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Synthesis and biological evaluation of 4-(1,2,3-triazol-1-yl)coumarin derivatives as potential antitumor agents

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ABSTRACT

In this research, a series of 4-(1,2,3-triazol-1-yl)coumarin conjugates were synthesized and their anticancer activities were evaluated in vitro against three human cancer cell lines, including human breast carcinoma MCF-7 cell, colon carcinoma SW480 cell and lung carcinoma A549 cell. To increase the biological potency, structural optimization campaign was conducted focusing on the C-4 position of 1,2,3-triazole and the C-6, C-7 positions of coumarin. In addition, to further evaluate the role of 1,2,3-triazole and coumarin for antiproliferative activity, 9 compounds possessing 4-(piperazin-1-yl)coumarin framework and 3 derivatives baring quinoline core were also synthesized. By MTT assay in vitro, most of the compounds display attractive antitumor activities, especially **23**. Further flow cytometry assays demonstrate that compound **23** exerts the antiproliferative role through arresting G_2/M cell-cycle and inducing apoptosis.

Coumarin derivatives which are widely distributed in the plants[1,2] have been extensively investigated as anticoagulation, antiviral,[3–5] anti-inflammatory,[6,7] antibacterial[8] and anticancer[9–17] agents. Another promising group, 1,2,3-triazole, has emerged as one of the most important heterocycles in current medicinal chemistry[18–20] and its applications have also been extended to widespread diseases.[21–24] In recent years, a library of coumarin derivatives conjugated with 1,2,3-triazole were synthesized and proved to possess different bioactivity. As far as anticancer activity was concerned, H.M. Liu and his coworkers discovered 4-((1,2,3-triazol-1-yl)methyl)coumarin derivatives exhibiting obvious anticancer activity through inducing apoptosis.[25] Besides, novobiocin analogues with 1,2,3-triazole at the C-3 position of coumarin displayed potent cytotoxic activity against two breast cancer cell lines (SKBr-3 and MCF-7).[26] For anti-inflammatory activity, a family of 3-(1,2,3-triazol-1-yl)coumarins, effecting on inducible nitric oxide synthase, were synthesized and proved to reduce neutrophils in the LPS-inflamed subcutaneous tissue,[27] while, through inhibiting 5-lipoxygenase, triazole connected to C-7 position of coumarin by a methene can also cause remarkable anti-inflammatory activity.[28] In addition, compounds with 1,2,3-triazol-1-yl at C-3 position of coumarin revealed the inhibition of amyloid-β aggregation which plays a pathogenic role in the progression of Alzheimer's disease.[29] Compounds mentioned above are summarized in Figure 1.

While the conjugates of 1,2,3-triazole and coumarin fighting against different diseases have made significant progress, efficient molecules against cancer are still urgently needed. As for 4-(1,2,3-triazol-yl)coumarin derivatives, the synthesis methods have been reported,[30] however, so far their anticancer activities have rarely been investigated. In our preliminary experiments, we found 6-bromo-4-(4-phenyl-1,2,3-triazol-1-yl)coumarin (compound **1**) showed a moderate anticancer activity with the IC_{50} values of 9.45, 6.66, 11.23 μM against MCF-7, SW480 and A549, respectively, which inspired us to conduct the structural optimization of compound **1** for more potent anticancer agents. Our optimization focused on the following two aspects: (1) in view of the planarity caused by the conjugated system, introducing a series of chemical bridges ($-CH_2-NH-$, $-CH_2-O-$ or $-CH_2-S-$) between phenyl and 1,2,3-triazole may be helpful to eliminate the planarity, thereby ameliorate the druggability. Meanwhile, the rotatable bonds may also facilitate the compounds binding to its possible receptor through induced fit. (2) To improve the potency, different substitutions introduced to C-6 and C-7 positions of coumarin were taken into account. Moreover, it should be mentioned that in order to evaluate the contribution of 1,2,3-triazole and coumarin to the antiproliferative activity, respectively, the replacements of 1,2,3-triazole with piperazine and coumarin with quinoline were conducted and their biological activity were also measured.

The general procedures for the preparation of the 4-(1,2,3-triazol-1-yl)coumarin derivatives **1**–**23** and **6e** were efficiently synthesized according to the protocol outlined in Schemes 1–3. Different

