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Preparation of novel 1,2,3-triazole furocoumarin derivatives *via* click chemistry and their anti-vitiligo activity

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The extracts of *Psoralea corylifolia* L. were often used for the repigmentation of leukoderma (vitiligo) in traditional Uygur medicine thousands years ago. Nowadays, its active ingredient, furocoumarins, has been clinically applied since it exhibited strong photosensitivity. Thus, a new series of furocoumarin derivatives (**8a–8o**) containing 1,2,3-triazole were designed and synthesized based on our previous work. After biological evaluation for melanin contents and tyrosinase activity in B16 murine cells, the SAR was summarized. The results indicated that five compounds (**8a**, **8j**, **8m–8o**) were more potent than the positive control (8-MOP) on melanogenesis. Among them, **8a** and **8o** showed the best stimulating effect on tyrosinase activity as well, and were submitted for further pharmacological study of anti-vitiligo.

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1 Introduction

Vitiligo is an acquired pigmentary disorder of the skin characterized by circumscribed depigmented macules due to the destruction of the melanocyte and subsequent obstruction of melanin synthesis (Fig. 1).^{1,2} The prevalence of vitiligo is often referred to as 0.5–2% of the world's population.³ The origin of vitiligo is thought to be a complex interplay of genetics, environment, oxidative stress, and autoimmunity.^{4,5} And the autoimmune theory is the leading hypothesis that is supported by strong evidence.⁶

In humans, melanin is the primary determinant of skin color and thought to protect skin cells from UVB radiation damage, reducing the risk of cancer.⁷ It is produced by melanocytes which are found in the basal layer of the epidermis and regulated by enzymatic cascade, including tyrosinase (TYR), tyrosinase-related protein 1 (TRP-1) and tyrosinase-related protein 2 (TRP-2).⁸ Among them, TYR is the rate-limiting enzyme and is mainly involved in two distinct reactions of melanin synthesis: firstly, the hydroxylation of a monophenol and secondly, the conversion of an *o*-diphenol to the corresponding *o*-quinone.^{9,10}

Presently, there are several drugs used for the treatment of vitiligo including photosensitizer (8-MOP, khellin), topical corticosteroids (dexamethasone), calcineurin inhibitors (tacrolimus), vitamin D3 analogs (tacalcitol),¹¹ and JAK inhibitors

(ruxolitinib, baricitinib, tofacitinib) (Fig. 2), which are often used for myelodysplastic disorders, were recently proven to be efficacious for vitiligo based on a large number of clinical cases.^{12,13}

Traditional Chinese medicine is an important source of modern drugs. In Uygur medicine, the extract of *Psoralea corylifolia* L. (Fig. 3) was often used for repigmentation of vitiligo with natural sunlight and initially recorded in 'Yao Yong Zong Ku' around 300 years ago. Its active ingredient,



Fig. 1 Vitiligo with typical lesions of the face and trunk.

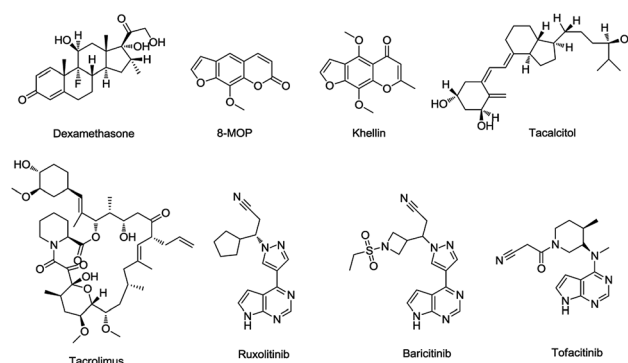


Fig. 2 Structures of commonly used drugs for vitiligo.

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Fig. 3 The plant of the *Psoralea corylifolia* L.

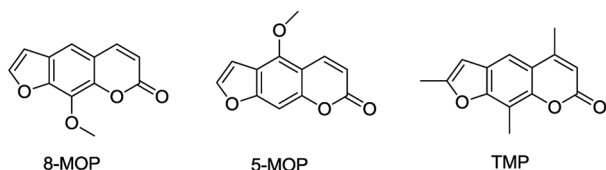


Fig. 4 The structures of the furocoumarins used for vitiligo.

furocoumarins, has been clinically applied, including 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP) and 4,5,8-trimethylpsoralen (TMP) (Fig. 4). Further research proved that these compounds exhibited strong photosensitivity,¹⁴ which may be beneficial for the repigmentation of skin with subsequent exposure to long-waved ultraviolet radiation.¹⁵ In spite of some undesired side effects,^{16,17} the therapy is still the most effective way to treat the disease today.

Unfortunately, the targets of furocoumarin for the therapies was still unknown due to the complexity of pathogenesis, and few derivatives with anti-vitiligo activity were reported.^{18–20} During past few years, many molecules with superior effect on melanogenesis and tyrosinase activity were isolated or synthesized by our group.^{21–24} The preliminary SAR of furocoumarins on vitiligo was outlined in Fig. 5 based on these studies.

1,2,3-Triazole and its derivatives showed particular promise as amide bond isosteres, given their diverse biological properties and facile synthesis from readily available azide and alkyne.^{25–28} The moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding of biomolecular targets and increasing water solubility.²⁹

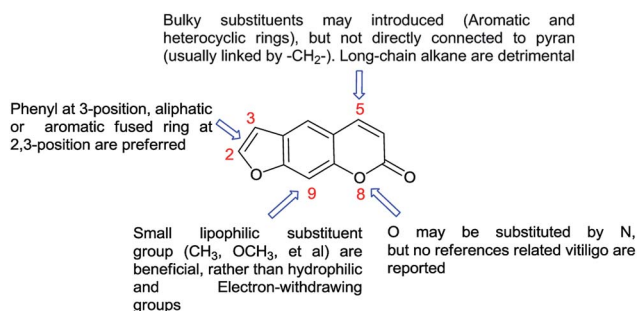


Fig. 5 The SAR of furocoumarins on vitiligo.

