Chinese Chemical Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Discovery of novel dual inhibitors of VEGFR and PI3K kinases containing 2-ureidothiazole scaffold

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ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form 15 May 2015
Accepted 10 August 2015
Available online xxx

Keywords:
2-Aminothiazole
VEGFR
PI3K
Anticancer

ABSTRACT

A series of compounds possessing 2-(3-phenyl) ureidothiazol-4-formamide derivatives with a 2-ureidothiazole scaffold were designed and synthesized. Some compounds demonstrated inhibition of cell proliferation against both MDA-MB-231 and HepG2 cell lines using Sorafenib as the positive control. Compounds **6i** showed a good to moderate inhibition on VEGFR-2 and PI3Kα which was proved by further molecular docking study. This study suggests that compound **6i** is a potential dual inhibitor of VEGFR-2 and PI3Kα and is applicable for further investigation.

1. Introduction

Angiogenesis, the process by which new blood vessels grow from a body's vasculature, is fundamental to physiological processes of reproduction and wound healing. Disturbances in this process are associated with pathological conditions like rheumatoid arthritis, age-related macular degeneration, diabetic retinopathy, and are highly related to tumor progression and metastasis [1,2]. It has been confirmed that blocking angiogenesis is an efficient and prospective approach for cancer therapy. VEGFRs (vascular endothelial growth factor receptors) are key regulatory and signaling molecules involved in angiogenesis and consist of three subtypes: VEGFR-1, VEGFR-2, and VEGFR-3 [3]. Overexpression of VEGFRs serves as a potential target for anticancer agents. In other words, a drug can be designed based on the overexpressed genetic marker. Currently an extensive array of VEGFR inhibitors is entering clinics and/or achieving approval from FDA, such as bevacizumab, sorafenib, sunitinib, pazopanib and vandetanib, while many are still in preclinical development [4,5].

The phosphatidylinositol 3-kinases (PI3Ks) are members of a unique group of intracellular lipid kinases [6]. The PI3K family is involved in numerous cellular functions including proliferation, adhesion, migtation, invasion, metabolism and survival [7]. Frequent occurrences of aberrant signaling mediated by PI3Ks in human cancers have made them attractive targets for the design of small molecule inhibitors.

Although antiangiogenesis has shown to be a promising strategy for cancer therapy, VEGFR inhibitors often encounter resistance to novel therapeutic agents or chemotherapeutics after a period of treatment. One important explanation is that many other pathways are activated during antiangiogenic treatment to counteract the therapeutic efficacy [8]. The PI3K/Akt signaling pathway is one that has proven to be a bypass or compensatory pathway and can become overactive in the presence of cancers or certain agents [9,10]. PI3Ks upregulate angiogenic cytokines due to tumor hypoxia, or oncogene stimulation, and alter endothelial cell responses to them. These cytokines signal through the receptors VEGFR, FGFR, and Tie-2 to potentiate cell proliferation, migration, differentiation into tubules, and "invasion" of these capillary sprouts into extracellular matrix [11]. Therefore, blocking activation of the PI3K/Akt pathway during antiangiogenesis therapy could reduce tumor progression.

However, VEGFRs and PI3Ks are from different kinases families so it is a challenge to effectively design dual inhibitors of VEGFRs

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http://dx.doi.org/10.1016/j.cclet.2015.09.008
1001-8417/

and PI3Ks. As of now, there are no reports on an agent that targets both enzymes. Our investigation was induced by the lack of such an agent and the possibility of discovering VEGFR and PI3K dual inhibitors with novel scaffold. With this purpose, we searched the Ambinter and Chemspider libraries by the combinatory approach of SVM (support vector machine) and docking and were able to identify a one hit compound **5a** containing imidazo[2,1-b]thiazole scaffold. Based on this hit compound, a series of 2-aminothiazol-4-acetamide and 2-aminothiazol-4-carboxamide derivatives was designed and synthesized. All compounds were evaluated for their *in vitro* cytotoxicity against human HepG2 and MDA-MB-231 cell lines. Kinase inhibition and molecular docking were also studied. The results showed that compounds **6i** and **6j** containing 2-Ureidothiazol scaffold have good PI3K and moderate VEGRF inhibitory activity along with potency against both MDA-MB-231 and HepG2 cell lines.

