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Design, Synthesis and Biological Evaluation of Novel Tetrahydroisoquinoline Derivatives as Potential Antitumor Candidate

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Abstract

A novel class of tetrahydroisoquinoline derivatives were designed and synthesized as antitumor agents and evaluated for their *in vitro* and *in vivo* biological activities. The antiproliferative activities of all the target compounds on HUVEC, MCF-7 and HT-29 were evaluated. Compared with Colchicine (1.04×10^{-2} μM)**, 17d** and **17e** exhibited outstanding

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activity on MCF-7 with IC_{50} values 0.26×10^{-2} μM and 0.89×10^{-3} μM in cell cytotoxicity assay. The tubulin polymerization assay demonstrated that **17d** and **17e** exhibited better inhibition rate. In the MCF-7-xenograft mouse model which were treated with **17d** and **17e** by intraperitoneal injection, the tumor weight was decreased at same rate with Tamoxifen, and relative tumor proliferation rates were 59.48 % and 41.33 %, while Tamoxifen was 45.08 % with a daily dose of 20 mg/kg, which were demonstrated potent *in vivo* efficacy.

Keywords: tetrahydroisoquinoline derivatives, MCF-7, selectivity, antitumor

1. Introduction

Tubulin, a globular protein, is consists of five distinct families, α, β, δ, ε and ζ, among which α- tubulin and β- tubulin build the microtubule [1, 2]. Microtubules are long, hollow cylinders of tubulin dimmers, playing critical roles in cell division, formation and maintenance of cell shape, motility, cell signaling, secretion, and intracellular transport [3-5]. It is why molecules acting on the cellular microtubule dynamics form one of the largest groups of effective chemotherapeutics used against cancer.

Podophyllotoxin was a non-alkaloid toxic lignin extracted from the roots and rhizomes of Podophyllum species. Podophyllotoxin had been extensively researched as a cytotoxic agent, exhibiting potent anticancer activity toward numerous cancer cell lines by inhibit both tubulin polymerization and DNA topoisomerase-II. However, the systemic toxicity of Podophyllotoxin limited its clinical application as a medicinal drug [6]. According to the biological properties of Podophyllotoxin, lots of derivatives were semi-synthesized [7, 8], such as Etoposide and Teniposide (semis synthetic derivatives of Podophyllotoxin), and used in cancer chemotherapy against various cancer [9]. According to the structure of microtubule assembly inhibitor Podophyllotoxin **3** and Topo II inhibitor Etoposide [10], Akira's team developed compounds **1** and **2**（Fig **1**）with the de-hydroxyl C ring, exhibited cytotoxicity due to inhibition of microtubule assembly [11]. However, compound **1** did not inhibit Topo II activity. It was reported that the aza-podophyllotoxin, based on the deoxidized derivatives of Podophyllotoxin (Compound **3**, Fig **1**) exhibited tubulin polymerization inhibition ability [12, 13].

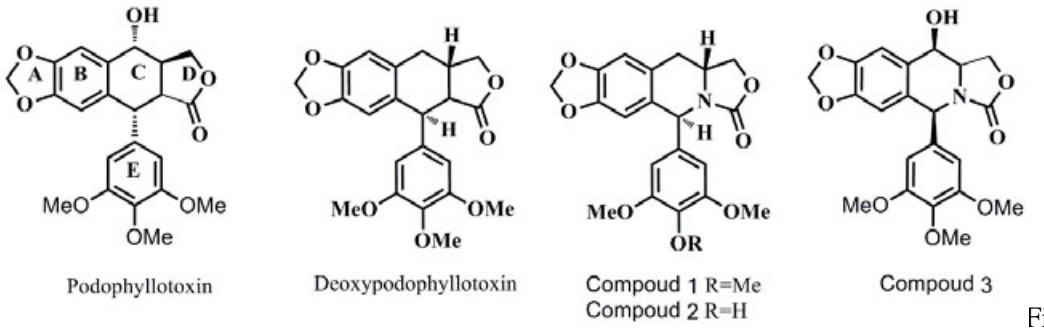


Fig **1**.

The structure of Podophyllotoxin and its derivatives

Isoquinoline alkaloid was a class of natural products that possess a broad spectrum of pharmacological actions, particularly anticancer activity [14]. Tetrahydroisoquinoline, one of the most important heterocyclic scaffolds, can be found in various pharmaceutically important antitumor antibiotics. Tetrahydroisoquinoline derivatives (Fig **2**, compound **4**, **5**) which were developed by Ramanivas *et al*. had shown significant activity against human prostate cancer cell line (DU-145) with IC_{50} value 0.72 and 1.23 μM respectively [15]. Comparing with CA-4, compounds **6**, **7**, **8** developed by Leese *et al.* manifest better anti-proliferation activity against human burkitt lymphoma cells [16].

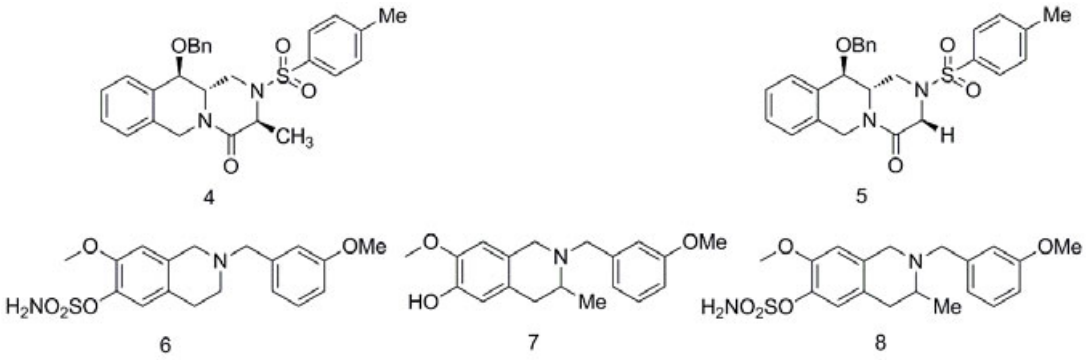


Fig **2**. The structure of tetrahydroisoquinoline derivatives

In recent years, it was found that the phenyl acrylic acid series ferulic acid [17], hydroxy cinnamic acid [18] and cinnamon acid [19] which have preferable antitumor effect, inducing apoptosis, sensitization effect of chemotherapy, radiation protection, etc. may correlated with benzene acrylic.

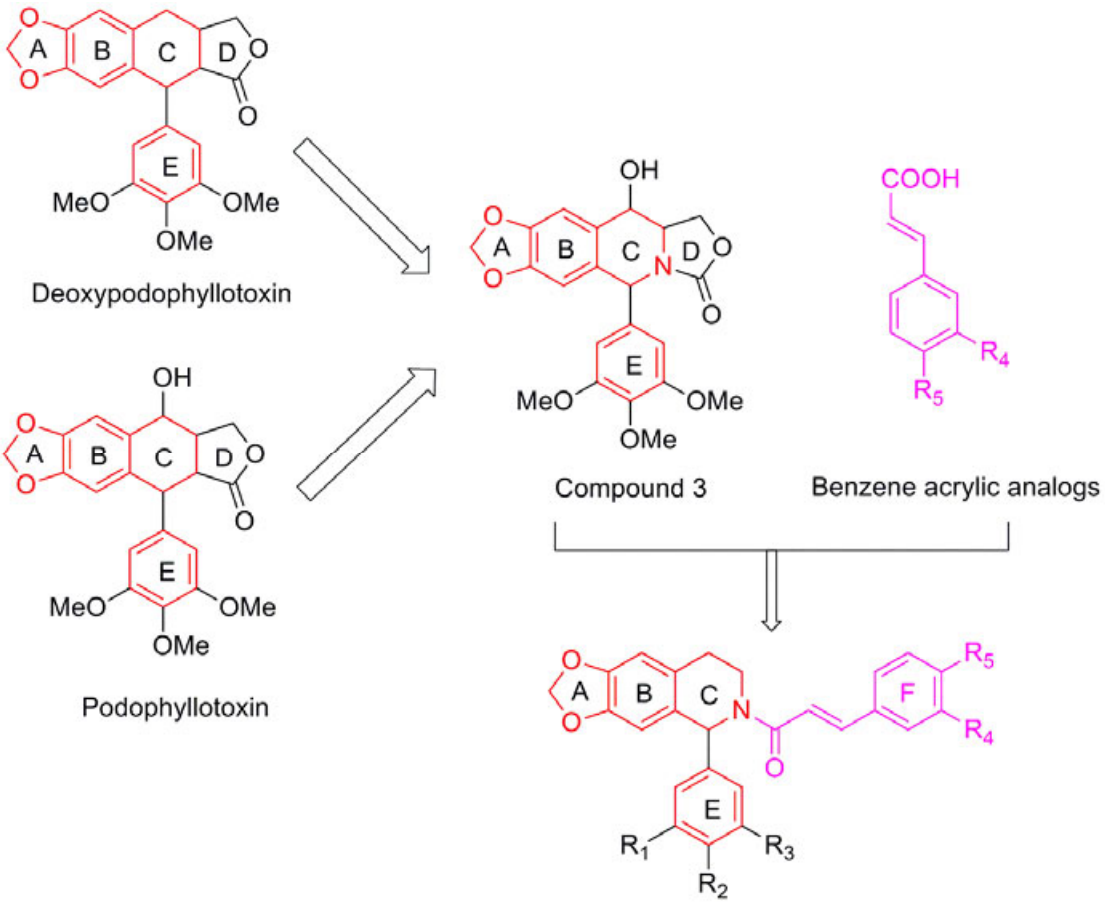


Fig **3**. Design of the tetrahydroisoquinoline derivatives

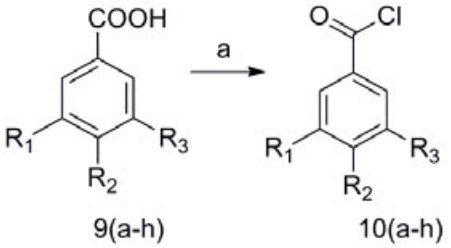
Based on the above structural requirements that the A and E rings of the Podophyllotoxin and tetrahydroisoquinoline were important to the activity, we postulated that the hydroxyl on C ring and D ring was not the essential group for antineoplastic activity of Podophyllotoxin. Therefore, we design and synthesis deoxypodophyllotoxin derivatives with benzene acrylic group, which can also be referred as opened D rings, to promote efficacy and selectivity to tumor.

