Abstract

This thesis concludes my contribution to research of HIV-1 capsid assembly inhibitors. It has been shown that 2,4-disubstituted quinazoline derivatives are able to inhibit this process both, in competitive biochemical assay based on the AlphaScreen technology as well as in tissue cultures. The main objective of the work was to prepare the aforementioned quinazolines, to design and prepare new candidates with higher activity based on results of biochemical tests, and also to try to increase the solubility of otherwise poorly soluble compounds.

Disubstituted quinazolines are relatively easily accessible from the commercially available anthranilic acid derivatives. These are converted to the corresponding quinazolin-4(3*H*)-ones by the condensation reactions. In this work, two methods were used for the preparation of quinazolin-4(3*H*)-ones: reaction of acyl chlorides with aromatic anthranilamides provided 2-arylamidobenzamides whose subsequent cyclisation under basic conditions led to derivatives of 2-arylquinazolin-4(3*H*)-one; reaction of anthranilic acid esters with aromatic nitriles, which afforded desired quinazolin-4(3*H*)-one in one reaction step. Chlorination of 2-arylquinazolin-4(3*H*)-ones using $POCl_3$ then led to 2-aryl-4-chloroderivatives as key intermediates. Nucleophilic substitution of 4-chloroderivatives by aromatic and aliphatic amines then provided desired *N*-substituted-2-arylquinazolin-4-amines. The most common method of nucleophilic substitution was acid-catalyzed reaction. The complementary method was run under basic conditions – particularly suitable in the case of non-reactive sterically hindered anilines.

A number of focused libraries of *N*-substituted-2-arylquinazolin-4-amines were prepared by the methodology described above. Ability of these compounds to inhibit HIV-1 capsid assembly was tested in a biochemical assay (AlphaScreen) and some compounds were tested in tissue culture assays, too. Synthesis of the compounds, reaction yields, their approximate solubility and the results of biochemical tests of these compounds are discussed within the thesis.