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Heterocyclic core analogs of a direct thrombin inhibitor

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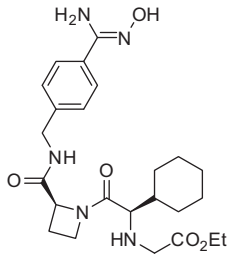
ABSTRACT

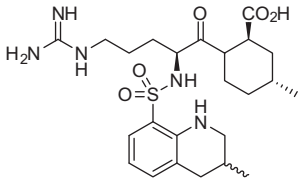
Thrombin is a serine protease that plays a key role in blood clotting. Pyrrolidine **1** is a potent thrombin inhibitor discovered at Merck several years ago. Seven analogs (**2**–**8**) of **1** in which the pyrrolidine core was replaced with various heterocycles were prepared and evaluated for activity against thrombin, clotting factors VIIa, IXa, Xa, and XIIa, and trypsin. The thiomorpholine analog **6** was the most active, essentially matching the thrombin inhibitory activity of **1** with slightly improved selectivity over trypsin.

Thrombotic events (stroke, heart attack, etc.) are an important cause of morbidity and mortality, especially in older patients.[1] A safe and effective drug that could prevent thrombotic events would clearly have a significant positive impact on life expectancy and quality of life. Fortunately, thrombogenesis is a complicated biological process involving a number of enzymes that provide attractive targets for potential new therapies.[2] Several approved drugs, including Warfarin (a vitamin K epoxide reductase inhibitor), Dabigatran (a thrombin inhibitor), Rivaroxaban and Apixaban (factor Xa inhibitors) are currently used prophylactically to reduce the risk of thrombotic events.[3] Unfortunately, current therapy suffers from significant side effects. Bleeding, in particular, remains a significant concern. Thus, there remains an unmet medical need for improved antithrombotic agents that would not have the bleeding liability of current drugs. This is a very active field of research and, in addition to those drugs already on the market, numerous compounds employing a variety of mechanisms are in development.[4–6]

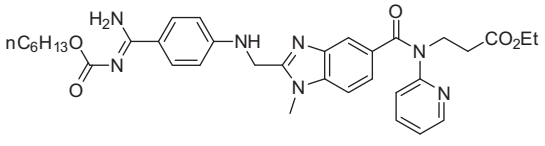
Thrombin (Factor IIa) is a serine protease that plays a key role in blood clotting. Selective thrombin inhibition is an established mechanism for thromboembolism prevention.[7,8] Three small molecule thrombin inhibitors have reached the market. The first, Ximelagatran, was subsequently withdrawn due to unacceptable liver toxicity.[7] Two newer direct thrombin inhibitors, Dabigatran and Argatroban, are currently on the market. Numerous other thrombin and Factor Xa inhibitors are in various stages of development.[9]



Ximelagatran



Argatroban



Dabigatran

Pyrrolidine **1** is a potent thrombin inhibitor discovered[10] at Merck several years ago as part of a program directed at finding clinically useful thrombin inhibitors.[10–13]

