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Research paper

Discovery of 4-((*N*-(2-(dimethylamino)ethyl)acrylamido)methyl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl) benzamide (CHMFL-PDGFR-159) as a highly selective type II PDGFRα kinase inhibitor for PDGFRα driving chronic eosinophilic leukemia

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ABSTRACT

Through exploration of the non-highly conserved allosteric hydrophobic pocket generated by DFG-out shifting in the inactive conformation, we discovered a highly selective type II PDGFRα kinase inhibitor **15i** (CHMFL-PDGFRα-159), which exhibited strong potency against purified PDGFRα (IC_{50}: 132 nM) but not structurally similar PDGFRβ, ABL, c-KIT and VEGFR2 kinases. In addition, it displayed a high selectivity profile (S score (10) = 0.02) at the concentration of 1 μM among 468 kinases/mutants in the KINOMEscan profiling. X-ray crystal structure of **15i** in complex with PDGFRα revealed a distinct binding feature in the allosteric hydrophobic pocket which might help to expand the diversity of type II kinase inhibitors. Compound **15i** potently inhibited the proliferation of PDGFRα driving Chronic Eosinophilic Leukemia (CEL) cell line EOL-1 through strong blockage of PDGFRα mediated signaling pathways, arresting cell cycle progression, and induction of apoptosis. Furthermore, compound **15i** effectively suppressed the EOL-1 tumor progression in the xenograft model and increased the survival rate in the engraftment tumor model.

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Abbreviations used: PDGFR, platelet-derived growth factor receptor; RTK, Receptor Tyrosine Kinases; ABL kinase, Abelson kinase; KIT kinase, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; RTK, receptor tyrosine kinase; CEL, Chronic Eosinophilic Leukemia; GISTs, Gastrointestinal Stromal Tumors; SAR, structure-activity relationship; NSCLC, non-small cell lung cancer; STAT3, signal transducer and activator of transcription 3; ERK, extracellular regulated protein kinases; PARP, poly ADP-ribose polymerase; PK, pharmacokinetics; PD, Pharmacodynamics; IHC, immunohistochemistry; HE, hematoxylin-eosin; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; TGI, tumor growth inhibition; IP, intraperitoneal injection.

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1. Introduction

Platelet-derived growth factor receptors (PDGFRs), including PDGFRα and PDGFRβ, are class III receptor tyrosine kinases (RTK) that can be activated by PDGFs and play important roles in the basic physiological functions, such as organogenesis and angiogenesis [1–3]. Dysregulation of PDGFRs, especially PDGFRα, has been observed in a variety of human tumors including sarcomas, gastrointestinal stromal tumors (GISTs), glioblastomas and chronic eosinophilic leukemia (CEL) etc. [4–6] Due to the critical role of PDGFRα in tumorigenesis, it has been extensively explored as a drug discovery target. To date, a number of kinase inhibitors have been reported to bear PDGFRs activities, such as compounds **1** (Imatinib) [7,8], **2** (Sunitinib) [9], **3** (Ponatinib) [10], **4** (Axitinib) [11], **5** (Masitinib) [12], **6** (Crenolanib) [13], **7** (Nintedanib) [14], **8** (Linfanib) [15,16] and **9** (Amuvatinib) [16] (Fig. 1). However, all of these inhibitors are multiple-target compounds and highly selective PDGFRα inhibitor is in urgent need both for fundamental research and clinical application.

Besides PDGFRs, class III RTK family also includes c-KIT, FLT3 and CSF1R [17]. Structurally, class III RTKs are comprised by five extracellular immunoglobulin-like repeats and a kinase insert separating the ATP-binding and phosphotransferase regions of the kinase domain. The ATP-binding pockets of type III RTK family are highly conserved, which makes it quite challenging to develop selective inhibitors. Type II inhibitors that bind to the inactive (DFG out) conformation of the kinase, sometimes can take advantage of the additional DFG-shift generated allosteric pocket to achieve higher selectivity [18]. Given this fact, we postulated that modification of the DFG region-binding moiety of the suitable pharmacophore might lead to more selective inhibitors. Inspired by this assumption and via the structure-guided drug design approach, starting from the known BCR-ABL/cKIT inhibitor imatinib that also bears PDGFR activity, we discovered a highly selective type II PDGFRα inhibitor **15i** (CHMFL-PDGFRα-159) (Fig. 2).

