 6.19; Found: C 74.3; H 5.48; N 5.95.

(1E,4E)-1-(2-fluorophenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5h)** Yield:

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 8 of 10

50.4%; yellow powder; mp: 155–157 °C; IR (KBr, cm^{-1}) v: 3445, 1653, 1620, 1582, 1506, 1481, 1398, 1223, 984; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.79 (s, 1H, Qu-2-H), 8.31 (d, J = 8.0 Hz, 1H, F–Ar–CH=), 7.77–7.85 (m, 3H, Qu-5,7-H, Ar–CH=), 7.67 (d, J = 16.5 Hz, 1H, F–Ar-6-H), 7.59 (m, 1H, Qu-6-H), 7.53 (m, 1H, F–Ar-4-H), 7.29–7.43 (m, 4H, Ar-3,5-H, F–Ar-3,5-H), 7.05–7.14 (m, 3H, Ar-4-H, F–Ar–C=CH, Ar–C=CH), 6.95 (d, J = 16.5 Hz, 1H, Ar-6-H), 2.76 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 188.8, 167.1, 153.2, 151.7, 151.1, 136.9, 136.6, 136.0, 134.5, 131.9, 131.9, 129.3, 128.4, 128.1, 127.8, 127.8, 127.6, 126.6, 124.5, 123.6, 121.1, 116.4, 17.8; Anal. Calcd for C$_{25}$H$_{19}$FN$_2$O$_2$: C 76.08; H 4.67; N 6.83; Found: C 75.81; H 4.53; N 7.04.

(1E,4E)-1-(2-chlorophenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5i)** Yield: 41.8%; yellow powder; mp: 152–154 °C; IR (KBr, cm^{-1}) v: 3443, 1655, 1616, 1595, 1481, 1406, 1358, 1229, 979; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.79 (s, 1H, Qu-2-H), 8.30 (d, J = 8.5 Hz, 1H, Cl–Ar–CH=), 7.96 (d, J = 16.5 Hz, 1H, Ar–CH=), 7.76–7.85 (m, 3H, Qu-5,6,7-H), 7.50-7.59 (m, 3H, Ar-3-H, Cl–Ar-3,6-H), 7.38-7.40 (m, 2H, Cl–Ar-4,5-H), 7.29–7.39 (m, 2H, Cl–Ar–C=CH, Ar–C=CH), 7.14–7.25 (m, 2H, Ar-4,5-H), 6.81 (d, J = 16.0 Hz, 1H, Ar-6-H), 2.77 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 188.7, 167.1, 153.2, 151.7, 151.1, 139.2, 137.2, 136.6, 135.4, 134.6, 131.7, 131.3, 130.3, 128.4, 128.3, 128.1, 127.7, 127.6, 127.1, 126.6, 123.6, 121.1, 116.1, 17.8; Anal. Calcd for C$_{26}$H$_{19}$ClN$_2$O$_2$: C 73.15; H 4.49; N 6.56; Found: C 73.04; H 4.74; N 6.76%.

(1E,4E)-1-(4-chlorophenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5j)** Yield: 58.6%; yellow powder; mp: 161–163 °C; IR (KBr, cm^{-1}) v: 3445, 1647, 1616, 1576, 1481, 1406, 1358, 1227, 937; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.79 (s, 1H, Qu-2-H), 8.20-8.34 (m, 3H, Qu-5,6,7-H), 7.72–7.86 (m, 4H, Ar–CH=, Ar-3-H, Cl–Ar–C=CH, Cl–Ar=CH), 7.52–7.64 (m, 4H, Cl–Ar-2,3,5,6-H), 7.41-7.42 (m, 1H, Ar-5-H), 7.30–7.32 (m, 1H, Ar-4-H), 7.11–7.14 (d, J = 15.0 Hz, 1H, Ar-6-H), 6.93–6.96 (d, J = 15.0 Hz, 1H, Ar–C=CH), 2.77 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 188.6, 167.1, 153.2, 153.1, 151.7, 151.1, 141.9, 136.9, 136.7, 134.6, 131.7, 129.5, 129.2, 128.4, 128.1, 127.6, 127.2, 126.7, 125.8, 123.6, 121.1, 17.8; Anal. Calcd for C$_{26}$H$_{19}$ClN$_2$O$_2$: C 73.15; H 4.49; N 6.56; Found: C 73.36; H 4.65; N 6.86.

