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Synthesis, structure-activity relationships and biological evaluation of barbigerone analogues as anti-proliferative and anti-angiogenesis agents

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Abstract

A series of barbigerone analogues (**7a-7w**, **13a-13x**) were designed, synthesized and biologically evaluated for their anti-proliferative and anti-angiogenic activities. Among these compounds, compound **13a** exhibited the most potent inhibitory effect on the proliferation of HUVECs, HepG2, A375, U251, B16, and HCT116 cells (IC_{50} = 3.80, 0.28, 1.58, 3.50, 1.09 and 0.68 μM, respectively). Compound **13a** inhibited the angiogenesis in zebrafish embryo assay in a concentration-dependent manner. Furthermore, **13a** also effectively inhibited the migration and capillary like tube formation of human umbilical vein endothelial cell *in vitro*. These results support the further investigation of this class of compounds as potential anti-proliferative and anti-angiogenesis agents.

Keywords: barbigerone; isoflavone; anti-proliferative; anti-angiogenesis

Angiogenesis, which is the growth of new blood vessels from the pre-existing vasculature of a host, is a critical process for the growth and metastasis of most cancerous tumors,[1] and its inhibition is now a well-established therapeutic strategy for cancer patients.[2-4] Angiogenesis is a very complex process and involves a number of distinct steps, such as endothelial cell activation, migration, proliferation, formation of capillary tubes of endothelial cells, their invasion, and metastasis.[5,6] In tumors, angiogenesis causes the growth of new blood vessels that supply necessary oxygen and nutrient for the growth of tumor tissue.[7] It has been shown that, without angiogenesis, a solid tumor cannot deteriorate beyond a critical size and metastasize

to other organs.[8] Therefore, inhibition of angiogenesis is a promising approach to the development of anticancer therapy.

Barbigerone (**Figure 1**) is one of the naturally occurring pyranoisoflavones, which was first isolated from the seeds of a leguminous plant *Tephrosia barbigera*.[9] It has been reported to have a wide range of biological activities such as antioxidant,[10] antiplasmodial[11] and anti-cancer activity.[12,13] Our previous study has shown that barbigerone exhibited antitumor activity by inducing apoptosis and inhibiting angiogenesis in murine or human cancer cells.[12,13] Recently, Yang and coworkers[14] have reported the total synthesis of barbigerone and its four analogues (**7a**, **7b**, **7t** and **7u** in this study), but they didn't study the biological activity of these compounds. To the best of our knowledge, there has been no study focusing on structural modification of barbigerone associated with potential anti-cancer and anti-angiogenic activities. During our continued efforts to screen natural and synthetic compounds for anti-tumor effects, [15-18] a novel series of barbigerone analogues have been designed, synthesized and evaluated for their anti-proliferative and anti-angiogenic activities.

Please insert **Figure 1** here.

In this paper, a series of barbigerone analogues (**7a-7w**, **13a-13x**) were designed, synthesized and biologically evaluated for their anti-proliferative and anti-angiogenic activities. Among these compounds, compound **13a** exhibited the most potent inhibitory effect on the proliferation of HUVECs, HepG2, A375, U251, B16, and HCT116 cells (IC_{50} = 3.80, 0.28, 1.58, 3.50, 1.09 and 0.68 μM, respectively). Compound **13a** inhibited the angiogenesis in zebrafish embryo assay in a

concentration-dependent manner. Furthermore, **13a** also effectively inhibited the migration and capillary like tube formation of human umbilical vein endothelial cell *in vitro*.

Barbigerone analogues **7a** – **7w** were prepared by the synthesis route outlined in **Scheme 1**. The 4-hydroxyl of compound **1** was protected with 3,4-dihydro-2H-Pyran in dichloromethane in the presence of pyridinium p-toluenesulfonate (PPTS) to give the THP ether **2**, which condensation with N,N-dimethylformamide dimethylacetal (DMF-DMA) provided the enamine **3**, The crude **3** was directly treated with I_2 in the presence of pyridine at room temperature for 24 h, followed by neutralizing with saturated $Na_2S_2O_3$ and extract with $CHCl_3$, compound **4** was obtained.[19,20] The obtained compound **4** was refluxed in CH_3OH-THF (1:1) in the presence of *p*-toluenesulfonic acid for 1 h to give compound **5**. Following a literature method,[21-23] a condensation reaction between **5** and 1,1-diethoxy-3-methyl-2-butene in p-xylene in the presence of picoline as base brought about the desired ring closure in position 8 of **5** to give the key intermediate **6**, which coupling with commercial available substituted phenylboronic acids in a Suzuki-Miyaura reaction[19,20,24] led to the target products **7a** – **7w**.