As depicted in Fig. 5, it is quite clear that more structure modification should be proceed on C-5 position of the furocoumarin to improve this efficiency. Thus, a new series of derivatives containing 1,2,3-triazole group was synthesized, which may be developed as better candidates for the vitiligo.

2 Results and discussion

2.1 Chemistry

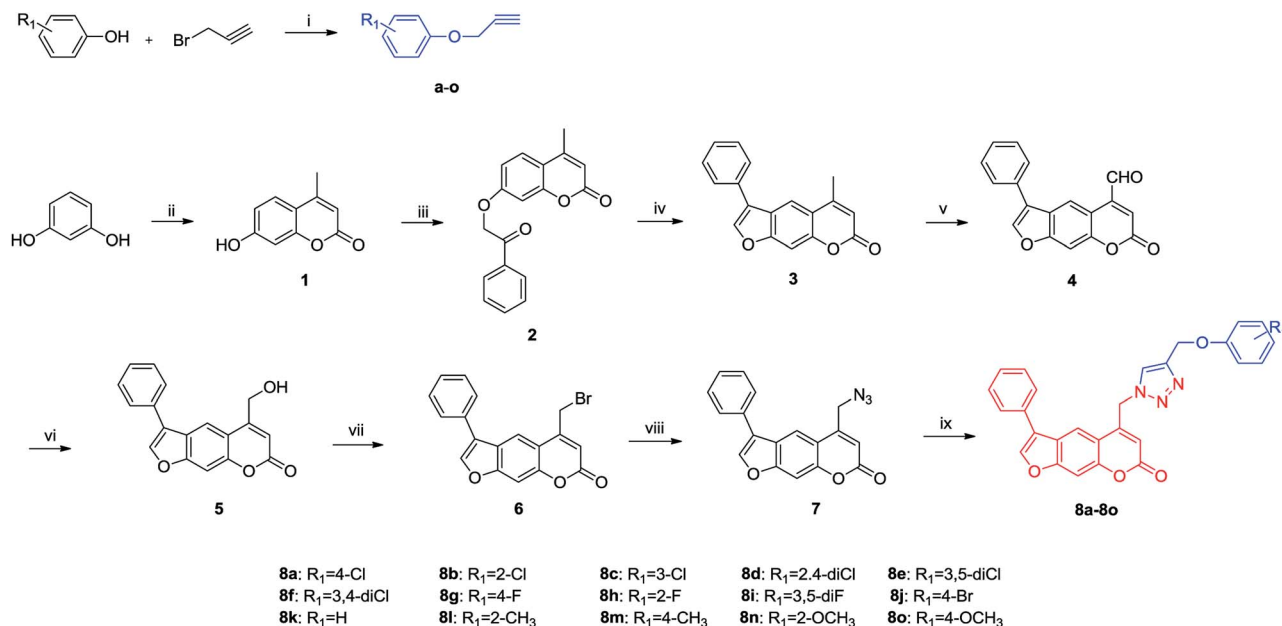
The synthetic route for the target compounds is outlined in Scheme 1. First, the commercially available material resorcinone was converted to the desired intermediate 4-methylumbelliferone **1** at a 92% yield *via* Pechmann reaction.^{30,31} Then, Williamson reaction between **1** and 2-bromoacetophenone in the presence of potassium carbonate afforded intermediate **2**, which was cyclized in 4% KOH ethanolic solution to form **3**.³² Selenium dioxide was applied in selective oxidation of compound **3** to produce 5-carbaldehyde **4**. After that, it was further reduced with NaBH_4 to achieve alcohol **5** in 76% yield.^{33,34} Bromination and azidation of hydroxy with PBr_3 and NaN_3 successively gave the key intermediate **7**. Finally, compound **7** was converted to the target **8a–8o** through click chemistry with different alkyne **a–o**.³⁵

2.2 Biological evaluation

Compounds **8a–8o** were evaluated for their activity on melanin synthesis in murine B16 cells, with a known method.³⁶ According to the results in Fig. 6, the reference drug 8-MOP enhanced the melanin synthesis by $126.03 \pm 2.97\%$ at $50 \mu\text{m}$ as compared to the blank control. Most of synthesized compounds could increase the melanin content, especially for **8a**, **8j**, **8m–8o**, which were more potent than the positive control (8-MOP) with a value from 134% to 211%. For example, derivatives bearing EDG (**8l–8o**) on benzene exhibited a stronger effect than unsubstituted **8k**. The OCH_3 group contributed more than CH_3 to the activity, such as **8o** > **8m**, **8n** > **8l**. And it seemed that the *para*-position may be superior for the substituent to improve melanin synthesis (**8m** > **8l**, **8o** > **8n**). Among these halogenated derivatives (**8a–8j**), ones with $-\text{Cl}$ and $-\text{Br}$ showed higher activity compared with $-\text{F}$ (**8a**, **8j** > **8g**, **8b** > **8h**). The position of the halogen on benzene also played an important role for their efficacy, the shift of $-\text{Cl}$ substituent from the *para*- (**8a**, 166%) into the *ortho*- or *meta*-position led to **8b** (118%) or **8c** (106%) separately, which induced a decreased value in melanin content. The similar result was observed in compounds **8g** and **8h**, substituted with $-\text{F}$ group as well. However, introduction of a second $-\text{F}$ or $-\text{Cl}$ to the benzene may not strengthen this ability (**8a** > **8d–8f**, **8g** > **8i**), and it is apparent that the presence of a halogen group in the *para*-position of the phenyl ring was crucial for melanogenesis (**8d** > **8f** > **8e**).

