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Design and synthesis of new triazoles linked to xanthotoxin for potent and highly selective anti-gastric cancer agents

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ABSTRACT

Two series of xanthotoxin-triazole derivatives were designed, synthesized, and studied for their antiproliferative properties. The in vitro cytotoxicity of the compounds in the AGS cancer cell line and the L02 normal cell line was evaluated via MTT assay. Among the synthesized compounds, 9-((1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-7*H*-furo[3,2-*g*]chromen-7-one (**6p**) was found to have the greatest antiproliferative activity against AGS cells (IC_{50} = 7.5 μM) and showed better activity than the lead compound (xanthotoxin, IC_{50} > 100 μM) and the reference drug (5-fluorouracil, IC_{50} = 29.6 μM) did. The IC_{50} value of **6p** in L02 cells was 13.3 times higher than that in the AGS cells. Therefore, the compound exhibited better therapeutic activity and specificity compared with the positive control 5-fluorouracil. Cell cycle analysis revealed that compound **6p** inhibited cell growth via the induction of S/G2 phase arrest in AGS cells. Compound **6p** was identified as a promising lead compound for the further development and identification of 1,2,3-triazole-based anticancer agents.

Over the past few decades, cancer has been the second most common life-threatening disease after cardiovascular disease. Gastric cancer is one of the most frequent causes of cancer-related deaths.[1] Despite the enormous advances in cancer treatment, it remains the second most common cause of death worldwide because of ineffective chemotherapy, caused by drug resistance, and the inability of many drugs to differentiate between normal cells and cancerous cells.[2] Thus, there is an urgent need for a systematic approach to the development of new chemotherapeutic agents with superior efficacy, lower toxicity, and better selectivity.

Furanocoumarins occupy an important place in the subject of natural products and synthetic organic chemistry. They possess antileukodermal, vasodilatory, and anticancer activities.[3–5] Xanthotoxin and imperatorin (Fig. 1) are two important derivatives of furanocoumarin: it has been reported that xanthotoxin and its derivatives clearly inhibited the growth of tumor cells[4] and the administration of imperatorin was reported to inhibit tumor growth and block tumor angiogenesis in a xenograft tumor model.[6]

Nitrogen heterocycles have been extensively investigated in the literature owing to their role as active pharmacophores. Among them, substituted 1,2,3-triazoles are an indispensable structural motif of compounds that display a broad spectrum of biological activities and are widely used in organic synthesis, medicinal chemistry, and material science. For example, 1,2,3-triazoles are reported to possess diverse pharmacological effects, including anticancer[7,8] (compound **A** and **B**; Fig. 1), immunosuppressant,[9] antimicrobial,[10,11] antimalarial,[12] and anti-inflammatory[13] activities. Compounds containing 1,2,3-triazole actively participate in hydrogen bonding and dipole-dipole interactions owing to their strong dipole moments; moreover, it is extremely resistant to hydrolysis and remains stable in oxidative and reductive conditions.[14] Recently, a molecular hybridization approach that combines two pharmacophores to yield a single molecule with the additive biological properties has been favored by medicinal chemists.[15] These hybrids combine two active moieties in a single molecule with the goal of creating a chemical entity that is medically more effective than the individual constituents. We envisaged that the integration of the xanthotoxin and 1,2,3-triazole moieties into one molecular platform could potentially produce novel compounds with significant synergistic antitumor properties. Additionally, 1,2,4-triazole is an isostere of 1,2,3-triazole. Herein, we have described our work towards the design, synthesis, and evaluation of new xanthotoxin-linked 1,2,3-triazoles (**6a**–**6r**) (Fig. 1) and new xanthotoxin-linked 1,2,4-triazoles (**9 a**–**9 g**) (Fig. 1) for their cytotoxicity in the gastric cancer cell line, AGS, and the human normal liver cell line, L-02.

