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Process related and degradation impurities in anti-inflammatory drug Roflumilast

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ABSTRACT

A detail study was undertaken to investigate origin of Roflumilast drug substance related impurities. These impurities were synthetically prepared and characterized by IR, NMR and Mass, in order to have proper process control. These impurities are N-(3,5-Dichloropyridin-4-yl)-3,4-bis(difluoromethoxy)benzamide (Roflumilast impurity-I), 4-(Cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-3-(difluoromethoxy)benzamide (Roflumilast impurity-II), 3,4-Bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)benzamide (Roflumilast impurity-III), 3-Cyclobutyl-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (Roflumilast impurity-IV), 3-(But-3-en-1-yloxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (Roflumilast impurity-V), 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)-N-(pyridin-4-yl)benzamide (Roflumilast impurity-VI), N-(3-Chloropyridin-4-yl)-3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamide (Roflumilast impurity-VII) and 3,5-Dichloro-4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamido]pyridine-1-oxide (Roflumilast impurity -VIII).

Key words: Roflumilast, Related Substances, Control, Synthesis, Characterization.

INTRODUCTION

Roflumilast (trade names *Daxas, Daliresp*) is a drug that acts as a selective, long-acting inhibitor of the enzyme PDE-4. It has anti-inflammatory effects and is used as an orally administered drug for the treatment of inflammatory conditions of the lungs such as Chronic Obstructive Pulmonary Disease (COPD) [1-5]. Recently, '*Daxas'* was approved in the EU for severe COPD associated with chronic bronchitis. Also, '*Daliresp'* gained FDA approval in the US for reducing COPD exacerbations.

There are many synthetic routes available on synthesis of Roflumilast. However, the literature search revealed the absence of much work on study of Roflumilast impurities profile and possible degradation products. The impurity profile in the present work is different from the earlier reported study. In this article we have reported various probable process related impurities and degradation products of Roflumilast. The path way for their formation and synthesis of these impurities is also described.

EXPERIMENTAL SECTION

Melting points are measured in open capillary tubes and are uncorrected. The ^{1}H NMR spectra was recorded in $CDCl_3$ on Mercury plus Varian 500 MHz FT NMR spectrometer. The chemical shifts were reported in ppm relative

to TMS (δ 0.00 ppm) as internal standard. IR spectra were recorded on a Perkin-Elmer FT-IR instrument (KBr pellet method). Mass spectra were recorded using a 4000-Q-trap LC-MS/MS mass spectrometer. The solvents and reagents were used without further purification.

1. *N*-(3,5-Dichloropyridin-4-yl)-3,4-bis(difluoromethoxy)benzamide [Roflumilast impurity-I]

a)Preparation of 3,4-Di(difluoromethoxy)benzaldehyde (9):

To a suspension of **4** (10 g, 0.05 mol), potassium carbonate (13.2g, 0.09 mol) in *N,N*-Dimethylformamide (150 ml) was added **3** (10.5g, 0.07 mol) at 20-30°C. The resultant reaction mixture was heated to 90-100°C and stirred at this temperature for completion of reaction which takes about 3 hrs. Thereafter, the reaction mass was cooled to 20-30°C. The unwanted inorganic solid was filtered and washed with *N,N*-Dimethylformamide (10 ml). The combined filtrate was distilled and the product was isolated by column chromatography using 8% v/v ethyl acetate and hexanes. Yield: 11g; Yellow liquid; Mass (m/z): 238 $[M]^+$; IR (KBr): 2846, 2741, 1697, 1606, 1509, 14371383 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 6.46-6.78 (*2t*, 2H), 7.43 (*d*, 1H), 7.78 (*m*, 2H), 9.96 (*s*, 1H).

b)Preparation of 3,4-Di(difluoromethoxy)benzoic acid (11):

To a cooled solution of **9 (**5 g, 0.02 mol) in methanol (50 ml) was added 50% w/v aqueous potassium hydroxide solution (6 ml) at 0-5°C. The reaction mass was stirred for 5 min at this temperature and 30% aqueous hydrogen peroxide (10.82 ml, 0.10 mol) was slowly added over a period of 15 min. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction which takes about 2 hrs. Thereafter, the reaction mass was cooled and water (150 ml) was added at 0-5°C. A solution of ~35% concentrated hydrochloric acid (5 ml) was added for crystallization. It was filtered, washed with water and dried.