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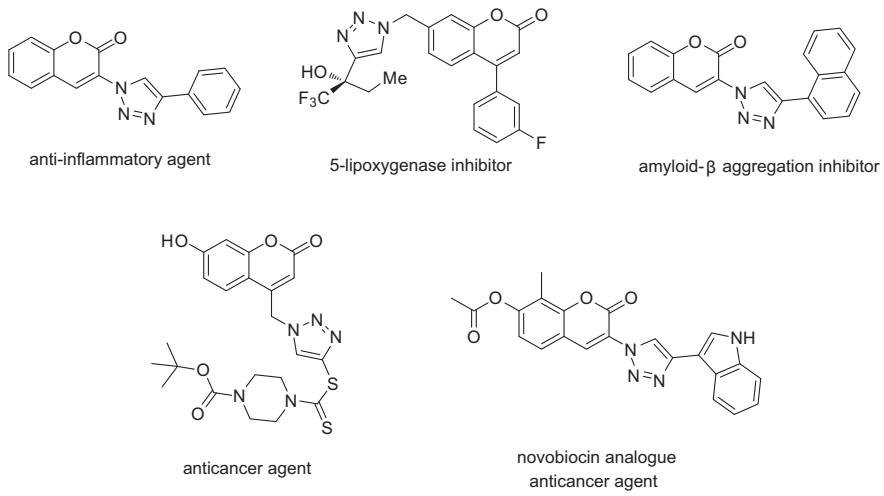
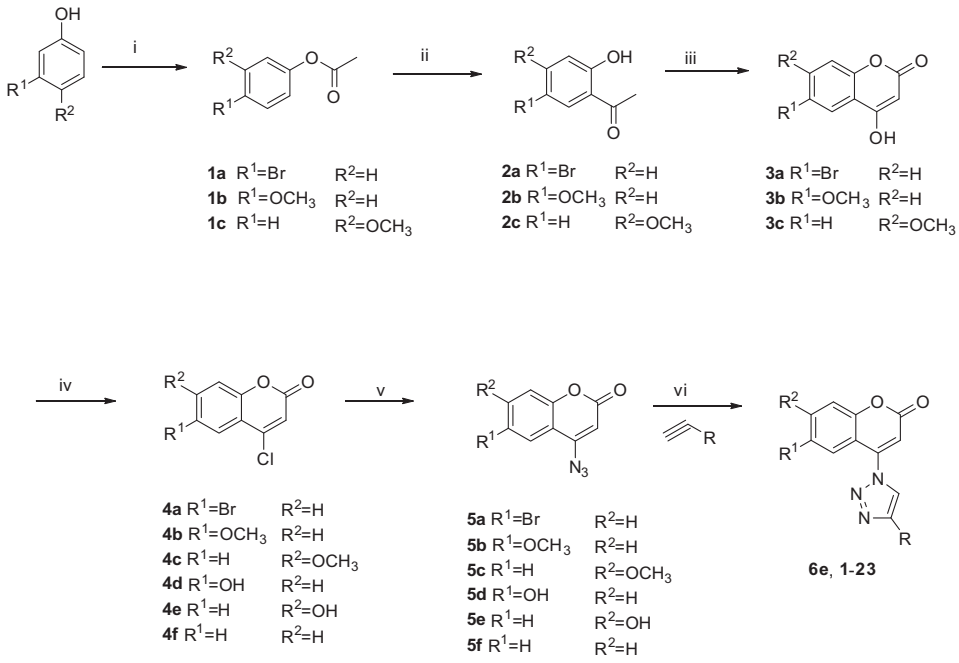


Figure 1. Structures of coumarin derivatives conjugated with 1,2,3-triazole.



Scheme 1. Reagents and conditions: (i) acetic anhydride, pyridine, 100 °C, 3.5 h, 82–98%; (ii) $AlCl_3$, 150 °C, 3.5 h, 70–75%; (iii) diethyl carbonate, NaH, Toluene, 100 °C, 4 h, 67–86%; (iv) $POCl_3$, Triethylamine, reflux, 1 h, 70–85%; (v) NaN_3, NMP, rt, 69–82%; (vi) *t*-BuOH, Cu, $CuSO_4{\cdot}5H_2O$, 65 °C, 49–80%.

phenol derivatives were reacted with acetic anhydride at 100 °C to prepare the esters **1a**–**1c**, which were further subjected to the Fries rearrangement reaction with *o*-hydroxyacetophenone **2a**–**2c** in the presence of aluminum chloride at 150 °C. Compounds **3a**–**3c**, which are crucial to the synthesis of all 4-(1,2,3-triazol-1-yl)coumarin derivatives, were synthesized from *o*-hydroxyacetophenone derivatives by reacting with diethyl carbonate and sodium hydride at 100 °C. Compounds **4a**–**4c**, with a chlorine group at the C-4 position of the coumarin ring, were synthesized in 60–97% yield by treatment of **3a**–**3c** compounds with phosphorus oxychloride ($POCl_3$) and triethylamine. The product (**4b** and **4c**) in dichloromethane was then hydrolyzed with BBr_3 at cooled temperature to obtain the 4-chloro-6-hydroxycoumarin (**4d** and **4e**) (Scheme 2). The treatment of 4-azido-coumarin compounds (**5a**–**5f**) which were obtained through 4-chloro-coumarin derivatives in the presence of NaN_3 at room temperature, and alkynes (Scheme 3), afforded the 4-(1,2,3-triazol-1-yl) coumarin derivatives in tert-butyl alcohol at 65 °C with copper sulfate pentahydrate and copper as CuAAC.[31] Furthermore, 4-fluorobenzene-1-sulfonyl chloride, methanesulfonyl chloride or morpholine derivative (**12a**) were reacted with compound **6e** or **16** to prepare target compounds **18**, **19** and **17** (Scheme 2).

To further measure the contribution of 1,2,3-triazole and coumarin to the antiproliferative activity, we next replaced them with piperazine and quinoline, respectively (Scheme 4 and 5). As outlined in Scheme 4, each candidate was obtained starting from 4-chlorocoumarin (**4f**) and the synthesis began with the substitution of piperazine or 2-(piperazin-1-yl)ethanol to obtain **6a** and **6b**. The 4-(4-benzylpiperazin-1-yl)coumarin analogues **24**–**30** were prepared by the reaction of the corresponding benzaldehyde with **6a**. On the other hand, analogues **31** and **32** were synthesized from **6b** in two steps. In addition, the syntheses of 6-bromoquinolin-4-ol, **2g**, was accomplished according to the cyclization of **1g** in boiling diphenyl ether, which was achieved with 4-bromoaniline in