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Synthesis and evaluation of pyrrolotriazine based molecules as PI3 kinase inhibitors

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ABSTRACT

Over activation of the PI3K/ Akt/ mTOR pathway is found in most cancer tumor types. Controlled regulation of this pathway using PI3K inhibitors can provide therapeutic significance in cancer treatment. Herein, we report the synthesis and evaluation of pyrrolotriazine based novel small molecules as pan-PI3K inhibitors. The SAR studies based on *in vitro* potency along with microsomal metabolic stability screening, identified **18** as a preclinical lead found to be suitable for *in vivo* evaluation. The identified lead was also found to be a selective inhibitor of PI3K isoforms and mTOR when screened across a panel of 23 homologous kinases.

The development of inhibitors for the PI3K/ AKT/ mTOR signalling pathway is an attractive area of research in oncology due to association of this pathway in several oncogenic malignancies.[1-4] The PI3 kinase (PI3K) signaling pathway controls cellular growth as well as survival via regulation of widely divergent physiological processes, i.e. cell cycle progression, differentiation, transcription, translation and apoptosis. Constitutive activation of PI3K alpha has been implicated in both pathogenesis as well as progression of large variety of solid tumors. There are many literature reports which demonstrate that the PI3K alpha (PI3Kα) signaling pathway is frequently deregulated in most cancer types.[5-8] Strong validation exists in the literature for the development of novel anticancer strategies exploiting inhibitors for PI3K isoforms. In recent years, interest in PI3K inhibitors has been intensifying and a large number of compounds in pre-clinical and clinical development have shown strong anti-tumor activity in animal models.[9] Currently, there are several PI3Kα inhibitors in various phases of pre-clinical and clinical development,[10-11] with BEZ235, GDC0941, XL765, PKI587 representing the most advanced development candidates and are in Phase I/II clinical trials.[121]

During our efforts towards the development of small molecule inhibitors for PI3 kinase (PI3Kα), we identified novel inhibitors for PI3Kα based on the pyrrolotriazine heterocyclic core **11** in figure 1. Herein, we describe the Structure Activity Relationship (SAR) and other pre-clinical findings leading to the development of pyrrolotriazine based molecules as inhibitors of PI3Kα. Our screening assay identified compound **8**, as a 1.1 uM (IC_{50}) inhibitor of PI3Kα. With this encouraging result we initiated an effort to develop an understanding of the SAR and synthesized selected molecules with the pyrrolotriazine core.

Synthetic Scheme 1 and its minor variations were used to synthesize a series of molecules to evaluate the pharmacophore space and to define the *in vitro* kinase activity as well as their cell based potency using cellular anti-proliferative assays.[13] Compounds **2** and **12**, served as key intermediates to facilitate the synthesis of various analogs of interest and the data from this structure activity relationship study is presented in tables 1, 2 and 3. The complete detail about the chemical synthesis and biological evaluation of all molecules mentioned in table 1-3 is provided in supporting document.

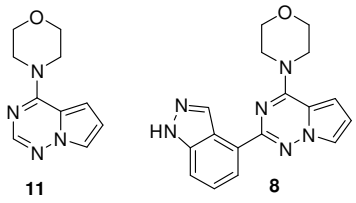

Figure 1: Initial hits

The PI3Kα enzyme inhibitory activity of all the compounds was determined using Homogeneous Time Resolved Fluorescence

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