Yield: 5 g; M.P.: 103-106°C; White Crystalline Solid; Mass (m/z): 253 $[M-H]^-$; IR (KBr): 2537, 1700, 1614, 1594, 1515, 1446, 1378, 1277 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 6.44 -6.77 (*2t*, 2H), 7.35 (*d*, 1H), 8.00 (*m*, 2H).

c) Preparation of *N*-(3,5-Dichloropyridin-4-yl)-3,4-bis(difluoromethoxy)benzamide [Roflumilast impurity-I]:

To a solution of **11 (**2 g, 0.008 mol) in toluene (20 ml) was added *N,N*-Dimethylformamide (0.2 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (1.48 g, 0.012 mol) was slowly added over a period of 20 min at 70-80°C. It was stirred at this temperature for completion of the reaction for ~2 hrs. Thionyl chloride was distilled out at 40-50°C to get oil. In another flask a mixture of **8** (2.57 g, 0.015 mol) and potassium *tert*-butoxide (1.76 g, 0.015 mol) in *N,N*-Dimethylformamide (10 ml) was stirred at 10-15°C for 45 min. Thereafter, the reaction mass was cooled to 0-5°C and added a solution of above prepared 3,4-Di(difluoromethoxy)benzoyl chloride in *N,N*-Dimethylformamide (10 ml) slowly over a period of 30 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction which takes ~1 hr. Thereafter, the reaction mixture was cooled and quenched with water (20 ml). It was acidified with conc. hydrochloric acid (p^H adjusted to 2). The resultant reaction mixture was filtered, washed with water (20 ml) to obtain crude product which was further stirred in sodium hydroxide solution (p^H adjusted to 9-10) and the slurry was filtered to obtain pure compound.

Yield: 2.2 g; M.P: 133-135°C; White Crystalline Solid; Mass (m/z); 398 $[M+H]^+$, 400 $[M+H+2]^+$, 402 $[M+H+4]^+$; IR (KBr): 3285, 3136, 1658, 1609, 1594, 1559, 1499, 1405, 1299 cm^{-1}; ^1H NMR (500 MHz,$CDCl_3$): *δ(ppm)*: 7.16-7.50 (*m*, 2H), 7.56 (*d*, 1H), 7.95 (*s*, 1H), 8.01 (*d*, 1H), 8.76 (*s*, 2H), 10.82 (*brs*, 1H).

2. 4-(Cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-3-(difluoromethoxy)benzamide [Roflumilast impurity-II] :

a)Preparation of 4-Cyclopropylmethoxy-3-hydroxy benzaldehyde :

To a suspension of **2** (20 g, 0.145 mol), potassium carbonate (20 g, 0.145 mol) in acetone (200 ml) was added **5** (19.5 g, 0.145 mol) at 20-30°C. The resultant reaction mixture was heated to 45-50°C and stirred at this temperature for completion of reaction which takes about 4 hrs. Thereafter, the reaction mass was cooled to 20-30°C. The inorganic solid was filtered and washed with acetone (20 ml). The combined filtrate was distilled and the product was isolated by column chromatography using 5% v/v ethyl acetate and hexanes.

