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Design, Synthesis and Biological Evaluation of Novel 5-Hydroxy-2-methyl-4*H*-pyran-4-one Derivatives as Antiglioma Agents

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ABSTRACT

D-2-hydroxyglutarate (*D*-2HG) is frequently found in human brain cancers. Approximately 50%~80% of grade II glioma patients have a high level of *D*-2HG production, which can lead to cancer initiation. In this study, a series of novel 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives were designed and synthesized as antiglioma agents, and the related structure-activity relationships are discussed. Among these novel compounds, **4a** exhibited promising anti-proliferative activity against glioma HT1080 cells and U87 cells with an IC_{50} of 1.43 μM and 4.6 μM respectively. Further studies found that the most active compound (**4a**) shows an 86.3% inhibitory rate against intracellular production of *D*-2HG at 1 μM, and dramatic inhibitory effects, even at 1 μM on colony formation and migration of U87 and HT1080 cells.

Keywords: 5-hydroxy-2-methyl-*4H*-pyran-4-one, antitumor, *D*-2-hydroxyglutarate

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1. Introduction

Excessive accumulation of intracellular *D*-2-hydroxyglutarate (*D*-2HG), which is a product of mutations of residue 132 (R132) in isocitrate dehydrogenase 1 (IDH1) results in hypermethylation of histone and DNA by competitive inhibition of several α-KG-dependent dioxygenases including histone demethylases and 5-methylcytosine hydroxylases in the TET family.[1] The newly produced *D*-2HG has been proposed to act as an oncogenic metabolite inducing dysregulation of methylation, and thus elevating risk of malignant tumors.[2]

AGI-5198 (**Fig. 1**) has been reported to inhibit the production of cellular *D*-2HG and impair the growth of IDH1 mutant glioma both *in vitro* and *in vivo*. The potential clinical utility of such *D*-2HG scavengers has been identified and much interest has been attracted to this area. To date however, only four chemo-types of mutant IDH1 inhibitors with *D*-2HG scavenging effects, have been reported[3] in addition to **AGI-5198**. These are shown in **Fig. 1**. Consequently, exploration of structurally different types of *D*-2HG scavengers is necessary for the further confirmation of the feasibility of this antitumor strategy.

In the current study, several novel 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives that could be easily synthesized by Aldol reaction were designed by application of bioisosterism and a scaffold hopping strategy based on an analysis of the structures of previously reported *D*-2HG inhibitors (**Fig. 1**), and evaluated as *D*-2HG scavengers. The compound (**4a**) was identified and showed a promising *D*-2HG production inhibitory effect as well as anti-proliferative activity against glioma cells, including cell growth, colony formation and migration inhibitory effects,.

2. Chemistry

Compound **SYC-435** shown in **Fig. 1**, was reported to be an excellent potent inhibitor of mutant IDH1 with IC_{50} values as low as 190 nM.[3f] The X-ray structures of IDH1 (R132H) in a complex with NADPH and the inhibitor **SYC-435** indicate that the 4-methyl-1-hydroxypyridin-2-one moiety of **SYC-435** is the critical

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pharmacophore, for it forms several key H-bonds, and enjoys electrostatic and hydrophobic interactions with the protein. To enrich the type of inhibitor, compounds of **series I** were designed by replacing the 4-methyl-1-hydroxy-pyridin-2-one moiety (A ring) of **SYC-435** with one of its bioisosters, the 5-hydroxy-2-methyl-4*H*-pyran-4-one, and the resulting compound was synthesized. Since the space of the active pocket of IDH1 protein is bigger, and all the other reported inhibitors, including **AGI-5198**, **VVS**, **GSK-321** and **BRD-2879**, appear to have an essentially triangular skeleton, compounds of series II were designed by introducing a second 5-hydroxy-2-methyl-4*H*-pyran-4-one moiety at the benzyl α-carbon position of the compounds in series I. The synthetic route of the designed compounds in **Fig. 1** is outlined in **Scheme 1** (**series I**: 3a~3e, **series II**: 4a~4f).

