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Research Article

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Synthesis of Aspirin Prodrugs of *β*-Cyclodextrin on the Primary/Secondary Hydroxyl Sides

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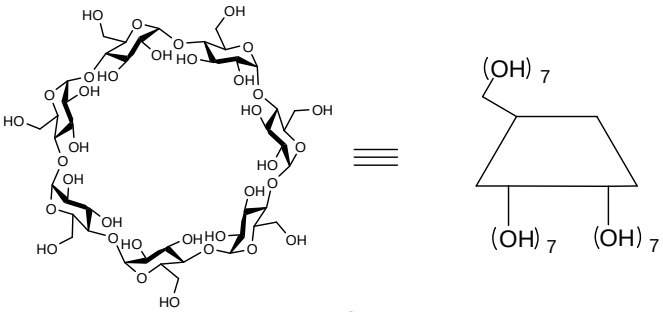
ABSTRACT

Aspirin was covalently conjugated to the primary/secondary hydroxyl groups of β-cyclodextrin in different solvents using different reagents for acylation. In pyridine, β-cyclodextrin reacted with acetylsalicylic acid chloride to produce the aspirin conjugates on the primary hydroxyl side, and in a carbonate buffer solution of N, N-dimethylformamide, β-cyclodextrin reacted with N-(2-acetoxybenzoyl)imidazole to give the aspirin conjugates on the secondary hydroxyl side.

Keywords: Aspirin, *β*-Cyclodextrin, Conjugation, Hydroxyl side, Prodrug.

INTRODUCTION

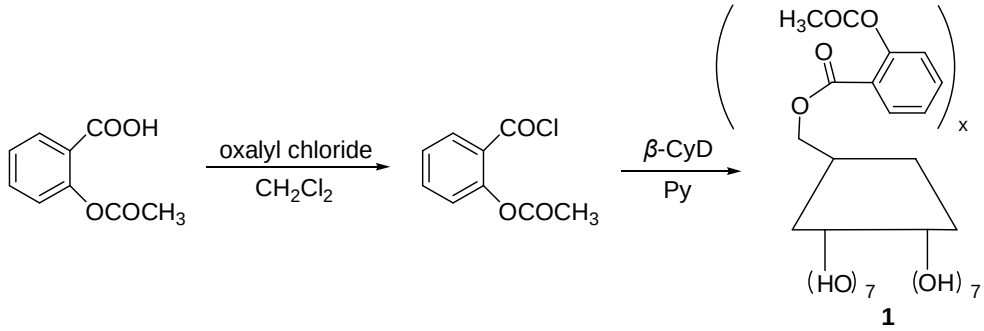
Aspirin, also known as acetylsalicylic acid, is an effective drug in the treatment for inflammatory and fever diseases, and new uses are being discovered all the time [1,2]. However, oral administration of aspirin induces gastric irritation and bleeding from cyclooxygenase inhibition in the mucosa [3-5]. Therefore, many prodrugs of aspirin based on non-acidic latentiated derivatives are synthesized and used [6-10]. In addition, a colon-targeting delivery system of aspirin is expected to be a promising formulation, and may decrease side-effects of upper gastrointestinal tracts.



Scheme 1

β-cyclodextrin (*β*-CyD) is a well-known cyclic oligosaccharide consisted of 7 α-1,4-linked D-glucopyranose units (Scheme 1), which possesses the secondary hydroxyl groups on its more open side and the primary hydroxyl groups on the other narrow side. It has been widely used as an excipient in the pharmaceutical industry for improving some properties of drugs, such as solubility, stability, absorption and/or bioavailability, by forming the inclusion complexes [11]. On the other hand, *β*-CyD is hardly hydrolyzed and only slightly absorbed through the stomach and small intestine. However, *β*-CyD can be bio-degradated into small saccharides by colonic microflora. This biodegradable property makes *β*-CyD useful as a colon-targeting material [12]. Therefore, *β*-CyD's conjugates, where a drug is covalently bonded to *β*-CyD, may serve as a source of colon-specific delivery system of drugs. In recent years, several *β*-CyD-drug conjugates and their pharmaceutical properties have been reported [13]. Herein,

we report the synthesis of aspirin prodrugs of *β*-CyD on the primary/secondary hydroxyl sides (Scheme 2 and 3).