After that, all these derivatives were further studied for their stimulating effect on tyrosinase.³⁷ As shown in Fig. 7, only two compounds (**8a**, **8o**) showed a higher value than 8-MOP. And it can be noticed that the $-\text{Cl}$, and $-\text{OCH}_3$ groups might be favorable to enhance the activity among these monosubstituted compounds, since the value of them were all over 110% (**8a–8c**,





Scheme 1 Synthesis of furocoumarin derivatives containing 1,2,3-triazole (**8a–8o**). Reagents and conditions: (i) DMF, K₂CO₃, 70 °C (ii) ethyl acetoacetate, H₂SO₄, 60 °C (iii) 2-bromoacetophenone, K₂CO₃, acetone, reflux (iv) 4% KOH ethanolic solution, reflux (v) SeO₂, xylene, reflux (vi): NaBH₄, methanol, rt (vii): PBr₃, THF, 0 °C–rt (viii): NaN₃, CH₃CN, reflux (ix) **a–o**, CuSO₄·5H₂O, Cu, *t*-BuOH : H₂O = 1 : 3, 80 °C.

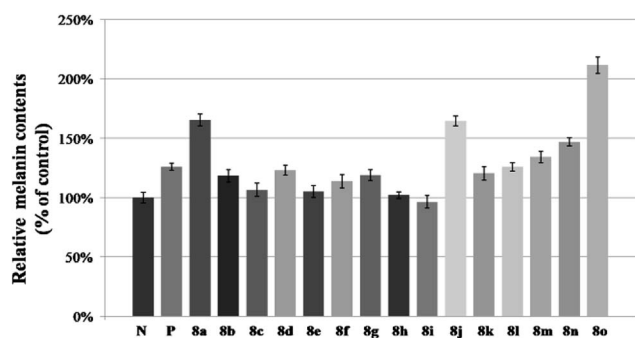


Fig. 6 Stimulation of melanin content of B16 cells by **8a–8o**. N means negative control; P means positive control (**8-MOP**); the B16 cells was treated with 50 μM different furocoumarin derivatives for 48 h. After that, melanin content was measured directly. Values are expressed as the mean ± SD of three separate experiments, *P* < 0.05.

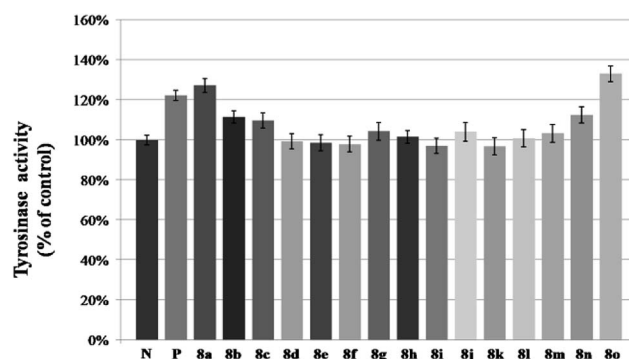


Fig. 7 Stimulation of tyrosinase activity of B16 cells by **8a–8o**. N means negative control; P means positive control (**8-MOP**). B16 cells was treated with 50 μM different furocoumarin derivatives for 48 h. After that, tyrosinase activity was measured directly. The data are the mean ± SD of three experiments, *P* < 0.05.

8n–8o > 110%). Changing the position of –Cl on benzene ring weakened stimulatory efficiency (**8a** > **8b** or **8c**), indicating that the presence of a substituent in the *para*-position may be beneficial for the enzyme activation, and it was also applicable for the OCH₃ group (**8o** > **8n**). Nevertheless, dihalide derivatives possessed a lower activity than mono- ones. Additionally, the effect of most potential **8a**, **8n**, on both melanin synthesis and tyrosinase activity, were positively in a concentration dependent manner as depicted in Fig. 8.

3 Experimental

3.1 Chemistry

Reagents and solvents were purchased from Sigma, and used without further purification. Thin-layer chromatography (TLC)

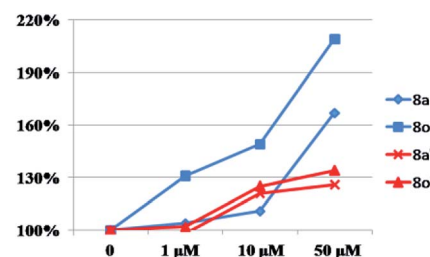


Fig. 8 The concentration dependent manner of **8a**, **8o** on melanin synthesis and tyrosinase activity. “♦”, “■” and “x”, “▲” means the effect of **8a**, **8o** on melanin synthesis (in blue) and tyrosinase activity (in red) separately at different concentration in B16 cells.



was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200–300 mesh). Melting points were determined on a Buchi B-540 apparatus and uncorrected. All the NMR spectra were recorded with a Varian 400 MHz NMR spectrometer in CDCl₃ or acetone-*d*₆, using TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded on AB SCIEX QSTAR Elite quadrupole time-of-flight mass spectrometry. The IR data were recorded on a Thermo Fisher Scientific Nicolet 6700 FT-IR infrared spectrometer (KBr).

3.1.1 General procedure of preparation of alkyne a–o. To substituted phenol (3.50 mmol) and potassium carbonate (10.5 mmol, 1.45 g) in DMF was added 3-bromopropyne (4.20 mmol, 500 mg) and stirred at 70 °C overnight. Then the mixture was quenched with water, extraction was with DCM (20 mL × 3) and the combined organic layer was washed by saturated sodium chloride solution for three times, dried by anhydrous Na₂SO₄ and concentrated under reduced pressure to give a oil or solid, which was purified by silica gel chromatography.

a: ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.67 (d, *J* = 2.4 Hz, 2H), 2.52 (t, *J* = 2.4 Hz, 1H).

d: ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 2.5 Hz, 1H), 7.20 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 4.76 (d, *J* = 2.4 Hz, 2H), 2.55 (t, *J* = 2.3 Hz, 1H).

e: ¹H NMR (400 MHz, CDCl₃) δ 7.01 (t, *J* = 1.7 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 2H), 4.67 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H).

k: ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.29 (m, 2H), 7.05–6.97 (m, 3H), 4.71 (d, *J* = 2.4 Hz, 2H), 2.53 (t, *J* = 2.4 Hz, 1H).

l: ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.21, (m, 2H), 7.06–6.95 (m, 2H), 4.76 (d, *J* = 2.4 Hz, 2H), 2.56 (t, *J* = 2.4 Hz, 1H), 2.34 (s, 3H).

o: ¹H NMR (400 MHz, CDCl₃) δ 6.93 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 4.64 (d, *J* = 2.4 Hz, 2H), 3.77 (s, 3H), 2.51 (t, *J* = 2.3 Hz, 1H).

