Abstract

This thesis is engaged in the synthesis of polysubstituted pyrimidines with anti-inflammatory properties. Such molecules can inhibit production of prostaglandin E_2 (PGE_2). The aim of this study was to enhance water-solubility and anti-inflammatory efficacy of such derivatives via structural modifications of the lead scaffold. Among applied synthetic tools, the Suzuki-Miyaura cross-coupling was the prevalent reaction, however, many other synthetic procedures (Heck reaction, condensation, borylation, ozonolysis, nucleophilic substitution, etc.) were utilized as well. Overall, 43 final products were prepared. The anti-inflammatory efficacy (inhibition of PGE_2 production) was successfully increased as the most potent compound achieved three orders of magnitude higher activity compared to the current lead structure WQE-134. Furthermore, no general influence of the length of the substituent in the C5 position of pyrimidine (C5pyr) on the anti-inflammatory efficacy of synthesized compounds was observed. Significant bioavailability obstacle in future development of the current lead WQE-134 is its poor solubility which was successfully enhanced by introduction of heteroatom bearing moieties to C5pyr. The most water-soluble compound achieved two orders of magnitude higher solubility than WQE-134 while biological activity decreased only slightly. Finally, WQE-134 biotinylated in C5pyr via pegylated linker was synthesized and will be used in pulldown experiments in order to clarify the mechanism of action of studied analogues.

Keywords: polysubstituted pyrimidines, anti-inflammatory properties, prostaglandin E_2, structure-activity relationship study, cross-coupling reactions, solubility