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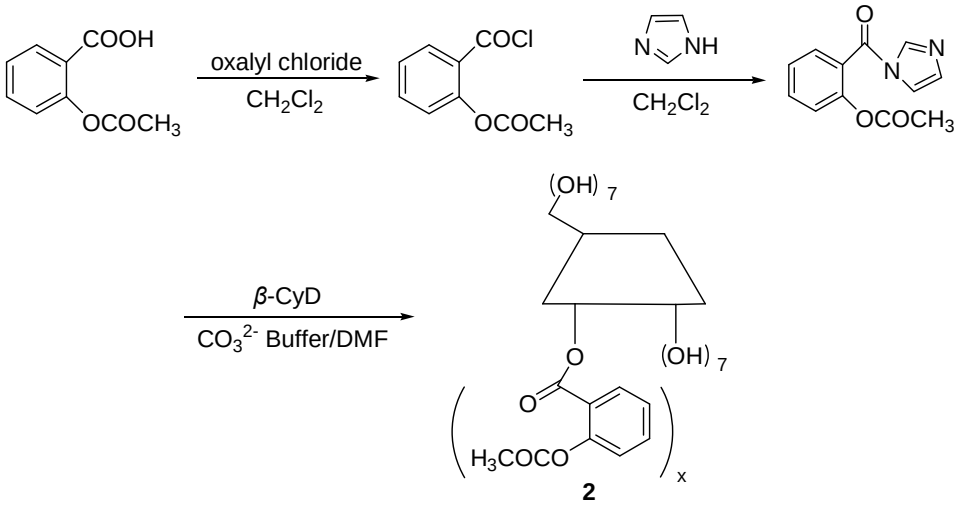
Scheme 2. The synthesis routes of the aspirin conjugates on the primary hydroxyl side of *β*-CyD



2

Scheme 3. The synthesis routes of the aspirin conjugates on the secondary hydroxyl side of *β*-CyD

EXPERIMENTAL SECTION

β-CyD was recrystallized twice from distilled water and dried under reduced pressure at 110 °C for 24 h before use. Pyridine (Py) was freshly distilled over CaH_2 and stored over 4A molecular sieves. Dichloromethane (DCM) was dried by $CaCl_2$ for 12 h and distilled prior to use. All other chemical materials and reagents were of commercial grade, and used without further purification. 0.2 *M* carbonate buffer (*pH* 9.9) was prepared by mixing equal volumes of 0.2 *M* sodium carbonate and 0.2 *M* sodium bicarbonate. NMR spectra were carried out on Bruker AM-600 (^{13}C 150 MHz) in DMSO-d_6 solutions with tetramethylsilane (TMS) as a standard.

Synthesis of the aspirin conjugates of β-CyD on the primary hydroxyl side

To a solution of acetylsalicylic acid (0.33g, 1.83 mmol) in 20 cm^3 DCM, oxalyl chloride (0.60 cm^3) was added at room temperature. After the addition of three drops of dry DMF, evolution of gas occurred. The mixture was stirred overnight. After completion of the reaction, the excess oxalyl chloride was removed in vacuo. The residue was dissolved in pyridine (10 cm^3), added to a solution of *β*-CyD (4.2 g, 3.70 mmol) in pyridine (70 cm^3) in an ice bath. The reaction mixture was kept with stirring in ice bath for 8 h, and then the temperature was raised to room temperature for 24 h. A small amount of water was added to quench the reaction and the solvent was removed under vacuum at 50 °C. The residue was dissolved in a small amount of DMF, to which was added 300 cm^3 of acetone. The precipitate was filtered and washed with acetone (20 cm^3). The crude products were isolated by an open RP-18 column using H_2O-MeOH (10%-20%-80%) as eluents. Thus, **1** was obtained in 38% yields (0.77 g), x = 1.2 (Average degree of substitution). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 20.8, 60.2, 64.5 (C-6′), 69.4, 72.2-73.7, 81.4-82.8, 102.1-103.1, 122.0-156.4 (the aromatic carbons), 165.9, 169.4.

Synthesis of the aspirin conjugates of β-CyD on the secondary hydroxyl side

To a solution of acetylsalicylic acid (0.33g, 1.83 mmol) in 20 cm^3 DCM, oxalyl chloride (0.60 cm^3) was added at room temperature. After the addition of three drops of dry DMF, evolution of gas occurred. The mixture was stirred overnight. After completion of the reaction, the excess oxalyl chloride was removed in vacuo. The residue was dissolved in DCM (4 cm^3), added dropwise to a solution of imidazole (0.25 g, 3.68 mmol) in DCM (4 cm^3) in an ice bath. The reaction mixture was kept with stirring in ice bath for 2 h, and allowed to warm to room temperature for

another 2 h. Then the reaction mixture was filtered, evaporated in vacuo, and the residue was dissolved in DMF (30 cm^3). To the solution, *β*-CyD (1.0 g, 0.88 mmol) and 6 cm^3 of 0.2 *M* carbonate buffer were added. The reaction mixture was heated at 60 ℃ for 1 h. Then the mixture was neutralized with 1 *M* HCl, evaporated in vacuo to a volume of ca. 5 cm^3, and 300 cm^3 acetone was added to precipitate cyclodextrin derivatives. The crude products were isolated by an open RP-18 column using H_2O-MeOH (10%-20%-80%) as eluents. Thus, **2** was obtained in 27% yields (0.34 g), x = 1.8 (Average degree of substitution). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 20.8, 60.4, 70.1-73.9, 75.0, 78.6 (C-4′), 81.4-82.1, 98.8 (C-1′), 102.0-102.4, 123.2-158.5 (the aromatic carbons), 166.1, 169.5.

