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

Harry Chobanian, Barbara Pio, Yan Guo, Hong Shen, Mark Huffman, Maria Madeira, Gino Salituro, Jenna Terebetski, James Ormes, Nina Jochnowitz, Lizbeth Hoos, Yuchen Zhou, Dale Lewis, Brian Hawes, Lyndon Mitnaul, Kim O'Neill, Kenneth Ellsworth, Liangsu Wang, Tesfaye Biftu, Joseph Duffy

Merck and Co. Inc, Kenilworth, NJ, USA

Modification of the previously disclosed (*S*)-*N*-(2-(aminomethyl)-5-chlorobenzyl)-1-((*R*)-2-hydroxy-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.