2. Experimental

2.1. General

^{1}H NMR, ^{13}C NMR spectra were determined on Bruker ARX-400, 400 Hz spectrometers with tetramethylsilane (TMS) as the internal standard and DMSO-d_6, $CDCl_3$ as the solvent (Chemical shifts in ppm). Splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; m: multiplet. Mass spectra were carried out using a Waters Micromass Q-TOF Premier Mass Spectrometer. Melting points were determined in open glass capillaries with a SGW X-4 digital apparatus and were uncorrected. Follow-up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected glass plates and the spots were detected by exposure to UV-lamp at λ254 and λ365. Unless otherwise noted, all solvents and reagents were commercially available and used without further purification.

2.2. General procedure for preparation of compounds **2a–2n**

To a solution of compound ethyl 2-aminothiazole-4-acetate (**1**) (10 mmol) or ethyl 2-aminothiazole-4-carboxylate (**2**) (10 mmol) in anhydrous THF (10 mL), NMM (15 mmol) and substituted benzoyl chlorides (11 mmol) or substituted isocyanatobenzenes (11 mmol) were added with stirring at r.t. for 12 h. The solution was cautiously basified with 15% NH_4OH to pH 7, then poured into CH_2Cl_2, separated, washed and concentrated to result in four kinds of esters **1a–1n**, respectively. The crude product **1a–1n** was dissolved in EtOH–H_2O–NaOH (700 mL:300 mL:60 g) and refluxed for another 0.5 h, then acidified to pH 3–4 with concentrated HCl to afford white solid precipitation. After filtration, wash with water and dry, the desired compounds **2a–2n** were obtained.

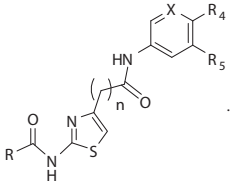
2.3. General procedure for preparation of compounds **3a–3b**, **4a–4b**

A mixture of 2-chloro-5-nitropyridine (**3**) (50 mmol), morpholine (100 mmol), and K_2CO_3 (100 mmol) in THF (50 mL) were stirred at 80 C for 4 h. And then the mixture was concentrated to 20 mL and poured into water (100 mL), the yellow solid precipitation formed. After filtration, wash with purified water and dry, the desired compound **3a** was obtained. **3b** Was got with the same method. The mixture of **3a–3b** (20 mmol) and Pd/C (20%, 500 mg) in methanol was hydrogenated at atmosphere at r.t. for 12 h, followed by filtration and concentration to afford compounds **4a–4b**.

2.4. General procedure for preparation of compound **4c**

5-amino-2-hydroxybenzoic acid (**4**) (100 mmol), methanol (80 mL) and H_2SO_4 (15 mL) were stirred at 80 C for 24 h, then cold to r.t. and pale yellow solid precipitation formed. After filtration, the crude product was dissolved in 200 mL ethyl acetate

Table 1
The 2-benzamidothiazole-4-amide derivatives and IC_{50} values against the liver cancer cell and human breast cancer cell line of compounds **5a–5r**.



5a-5r

Compound	R	R4	R5	X	n	IC_{50} (μmol/L)	
						HepG2	MDA-MB-231
5a	Ph	OCH_3	H	N	1	100.0	25.0
5b	Ph	Cl	H	N	1	63.6	2.7
5c	Ph	$NHCH_3$	H	N	1	>100	51.7
5d	Ph	OH	$COOCH_3$	CH	1	>100	39.5
5e	Ph		H	N	1	74.4	53.7
5f	2-chlorophenyl	OCH_3	H	N	1	>100	12.1
5g	3-chlorophenyl	OCH_3	H	N	1	>100	21.1
5h	4-chlorophenyl	OCH_3	H	N	1	>100	6.3
5i	3-trifluoromethylphenyl phenyl	OCH_3	H	N	1	>100	29.4
5j	2,4-dichlorophenyl	OCH_3	H	N	1	>100	3.7
5k	2-chlorophenyl	Cl	H	N	1	>100	2.5
5l	3-chlorophenyl	Cl	H	N	1	>100	18.5
5m	4-chlorophenyl	Cl	H	N	1	>100	2.4
5n	2,4-dichlorophenyl	Cl	H	N	1	>100	1.7
5o	3,4-dichlorophenyl	Cl	H	N	1	24.7	9.6
5p	2,4-dichlorophenyl	OCH_3	H	N	0	85.7	15.2
5q	2,4-dichlorophenyl	Cl	H	N	0	66.5	5.8
5r	2,4-dichlorophenyl	OH	$COOCH_3$	CH	0	45.0	19.4
Sorafenib						33.7	5.2

