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Original article

Cyclopentyl-pyrimidine based analogues as novel and potent IGF-1R inhibitor

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ABSTRACT

A series of novel 2-amino-4-pyrazolecyclopentylpyrimidines have been prepared and evaluated as IGF-1R tyrosin kinase inhibitors. The *in vitro* activity was found to depend strongly on the substitution pattern in the 2- amino ring, 4-pyrazolo moieties and size of fused saturated ring with the central pyrimidine core. A stepwise optimization by combination of active fragments led to discovery of compound **6f** and **6k**, two structures with IGF-1R IC_{50} of 20 nM and 10 nM, respectively. **6f** was further profiled for its anti cancer activity across various cell lines and pharmacokinetic studies in Sprague Dawley rats.

1. Introduction

Insulin-like growth factor receptor (IGF1R) is a transmembrane receptor tyrosin kinase. The IGF signalling cascade involves interactions between receptors, ligands, binding proteins, and downstream enzymes. Upon ligand binding, it's known to activate two signalling pathways of great importance in cancer biology, the Pi3K-AKT-mTOR pathway and the Ras-Raf-MEK pathway [1]. Dysregulation of the IGF-IR signalling pathway have been implicated in the development of many types of tumours, including colon, breast, pancreatic, multiple myeloma, and sarcoma [2,3]. Insulin-like growth factors and their receptor tyrosine kinase, IGF-IR, have been involved in the development and progression of cancer, by contributing towards proliferative, antiapoptotic, and proangiogenic signalling. Agents that inhibit IGF-IR activity at the receptor level may be useful in treatment of various cancers [4,5].

Various methods of inhibition of IGF-1R have been evaluated to bring about a desired clinical response. A plethora of monoclonal anti-bodies are in various stages of clinical trials. These antibodies are IGF-1R specific and are thus extremely useful tool to evaluate the clinical relevance of IGF-1R inhibition. As compared to mAbs there are relatively fewer small molecule IGF-1R inhibitors in various stages of clinical trials. The most advanced of them, Linsitinib (OSI906), a Phase III clinical candidate from OSI Pharmaceuticals [6], is presently being evaluated for adrenocortical carcinoma. It is also undergoing preclinical evaluation as either a single agent or in combination with various other anti-cancer agents. Though only a few of these inhibitors are being evaluated in clinical trials, there are multiple scaffolds known as IGF-1R inhibitors. OSI-906 is imidazo[1,5-a]pyrazines scaffold [7,8]. Various other scaffolds like benzimidazoles [9–13], 3-cyanoquinoline [14,15], isoquinolinedione [16], Pyrrolo-[1,2-f][1,2,4]triazine [17], 2,4-bis-

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arylamino-1,3-pyrimidines [18] have been reported in the literature. A hydantoin core as a non ATP competitive IGF-1R inhibitor [19] has also been reported by Buchanan et al. In addition to these scaffolds imidazo[1,2-α]pyridines [20–22] and 1H-pyrrolo[2,3-b] pyridines [23–25] have also been reported from various pharmaceutical companies as IGF-1R inhibitors. The concept of allosteric inhibition as IGF-1R inhibitors have also been explored [26].