Yield: 15g; Yellow liquid; Mass (m/z); 193 $[M+H]^+$; IR (KBr): 3228, 2934, 1676, 1607, 1581, 1506, 1461, 1408, 1343, 1276 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 0.38 & 0.69 (2*m*, 4H), 1.32 (*m*, 1H), 3.97 (*d*, 2H), 5.87 (*s*, 1H), 6.92 (*d*, 1H), 7.40(*d*, 1H), 7.45(*s*, 1H), 9.83 (*s*, 1H).

b)Preparation of 4-Cyclopropylmethoxy-3-difluoromethoxy benzaldehyde (12):
To a suspension of 4-Cyclopropylmethoxy-3-hydroxybenzaldehyde (5 g, 0.026 mol), potassium carbonate (6.4 g, 0.046 mol) in *N*,*N*-Dimethylformamide (50 ml) was added 3 **(**5.1 g, 0.033 mol) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and stirred at this temperature for completion of reaction for ~3 hrs. Thereafter, the reaction mass was cooled to 20-30°C. The reaction mass was filtered and washed with *N*,*N*-Dimethylformamide (5 ml). The combined filtrate was distilled and the product was isolated by column chromatography using 5% v/v ethyl acetate and hexanes.

Yield: 4g; Yellow liquid; Mass (m/z); 243 $[M+H]^+$; IR (KBr): 3086, 3011, 2933, 1692, 1604, 1582, 1509, 1440, 1382, 1313, 1280 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 0.38 (m, 2H), 0.68 (m, 2H), 1.32 (*m*, 1H), 4.0 (d, 2H), 6.49, 6.64 & 6.79 (*t*, 1H), 7.04 (d, 1H), 7.71 (d, 1H), 7.73 (s, 1H). 9.86 (brs, 1H).

c) Preparation of 4-Cyclopropylmethoxy-3-difluoromethoxybenzoic acid :
To a cooled solution of **12 (**3 g, 0.012 mol) in methanol (30 ml), 50% w/v aqueous potassium hydroxide solution (3.6 ml) was added at 0-5°C. The reaction mass was stirred for 30 min at this temperature and 30% aqueous hydrogen peroxide (6.32 ml, 0.0557 mol) was added slowly over a period of 15 min. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction for ~ 6 hrs. Thereafter, the reaction mass was cooled and water (90 ml) was added at 0-5°C. A solution of ~35% concentrated hydrochloric acid (3 ml) was added in the reaction solution for product crystallization. A generated crystal were collected by filtration and washed with water and dried under vacuum at 40-45°C.

Yield: 3 g; M.P.: 143-146°C; White Crystalline Solid; IR (KBr): 3089, 2876, 1688, 1607, 1579, 1514, 1444, 1411, 1277 cm^{-1}; Mass (m/z): 257 $[M-H]^-$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 0.38 & 0.67 (*2d*, 4H), 1.32 (*m*, 1H), 3.95 (*d*, 2H), 6.48, 6.63& 6.78 (*t*, 1H), 6.98 (*d*, 1H), 7.90 (*s*, 1H), 7.96 (*d*, 1H).

d)Preparation of 4-(Cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-3-(difluoro-methoxy)benzamide (Roflumilast impurity II)
To a solution of 4-Cyclopropylmethoxy-3-difluoromethoxybenzoic acid **(**2 g, 0.008 mol) in toluene (30 ml) was added *N*,*N*-Dimethylformamide (0.2 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (1.38 g, 0.012 mol) was added slowly over a period of 20 min at 70-80°C. The reaction mixture was stirred at this temperature for completion of the reaction for ~ 2 hrs. Thionyl chloride was distilled out at 40-50°C to get oily residue. In another flask, a mixture of **8** (2.53 g, 0.015 mol) and potassium *tert*-butoxide (1.74g, 0.015 mol) in *N*,*N*-Dimethylformamide (15 ml) was stirred at 10-15°C for 1 hr. Thereafter, the reaction mass was cooled to 0-5°C and added a solution of above prepared 4-Cyclopropylmethoxy-3-difluoromethoxybenzoylchloride by dissolving in *N*,*N*-Dimethylformamide (5 ml) slowly over a period of 20 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction for ~1 hr. Thereafter, the reaction mixture was cooled and quenched with water (20 ml). It was acidified with conc. hydrochloric acid (p^H was adjusted to 2). The resultant reaction mixture was filtered, washed with water (20 ml) to obtain crude product. The crude wet product was stirred in sodium hydroxide solution (p^H adjusted to 9.0-10.0) and the product was isolated by filtration. It was dried at 40-45°C under reduced pressure to obtain the dry product.