Please insert **Scheme 1** here.

Compounds **13a** – **13x** were synthesized by the method shown in **Scheme 2**. Having completed the synthesis of compound **4** in **Scheme 1**, we focus on the synthesis of (2,4,5-trimethoxyphenyl)boronic acid **10**. Trimethoxybenzene **8** was brominated in 92.3 % yield to the bromide **9**, which reacted with n-BuLi and trimethyl

borate to provide the intermediate (2,4,5-trimethoxyphenyl)boronic acid **10**. Compound **11** was obtained by a Suzuki-Miyaura coupling reaction between of O-THP-protected iodochromanone **4** and (2,4,5-trimethoxyphenyl)boronic acid **10**. Deprotection of the THP group was performed by treatment with *p*-toluenesulfonic acid, leading to the key intermediate **12**, followed by an esterification or etherification of the liberated phenol with alkyl halide, substituted benzyl halide and substituted aryl acid to afford the final desired products **13a** – **13x**.

Please insert **Scheme 2** here.

These barbigerone analogues (**7a – 7w** and **13a – 13x**) were evaluated for their anti-proliferative activity in human umbilical vein endothelial cells (HUVECs), HepG2 (hepatocellular carcinoma), A375 (melanoma), U251 (glioma), B16 (melanoma), and HCT116 (colorectal carcinoma) using MTT method. HUVECs were used to evaluate their in vitro inhibitory effects on the proliferation of endothelial cells that are closely related to angiogenesis. The compounds that exhibited IC_{50} > 10.0 μM were considered to be inactive on the respective cancer cell lines. The results were summarized in **Table 1**. Among these compounds, compound **13a** displayed the most potent anti-proliferative activity than barbigerone against HUVECs, HepG2, A375, U251, B16, and HCT116 cells.

Please insert **Table 1** here.

To study the structure – activity relationships (SAR) of barbigerone, the substitutes of the B-ring were discussed firstly. Based on the anti-proliferative activity of **7a – 7w**, we found that the substituents of the B-ring greatly affected on anti-proliferative

activity of the compounds in this series. The introduction of electro–withdraw groups (CN, CF_3, Cl, F, CHO, $COCH_3$) to the B-ring has proven to be detrimental to antitumor activity. It's interesting to point out that **7o** and **7p** containing CF_3 group at *para*-position of the B-ring slightly decrease the anti-proliferative activity. The replacement of the 2,4,5-trimethoxy group with various methoxyl, ethoxyl and hydroxyl groups (3-methoxy in **7a**, 3,4-dimethoxy in **7b**, 4-methoxy in **7c**, 2,4-dimethoxy in **7d**, 2,3,4-trimethoxy in **7f**, 2-F-3-methoxy in **7g**, 4-hydroxyl in **7i**, 3,5-dimethoxy in **7r**, 2-ethoxy in **7s**, 2,5-dimethoxy in **7t**, 3,4,5-trimethoxy in **7u**, 2-methoxy in **7v**, 4-ethoxy in **7w**) resulted in a remarkable decrease the anti-proliferative activity. These results indicated the pattern of substitution in the B-ring is closely related to the biological activity of this class of compounds. Thus, the 2,4,5-trimethoxy group seems to be the optimal substituent on the B-ring.

Since 2,4,5-trimethoxy group is proved the most potent group in the B-ring, it was retained during the structure-activity relationship studies focused at the C-5 position of the A-ring. Introduction ester groups (**13f** and **13g**) at the C-5 position, results in a significant decrease the anti-proliferative activity. The replacement of benzopyran ring with alkoxyl groups at the C-5 position (**13a**，**13b**，**13c**，**13e**) resulting in increased the anti-proliferative activity, whereas 2-morpholinoethoxy group (**13n**) decrease the anti-proliferative activity. The replacement of benzopyran ring with various substituted benzoyloxyl groups (**13h**-**13x**) resulted in a maintained or improved the anti-proliferative activity, whereas the substitution of benzyloxyl group (**13d**) remarkable decreased the anti-proliferative activity. In summary, the

information of SAR provided us a guideline to improve the inhibitory activity in the future structural modification.

