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Research paper

"Hit" to lead optimization and chemoinformatic studies for a new series of Autotaxin inhibitors

Elli-Anna Stylianaki [a,1], Christiana Magkrioti [a,1], Eleni M. Ladopoulou [a,b], Konstantinos D. Papavasileiou [c,d], Panagiotis Lagarias [c], Georgia Melagraki [e], Martina Samiotaki [a], George Panayotou [a], Skarlatos G. Dedos [b], Antreas Afantitis [c,d,**], Vassilis Aidinis [a,***], Alexios N. Matralis [a,*]

Herein, the potency optimization efforts of a new series of Autotaxin inhibitors, namely 2-substituted-2,6-dihydro-4H-thieno[3,4-c]pyrazol-1-substituted amide, is described using a previously identified novel chemical scaffold as a "hit". The mode of inhibition of the most promising ATX inhibitors was investigated, while their cellular activity, aqueous solubility and cytotoxicity were evaluated. Our pharmacological results were corroborated by chemoinformatic tools (molecular docking and molecular dynamics simulations) deployed, to provide insight into the binding mechanism of the synthesized inhibitors to ATX.

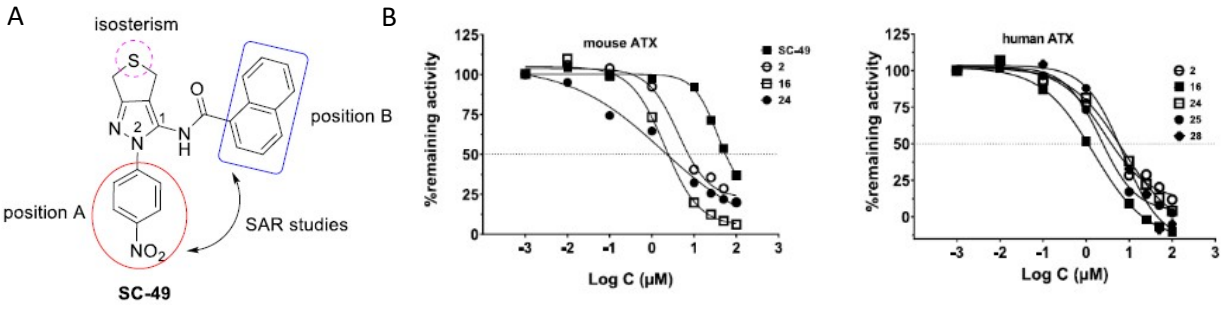

Figure. A. Structure-Activity Relationship studies were performed after the synthesis of 29 derivatives from the initial "hit" compound SC-49. Preliminary SAR studies followed by isosterism afforded derivatives (**16**, **24** and **25**) which exhibited a much more improved inhibitory activity, compared to the "hit" analogue, against ATX, accompanied by a better physicochemical profile (aqueous solubility and cytotoxicity). **B**. Graphs of the dose response curves of mouse (left) and human (right) ATX inhibition by different concentrations of representative compounds