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Research paper

Discovery of novel diaryl urea derivatives bearing a triazole moiety as potential antitumor agents

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ABSTRACT

Herein, we report a novel series of diaryl urea derivatives bearing a triazole moiety, from which potent antitumor agents have been identified. With a modified triazole, most compounds showed high level activity in both cellular and enzymatic assays, accompanied with a suitable $ClogD_{7.4}$ value. The most active compound, **13i**, effectively suppressed proliferation of HT-29, H460 and MDA-MB-231 cancer cells, with IC_{50} values of 0.90, 0.85 and 1.54 μM, respectively. Compound **13i** also exhibited significant inhibition of tyrosine kinases including c-Kit, RET and FLT3. Furthermore, compound **13i** could obviously induce apoptosis of HT-29 cells in a concentration-dependent manner. The study of structure-activity relationships also revealed that a hydrophilic tail at the 4-position of the triazole was crucial for high activity of the compound.

1. Introduction

Cancer is a serious worldwide public health concern. Most patients suffering from cancer have a poor prognosis due to its high mortality rate and incidence of relapse. Therefore, there is still an urgent need for new antitumor agents with improved efficacy.

In the past two decades, multikinase inhibitors, such as sunitinib, imatinib, and sorafenib have received great attention and have yielded great benefits in numerous clinical cancer cases [1–4]. The simultaneous inhibition of multiple targets can create a synergistic anti-cancer effect. This strategy is proven to efficiently interrupt complex oncogenic pathways and reduce the possibility of developing drug resistance [5]. Sorafenib, a well-known multikinase inhibitor, potently suppresses several receptor tyrosine kinases, including PDGFR-β, VEGFR-2, VEGFR-3, FLT3, Kit, and RET, as well as the downstream protein Raf. In addition, it demonstrates significant inhibition across a broad spectrum of tumour types [6–8]. Thus far, it has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal carcinoma (RCC), unresectable hepatocellular carcinoma (HCC), and differentiated thyroid carcinoma (DTC). In addition, its applications in breast, lung, and colorectal carcinomas are being evaluated in clinic, and the results are eagerly awaited [9–12].

Despite its outstanding antitumor activity, the overall bioavailability of sorafenib is limited, mainly because of its poor water-solubility which is ascribed to the high hydrophobicity of its chemical structure [13,14]. We considered rational optimization of sorafenib a feasible approach to develop novel antitumor agents, placing equal attention and importance on their antitumor potency as well as their hydrophilicity.

As reported previously, the diaryl urea framework plays a pivotal role in the complexation of sorafenib with enzymes through hydrogen bonding and hydrophobic interactions [15], which prompted us to retain this functional template in the design of new compounds. In previous study, we have reported a series of compounds based on a 2-(4-(2-(dimethylamino)ethyl)-4*H*-1,2,4-triazol-3-yl)pyridine moiety as potent antitumor agents [16]. Structure-activity relationships revealed that an optimized triazole was crucial for high activity. Thus, in the current research, we developed a strategy to investigate hybrids of diaryl urea and triazole for application as antitumor agents.

Here, we reported the design, synthesis and biological evaluation of a series of diaryl urea derivatives bearing a triazole moiety, to identify their potential as antitumor agents (Fig. 1). The new

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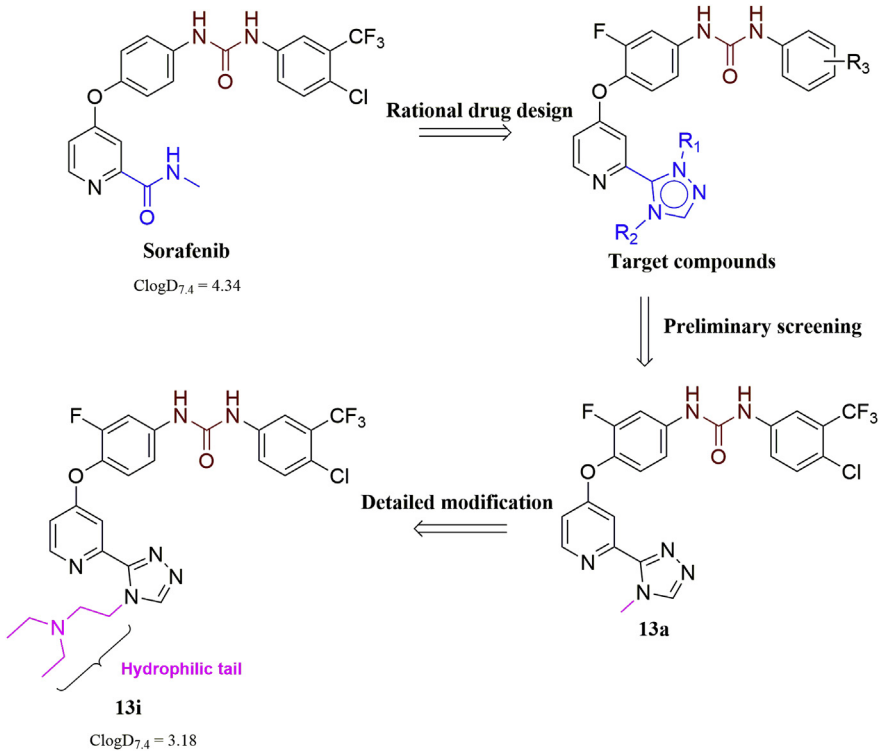


