Abstract (English)

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Title: Synthesis of a combinatorial compound library based on the double click reaction

Click chemistry is a powerful tool in drug discovery. It is very efficient in creating compound libraries through the combinatorial methodology. The copper(I)-catalyzed 1,2,3-triazole-forming reaction between azides and terminal alkynes has become the gold standard of click chemistry due to high reaction efficiency, mild reaction conditions, chemo- and regioselectivities. The molecules with triazole moiety display a broad spectrum of favorable properties and have been used in the development of antibacterial, antiviral, anti-inflammatory, anticancer, and anti-tubercular agents. This work focused on preparing a compound library using double-click reactions. Firstly, we synthesized several compounds with two alkyne groups ("alkyne cores") and a diverse group of structurally simple azides. In the next step, one equivalent of alkyne core was reacted with two equivalents of all prepared azides. The reaction between each alkyne core and ten azides yielded 100 compounds. The prepared libraries of compounds were assayed on several validated pharmacological targets, including human butyryl- and acetylcholinesterase, penicillin-binding protein 1b, InhA, and MurA. Inhibition of butyrylcholinesterase and InhA was observed, thus clearly demonstrating the validity of the initial idea. As a continuation of this work, various methods will be used to identify compounds causing inhibition from the compound mixtures.

Keywords: azide–alkyne cycloaddition; click chemistry; combinatorial chemistry; compound library