(1E,4E)-1-(2-chloro-5-nitrophenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5k)** Yield: 54.5%; yellow powder; mp: 198–200 °C; IR (KBr, cm^{-1}) v: 3420, 1676, 1626, 1560, 1522, 1479, 1402, 1348, 1221, 980; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.78 (s, 1H, Qu-2-H), 8.39 (s, 1H, Cl–Ar-6-H), 8.32 (d, J = 8.0 Hz, 1H, Cl–Ar-4-H), 8.13 (d, J = 8.3 Hz, 1H, Qu-5-H), 7.76-7.88 (m, 4H, Ar–CH=, Cl–Ar–CH=, Qu-6, 7-H), 7.45–7.59 (m, 3H, Ar-3-H, Cl–Ar-3-H, Cl–Ar–C=CH), 7.23–7.40 (m, 2H, Ar-4,5-H), 7.10 (d, J = 12.5 Hz, 1H, Ar–C=CH), 6.93 (d, J = 16.0 Hz, 1H, Ar-6-H), 2.75 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 187.8, 167.1, 153.1, 151.8, 151.0, 146.7, 141.6, 138.2, 136.7, 136.6, 134.6, 132.0, 131.3, 130.1, 128.6, 127.7, 126.9, 126.7, 125.1, 123.7, 122.5, 120.9, 116.1, 17.7; Anal. Calcd for C$_{26}$H$_{18}$ClN$_3$O$_4$: C 66.18; H 3.84; N 8.90; Found: C 66.30; H 3.84; N 8.86.

(1E,4E)-1-(2,4-dichlorophenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5l)** Yield: 58.6%; yellow powder; mp: 175–178 °C; IR (KBr, cm^{-1}) v: 3445, 1653, 1618, 1576, 1481, 1408, 1358, 1229, 984; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.79 (s, 1H, Qu-2-H), 8.30 (d, J = 8.0 Hz, 1H, Cl–Ar–CH=), 7.76–7.94 (m, 3H, Ar–CH=, Qu-5,7-H), 7.53–7.57 (m, 2H, Qu-6-H, Cl–Ar-3-H), 7.38–7.47 (m, 3H, Ar-3-H, Cl–Ar-5,6-H), 7.29–7.31 (m, 2H, Cl–Ar-4-H), 7.38–7.41 (m, 2H, Cl–Ar–C=CH, Ar-5-H), 7.15–7.17 (m, 2H, Ar–C=CH, Ar-4H), 6.78 (d, J = 16.5 Hz, 1H, Ar-6-H), 2.77 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 188.5, 167.1, 153.2, 151.8, 151.1, 139.1, 137.5, 136.7, 135.4, 134.6, 134.1, 133.3, 131.8, 131.7, 129.2, 128.4, 128.0, 127.6, 127.4, 126.7, 125.8, 123.6, 121.0, 116.1, 17.7; Anal. Calcd for C$_{26}$H$_{18}$Cl$_2$N$_2$O$_2$: C 67.69; H 3.93; N 6.07; Found: C 67.27; H 4.03; N 5.96%.

(1E,4E)-1-(2,6-dichlorophenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5m)** Yield: 56.1%; yellow powder; mp: 161–163 °C; IR (KBr, cm^{-1}) v: 3421, 1676, 1620, 1587, 1481, 1400, 1359, 1225, 984; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.76 (s, 1H, Qu-2-H), 8.28 (d, J = 8.5 Hz, 1H, Ar–CH=), 7.73–7.85 (m, 3H, Cl–Ar–CH=, Qu-5,7-H), 7.52–7.59 (m, 3H, Cl–Ar-3,5-H, Qu-6-H), 7.29–7.41 (m, 4H, Ar-3, 5-H, Cl–Ar-4-H, Cl–Ar–C=CH), 7.16 (m, 1H, Ar-4-H), 7.07 (d, J = 16.0 Hz, 1H, Ar–C=CH), 6.98 (d, J = 17.0 Hz, 1H, Ar-6-H), 2.75 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 188.96, 167.10, 153.15, 151.70, 150.99, 137.59, 136.75, 135.68, 135.17, 134.57, 132.97, 131.85, 129.88, 128.85, 128.36, 127.88, 127.65, 127.45, 126.72, 123.60, 121.04, 116.02, 17.79; Anal. Calcd for C$_{26}$H$_{18}$Cl$_2$N$_2$O$_2$ (461): C, 67.69; H, 3.93; N, 6.07; N, 7.07%. Found: 67.36; H, 3.96; N, 5.84%.

