Expeditious Approach to the Synthesis of Betrixaban

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Abstract A new scalable route to synthesize the factor Xa (FXa) inhibitor betrixaban is disclosed. The product is obtained in a seven-step reaction sequence (in five stages using two one-pot reactions) starting from easily accessible 4-(N,N-dimethylcarbamimidoyl)benzoate. Effective isolation of intermediates, use of cost-effective amide formation and 2-methyltetrahydrofuran as an effective reaction solvent as well as for extraction in three of the stages, are key features. The strategy provides the desired product in 38% overall yield with high purity (>98%).

Key words betrixaban, factor Xa (FXa) inhibitor, anticoagulant, one-pot reaction, amidation

Betrixaban (1: Figure 1) is an oral anticoagulant that acts as a direct factor Xa (FXa) inhibitor, sold under the brand name BEVYXXA, for the prevention and treatment of arterial and venous thrombosis.1-4 It was initially developed by Millenium Pharmaceuticals. Later, Portola pharmaceuticals acquired the rights and co-developed it with Merck. Betrixaban has relatively low levels of renal excretion compared to other direct oral anti-coagulants (DOAC) and is not metabolized by CYP3A4.5

Due to the important activity of betrixaban in the prevention of venous thromboembolism (VTE), several strategies for its synthesis have been reported.4,6-9 For example, the original approach by Kanter and co-workers (Scheme 1a) begins with the coupling of 5-methoxy-2-nitrobenzoic acid (2) with 2-amino-5-chloropyridine (3) in the presence of POCl3 and pyridine in acetonitrile to yield nitroamide 4, which, upon hydrogenation, provided the amino amide intermediate 5.

Figure 1 Structure of betrixaban

Scheme 1 Selected previous approaches to betrixaban (1)
Treatment of 5 with 4-cyanobenzoyl chloride (6)/pyridine gave the cyano precursor 7, and reaction of the latter with lithium dimethylamide afforded the target molecule 1. Alternatively, a modified route has been developed by Song and co-workers (Scheme 1b), wherein the amidine 10 is prepared from the reaction of ethyl 4-cyanobenzoate (8) with lithium dimethylamide (9) followed by hydrolysis of the ester using lithium hydroxide in THF/H2O and acidification with HCl. Next, the coupling of amidine 10 with amino-amide 5, in the presence of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI·HCl) in DMF or dimethylacetamide, gave betrixaban (1). Later in 2015, Wang and co-workers reported a reaction sequence (Scheme 1c) starting from the reduction of 5-methoxy-2-nitrobenzoic acid (2) to 2-amino-5-methoxybenzoic acid (11), wherein the dechlorination is avoided. Subsequently, the coupling of 11 with 6, in the presence of triethylamine, gave amidocarboxylic acid 12, which was subjected to amide formation with 2-amino-5-chloropyridine (3) to form the intermediate 7, followed by conversion of the cyano group into an amidine, leading to the target molecule 1.

However, these routes suffer from one of the following drawbacks: (1) dechlorination during the reduction of the nitro group leads to an impurity that is difficult to separate; (2) the use of expensive coupling agents and/or (3) tedious work-up procedures. These observations encouraged us to find an alternative approach to a scalable synthesis of betrixaban by circumventing the above disadvantages. In this direction, we planned the synthesis of betrixaban starting from N,N-dimethyl benzimididamide 13 in a protected form for easy isolation of all the intermediates involving the late-stage coupling of 5-chloropyridin-2-amine (3).

In our strategy (Scheme 2), initially, methyl 4-(N,N-dimethylcarbamimidoyl)benzoate (13), prepared by following a reported procedure, was protected as its tosylate by using tosyl chloride in the presence of triethylamine in 2-methyltetrahydrofuran (2-MeTHF). Subsequent LiOH-mediated hydrolysis provided (E)-4-(N,N-dimethyl-N'-tosylcarbamimidoyl)benzoic acid (14) in 85% yield. Coupling of acid 14 with commercially available methyl-5-amino-5-methoxybenzoate (15), in the presence of POCl₃ in 2-MeTHF, afforded the corresponding amide ester, which, upon treatment with LiOH in water, delivered the amido-benzoic acid 16 in 81% yield. The amide formation of 16 with 5-chloropyridin-2-amine (3) was carried out in a two-step sequence to avoid expensive coupling reagents.

Firstly, acid 16 was converted into benzoxazine 17 using POCl₃, Et₃N/DMAP in 2-MeTHF in 82% yield. Then, DBU-promoted ring opening of 17 with amine 3 in toluene under reflux gave the tosyl-protected betrixaban 18 in 87% yield. Finally, deotosylation of 18 proceeded well with trifluoroacetic acid (TFA) in methanol to give betrixaban (1) in 78% yield. It is important to note that the use of 2-MeTHF (immiscible in water) as the solvent permits easy separation during the workup, and the organic layer containing the product can be directly used for the next reaction in the same solvent. Furthermore, this strategy avoids the requirement of additional solvent for extraction and isolation of intermediates in two stages.