The anti-angiogenic activity of the most potent compound **13a** was tested using zebrafish embryos which represent an excellent animal model for the study of angiogenesis.[25] Zebrafish embryos were treated with barbigerone (1.25 or 2.5 μM), **13a** (1.25 or 2.5 μM) or vehicle for 24 h. As shown in **Figure 2**, the control group had normal vessel development, in which the subintestinal vessel (SIV) formed as a smooth basket-like structure. In the group treated with **13a** and barbigerone, the formation of SIV was considerably inhibited compared with that of the vehicle control group, indicating a dose-dependent inhibition pattern. Therefore, the anti-angiogenic activity of **13a** was further studied.

Please insert **Figure 2** here.

Endothelial cell migration is an essential step in angiogenesis. Inhibition on this process will block the formation of new blood vessels.[26, 27] Therefore, compound **13a** was tested for possible inhibition of endothelial cell migration in a wound-healing migration assay. As illustrated in **Figure 3**, the HUVECs actively migrated into the wound area (between the two white lines) under the compound-free condition (vehicle). At a concentration of 0.5 μM, the HUVECs migratory rates of **13a** and barbigerone were 35.36±4.13 % and 74.26±4.72 %, respectively. While the tested compounds' concentration reached 1.0 μM, the HUVECs migratory rates of **13a** and barbigerone were 8.45±2.91 % and 1.65±8.69 %, respectively. The results showed that compound **13a** and barbigerone exerted potent inhibitory effect on the migration

of HUVECs in a dose-dependent manner. Compound **13a** statistically exerted the higher potent inhibitory effect on the migration of HUVECs, reaching a 4.9-fold improvement over barbigerone at a concentration of 1.0 μM.

Please insert **Figure 3** here.

In the later stages of angiogenesis, tube formation of endothelial cell is also an important process.[26] Inhibition on the formation of capillary-like tube networks will terminate the development of new blood vessels. To further characterize the anti-angiogenesis activity of **13a**, we investigated the inhibitory effect of tube formation by plating HUVECs on matrigel substratum. As shown in **Figure 4A**, in the vehicle group, HUVECs showed high mobility on matrigel and formation of tube-like structures was observed in 8 h. In comparison with the vehicle group, treatment of HUVECs with **13a** or barbigerone at the concentration of 1.0 μM could induce 78.21 ±4.86 % and 23.74±7.6 % inhibition of tube-like structure formation respectively. Moreover, the inhibitory rates of tube formation treated with **13a** and barbigerone at a concentration of 5.0μM were 88.33±3.5 % and 65.37±1.78 % respectively (**Figure 4B**). The results demonstrated that compound **13a** and barbigerone could effectively inhibit tube formation of HUVECs in a dose-dependent manner. Our observation indicated that **13a** approximately achieved a 3.3-fold improvement in the inhibition of tube formation compared to that of barbigerone at the same concentration of 1.0 μM.

Please insert **Figure 4** here.

Angiogenesis is a highly regulated process that involves a complex cascade of events, and its inhibition is now a well-established therapeutic strategy for cancer

patients. Herein, a series of barbigerone analogues were synthesized and their anti-angiogenesis and anti-proliferative activities were tested. Among these compounds, compound **13a** exhibited the most potent inhibitory effect on the proliferation of HUVECs, HepG2, A375, U251, B16, and HCT116 cells (IC_{50} = 3.80, 0.28, 1.58, 3.50, 1.09 and 0.68 μM, respectively). Compound **13a** inhibited the angiogenesis in zebrafish embryo assay in a concentration-dependent manner. Furthermore, **13a** also effectively inhibited the migration and capillary like tube formation of human umbilical vein endothelial cell *in vitro*. In conclusion, the preliminary *in vitro* anti-angiogenic activities of these compounds possess potential for design of better future molecules targeting tumor angiogenesis. In the future research we will be exploring for a clear structure-activity relationship of this type of compound and studying on their mechanism of anti-angiogenesis activity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: .