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and 100 mL H_2O. The resulting solution was cautiously basified with 15% NH_4OH to pH 8–9, then separated, washed and concentrated to get **4c**.

2.5. General procedure for preparation of compounds *5a–5r*, *6a–6o*

A solution of the **2a** (1 mmol) and **4a** (1 mmol), EDCI (1 mmol), HOBt (1 mmol), and DIPEA (3 mmol) in anhydrous THF (10 mL) was stirred for 24 h. The reaction was quenched with 1 M NaOH (20 mL) and extracted with ethyl acetate (3 × 20 mL), the organic layer was washed with 1 mol/L HCl (3 × 20 mL), water (20 mL), dried with Na_2SO_4 and evaporated to give compound **5a** as a white solid. Other title compounds **5b–5r**, **6a–6o** were synthesized as the same procedure.

2.6. Molecular docking methodology

The molecular docking of the representative compound **6i** with kinases was carried out using Discovery Studio.3.1/ CDOCKER protocol (Accelrys Software Inc.). The protein crystallographic structure, VEGFR (PDB entry 2QU5) and PI3K (PDB entry 3L54) were downloaded from the Protein Data Bank (PDB). The general procedure is as followed: (1) ligand and receptor preparation, (2) protocol generation, (3) docking and (4) analysis of the results.

