Universität Basel

Research Project

Bioactive natural products - linking chemical and biological information for lead discovery, preliminary SAR and assessment of undesired pharmacological properties

Third-party funded project

Project title Bioactive natural products - linking chemical and biological information for lead discovery, preliminary SAR and assessment of undesired pharmacological properties
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Department
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Status Completed

1. Background

Small molecule natural products are a prolific source of inspiration for the development of new drugs, and essential tools in basic biomedical research as probes of biological functions. The contribution of academic laboratories in natural products discovery has been essential. The limiting factor of traditional approaches in bioactivity-directed natural product research has been the tedious process of purification and identification of active molecules from a highly complex extract matrix. Recent technological advances enable substantial improvements in efficiency via a consequential miniaturization of the screening and discovery process, and automation of certain process steps.

2. Specific Aims

The aim of the project is to discover small molecule natural products leads from plants and fungi acting against clinically relevant and/or emerging targets in important disease areas. The targets have been selected on the basis of specific criteria, such as (i) novelty and importance of target; (ii) lack of specific/selective inhibitors; (iii) need for enhancement of structural diversity of ligands; (iv) difficulty/impossibility to use rational drug discovery approaches; (v) access to animal models. Indications include CNS (selective GABA-A receptor agonists), inflammation and cancer (modulation of angiogenesis and lymphangiogenesis, inhibition of PI3 kinases). In addition, a screening for hERG channel inhibition will be carried out as the currently most critical anti-target in drug discovery & development.

3. Methods

An extract library and a technology platform for the miniaturized discovery of natural products will be used. The library consists of currently 1000 plant and fungal extracts. An ethnomedicine-based focussed sub-library will be specifically tested for GABAA receptor agonistic properties. All process steps in the screening and consecutive lead identification are miniaturized, in part automated, and based on the 96-well microtiter footprint. Most of the assays are via external collaborations, and some assays involving cell signalling are established in-house. Prioritized extracts are submitted to HPLC-based activity profiling with microtiter-based fractionation of column effluent, and simultaneous on-line spectroscopic (PDA, ion-trap ESI and APCI-MS, and ESI-TOF) analysis. Compound dereplication and identification is supported by off-line microprobe NMR spectroscopy. Around the active target molecules, structurally related compounds will be characterized to generate small “virtual” libraries for preliminary structure activity relationships. Calculation of physico-chemical data and secondary bioassays will characterize leads, and

shortlisted compounds will be tested *in vivo* for proof of concept.ă For this purpose, compounds of interest are isolated in a targeted manner in amounts of up to several hundred mg.

4. Expected Value of the Project

We anticipate the discovery of several new structural templates for the targets, and some compounds with confirmed in vivo activity. The use of functional assays and complex endpoints, combined with efficient tracking of activity and early dereplication enable the focussed identification of structurally novel molecules with possibly new and unexpected modes of action. These molecules may serve as new drug leads and/or as tools for basic biomedical research. The screening and profiling for natural product hERGchannel blockers will be pioneering work in the field and will provide important information on possible drug interactions with natural products contained in herbal medicines, food and food supplements.

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Follow-up project of 5778 Library based discovery of natural product leads - a miniaturized approach

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