RESULTS AND DISCUSSION

Of the three types of hydroxyl groups present in *β*-CyD, those at the 6-position are the most basic and often most nucleophilic, those at the 2-position are the most acidic, and those at the 3-position are the most inaccessible. Under normal circumstances, a more reactive electrophilic reagent attacks the 6-position. In addition, carbonate buffer (*pH* 9.9) can efficiently activate the C-2 OH of *β*-CyD, and regioselectively promote reactions at the secondary hydroxyl side [14]. Therefore, aspirin was covalently conjugated to the primary or secondary hydroxyl groups of *β*-CyD using different reagents for acylation. In pyridine, using acetylsalicylic acid chloride as an acylating reagent, aspirin was covalently conjugated to the primary hydroxyl groups of *β*-CyD. In a carbonate buffer solution of DMF, using *N*-(2-acetoxybenzoyl)imidazole as an acylating reagent, aspirin was covalently conjugated to the secondary hydroxyl groups of *β*-CyD. Different degrees of substitution (DS) were obtained by adjusting the ratio of *β*-CyD and acylating reagent.

In order to interpret the positions of aspirin conjugated to *β*-CyD, ^{13}C NMR spectra were used. ^{13}C NMR spectra is an effective technique for the analysis of cyclic oligosaccharides. As elegantly explaind by Breslow [15], usually, arylation of a hydroxyl group of *β*-CyD leads to a downfield chemical shift of the carbon carrying the hydroxyl (*α*-carbon), but a small upfield chemical shift of *β*-carbon and a still smaller shift of *γ*-carbon. In the ^{13}C NMR spectra of **1**, the peak at δ = 64.5 ppm (C-6′) clearly indicate that the substituents were at the 6-positions of *β*-CyD on the primary hydroxyl side. In the ^{13}C NMR spectra of **2**, the peak at δ = 98.8 ppm (C-1′) and 78.6 ppm (C-4′) indicate that the substituents were at the 2 and 3-positions of *β*-CyD on the secondary hydroxyl side.

CONCLUSION

Two kinds of aspirin conjugates, where aspirin were covalently bonded to the primary or secondary hydroxyl groups of *β*-CyD, were synthesized, i. e., in pyridine, using acetylsalicylic acid chloride as an acylating reagent, aspirin was covalently conjugated to the primary hydroxyl side of *β*-CyD, and in a carbonate buffer solution of DMF, using *N*-(2-acetoxybenzoyl)imidazole as an acylating reagent, aspirin was covalently conjugated to the secondary hydroxyl side of *β*-CyD. The release behaviors of aspirin conjugates are in progress.

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REFERENCES

[1] KD Rainsford. Aspirin and Related Drugs, Taylor & Francis, London. **2004**.
[2] KD Rainsford. *Subcell Biochem.*, **2007**, 42, 3-27.
[3] MM Wolfe; DR Lichtenstein; G Singh. *N. Engl. J. Med.*, **1999**, 340, 1888-1899.
[4] S Ghajar; MR Sohrabi. *J. Chem. Pharm. Res.*, **2012**, 4, 814-821.
[5] JK Savjani; AK Gajjar; AK Gajjar. *J. Chem. Pharm. Res.*, **2011**, 3, 160-168.
[6] LM Moriarty; MN Lally; CG Carolan; M Jones; JM Clancy; JF Gilmer. *J. Med. Chem.*, **2008**, 51, 7991–7999.
[7] AR Bendale; SB Narkhede; AG Jadhav; G Vidyasagar. *J. Chem. Pharm. Res.*, **2010**, 2, 225-233.
[8] ZZ Wang; JY Ma. *J. Chem. Pharm. Res.*, **2012**, 4, 580-582.
[9] JF Gilmer; LM Moriarty; MN Lally; JM Clancy. *Eur. J. Pharm. Sci.*, **2002**, 16, 297-304.
[10] NM Nielsen; H Bundgaard. *J. Med. Chem.*, **1989**, 32, 727-734.
[11] M Kreer; G Swami; R Kumar; K Kanwar; P Kaur; P Singh; A Kaur. *J. Chem. Pharm. Res.*, **2010**, 2, 851-860.
[12] GVD Mooter. *Expert Opin. Drug Deliv.*, **2006**, 3, 111-125.
[13] KI Singh; J Singh; D Sharma; A Sharma. *Int. J. Pharm. Sci. Res.*, **2012**, 3, 637-647.
[14] ZZ Wang; MY Liu; RH Lu; XY Fu; GD Dai. *Monatsh. Chem.*, **2011**, 142, 1283-1287.
[15] A Ueno; R Breslow. *Tetrahedron Lett.*, **1982**, 23, 3451-3454.