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Isolation, synthesis and structure confirmation of the impurity in crude roflumilast product

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Abstract An impurity was isolated from crude synthesized roflumilast and characterized by ^{1}H NMR, ^{13}C NMR, and HR-MS, which confirmed the structure as *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide. To further verify the structure, this compound was synthesized from 4-difluoromethoxy-3-hydroxybenzaldehyde. Comparison of the ^{1}H NMR, ^{13}C NMR, HR-MS, and the HPLC spectrum of the impurity and the authentic sample indicated that this impurity was *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide. This demonstrated the significance of monitoring the reaction process of roflumilast.

Keywords Impurity · PDE-4 inhibitor · Roflumilast · Structure confirmation · Synthesis

Introduction

Roflumilast, one of the second generation PDE-4 inhibitors, was developed by Altana AG and first put into the market in Europe for the treatment of COPD in July,

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2010 [1]. It has displayed high efficacy and a good safety profile and is currently widely used for the treatment of COPD, athsma, and other inflammatory diseases [2–4].

The synthetic methods of roflumilast have been intensively studied [5–7], but there are only a few reports related to impurities in roflumilast. Cook et al. [8] described the process and impurities in the synthesis of 3-cyclopentyloxy-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (INN: piclamilast). This paved the way to the study of the impurities in roflumilast synthesis. It was reported that, when the synthetic method of piclamilast is applied analogously to roflumilast, it leads to the formation of more than 3 % *N*-(3,5-dichloropyrid-4-yl)-3-cyclopropyl-methoxy-4-hydroxybenzamide [9]. In addition, this compound was also detected when sodium hydroxide was employed in the synthesis of roflumilast [10]. In this paper, we present another impurity in the synthesis of roflumilast, and the characterization of its structure shows it to be *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide. This compound was then synthesized to make comparisons. The comparison of the impurity and the authentic compound indicated that this compound was *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide.

Results and discussion

Generally, roflumilast is synthesized via O-alkylation, oxidation, chlorination of the corresponding carboxylic acid and N-acylation reaction of 3,5-dichloropyridine-4-amine. And it is obvious that the N-acylation reaction is the crucial step in the synthesis due to the low nucleophilic ability of 3,5-dichloropyridine-4-amine. Several alkalis have been employed to activate the amine group, including potassium *tert*-butoxide, sodium hydride, and sodium hydroxide [9–11]. So ,we followed the general procedure to synthesize roflumilast from 4-difluoromethoxy-3-hydroxybenzaldehyde and bromomethyl cyclopropane and put effort into the study of sodium hydride because of its cleanliness and high activity. In the process, a new impurity was detected and successfully separated from the crude roflumilast product. It was characterized by ^{1}H NMR, ^{13}C NMR, and HR-MS, which indicated the chemical structure to be compound **1** in Fig. 1.

To further confirm the impurity structure, we synthesized compound **1** from 4-difluoromethoxy-3-hydroxybenzaldehyde (Fig. 1). The oxidation of aldehyde has been widely reported to give the corresponding carboxylic acid [8, 12]. As seen in Fig. 1, the oxidation of compound **2** was achieved by sulfamic acid and sodium chlorite in acetonitrile and yielded compound **3**. It was then chloridized by $SOCl_2$ to give compound **4**. Just as in the synthesis of roflumilast, it is difficult to carry out the obvious amidation reactions of compounds **4** and **5**. This was probably a consequence of the steric congestion around the amino group and the electron attractive effect of the aromatic pyridine ring. Due to the high activity of sodium hydride in the synthesis of roflumilast, it was still employed to make the amine more nucleophilic in the reaction of synthesizing compound **1**. An amount of 1 M Eq of sodium hydride seemed to be enough. Considering the hydroxyl

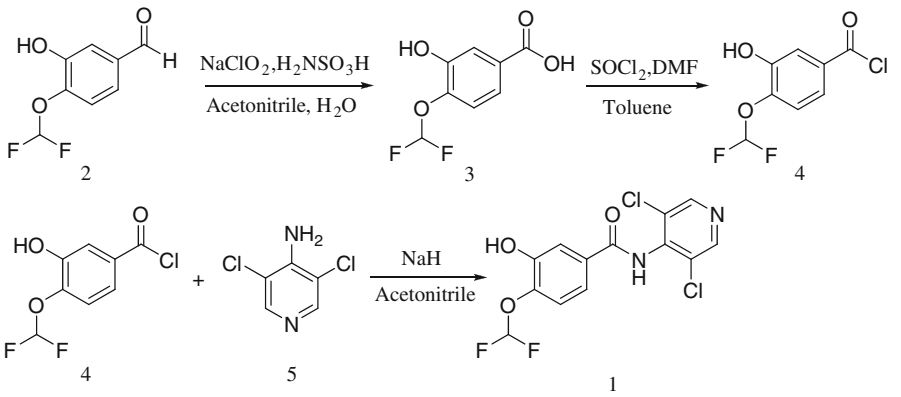

Fig. 1 Synthesis of *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide

group in compound **5**, it consumed another mole of sodium hydride. Hence, it was necessary to use more than 2 Eq of sodium hydride to achieve compound **1**. Thus, the amine **5** was added to the suspension of the sodium hydride, giving the amino anion and unreacted sodium hydride. Then, the acid chloride **4** was added slowly to the suspension to give product **1**. Later, the purified compound **1** was characterized by ^{1}H NMR, ^{13}C NMR, and HR-MS, which showed the identity of the impurity isolated from crude roflumilast product. In addition, comparison of the HPLC spectrum between them also confirmed that the impurity was *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide. Considering the synthetic method of roflumilast, it was probably that the alkylation reaction of compound **2** was not processed completely, thus contributing to the formation of compound **1** after multistep reactions. It can be reduced by the complete alkylation reaction of the raw material, and showed the great importance of monitoring the reaction process.