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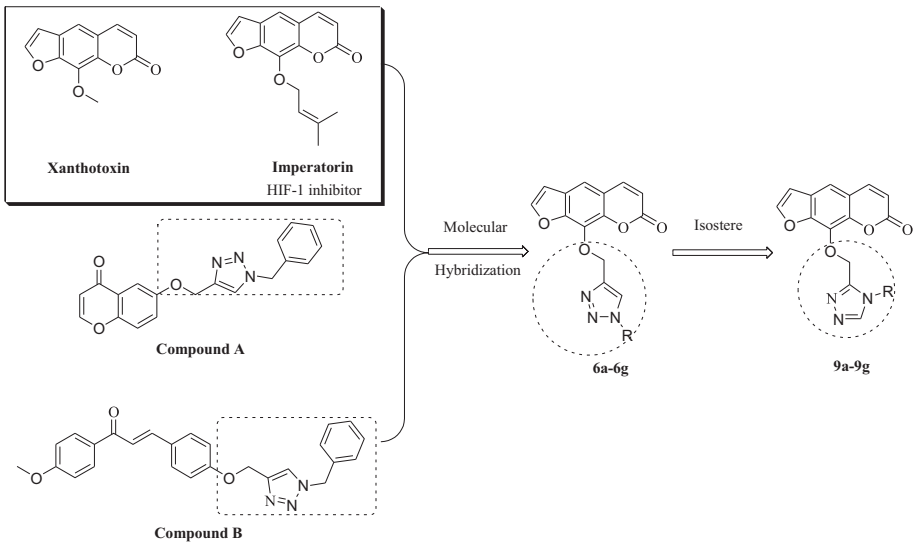
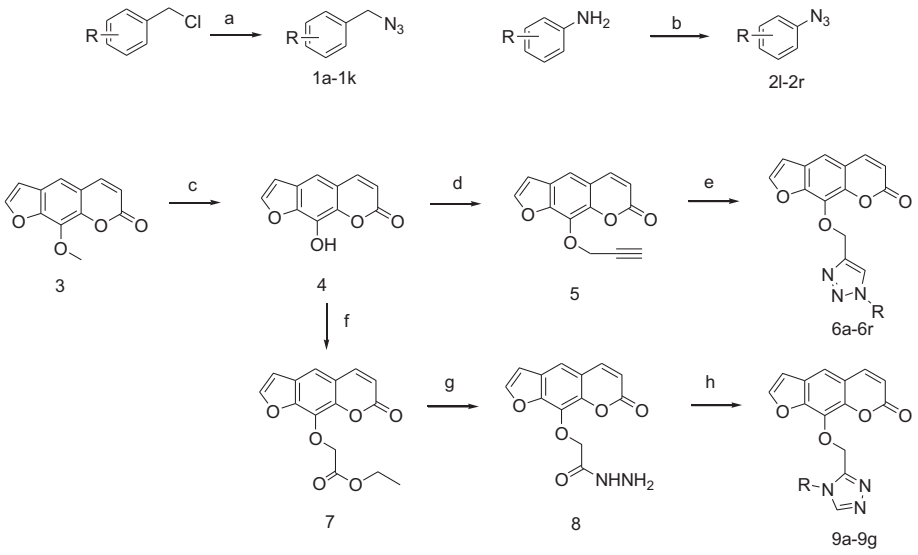


Fig. 1. Design of target compound **6a**–**6r** and **9a**–**9**g.



Scheme 1. Reagents and conditions: (a) NaN_3, DMF, rt; (b) (i) $NaNO_2$, HCl, 0 °C, 45 min; (ii) NaN_3, H_2O, 0 °C; (c) BBr_3, CH_2Cl_2, 0 °C, 12 h; (d) K_2CO_3, propargyl bromide, acetone, 56 °C; (e) 1a–1k or 2l–2r, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, CH_2Cl_2/H_2O (1:1), 40 °C; (f) K_2CO_3, ethyl bromoacetate, acetone, 56 °C; (g) hydrazine hydrate, ethyl alcohol, 78 °C; (h) (i) dimethylacetal, acetonitrile, 60 °C, 1 h; (ii) various aromatic amine, glacial acetic acid, 120 °C.

The synthetic outlines for the synthesis of the starting and target compounds are presented in Scheme 1. First, xanthotoxin (**3**) was treated with 1 M BBr_3 in anhydrous methylene chloride at 0 °C to yield 9-hydroxy-7*H*-furo[3,2-*g*]chromen-7-one (**4**) via a reported procedure.[16] In the next step, 9-(prop-2-ynyloxy)-7*H*-furo[3,2-*g*]chromen-7-one (**5**) was obtained by the reaction of propargyl bromide and compound **4** in the presence of anhydrous potassium carbonate and dry acetone at 56 °C for 12 h.[17] Then, the target compounds **6a**–**6r** were obtained by the reaction of various intermediates (**1a**–**1k** or **2l**–**2r**), sodium ascorbate, and $CuSO_4{\cdot}5H_2O$ in dichloromethane:water (5:1) at 40 °C for 12–24 h.[18,19] Additionally, 9-hydroxy-7*H*-furo[3,2-*g*]chromen-7-one (**4**) was treated with ethyl bromoacetate in the presence of anhydrous potassium carbonate in dry acetone at 56 °C for 12 h to yield intermediate **7**. Hydrazinolysis of the latter afforded the acid hydrazides **8**, which were mingled with *N*,*N*-dimethylformamide dimethyl acetal and aniline to yield the target compounds **9a**–**9g**.[20]

The synthetic outlines for the synthesis of the starting and compared compounds **10**–**11** are presented in Scheme 2. 1-(4-(trifluoromethyl)phenyl)-4-methyl-1*H*-1,2,3-triazole (**10**) was obtained by the reaction of propionaldehyde, malononitrile, 1-azido-4-(trifluoromethyl)benzene (**2p**) and DBU in DMSO at 50 °C.[21] 4-Fluorobenzenamine was mingled with *N*,*N*-dimethylformamide dimethyl acetal and acetohydrazide to yield the target compound 4-(4-fluorophenyl)-3-methyl-4*H*-1,2,4-triazole (**11**).[20] All compounds submitted for biological testing were recrystallized to consistent melting point and judged as >95% pure by HPLC and identified via IR, ^1H NMR, and ^{13}C NMR spectrometry and high resolution mass spectrometry (HRMS).

The antiproliferative activity of the synthesized compounds was evaluated against the cultured human AGS cell line, with xanthotoxin tested as a comparative compound. In addition, the clinically prescribed powerful antineoplastic drug 5-fluorouracil (5FU) was used as a reference drug. The screening procedure was based on