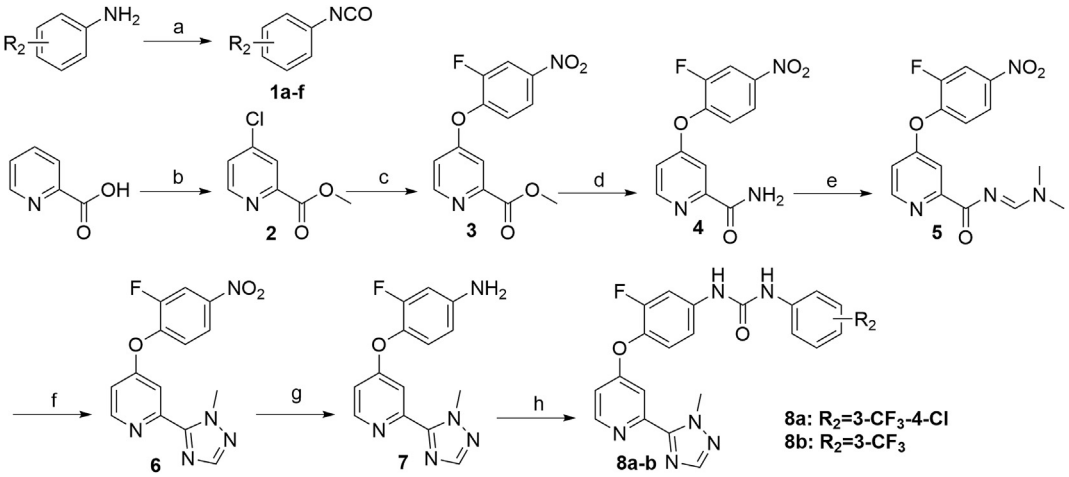
Fig. 1. Design strategy of the target compounds.

compounds were screened in HT-29, H460, and MDA-MB-231 cancer cells, and against a kinase panel comprising c-Kit, RET, FLT3, B-Raf, and VEGFR-2. Additionally, cell apoptosis induced by compound **13i** was evaluated in HT-29 cells.

2. Results and discussion

2.1. Chemistry

The general route to prepare compounds **8a** and **8b** is described in Scheme 1. The appropriate aniline was reacted with triphosgene in refluxing toluene to give the corresponding isocyanate **1a**–**f** as a solid or an oil. The synthesis of intermediate **2** was achieved in two steps from picolinic acid, which has been described in detail in our previous study [16]. A nucleophilic substitution of **2** with 2-fluoro-4-nitrophenol in refluxing chlorobenzene yielded the crude product of **3**, which was purified by recrystallization in absolute ethanol. Aminolysis of **3** with ammonia in acetone led to the desired intermediate **4**, which then reacted with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) to generate **5** in a high yield. Intermediate **6** was obtained by cyclization of **5** with methylhydrazine under a modified condition, as previously reported [17]. Then, intermediate **6** was reduced using hydrazine hydrate, to efficiently yield amine **7**. Ureas **8a** and **8b** were obtained by reaction of



Scheme 1. Reagents and conditions: (a) triphosgene, toluene, reflux, 7–10 h; (b) (i) $SOCl_2$, NaBr, chlorobenzene, 50 °C, 30 min, 85 °C, 20 h; (ii) MeOH, toluene, 0–15 °C, 1.5 h; (c) 2-fluoro-4-nitrophenol, chlorobenzene, reflux, 12 h; (d) $NH_3 \cdot H_2O$, acetone, 50 °C, 3 h; (e) DMF-DMA, CH_2Cl_2, reflux, 2–3 h; (f) CH_3NHNH_2, HOAC, 90 °C, 3 h; (g) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 3–6 h; (h) **1a**–**b**, CH_2Cl_2, rt, 5 h.