3.1.2 Preparation of 7-hydroxy-4-methyl-2H-chromen-2-one (1). To an ice-cold solution of resorcinol (2.0 g, 18.2 mol) in dioxane, conc. H₂SO₄ (0.5 mL) was added dropwise under 20 °C. After that, ethyl acetoacetate (2.8 g, 21.8 mmol) was added, and the mixture was heated to 60 °C for 4 h. Then, the mixture was poured into cold water, and the precipitate was filtered and dried under reduced pressure. The resulting mixture was recrystallized from methanol to give **1** as white needle crystals. Yield 92%, mp 202–204 °C.

3.1.3 Preparation of 4-methyl-7-(2-oxo-2-phenylethoxy)-2H-chromen-2-one (2). A mixture of **1** (0.88 g, 5.0 mmol) with 2-bromoacetophenone (1.49 g, 7.5 mmol) and anhydrous K₂CO₃ (1.4 g, 10 mmol) in acetone (50 mL) was refluxed under stirring for 4 h. After cooling, the reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography with petroleum ether/ethyl acetate to give intermediate **2**. Yield 90%, white solid, mp 162–164 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.51 (m, 7.55–

7.48, 3H), 6.94 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.13 (d, *J* = 1.1 Hz, 1H), 5.38 (s, 2H), 2.38 (d, *J* = 1.1 Hz, 3H).

3.1.4 Preparation of 5-methyl-3-phenyl-7H-furo[3,2-*g*]chromen-7-one (3). To an ethanolic solution (100 mL) of intermediate **2** (2.94 g, 10 mmol) was added a 4% ethanol potassium hydroxide solution (20 mL) and the mixture was refluxed for 4 h. After cooling, the solution was acidified with 1 M hydrochloric acid and extracted with ethyl acetate three times. The organic phase was dried over night and evaporated under reduced pressure. The resulting residue was purified by silica gel chromatography with petroleum ether/ethyl acetate to give compound **3**. Yield 95%, white solid, mp 171–173 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.83 (s, 1H), 7.64 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.50–7.56 (m, 3H), 7.44 (td, *J* = 7.4, 1.1 Hz, 1H), 6.29 (s, 1H), 2.52 (s, 3H).

3.1.5 Preparation of 7-oxo-3-phenyl-7H-furo[3,2-*g*]chromene-5-carbaldehyde (4). Powdered SeO₂ (3.33 g, 30 mmol) was added to a solution of **3** (5.52 g, 20 mmol) in 20 mL of hot dry xylene and the mixture were refluxed for 24 h with vigorous stirring under the nitrogen. The reaction mixture was filtered to remove black Se, and the deep orange filtrate was allowed to stand overnight. Almost pure crystals of **4** could be separated from the solution. Yield 63%, yellow solid, mp 148–150 °C; ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 9.10 (s, 1H), 7.87 (s, 1H), 7.66 (d, *J* = 7.4 Hz, 2H), 7.59–7.49 (m, 3H), 7.44 (t, *J* = 7.2 Hz, 1H), 6.86 (s, 1H).

3.1.6 Preparation of 5-(hydroxymethyl)-3-phenyl-7H-furo[3,2-*g*]chromen-7-one (5). Compound **4** (5.80 g, 20 mmol) was dissolved in ethanol (130 mL), sodium borohydride (380 mg, 10.0 mmol) was added, and the solution was stirred for 2 h at room temperature. Thereafter the suspension was carefully hydrolyzed with 1 M HCl (20 mL), diluted with H₂O and extracted three times with DCM. The organic phase was washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford alcohol **5**. Yield 76%, white solid, mp 99–100 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (s, 1H), 7.79 (s, 1H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.55–7.47 (m, 2H), 7.46–7.38 (m, 2H), 6.62 (s, 1H), 4.97 (s, 2H).

3.1.7. Preparation of 5-(bromomethyl)-3-phenyl-7H-furo[3,2-*g*]chromen-7-one (6). A mixture of **5** (2.92 g, 10 mmol) in anhydrous THF (25 mL) was cooled to 0 °C, a solution of PBr₃ (0.95 mL, 10 mmol) in THF (2 mL) was added dropwise in ice-bath and stirred at room temperature. After the raw material consumed, the mixture was neutralized with NaHCO₃ and extracted with DCM two times. The organic phase was evaporated under reduced pressure and purified by silica gel chromatography with petroleum ether/ethyl acetate to give **6**. Yield 88%, light yellow solid, mp 175–177 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.86 (s, 1H), 7.68–7.61 (m, 3H), 7.58–7.53 (m, 3H), 6.53 (s, 1H), 4.57 (s, 2H).

3.1.8 Preparation of 5-(azidomethyl)-3-phenyl-7H-furo[3,2-*g*]chromen-7-one (7). To **6** (3.55 g, 10 mmol) in acetonitrile was added sodium azide (0.96 g, 14.8 mmol) and stirred at reflux for 12 h. The resulting mixture was evaporated under reduced pressure and purified by silica gel chromatography with petroleum ether/ethyl acetate to give compound **7**. Yield 81%, yellow



solid, mp 188–190 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (s, 1H), 7.85 (s, 1H), 7.62 (d, $J = 7.3$, 2H), 7.58–7.53 (m, 3H), 7.45 (t, $J = 7.4$, 1H), 6.53 (s, 1H), 4.64 (s, 2H).

3.1.9 General procedure of preparation of 8a–8o. To compound 7 (0.32 g, 1.0 mmol) and alkyne a–o (1.2 mmol) in 20 mL mixture ($V_{\text{tert-butanol}}/V_{\text{H}_2\text{O}} = 3 : 1$) were added copper sulfate pentahydrate (0.44 mg, 1.75 mmol) and copper (0.06 g, 1.0 mmol). The reaction was stirred at 80 °C overnight. Then the suspension was extracted with DCM (10 mL \times 2), the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography to afford final compounds 8a–8o.

