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Research paper

Synthesis and biological evaluation of novel indole-pyrimidine hybrids bearing morpholine and thiomorpholine moieties

Peng-Cheng Diao [a, 1], Qiu Li [a, 1], Meng-Jin Hu [a], Yu-Feng Ma [a], Wen-Wei You [a], Kwon Ho Hong [b, **], Pei-Liang Zhao [a, *]

[a] Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Science, Southern Medical University, Guangzhou 510515, PR China

[b] Department of Medicinal Chemistry, Institute for Therapeutics Discovery and Development, College of Pharmacy, University of Minnesota, Minneapolis 55414, United States

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ABSTRACT

Based on our previous screening hit compound **1**, a series of novel indole-pyrimidine hybrids possessing morpholine or thiomorpholine moiety were synthesized *via* an efficient one-pot multistep synthetic method. The antiproliferative activities of the synthesized compounds were evaluated *in vitro* against four cancer cell lines including HeLa, MDA-MB-231, MCF-7, and HCT116. The results revealed that most compounds possessed moderate to excellent potency. The IC_{50} values of the most promising compound **15** are 0.29, 4.04, and 9.48 μM against MCF-7, HeLa, and HCT116 cell lines, respectively, which are 48.0, 4.9, and 1.8 folds more active than the lead compound **1**. Moreover, fluorescence-activated cell sorting analysis revealed that compound **14** showing the highest activity against HeLa ($IC_{50} = 2.51$ μM) displayed a significant effect on G_2/M cell-cycle arrest in a concentration-dependent manner in HeLa cell line. In addition, representative nine active hybrids were evaluated for tubulin polymerization inhibitory activities, and compound **15** exhibited the most potent anti-tubulin activity showing 42% inhibition at 10 μM. These preliminary results encourage a further investigation on indole-pyrimidine hybrids for the development of potent anticancer agents that inhibit tubulin polymerization.

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1. Introduction

In recent decades, microtubules have been important molecular targets for the development of anticancer drugs due to their crucial roles in the regulating cancer cell survival and progression including cellular signaling, motility, cell shape maintenance, secretion, intercellular transport and spindle formation during mitosis [1–4]. Inhibiting tubulin polymerization or interfering with microtubule disassembly ultimately leads to cell cycle arrest or apoptosis of cancer cells [5–7]. Hence, there are commonly two major categories of anti-tubulin agents: inhibitors of the tubulin polymerization and stabilizers of the microtubule structure.

Recently, our research group discovered indole-pyrimidine hybrid **1**, having piperazine on the pyrimidine moiety (Fig. 1), as a potent inhibitor of the polymerization of tubulin with a low toxicity [8]. The agent shows low IC_{50} values ranged from 5.01 to 14.36 μM against four cancer cell lines and does not affect the normal human embryonic kidney cells, HEK-293. Interest towards morpholine- or thiomorpholine-containing indole or pyrimidine systems as anticancer agents has increased due to their important chemopreventive and chemotherapeutic effects on cancer [9–14]. As shown in Fig. 1, pyrimidine derivative BKM-120 containing two morpholine groups manifests a great antiproliferative activity against PI3K-deregulated cell lines (GI_{50} values against A2780, U87MG, MCF7 and DU145 are 0.1–0.7 nM), and is currently in phase III clinical trials for the treatment of advanced breast cancer [15,16]. In addition, Kryštof and coworkers reported that thiomorpholine-containing pyrimidine compound **3** exhibited potential antitumor activities against a panel of cancer cell lines [17]. More interestingly, indole-pyrimidine hybrid **4** with a morpholine group was identified as a potent PI3K inhibitor with a low nanomolar IC_{50} value and used in the treatment of PI3K-mediated

* Corresponding author.
** Corresponding author.
E-mail addresses: hong0207@umn.edu (K.H. Hong), plzhao@smu.edu.cn (P.-L. Zhao).
[1] These authors contributed equally to this work.

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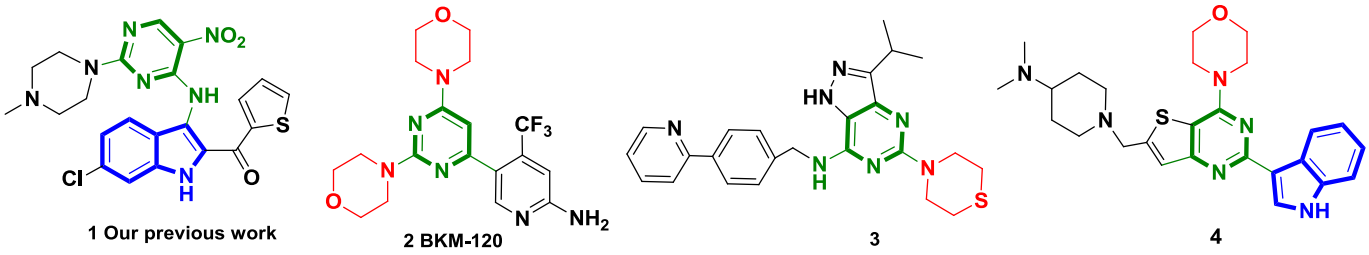

Fig. 1. Our previously reported the indole-pyrimidine hybrid **1** and selected morpholine or thiomorpholine-linked pyrimidine and indole derivatives with antitumor activity.

disorders such as inflammation and cancer [18].

