SELECTIVE AND POTENT 3-AMINO-2-PYRIDINONE ACETAMIDE THROMBIN INHIBITORS INCORPORATING HETEROBICYCLIC P1-ARGININE MIMETICS

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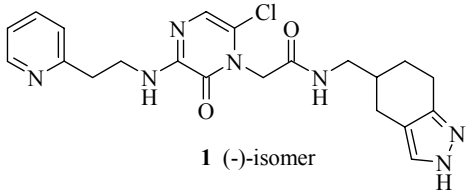
The major goal of pharmaceutical chemists dealing with development, synthesis and optimisation of new thrombin inhibitors is to convert *in vitro* active and selective inhibitors into *in vivo* orally bioavailable anticoagulants with the proper pharmaco-dynamical and pharmacokinetical profile which would enable one- or twice daily dosing and which would have advantages of safety and efficiency in comparison with classical and novel parenteral anticoagulants being used in therapy. The development of novel thrombin inhibitors containing weakly basic arginine side chain mimetics was coupled with the desire to overcome the limitations imposed by the amidine and guanidine moieties, whose high basicity reduces both bioavailability following peroral application, and selectivity for thrombin against trypsin. According to our structure activity relationship studies, we were interested in preparing a series of 2-(3-amino-6-methyl-2-oxo-2*H*-pyridin-1-yl)acetamide and 2-(3-amino-6-chloro-2-oxo-2*H*-pyrazin-1-yl)acet-amide template-based thrombin inhibitors incorporating novel, weakly basic, partially saturated, heterobicyclic arginine side chain mimetics at the P1 part of the inhibitor [1-7]. We prepared a series of highly selective and potent thrombin inhibitors represented by inhibitor **1** with the Ki value for thrombin of 40 nM and more that 2400-fold selectivity against trypsin and studied the influence of chirality on thrombin inhibitory potency [5-8].



1 (-)-isomer

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