(1E,4E)-1-(2,5-dimethoxyphenyl)-5-(2-((8-methylquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one **(5n)** Yield: 43.6%; yellow powder; mp: 176–178 °C; IR (KBr, cm^{-1}) v: 3445, 1647, 1616, 1570, 1491, 1373, 1211, 984; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 8.79 (s, 1H, Qu-2-H), 8.30 (d, J = 8.6 Hz, 1H, CH$_3$O–Ar–CH=), 7.75–7.92 (m, 4H, Ar–CH=, Qu-5,6,7-H), 7.50–7.59 (m, 2H, Ar-3,5-H), 7.39

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 9 of 10

(m, 1H, Ar-4-H), 7.15–7.29 (m, 2H, CH$_3$O–Ar–C=CH, Ar–C=CH), 6.98 (s, 1H, CH$_3$O–Ar-6-H), 6.89–6.93 (m, 2H, Ar-6-H, CH$_3$O–Ar-3-H), 6.81 (d, J = 8.6 Hz, 1H, CH$_3$O–Ar-4-H), 3.77 (s, 6H, 2CH$_3$O), 2.76 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 189.25, 167.14, 153.57, 153.18, 151.66, 151.03, 138.78, 136.58, 136.25, 134.51, 131.45, 128.41, 128.23, 127.55, 127.24, 126.58, 124.21, 123.54, 121.16, 120.94, 117.61, 116.16, 113.22, 112.47, 56.08, 55.85, 17.75. Anal. Calcd for C$_{28}$H$_{24}$N$_2$O$_4$ (453): C, 74.32; H, 5.35; N, 6.19; %. Found: C, 74.55; H, 5.68; N, 5.95%.

Cell culture

Human gastric cancer cell line MGC-803, human prostate cancer cell line PC3, and human breast cancer cell line Bcap-37 and one normal cell line NIH3T3 were obtained from Cell Bank of Type Culture Collection of Chinese Academy of Sciences (Shanghai, China). NIH3T3 was routinely maintained in a DMEM medium, while all the other cell lines were cultured in a 1640 medium. All the cells were grown in the medium supplemented with 10% FBS at 37 °C with 5% CO$_2$.

MTT assay

The growth-inhibitory effects of the test compounds were determined on MGC-803, PC3, Bcap-37, and NIH3T3 cells. All cell types were seeded into 96-well plates at a density of 2×10^3 cells/well 100 μL of the proper culture medium and incubated with increasing concentrations of the compounds at 37 °C under cell culturing conditions. An MTT assay (Roche Molecular Biochemicals, 1465-007) was performed 72 h later according to the instructions provided by Roche. The precipitated formazan crystals were dissolved in SDS, and the absorbance was read at 595 nm with a microplate reader (BIO-RAD, model 680), which is directly proportional to the number of living cells in culture. The experiment was performed in triplicate. The percentage cytotoxicity was calculated using the formula.

$$\%\text{Cytotoxicity} = [(\text{Control}_{abs} - \text{Blank}_{abs}) - (\text{Test}_{abs} - \text{Blank}_{abs})]/ (\text{Control}_{abs} - \text{Blank}_{abs}) \times 100$$

AO/EB staining

Cells were seeded in 6-well culture plates at a density of 5×10^4 cells/mL in 0.6 mL of medium and allowed to adhere to the plates overnight. The cells were incubated with different concentrations of compounds or vehicle solution (0.1% DMSO) in a medium containing 10% FBS for 12 h. After the treatment, the cover slip with monolayer cells was inverted on the glass slide with 20 μL of AO/EB stain (100 μg/mL), and finally analyzed for morphological characteristics of cell apoptosis under a fluorescence microscope (Olympus Co., Japan).