2. Chemistry

2.1. Design of compounds

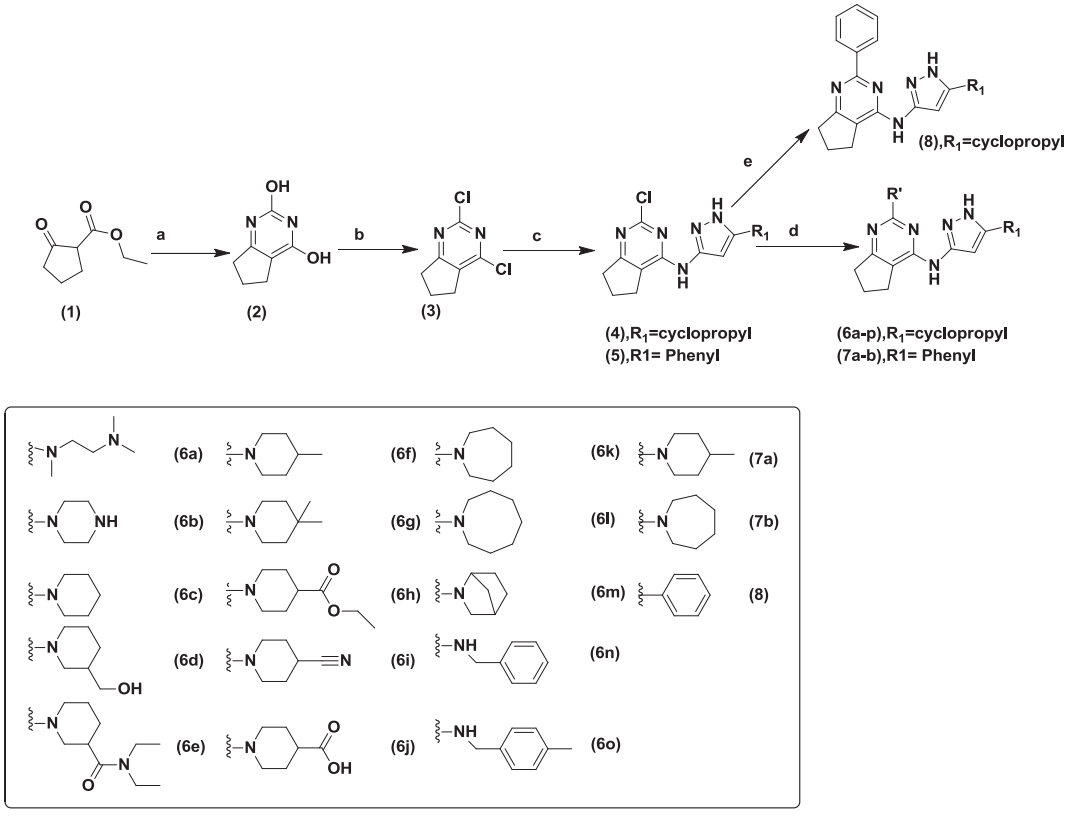
In a quest to discover a new class of IGF-1R inhibitors our group focused upon the discovery of a cyclopentyl-pyrimidine scaffold. The rational for the design of a cyclopentyl-pyrimidine core was a combination of factors to generate a novel core and was primarily driven by docking studies. Herein we report detailed SAR of the cyclopentyl-pyrimidine scaffold and its optimization to result in a low nM IGF-1R inhibitor. Using a classical approach for inhibiting kinases we planned on choosing a hinge-binding motif. Based on literature precedence we planned to decorate the cyclopentyl-pyrimidine core with a 5-cyclopropyl-1H-pyrazol-3-amine to introduce hinge binding capabilities. This amino pyrazole moiety has been used as a hinge binding motif in other kinase inhibitor programs. The designed compounds were validated by docking studies. The docked compounds were compared to the co-crystallized ligand of a pyrrolo-[1,2-f][1,2,4]triazine based compound (BMS754807 from Bristol Myers Squibb), in terms of docked conformations, hinge interactions, hydrophobic interactions, active site occupancy and also for unfavourable contacts [27].

2.2. Synthesis of target compounds

The synthesis of the desired analogs were executed via a four step parallel synthesis protocol as explained in Schemes 1–3. To investigate the importance of 4-methyl piperdine, a series of 2-substituted pyrimidine analogs (**6a-6o, 7a-b, 8**) were synthesized as described in Scheme 1. The key precursor of cyclopentyl dichloropyrimidine (**3**) was obtained from dihydroxy pyrimidine (**2**) upon treatment with $POCl_3$. The dihydroxypirimidine was obtained from commercially available corresponding beta-ketoesters (**1**), via initial cyclisation with urea [28]. The key intermediate, cyclopentyl dichloropyrimidine (**3**) was selectively substituted with 5-cyclopropyl-1H-pyrazol-3-amine and 5-phenyl-1H-pyrazol-3-amine at the 4-chloro position, to build-in the desired hinge binding motif thus yielding **4** and **5** respectively. The 2-chloro of the pyrimidine (**4** and **5**) reacted under much harsher conditions to facilitate a detailed SAR. Using this synthetic scheme derivatives **6a**–**6o** and **7a**–**b** were synthesized [29]. Compound **8** was synthesized by the treatment of 2-chloropyrimidine (**4**) with phenyl boronic acid under microwave condition (Scheme 1).

3. Results and discussion

The first set of SAR was focused on the 2-chloro position of the pyrimidine core to identify the best substitution at that site. The initial SAR set included amino substitutions of the chloro group. The chloro moiety was substituted with aliphatic amine (**6a**), piperazine (**6b**), piperidine (**6c**) and substituted piperidines (**6d**–**6j**). The piperidine substitution (**6c**) yielded excellent IC_{50} of 32 nM Table 1. Compound **6c** when docked exhibited 3 hinge H-



Scheme 1. Reagents and conditions: (a) Urea, Cat. HCl, ethanol, 80 °C, 5 h (b) $POCl_3$, 110 °C, 12 h (c) Et_3N, 5-cyclopropyl-1H-pyrazol-3-amine (for compound 4)/5-phenyl-1H-pyrazol-3-amine (for compound 5), 80 °C ethanol, 48 h (d) corresponding amine, NEt_3, IPA, 180 °C, 12 h sealed tube (e) $PhB(OH)_3$, $Pd(PPh_3)_4$, $NaHCO_3$, DME, 180 °C, 55 min, microwave.