3.1.9.1 5-((4-((3-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8a). Yield 84%, light yellow solid, mp 180–182 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.58–7.53 (m, 5H), 7.48–7.41 (m, 1H), 7.21 (d, $J = 9.0$ Hz, 2H), 6.88 (d, $J = 9.0$ Hz, 2H), 6.05 (s, 1H), 5.80 (s, 2H), 5.21 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.06, 157.52, 156.70, 152.07, 148.18, 143.47, 130.56, 129.60, 129.54, 128.48, 127.65, 124.70, 123.40, 122.48, 116.24, 115.20, 114.02, 113.62, 101.06, 62.33, 50.95; IR (KBr) ν : 2925, 1732, 1635, 1576, 1489, 1240, 1151, 823 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{19}\text{ClN}_3\text{O}_4[\text{M} + \text{H}]^+$ 484.0986, found 484.0993.

3.1.9.2 5-((4-((2-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8b). Yield 86%, light yellow solid, mp 198–201 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 7.59–7.50 (m, 5H), 7.48–7.40 (m, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.22–7.15 (m, 1H), 7.06 (d, $J = 8.2$ Hz, 1H), 6.94–6.87 (m, 1H), 6.02 (s, 1H), 5.81 (s, 2H), 5.33 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.05, 157.51, 153.66, 152.08, 148.24, 145.51, 143.42, 132.60, 131.02, 130.57, 129.53, 128.95, 128.46, 127.98, 127.67, 124.68, 123.49, 122.51, 115.16, 114.57, 113.92, 101.05, 63.52, 50.90; IR (KBr) ν : 2926, 1719, 1634, 1484, 1273, 1152, 1067, 754 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{19}\text{ClN}_3\text{O}_4[\text{M} + \text{H}]^+$ 484.0986, found 484.0977.

3.1.9.3 5-((4-((3-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8c). Yield 82%, light yellow solid, mp 110–111 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.59–7.52 (m, 5H), 7.48–7.41 (m, 1H), 7.22–7.15 (m, 1H), 6.99–6.92 (m, 2H), 6.85 (d, $J = 8.6$ Hz, 1H), 6.06 (s, 1H), 5.81 (s, 2H), 5.22 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.06, 158.84, 157.53, 152.09, 148.17, 143.45, 135.14, 131.06, 130.56, 130.50, 129.54, 128.48, 127.67, 123.36, 121.83, 115.56, 115.21, 114.04, 113.64, 113.22, 110.17, 108.07, 101.08, 62.27, 50.96; IR (KBr) ν : 2924, 1733, 1635, 1457, 1274, 1152 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{19}\text{ClN}_3\text{O}_4[\text{M} + \text{H}]^+$ 484.0986, found 484.1004.

3.1.9.4 5-((4-((2,4-Dichlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8d). Yield 86%, light yellow solid, mp 121–123 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.59–7.50 (m, 5H), 7.48–7.41 (m, 1H), 7.32 (d, $J = 2.4$ Hz, 1H), 7.14 (dd, $J = 8.8$, 2.5 Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 1H), 6.03 (s, 1H), 5.81 (s, 2H), 5.30 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.13, 157.53, 155.69, 152.48, 148.16, 143.47, 142.31, 131.06, 130.29, 129.53, 128.99, 128.47, 127.87, 127.65, 125.78, 124.70, 123.58, 115.35,

115.14, 113.98, 110.98, 101.09, 63.68, 50.95; IR (KBr) ν : 2925, 1733, 1635, 1576, 1473, 1271 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 518.0669, found 518.0680.

3.1.9.5 5-((4-((3,5-Dichlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8e). Yield 88%, light yellow solid, mp 223–224 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.57–7.51 (m, 5H), 7.48–7.41 (m, 1H), 6.97 (t, $J = 1.8$ Hz, 1H), 6.87 (d, $J = 1.7$ Hz, 2H), 6.07 (s, 1H), 5.82 (s, 2H), 5.20 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.04, 157.32, 156.52, 152.79, 148.11, 143.48, 131.06, 129.54, 129.41, 128.99, 128.49, 127.66, 124.73, 123.47, 121.98, 115.20, 114.06, 113.77, 109.69, 101.10, 62.44, 50.98; IR (KBr) ν : 2926, 1732, 1634, 1571, 1457, 1273, 1150, 1074 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 518.0669, found 518.0651.

3.1.9.6 5-((4-((3,4-Dichlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8f). Yield 80%, light yellow solid, mp 159–161 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.59–7.52 (m, 5H), 7.49–7.41 (m, 1H), 7.30 (d, $J = 8.9$ Hz, 1H), 7.07 (d, $J = 2.9$ Hz, 1H), 6.82 (dd, $J = 9.0$, 2.9 Hz, 1H), 6.06 (s, 1H), 5.81 (s, 2H), 5.20 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.05, 157.54, 157.10, 156.31, 152.08, 148.13, 143.49, 130.95, 129.53, 128.48, 127.65, 124.72, 123.47, 122.49, 117.05, 115.19, 114.77, 114.05, 113.60, 110.15, 101.09, 62.46, 50.98; IR (KBr) ν : 2924, 1733, 1653, 1576, 1473, 1274, 1048 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 518.0669, found 518.0682.

3.1.9.7 5-((4-((4-Fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8g). Yield 82%, light yellow solid, mp 184–185 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.59–7.50 (m, 6H), 7.48–7.41 (m, 1H), 6.99–6.85 (m, 4H), 6.04 (s, 1H), 5.80 (s, 2H), 5.19 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.06, 157.50, 156.54, 154.20, 152.05, 148.24, 143.45, 131.02, 129.53, 128.93, 128.46, 127.65, 124.67, 123.40, 122.48, 116.21, 115.98, 115.20, 113.95, 113.63, 101.03, 62.71, 50.90; IR (KBr) ν : 2926, 1732, 1634, 1576, 1506, 1389, 1202, 1152, 1040 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{19}\text{FN}_3\text{O}_4[\text{M} + \text{H}]^+$ 468.1354, found 468.1367.