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Table Captions

Table 1. The anti-proliferative activities of tested compounds against HUVECs and five cancer cell lines.

Scheme Captions

Scheme 1. Reagents and conditions: (a) DHP, PPTS, CH_2Cl_2, r.t., 4 h; (b) DMF-DMA, 95 °C, 3 h; (c) I_2, pyridine, $CHCl_3$, r.t., 12 h (91.7% for three steps); (d) pTsOH, CH_3OH, THF, 60 °C, 1 h (94.9%); (e) 1,1-diethoxy-3-methyl-2-butene, 3-picoline, xylene, reflux, 24 h (48.4%); (f) $ArB(OH)_2$, 10 % Pd/C, Na_2CO_3, H_2O, DME, 45 °C, 1 h (49.6%–89.7%).

Scheme 2. Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C (92.3%); (b) *n*-BuLi, trimethyl borate, THF, -78 °C (37.7%); (c) 10 % Pd/C, Na_2CO_3, H_2O, DME, 45 °C, 1 h (61.4%); (d) pTsOH, CH_3OH, THF, 60 °C, 1 h (87.1%); (e) RX, K_2CO_3, Acetone, r.t., overnight, or RCOOH, DCC, DMAP, CH_2Cl_2, r.t., overnight (18.7%-99.4%).

Figure Captions

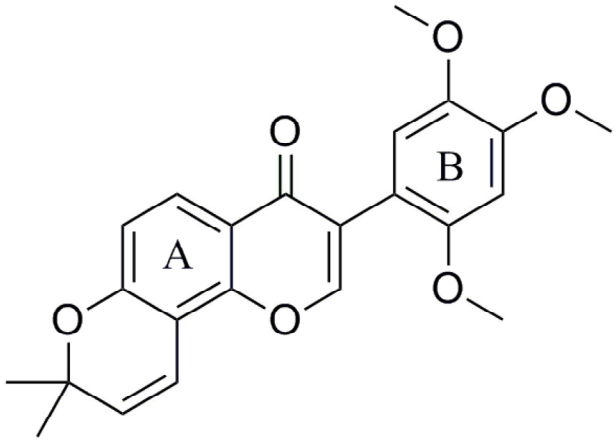
Figure 1. Chemical structure of barbigerone.

Figure 2. Effects of **13a** and barbigerone on the formation of subintestinal vessel

(SIV) in zebrafish embryos assay. Zebrafish embryos were incubated with **13a** or barbigerone at 1.25 or 2.5 μM for 24 h.

Figure 3. Effects on the HUVECs migration. (A) HUVECs were wounded with pipette and treated with vehicle, indicated concentrations of compound **13a** or barbigerone. At 0 h or 24 h, photographs were taken by an OLYMPUS digital camera (magnification 50×). (B) Rates of migration impacted by compound **13a** and barbigerone on the HUVECs. Data represented the mean±standard deviation (SD) from three independent experiments. $^{**}P < 0.01$; $^{***}P < 0.005$.

Figure 4. Effects on the HUVECs tube formation. (A) HUVECs (1×10^4 cells) suspended in EBM-2 containing vehicle, compound **13a** (1.0 or 5.0 μM) or barbigerone (1.0 or 5.0 μM) were added to the Matrigel. After incubation for 8 h at 37 ^{o}C, capillary networks were photographed and quantified (magnification: 100×). (B) Rates of tube formation impacted by compound **13a** or barbigerone on the HUVECs. The number of intact tubes was counted in five randomly chosen regions and expressed as the percentage of that of the vehicle group. The results were expressed as mean±SD. $^{**}P < 0.01$; $^{***}P < 0.005$.