A novel, convergent approach for the convenient and scalable synthesis of betrixaban has been developed by using methyl 4-(N,N-dimethylcarbamimidoyl)benzoate, methyl 2-amino-5-methoxybenzoate and 2-amino-5-chloropyridine as starting materials. The unique features of this sequence, including effective isolation of intermediates due to the presence of a tosyl group, use of cost-effective amide formation reactions, and 2-MeTHF as solvent medium for both the reaction and the extraction of the product in three steps, make this an attractive process. Furthermore, avoidance of nitro-group reduction and a late-stage Pinner reaction are added advantages to avoid the formation of the dechlorinated impurity and tedious work-up procedures (shortcomings in previous approaches). We believe that the developed approach is convenient for scale-up as well as for the synthesis of novel analogues.

All the starting materials, reagents and solvents were used as received without further purification, unless otherwise stated. Reactions were analysed by thin-layer chromatography (TLC) on silica and compounds were visualized with UV-light. ¹H NMR and ¹³C NMR spectra were recorded with a 500 MHz Agilent spectrometer in either CDCl₃ or DMSO-d₆ with TMS as an internal standard. IR spectra were obtained with a Bruker-Alpha, Opus 8.2 spectrometer. Mass spectra were obtained with an AB SCIEX QTRAP 5500 LCMS/MS System. High-resolution mass spectra were recorded with either a TOF or double focusing spectrometer.
To a mixture of methyl 4-(N,N-dimethylcarbamimidoyl)benzoate (13) (13 g, 0.063 mol) and triethylamine (14.66 g, 0.145 mol) in 2-Me THF (130 mL) under a nitrogen atmosphere was added tosyl chloride (15.61 g, 0.082 mol) dropwise at 10 °C. Then, the mixture was allowed to warm to r.t. and stirred until completion (2 h, monitored by TLC). Upon completion, the mixture was cooled to 10 °C, the reaction was quenched with water (100 mL), and the aqueous layer was washed with saturated aqueous sodium bicarbonate (50 mL). To the organic layer was added LiOH (1.73 g, 0.072 mol) solution in water at 20 °C and the mixture was stirred at r.t. for 2 h. Upon completion, the white precipitate was added a solution of sodium bicarbonate (75 mL) and brine (50 mL). The aqueous layer was quenched with water (100 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate (75 mL) and brine (50 mL). The organic layer was concentrated in vacuo below 50 °C to give the crude benzoazinone 17 which was used further without any purification.

Yield: 78% (13.83 g); mp 217–219 °C.

HRMS (ESI): m/z [M + H]+ calcd for C_{25}H_{24}N_{3}O_{5}S: 478.1437; found: 478.1442.

To a stirred solution of benzoazinone 17 (12 g, 0.025 mol) in toluene (72 mL) under a nitrogen atmosphere, was added 2-aminoo-5-chloropyridine 3 (4.19 g, 0.033 mol) and the mixture stirred for 12 h under reflux. Upon completion, the reaction mixture was cooled to r.t., filtered, and the solid was dried under vacuum to afford betrixaban (18).

Yield: 87% (13.25 g); mp 236–238 °C.

HRMS (ESI): m/z [M + H]+ calcd for C_{36}H_{43}ClN_{2}O_{5}S: 606.1472; found: 606.1584.
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1H NMR (500 MHz, DMSO-d6): δ = 11.13 (s, 1 H), 11.07 (s, 1 H), 9.49 (s, 1 H), 9.37 (s, 1 H), 8.27 (d, J = 2.0 Hz, 1 H), 8.10 (d, J = 9.0 Hz, 1 H), 8.08 (d, J = 8.5 Hz, 2 H), 7.96 (m, 2 H), 7.74 (d, J = 8.5 Hz, 2 H), 7.42 (d, J = 3.0 Hz, 1 H), 7.18 (dd, J = 9.0, 3.0 Hz, 1 H), 3.85 (s, 3 H), 3.27 (s, 3 H), 2.97 (s, 3 H).

13C NMR (125 MHz, DMSO-d6): δ = 167.1, 163.9, 163.8, 155.6, 150.5, 146.3, 137.8, 137.4, 132.2, 130.2, 128.6, 127.7, 126.8, 125.8, 124.9, 118.1, 116.2, 113.8, 55.5, 41.8.

IR (neat): 3382–2945, 1649, 1607, 1212, 1178, 846, 690 cm⁻¹.

MS (ESI): m/z = 452.4 [M + H]+.

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Supporting Information

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References

(9) Pinto, D. J.; Qiao, J. X.; Gangor, T.; Lam, P. Y. S.; Li, Y.-L. PCT Int. Appl. WO2004083174, 2004; A2 20040930, 2004