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Research paper

Design, synthesis and biological evaluation of a series of novel 2-benzamide-4-(6-oxy-N-methyl-1-naphthamide)-pyridine derivatives as potent fibroblast growth factor receptor (FGFR) inhibitors

Manman Wei [a, d, 1], Xia Peng [b, d, 1], Li Xing [a], Yang Dai [b, d], Ruimin Huang [c, d], Meiyu Geng [b, d], Ao Zhang [a, c, d], Jing Ai [b, d, **], Zilan Song [a, d, *]

[a] CAS Key Laboratory of Receptor Research and the State Key Laboratory for Drug Research, Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai, 201203, China
[b] Division of Anti-tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai, 201203, China
[c] School of Life Science and Technology, ShanghaiTech University, Shanghai, 200031, China
[d] University of Chinese Academy of Sciences, 19A Yuquan Road, Beijing, 100049, China

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ABSTRACT

Starting from the phase II clinical FGFR inhibitor lucitanib (**2**), we conducted a medicinal chemistry approach by opening the central quinoline skeleton coupled with a scaffold hopping process thus leading to a series of novel 2-benzamide-4-(6-oxy-N-methyl-1-naphthamide)-pyridine derivatives. Compound **25a** was identified to show selective and equally high potency against FGFR1/2 and VEGFR2 with IC_{50} values less than 5.0 nM. Significant antiproliferative effects on both FGFR1/2 and VEGFR2 aberrant cancer cells were observed. In the SNU-16 xenograft model, compound **25a** showed tumor growth inhibition rates of 25.0% and 81.0% at doses of 10 mg/kg and 50 mg/kg, respectively, with 5% and 10%body weight loss. In view of the synergistic potential of FGFs and VEGFs in tumor angiogenesis observed in preclinical studies, the FGFR/VEGFR2 dual inhibitor **25a** may achieve better clinical benefits.

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1. Introduction

The fibroblast growth factor receptors (FGFRs) are a family of highly conserved transmembrane tyrosine kinases (RTKs), which constitute four members (FGFR1-4) [1–4]. The FGF-FGFR axis is involved in signal transduction pathways that regulate cell proliferation, differentiation, embryonic development, migration, survival, angiogenesis and organogenesis [3,5–8]. Over the past decades, several genomic alterations in the FGF-FGFR axis including activation mutations, gene amplifications, and chromosomal translocations have been identified in a broad spectrum of human tumors as oncogenic drivers, thus offering a new strategy to develop molecular targeted personalized medicine based on the FGFR activation status in cancer patients [9–15]. Since FGFR, like other RTKs (EGFR, VEGFR2), shares a ubiquitous intracellular signaling pathway, cancer cells are prone to escape the FGFR inhibition by either genomic mutations or by shifting to parallel signaling pathways [16–20]. Accordingly, the currently approved FGFR inhibitors are multi-target inhibitors (e.g. lenvatinib [21], nintedanib [22], pazopanib [23]) exerting antitumor efficacy primarily through targeting other RTKs rather than FGFRs [8]. Therefore, there is a need to develop more selective inhibitors to suppress tumors clearly through targeting FGFRs by using FGFR activation status as a biomarker to stratify patients [24,25]. To this end, several FGFR-selective inhibitors, including AZD4547 (**1**) [26] and BGJ398 (**3**) [27] (Fig. 1) have been in extensive clinic trials, and the outcome of these investigations will be useful to validate FGFR inhibitors as single anticancer therapies [28,29]. On the other hand, it is known that tumor angiogenesis is augmented by cross-talking between

* Corresponding author. CAS Key Laboratory of Receptor Research and the State Key Laboratory for Drug Research, Shanghai Institute of *Materia Medica* (SIMM), Chinese Academy of Sciences, Shanghai, 201203, China
** Corresponding author. Division of Anti-tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of *Materia Medica* (SIMM), Chinese Academy of Sciences, Shanghai, 201203, China.
E-mail addresses: jai@simm.ac.cn (J. Ai), songalan@simm.ac.cn (Z. Song).
[1] These two authors contributed to this work equally.

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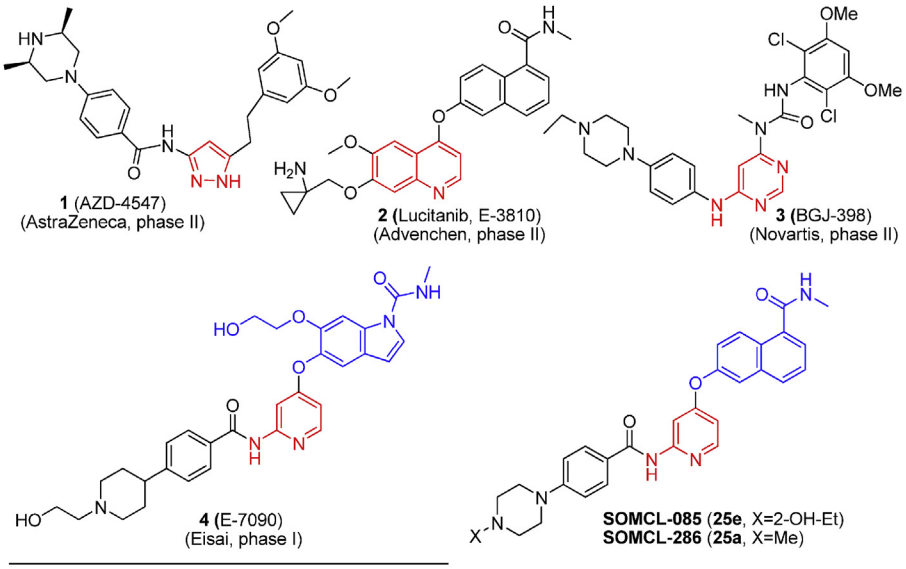

Fig. 1. Representative FGFR inhibitors.