Yield: 2.2 g; White Crystalline Solid; M.P.: 116-118°C; IR (KBr): 3448, 3259, 1655, 1612, 1534, 1502, 1401, 1384, 1350, 1300, 1210 cm^{-1}; Mass (m/z): 400.99 $[M-H]^-$, 402.99 $[M-H+2]^-$, ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 0.38& 0.60 (*2m*, 4H), 1.28 (*m*, 1H), 4.01 (*d*, 2H), 7.02,7.16 & 7.31 (*t*, 1H), 7.32 (*d*, 1H), 7.82 (*s*, 2H), 7.94 (*d*, 1H), 8.75 (*s*, 1H), 10.57 (*brs*, 1H).

3. 3,4-Bis(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)benzamide [Roflumilast impurity-III]:
a)Preparation of 3,4-Di(cyclopropylmethoxy)benzaldehyde :
To a suspension of **2** (10 g, 0.07 mol), potassium carbonate (40 g, 0.29 mol) in a mixture of acetonitrile (100 ml) and acetone (100 ml), **5 (**39.13 g, 0.29 mol) was added at 20-30°C. The resultant reaction mixture was heated to 45-50°C and stirred at this temperature for completion of reaction for ~ 22 hrs. Thereafter, the reaction mass was cooled to 20-30°C. The unwanted solid was filtered and washed with acetone (20 ml). The combined filtrate was distilled under reduced pressure to obtain the desired product.

Yield: 15g; Yellow Crystalline Solid; M.P.: 46-48°C; IR (KBr): 3082, 3068, 3028, 2911, 2866, 1690, 1679, 1598, 1587, 1509, 1459, 1437, 1410, 1273 cm^{-1}; Mass (m/z): 247 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 0.39 & 0.66 (*2m*, 8H), 1.34 (*s*, 2H), 3.94 (*m*, 4H), 6.96 (*d*, 1H), 7.42 (*m*, 2H), 9.82 (*s*, 1H).

b)Preparation of 3,4-Di(cyclopropylmethoxy)benzoic acid :
To a cooled solution of 3,4-Di(cyclopropylmethoxy)benzaldehyde **(**12 g, 0.05 mol) in methanol (120 ml), 50% w/v aqueous potassium hydroxide solution (14.4 ml) was added at 0-5°C. The reaction mass was stirred for 5 min at this temperature and 30% aqueous hydrogen peroxide (25.13 ml, 0.22 mol) was slowly added over a period of 15 min. The reaction temperature was raised to 20-30°C and stirred at this temperature for 6 h for completion of the reaction. Thereafter, the reaction mass was cooled and water (360 ml) was added at 0-5°C. A solution of ~35% concentrated hydrochloric acid (12 ml) was added to reaction solution for product crystallization. The product precipitated was collected by filtration and washed with water. It was dried at 40-45°C under reduced pressure to obtain the dry product.

Yield: 12 g; White Crystalline Solid; M.P.:152-154°; IR (KBr): 3080, 3002, 2952, 1679, 1600, 1586, 1590, 1468, 1445, 1430 1349, 1308, 1283 cm^{-1}; Mass (m/z): 263 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 261 $[M-H]^-$; 0.38& 0.64 (*2m*, 8H), 1.34 (*m*, 2H), 3.93 (*m*, 2H), 6.90 (*d*, 1H), 7.61 (*s*, 1H), 7.72 (*d*, 1H).