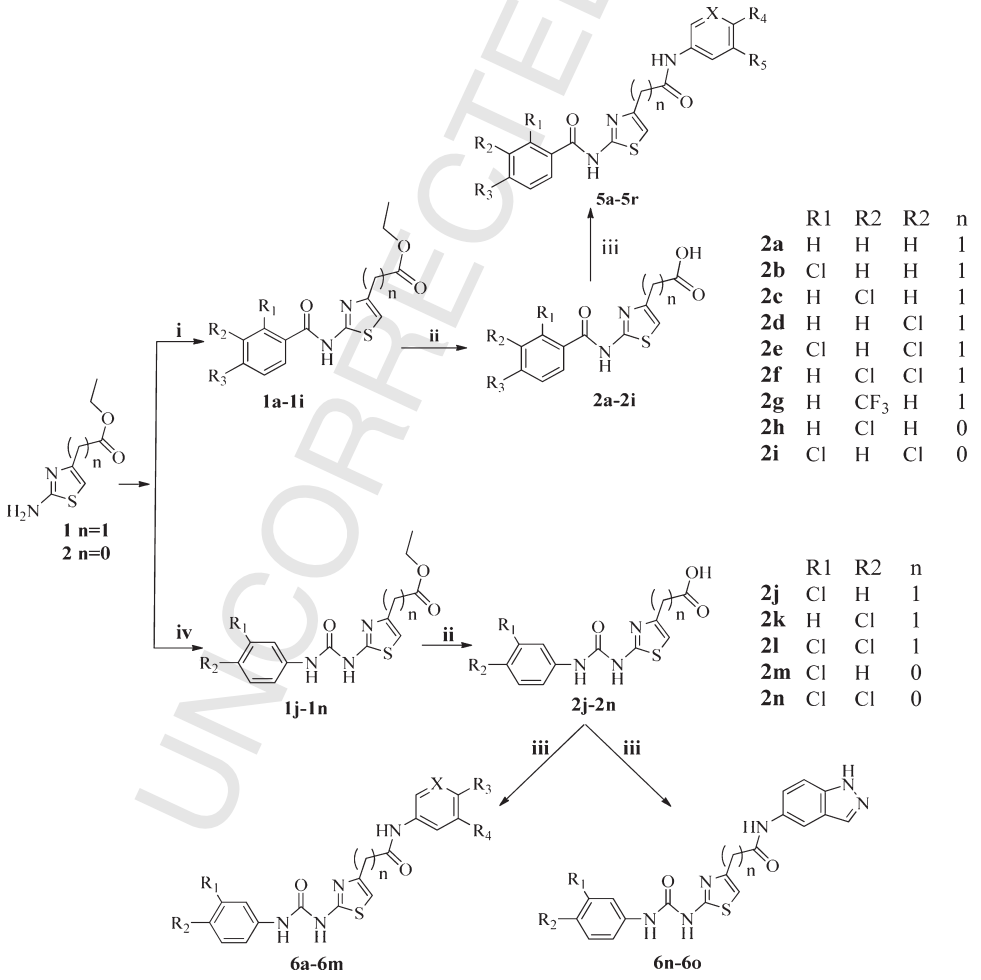
3. Results and discussion

3.1. High-throughput virtual screening

Virtual screening against Ambinter and in-house libraries was conducted using the similar methods and computational procedures as those described in a recently published paper [12–14]. Initially, SVM models of VEGFR and PI3K inhibitors were used to screen the compounds and received many SVM virtual hits. The hits were evaluated by Lipinsky's rule of five, and compounds that passed Lipinsky's rule were selected for further screening *via* molecular docking. Finally, compound **5a** (Ambinter ID 15893411) was identified as a virtual multi-target VEGFR and PI3K inhibitor. This compound and the other derivatives of **5a** were synthesized. The kinase assay result suggested that 2-aminothiazole is a potential scaffold and can be modified to get novel compounds with better antitumor activity.

3.2. Chemistry

The hit compound **5a** and target compounds **5b–5r**, **6a–6o** collected in Table 1 were prepared as shown in Scheme 1. Ethyl 2-aminothiazole-4-acetate (**1**) and ethyl 2-aminothiazole-4-carboxylate (**2**) were reacted with substituted benzoyl chlorides and substituted isocyanatobenzenes resulting in four different esters:



	R1	R2	R2	n
2a	H	H	H	1
2b	Cl	H	H	1
2c	H	Cl	H	1
2d	H	H	Cl	1
2e	Cl	H	Cl	1
2f	H	Cl	Cl	1
2g	H	CF_3	H	1
2h	H	Cl	H	0
2i	Cl	H	Cl	0

	R1	R2	n
2j	Cl	H	1
2k	H	Cl	1
2l	Cl	Cl	1
2m	Cl	H	0
2n	Cl	Cl	0

Scheme 1. Synthesis of compounds **2a–2n**, **5a–5r** and **6a–6o**. Reagents and conditions: (i) THF, substituted benzoyl chlorides, 12 h, r.t.; (ii) EtOH–H_2O–NaOH (1.5 mol/L), reflux, 0.5 h, then HCl (2 mol/L); (iii) amines, DIPEA, HOBt, EDCI, THF, 12 h, r.t.; (iv) THF, substituted isocyanatobenzenes, 12 h, r.t.

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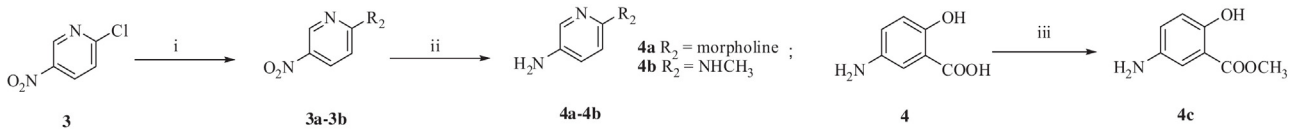


Scheme 2. Synthesis of compounds **4a–4c**. Reagents and conditions: (i) morpholine or methylamine hydrochloride THF, K_2CO_3, reflux, 4 h; (ii) H_2, Pd/C, r.t., 12 h; (iii) methanol, H_2SO_4, reflux, 24 h.

