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Original article

Design, synthesis and docking studies of novel thienopyrimidine derivatives bearing chromone moiety as mTOR/PI3Kα inhibitors

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ABSTRACT

Two series of thienopyrimidine derivatives (**10a**–**k**, **16a**–**j**) bearing chromone moiety were designed and synthesized. All the compounds were evaluated for inhibitory activity against mTOR kinase at a concentration of 10uM. Four selected compounds were further evaluated for the IC_{50} values against mTOR kinase, PI3Kα kinase and two cancer cell lines. Some of the target compounds exhibited moderate to excellent mTOR/PI3Kα kinase inhibitory activity and cytotoxicity. The most promising compound **16i** showed good inhibitory activity against mTOR/PI3Kα kinase and good antitumor potency for H460 and PC-3 cell lines with IC_{50} values of 0.16 ± 0.03 μM, 2.35 ± 0.19 μM, 1.20 ± 0.23 μM and 0.85 ± 0.04 μM, which were 8.6, >5, 7.9 and 19.1 times more active than compound **I** (1.37 ± 0.07 μM, >10 μM, 9.52 ± 0.29 μM, 16.27 ± 0.54 μM), respectively. Structure–activity relationships (SARs) and docking studies indicated that the chromone moiety is necessary for the potent antitumor activity and cytotoxicity of these compounds. Substitution of the chromone moiety at the 6-position has a significant impact to the inhibitory activity, in particular a carboxylic acid group, produced the best potency.

1. Introduction

The PI3K-Akt-mTOR signaling pathway plays a key role in cell proliferation, migration, survival, and angiogenesis, and developing mTOR/PI3Kα inhibitors is one of the research hotspots in molecular targeted therapy for the treatment of human cancer [1,2].

In recent years, a growing number of studies based on the (fused-)pyrimidine/triazine scaffolds towards antitumor activity have been carried out [3–7]. Among them, GDC-0941 (Fig. 1), which is a potent, orally bioavailable inhibitor of PI3K, exerted antitumor activity against an array of human tumor cell lines and is currently undergoing Phase II clinical trials [5]. Further optimization of GDC-0941 led to several backup clinical candidates with similar structures, such as GNE-490 and GNE-493 [4] (Fig. 1). Compound **I** (Fig. 1) is a triazine-hydrazone derivative which exhibited potent anti-tumor activity with an mTOR IC_{50} value of 0.27 μM [6]. To our knowledge, few studies based on pyrimidine- or triazine-hydrazones as mTOR inhibitors have been reported to date. Importantly, the hydrazinyl group or its mimics are key pharmacophores in the design of different potential anticancer agents [7]. Therefore, the research on this aspect seemed to be an attractive task.

In our previous research [8–10], several series of 2-hydrazinyl-4-morpholinothieno[3,2-*d*]pyrimidines which demonstrated potent antitumor activity were designed and synthesized, and SARs were discussed and summarized. The results showed that most of them exhibited excellent cytotoxicity but possessed disappointing *in vivo* antitumor activity, such as the representative compounds **II** [9] and **III** [10] (Fig. 1). This work also showed that introduction of indole-hydrazone to the target compound benefitted the antitumor activity.

In continuation of our previous research towards compounds which possessed excellent antitumor activity, further indole-hydrazone studies were carried out and are reported herein. Through analysis of the SARs and the results of docking with mTOR/

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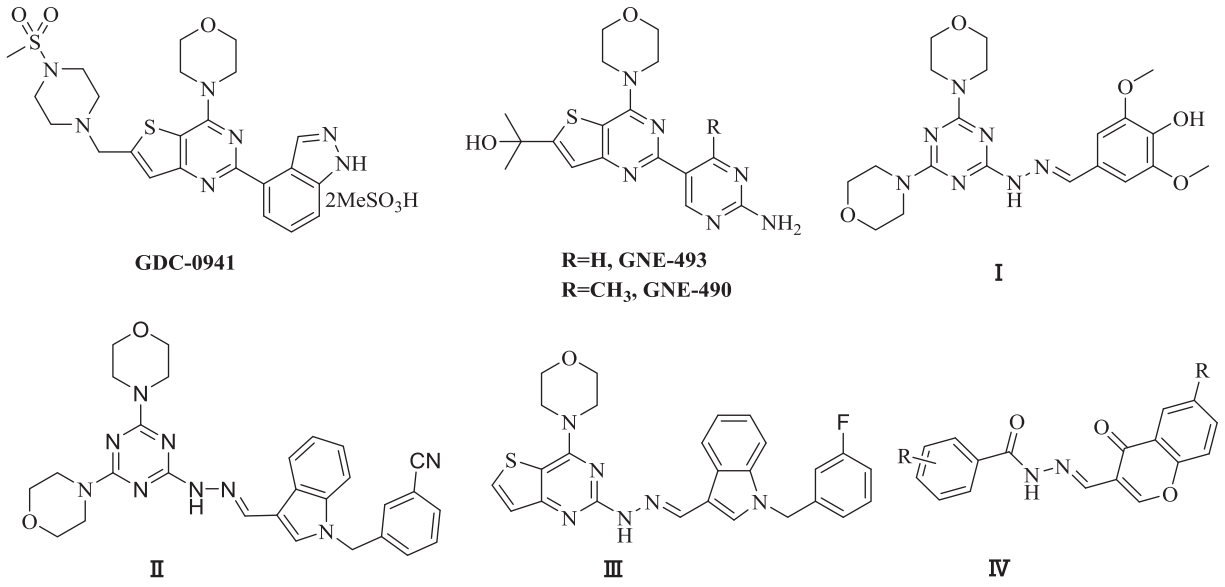

Fig. 1. Structures of some reported (fused-)pyrimidine/triazines and compounds reported in previous research.