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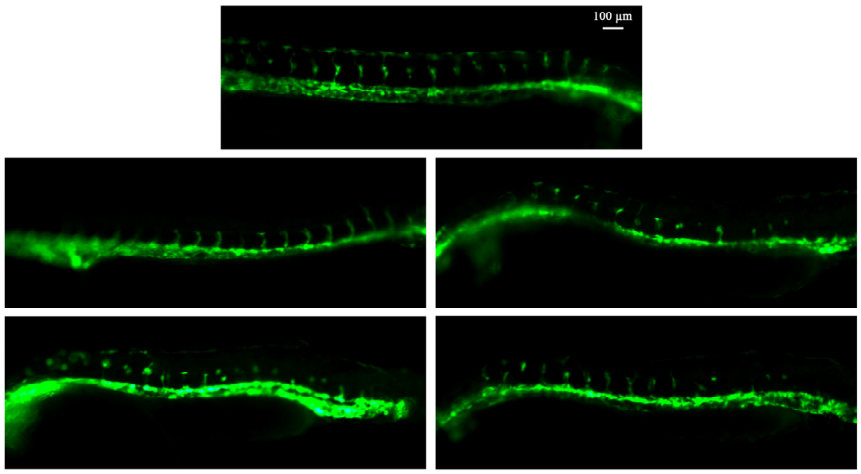

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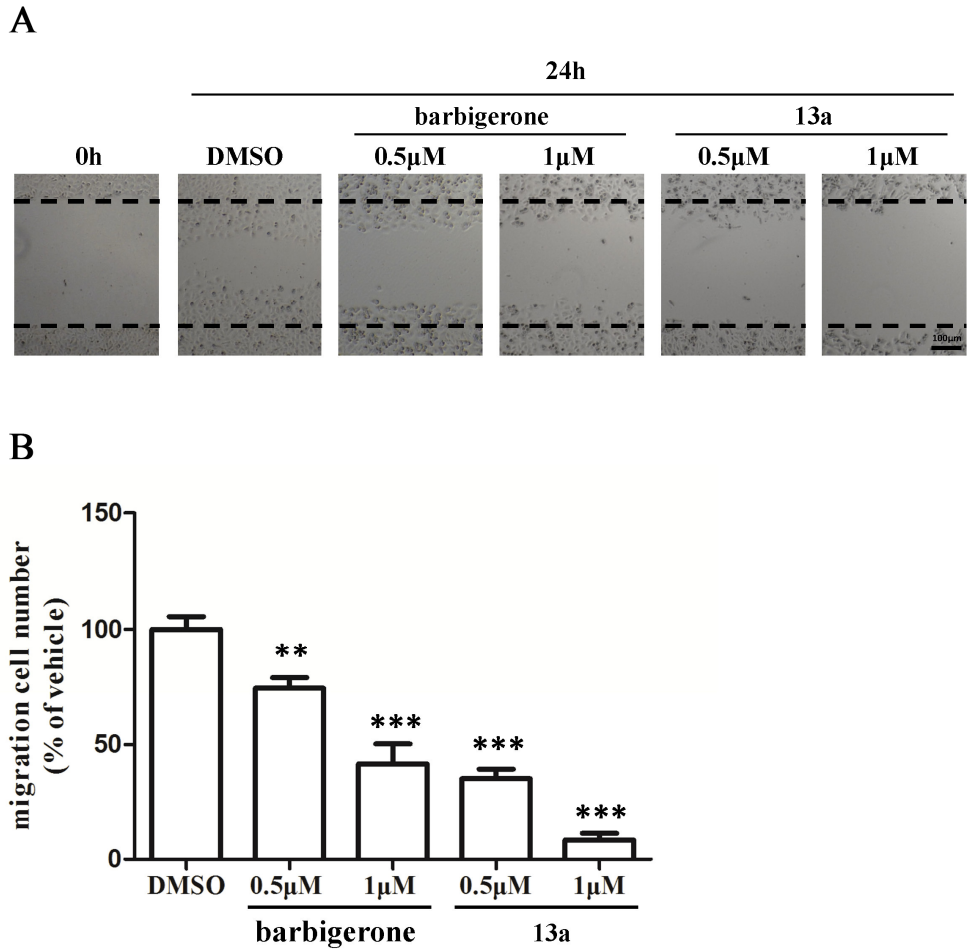