1a–1n. Compounds **1a–1n** were directly refluxed in EtOH–H_2O–NaOH and acidified to get **2a–2b** [15]. Compounds **3a–3b** were obtained from 2-chloro-5-nitropyridine (**3**) and other amines as shown in Scheme 2 [16]. The nitro-group on compounds **3a–3b** was reduced to an amino group by hydrogen using Pd/C as catalyst at atmospheric pressure and room temperature to get compounds **4a–4b** as shown in Scheme 2. 5-Amino-2-hydroxybenzoic acid (**4**) was esterified with methanol and catalyzed by H_2SO_4 to get compound **4c**. The target compounds were prepared *via* coupling **2a–2n** with **4a–4c** and other commercially available amines using DIPEA, HOBt, EDCI [17]. If necessary, silica-gel column chromatography was used with dichloromethane-methanol system as eluant.

3.3. Biological evaluation

3.3.1. Antiproliferative activity and Structure-activity relationship

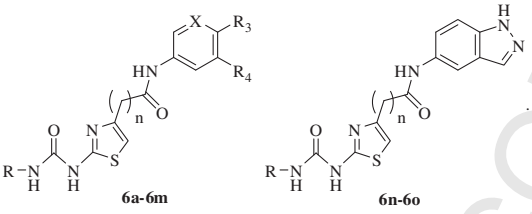
As shown in Table 1, the hit compound **5a** and other 2-benzamidothiazol-4-amide derivatives **5b–5r** were evaluated against HepG2 and MDA-MB-231 cell lines with Sorafenib as the positive control by MTT assay. The cells were treated with compounds in the range of 0.1–100 μmol/L for 48 h.

The results showed that these compounds have selective inhibition against the MDA-MB-231 cell line compared to the HepG2 cell line. Five of the compounds that have IC_{50} values ranging from 1.7 μmol/L to 3.7 μmol/L were more potent than Sorafenib (IC_{50} 5.2 μmol/L). Compounds **5a**, **5f–5j**, **5p** possess a methoxy group while compounds **5b**, **5k–5o**, **5q** possess a chloro group on position 2 of the pyridine ring. The chloro compounds were more potent than the corresponding methoxyl derivatives. The activity of **5f–5j** for the MDA-MB-231 cell line gradually increased in conjunction with substitutions by 3-chloro, 2-chloro, 4-chloro, and 2,4-chloro on the benzene ring and this sequence was consistent with the activity of compounds **5k–5n**. However, compound **5o** with 3,4-dichloro substituted on benzene ring can more so increase the activity against HepG2 and decrease the activity for MDA-MB-231 compared to compound **5n**, which was the 2,4-dichloro substituted on the benzene ring. The activity of compound **5e** showed that pyridine substituted by a bulk group increased the activity for HepG2 and decreased the activity for MDA-MB-231 when contrasted to hit compound **5a**. After removal of the methane group to yield derivatives of compound **2**, the activity for HepG2 increased while the activity for MDA-MB-231 remained unaltered, as suggested by **5p** *vs* **5j**, **5q** *vs* **5n**. In an attempt to replace the pyridine ring with to get compound **5r**, the activity stayed moderate against the two cell lines. The above observation indicated that a pyridine ring on position 2 substituted by a chloro group was crucial for antitumor activity.

Based on 2-benzamidothiazole derivatives, a series of 2-(3-phenyl)ureidothiazole derivatives containing a urea group was synthesized as listed in Table 2. Overall, the cytotoxicity activity against HepG2 greatly increased while the activity for MDA-MB-231 remained constant. Compounds **6f** and **6g–6o** have IC_{50} values ranging from 6.4 μmol/L to 20.8 μmol/L for HepG2, and **6d–6o** have IC_{50} values ranging from 1.6 μmol/L to 4.6 μmol/L for MDA-MB-231. These compounds were more potent than Sorafenib (IC_{50} 33.7 μmol/L and 5.2 μmol/L, respectively).

SARs suggested that substitution by 3-chloro on the benzene ring more reactive than the substitution of 4-chloro for HepG2, **6a** *vs* **6b**, and **6d** *vs* **6e**. Contrarily, the results for the MDA-MB-231 cell

Table 2
The 2-(3-phenyl) ureidothiazole-4-amide derivatives and IC_{50} values against the liver cancer cell and human breast cancer cell line of compounds **6a–6o**.



