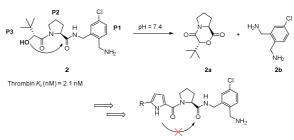
Improved Stability of Proline-derived Direct Thrombin Inhibitors through Hydroxyl to Heterocycle Replacement

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Modification of the previously disclosed (*S*)-*N*-(2-(aminomethyl)-5-chlorobenzyl)-1-((*R*)-2hydroxy-3,3-dimethylbutanoyl)pyrrolidine-2-carboxamide **2** by optimization of the P3 group afforded novel, low molecular weight thrombin inhibitors. Heterocycle replacement of the hydroxyl functional group helped maintain thrombin in vitro potency while improving the chemical stability and pharmacokinetic profile. These modifications led to the identification of compound **10**, which showed excellent selectivity over related serine proteases as well as in vivo efficacy in the rat arteriovenous shunt. Compound **10** exhibited significantly improved chemical stability and PK properties over **2**, and may be utilized as a structurally differentiated preclinical tool comparator to dabigatran etexilate to interrogate the on- and off-target effects of oral direct thrombin inhibitors.

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10: R = Me, Thrombin K_i = 9.6 nM **12**: R = CI, Thrombin K_i = 11 nM