[Figure 1]

[Scheme 1]

2.1. Synthesis of the target compounds in series I

The synthesis of the precursor allomaltol (**1**) was performed in two steps, starting with the reaction of kojic acid (5-hydroxy-2-(hydroxylmethyl)-4H-pyran-4-one) with thionylchloride, yielded product then reduction with zinc powder under acidic conditions[4]. Due to the position-6 show higher reactivity than position-3 on the pyrone ring of **1**, appropriate functionalization at position-6 can easily be achieved by the Aldol reaction. Thus, compound **3a**~**3e** was synthesized by condensation of allomaltol (**1**) (1.0 eq) with different aldehydes (1.2 eq) in the presence of a catalyst, triethylene diamine (DABCO, 1.2 eq)[5], then the α–hydroxyl group was reduced using triethylsilicane (5.0 eq.) and trifluoroacetic acid (5.0 eq.) in CH_2Cl_2.

2.2. Synthesis of the target compounds in series II

The Aldol reaction of 5-hydroxy-2 -methyl-4*H*-pyran-4-one, carried out with different aldehydes, leads to variously substituted double 5-hydroxy-2 -methyl-4*H*-pyran-4-one [6]. It has been reported substituted double kojic acid

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derivatives can be synthesized by microwave-assisted condensation of kojic acid with aldehydes[7]. Here we report a simple method with which to synthesize compounds **4a**-**4f** by condensation of allomaltol (**1)** (1 eq) with different aldehydes (0.5 eq) in the presence of a catalyst, triethylene diamine (DABCO, 1.2 eq).

3. Results and Discussion

3.1. Inhibition of proliferation of human glioma cells

First, the growth inhibitory activities of the synthetic compounds in human brain glioma HT1080 cells and U87 cells were evaluated with an MTT assay. As shown in **Table 1**, compound **4a** showed the best anti-proliferative activity, with an IC_{50} of 1.43 ± 0.2 μM and 4.6 ± 0.3 μM against HT1080 cell and U87 cell respectively. Based on these MTT results, some preliminary structure-activity relationships (SAR) could be summarized as follows: (a) a long R group containing a phenyl ring may be necessary for activity (**4a** *vs* **4e** and **4f**), (b) substitution on the phenyl ring would reduce the activity (**4a** *vs* **4b** and **4c**), and (c) when the benzene is connected through an alkyl chain, the activity will disappear (**4a** *vs* **4d**).

[Table 1]

3.2. Inhibition of D-2HG Production

D-2HG is the specific product of the mutant IDH1 protein, which is often detected in IDH1-mutant cells including gliomas, and can be used as a biomarker for cancer cells' activity.[3a, 3b, 3d, 8] So in order to ascertain if the cytotoxicity of the compounds resulted from the decline of intracellular *D*-2HG, the *D*-2HG level was tested using a human fibrosarcoma HT1080 cell line which harbors an IDH1 mutant gene and has relatively high cellular *D*-2HG accumulation in the absence or presence of **4a**. The intracellular *D*-2HG concentrations were quantitatively determined by HPLC-MS (standard curve line is shown in **Fig. S3**, R=0.9966). As shown in **Fig. 2**, we found that *D*-2HG levels decreased significantly from 23.25 ± 4.03 μg/mL in non-treated cells to 3.14 ± 0.77 μg/mL after treatment of the cells with 1 μM of compound **4a**. For a positive control, it decreased to 3.05 ± 0.70 μg/mL after

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treatment with 1 μM **AGI-5198**. Here, compound **4a** shows excellent *in cellular D*-2HG inhibitory activity.

[Figure 2]

3.3. Inhibition of migration of human glioma cells

Zhu Jian et al. have found that human glioma cells with high *D*-2HG levels have a faster migration rate than normal human glioma cells.[8a] Meanwhile, Luyuan Li et al. have reported that the first mutant IDH1 inhibitor **AGI-5198** inhibits the migration of human glioma cells with the IDH1 mutation.[9] Accordingly, the migration of human brain glioma U87 cells and human fibrosarcoma HT1080 cell line were assessed with a scratch assay in the presence or absence of **4a**. As depicted in **Figs. 3A** and **3B**, the migration rate of U87 decreased in 12 h from 100% to 51.3% and in 24 h to 17.5% relative to the blank control. However, after treatment with 1 μM **4a**, the migration rate decreased in 12 h from 100% to 82.8% and in 24 h to 69.5% respectively. In the positive control (**AGI-5198**), the decreases were from 100% to 84.0% in 12 h and to 51.0% in 24 h . Because the migration rate of HT1080 cells is faster, we shortened the interval time to 6 h. As shown in **Fig. 3C** and **3D**, the scratch area in 6 h was 58.7%, 61.0%, and 70.0% for the control, 1 μM **4a**, and 10 μM **AGI-5198** group respectively**,** and in 12 h was 23.3%, 43.5%, and 56% for control, 1 μM **4a**, and 10 μM **AGI-5198** group respectively**.** Our studies demonstrated that compound **4a** is a potent *D*-2HG scavenger which also exhibits an obvious inhibitory effect on the migration of U87 and HT1080 cells.