Compound	R	R3	R4	X	n	IC_{50} (μmol/L)	
						HepG2	MDA-MB-231
6a	3-chlorophenyl	OCH_3	H	N	1	55.0	23.1
6b	4-chlorophenyl	OCH_3	H	N	1	>100	11.0
6c	3,4-dichlorophenyl	OCH_3	H	N	1	>100	14.7
6d	3-chlorophenyl	Cl	H	N	1	45.5	3.6
6e	4-chlorophenyl	Cl	H	N	1	77.7	3.3
6f	3,4-dichlorophenyl	Cl	H	N	1	20.8	2.2
6g	3,4-dichlorophenyl	OH	$COOCH_3$	CH	1	>100	4.3
6h	3-chlorophenyl	OH	$COOCH_3$	CH	0	8.4	2.2
6i	3,4-dichlorophenyl	OH	$COOCH_3$	CH	0	7.4	3.7
6j	3-chlorophenyl	Cl	H	N	0	8.3	1.6
6k	3,4-dichlorophenyl	Cl	H	N	0	7.5	4.0
6l	3,4-dichlorophenyl	F	H	N	0	6.4	4.1
6m	3,4-dichlorophenyl	$NHCH_3$	H	N	0	26.5	2.6
6n	3-chlorophenyl				0	14.7	4.6
6o	3,4-dichlorophenyl				0	15.0	3.1
Sorafenib						33.7	5.2

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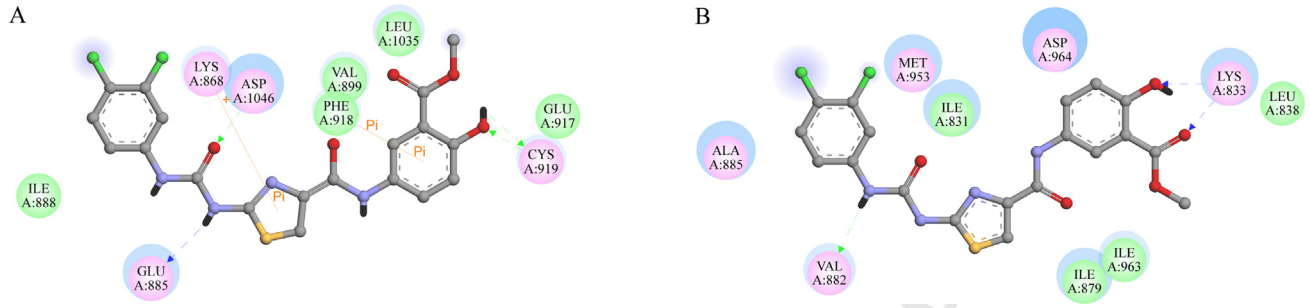

Fig. 1. 2D-presentation for the binding interactions of compound **6i** with VEGFR and PI3K kinase domain. (A) Compound **6i** with VEGFR; (B) compound **6i** with PI3K.

line were the reverse of the latter. 3,4-Dichloro substituted on benzene ring increased the activity in both HepG2 and MDA-MB-231. Similar results were produced for the 2-benzamidothiazole derivatives in which the chloro group was better than the methoxy group on position 2 of the pyridine ring.

In order to increase the rigidity of compounds and shorten the length of the chain, methane was removed in order to synthesize a series of 2-(3-phenyl) ureidothiazole-4-formamide derivatives **6h**–**6o**. The best results were obtained with compounds **6h**–**6l**. This may be attributed to hydrogen bond formation at the receptor site. Basis on compounds **5d**, **5r**, **6g**, compounds **6h**, **6i** were synthesized and exhibited good activity in the two cell lines. Compound **6l** was produced by exchanging the chloro group with a fluoro group on **6k**. The activity had no significant increase. We tried changing the pyridine ring to indazole and received compounds **6n** and **6o**, which resulted in decreased activity against HepG2 and the same activity for MDA-MB-231.

By observing anticancer activity from the data in Table 1 and Table 2, it was concluded that compounds **5a**–**5r** possess an amide linker while compounds **6a**–**6o** have a urea group linker. The best results were obtained with compounds **6h**–**6l**, which exhibited high potency against HepG2 and MDA-MB-231 cell lines with a urea linker. It was decided that the urea and 4-formamide are optimum for this series of compounds against HepG2 and MDA-MB-231 cell lines.