3.1.9.8 5-((4-((2-Fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8h). Yield 85%, light yellow solid, mp 166–167 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.61–7.49 (m, 5H), 7.47–7.40 (m, 1H), 7.12–6.96 (m, 3H), 6.96–6.85 (m, 1H), 6.01 (s, 1H), 5.80 (s, 2H), 5.30 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.03, 157.50, 154.29, 152.06, 148.21, 146.00, 143.42, 132.45, 131.05, 130.56, 129.52, 128.97, 128.45, 127.66, 124.58, 122.41, 116.46, 115.19, 113.94, 113.66, 101.03, 63.65, 50.94; IR (KBr) ν : 2925, 1733, 1634, 1506, 1457, 1257, 1152, 1047 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{19}\text{FN}_3\text{O}_4[\text{M} + \text{H}]^+$ 468.1354, found 468.1371.

3.1.9.9 5-((4-((3,5-Difluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (8i). Yield 83%, light yellow solid, mp 210–212 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.59–7.52 (m, 5H), 7.47–7.43 (m, 1H), 6.50 (d, $J = 8.8$ Hz, 2H), 6.43 (t, $J = 8.9$ Hz, 1H), 6.06 (s, 1H), 5.82 (s, 2H), 5.19 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.04, 157.54, 155.60, 152.09, 148.12, 143.48, 131.06, 129.54, 128.99, 128.49, 127.66, 124.74, 123.02, 122.53, 115.20,



114.05, 113.58, 109.19, 101.09, 62.49, 50.98; IR (KBr) ν : 2923, 1732, 1599, 1465, 1275, 1152, 1042, 996 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{18}\text{F}_2\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 486.1260, found 486.1248.

3.1.9.10 5-((4-(4-Bromophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (**8j**). Yield 84%, light yellow solid, mp 104–105 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.59–7.51 (m, 5H), 7.48–7.41 (m, 1H), 7.35 (d, $J = 8.9$ Hz, 2H), 6.84 (d, $J = 8.9$ Hz, 2H), 6.05 (s, 1H), 5.80 (s, 2H), 5.20 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.06, 157.52, 157.21, 153.19, 152.07, 148.17, 143.47, 132.54, 129.54, 128.48, 127.65, 124.69, 123.41, 122.49, 116.75, 115.20, 114.03, 113.85, 113.62, 101.07, 62.25, 50.95; IR (KBr) ν : 2926, 1733, 1635, 1576, 1489, 1457, 1276, 1150 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{19}\text{BrN}_3\text{O}_4[\text{M} + \text{H}]^+$ 528.0553, found 528.0571.

3.1.9.11 5-((4-(Phenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (**8k**). Yield 85%, light yellow solid, mp 152–154 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.61–7.50 (m, 5H), 7.48–7.41 (m, 1H), 7.30–7.24 (m, 2H), 7.00–6.92 (m, 3H), 6.05 (s, 1H), 5.80 (s, 2H), 5.24 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.07, 158.12, 157.51, 152.08, 148.24, 143.42, 130.57, 129.72, 129.53, 128.46, 127.67, 124.68, 123.32, 122.52, 121.59, 115.23, 114.91, 114.00, 113.67, 101.03, 62.09, 50.90; IR (KBr) ν : 2925, 1732, 1634, 1490, 1274, 1150, 1047 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{20}\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 450.1448, found 450.1433.

3.1.9.12 5-((4-(*o*-Tolyloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (**8l**). Yield 89%, light yellow solid, mp 160–161 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.86 (s, 1H), 7.68 (s, 1H), 7.61–7.50 (m, 5H), 7.48–7.41 (m, 1H), 7.08–7.17 (m, 2H), 6.96–6.83 (m, 2H), 6.04 (s, 1H), 5.81 (s, 2H), 5.25 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.09, 157.51, 156.28, 152.08, 148.31, 143.39, 131.02, 130.57, 129.53, 128.46, 127.67, 127.01, 124.68, 122.52, 121.31, 115.19, 113.89, 113.69, 111.70, 101.07, 62.41, 50.92, 29.86; IR (KBr) ν : 2925, 1733, 1635, 1460, 1273, 1152, 1046 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 464.1605, found 464.1616.

3.1.9.13 5-((4-(*p*-Tolyloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (**8m**). Yield 91%, light yellow solid, mp 218–220 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.60–7.51 (m, 5H), 7.48–7.41 (m, 1H), 7.06 (d, $J = 8.1$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.05 (s, 1H), 5.79 (s, 2H), 5.20 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.07, 157.50, 156.00, 152.08, 148.23, 143.45, 143.37, 130.89, 130.57, 130.15, 129.54, 128.46, 127.67, 124.67, 122.52, 115.28, 115.23, 114.81, 114.06, 113.99, 113.68, 101.05, 62.26, 50.98, 29.85; IR (KBr) ν : 2925, 1733, 1647, 1508, 1457, 1388, 1228, 1151, 1050 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$ 464.1605, found 464.1589.

3.1.9.14 5-((4-(2-Methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (**8n**). Yield 90%, light yellow solid, mp 172–173 °C; ^1H NMR (600 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.59–7.51 (m, 5H), 7.48–7.41 (m, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 6.95–6.90 (m, 1H), 6.89–6.81 (m, 2H), 6.05 (s, 1H), 5.78 (s, 2H), 5.32 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.06, 157.52, 156.69, 152.11, 148.21, 147.44, 145.97, 143.39, 130.57, 130.18, 129.54, 128.45, 127.68, 124.67, 123.44, 122.39, 121.02, 115.30, 114.94, 114.09, 113.70, 112.08,

101.02, 63.48, 55.96, 50.90; IR (KBr) ν : 2926, 1733, 1635, 1505, 1457, 1388, 1253, 1150, 1074, 1026 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{N}_3\text{O}_5[\text{M} + \text{H}]^+$ 480.1554, found 480.1539.