As the heterocyclic compounds consisting of multiple cores receive much attention in recent years [19–23], and in view of the above mentioned prominence, we have focused on the design and efficient synthesis of novel indole-pyrimidine systems bearing a morpholine or thiomorpholine moiety. In the present study, morpholine and thiomorpholine moieties replaced the piperazine group of the C-2 position of the pyrimidine moiety of compound **1** (Fig. 2) and a series of novel hybrids of indole-pyrimidine containing a morpholine or thiomorpholine ring **11**–**32** were synthesized *via* an efficient one-pot multistep synthetic methodology. Furthermore, these compounds were evaluated for the antiproliferative and tubulin polymerization inhibitory activities.

2. Chemistry

The synthesis of the target compounds **11**–**32** was illustrated in Scheme 1. Substituted ethyl (2-cyanophenyl)carbamates **6** were obtained by condensation of the appropriately substituted 2-aminobenzonitriles **5** and ethyl chloroformate under reflux. The subsequent Thorpe–Ziegler cyclization with various α-bromoketones using K_2CO_3 as a base in dimethylformamide provided the common intermediates *N*-1-ethoxycarbonyl-2-substituted-3-aminoindoles **7**. These intermediates were subsequently *N*-deprotected by alkaline hydrolysis using NaOH in aqueous ethanol to generate the corresponding 3-amino-1H-indoles **8**, as illustrated in detail in our previously reported approach [24].

The expected indole-pyrimidine derivatives **11**–**32**, containing a morpholine or thiomorpholine ring, were generally obtained *via* a one-pot, multistep synthetic operation of equimolar amounts of substituted 3-amino-indoles **7** or **8**, 2,4-dichloro-5-nitropyrimidne **9** and morpholine or thiomorpholine in dry acetone (Scheme 1). The structures of target compounds **11**–**32** were characterized with spectroscopic techniques including ^{1}H NMR, ^{13}C NMR and HRMS, and the spectral data agree with the proposed structures.

3. Results and discussion

3.1. In vitro antiproliferative activity

The synthesized compounds **11**–**32** were evaluated for their *in vitro* antiproliferative activities against four human cancer cell lines including HeLa, MDA-MB-231, MCF-7, and HCT116 using the MTT assay [25]. The assay results expressed as IC_{50} (μM) were summarized in Table 1 and compared with the inhibitory activities of two reference compounds, CA-4, a potent natural tubulin-binding anticancer agent, and our previously reported compound **1**. Here, the IC_{50} value represents the concentration of a compound resulting in 50% inhibition of cell growth after 48 h incubation, and is the average of three independent experiments.

As shown in Table 1, it is clear that the first series of indole-pyrimidine hybrids (**11**–**29**) bearing a morpholine ring at the C-2 position of the pyrimidine, exhibit generally higher potency than the corresponding hybrids (**30**–**32**) with a thiomorpholine ring, indicating that the morpholine substitution on the pyrimidine ring might play a crucial role in modulating the antitumor activity.

Among the morpholine series (**11**–**29**), most compounds showed moderate to excellent antiproliferative activities against the four tested cancer cell lines. The IC_{50} values of the most promising compound **15** were 0.29, 4.04, and 9.48 μM against MCF-7, HeLa, and HCT116 cell lines, respectively, which indicated that this compound was 48.0, 4.9, and 1.8 folds more active than the lead compound **1**. More interestingly, compound **17** showed potent *in vitro* antiproliferative activities against all the tested cancer cell lines with the IC_{50} values ranged from 2.13 to 5.52 μM. Notably, compound **17** was two folds more active than positive control CA-4 in inhibiting HCT116 cell proliferation with IC_{50} value of 2.99 μM. It was worth noting that, the compound did not affect the normal human embryonic kidney cells, HEK-293.

Further analysis clearly revealed that different antiproliferative activities were observed when various substituents R^1, R^2, R^3 were

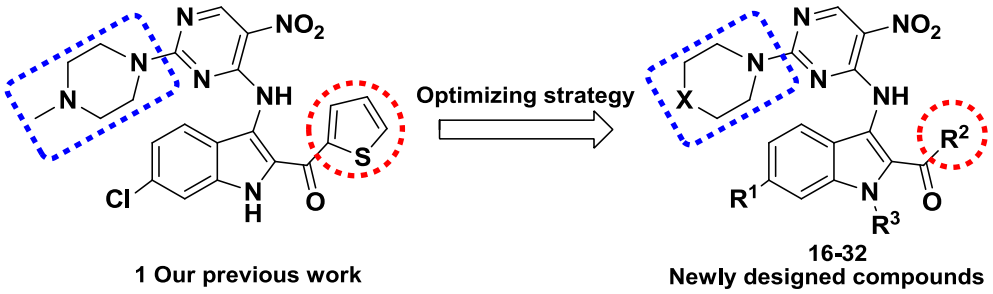

Fig. 2. Design strategy of the title compounds.

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