3.3.2. *Kinase inhibition*

Compounds **5n**, **6f**, **6i** and **6j** were selected for further evaluation in VEGFR2 and PI3Kα kinases inhibition assays at the concentration of 20 μmol/L with Staurosporine and PI103 as controls, respectively. As the kinase assay results reveal in Table 3 compound **5n** showed no obvious kinase inhibition against both VEGFR2 and PI3K kinases. Compound **6f** showed selective kinases inhibition with lower for VEGFR2 (7.03%) but better against PI3Kα (38.77%). Furthermore, compounds **6f**, **6i** and **6j** exhibit moderate inhibitory activities against VEGFR2 kinase within the range of 26–36% and good PI3Kα inhibitory activity in the range of 38–58%. This result is consistent with cell cytotoxicity activity. Our findings suggest that compounds **6i** and **6j** exhibit good PI3Kα inhibitory activity and moderate VEGFR-2 inhibitory activities, while compound **6f** showed moderate PI3Kα inhibitory activity and slightly weaker VEGFR-2 inhibitory activity.

Table 3
Inhibitory activity of compounds selected with two kinases (inhibitory rate, %) at 20 μmol/L.

Compound	VEGFR2 (%)	PI3Kα (%)
5n	8.82	2.03
6f	7.03	38.77
6i	36.58	58.44
6j	26.95	54.26
Staurosporine	99.71	–
PI103	–	99.94

3.4. *Molecular docking*

In order to better understand the interaction between compounds and VEGFR and PI3K kinases, compound **6i** was selected as a representative example for this series of compounds for molecular docking studies using the Discovery Studio 3.1/CDOCKER protocol [18,19]. The VEGFR-2 docking study revealed that the **6i** formed three strong hydrogen bonds, one π–π interaction, and one cation–π interaction between the binding site and the ligand (Fig. 1A). Two hydrogen bonds were formed between phenolic hydroxyl and CYS919, and the other one was formed between the urea hydrogen atom and GLU885. The π–π interaction and cation–π interaction were formed with PHE918 and LYS868, respectively.

Compound **6i** was also docked onto the PI3K-binding domain. Fig. 1B demonstrates that the ligand **6i** formed three hydrogen bonds with the protein. The phenolic hydroxyl oxygen atom and carbonyl oxygen atom as hydrogen bond acceptor formed two hydrogen bonds with LYS833. Also the urea group as hydrogen bond donors formed one hydrogen bond with VAL882. The docking analysis indicated that compound **6i** fit into the binding site of VEGFR and PI3K kinases suggesting that this compound may be a potent VEGFR and PI3K inhibitor.

The docking analysis indicated that compound **6i** fit into the binding site of VEGFR and PI3K kinases suggesting that this compound may be a potent VEGFR and PI3K inhibitor.

4. Conclusion

In summary, a series of novel compounds possessing a 2-aminothiazole scaffold were prepared. Most of the modified compounds showed tantamount or better cytotoxicity against either HepG2 or MDA-MB-231 cell lines. Compounds **6h**–**6l** showed higher and better potency against the two cancer cell lines than Sorafenib. SARs studies indicated that a benzene ring and thiazole ring linked by urea, and as well as removal of the methane group, are crucial for the antitumor activity. The molecular docking studies and the results of kinase inhibition assay *in vitro* suggest that compound **6i** may be a potent VEGFR-2 and PI3Kα dual inhibitor. The 2-aminothiazole scaffold may be considered a promising structure for future designs of VEGFR-2 and PI3Kα dual inhibitors. Q4

Acknowledgments

The authors would like to thank the financial supports from the NSFC (No. 21272134) and Shenzhen Municipal government SZSITIC Q5 (Nos. JCYJ20130402145002384, ZDSY20120619141412872).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.09.008.

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Please cite this article in press as: L. Li, et al., Discovery of novel dual inhibitors of VEGFR and PI3K kinases containing 2-ureidothiazole scaffold, Chin. Chem. Lett. (2015), http://dx.doi.org/10.1016/j.cclet.2015.09.008