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Thienopyrimidine-based $P2Y_{12}$ platelet aggregation inhibitors

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ABSTRACT

Herein we describe the design and synthesis of a novel series of potent thienopyrimidine $P2Y_{12}$ inhibitors and the negative impact protein binding has on the inhibition of platelet aggregation.

The success of Plavix® (clopidogrel) in inhibiting platelet aggregation and the subsequent discovery of the $P2Y_{12}$ receptor as the mechanism of action validates the inhibition of the $P2Y_{12}$ receptor as a viable strategy for platelet aggregation inhibition.[1,2] Whereas clopidogrel is an irreversible inhibitor of the $P2Y_{12}$ receptor, we were interested in developing a reversible inhibitor.[3] AZD-6140, an orally active $P2Y_{12}$ reversible inhibitor in clinical evaluation for acute coronary syndrome (ACS), shown in Figure 1 has a total of six chiral centers (four contiguous).[4] One of our goals was to develop a less complex adenosine diphosphate (ADP)-stimulated $P2Y_{12}$ antagonist while retaining the hydrophilic and hydrophobic regions as in AZD6140.[5]

We, along with others, investigated the thienopyrimidine core as a potential candidate for platelet inhibition.[6] Our efforts were concentrated on the central theme of a hydrophobic northern region with a hydrophilic southern region as exemplified by compound **21k**.

The synthesis of the chloro intermediates **5** and **7** are outlined in Scheme 1. Butyraldehyde **1** and methyl cyanoacetate **2** were combined in the presence of elemental sulfur and triethylamine in the classic Gewald synthesis to give aminothiophene **3** in 70% yield.[7,8]

Aminothiophene **3** reacted with potassium cyanate in acetic acid at room temperature for 18 h to give thienopyrimidinedione **4** in 65% yield. Thienopyrimidinedione **4** was converted to the 4,6-dichlorothienopyrimidine 5 using phenylphosphonic dichloride at 150 °C and then quenched in ice water to give the desired product in >95% yield. At atmospheric pressure, thienopyrimidinone **4** and $POCl_3$ with catalytic *N*,*N*-dimethylformamide (DMF) gave yields ranging from 0% to 30%. Use of a sealed tube (150 °C) gave improved yields (80–95%), but for larger scale reactions, phenylphosphonic dichloride in place of phosphorus oxychloride allowed the elimination of sealed pressure vessels while maintaining high yields of 4,6-dichlorothienopyrimidine **5**. Thiophene **3** is reacted with formamide at 130 °C for 12 h to give thienopyrimidinone **6** in 75% yield. Conversion of thienopyrimidinone **6** to thienopyrimidine **7** was accomplished using thionyl chloride and DMF at 80 °C in 86% yield.

Scheme 2 outlines the synthesis of the C-6 hydrogen analogs. Displacement of the C-4 chloro group of **7** with boc-piperazine **8** was accomplished at room temperature in the presence of diisopropylethylamine (DIEA) to give thienopyrimidine **9** in 70–90% yield. For exploration of the substituents at C-6, the BOC group of

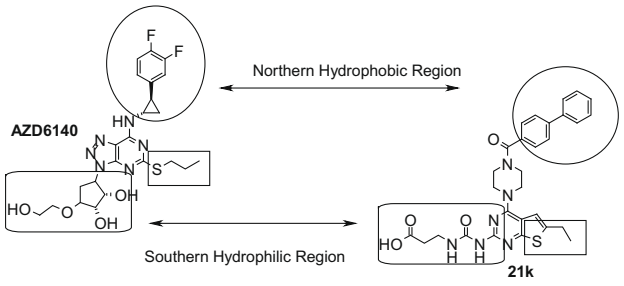

Figure 1. Comparison of AZD6140 to the thienopyrimidine compound **21k** highlighting the hydrophilic and hydrophobic regions of each molecule.

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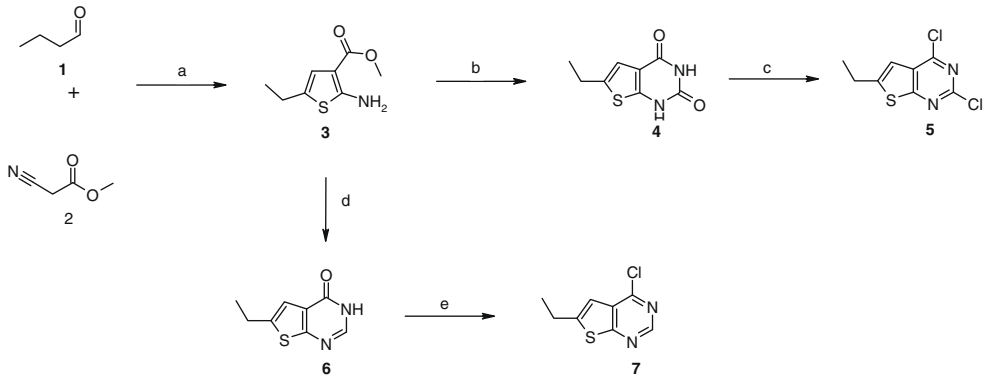
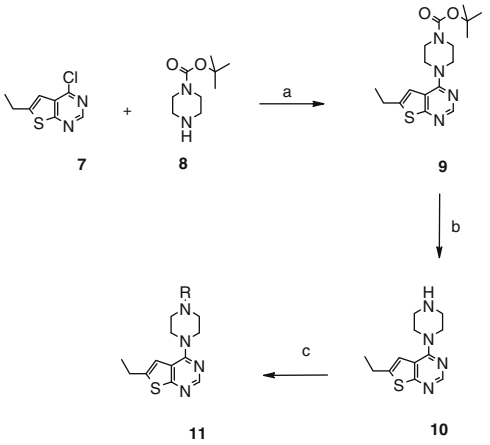
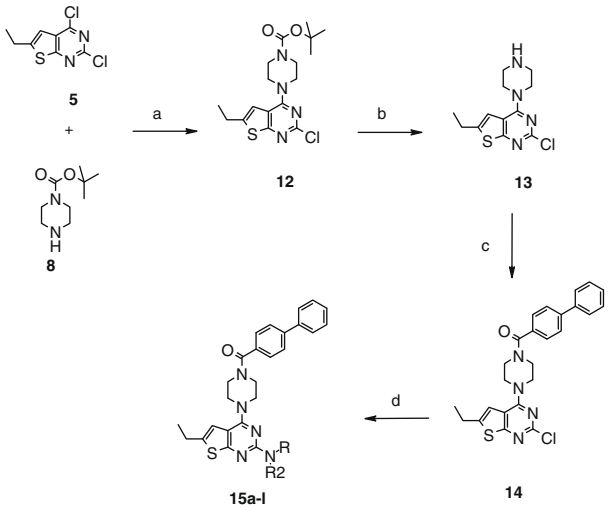