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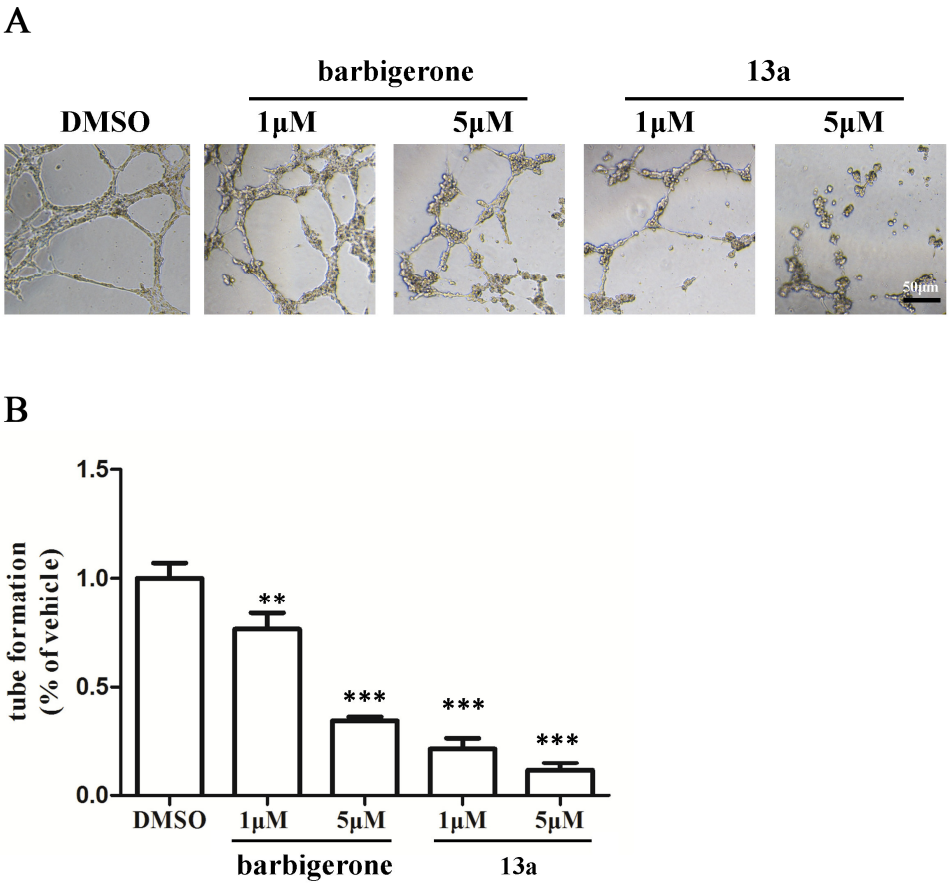

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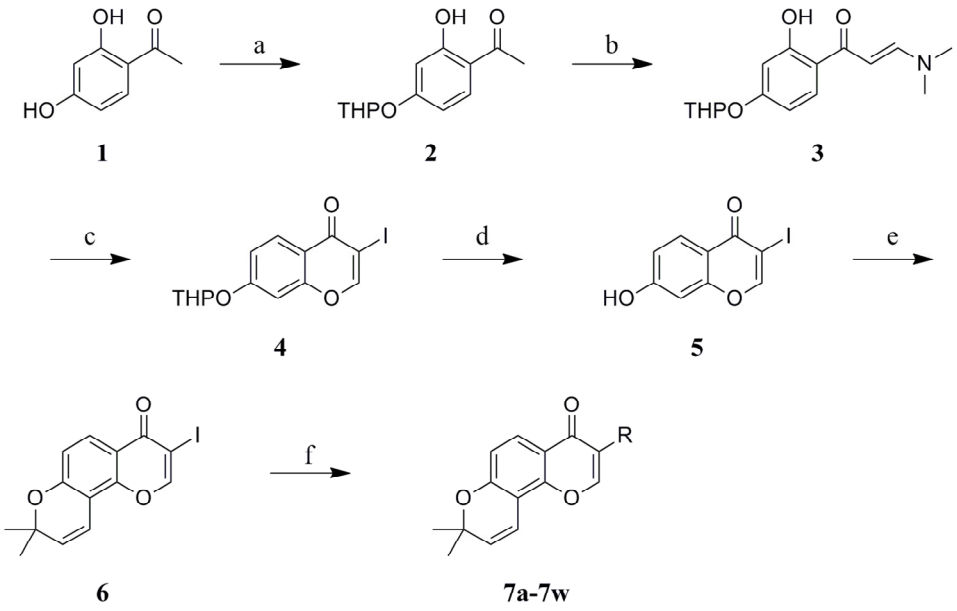