2. Chemistry

The target compounds were reached as follows. Compounds **12(a-h)** were prepared by substituted benzoic acid and aromatic amine, in the presence of $SOCl_2$ [20]. Intermediates **13(a-h)** were gained by reacting **12(a-h)** with substituted benzaldehyde in the presence of $POCl_3$ (Bischler-Napieralsk [21] reaction), which were then reduced by $NaBH_4$ to achieve **14(a-h)**. Compounds **16(a-l)** were obtained from different substituted cinnamic acid via

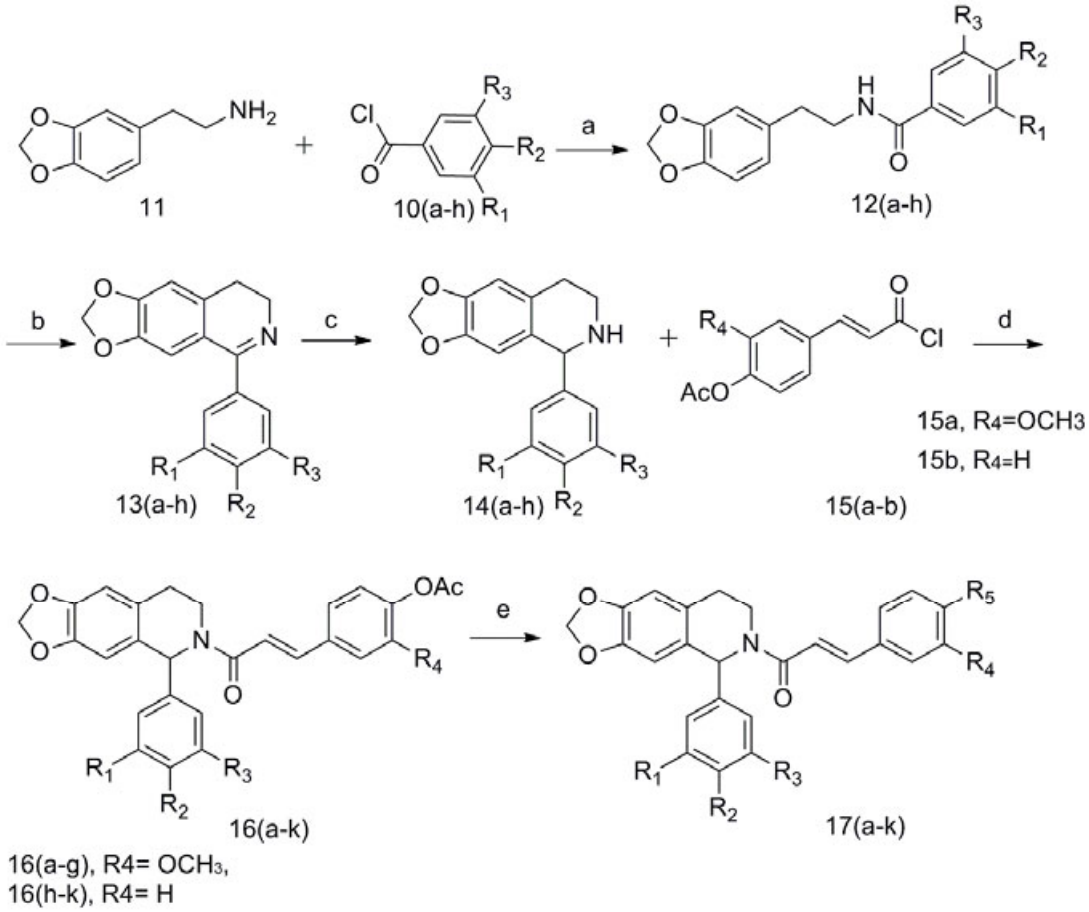
$SOCl_2$-catalyzed amidation reaction [22] followed by hydrolization to achieve compounds **17(a-k)**. Target compounds **19(c-e)** were prepared by etherification with the commercially available amine in the presence of KI [23].

Scheme 1. Synthesis of Compounds 10(a-h)



	R_1	R_2	R_3
10a	H	CH_3	H
10b	H	Cl	H
10c	H	NO_2	H
10d	H	OCH_3	H
10e	H	OCH_3	OCH_3
10f	H	OCH_3	OH
10g	H	H	H
10h	OCH_3	OCH_3	OCH_3

Reagents and conditions: (a) $SOCl_2$, toluene 77 °C, 4h.



	R1	R2	R3	R4	R5
17a	H	CH_3	H	OCH_3	OH
17b	H	Cl	H	OCH_3	OH
17c	H	NO_2	H	OCH_3	OH
17d	H	OCH_3	H	OCH_3	OH
17e	H	OCH_3	OCH_3	OCH_3	OH

	R1	R2	R3	R4	R5
17f	H	OCH_3	OH	OCH_3	OH
17g	H	H	H	OCH_3	OH
17h	OCH_3	OCH_3	OCH_3	H	OH
17i	H	NO_2	H	H	OH
17j	H	OCH_3	H	H	OH
17k	H	OCH_3	OCH_3	H	OH

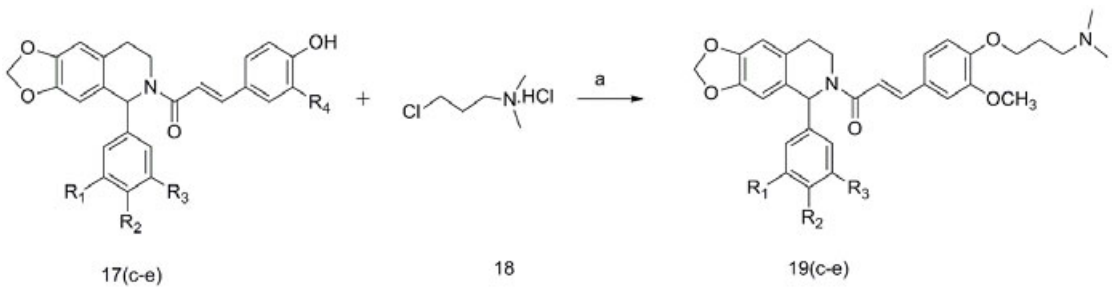
Reagents and conditions: (a) NaOH (aq), CH_2Cl_2, 0 °C, 2.5h; (b) $POCl_3$, Toluene 115 °C, 7h; (c) $NaBH_4$, 0 °C, CH_3OH, 4h; (d) Et_3N, CH_2Cl_2, 0 °C, 2.5h; (e) NaOH (aq), CH_3OH, r.t, 24h.

In the preparation of cinnamic acid chloride, because homemade acetylated cinnamic acid was cloudy in a solvent would result the reaction yield significantly reduced, DMF was used as co-solvent solution.

Scheme 2. Synthesis of Compounds 17(a-k)

During Bischler-Napieralski [21] reaction, the $POCl_3$ should be added below 95 °C, otherwise, the reaction process would produce a large quantity of thick black gum, leading to the failure of the reaction.

Scheme 3. Synthesis of Compounds 19(c-e)

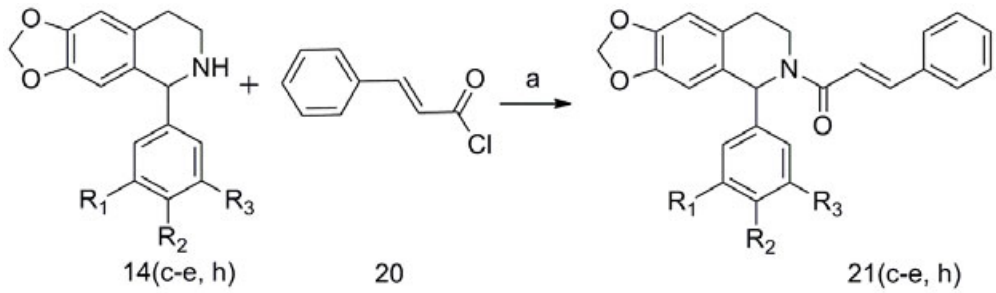


17(c-e) 18 19(c-e)

	R1	R2	R3
19c	H	NO_2	H
19d	H	OCH_3	H
19e	H	OCH_3	OCH_3

Reagents and conditions: (a) K_2CO_3, KI, isopropanol, r.t, 3h

Scheme 4. Synthesis of Compounds 21(c-f)



14(c-e, h) 20 21(c-e, h)

	R1	R2	R3
21c	H	NO_2	H
21d	H	OCH_3	H
21e	H	OCH_3	OCH_3
21h	OCH_3	OCH_3	OCH_3

Reagents and conditions: (a) Et_3N, CH_2Cl_2, 0 °C, 2.5 h.