[Figure 3]

3.4. Inhibition of colony formation of human glioma cells

Luyuan Li et al. have reported that the first mutant IDH1 inhibitor **AGI-5198** with an *D*-2HG inhibitory effect can also inhibit the colony formation of human glioma cells with an IDH1 mutation.[9] Thus, U87 and H1080 cells were further employed to examine the colony formation inhibitory activity of **4a**. The results (**Fig. 4**) show that the colony formation of both U87 and H1080 cells were significantly

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inhibited after the addition of **4a** in a concentration-dependent manner. The colony inhibitory rate against U87 cells was 11.3% (after the treatment of 0.5 μM **4a**) and 96.8% (after the treatment of 1 μM 4a). For HT1080 cells, complete suppression with an inhibition rate of 99.5% was also observed at the higher concentration of **4a** (1 μM). More importantly, compound **4a** also showed a strong inhibitory effect (75.0%) on colony formation of H1080 cells at a low concentration (0.5 μM). These more significant colony formation inhibitory effects of **4a** against the cells that express the mutant IDH1 highly suggest that these effects are likely to be attributed to the elimination of *D*-2HG.

[Figure 4]

3.5. Inhibition of mutant IDH1 (R132H).

Considering **4a** shows potent *D*-2HG elimination activity, as well as obvious inhibition of antiproliferation, migration and colony formation, we investigated the effect of **4a** on mutant IDH1, whose mutation is the critical cause of the high intracellular *D*-2HG levels. Recombinant IDH1 (R132H), the predominant (>90%) mutation found in IDH1 associated gliomas, was used for enzyme inhibitory activity screening. The purity of the recombinant IDH1 (R132H) protein is > 98% (**Fig. S1** in supporting information - SI), and activity of the enzyme is good (**Fig. S2** in SI). The IDH1 (R132H) inhibitory activities (IC_{50}) of all the synthesized 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives are shown in **Table 1**. It was found that all of the compounds, including the active compound (**4a**) showed no obvious activity (IC_{50} > 20 μM) against IDH1 (R132H). These compounds therefore are much weaker than the positive control **AGI-5198** (0.08 ± 0.01 μM). Combined with the *D*-2HG production inhibition activity, we were puzzled because **4a** exhibits good *D*-2HG production inhibitory activity but no obvious IDH1 directly inhibitory activity compared with **AGI-5198**. Therefore, **4a** may employ a different inhibitory mechanism instead of combining with mutant IDH1 directly, and accordingly, we will in the future conduct an intensive study of the *D*-2HG inhibitory mechanism of this class of compounds.

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[Table 1]

4. Conclusion

In this study, two series of 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives were synthesized, and their bioactivities were evaluated. Among these compounds, one potent antiglioma agent (**4a**), which harbors excellent intracellular *D*-2HG scavenging activity was identified. Biological activity studies also indicated the significantly inhibitory effects of **4a** on the migration and colony formation of human glioma cells, suggesting that **4a** may be a promising *D*-2HG scavenger and have development potential as an antiglioma agent. Obvious *D*-2HG inhibition activity but no obvious mutant IDH1 inhibitory activity of **4a** implied that our compounds may adopt a different inhibitory mechanism rather than combining with mutant IDH1 directly. Further studies of the mechanism of *D*-2HG elimination are in progress and it is hoped that we could successfully resolve this. These findings may be useful for the further develop of antiglioma agents with novel mechanisms.

Acknowledgments

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Conflict Of Interest

The authors declare no competing interests.

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Figure Captions

Figure 1. Design strategy of 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives.

Figure 2. *D*-2HG production inhibitory effects of **4a** in HT1080 Cells. Red peak represents control, blue for compounds **4a** (1 μM), and green for positive control (AGI-5198, 1 μM).

Figure 3. Cell migration inhibition assay. (A) Compound **4a** inhibit U87 cell migration (photo), samples were photographed per 12 h after the addition of 1 μM **4a** or 10 μM **AGI-5198**; (B) Scratch area analysis of (A). (C) Compound **4a** inhibit HT1080 cell migration (photo), samples were photoed per 6 h after the addition of 1 μM **4a** or 10 μM **AGI-5198**; (D) Scratch area analysis of (C).