Scheme 1. Synthesis of the thienopyrimidine cores **5** and **7**. Reagents and conditions: (a) sulfur, triethylamine, DMF, rt, 18 h (70%); (b) acetic acid, H_2O, KOCN, rt, 18 h (64%); (c) phenylphosphonic dichloride, 150 °C, 3 h (95%); (d) formamide, ammonium formate, 135 °C, 12 h (75%); (e) thionyl chloride, DMF, 80 °C, 3 h (86%).



Scheme 2. Synthesis of C-6 hydrogen-substituted thienopyrimidine analogs **11a–h**. Reagents and conditions: (a) THF, DIEA, rt, 6 h (70–90%); (b) hydrochloric acid, methanol, rt, 3 h (quant); (c) DMF, DIEA, rt, 18 h (30–90%).



Scheme 3. Synthesis of the C-6 amino-substituted thienopyrimidine analogs **15a–l**. Reagents and conditions: (a) THF, DIEA, rt, 6 h (70–90%); (b) hydrochloric acid, methanol, rt, 3 h (quant); (c) DMF, DIEA, rt, 1 h (94%); (d) DIEA, NMP, 130 °C, 18 h (40–90%).

thienopyrimidine **9** was removed using HCl in methanol to give thienopyrimidine **10** in quantitative yield. Thienopyrimidine **10** was either acylated with the appropriate acid chloride using DIEA as base at room temperature to give thienopyrimidines **11a–h** in 30–60% yield or coupled with the appropriate acid using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) in comparable yields.

Scheme 3 outlines the synthesis of the C-6 nitrogen analogs. BOC deprotection of **12** and acylation of piperazine **13** were accomplished using the same procedures in similar yields to those of the C-6 hydrogen analogs. The C-6 chloro group of **14** was displaced using an appropriate amine with DIEA in 1-methyl-2-pyrrolidinone (NMP) at 105 °C to give the corresponding thienopyrimidines 15a–l in 40–90% yield.

Scheme 4 outlines the synthesis of urea analogs **21a–k**. The C-6 chloro group of **12** is displaced with sodium azide in NMP at 130 °C to give azide **16** in 77% yield. Azide **16** was reduced using trimethylphosphine in tetrahydrofuran (THF) to give amine **17** in 85% yield. Amine **17** was heated in pyridine with ethyl-3-isocyanatopropionate at 80 °C to give urea **18** (81%) followed by BOC deprotection to give **19** in quantitative yield. Acylation of **19** to give the intermediate esters **20a–k** in 30–60% yield and subsequent hydrolysis was accomplished in 50–90% yield using lithium hydroxide to give thienopyrimidines **21a–k**.

The $P2Y_{12}$ binding assay used for this study uses recombinant human $P2Y_{12}$ transfected Chinese Hamster Ovary (CHO) cell membranes.[9] The $P2Y_{12}$ binding assay with added protein, human serum albumin (HSA) and alpha-1 acid glycoprotein (AGP), was used to give a readout on the protein binding of our inhibitors before going into the human platelet rich plasma (hPRP) aggregation functional assay.[10,11] A large portion of the discrepancies between the $P2Y_{12}$ binding and functional assays, nM versus μM, are likely due to the increased amount of protein in the hPRP aggregation assay as compared with the $P2Y_{12}$ binding assay.

In keeping with the hydrophobic nature of the northern substituent we first looked at several hydrophobic substituents on the piperazine ring while keeping C-6 as H (Table 1). Biphenyl **11c** was the most active compound in the $P2Y_{12}$ binding assay, followed by naphthyl carbamate **11g**, indicating that larger, hydrophobic groups were preferred. All of the compounds lacking a C-6 substituent displayed poor activity in the hPRP aggregation assay.

Table 2 lists analogs containing C-6 nitrogen based substituents with the 4-biphenylacetyl group as the northern piperazine substituent. Substituents with carbonyl groups directly attached to (**21k**) or one atom removed from (**15h** and **15k**) the C-6 nitrogen were the most active in both the $P2Y_{12}$ binding and hPRP aggregation assays. Moving the carbonyl even further away from the C-6 nitrogen, as in **15c** and **15g,** resulted in a 10–15-fold decrease in