Synthesis and Biological Evaluation of Pyrroquinoline Pseudo-Natural Products

Reporting

Project Information

pyrroQuin

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Periodic Reporting for period 1 - pyrroQuin (Synthesis and Biological Evaluation of Pyrroquinoline Pseudo-Natural Products)

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Summary of the context and overall objectives of the project

Natural products (NPs) and their structural scaffolds are a rich source of small molecule tools for chemical biology and drug candidates due to their inherent activity exploited by nature.[1] In the past,

natural product scaffolds were modified through chemical synthesis or simplified for the discovery of novel biologically active molecules.[2] In a new approach, natural product fragments[3] are combined in a biosynthetically unrelated manner to afford novel chemotypes with unknown biological activity. These compounds are termed pseudo natural products (pseudo NPs)[4], and a proof of concept has been established by the Waldmann group in several examples.[2] The biological activities of the obtained compounds were completely unrelated to the natural products the fragments were sourced from.
The purpose of this project was to explore the synthesis of members of the novel pseudo NP class pyrroquinoline (PQ) and investigating their biological activity with a target agnostic morphological profiling method called “cell painting”. PQs are a combination of tetrahydroquinoline and pyrrolidine fragments in manners not observed through biosynthesis. For this proposal, two scaffolds were designed where the fragments are combined to an edge-on fused as well as a bridged scaffold. Through the use of cell painting we are able to stream line the biological characterisation of the compounds without using a large number of primary assays. The morphological changes observed in cells upon compound treatment can give us direct indications on the involved cellular targets.

References
[1] G. M. Cragg, D. J. Newman, Biochim Biophys Acta 2013, 1830, 3670-3695.
[2] a) G. Karageorgis, H. Waldmann, Synthesis 2018, 51, 55-66; b) G. S. Cremosnik, J. Liu, H. Waldmann, Nat Prod Rep 2020, 37, 1497-1510; c) M. Grigalunas, A. Burhop, A. Christoforow, H. Waldmann, Curr Opin Chem Biol 2020, 56, 111-118.
[3] B. Over, S. Wetzel, C. Grutter, Y. Nakai, S. Renner, D. Rauh, H. Waldmann, Nat. Chem. 2013, 5, 21-28.
[4] G. Karageorgis, D. J. Foley, L. Laraia, H. Waldmann, Nat. Chem. 2020, 12, 227-235.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

During this fellowship, diastereoselective synthesis routes to both proposed scaffolds were developed. The methodology allowed for the generation of diverse libraries in a few steps. Further, synthetic handles were introduced into the scaffolds enabling late-stage functionalisation and derivatisations. The obtained libraries (> 100 compounds) were tested in several primary assays available in our in-house screening facility and were found to be potent inhibitors of cellular pathways involved in cancer. Morphological profiling of the compounds further enabled the generation of target hypothesis leading the search for cellular targets. Subsequently, we prepared probes for target identification according to the observed structure activity relationship. Efforts to identify and validate the cellular targets are still ongoing. It is expected that these PQ pseudo NPs will expand our understanding of the involved cellular pathway and potentially lead to novel therapeutic approaches. The dissemination of these results is planned after finishing the biological studies and publication in a high impact chemical biology journal is expected due to the importance of the involved cellular pathways in cancer biology. Additional to the proposed work, the data obtained from the morphological profiling was used in a statistical analysis involving other PQ scaffolds to determine the effects of fusion patterns,

regioisomeric combinations and saturation states on the biological activity. This study has recently been published in Angewandte Chemie, a high impact chemistry journal.[5]

References

[5] J. Liu, G. S. Cremosnik, F. Otte, A. Pahl, S. Sievers, C. Strohmann, H. Waldmann, Angew Chem Int Ed Engl 2021, 60, 4648–4656.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

The project relied heavily on the morphological cell painting assay to guide our biological studies. We will be able to further demonstrate the utility of such phenotypic assays to the chemical biology community and that they are a powerful tool for the discovery of novel biologically active molecules. In combination with specific primary assays, we were able to find new regulatory mechanisms of cell signalling pathways and unveil potentially therapeutic targets for cancers governed by said pathways.

Further, in an independent study using eight different PQ scaffolds, we were able to demonstrate that cells exhibit distinguishable phenotypes when treated with PQs varying in saturation states, arrangement of fragments and regioisomers. These findings strengthen the value of the cell painting assay.

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