Author: Tomasz Frączek, M. Sc.

Supervisor: Piotr Paneth, Ph. D., D. Sc.

Affiliation: Institute of Applied Radiation Chemistry, Department of Chemistry, Lodz University of Technology

Design of HIV reverse transcriptase inhibitors

During the course of my PhD studies I attempted to rationally design and synthesize new non-nucleoside inhibitors of HIV-1 reverse transcriptase. A search for new bioactive compounds usually requires synthesis and examination of a large number of compounds. To reduce this number I employed a molecular modeling approach, particularly the molecular docking. By performing a detailed analysis of several docking programs, I concluded that the most suitable program for my project is Glide. In order to organize the numerous structural data that resulted from that part of my research, I wrote a computer program for structure diagram generation that proved to be superior in many aspects to the existing programs. I designed several classes of compounds as potential reverse transcriptase inhibitors. The first class of compounds that I synthesized were derivatives of 1,2,4-triazole, some of which were found to possess the desired activity, although with moderate potency. I attempted to optimize the most active compound, N-(2-chloro-4-carboxyphenyl)-2-((4-benzyl-5-methyl-4H-1,2,4-triazol-3-yl)sulfa-nyl)acetamide, with poor results. I was forced to abandon this direction of study, and design completely new compounds. I decided on diaryl ethers, which turned out to be significantly more potent than 1,2,4-triazoles, with activities comparable to clinically used reverse transcriptase inhibitors. Collaboration with people from the Ghent University allowed measuring the antiviral activity and cytotoxicity of the new compounds. Among them, 2-[4-

(4-{2-[4-chloro-3-(3-chloro-5-cyanophenoxy)phenoxy]acetyl}phenoxy)phenoxy]acetic acid demonstrated a pronounced antiviral activity below the cytotoxic concentration.

Łódź, 04.07.2017

Tomasz Frąckowiak