c) Preparation of 3,4-Bis(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)benzamide [Roflumilast impurity-III]:
To a solution of 3,4-Di(cyclopropylmethoxy)benzoic acid **(**2 g, 0.008 mol) in toluene (20 ml) was added *N*,*N*-Dimethylformamide (0.2 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (1.48 g, 0.01 mol) was slowly added over a period of 10 min at 70-80°C. The reaction mass was stirred at this temperature for completion of the reaction which takes about 2 hrs. Thionyl chloride was distilled out at 40-50°C to get an oily mass. In another flask, a mixture of **8** (2.57 g, 0.016 mol) and potassium *tert*-butoxide (1.77g, 0.016 mol) in *N*,*N*-Dimethylformamide (15 ml) was stirred at 10-15°C for 45 min. Thereafter, the reaction mass was cooled to 0-5°C and added a solution of above prepared 4- 3,4-Dicyclopropylmethoxybenzoylchloride in *N*,*N*-Dimethylformamide (7 ml) slowly over a period of 15 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction which takes about 1 hr. Thereafter, the reaction mixture was cooled and quenched with water (20 ml) and acidified with concentrated hydrochloric acid (p^H adjusted to 2). The resultant reaction mixture was filtered, washed with water (20 ml) and the wet filtered product was stirred in aqueous sodium hydroxide solution (p^H adjusted to 9-10). The product was filtered, washed with water to neutral pH and dried at 40-45°C under reduced pressure to obtain pure compound.

Yield: 2 g; White Crystalline Solid; M.P.: 200-203°C; IR (KBr): 3281, 3084, 2939, 2871, 1665, 1598, 1586, 1558, 1499, 1477, 1409, 1377, 1303, 1278, 1250 cm^{-1}; Mass (m/z): 407.09 $[M+H]^+$, 409.09$[M+H+2]^+$, 411 $[M+H+4]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*; 0.35 & 0.59 (*2m*, 8H), 1.26 (*m*, 2H), 3.91 (*d*, 4H), 7.09 (*d*, 1H), 7.56 (*s*, 1H), 7.63 (*d*, 1H), 8.73 (*s*, 2H), 10.40 (*brs*, 1H).

4. 3-Cyclobutyl-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide [Roflumilast impurity-IV]:
a)Preparation of 4-Difluoromethoxy-3-cyclobutylbenzaldehyde:
To a suspension of **4** (10 g, 0.05 mol), potassium carbonate (13.2 g, 0.01 mol) in acetonitrile (100 ml) was added **14 (**9.3 g, 0.07 mol) at 20-30°C. The resultant reaction mixture was heated to 80-85°C and stirred at this temperature for completion of reaction which takes about 30 hrs. Thereafter, the reaction mass was cooled to 20-30°C. The reaction mass was filtered and washed with acetonitrile (20 ml). The combined filtrate was distilled and the product was isolated by column chromatography using 5% v/v ethyl acetate and hexanes. The ethyl acetate and hexanes layers were removed under reduced pressure to give the desired product.

Yield: 6 g; Yellow liquid; IR (KBr): 3078, 2991, 2948, 2740, 1695, 1599, 1505, 1469, 1435, 1392, 1276 cm^{-1}; Mass (m/z): 243 $[M+H]^{+1}$; H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 1.59& 1.75 (*2m*, 2H), 2.22& 2.52 (*2m*, 4H), 4.76 (*m*, 1H), 6.44, 6.69 & 6.94 (*t*, 1H), 7.30 (*m*, 2H), 7.44 (*m*, 1H), 9.92 (*s*, 1H).

b)Preparation of 4-Difluoromethoxy-3-cyclobutylbenzoic acid:
To a cooled solution of 4-difluoromethoxy-3-cyclobutylbenzaldehyde **(**5.5 g, 0.023 mol) in methanol (55 ml) was added 50% w/v aqueous potassium hydroxide solution (6.6 ml) at 0-5°C. The reaction mass was stirred for 5 min at

this temperature and 30% aqueous hydrogen peroxide (11.58 ml, 0.11 mol) was slowly added over a period of 15 min. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction which takes about 4 hrs. Thereafter, the reaction mass was cooled and water (165 ml) was added at 0-5°C. A solution of ~35% concentrated hydrochloric acid (5.5 ml) was added to the reaction mass during which product was precipitated out. The product was isolated by filtration, washed with water to neutral pH and the wet product was dried at 40-45°C under reduced pressure.