FGF ligands, VEGFRs, and inflammatory mediators in tumor stroma, and the synergistic effects of FGFs and VEGFs in tumor angiogenesis have been observed in preclinical studies [16,30–32]. Therefore, compared to the previous multi-target FGFR inhibitors with less potency against FGFR, development of selective FGFR/VEGFR2 dual inhibitors with equal or even greater potency against FGFR would be an appealing combination [16,17].

The crystal structure of **1** [34] with FGFR1 demonstrates that the 3,5-dimethoxy-phenyl moiety occupies the hydrophobic pocket to form a hydrogen bond with the Asp641 residue. The pyrazole core located in the hinge region forms two hydrogen bonds with the carbonyl of the Glu562 and the NH of the Tyr563 residues. The substituted benzamide extends toward solvent, making two hydrogen bonds with the carbonyl of Ala564 and the NH of Gly485. The binding mode of another non-selective clinically being investigated FGFR inhibitor lucitanib (**2**) [33,34] with FGFR1 is similar to that of **1**. The *N*-methyl-1-naphthamide fragment forms two hydrogen bonds with the carbonyl of the Glu531 and the NH of the Asp641 residues, and extends to the hydrophobic pocket. The quinoline moiety forms a hydrogen bond with the NH of the Ala564 residue in the hinge region.

In view of the similar binding patterns of **1** and **2** with FGFR1, we envisioned that opening the quinoline fragment of **2** and introducing an amide bond as the hydrogen bond acceptor and donor would generate structurally flexible new FGFR inhibitors retaining similar hydrogen bonding networks (Fig. 2). Following this approach, we identified compound **SOMCL-085** [35] (**25e**, Fig. 1) that showed nearly equal potency against FGFR and VEGFR2 (Fig. 2). Encouraged by this result, a series of novel 2-benzamide-4-aryloxypyridine derivatives were developed and a systemic SAR study was conducted leing to the discovery of the preclinical compound **SOMCL-286** (**25a**). Notably, during completion of our study, Eisai disclosed its phase I clinical compound **4** (E−7090) [36], which also bears a 4-aryloxy-2-aminopyridine framework, but with a different head group. This compound showed high potency against FGFR1-3 (0.5–1.2 nM), but weaker potency against VEGFR2 (16 nM), which is different from our FGFR/VEGFR2 dual inhibitor profile. Herein, we report the structure-activity relationship study of our 2-benzamide-4-(6-oxy-N-methyl-1-naphthamide)pyridine series and the pharmacological profiling of the FGFR/VEGFR dual inhibitor **25a**.

2. Chemistry

The synthesis of 2-benzamide-4-aryloxypyridine derivatives is outlined in Schemes 1–5. Nucleophilic displacement of the C-4 fluoro atom of ethyl 4-fluorobenzoates with substituted piperazines afforded compounds **6a-i** in 68–89% yields. Similarly, nucleophilic displacement of the C-2 bromo groups of ethyl 2-bromothiazole-4-carboxylate (**8a**) and ethyl 2-bromooxazole-4-carboxylate (**8b**) and the C-2 chloro group of methyl 2-chloropyrimidine-5-carboxylate (**11**) afforded **9a**, **9b** and **12** in 70–82% yields, respectively. Hydrolysis of **6a-i, 9a, 9b** and **12** afforded the corresponding acids, which were then transformed to acyl chlorides by treating with thionyl chloride and subsequently reacted with ammonium hydroxide to afford primary amide intermediates **7a-i, 10a**, **10b and 13** in 33–70% yields (Scheme 1).

Condensation of 6-(2-chloropyridin-4-yloxy)-1-naphthoic acid (**14**) [37] with CH_3NH_2 afforded intermediate **15** in 96% yield. Compounds **19a-d** were prepared by Buchwald-Hartwig cross-coupling of **15** with benzamides **7a-d** followed by deprotection with CF_3COOH in 49–58% yields for two steps. Treatment of (2-bromoethoxy) (*tert*-butyl)diphenylsilane with 1H-pyrazole-4-carboxamide afforded intermediate **18**, which was converted to compound **20** via cross-coupling with **15** followed by deprotection with CsF in 17% overall yield. Compounds **21a-b** were obtained by cross-coupling of **15** with **10a-b** in 69% and 55% yield, respectively. Similarly, cross-coupling of **15** with **13** followed by deprotection with CF_3COOH afforded compound **22** in 51% yield for two steps (Scheme 2).

Condensation of 6-(2-chloropyridin-4-yloxy)-1-naphthoic acid (**14**) with MeOH afforded **23a** in 95% yield. 2-Chloro-4-(6-oxy-substituted)-pyridine derivatives **23b-e** were synthesized by nucleophilic substitution of 2-chloro-4-nitropyridine with the corresponding phenol derivatives in 40–71% yields. Similarly, nucleophilic displacement of 2,4-dichloropyridine with 2-(3,5-dimethoxyphenyl)ethanol [38] or 2-(2,6-dichloro-3,5-dimethoxyphenyl)ethanol [39] afforded **23f** or **23g** in 71% or 66% yield, respectively. Intermediates **23h-i** were prepared by nucleophilic displacement of 2,6-difluoro-3,5-dimethoxybenzyl methanesulfonate [40] or 1-(3,5-dicholoropyridin- 4-yl)ethyl methanesulfonate [41] with 6-chloropyridin-3-ol in 65% or 61% yield respectively. Compounds **24a-i** were prepared in 52–72%

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