3. Biological evaluation

3.1 *In vitro* antiproliferative activities

To test the anticancer activities of the synthesized compounds, firstly we evaluated antiproliferative activities of compounds against HUVEC (Umbilical Vein Endothelial Cells), HT-29 (Colonic Carcinoma Cells) and MCF-7 (Breast Cancer Cells). Colchicine was taken as the positive control. The results were summarized in (Table **1**). From the results of the SRB assay, it was found that compound **19c** showed better potency against HUVEC and HT-29, compounds **17d** and **17e** showed the extraordinary activity against MCF-7. The results expressed as IC_{50} values, are reported in Table **1**.

Table **1.** In vitro inhibitory activity of target compounds against human cancer cells ($\bar{x} \pm s$, n=3)

Compound	IC_{50}/μM		
	HUVEC	MCF-7	HT-29
17a	7.00±3.50	6.00±1.02	2.98±0.10
17b	2.86±0.36	5.53±0.49	5.22±0.15
17c	334.00±13.04	135.97±7.32	4.53±0.63
17d	5.86±2.74	**$0.26\times10^{-2}\pm0.40\times10^{-3}$**	2.54±0.19
17e	11.14±2.89	**$0.89\times10^{-3}\pm0.28\times10^{-3}$**	6.43±0.99
17f	2.45±0.74	10.63±0.57	2.09±0.15
17g	10.74±7.00	13.58±0.91	3.37±0.44
17h	11.97±3.83	23.50±5.00	9.83±2.84
17i	4.59±0.62	22.44±3.52	12.05±7.08
17j	12.03±4.39	145.16±25.16	10.59±5.63
17k	81.08±7.34	74.41±27.78	7.95±0.96
19d	1.71±0.39	2.44±0.44	1.77±0.72

19e	1.78±0.62	3.91±1.29	1.54±0.79
19c	**0.78±0.19**	2.47±0.59	**0.35±0.08**
22d	149.20±35.52	49.31±3.80	39.01±6.12
22e	16.78±13.17	28.83±4.01	12.38±2.64
22f	19.52±8.04	124.41±6.32	47.7±12.49
22c	23.72±19.09	53.43±12.49	5.90±0.96
Colchicine	1.88±0.43	$1.04\times10^{-2}\pm0.28\times10^{-2}$	$3.22\times10^{-2}\pm1.30\times10^{-2}$

The anti-proliferative activities of compounds against all the tested cell lines were determined using the SRB assay, colchicine was taken as the positive control. The results were expressed as the IC_{50}.

3.2 Inhibition of tubulin polymerization

To investigate the mechanism of antiproliferative activity of compound **17d** and **17e**, the inhibition of tubulin polymerization were evaluated. CA-4 was taken as a positive control. As shown in (Table **2**), compounds **17d** and **17e** which exhibit similar inhibitory effect to CA-4, proved to be better inhibitors of tubulin polymerization, in a dose-dependent manner.

Table **2.** Tubulin polymerization inhibitory effect of compounds

Group	**α-tubulin**
Negative control	0.68
Solvent control	0.63
17d (50 nM)	0.52
17d (500 nM)	0.21
17d (1000 nM)	0.13
17e (50 nM)	0.33
17e (500 nM)	0.15

17e (1000 nM)	0.11
CA-4 (50 nM)	0.53
CA-4 (500 nM)	0.34
CA-4 (1000 nM)	0.22

Data values of **17d, 17e** and **CA-4** were determined from the tubulin polymerization assay, **CA-4** was taken as a positive control.

3.3 Antitumor activity *in vivo*

17d and **17e** were selected for further *in vivo* antitumor activity studies on human breast cancer MCF-7 xenograft model, while tamoxifen was chosen as reference. As showed in Fig **4**, remarkable antitumor effects were observed in mice treated with compounds **17d** and **17e** which were administered intraperitoneally (i.p.) for 30 consecutive days. Furthermore, compound **17e** showed better *in vivo* antitumor potency than tamoxifen.

The relative tumor proliferation rates of **17d** and **17e** were 59.48 % and 41.33 % separately at the dose of 20 mg/kg while 45.08 % of tamoxifen at the same dose. In addition, no significant body weight loss or any other obvious signs of toxicity were observed for all of the **17d** and **17e** treated mice during the whole research which means that just like tamoxifen, the compounds **17d** and **17e** had weak influence on normal cell.

Table **3.** *In vivo* Anti-tumor activity on female BALB/c nude mice/MCF-7 xenograft mode ($\bar{x} \pm S$, n= 6)

		Control	**Tamoxifen**	**17d**	**17e**
1	**Tumor volume**	0.098±0.026	0.098±0.024	0.099±0.046	0.098±0.041
2	**Tumor volume**	0.171±0.057	0.154±0.030	0.161±0.087	0.141±0.048
	RTV	1.742±0.234	1.592±0.157	1.627±0.233	1.480±0.150*
	T/C		91.41%	93.38%	84.95%
3	**Tumor volume**	0.631±0.276	0.445±0.116	0.494±0.164	0.355±0.074*
	RTV	6.382±1.415	4.608±1.115*	5.547±2.343	3.909±0.860**
	T/C		72.21%	86.91%	61.25%

4	**Tumor volume**	1.564±0.452	0.822±0.189**	0.972±0.315*	0.684±0.186**
	RTV	16.337±4.647	8.760±2.877**	10.904±4.294	7.758±3.395**
	T/C		53.62%	66.74%	47.49%
5	**Tumor volume**	3.748±1.197	1.672±0.260**	1.992±0.302**	1.457±0.167**
	RTV	39.988±14.875	18.025±5.342**	23.785±11.251	16.526±4.809**
	T/C		45.08%	59.48%	41.33%

*P＜0.05， **P＜0.01; **RTV**: relative tumor volume, **T/C:** relative tumor proliferation rates

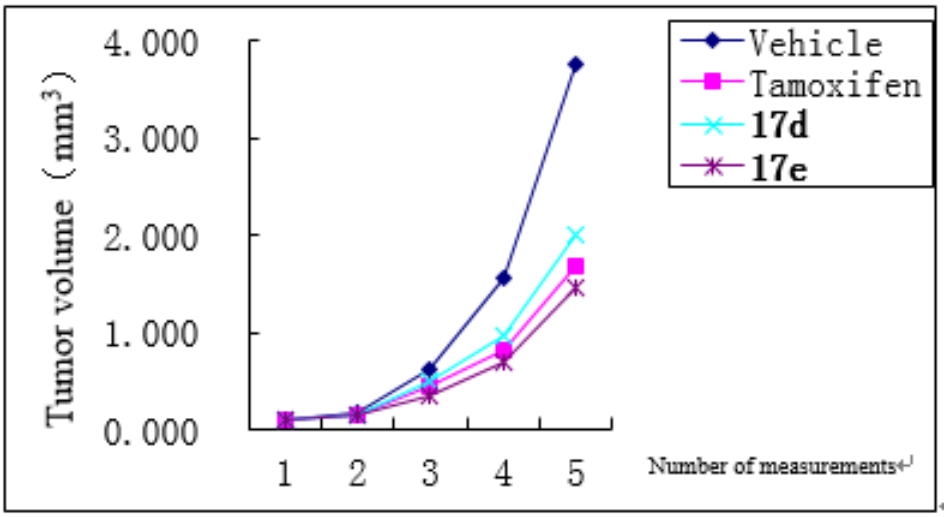


Fig **4.** Anti-tumor activity of **17d** and **17e** assessed using female BALB/c nude mice/MCF-7 xenograft model. Mice were assessed for tumor growth. **17d**, **17e** and Tamoxifen were administrated at a dose of 20 mg/kg once daily for 30 days. Tamoxifen as a positive control. (Measure once every six days, Significance levels p <0.05 and p <0.05 as compared with the respective control)

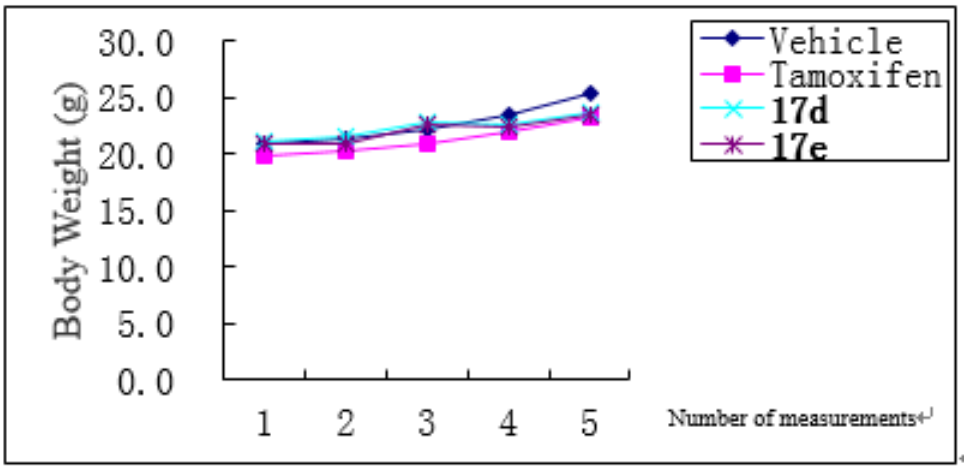


Fig **5.** Anti-tumor activity of **17d** and **17e** assessed using female BALB/c nude mice/MCF-7 xenograft model. Mice were assessed for body weight. **17d**, **17e** and Tamoxifen were administrated at a dose of 20 mg/kg once daily for 30 days. Tamoxifen as a positive control. (Measure once every six days, Significance levels $p > 0.05$ and $p > 0.05$ as compared with the respective control)

4. Discussion

(1) According to the biological evaluation of Podophyllotoxin deritives, we had proved that the D ring of Podophyllotoxin moiety could be replaced with phenyl acrylic acid, which promote activity and target selectivity. (2) During the antiproliferative activities *in vitro*, it was found that when the substituent on the E ring was the electron-withdraw group, 4-NO_2, the antiproliferative activities of compounds were lower, or even missing, mean that the introduction of electron-withdraw group on the E ring decreases the antiproliferative activity. (3) On the E ring, the electron-donating group may have improved the inhibition of tubulin. When the substitutions on the E ring are electro-donating group such as 3, 4-$(OCH_3)_2$ and 3-OCH_3, the inhibitory activity is higher, and selectively inhibit MCF-7 cells. (4) In addition, R4 and R5 also play an important role on the F ring, for example, the pharmacological activity of ferulic acid series was better than that of the series of cinnamon acid and hydroxy cinnamic acid. Thus, the substituent on the benzene ring is an important factor in determining the activity of compounds. (5) After western blot, flow cytometry analysis was also performed, while the data was not enclosed. It is proved that the anti-mitotic drugs arrest cell cycle at G2/M phase in cancer cells due to destruction of the microtubular cytoskeleton, so we can conclude that the cytotoxicity of **17d** and **17e** might not be because of tubulin inhibition. So the mechanism of their cytotoxicity in very low concentration cannot be tubulin inhibition. Above all, the tumor selectivity to MCF-7 cell and mechanism of **17d** and **17e** need further confirmation and research.