1 **2** **3**

4 **5**

6 **7a-7w**

7a R = 3-methoxyphenyl
7b R = 3,4-dimethoxyphenyl
7c R = 4-methoxyphenyl
7d R = 2,4-dimethoxyphenyl
7e R = benzo[d][1,3]dioxol-5-yl
7f R = 2,3,4-trimethoxyphenyl
7g R = 2-fluoro-3-methoxyphenyl
7h R = 4-acetylphenyl
7i R = 4-hydroxyphenyl
7j R = 2,3-dihydrobenzo[b][1,4]dioxin-6-yl
7k R = 4-formylphenyl
7l R = 4-cyanophenyl
7m R = 3-formylphenyl
7n R = 4-chloro-3-(trifluoromethyl)phenyl
7o R = 2-chloro-4-(trifluoromethyl)phenyl
7p R = 4-(trifluoromethyl)phenyl
7q R = 3-(trifluoromethyl)phenyl
7r R = 3,5-dimethoxyphenyl
7s R = 2-ethoxyphenyl
7t R = 2,5-dimethoxyphenyl
7u R = 3,4,5-trimethoxyphenyl
7v R = 2-methoxyphenyl
7w R = 4-ethoxyphenyl

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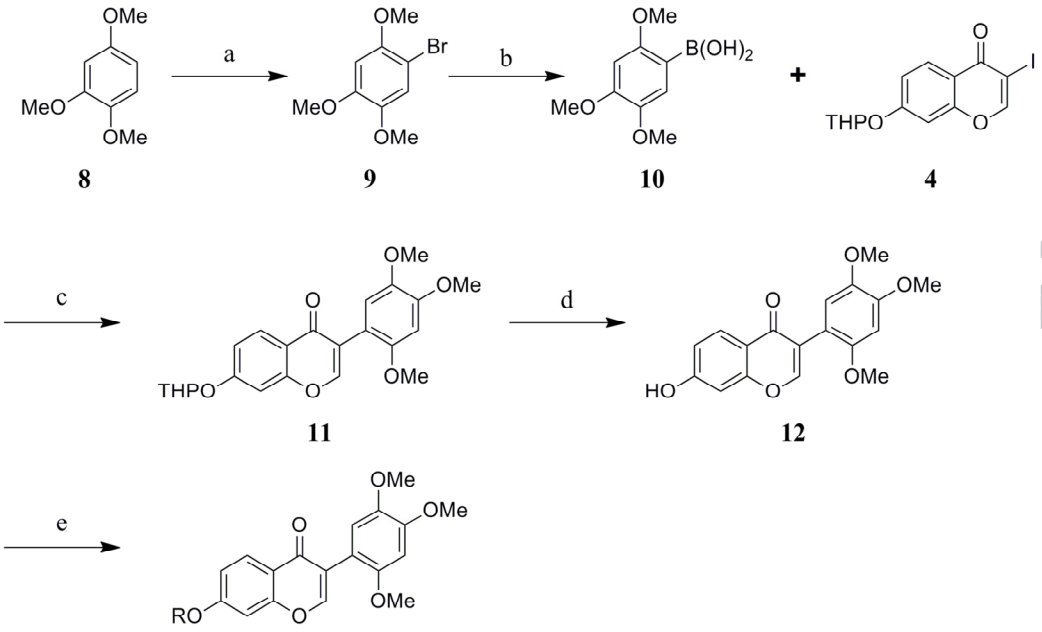

13a: R = 3-methyl-2-butyenyl
13b: R = allyl
13c: R = 2-propynyl
13d: R = benzyl
13e: R = Methyl
13f: R = 3-methoxybenzoyl
13g: R = 2-(3-(trifluoromethyl)phenyl)acetyl
13h: R = 2-fluorobenzyl
13i: R = 4-fluorobenzyl
13j: R = 4-bromobenzyl
13k: R = 2-methylbenzyl
13l: R = 4-nitrobenzyl
13m: R = 2-(trifluoromethyl)benzyl
13n: R = 2-morpholinoethyl
13o: R = 4-cyanobenzyl
13p: R = 2-cyanobenzyl
13q: R = 3-fluorobenzyl
13r: R = 4-chlorobenzyl
13s: R = 3-chlorobenzyl
13t: R = 2-chlorobenzyl
13u: R = 3-bromobenzyl
13v: R = 2-bromobenzyl
13w: R = 4-(trifluoromethyl)benzyl
13x: R = 3-(trifluoromethyl)benzyl

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291

292 **Table 1**. The antiproliferative activities of test compounds against HUVECs and five

293 cancer cell lines.