Hoechst 33,258 staining

Cells were seeded in 6-well culture plates at a density of 5×10^4 cells/mL in 0.6 mL of medium and allowed to adhere to the plates overnight. The cells were incubated with different concentrations of compounds or vehicle solution (0.1% DMSO) in a medium containing 10% FBS for 12 h. After the treatment, the cells were fixed with 4% paraformaldehyde for 10 min, followed by incubation with Hoechst 33,258 staining solution (Beyotime) for 5 min and finally analyzed for morphological characteristics of cell apoptosis under a fluorescence microscope (Olympus Co., Japan).

Flow cytometry analysis

To further quantitative analysis of apoptosis, the cells were washed with PBS, stained with annexinV-FITC and propidium iodide (PI) using the AnnexinV-FITC kit (Key-GEN BioTECH). The cells were then subjected to flow cytometry according to manufacturer's instructions and the stained cells were analyzed by FACS can flow cytometer (Becton–Dickinson, CA, USA).

Statistical analysis

All statistical analysis was performed with SPSS Version 19.0. Data was analyzed by one-way ANOVA. Mean separations were performed using the least significant difference method. Each experiment was replicated thrice, and all experiments yielded similar results. Measurements from all the replicates were combined, and treatment effects were analyzed.

Authors' contributions

HL and SY synthesized the compounds and carried out most of the bioassay experiments. DH took part in the compound structural elucidation and bioassay experiments. WX carried out some structure elucidation experiments. PX assisted in structural elucidation experiments. All authors read and approved the final manuscript.

Author details

[1] Guizhou Fruit Institute, Guizhou Academy of Agricultural Sciences, Guiyang 550006, P. R. China. [2] R&D Center, Sinphar Tian-Li Pharmaceutical Co., Ltd, Hangzhou 311100, P. R. China. [3] State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, P. R. China. [4] Ctr for R&D of Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China.