Figure 4. Colony formation assay of U87 and HT1080 cells. Gray column represents U87 cell line, the other HT1080 (black column). 0.5 and 1 μM **4a** were added with cells and colonies were counted after 8 days. 5 and 20 μM **AGI-5198** were positive control drug.

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Table 1. Mutant IDH1 (R132H) inhibitory activities and cytotoxicity against glioma HT1080 cell line and U87 cell line of 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives.

Compound	IC_{50} for MTT (μM)[a]		IC_{50} for IDH1 (μM)[a]
	HT1080	U87	
AGI-5198[b]	ND	20.1 ± 2.1	0.08 ± 0.01
3a	> 50	> 50	> 50
3b	> 50	> 50	> 50
3c	> 50	> 50	> 50
3d	24.4 ± 0.4	> 50	> 50
3e	> 50	> 50	> 50
4a	1.43 ± 0.2	4.6 ± 0.3	23.1 ± 2.8
4b	2.6 ± 0.3	5.2 ± 0.2	32.0 ± 2.9
4c	3.06 ± 0.2	> 50	> 50
4d	> 50	27.2 ± 1.5	> 50
4e	26.6 ± 0.4	29.5 ± 0.5	> 50
4f	28.3 ± 0.6	30.9 ± 1.1	> 50

[a] All dates represent mean ± S.D. from different experiments performed in triplicate.

[b] **AGI-5198** acted as a positive control for IDH1(R132H) inhibitory activities assays and MTT assays.

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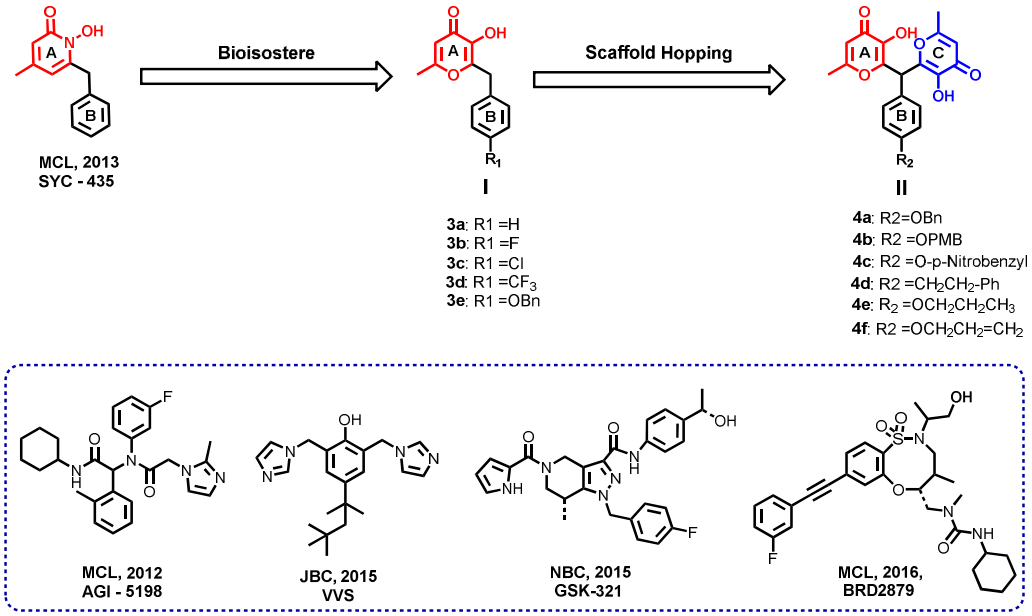

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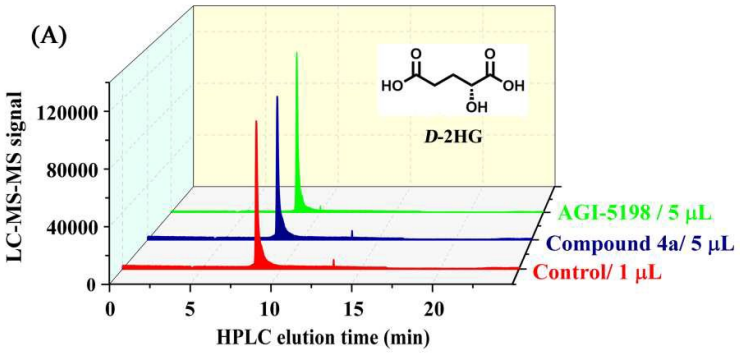