5. Conclusions

In summary, we had developed a series of tetrahydroisoquinoline derivatives and explored their antiproliferative activity against a panel of three cancer cell lines. Most of the compounds displayed inhibition activity, especially **17d** and **17e**， which exhibit selectivity to MCF-7 cell. In addition, compounds **17d** and **17e** demonstrated potent *in vivo* efficacy and had very little influence on body weight. These results demonstrate that **17d** and **17e** are promising lead compounds and could be taken for further exploration.

6. Experimental section

6.1 General information. All reagents and anhydrous solvents were obtained from commercial sources and used without further purification unless noted otherwise. Melting points were taken on a WRS-1B melting point apparatus, uncorrected and reported in degrees Centigrade. ^{1}HNMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 (400 MHz) using TMS as internal standard. ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 100 MHz spectrometer, a Bruker 150 MHz spectrometer, using TMS as internal standard.

6.2 Abbreviations used. $CDCl_3$, Deuterochloroform; DMF, N, N-dimethylformamide; ESI-MS, Electron spray ionization mass spectrum; h, Hour; IR, Infrared absorption spectrum; min, Minute; mp, Melting point; NMR, Nuclear magnetic resonance; SRB, Sulforhodamine B; TLC, Thin layer chromatography; DMSO, dimethylsulfoxide; δ(ppm), chemical shift.

Synthesis of *N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4-methoxybenzamide (12d) A mixture of compound **9d** (7.6 g, 50 mmol), $SOCl_2$ 10 mL， toluene 50 mL were added to a round bottom flask. The reaction mixture was heated to 77 °C for 4 h with stirring, then evaporated with toluene under reduced pressure to remove excess thionyl chloride to give compound **10d**.

In a three-neck flask, compound **11** (7.4 g, 45 mmol) was added, NaOH (2.0 g, 50 mmol) and CH_2Cl_2 50 mL, Compound **10d** dissolved in CH_2Cl_2 (10 mL) solution was added drop wise under ice-cooling. After the addition was complete, the reaction was continued for 2.5 h. The reaction mixture was washed with 1% dilute hydrochloric acid (150 mL × 3), 1 mol/L NaOH aqueous solution (150 mL × 3), saturated sodium chloride solution (100 mL × 3) after

washing separately, died with sodium sulphate and evaporated in vacuo. The residues were recrystallized with anhydrous ethanol to afford white solid (10.5 g, yield 78.1 %). mp 120.2-122.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.8 Hz, 2H, Ar**H**), 6.89 (d, *J* = 8.8 Hz, 2H, Ar**H**), 6.75 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.72 (s, 1H, Ar**H**), 6.67 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.13 (s, 1H, N**H**), 5.03 (s, 2H, OC**H**$_2$O), 3.83 (s, 3H, OC**H**$_3$), 3.67-3.62 (m, 2H, NHC**H**$_2$CH$_2$), 2.83 (t, *J* = 6.8 Hz, 2H, NHCH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 162.1, 147.9, 146.2, 132.7, 128.6, 126.9, 121.6, 113.7, 109.0, 108.3, 100.9, 55.3, 41.2, 35.5; IR (KBr, cm^{-1}) υ: 3348.8, 2971.8, 2880.9, 1640.0, 1547.4, 1501.4, 1253.9, 928.1, 847.7, 815.7; ESI-Mass for **$C_{17}H_{17}NO_4$**: m/z $(M+H)^+$ 300.04.

5-(4-methoxyphenyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (14d).

A solution of the prepared Compound **12d** (6.0 g, 20 mmol), $POCl_3$ (12.3 mL, 40 mmol) in toluene 40 mL was stirred at 115 °C for 7 h. The reaction mixture was evaporated in vacuo. The residues were partitioned between CH_2Cl_2 and water. The organic phase was dried over sodium sulphate and evaporated in vacuo to give the **13d** (4.6 g, yield 81.7 %).

A mixture of **13d** (4.6 g, 16 mmol) was dissolved in CH_3OH (20 mL), and $NaBH_4$ (1.1 g, 29 mmol) was added portion-wise under ice-cooling, and stirred 4h at 0 °C . The reaction mixture was evaporated. The residues were partitioned between CH_2Cl_2 and water. The organic phase was dried over sodium sulphate and evaporated in vacuo. The residue was recrystallized from 40 mL of methanol to give a white solid (3.5 g, yield 76.0 %). mp 98.5-100.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H, Ar**H**), 6.64 (d, *J* = 8.4 Hz, 2H, Ar**H**), 6.58 (s,1H, Ar**H**), 6.21 (s, 1H, Ar**H**), 5.83 (s, 2H, OC**H**$_2$O), 4.95 (s, 1H, C**H**NH), 3.78 (s, 3H, OC**H**$_3$), 3.23-3.1 (m, 1H, NHC**H**$_2$CH$_2$), 3.04-2.97 (m, 1H, NHC**H**$_2$CH$_2$), 2.95-2.88 (m, 1H, NHCH$_2$C**H**$_2$), 2.73-2.67 (m, 1H, NHCH$_2$C**H**$_2$), 2.58 (br, 1H, N**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 146.0, 145.6, 136.6, 131.2, 129.9, 128.4, 113.8, 108.4, 107.9, 100.5, 61.3, 55.2, 42.0, 29.6; IR (KBr, cm^{-1}) υ: 3238.5, 2929.6, 2874.5, 1610.1, 1509.9, 1479.0, 1374.8, 123.1, 1033.0, 933.0, 813.3; ESI-Mass for **$C_{17}H_{17}NO_3$**: m/z $(M+H)^+$ 283.97.

(*E*)-2-methoxy-4-(3-(5-(4-methoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5*H*)-yl)-3-oxoprop-1-en-1-yl)phenyl acetate (16d). A mixture of **14d** (1.0 g, 3.4 mmol), Et_3N (3.5 mL, 25.3mmol) in CH_2Cl_2 (30 mL), compound **15a** (1.30g, 5.1mmol) dissolved in CH_2Cl_2 (10 mL) solution was added drop wise under ice-cooling. After the addition was complete, the mixture was stirred for 2.5 h and monitored by TLC. The reaction mixture was washed with 1 % dilute hydrochloric acid (150 mL × 3), 1 mol/L NaOH aqueous

solution (150 mL × 3), saturated sodium chloride solution (100 mL × 3) after washing separately, died with sodium sulphate and evaporated in vacuo. The residues were recrystallized with anhydrous ethanol to afford yellow solid (1.1g, yield 60.1 %). mp 95.8-97.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.2 Hz, 1H, CH=C**H-**Ar), 7.21 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.13 (d, *J* = 7.6 Hz, 2H, Ar**H**), 7.06 (s, 1H, Ar**H**), 7.02 (d, *J* = 8.4 Hz, 1H, Ar**H**), 6.90 (s, 1H, Ar**H**), 6.85-6.80 (m, 3H, C**H**=CH**-**Ar**,** Ar**H**), 6.54 (s, 1H, Ar**H**), 5.93 (d, *J* = 8.4 Hz, 1H, OC**H**$_2$O), 3.95-3.90 (m, 1H, NC**H**$_2$CH$_2$), 3.86 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.54 -3.47 (m, 1H, NC**H**$_2$CH$_2$), 2.99-2.87 (m, 1H, NCH$_2$C**H**$_2$), 2.78-2.65 (m, 1H, NCH$_2$ C**H**$_2$), 2.32 (s, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$). δ: 168.8, 165.0, 158.8, 151.2, 146.7, 146.2, 142.5, 140.7, 134.5, 134.3, 129.9, 128.57, 128.50, 127.4, 123.1, 120.3, 117.6, 113.9, 113.5, 111.5, 108.5, 108.1, 100.9, 55.9, 55.2, 55.0, 39.6, 29.4, 20.6; IR (KBr, cm^{-1}) υ: 3003.3, 2932.5, 2362.7, 1764.6, 1646.8, 1604.2, 1434.4, 1242.2, 1035.3, 941.2, 826.7; ESI-Mass for **C$_{29}$H$_{27}$NO$_7$**: m/z (M+H) $^+$ 501.98.