PI3Kα kinase, a new compound library was built with structural modifications at thienopyrimidine moiety and indole-hydrazone groups (Fig. 1). Firstly, a series of thieno[3, 2-*d*]pyrimidines **10a**–**k** (Fig. 2) were designed by replacing the *N*-benzyl indole or *N*-benzyl benzimidazole moieties of compounds **II** and **III** with active pharmacophore chromone moiety which was proved in our previously research [11]. However, this series of compounds showed poor cytotoxicity [12] and moderate mTOR kinase inhibitory activity. Further investigations were carried out in detail to study the effects of the thienopyrimidine scaffold on the antitumor activity. Therefore, the fusion between the thienyl and pyrimidine in the scaffold was changed according to the theory of isostere principle, resulting in the series of thieno[2, 3-*d*]pyrimidines **16a**–**j** (Fig. 2). The inhibitory activity against mTOR kinase and cytotoxicity of compounds **16a**–**j** were better than that of compounds **10a**–**k**.

Considering the high potency of GDC-0941 and its analogous on lung and prostate cancer cells, herein we disclose the design, synthesis and inhibitory activity of novel thieno[2,3-d]pyrimidine bearing a chromone moiety against mTOR kinase, as well as the cytotoxicity against H460 (lung) and PC-3 (prostate) cancer cell lines. Further evaluation was carried out against PI3Kα kinase to confirm the types of target compounds, selective or mixed type inhibitors. Moreover, docking studies are presented providing a rationale for the observed activity.

2. Chemistry

The preparation of target compounds **10a**–**k** and **16a**–**j** is described in Schemes 1 and 2. The structures and the predicted cLogp values of target compounds are shown in Table 1.

The substituted 4-oxo-*4H*-chromene-3-carbaldehydes **4a**–**k** were synthesized through the procedures reported previously by our group (Scheme 1) [11,13].

The synthesis of compounds **10a**–**k** was similar to the procedures previously reported [8–10,12]. The key intermediate **9** condensed with substituted 4-oxo-*4H*-chromene-3-carbaldehydes **4a**–**k** to afford target compounds **10a**–**k**, respectively.

Compounds **16a**–**j** were synthesized from methyl 2-

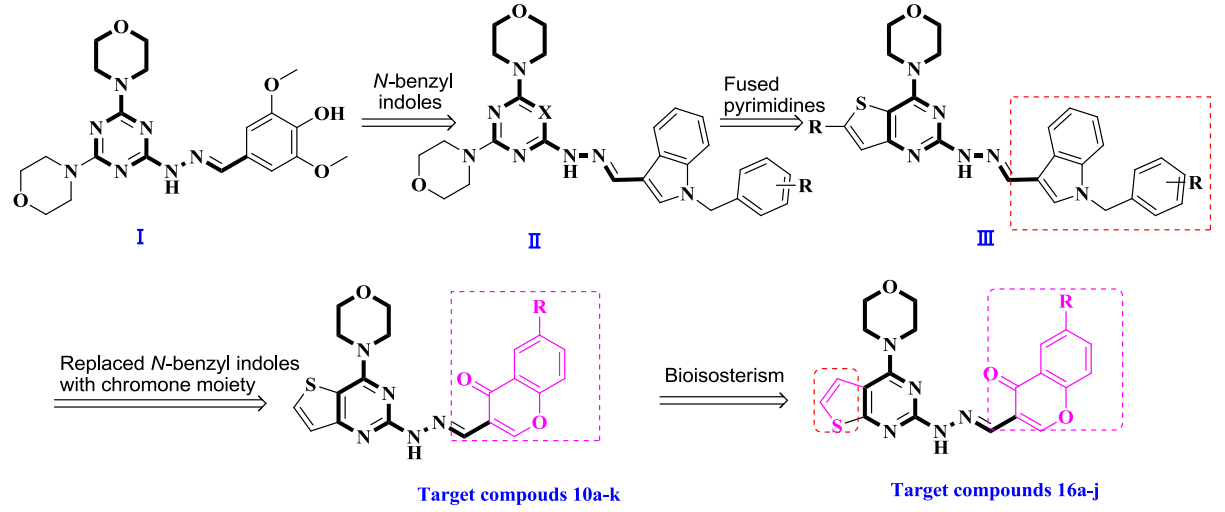

Fig. 2. Structures and design strategy for target compounds **10a**–**k** and **16a**–**j**.