P047 Design of a novel class of potent and highly isoform selective PI3Kγ inhibitors

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PI3Kγ plays a crucial role in mediating leukocyte chemotaxis and there is a great interest to discover selective PI3Kγ inhibitors to treat inflammatory diseases. We describe herein the discovery of a potent (IC_{50}=30nM) and isoform selective chemical series of PI3Kγ inhibitors bearing a phenol thiazolidine dione moiety. Preliminary structure activity relationships mostly focused on the phenol replacement with the goal to increase PI3Kγ/α selectivity. Ultimately, introduction of a fluorine atom on the phenol ring greatly enhanced selectivity (30-fold). Analysis of the crystallographic structure fully supported our observation where the fluorine atom points out to a non-conserved region of the binding site (e.g., $Ala^{\gamma}/Ser^{\alpha}$). In addition, compound appeared to be highly selective versus PI3Kδ and β and against a wide panel of protein kinases. This selectivity profile was further corroborated in cells where it preferentially inhibited a class Ib dependent chemokine-induced (MCP-1) Akt phosphorylation (EC_{50}= 400nM) versus a class Ia dependent CSF induced pathway (EC_{50}= 4.7μM). Upon oral administration, it reduced neutrophil recruitment (40%) comparable with inhibition of PI3Kγ knock out mice (50%). This compound is amongst the first published PI3Kγ inhibitors showing selectivity against the class Ia PI3K isoforms.