(*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(5-(4-methoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4, 5-g]isoquinolin-6(5*H*)-yl)prop-2-en-1-one (17d). To a mixture of **16d** (1.1 g, 2.2 mmol) in methanol 30 mL, 10 mL NaOH (9.4 × 10^{-2} g, 24 mmol) in aqueous methanol was added. The reaction mixture was stirred at room temperature for 24 h, then evaporated. The residue was diluted with 3% HCl (liq.) was slowly added drop wise to pH = 4-5 to give a yellow solid, filtration and drying. The crude product was purified on silica using (Ethyl acetate/PE = 2:1) to provide the title compound as an off-white solid (0.58 g, yield 58 %). mp 106.5-108.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.0Hz, 1H, CH = C**H-**Ar), 7.22-7.09 (m, 3H, Ar**H**), 6.98 (br, 1H, Ar**H**), 6.91 (d, *J* = 8.0Hz, 2H, Ar**H**), 6.81 (d, *J* = 8.0Hz, 2H, Ar**H**), 6.73(d, *J* = 16.0, 1H, C**H** = CH**-**Ar), 6.64 (s, 1H, Ar**H**), 6.55 (s, 1H, C**H**N), 5.93 (d, *J* = 7.2Hz, 2H, OC**H**$_2$O), 3.98-3.94 (m, 1H, NC**H**$_2$CH$_2$), 3.92 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.53-3.46 (m, 1H, NC**H**$_2$CH$_2$), 2.98-2.94 (m, 1H, NCH$_2$C**H**$_2$), 2.78-2.64 (m, 1H, NCH$_2$C**H**$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5, 158.9, 147.3, 146.7, 146.3, 143.4, 134.7, 129.9, 128.7, 128.6, 127.9, 127.6, 121.9，114.8, 113.9, 113.6, 110.0, 108.6, 108.2, 101.0, 56.0, 55.3, 55.0, 39.6, 29.4; IR (KBr, cm^{-1}) υ: 3423.0, 2932.1, 1640.2, 1510.9, 1433.9, 1239.4, 924.2, 817.2; ESI-Mass for **C$_{27}$H$_{25}$NO$_6$**: m/z (M-H) $^+$ 458.25.

(*E*)-1-(5-(4- methylphenyl)-7,8-dihydro-[1, 3] dioxole and [4,5-g] isoquinoline-6(5H)-yl)-3- (4-hydroxy-3-methoxyphenyl) prop-2-en-1-one (**17a**). Compound **17a** was prepared from **16a** according to procedure used for **17d** synthesis. White solid, yield 60 %, mp 110.7-112.9 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.2 Hz, 1H, CH=C**H-**Ar), 7.18 (d, *J* = 7.2 Hz, 1H, Ar**H**), 7.11-7.092 (m, 4H, Ar**H**), 6.98(s, 1H, Ar**H**), 6.92 (d, *J* = 8.4 Hz,

2H, Ar**H**), 6.77 (d, *J* = 15.2 Hz, 1H, C**H**=CH-Ar), 6.64 (s, 1H, Ar**H**), 6.56 (s, 1H, C**H**N), 5.94 (d, *J* = 7.8 Hz, 2H, OC**H**$_2$O), 4.03-3.99 (m, 1H, NC**H**$_2$CH$_2$), 3.92 (s, 3H, OC**H**$_3$), 3.54-3.49 (m, 1H, NC**H**$_2$CH$_2$), 2.95-2.91 (m, 1H, NCH$_2$C**H**$_2$), 2.78-2.69 (m, 1H, NCH$_2$C**H**$_2$), 2.31 (s, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 147.4, 146.7, 143.4, 139.5, 137.1, 128.3, 128.9, 128.6, 127.8, 127.6, 127.3, 121.9, 114.8, 114.7, 110.0, 108.6, 108.1, 101.0, 56.0, 39.8, 29.4, 21.1; IR (KBr, cm^{-1}) υ: 3173.1, 2590.9, 1640.7, 1575.1, 1511.1, 1454.3, 1279.2, 1034.4, 921.5, 813.8; ESI-Mass for **$C_{27}H_{25}NO_5$**: m/z $(M+H)^+$ 444.10.

(*E*)-1-(5-(4-chlorophenyl)-7,8-dihydro-[1,3]dioxole and[4,5-g]isoquinoline-6(5H)-yl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (**17b**). Compound **17b** was prepared from **16b** according to procedure used for **17d** synthesis White solid, yield 57 %, mp 108.7-110.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.2 Hz, 1H, CH=C**H**-Ar), 7.26-7.24 (m, 4H, Ar**H**), 7.11 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.99(s, 1H, Ar**H**), 6.92 (d, *J* = 8.4 Hz, 2H, Ar**H**), 6.76 (d, *J* = 15.2 Hz, 1H, C**H**=CH-Ar), 6.65 (s, 1H, Ar**H**), 6.54 (s, 1H, C**H**N), 5.94(d, *J* = 7.9Hz, 2H, OC**H**$_2$O), 3.98-3.95 (m, 1H, NC**H**$_2$CH$_2$), 3.92 (s, 3H, OC**H**$_3$), 3.52-3.45 (m, 1H, NC**H**$_2$CH$_2$), 2.95-2.91 (m, 1H, NCH$_2$C**H**$_2$), 2.77-2.73 (m, 1H, NCH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 147.4, 146.9, 146.7, 146.3, 143.7, 140.8, 133.2, 129.9, 128.7, 128.3, 127.9, 127.7, 121.9, 114.7, 114.3, 110.0, 108.4, 108.3, 101.0, 55.9, 55.0, 39.9, 29.2; IR (KBr, cm^{-1}) υ: 3182.2, 2933.6, 1640.8, 1590.3, 1511.2, 1430.9, 1275.1, 1235.9, 1035.9, 922.3, 844.9, 812.3; ESI-Mass for **$C_{26}H_{22}Cl\ NO_5$**: m/z $(M+H)^+$ 464.06.

(*E*)-1-(5-(4-nitrophenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinoline-6(5H)-yl)-3-(4-hydroxy-3-methoxyphenyl) prop-2-en-1-one (**17c**). Compound **17c** was prepared from **16c** according to procedure used for **17d** synthesis. Yellow solid, yield 68 %. mp 104.3-105.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15(d, *J* = 7.2 Hz, 2H, Ar**H**), 7.74 (d, *J* = 16.0 Hz, 1H, CH=C**H**-Ar), 7.48 (d, *J* = 7.2 Hz, 2H, Ar**H**), 7.13 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.00 (s, 1H, Ar**H**), 6.96 (s, 1H, Ar**H**), 6.93 (d, *J* = 7.2 Hz, 1H, Ar**H**), 6.78 (d, *J* = 16.0 Hz, 1H, C**H**=CH-Ar), 6.69 (s, 1H, Ar**H**), 6.56 (s, 1H, C**H**N), 5.97 (d, *J* = 5.2 Hz, 2H, OCH_2O), 4.03-3.99 (m, 1H, NC**H**$_2$CH$_2$), 3.93 (s, 3H, OC**H**$_3$), 3.56-3.51(m, 1H, NC**H**$_2$CH$_2$), 3.01-2.97 (m, 1H, NCH$_2$C**H**$_2$), 2.78-2.72 (m, 1H, NCH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.6, 147.7, 147.3, 147.2, 146.8, 146.6, 144.3, 129.3, 127.9, 127.6, 127.2, 123.5, 122.1, 114.9, 114.0, 110.1, 108.5, 108.3, 101.2, 56.0, 55.3, 40.5, 29.1; IR (KBr, cm^{-1}) υ: 3440.1, 2931.4, 1641.4, 1596.5, 1515.0, 1430.2, 1346.9, 1274.5, 1238.4, 1036.1, 924.6, 815.5; ESI-Mass for **$C_{26}H_{22}N_2O_7$**: m/z $(M-H)^+$ 473.21.

(*E*)-1-(5-(3,4-dimethoxyphenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinolinemorpholine-6(5H)-yl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (**17e**). Compound **17e** was prepared from **16e** according to procedure used for **17d** synthesis. White solid, yield 59 %, mp 120.7-123.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.2 Hz, 1H, CH=C**H**-Ar), 7.11 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.99 (s, 2H, Ar**H**), 6.91 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.77-6.73 (m, 2H, Ar**H**, C**H**=CH-Ar), 6.66 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.57 (s,1H, C**H**N), 5.95 (d, *J* = 6.4 Hz, 2H, OC$\mathbf{H}_2$O), 3.99-3.94 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 3.92 (s, 3H, OC$\mathbf{H}_3$), 3.84-3.76 (m, 6H, OC$\mathbf{H}_3$×2), 3.54-3.47 (m, 1H,NC$\mathbf{H}_2$CH$_2$), 2.98-2.91 (m, 1H, NCH$_2$C$\mathbf{H}_2$), 2.78-2.74 (m, 1H, NCH$_2$C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 148.9, 148.4, 147.5, 146.8, 146.2, 143.4, 135.2, 135.1, 128.5, 127.8, 127.6, 121.8, 121.0, 114.9, 114.7, 112.3, 110.5, 110.1, 108.6, 108.2, 100.9, 56.0, 55.9, 55.3, 39.7, 29.4; IR (KBr, cm^{-1}) υ: 3425.2, 2932.3, 1639.8, 1590.6, 1511.8, 1443.7, 1265.7, 1236.3, 1032.9, 927.8, 817.9; ESI-Mass for **$C_{28}H_{27}NO_7$**: m/z (M-H)$^+$ 488.18.