2. Results and discussion

2.1. Chemistry and structure-activity relationship (SAR) investigation

As depicted in Scheme 1, compounds **13a-n** were prepared starting from amidation reaction between 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**10**) and corresponding substituted benzoyl chloride or benzoic acid derivatives to form intermediates **11a-f**. Then, compounds **11a-b** were treated with NaN_3 and subsequently the azido groups were hydrogenated to yield the amine intermediates **12a-b**. Compound **12c** was generated by deprotection of the Boc group under acidic condition from **11c**. For the synthesis of compounds **12d-f**, the nitro groups in **11d-f** were hydrogenated to afford the amine products directly. Finally, amidation reaction between amine analogs **12a-f** and R4-substituted acyl chloride derivatives furnished the target compounds **13a-n**. Compounds **15a-r** were prepared beginning with nucleophilic substitution reaction of intermediate **11a** with different substituted amines to give intermediates **14a-e**. Then amidation reaction between amine analogs **14a-e** and a panel of R5-substituted acyl chloride derivatives afforded the products **15a-r**.

For SAR exploration, we used IL3 independent BaF3 cells expressing the fusion kinases TEL-PDGFRα, TEL-PDGFRβ, TEL-c-KIT and TEL-VEGFR2 as the primary readout of the activity and selectivity of the compounds. Ideally in this assay the highly selective

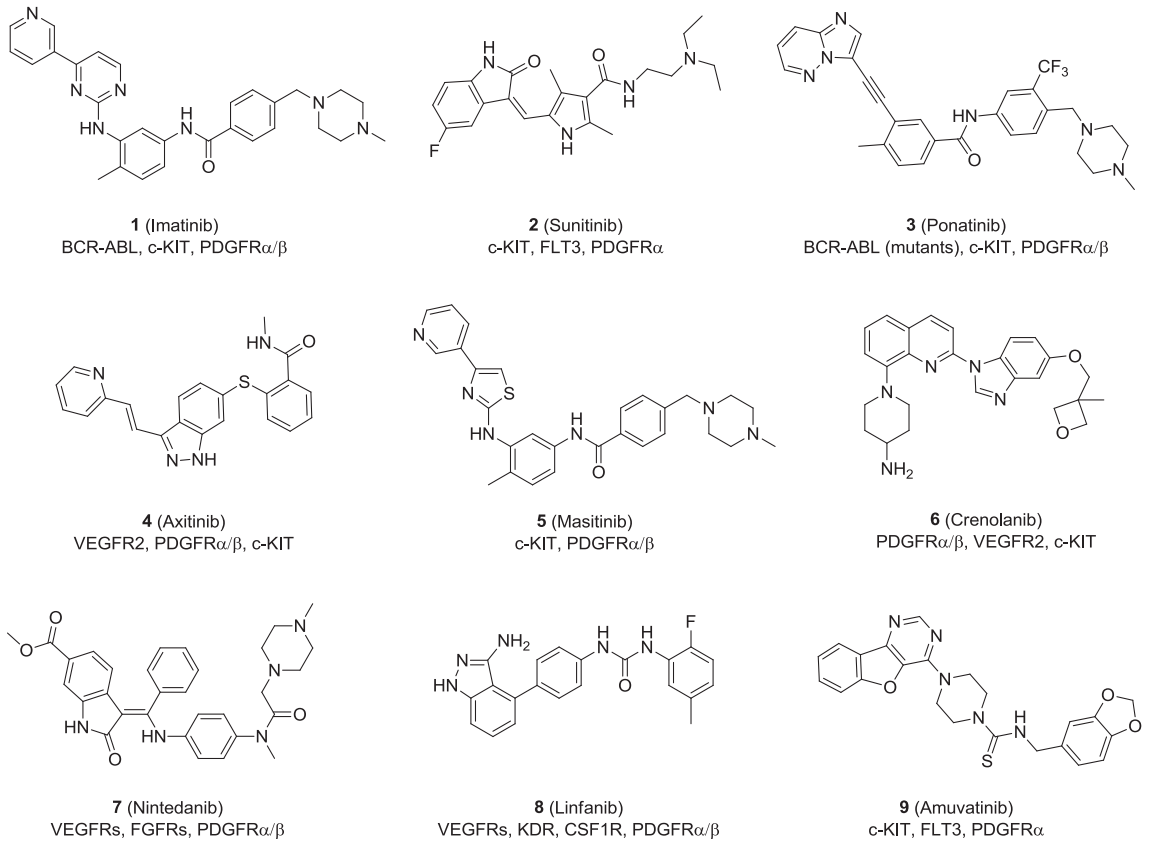

Fig. 1. Representative multi-target kinase inhibitors with PDGFRs activity.

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