Luo *et al. Chemistry Central Journal* (2017) 11:23

Page 10 of 10

References
1. Twombly R (2005) Cancer surpasses heart disease as leading cause of death for all but the very elderly. J Natl Cancer 97:330–331
2. Nichols L, Saunders R, Knollmann FD (2012) Causes of death of patients with lung cancer. Arch Pathol Lab Med 136:1552–1557
3. Karthikeyan C, Solomon VR, Lee H, Trivedi P (2013) Design, synthesis and biological evaluation of some isatin-linked chalcones asnovel anti-breast cancer agents: a molecular hybridization approach. Biomed Prev Nutr 3:325–330
4. Fedele P, Marino A, Orlando L, Schiavone P, Nacci A, Sponziello F, Rizzo P, Calvani N, Mazzoni E, Cinefra M, Cinieri S (2012) Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. Eur J Cancer 48:24–29
5. Huang W, Zhang J, Dorn HC, Zhang C (2013) Assembly of bio-nanoparticles for double controlled drug release. PLoS ONE 8:e74679
6. Sanmartín C, Plano D, Domínguez E, Font M, Calvo A, Prior C, Encío I, Palop AJ (2009) Synthesis and pharmacological screening of several aroyl and heteroaroyl selenylacetic acid derivatives as cytotoxic and antiproliferative agents. Molecules 14:3313–3338
7. Wu Y, Liu F (2013) Targeting mTOR: evaluating the therapeutic potential of resveratrol for cancer treatment. Anti-Cancer Agent Me 13:1032–1038
8. Li X, Xu W (2006) Recent patent therapeutic agents for cancer. Recent Pat Anti Cancer Drug Discov 1:1–30
9. Baker DD, Chu M, Oza U, Rajgarhia V (2007) The value of natural products to future pharmaceutical discovery. Nat Prod Rep 24:1225–1244
10. Butler MS (2005) Natural products to drugs: natural product derived compounds in clinical trials. Nat Prod Rep 22:162–195
11. Padhye S, Chavan D, Pandey S, Deshpande J, Swamy KV, Sarkar FH (2010) Perspectives on chemopreventive and therapeutic potential of curcumin analogs in medicinal chemistry. Mini Rev Med Chem 10:372–387
12. Menon VP, Sudheer AR (2007) Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol 595:105–125
13. Barclay LR, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A, Uno H (2000) On the antioxidant mechanism of curcumin: classical methods are needed to determine antioxidant mechanism and activity. Org Lett 2:2841–2843
14. Jurenka JS (2009) Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. Altern Med Rev 14:141–153
15. Jordan WC, Drew CR (1996) Curcumin-a natural herb with anti-HIV activity. J Natl Med Assoc 88:333
16. Sui Z, Salto R, Li J, Craik C, de Montellano PRO (1993) Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. Bioorg Med Chem 1:415–422
17. Beevers CS, Huang S (2011) Pharmacological and clinical properties of curcumin. Botanics Targets Ther. 1:5–18
18. Aggarwal BB, Kumar A, Bharti AC (2003) Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 23:363–398
19. Liu Z, Sun Y, Ren L, Huang Y, Cai Y, Weng Q, Shen X, Li X, Liang G, Wang Y (2013) Evaluation of a curcumin analog as an anti-cancer agent inducing ER stress-mediated apoptosis in non-small cell lung cancer cells. BMC Cancer 13:494
20. Nagaraju GP, Zhu S, Wen J, Farris AB, Adsay VN, Diaz R, Snyder JP, Mamoru S, El-Rayes BF (2013) Novel synthetic curcumin analogues EF31 and UBS109 are potent DNA hypomethylating agents in pancreatic cancer. Cancer Lett 341:195–203
21. Lev-Ari S, Starr A, Katzburg S, Berkovich L, Rimmon A, Ben-Yosef R, Vexler A, Ron I, Earon G (2014) Curcumin induces apoptosis and inhibits growth of orthotopic human non-small cell lung cancer xenografts. J Nutr Biochem 25:843–850
22. Bairwa K, Grover J, Kania M, Jachak SM (2014) Recent developments in chemistry and biology of curcumin analogues. RSC Adv 4:13946–13978
23. Chandru H, Sharada AC, Bettadaiah BK, Kumar CS, Rangappa KS, Sunila Jayashree K (2007) In vivo growth inhibitory and anti-angiogenic effects of synthetic novel dienone cyclopropoxy curcumin analogs on mouse Ehrlich ascites tumor. Bioorg Med Chem 15:7696–7703
24. Luo H, Yang S, Cai Y, Peng Z, Liu T (2014) Synthesis and biological evaluation of novel 6-chloro-quinazolin derivatives as potential antitumor agents. Eur J Med Chem 84:746–752
25. Luo S, Yang S, Zhao Q, Xiang H (2014) Synthesis and antitumor properties of novel curcumin analogs. Med Chem Res 23:2584–2595
26. Luo H, Liu J, Jin L, Hu D, Chen Z, Yang S, Wu J, Song B (2013) Synthesis and antiviral bioactivity of novel (1*E*,4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy) phenyl)-1,4-pentadien-3-one derivatives. Eur J Med Chem 63:662–669
27. Elmore S (2007) Apoptosis: a review of programmed cell death. Toxicol Pathol 35:495–516
28. Lowe SW, Lin AW (2000) Apoptosis in cancer. Carcinogenesis 21:485–495
29. Huang HL, Liu YJ, Zeng CH, Yao JH, Liang ZH, Li ZZ, Wu FH (2010) Studies of ruthenium(II) polypyridyl complexes on cytotoxicity in vitro, apoptosis, DNA-binding and antioxidant activity. J Mol Struct 966:136–143
30. Gao L, Shen L, Yu M, Ni J, Dong X, Zhou Y, Wu S (2014) Colon cancer cells treated with 5-fluorouracil exhibit changes in polylactosamine-type N-glycans. Mol Med Rep 9:1697–1702
31. Min Z, Wang L, Jin J, Wang X, Zhu B, Chen H, Cheng Y (2014) Pyrroloquinoline quinone induces cancer cell apoptosis via mitochondrial-dependent pathway and down-regulating cellular bcl-2 protein expression. J Cancer 5:609–624
32. Chan CK, Goh BH, Kamarudin MN, Kadir HA (2012) Aqueous fraction of Nephelium ramboutan-ake rind induces mitochondrial-mediated apoptosis in HT-29 human colorectal adenocarcinoma cells. Molecules 17:6633–6657
33. Liu G, Song BA, Sang WJ, Yang S, Jin LH, Ding X (2004) Synthesis and bioactivity of N-aryl-4-aminoquinazoline compounds. Chin J Org Chem 10:1296–1299
34. McGookin A, Heilbron IM (1924) CCLXXV.—The isomerism of the styryl alkyl ketones. Part I. The isomerism of 2-hydroxystyryl methyl ketone. J Chem Soc Trans 125:2099–2105