(*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(5-(3-hydroxy-4-methoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)prop-2-en-1-one(**17f**). Compound **17f** was prepared from **16f** according to procedure used for **17d** synthesis. White solid, yield 45 %， mp 132.4-134.9°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 15.2 Hz, 1H, CH=C**H**-Ar), 7.09 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.97 (s, 1H, Ar**H**), 6.90 (d, *J* = 8.4 Hz, 1H, Ar**H**), 6.86-6.82 (m, 2H, Ar**H**), 6.79 (s, 1H, Ar**H**), 6.76-6.69 (m,2H, Ar**H**,C**H**=CH-Ar), 6.62 (s, 1H, Ar**H**), 6.54-6.46 (m,1H, Ar**H**), 5.93 (br, 2H, OC$\mathbf{H}_2$O), 4.14-4.09 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 3.91 (s, 3H, OC$\mathbf{H}_3$), 3.85 (s, 3H, OC$\mathbf{H}_3$), 3.55-3.51 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 2.95-2.86 (m, 1H, NCH$_2$C$\mathbf{H}_2$), 2.76-2.63 (m, 1H, NCH$_2$C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 147.3, 146.6, 146.2, 145.8, 145.2, 143.4, 135.7, 128.5, 127.8, 127.6, 127.5, 121.6, 120.6, 114.9, 114.7, 110.3, 109.9, 108.6, 108.1, 100.9, 55.9, 55.0, 39.7, 29.3; IR (KBr, cm^{-1}) υ: 3400.0, 2936.1, 1639.4, 1587.3, 1510.9, 1436.2, 1272.1, 1124.5, 1033.5, 924.4, 815.8; ESI-Mass for **$C_{27}H_{25}NO_7$**: m/z (M+H)$^+$ 476.18.

(*E*)-1-(1-(4-methoxyphenyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline-2(1H)-yl)-3- (4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (**17g**). Compound **17g** was prepared from **16g** according to procedure used for **17d** synthesis. White solid, yield 51 %, mp 120.7-122.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$). δ 7.71 (d, *J* = 15.2 Hz, 1H, CH=C**H**-Ar), 7.22(d, *J* = 8.4 Hz, 1H, Ar**H**), 7.12 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.99 (s, 2H, Ar**H**), 6.92(d, *J* = 8.0 Hz, 1H, Ar**H**), 6.82 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.78(d, *J* = 15.6 Hz, 1H, C**H**=CH-Ar), 6.66 (s, 1H, Ar**H**), 6.56 (s, 1H, C**H**N), 4.01-3.97 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 3.93 (s, 3H, OC$\mathbf{H}_3$), 3.89 (s, 3H, OC$\mathbf{H}_3$), 3.78 (s, 6H, OC$\mathbf{H}_3$×2), 3.50-3.44 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 2.99-2.95 (m, 1H, NCH$_2$C$\mathbf{H}_2$), 2.80-2.76

(m, 1H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 158.8, 148.0, 147.9, 147.6, 147.2, 143.4, 134.8, 130.0, 128.8, 127.5, 127.4, 126.4, 121.9, 115.2, 114.5, 113.5, 111.3, 111.1, 110.3, 56.0, 55.9, 55.2, 54.6, 39.9, 29.0; IR (KBr, cm^{-1}) υ: 3399.0, 3000.3, 2935.9, 2835.7, 1640.3, 1603.7, 1512.8, 1443.4, 1252.6, 1173.5, 1115.8, 1029.6, 976.7, 818.5; ESI-Mass for **$C_{28}H_{29}NO_6$**: m/z (M^+-H) 474.00.

(*E*)-1-(5-(4-methoxyphenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinolin-6(5H)-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**17j**). Compound **17j** was prepared from **16j** according to procedure used for **17d** synthesis. White solid, yield 50 %, mp 120.6-122.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 14.8 Hz, 1H, CH=C**H**-Ar), 7.39 (d, *J* = 7.2 Hz, 2H, Ar**H**), 7.20 (d, *J* = 8.4 Hz, 1H, Ar**H**), 7.12 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.90 (s, 1H, Ar**H**), 6.84-6.79 (m, 4H, Ar**H**), 6.75 (d, *J* = 14.8 Hz, 1H, C**H**=CH-Ar), 6.64 (s, 1H, Ar**H**), 6.54 (s, 1H, C**H**N), 5.93 (d, *J* = 8.4 Hz, 2H, OCH_2O), 3.98-3.93 (m, 1H, NCH_2CH_2), 3.77 (s, 3H, OCH_3), 3.53-3.46 (m, 1H, NCH_2CH_2), 2.96-2.89 (m, 1H, NCH_2CH_2), 2.78-2.73 (m, 1H, NCH_2CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 158.8, 158.3, 146.6, 146.2, 143.8, 134.3, 129.8, 129.7, 129.6, 128.5, 128.4, 127.4, 115.9, 113.9, 113.5, 108.5, 108.1, 100.9, 55.27, 55.22, 39.7, 29.3; IR (KBr, cm^{-1})υ: 3158.7, 2952.8, 1639.4, 1240.1, 1169.3, 977.9, 825.3; ESI-Mass for **$C_{26}H_{23}NO_5$**: m/z (M+H) $^+$430.17.

(*E*)-1-(5-(3,4-dimethoxyphenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinolinemorpholine-6(5H)-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**17k**). Compound **17k** was prepared from **16k** according to procedure used for **17d** synthesis. White solid, yield 52 %, mp 125.6-127.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68(d, *J* = 15.2 Hz, 1H, CH=C**H**-Ar), 7.38 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.99 (s, 1H, Ar**H**), 6.90 (s, 1H, Ar**H**), 6.85 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.74 (m, 2H, Ar**H**,C**H**=CH-Ar), 6.64 (br, 2H, Ar**H**), 6.55 (s, 1H, C**H**N), 5.93 (d, *J* = 10.8 Hz, 2H, OCH_2O), 3.98-3.94 (m, 1H, NCH_2CH_2),3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.54-3.49 (m, 1H, NCH_2CH_2), 2.99-2.92 (m, 1H, NCH_2CH_2), 2.79-2.75 (m,1H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 148.8, 148.3, 146.6, 146.1, 143.1, 135.2, 135.0, 129.6, 128.8, 127.7, 121.0, 117.2, 112.0, 110.2, 108.7, 108.5, 108.1, 107.9, 100.9, 55.9, 55.8, 55.2, 39.6, 29.4; IR (KBr, cm^{-1}) υ: 3159.4, 2935.2, 1639.3, 1444.5, 1236.1, 1032.6, 925.5, 824.5; ESI-Mass for **$C_{26}H_{23}NO_5$**: m/z (M+H) $^+$460.10.

(*E*)-1-(5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinoline-6(5H)-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**17h**). Compound **17h** was prepared from **16h** according to procedure used for **17d** synthesis. White solid, yield 44 %, mp 128.6-130.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67(d, *J* =15.6 Hz, 1H, CH=C**H**-Ar), 7.36 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.87-6.85 (m, 3H, Ar**H**), 6.76 (d, *J* = 15.2 Hz, 1H, C**H**=CH-Ar), 6.67-6.65 (m,1H, Ar**H**), 6.56 (s, 1H, Ar**H**), 6.51-6.41 (m, 2H, Ar**H,** C**H**N), 5.94 (d, *J* = 8.0 Hz, 2H, OC$\mathbf{H}_2$O), 4.01-3.98 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 3.81 (s, 3H, OC$\mathbf{H}_3$), 3.75 (s, 6H, OC$\mathbf{H}_3$×2), 3.57-3.49 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 3.00-2.92 (m, 1H, NCH$_2$C$\mathbf{H}_2$), 2.81-2.73 (m, 1H, NCH$_2$C$\mathbf{H}_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 158.5, 152.9, 146.6, 146.2, 143.8, 134.3, 129.8, 129.6, 128.5, 127.4, 115.9, 113.9, 113.5, 108.5, 108.1, 100.9, 55.7, 55.2, 55.22, 39.7, 29.3; IR (KBr, cm^{-1}) υ: 3159.7, 2937.0, 1639.3, 1125.9, 1038.0, 924.0, 826.5; ESI-Mass for $\mathbf{C_{28}H_{27}NO_7}$: m/z $(M+H)^+$490.00.

(*E*)-1-(5-(4-nitrophenyl)-7,8-dihydro-[1,3]dioxole and[4,5-g]isoquinoline-6(5H)-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**17i**). Compound **17i** was prepared from **16i** according to procedure used for **17d** synthesis. Yellow solid, yield 62 %, mp 107.7-109.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.4 Hz, 2H, Ar**H**), 7.72(d, *J* = 15.6 Hz, 1H, CH=C**H**-Ar), 7.46 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.40 (d, *J* = 7.6 Hz, 2H, Ar**H**), 6.94 (s,1H, Ar**H**), 6.84 (d, *J* = 7.6 Hz, 2H, Ar**H**), 6.76 (d, *J* = 15.2 Hz, 1H, C**H**=CH-Ar), 6.68 (s, 1H, Ar**H**), 6.55 (s, 1H, C**H**N), 5.97 (d, *J* = 6.4 Hz, 2H, OC$\mathbf{H}_2$O), 4.00-3.91 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 3.55-3.50 (m, 1H, NC$\mathbf{H}_2$CH$_2$), 2.99-2.93 (m, 1H, NCH$_2$C$\mathbf{H}_2$), 2.78-2.74 (m, 1H, NCH$_2$C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.3, 149.3, 147.3, 147.1, 146.6, 144.5, 129.7, 129.2, 127.8, 127.0, 123.5, 116.0, 113.3, 109.4, 108.5, 108.3, 101.2, 55.6, 40.7, 29.0; IR (KBr, cm^{-1}) υ: 3134.2, 1719.6, 1639.2, 1605.7, 1514.3, 1346.6, 1238.4, 1168.1, 923.6, 825.9; ESI-Mass for $\mathbf{C_{25}H_{20}N_2O_6}$: m/z $(M+H)^+$ 445.14.