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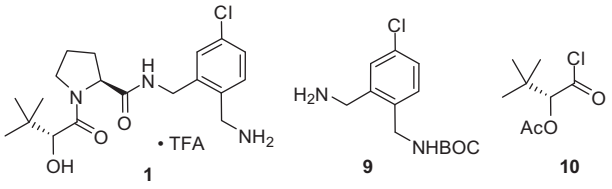
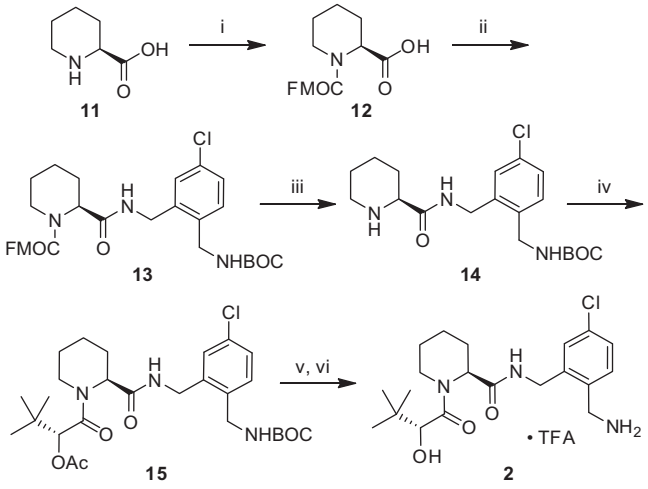
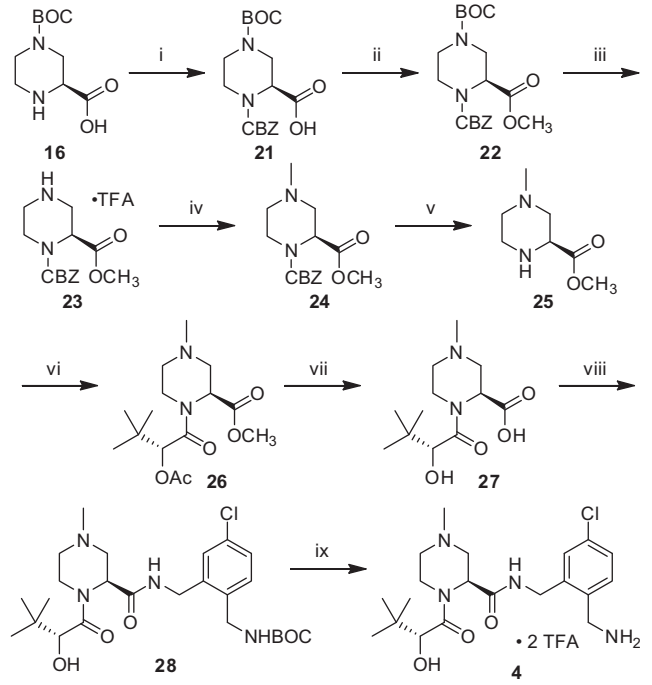


In their original report, Morissette et al. noted that reducing the core ring size (i.e. replacement of pyrrolidine with azetidine) resulted in reduced thrombin inhibitory activity.[10] However, the effect of ring expansion was unknown. In an attempt to discover an improved thrombin inhibitor, and to more fully elucidate the SAR of the heterocyclic core of **1**, we prepared and report herein a series of six-membered heterocyclic core analogs of **1**.

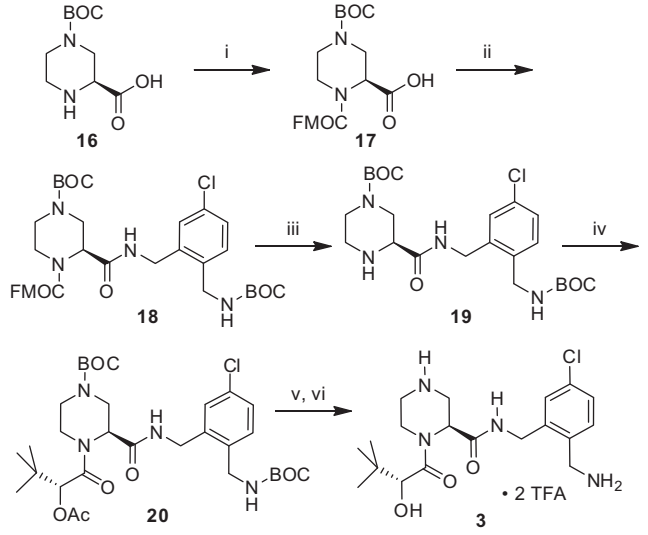


Scheme 1. Reagents and conditions: (i) FMOC-Cl, Na_2CO_3, 1,4-dioxane, water, 16 h, room temp, 52%; (ii) **9**, EDC, HOBT, DMF, 16 h, room temp, 70%; (iii) piperidine, CH_2Cl_2, 1 h, room temp, 80%; (iv) **10**, Et_3N, THF, −10 °C to room temp, 1 h, 65%; (v) K_2CO_3, CH_3OH, room temp, 30 m; (vi) TFA, CH_2Cl_2, room temp, 2 h, 30% for two steps.

