Communication

Concise Synthesis of Sibrafiban and Lamifiban, Two Non-Peptide Fibrinogen Receptor (GP IIb/IIIa) Antagonists

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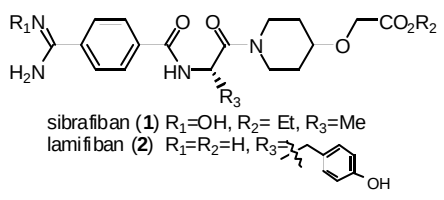
The total synthesis of the non-peptide fibrinogen receptor antagonists, sibrafiban (**1**) (Ro 48-3657) and lamifiban (**2**) (Ro 44-9883), is described. Both contain 4-hydroxypiperidine unit and the same solid-phase synthesis method was used as a key step. Connection of a secondary alcohol to the DHP-resin, followed by iterative saponification and coupling sequences, provided novel drugs.

INTRODUCTION

Dihydropyran (DHP)-linked polystyrene resin has become a valuable solid support for the high-throughput synthesis of oxygen-linked substrates.[1-9] The acetal, which in fact corresponds to a tetrahydropyran ether, should withstand a wide range of conditions including strong bases. The DHP-resin has provided the "traceless" linker in this solid phase peptide synthesis (SPPS) of literature. Since the integrity of the chiral center can be compromised in peptide synthesis using this approach, it is usually only used for side chain attachment or nonpeptide synthesis. In this letter, we report an *O*-attachment/saponification approach by employing DHP HM resin that provides a general and straightforward method for the synthesis of sibrafiban (**1**)[10,11] and lamifiban (**2**)[12,13] (see Diagram 1). Compounds **1** and **2** were both designed based on the integrin tripeptide recognition motif, Arg-Gly-Asp (RGD). According to recent studies[14] these compounds must have a carboxylate and an ammonium functionality within a distance of 11-15 Å to be effective inhibitors. Moreover, it has been shown that the basic function can be either a guanidine, which is the natural function of the RGD sequence, or an amine such as piperidine or a benzamidine moiety. They are also small organic molecular inhibitors of all platelet fibrinogen receptor glycoprotein IIb/IIIa (GPIIb/IIIa) blockers[15] and have been evaluated for their ability to prevent platelet aggregation. They are currently in clinical development as injectable antithrombotic agents for the treatment and prevention of acute coronary syndromes.

Diagram 1

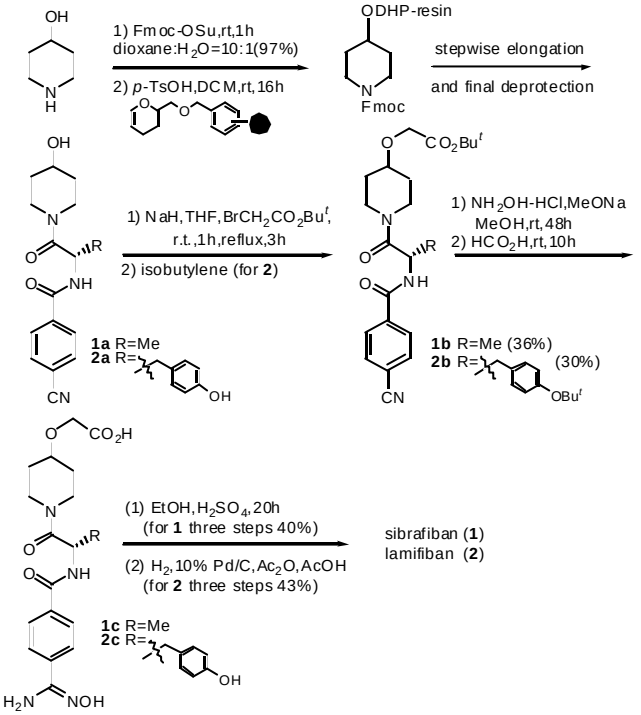


sibrafiban (**1**) R_1=OH, R_2= Et, R_3=Me
lamifiban (**2**) R_1=R_2=H, R_3=

RESULTS AND DISCUSSION

As shown in Diagram 2, 4-hydroxypiperidine reacted with *N*-(9H-fluoren-2-yl-methoxycarbonyloxy)succinimide (Fmoc-Osu, 1.0 eq) to give Fmoc-protected 4-hydroxypiperidine in 97% yield, then the resultant product (1.2 eq) was coupled to DHP HM polystyrene resin (0.98 mmole/g) using *p*-toluenesulfonic acid (*p*-TsOH, 1.2 eq) in dichloromethane/dimethylformamide (1/1 = v/v) for 20 h to give the Fmoc-amine resin. Deprotection of the Fmoc-amine resin (20% piperidine in DMF, 30 min) followed by acylation with Fmoc-Ala-OH or Fmoc-Tyr-(OBu^t)-OH (2.0 eq) and PyBOP (2.1 eq) for two hours gave the resin-bound amide. This was followed by deprotection of the Fmoc-amine amide (20% piperidine in DMF, 30 min) and acylation with 4-cyanobenzoic acid (2 eq) and PyBOP (2 eq) for 2 h. When the desired cyano-alcohol was obtained, cleavage of the acetal from the DHP HM resin was performed in acidic conditions. Treatment of the crude alcohol, **1a** or **2a**, with sodium hydride (NaH, 2.2 eq) and *tert*-butyl bromoacetate (1.2 eq) gave the Ala-CO_2Bu^t-ester **1b** and Tyr-CO_2Bu^t-ester. To easily purify the Tyr-(OBu^t)-CO_2Bu^t-ester **2b**, we protected the hydroxy group of phenol using excess isobutylene in acidic conditions[16,17] to give the Tyr-(OBu^t)-CO_2Bu^t-ester **2b**. The resultant cyano esters, **1b** and **2b**, were obtained in 36% and 30% yield, respectively, from Fmoc-protected piperidine. With **1b** and **2b** in hand, we required an efficient conversion of the nitrile into the amidine or amidoxime.[15,18-24] Conversion of the benzonitrile, **1b** or **2b**, into the benzamidoxime, **1c** or **2c**, was successfully achieved by amidoxime formation of

Diagram 2



hydroxyl ammonium chloride (NH_2OH-HCl, 1.5 eq) and sodium methoxide (MeONa, 1.4 eq) in methanol. Without purification, the residue was deprotected by formic acid (5 mL) to afford amidoxime **1c** and **2c**. Finally, the amidoxime, **1c**, was reacted with ethanol (5 mL) and a catalytic amount of sulfuric acid to give sibrafiban (**1**) in 40% yield, while the amidoxime, **2c**, was converted to lamifiban (**2**) by hydrogenolysis using 10% palladium on activated carbon (Pd/C, 100 mg) and acetic anhydride (2 eq) in 43% yield. The described solid-phase synthesis can be used to generate sibrafiban (**1**) and lamifiban (**2**) for use in human antithrombotic therapy studies.[25]

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Key Words

Sibrafiban; Lamifiban; Integrin; Fibrinogen; DHP HM resin; Phase III; GPIIb/IIIa.

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