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Synthesis and anticancer effects evaluation of 1-alkyl-3-(6-(2-methoxy-3-sulfonylaminopyridin-5-yl)benzo[*d*]thiazol-2-yl)urea as anticancer agents with low toxicity

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ABSTRACT

As a PI3K and mTOR dual inhibitor, *N*-(2-chloro-5-(2-acetylaminobenzo[*d*]thiazol-6-yl)pyridin-3-yl)-4-fluorophenylsulfonamide displays toxicity when orally administrated. In the present study, alkylurea moiety replaced the acetamide group in the compound and a series of 1-alkyl-3-(6-(2,3-disubstituted pyridin-5-yl)benzo[*d*]thiazol-2-yl)urea derivatives were synthesized. The antiproliferative activities of the synthesized compounds in vitro were evaluated against HCT116, MCF-7, U87 MG and A549 cell lines. The compounds with potent antiproliferative activity were tested for their acute oral toxicity and inhibitory activity against PI3Ks and mTORC1. The results indicate that the compound attached a 2-(dialkylamino)ethylurea moiety at the 2-positeion of benzothiazole can retain the antiproliferative activity and inhibitory activity against PI3K and mTOR. In addition, their acute oral toxicity reduced dramatically. Moreover, compound **2f** can effectively inhibit tumor growth in a mice S180 homograft model. These findings suggest that 1-(2-dialkylaminoethyl)-3-(6-(2-methoxy-3-sulfonylaminopyridin-5-yl)benzo[*d*]thiazol-2-yl)urea derivatives can serve as potent PI3K inhibitors and anticancer agents with low toxicity.

1. Introduction

Benzothiazole derivatives exhibit a broad spectrum of biological activities such as antitumor, antimicrobial, anti-inflammatory, anticonvulsant and antidiabetic activity. The study progress of benzothiazole derivatives in medicinal chemistry has been reviewed.[1–3] There are hydrogen-bond acceptors and hydrogen-bond donor in the 2-aminobenzothiazole. Thus it is considered as a privileged drug scaffold in drug discovery.

Chemotherapy is one of the major approaches in cancer treatment. Traditional cytotoxic agents clinically used have been increasingly limited due to their high risk of toxicity, drug resistance and lack of selectivity. At present, the molecularly targeted therapies aiming at special targets have become effective approaches in cancer therapies. Kinases play an important role in tumor cell proliferation, survival and metastasis. Therefore, inhibitors against key kinases have emerged as novel targeted anticancer agents. PI3K (phosphoinositide 3-kinase) and mTOR (mammalian target of rapamycin) are critical nodes of PI3K/Akt/mTOR pathway, which are abnormally active in many tumor cells. For example, PIK3CA, the gene encoding for p110α (PI3Kα), is often over-expressed or mutate in a wide variety of cancer cell lines. Thus, targeting PI3K, especially PI3Kα, and/or mTOR has become an appealing strategy for cancer therapies.[4–6]

In recent years, a remarkable progress has been made in the design, synthesis and evaluation of PI3K and mTOR dual inhibitors,[7–12] and thereupon the pharmacophore of the dual inhibitors has been put forward.[13] Among the reported PI3K/mTOR dual inhibitors, *N*-(5-(quinilin-6-yl)-pyridin-3-yl)phenylsulfonamide is an important class of active compounds. GlaxoSmithKline identified GSK2126458 as a potent, orally bioavailable inhibitor of PI3Kα and mTOR.[14] Amgen designed, synthesized and evaluated several classes of *N*-(2,5-disubstitutedpyridin-3-yl)phenylsulfonamides. Therefore, they discovered that *N*-(2-chloro-5-(4-morpholinoquinilin-6-yl)pyridin-3-yl)-4-fluorophenylsulfonamide,[15] *N*-(2-chloro-5-(2-acetyl aminobenzo[*d*]thiazol-6-yl) pyridin-3-yl)-4-fluorophenylsulfonamide (compound **A**, Fig. 1),[16] *N*-(2-chloro-5-(2-acetylaminoimidazo[1,2-*b*]pyridazin-6-yl)pyridin-3-yl)-4-fluorophenylsulfonamide[17] and AMG 511[18] are excellent

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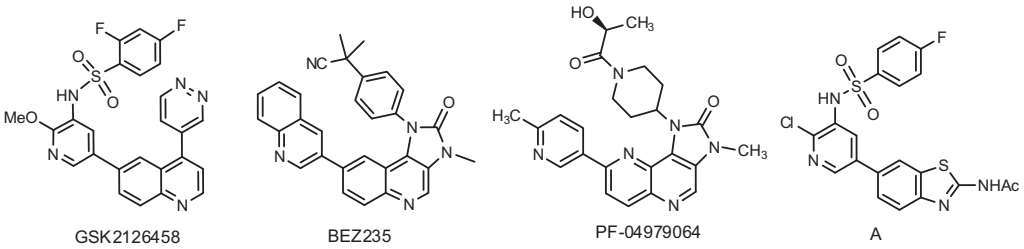

Figure 1. The structures of PI3K and mTOR dual inhibitors.