(B)

XIC of -MRM (4 pairs): 147.0/85.0 amu from Samples of Control, Compound **4a**/(1μM) and **AGI-5198**/ (1μM)							
Sample	Time (min)	Area (counts) $\times 10^6$	Height (cps) $\times 10^5$	Width (min)	Injection volume (μL)	*D*-2HG (μg/mL)	Inhibition ratio (%)
Control	8.4239	1.2473	1.0318	2.0913	1	23.25	0.00
Compound **4a**	8.2673	1.4395	1.2049	2.0093	5	3.14	86.49
AGI-5198	8.4192	1.3867	1.1618	1.9683	5	3.05	86.89

Figure 2. *D*-2HG production inhibitory effects of **4a** in HT1080 Cells. (A) Raw HPLC data, red peak represents control, blue for compounds **4a** (1 μM), and green for positive control (**AGI-5198**, 1 μM), and the injection volume of control group is 1 μL, while the injection volume of compound **4a**, **AGI-5198** group is 5 μL. (B) The quantitative analysis results according to the the peak and the standard curve line (**Fig. S3**).

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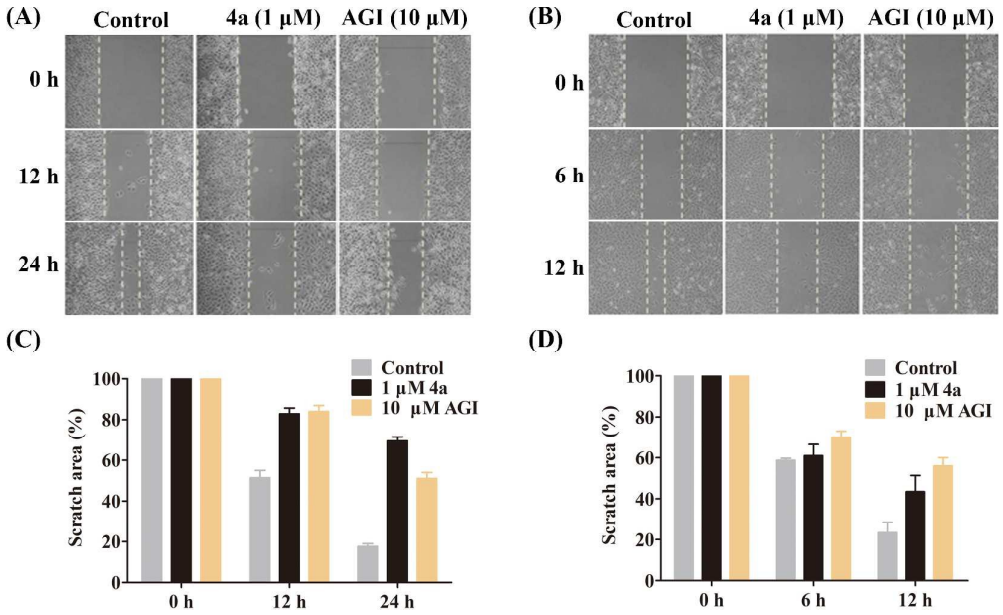

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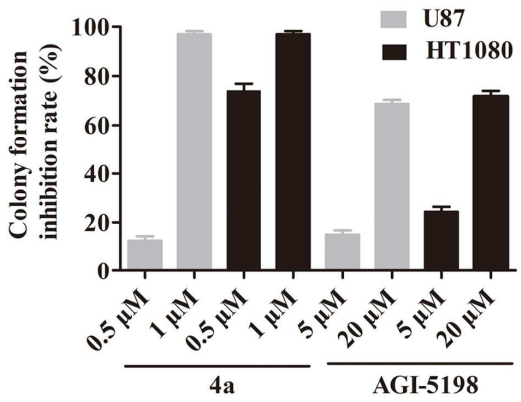