3.1.9.15 5-((4-(4-Methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-phenyl-7H-furo[3,2-g]chromen-7-one (**8o**). Yield 88%, light yellow solid, mp 195–197 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.60–7.50 (m, 5H), 7.48–7.41 (m, 1H), 6.93 (d, $J = 9.1$ Hz, 2H), 6.84 (d, $J = 9.1$ Hz, 2H), 6.03 (s, 1H), 5.79 (s, 2H), 5.19 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.07, 157.50, 154.47, 152.19, 151.82, 148.25, 143.46, 130.57, 129.54, 128.46, 127.67, 124.67, 122.51, 116.29, 116.08, 115.20, 114.84, 114.00, 113.67, 101.06, 62.88, 55.79, 50.98; IR (KBr) ν : 2927, 1717, 1631, 1574, 1439, 1388, 1257, 1151, 1082, 1109 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{N}_3\text{O}_5[\text{M} + \text{H}]^+$ 480.1554, found 480.1570.

3.2 Biological activity

3.2.1 Cell cultures. The murine B16 melanoma cell line was purchased from Chinese Academy of Sciences (Beijing, China). The cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM, Gibco Life Technologies, France) supplemented with 10% (v/v) FBS, penicillin G (100 U mL^{-1}) and streptomycin (100 mg mL^{-1}) (Gibco-BRL, Grand Island, NY, USA) in 5% CO_2 at 37 °C.

3.2.2 Cell viability measurement. The cell viability was assayed by adding CCK-8 solution. Generally speaking, the B16 cells were seeded in 96-well plates at a density of 8×10^3 cells per well and allowed to adhere for 24 h. The medium was replaced with medium containing samples diluted to the appropriate concentrations. The control cells were treated with DMSO at a final concentration of 0.1%. After 24 h, the culture medium of the cells was discarded, 10 μL of CCK-8 solution was added into each well and cells were incubated at 37 °C for another 2 h. The absorbance was measured at 450 nm using a Spectra Max M5 (Molecular Devices, USA). All assays were performed in triplicate. Absorbance of cells without treatment was regarded as 100% of cell survival. Cell viability was calculated using the following formula: cell viability (%) = $(A_{\text{sample}}/A_{\text{control}}) \times 100\%$.

3.2.3 Melanin measurement. B16 cells were seeded at a density of 2×10^5 cells per well in a 6-well plate. After overnight incubation, test samples were added to individual wells, cells were incubated for 48 h and washed twice with ice-cold PBS. After cells lysed, the harvested cells were centrifuged, and the pellet was dissolved by adding 1 N NaOH, followed by incubation at 80 °C for 1 h. Each lysate (150 μL) was put in a 96-well microplate, and measured spectro-photometrically at 405 nm by a multi-plate reader. Protein concentration of each sample was determined by BCA Protein Assay Kit (Biomed, Beijing). Intracellular melanin amount expressed as abs per μg protein was shown as a percentage value. The percentage value of the samples treated cells was calculated with respect to the untreated cells.

3.2.4 Tyrosinase activity assay. The assay for tyrosinase activity was carried out as previously described, with a slight modification.³⁷ B16 cells were seeded in a 6-well plate at



a density of 2×10^5 cells per well and allowed to attach for 24 h. Test samples were then added to individual wells. After a 24 h incubation, cells were washed with ice-cold PBS twice, lysed with 1% Triton X-100 solution containing 1% sodium deoxycholate for 30 min at -80°C , each lysate was centrifuged at 12 000g for 15 min to obtain the supernatant. After protein quantification and adjustment, 90 μL of the supernatant was incubated in duplicate with 10 μL of freshly prepared substrate solution (10 mM L-DOPA) in a well of a 96-well plate. Then the cells were incubated at 37°C in dark for 60 min, the absorbance was measured at 490 nm and the samples treated cells was presented as percentage against the untreated cells.