Synthesis of Compound **19d**. To a mixture of **18** (0.20 g, 1.3 mmol), K_2CO_3 (0.5 g, 3.6 mmlol), KI (0.1 g, 0.6 mmlol) in isopropanol 10 mL were stirred at room temperature for 3 h, which were add to the mixture of compounds **17d** (0.46 g, 1 mmol), K_2CO_3 (0.5 g, 3.6 mmol), and isopropanol 10 mL in a single neck flask. The mixture were reacted at 85 °C for 4 h then evaporated in *vacuo* to give the crude product. The crude product was purified on silica using MeOH/CH_2Cl_2 6 % to provide the title compound. Recrystallized with EtOH/PE = 10:1 to give a yellow solid (0.26 g, yield 45 %)

(*E*)-3-(4-(3-(dimethylamino)propoxy)-3-methoxy-phenyl)-1-(5-(4-methoxyphenyl) -7,8-di hydro-[1, 3]dioxole[4,5-g]isoquinoline-6(5H)-yl)prop-2-en-1-one (**19d**).
Yellow solid, yield 45 %, mp 150.4-153.9 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68(d, *J* = 15.2 Hz, 1H, CH=C**H**-Ar), 7.21 (d, *J* =8.0 Hz, 2H, Ar**H**), 7.09 (d, *J* = 7.6 Hz, 1H, Ar**H**), 7.02 (s, 1H, Ar**H**), 6.91-6.87 (m, 2H, Ar**H**), 6.81 (d, *J* = 8.4 Hz, 2H, Ar**H**), 6.75(d, *J* = 15.2 Hz, 1H, C**H**=CH-Ar), 6.63 (s, 1H, Ar**H**), 6.55 (s, 1H, C**H**N), 5.92 (d, *J* = 7.6 Hz, 2H, OC$\mathbf{H}_2$O), 4.10

(t, *J* = 6.8 Hz, 2H, OC**H**$_2$CH$_2$), 3.98-3.94 (m, 1H, NC**H**$_2$CH$_2$), 3.89 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.53-3.47 (m, 1H, NC**H**$_2$CH$_2$), 2.99-2.91 (m, 1H, NCH$_2$C**H**$_2$), 2.77-2.73 (m, 1H, NCH$_2$C**H**$_2$), 2.47 (t, *J* = 6.8 Hz, 2H, CH$_2$CH$_2$C**H**$_2$N), 2.25 (s, 6H, C**H**$_3$×2), 2.06-1.99 (m, 2H, CH$_2$C**H**$_2$CH$_2$N); ^{13}C NMR (100MHz, CDCl$_3$) δ 165.3, 158.7, 150.0, 149.3, 146.6, 146.2, 143.2, 134.6, 130.4, 129.8, 128.7, 128.6, 128.2, 127.5, 121.7, 114.9, 113.5, 112.5, 110.5, 108.5, 108.1, 100.9, 67.2, 56.2, 56.0, 55.2, 54.9, 45.4, 39.5, 29.4, 27.3; IR (KBr, cm^{-1}) υ: 3077.6, 2944.3, 2823.0, 1641.3, 1510.8, 1456.4, 1259.7, 1170.0, 1032.3, 922.0, 801.2; ESI-Mass for **C$_{32}$H$_{36}$N$_2$O$_6$**: m/z (M+H)$^+$ 545.37.

(*E*)-3-(4-(3-(dimethylamino)propoxy)-3-methoxy-phenyl)-1-(5-(3,4-dimethoxyphenyl)-7, 8-dihydro-[1, 3]dioxole and[4,5-g]isoquinoline-6(5H)-yl)prop-2-en-1-one (**19e**). Compound **19e** was prepared from **17e** according to procedure used for **19d** synthesis. Yellow solid, yield 42 %， mp 148.7-149.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, *J* = 15.6Hz, 1H, CH=C**H**-Ar), 7.11-7.09 (m, 1H, Ar**H**), 7.03 (s, 1H, Ar**H**), 6.99 (s, 1H, Ar**H**), 6.88 (d, *J* = 8.4, 1H, Ar**H**), 6.80 (s, 1H, Ar**H**), 6.76-6.73 (m, 2H, Ar**H,** C**H**=CH-Ar), 6.65 (d, *J* = 8.8Hz, 2H, Ar**H**), 6.56 (s, 1H, C**H**N), 5.93 (d, *J* = 10.4Hz, 2H, OC**H**$_2$O), 4.11 (t, *J* = 6.5Hz, 2H, OC**H**$_2$CH$_2$), 4.00-3.97 (m, 1H, NC**H**$_2$CH$_2$), 3.89 (s, 3H, OC**H**$_3$), 3.83-3.82 (m, 6H, OC**H**$_3$×2), 3.79-3.76 (m, 1H, NC**H**$_2$CH$_2$), 3.53-3.45 (m, 1H, NCH$_2$C**H**$_2$), 2.79-2.75 (m, 1H, NCH$_2$C**H**$_2$), 2.69 (t, *J* = 7.2Hz, 2H, CH$_2$CH$_2$C**H**$_2$N), 2.40 (s, 6H,C**H**$_3$×2), 2.15-2.08 (m, 2H, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.4, 149.3, 146.6, 143.0, 136.2, 131.1, 128.5, 128.4, 127.6, 127.5, 122.0, 121.6, 120.9, 115.2, 112.9, 112.1, 110.5, 108.1,100.9, 100.6, 68.8, 66.9, 56.1, 56.0, 55.9, 55.8, 51.4, 44.8, 43.8, 29.4; IR (KBr, cm^{-1}) υ: 3443.6, 2938.0, 1641.7, 1594.0, 1511.1, 1479.6, 1333.9, 1233.3, 1138.3, 1031.9, 932.9, 865.3; ESI-Mass for **C$_{33}$H$_{38}$N$_2$O$_7$**: m/z (M+H)$^+$ 575.24.

(*E*)-3-(4-(3-(dimethylamino)propoxy)-3-methoxy-phenyl)-1-(5-(4-nitrophenyl)-7, 1,8-hyd rogen-[1, 3]dioxole[4,5-g]isoquinoline-6(5H)-yl)prop-2-en-1-one (**19c**). Compound **19c** was prepared from **17c** according to procedure used for **19d** synthesis. Yellow solid, yield 50 %， mp 141.7-143.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.13 (d, *J* = 8.0Hz, 2H, Ar**H**), 7.72 (d, *J* = 15.2Hz, 1H, CH=C**H**-Ar), 7.47 (d, *J* = 8.0Hz, 2H, Ar**H**), 7.12(d, *J* = 8.0Hz, 1H, Ar**H**), 7.02 (s, 1H, Ar**H**), 6.95 (s, 1H, Ar**H**), 6.89 (d, *J* = 8.0Hz, 1H, Ar**H**), 6.78 (d, *J* = 16.0Hz, 1H, C**H**= CH-Ar), 6.68 (s, 1H, Ar**H**), 6.55 (s, 1H, C**H**N), 5.97 (d, *J*=5.6Hz, 2H, OC**H**$_2$O), 4.15 (t, *J* = 6.0Hz, 2H, OC**H**$_2$CH$_2$), 4.01-3.98(m, 1H, NC**H**$_2$CH$_2$),3.89 (s, 3H, OC**H**$_3$), 3.55-3.49 (m, 1H, NC**H**$_2$CH$_2$), 2.97 (t, *J* = 6.8Hz, 3H, CH$_2$CH$_2$C**H**$_2$N,NCH$_2$C**H**$_2$), 2.79-2.75 (m, 1H, NCH$_2$C**H**$_2$), 2.60 (s, 6H, C**H**$_3$×2), 2.30-2.24 (m, 2H, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.6, 149.4, 146.6, 143.9, 131.9, 130.0, 129.3, 128.5, 127.8, 127.0, 123.7,

123.5, 122.7, 121.7, 118.3, 114.6, 113.1, 110.7, 108.5, 108.3, 103.5, 101.2, 66.6, 56.1, 56.0, 55.2, 44.2, 29.1, 25.7; IR (KBr, cm^{-1}) υ: 3131.2, 3068.4, 2930.6, 2362.9, 1648.3, 1597.5, 1513.4, 1426.8, 1345.5, 1246.3, 1138.3, 1034.5, 812.6; ESI-Mass for $\mathbf{C_{31}H_{33}N_3O_7}$: m/z $(M-H)^+$ 558.26.

(*E*)-1-(5-(4-methoxyphenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinolin-6(5H)-yl)-3-phenyl-2-en-1-one (**21d**). Compound **21d** was prepared from **14d** according to procedure used for **16d** synthesis. White solid, yield 70 %, mp 105.7-107.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 15.4 Hz, 1H, CH=C**H**-Ar), 7.53-7.51 (m, 2H, Ar**H**), 7.39-7.35 (m, 3H, Ar**H**), 7.21 (d, *J* = 6.8 Hz, 2H, Ar**H**), 7.14 (s, 1H, Ar**H**), 6.90 (t, *J* = 6.4 Hz, 1H, Ar**H**), 6.83-6.80 (m, 2H, C**H**=CH-Ar, Ar**H**), 6.63 (s, 1H, Ar**H**), 6.54 (s, 1H, C**H**N), 5.91 (d, *J* = 6.8 Hz, 2H, OCH_2O), 4.00-3.93 (m, 1H, NCH_2CH_2), 3.76 (s, 3H, OCH_3), 3.53-3.45 (m, 1H, NCH_2CH_2), 2.97-2.88 (m, 1H, NCH_2CH_2), 2.77-2.72 (m, 1H, NCH_2CH_2); ^{13}C NMR (100MHz, $CDCl_3$) δ 158.9, 146.7, 146.3, 143.1, 135.3, 134.6, 129.9, 129.6, 128.8, 128.6, 128.5, 127.7, 127.5, 117.4, 113.6, 108.5, 108.1, 100.9, 55.2, 55.0, 39.6, 29.4; IR (KBr, cm^{-1}) υ: 3015.2, 2897.8, 2836.4, 1645.0, 1595.2, 1481.6, 1236.9, 1173.3, 1033.9, 918.6, 818.5; ESI-Mass for $\mathbf{C_{26}H_{23}NO_4}$: m/z $(M+H)^+$ 414.12.