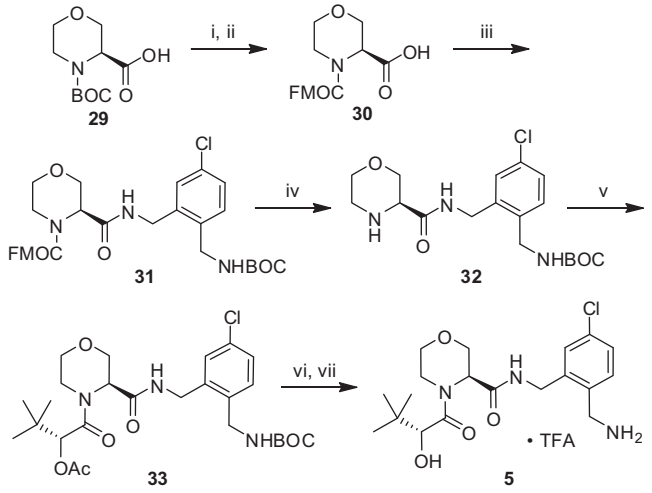


Scheme 3. Reagents and conditions: (i) CBZ-Cl, $NaHCO_3$, 1,4-dioxane, H_2O, room temp, 16 h, 82%; (ii) K_2CO_3, CH_3I, DMF, room temp, 2 h, 74%; (iii) TFA, CH_2Cl_2, room temp, 30 m, 97%; (iv) paraformaldehyde, Et_3N, $NaCNBH_3$, CH_3OH, AcOH, 0 °C to room temp, 2 h, 70%; (v) H_2 (1 atm), 10% Pd/C, CH_3OH, room temp, 3 h, 71%; (vi) **10**, Et_3N, CH_2Cl_2, room temp, 30 m, 40%; (vii) LiOH, THF, H_2O, CH_3OH, room temp, 2 h, 59%; (viii) **9**, EDC, HOBT, Et_3N, DMF, room temp, 16 h, 32%; (ix) TFA, CH_2Cl_2, room temp, 1 h, 73%.

We initially targeted the piperidine analog **2**. Starting with acid **11**,[14] **2** was readily synthesized as outlined in Scheme 1. Treatment of **11** with FMOC-Cl afforded the protected aminoacid **12** in good yield. The right-hand side chain was then introduced by EDC-mediated coupling of **12** with amine **9**,[10] to afford intermediate amide



Scheme 2. Reagents and conditions: (i) FMOC-Cl, Na_2CO_3, 1,4-dioxane, water, 0 °C to room temp, 16 h, 44%; (ii) **9**, EDC, HOBT, DMF, room temp, 16 h, 78%; (iii) piperidine, CH_2Cl_2, room temp, 2 h, 73%; (iv) **10**, Et_3N, THF, −5 °C to room temp, 1 h, 51%; (v) K_2CO_3, CH_3OH, room temp, 30 m; (vi) TFA, CH_2Cl_2, room temp, 2 h, 40% for two steps.



Scheme 4. Reagents and conditions: (i) TFA, CH_2Cl_2, room temp, 5 h; (ii) FMOC-Cl, K_2CO_3, 1,4-dioxane, H_2O, room temp, 3 h, 84% for two steps; (iii) **9**, EDC, HOBT, DMF, 0 °C to room temp, 5 h, 80%; (iv) piperidine, CH_2Cl_2, room temp, 1 h, 62%; (v) **10**, Et_3N, CH_2Cl_2, 0 °C to room temp, 16 h, 71%; (vi) K_2CO_3, CH_3OH, room temp, 30 m; (vii) TFA, CH_2Cl_2, 0 °C, 30 m, 48% for two steps.