J Develop Drugs 2016, 5:2(Suppl)
http://dx.doi.org/10.4172/2329-6631.C1.015

De novo design of novel inhibitors of the aspartic protease endothiapepsin exploiting dynamic combinatorial chemistry

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Structure-based design (SBD) is a powerful strategy to design and/or optimize bioactive compounds. Whereas, *de novo* SBD is rarely used, most reports on SBD are dealing with the optimization of an initial hit discovered by other means. Dynamic combinatorial chemistry has emerged as a powerful strategy to identify ligands for biological targets. In a dynamic combinatorial library (DCL), the connection bonds between the building blocks are reversible and continuously being made and broken. The composition of a DCL will respond to the addition of a target protein that selectively binds one or more library members and will extract such member(s) from the DCL. Here, we have demonstrated that the novel combination of *de novo* SBD and DCC is a highly efficient hit-identification strategy. We have designed a library of potential inhibitors (acyl hydrazones) generated from 5 aldehydes and 5 hydrazides and used DCC to identify the best binder(s). Upon addition of the aspartic protease endothiapepsin, the protein-bound library member(s) were characterized by saturation-transfer difference NMR spectroscopy (STD-NMR). The ligands identified were synthesized separately and tested for their biological activity using an enzyme-based fluorescence assay and shown to have IC50 values in the double-digit micromolar range. Subsequent co-crystallization experiments validated the predicted binding mode of the two most potent inhibitors, constituting a proof of concept that the combination of *de novo* SBD and DCC constitutes an efficient starting point for hit identification and optimization.

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Phenolic composition of Euphorbia macroclada by using UHPLC tandem mass spectrometry

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Euphorbia is one of the largest genus that belongs to the Euphorbiaceae family, and represented by 105 species in Turkey. *Euphorbia* species are named as 'Sütleğen' and 'Xaşil'. These species are commonly used in Turkish folk medicine for the treatment of rheumatism, swelling as well as a wart remover. In this study, root and aerial parts (stem, leave, flower and seed) of *Euphorbia macrolada* were collected in its flowering period. Powdered form of the dried plant material was weighed (1 gr) and macerated with methanol (3 times 10 mL) at 25°C for 24 hours. After filtration, the solvent was evaporated to obtain the crude extracts of different parts of *Euphorbia macrolada*. Phenolic components in the methanol extracts were analysed qualitatively and quantitatively by a previously validated LC-MS/MS method. With this method, 27 phenolic compounds were found in the plant.

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