(*E*)-1-(5-(3,4-dimethoxyphenyl)-7,8-dihydro-[1,3]dioxole and[4,5-g]isoquinolinemorpholine-6(5H)-yl)-3-phenyl-2-en-1-one (**21e**). Compound **21e** was prepared from **14e** according to procedure used for **16d** synthesis. White solid, yield 71 %, mp 107.6-109.8°C. ^{1}HNMR (400 MHz, $CDCl_3$). δ: 7.74(d, *J* =15.2 Hz, 1H, CH=C**H**-Ar), 7.54-7.52(m, 2H, Ar**H**), 7.37-7.35(m, 3H, Ar**H**), 7.00(s, 1H, Ar**H**), 6.93-6.90(m, 2H, Ar**H**, C**H**=CH-Ar), 6.74(d, *J* =8.0 Hz, 1H, Ar**H**), 6.67(s, 1H, Ar**H**), 6.64(s, 1H, Ar**H**),6.56(s, 1H, C**H**N), 5.93(d, *J* =10.0 Hz, 2H, OCH_2O), 3.99-3.95(m, 1H, NCH_2CH_2), 3.84(s, 6H, OCH_3×2), 3.54-3.48(m, 1H, NCH_2CH_2), 2.99-2.91(m, 1H, NCH_2CH_2), 2.79-2.71(m, 1H, NCH_2CH_2); ^{13}C-NMR (150 MHz, $CDCl_3$) δ:165.2, 148.8, 148.3, 146.6, 146.1, 143.1, 135.2, 135.0, 129.6, 128.8, 127.7, 127.5, 121.0, 117.2, 112.0, 110.2, 108.7, 108.5, 108.1, 107.9, 100.9, 55.9, 55.8, 55.2, 39.6, 29.4; IR (KBr, cm^{-1}) υ: 3014.4, 2955.5, 2925.7, 1643.3, 1483.2, 1454.7, 1230.5, 1191.3, 973.2, 921.1, 846.6; ESI-Mass for $\mathbf{C_{27}H_{25}NO_5}$: m/z $(M+H)^+$444.06.

(*E*)-1-(5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinoline-6(5H)- yl)-3-phenyl-2-en-1-one (**21f**). Compound **21f** was prepared from **14h** according to procedure used for **16d** synthesis. White solid, yield 68 %, mp 109.6-110.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.0 Hz, 1H, CH=C**H**-Ar), 7.54-7.51 (m, 2H, Ar**H**), 7.41-7.36

(m, 3H, Ar**H**), 6.95-6.87 (m, 2H, Ar**H,**C**H**=CH**-**Ar), 6.64 (s,1H, Ar**H**), 6.57 (s, 1H, Ar**H**), 6.52 (s, 1H, Ar**H**), 6.42 (s, 1H, C**H**N), 5.93(d, *J* = 14.8 Hz, 1H, OC**H**$_2$O), 4.01-3.97 (m, 1H, NC**H**$_2$CH$_2$), 3.82 (s, 3H, OC**H**$_3$), 3.77 (s, 6H, OC**H**$_3$×2), 3.57-3.51 (m, 1H, NC**H**$_2$CH$_2$), 2.98-2.91 (m, 1H, NCH$_2$C**H**$_2$), 2.80-2.75 (m, 1H, NCH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.9, 146.7, 146.3, 143.1, 135.3, 134.6, 129.9, 129.6, 128.8, 128.6, 128.5, 127.7, 127.5, 117.4, 113.6, 108.5, 108.1, 100.9, 55.2, 55.0, 39.6, 29.4; IR (KBr, cm^{-1}) υ: 2934.9, 2834.6, 1645.8, 1501.8, 1423.5, 1235.9, 1125.7, 923.4, 848.8; ESI-Mass for **C$_{28}$H$_{27}$NO$_6$**: m/z (M+H)$^+$474.30.

(*E*)-1-(5-(4-nitrophenyl)-7,8-dihydro-[1, 3]dioxole and[4,5-g]isoquinoline-6 (5H)-yl)-3-phenyl-2-en-1-one (**21c**). Compound **21c** was prepared from **14c** according to procedure used for **16d** synthesis. Yellow solid, yield 75 %, mp 113.6-114.9 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14(d, *J* = 8.4 Hz, 2H, Ar**H**), 7.78 (d, *J* =15.2 Hz, 1H, CH=C**H-**Ar), 7.53 (d, *J* = 4.4 Hz,2H, Ar**H**), 7.47 (d, *J* = 8.4 Hz, 2H, Ar**H**), 7.39-7.37 (m, 3H, Ar**H**), 6.95 (s, 1H, Ar**H**), 6.91 (d, *J* = 15.2 Hz, 1H, C**H**=CH**-**Ar), 6.69 (s, 1H, Ar**H**), 6.55 (s, 1H, C**H**N), 5.97 (d, *J* = 6.4 Hz, 2H, OC**H**$_2$O) , 4.01-3.97 (m, 1H, NC**H**$_2$CH$_2$), 3.55-3.48 (m, 1H, NC**H**$_2$CH$_2$), 2.99-2.93 (m, 1H, NCH$_2$C**H**$_2$), 2.78-2.74 (m, 1H, NCH$_2$C**H**$_2$); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.6, 149.4, 147.2, 147.0, 146.5, 144.0, 134.9, 129.9, 129.3, 128.8, 127.87, 127.80, 126.9, 123.5, 116.4, 55.2, 40.4, 29.0; IR (KBr, cm^{-1}) υ: 2890.1, 1644.3, 1492.1, 1442.4, 981.5, 856.4; ESI-Mass for **C$_{25}$H$_{20}$N$_2$O$_5$**: m/z (M+H)$^+$429.11.

6.3 *In vitro* anti-tumor activity

6.3.1 Anti-tumor activity by SRB assay

The anti-proliferation of compounds against HUVEC (human umbilical vein endothelial cells), MCF-7 (human breast cancer cells) and HT-29 (human colon cancer cells) were evaluated by SRB (sulforhodamine B) assay. Cells were seeded in 96-well culture plates (1×10^4 cells per well) and cultured for 12 h. Incubated (5 % CO_2, 95 % humidity, 37 °C) the cells with following treatment with the test compounds at increasing concentrations in the presence of 10 % FBS for 72 h. Then TCA was added and incubated at 4 °C for 1 h to fix the cells. After washing the distilled water, 100 μL of 0.057 % SRB solution was added to each well and incubated at 37 °C for 30 min and then quickly rinse the plates four times with 1 %（vol/vol）acetic acid to remove unbound dye. Use a blow dryer to dry the plates. 100 μL(10 mM)Tris-Base solution were added to each well and shake mechanically for 30 min, and then absorbance values at a wavelength of 515 nm were determined with the Spectramax

Microtiter Plate Luminometer (Molecular Devices, USA). The percentage of cell-inhibition was calculated using the formula below.

Inhibition rate (%) = (OD control -OD administration) / OD control × 100%， And calculate the IC_{50}.

6.3.2 Western blot

MCF-7 cells cultured overnight in a 12-well plate were treated with **17d**, **17e** and **CA-4** for 24 h. Subsequently, cells were lysed using Lysis Buffer (Kengen Biotech, China), and protein concentration was measured with coomassie brilliant blue G250 protein assay kit (Kengen Biotech, China). The lysate was subjected to a 15 % SDS-PAGE, and transferred to a WHATMAN membrane using iBlot™system (Invitrogen, Carlsbad, CA). Membranes were blocked with 3 % BSA in 1× Tris-buffered saline (TBS) at room temperature for 1 h and then incubated with primary antibodies at 4 °C overnight, followed by incubation with anti-rabbit IRDye 800CW secondary antibodies for 1 h at room temperature. All the blots were reported with total β-actin antibody as control. The signal of target proteins was detected by BIO-RAD Gel Doc XR and Bio-Rad 164-5051.

6.4 Antitumor activity *in vivo*

Four weeks old, female BALB/c nude mice (19–22 g) were purchased from the animal breeding laboratories of Academy of Military Medical Sciences. Thirty female BALB/c nude mice were randomly divided into four groups, 6 mice per group: a vehicle control group, a tamoxifen (20 mg/kg) treatment group, and **17d**, **17e** (20 mg/kg) treatment group. Human breast cancer xenografts were established by intraperitoneal injection of MCF-7 cells in right axillary subcutaneous of nude mice. When tumor volume reached 100 mm^3, treatment started with **17d** and **17e** injected intraperitoneally once daily at doses of 20 mg/kg or with tamoxifen injected intraperitoneally at doses of 20 mg/kg every day for 30 days. Vehicle control group were intraperitoneal injection of saline once daily. Tumor burden was measured every 6 days with a caliper.

(calculated volume (mm^3) = 1/2*length*width*width). After completing the treatment schedule, tumor-bearing mice were euthanized.

Statistical Analysis

Biological results are reported as means ±standard error. Statistical analysis was performed by using one-way analysis of variance. A P value of less than 0.05 was considered to be statistically significant.

Author Contributions

All authors have given approval to the final version of the manuscript.

Conflict of interest

The authors declare no competing financial interest.

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