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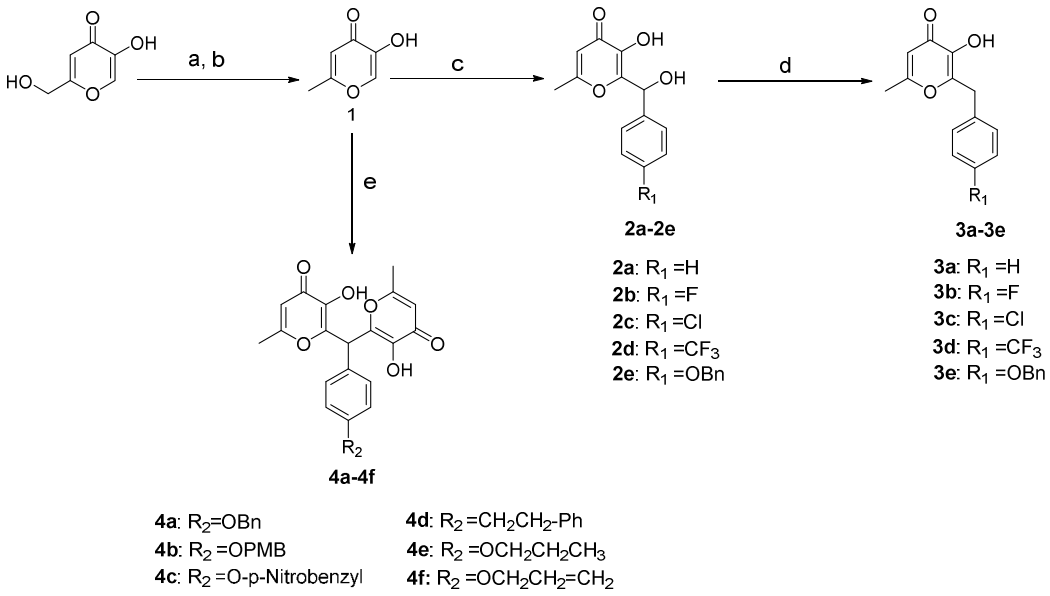

Scheme 1. Synthetic route to 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives Reagents and conditions: (a) $SOCl_2$, r.t., 1 h; (b) Zn, HCl, H_2O, 70 ^oC, 4 h; (c) aldehyde, DABCO, Dioxane:H_2O=1:1, r.t., 12 h. (d) Triethylsilane, CF_3COOH, CH_2Cl_2, r.t., overnight; (e) Aldehyde, DABCO, Dioxane:H_2O=1:1, 50 ^oC, 24 h ;

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Graphical Abstract

Design, Synthesis and Biological Evaluation of Novel 5-Hydroxy-2-methyl-4*H*-pyran-4-one Derivatives as Antiglioma Agents

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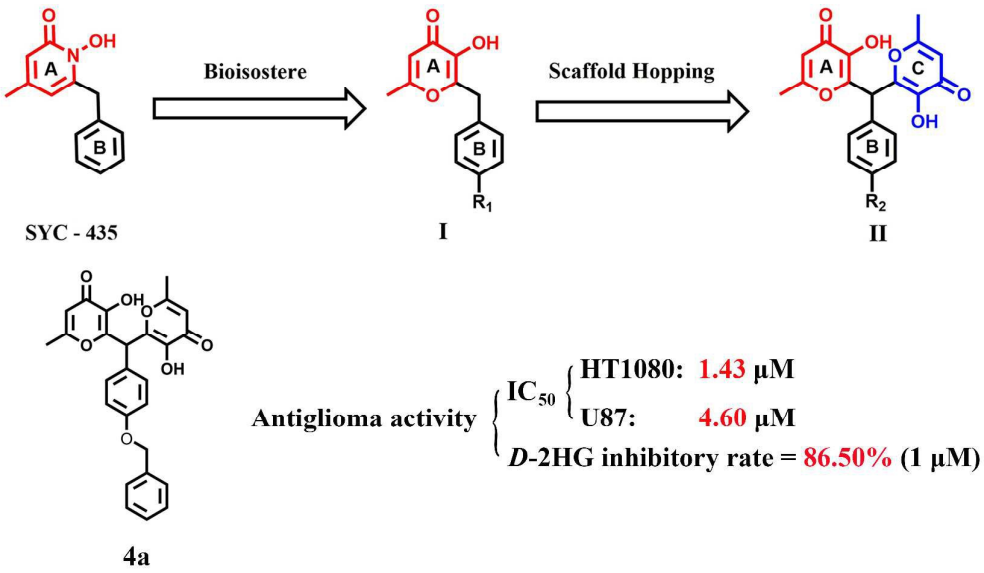

Two series of 5-hydroxy-2-methyl-4*H*-pyran-4-one derivatives were synthesized and their antiglioma activities were evaluated.