PI3Kα/mTOR dual inhibitors or selective PI3Kα inhibitor, and orally bioavailable anticancer agents as well. The pharmacophore of above compounds consists of the two ring nitrogen atoms in pyridine and quinoline. Another active compound, *N*-(2-methoxy-5-(acetylamino[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyridin-3-yl)-4-fluorophenylsulfonlyamide, having a pharmacophore similar to that of compound **A**, displays a potent anticancer effect.[19] Later, QSAR and pharmacophore of analogues of compound **A** were studied.[20] BEZ235[21] and PF-04979064[22] also possess a pharmacophore similar to compound **A**. As PI3Kα and mTOR dual inhibitors, they are in phase I/II clinical trials for treating solid tumors. Recently, it has been reported that VS-5584, a PI3K/mTOR dual inhibitor, can preferentially targets cancer stem cells.[23] This discovery may potentially bring a breakthrough to the treatment of cancer with small molecules. Thus, it is necessary to develop some new PI3K/mTOR dual inhibitors.

As a potent PI3K/mTOR dual inhibitor, compound **A** can inhibit tumor growth against a wide range of tumors with different genetic backgrounds. Its EC_{50} ranges from 0.26 mg/kg to 0.53 mg/kg against three established nude mice human cancer cell xenograft models. However, compound **A** displays significant peroral toxicity.[16] On the basis of the result, we suspect that the toxicity of compound **A** is unfavorable to its development into clinical trials. To overcome this problem, it is of vital importance to treat seriously the toxicity of compound **A**.

According to the co-crystal structure of compound **A** with PI3Kγ,[16] we proposed that the structure of an amide group may take the place of the water molecule bridge. Thereupon, we synthesized a series of 2-substituted-3-phenylsulfonylamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamides, and discovered that the designed compounds are novel PI3K inhibitors and anticancer agents.[24] In our previous work, we combined the benzamide moiety with 2-aminobenzothiazole to discover novel anticancer agents (strategy **A** in Fig. 2).[25] Recently, we discovered that 1-alkyl-3-(6-(2-methoxy-3-(4-fluorophenylsulfonylamino)pyridine-5-yl)-[1,2,4]triazolo-[1,5-*a*]pyridin-2-yl)urea derivatives can serve as potent PI3K inhibitors and anticancer agents with low toxicity.[26] In this work, we intend to replace the 2-acetylamino moiety in compound **A** with alkylamino or alkylurea moiety to search for the novel anticancer agents with low toxicity (strategy **B** in Fig. 2). Herein, we report our studies on the synthesis, biological activities and acute toxicity of designed compounds.

2. Results and discussion

2.1. Synthesis of designed compounds

The synthetic route of compounds **1** is outlined in Scheme 1. Commercially available 2-amino-6-bromobenzo[*d*]thiazole was used as starting material to prepare intermediates **3**, **4**, **5** and **6**. The details were previously described in our work.[25] The sulfonamides **7** were prepared from 5-bromopyridine derivatives according to the synthetic route reported in our previous work.[19] Catalyzed by $PdCl_2$(dppf), intermediate **7** was reacted with bis(pinacolato)diboron to produce corresponding arylboronic esters. Without isolation of arylboronic esters, intermediate **5**, or **6**, $PdCl_2$(dppf), water and potassium carbonate as well were added to the above reaction mixture. The resultant mixture was refluxed to produce compounds **1a**–**1d**. The preparation of arylboronic esters and Suzuki coupling were completed in one pot.

In Scheme 2, alkylurea moiety replaced the acetylamino group in compound **A** and compounds **2** were synthesized to probe the structure–activity relationship.

2-Amino-6-bromobenzo[*d*]thiazole was reacted successively with carbonyldimidazole (CDI) and alkylamine to yield compounds **8**. In the same way with the preparation of compounds **1**, intermediate **7** was reacted successively with bis(pinacolato)diboron and intermediate **8**, catalyzed by $PdCl_2$(dppf), to yield compounds **2a**–**2l**.

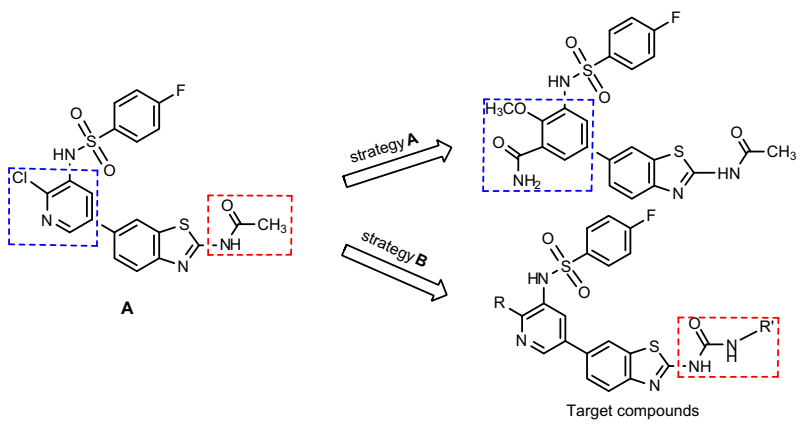

Figure 2. Optimizing strategy.