4 Conclusions

In summary, a novel series of furocoumarin derivatives bearing 1,2,3-triazole had been prepared *via* click chemistry. Two of them (**8a**, **8o**) could not only promote the melanin synthesis, but also the tyrosinase activity *in vitro* than positive control (8-MOP) in a concentration dependent manner, and the SAR was summarized. In light of our findings, it may provide scientific guidance for further structural modification of the furocoumarin, even if without knowing the specific targets of the disease. Further studies on action mechanism and animal experiment on transgenic mouse is under way.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 K. Ezzedine, V. Eleftheriadou, M. Whitton and N. van Geel, *Lancet*, 2015, **386**, 74–84.
- 2 M. Rodrigues, K. Ezzedine, I. Hamzavi, A. G. Pandya and J. E. Harris, *J. Am. Acad. Dermatol.*, 2017, **77**, 1–13.
- 3 K. Ezzedine, H. W. Lim, T. Suzuki, I. Katayama, I. Hamzavi, C. C. E. Lan, B. K. Goh, T. Anbar, C. Silva de Castro, A. Y. Lee, D. Parsad, N. van Geel, I. C. Le Poole, N. Oiso, L. Benzekri, R. Spritz, Y. Gauthier, S. K. Hann, M. Picardo and A. Taieb, *Pigm. Cell Melanoma Res.*, 2012, **25**, E1–E13.
- 4 N. C. Laddha, M. Dwivedi, M. S. Mansuri, A. R. Gani, M. Ansarullah, A. V. Ramachandran, S. Dalai and R. Begum, *Exp. Dermatol.*, 2013, **22**, 245–250.
- 5 S. Wang, R. Jin, R. Wang, Y. Hu, X. Dong and A. Xu, *RSC Adv.*, 2016, **6**, 106308–106315.
- 6 J. M. Richmond, M. L. Frisoli and J. E. Harris, *Curr. Opin. Immunol.*, 2013, **25**, 676–682.
- 7 P. Meredith and J. Riesz, *Photochem. Photobiol.*, 2004, **79**, 211–216.
- 8 M. Sandoval-Cruz, M. García-Carrasco, R. Sánchez-Porras, C. Mendoza-Pinto, M. Jiménez-Hernández, P. Munguía-Realpozo and A. Ruiz-Argüelles, *Autoimmun. Rev.*, 2011, **10**, 762–765.
- 9 M. M. García-Molina, J. L. Muñoz-Muñoz, F. Garcia-Molina, P. A. García-Ruiz and F. Garcia-Canovas, *J. Agric. Food Chem.*, 2012, **60**, 6447–6453.
- 10 Q. Wu, Z. Xu, Y. Duan, Y. Zhu, M. Oua and X. Xu, *RSC Adv.*, 2017, **7**, 28114–28123.
- 11 M. L. Felsten, A. Alikhan and V. Petronic-Rosic, *J. Am. Acad. Dermatol.*, 2011, **65**, 493–514.
- 12 W. Damsky and B. A. King, *J. Am. Acad. Dermatol.*, 2017, **76**, 736–744.
- 13 J. E. Harris, M. Rashighi, N. Nguyen, A. Jabbari, G. Ulerio, R. Clynes, A. M. Christiano and J. Mackay-Wiggan, *J. Am. Acad. Dermatol.*, 2016, **74**, 370–371.
- 14 W. L. Fowues, D. G. Griffith and E. L. Oginsky, *Nature*, 1958, **18**, 571–572.
- 15 T. B. Fitzpatrick, J. A. Parrish and M. A. Pathak, in *Phototherapy of vitiligo (idiopathic leukoderma) in sunlight and man*, Tokyo University Press, 1974, pp. 365–398.
- 16 L. M. Felsten, A. Alikhan and V. Petronic-Rosic, *J. Am. Acad. Dermatol.*, 2011, **65**, 473–491.
- 17 S. Tippisetty, D. Goudi, A. W. Mohammed and P. Jahan, *Toxicol. In Vitro*, 2013, **27**, 438–440.
- 18 A. Guiotto, P. Rodighiero, P. Manzini, G. Pastohi, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi, F. Dall'Acqua, M. Tamaro, G. Recchia and M. Cristofolini, *J. Med. Chem.*, 1984, **27**, 959–967.
- 19 H. Matsuda, N. Hirata, Y. Kawaguchi, M. Yamazaki, S. Naruto, M. Shibano, M. Taniguchi, K. Baba and M. Kubo, *Biol. Pharm. Bull.*, 2005, **28**, 1229–1233.
- 20 E. Chodurek, A. Orchel, J. Orchel, S. Kurkiewicz, N. Gawlik, Z. Dzierżewicz and K. Stepien, *Cell. Mol. Biol. Lett.*, 2012, **17**, 616–632.
- 21 C. Niu, G. X. Pang, G. Li, J. Dou, L. F. Nie, H. Himitt, K. Kabas and H. A. Hisa, *Bioorg. Med. Chem.*, 2016, **24**, 5960–5968.
- 22 L. Yin, G. X. Pang, C. Niu, J. Dou and H. A. Aisa, *Int. J. Mol. Med.*, 2018, **41**, 3727–3735.
- 23 C. Niu, D. Zang and H. A. Aisa, *Chem. Res. Chin. Univ.*, 2018, **34**, 408–414.
- 24 C. Niu and H. A. Aisa, *Molecules*, 2017, **22**, 1303–1330.
- 25 P. Yadav, K. Lal, A. Kumar, S. K. Guru, S. Jaglan and S. Bhushan, *Eur. J. Med. Chem.*, 2017, **126**, 944–953.
- 26 N. Pribut, C. G. L. Veale, A. E. Basson, W. A. L. van Otterlo and S. C. Pelly, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3700–3704.
- 27 S. Maračić, T. G. Kraljević, H. Č. Paljetak, M. Matijašić, D. Verbanac, M. Cetina and S. Raić-Malić, *Bioorg. Med. Chem.*, 2015, **23**, 7448–7463.
- 28 N. Fu, S. Wang, Y. Zhang, C. Zhang, D. Yang, L. Weng, B. Zhao and Li. Wang, *Eur. J. Med. Chem.*, 2017, **136**, 596–602.
- 29 N. S. Vatmurge, B. G. Hazra, V. S. Pore, F. Shirazi, P. S. Chavan and M. V. Deshpande, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2043–2047.



- 30 B. L. Zhang, C. Q. Fan, L. Dong, F. D. Wang and J. M. Yue, *Eur. J. Med. Chem.*, 2010, **45**, 5258–5264.
- 31 E. C. Gaudino, S. Tagliapietra, K. Martina, G. Palmisanob and G. Cravotto, *RSC Adv.*, 2016, **6**, 46394–46405.
- 32 A. Chilin, P. Manzini, S. Caffieri, P. Rodighiero and A. Guiotto, *J. Heterocycl. Chem.*, 2001, **38**, 431–434.
- 33 Q. Shen, Q. Peng, J. L. Sha, X. Liu, Z. Huang, X. Pu, L. Ma, Y. M. Li, A. S. C. Chan and L. Gu, *Eur. J. Med. Chem.*, 2005, **40**, 1307–1315.
- 34 R. O. Schönleber, J. Bendig, V. Hagen and B. Giese, *Bioorg. Med. Chem.*, 2002, **10**, 97–101.
- 35 Y. Hu, H. Shen, X. Zhang, Y. Liu and X. Sun, *RSC Adv.*, 2018, **8**, 23252–23256.
- 36 S. Y. Park, M. L. Jin, Y. H. Kim, Y. Kim and S. J. Lee, *Arch. Dermatol. Res.*, 2011, **303**, 737–744.
- 37 H. J. Kim, J. S. Kim, J. T. Woo, J. T. Woo, I. S. Lee and B. Y. Cha, *Acta Biochim. Biophys. Sin.*, 2015, **47**, 548–556.