Compds	IC_{50} (μM)					
	HepG2	**A375**	**U251**	**B16**	**HCT116**	**HUVEC**
barbigerone	1.77	1.85	4.10	1.23	2.36	7.45
7a	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7b	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7c	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7d	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7e	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7f	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7g	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7h	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7i	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7j	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7k	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7l	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7m	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7n	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7o	>10.0	8.90	2.50	3.55	3.80	>10.0
7p	>10.0	7.25	5.85	1.91	7.00	>10.0
7q	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0

7r	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7s	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7t	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7u	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7v	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
7w	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
13a	0.28	1.58	3.50	1.09	0.68	3.80
13b	3.45	4.75	5.90	5.10	6.60	>10.0
13c	4.95	3.68	6.45	4.50	8.05	>10.0
13d	1.32	1.64	6.75	2.33	2.28	9.75
13e	2.04	2.64	9.40	5.20	9.17	>10.0
13f	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
13g	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
13h	1.28	2.10	2.89	1.61	2.90	4.30
13i	1.00	1.72	3.20	1.12	0.95	>10.0
13j	1.05	1.00	>10.0	1.18	1.98	>10.0
13k	1.86	1.36	2.00	2.15	2.90	4.83
13l	2.50	>10.0	9.40	>10.0	>10.0	>10.0
13m	6.55	>10.0	>10.0	8.55	4.76	>10.0
13n	>10.0	>10.0	>10.0	>10.0	>10.0	>10.0
13o	4.23	1.55	6.18	7.00	4.22	10.0
13p	>10.0	0.99	0.98	2.14	>10.0	>10.0

13q	1.23	1.30	3.51	2.44	4.92	5.30
13r	0.94	1.02	0.47	2.40	4.45	4.40
13s	0.75	0.98	>10.0	2.28	1.33	>10.0
13t	1.69	2.02	>10.0	4.18	2.45	>10.0
13u	0.87	1.12	>10.0	4.40	1.20	>10.0
13v	2.18	2.85	>10.0	8.90	4.55	>10.0
13w	0.89	2.28	3.75	5.40	2.44	>10.0
13x	0.61	1.14	>10.0	>10.0	3.40	>10.0

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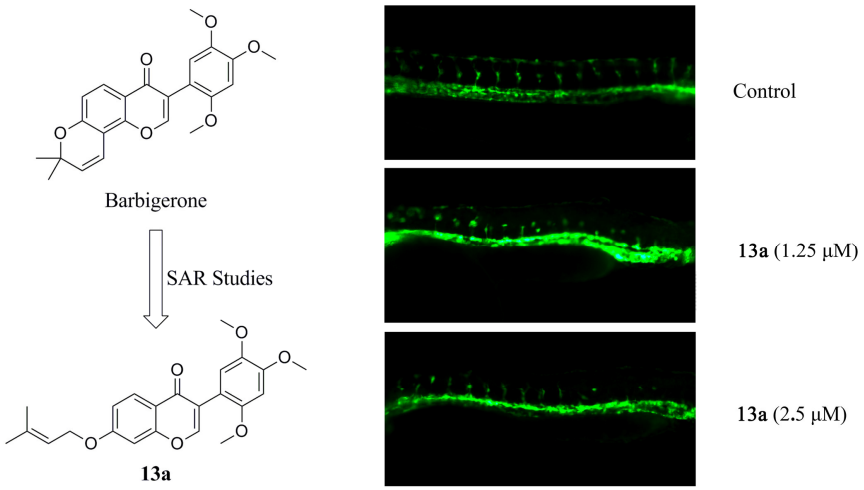

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