Conclusion

An impurity was separated from the synthesized roflumilast and characterized by ^{1}H NMR, ^{13}C NMR, and HR-MS, which confirmed the structure as *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide. To further verify the impurity structure, *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide was synthesized from 4-difluoromethoxy-3-hydroxybenzaldehyde via oxidation, chlorination, and amidation reaction. Comparisons between the impurity and the authentic compound confirmed that the impurity was indeed *N*-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-hydroxybenzamide. This could have significance for monitoring the industrial production process of roflumilast.

Experimental

Reagents and solvents were obtained from commercial suppliers. All reactions were monitored by thin layer chromatography using commercial silica gel plates. The purity of products was detected by HPLC on Agilent 1,100 series. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Inova-400, Bruker AV400 NMR, and Bruker avance III 600. HR-MS was recorded on MicroOTOF-Q II. Melting points were observed on a YRT-3 Melting Point Tester which was uncorrected.

The crude synthesized roflumilast was recrystallized in methanol/water = 90/10 (v/v). The filtrates were combined and concentrated. The residue was separated by silica gel column (petroleum ether/ethyl acetate = 3/1, V/V) to afford the impurity. ^{1}H NMR (CD_3OD, 400 MHz) δ: 8.62 (d, J = 2.8 Hz, 2H of pyridine), 7.56 (s, 1H of benzene), 7.50–7.48 (m, 1H of benzene), 7.25 (d, J = 8.4 Hz, 1H on benzene), 6.91 (t, J = 74.4 Hz, 1H on CF_2H); ^{13}C NMR (CD_3OD, 100 MHz) δ: 166.02 (C = O), 148.80, 147.92, 142.41 (3C on pyridine), 141.17, 131.28, 130.87, 120.72, 119.16, 116.73 (6C on benzene), 118.81, 116.27, 113.65 (CF_2H). HR-MS (ESI), calcd $C_{13}H_8Cl_2F_2N_2O_3$: $[M + H]^+$ m/z: 348.9958, found: 348.9940.

Synthesis of 4-difluoromethoxy-3-hydroxybenzoic acid (**3**) [12]

Compound **2** (53.16 mmol) was dissolved in 50 mL acetonitrile and added to the solution of sulfamic acid (74.42 mmol) in 50 mL water. Then, sodium chlorite (74.42 mmol) in 50 mL water was added slowly at 0–10 °C and the reaction mixture were stirred at 30 °C for 5 h. Then, the acetonitrile was evaporated and the mixture was extracted with ethyl acetate. The organic phases were combined, dried, and concentrated. The residue was purified by silica gel column (petroleum ether/ethyl acetate = 6/1, V/V) to give a white solid compound **3** 5.17 g, 90.4 %. Mp.164–165 °C; ^{1}H NMR (DMSO-d^6, 400 MHz) δ: 12.90 (s, 1H on COOH), 10.25 (s, 1H on OH), 7.53 (d, J = 1.2 Hz, 1H on benzene), 7.41–7.39 (m, 1H on benzne), 7.40 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H on beneze), 7.15 (t, J = 74.4 Hz, 1H on CF_2H); ^{13}C NMR (DMSO-d^6, 100 MHz) δ: 166.71 (C = O), 148.45, 142.31, 128.78, 120.95, 120.77, 118.03 (6C of benzene), 119.05, 116.48, 113.91 (CF_2H). HR-MS (ESI), calcd $C_8H_6F_2O_4$: $[M - H]^-$ m/z: 203.0156, found: 203.0080.

Synthesis of 4-difluoromethoxy-3-hydroxybenzoyl chloride (**4**) [8, 10]

Compound **3** (4.9 mmol) in 50 mL toluene was heated to reflux until dissolving and the water was removed by Dean-Stark apparatus. The solution was then cooled to 90 °C, and $SOCl_2$ (7.4 mmol) and several drops of DMF were added. The solution was heated at reflux for 3.0 h. Then, it was cooled to room temperature and concentrated to give compound **4** as a yellow oil.

Synthesis of *N*-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-3-hydroxybenzamide (**1**)

Sodium hydride (12.3 mmol) was slowly added to the mixture of compound **5** (4.9 mmol) in 30 mL anhydrous acetonitrile at 0–5 °C. After 2 h, the chloride **4** in anhydrous acetonitrile was added and the mixture was stirred at 0–15 °C for 1.5 h. After the solvent was evaporated, the residue was dissolved in ethyl acetate and washed successively by 1 mol/L hydrochloric acid and water. The organic phase was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column (petroleum ether/ethyl acetate = 3/1, V/V) to give a white solid 0.43 g, 25.2 %. ^{1}H NMR (DMSO-d^{6}, 600 MHz) δ: 10.61–10.58 (m, 2H, OH), 8.75 (s, 2H on pyridine), 7.57 (d, J = 1.8 Hz, 1H on benzene), 7.51 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H on benzene), 7.29 (d, J = 8.4 Hz, 1H on benzene), 7.18 (t, J = 74.4 Hz, 1H on CF_2H); ^{13}C NMR (DMSO-d^{6}, 150 MHz) δ: 164.19 (C = O), 148.59, 148.23, 141.76 (3C on pyridine), 141.26, 130.77, 130.72, 120.83, 119.07, 116.92 (6C on benzene), 118.07, 116.35, 114.64 (CF_2H). HR-MS (ESI), calcd $C_{13}H_8Cl_2F_2N_2O_3$: $[M - H]^-$ m/z: 346.9802, found: 346.9728.

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