Yield: 5 g; White Crystalline Solid; M.P.:103-106°C; IR (KBr): 2997, 2953, 2879, 1688, 1598, 1515, 1442, 1393, 1300, 1276, 1212 cm^{-1}; Mass (m/z): 257 $[M-H]^-$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 1.73 & 1.91 (*2m*, 2H), 2.23& 2.53 (2*m*, 4H), 4.75 (*t*, 1H), 6.53, 6.68 & 6.83 (*t*, 1H), 7.22 (*d*, 1H), 7.54 (*s*, 1H), 7.69 (*d*, 1H).

c) Preparation of 3- Cyclobutyl-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-benzamide [Roflumilast impurity-IV]:

To a solution of 4-Difluoromethoxy-3-cyclobutylbenzoic acid **(**2.5 g, 0.01 mol) in toluene (25 ml) was added *N*,*N*-Dimethylformamide (0.2 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (1.65 g, 0.014 mol) was added slowly over a period of 10 min at 70-80°C. The reaction mass was stirred at this temperature for completion of the reaction which takes about 2 hrs. Thionyl chloride was distilled out at 40-50°C to get an oily residue. In another flask, a mixture of **8** (2.99 g, 0.018 mol) and potassium *tert*-butoxide (2.06, 0.018 mol) in *N*,*N*-Dimethylformamide (15 ml) was stirred at 10-15°C for 45 min. Thereafter, the reaction mass was cooled to 0-5°C and a solution of above prepared 4-Difluoromethoxy-3-cyclobutylbenzoyl chloride dissolved in *N*,*N*-Dimethylformamide (10 ml) was added slowly over a period of 15 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for 1 h for completion of the reaction. Thereafter, the reaction mixture was cooled and quenched with water (25 ml). Ethyl acetate (40 ml) was added to it and it was stirred for 15 min. The layers were separated. The ethyl acetate layer was washed with 2N aqueous hydrochloric acid (20 ml) followed by 0.2% sodium hydroxide solution (20 ml) and finally with 5% aqueous sodium chloride solution (25 ml). The ethyl acetate layer was concentrated and the crude product was purified by using isopropanol.

Yield: 2.1 g; White Crystalline Solid; M.P.:132-135°C; IR (KBr): 3199, 2946, 1650, 1603, 1590, 1547, 1496, 1403, 1388, 1357, 1298, 1276 cm^{-1}; Mass (m/z): 403 $[M+H]^+$, 405 $[M+H+2]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 1.66 & 1.81 (2*m*, 2H), 2.12& 2.47 (2*m*, 4H), 4.85 (*t*, 1H), 7.07, 7.22 & 7.37(*t*, 1H), 7.36 (*d*, 1H), 7.54 (*s*, 1H), 7.66 (*d*, 1H), 8.77 (*s*, 2H), 10.65 (*brs*, 1H).

5. 3-(But-3-en-1-yloxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide [Roflumilast impurity - V]:

(a) Preparation of 4-Difluoromethoxy-3-(but-3-en-1-yloxy)benzaldehyde :

To a suspension of **4** (10 g, 0.05 mol), potassium carbonate (13.2 g, 0.09 mol) in acetonitrile (50 ml) was added **15** (9.3 g, 0.07 mol) at 20-30°C. The resultant reaction mixture was heated to 80-85°C and stirred at this temperature for 7 h for completion of reaction. Thereafter, the reaction mass was cooled to 20-30°C. The reaction mass was filtered and washed with acetonitrile (20 ml). The combined filtrate was distilled and the product was isolated by column chromatography using 5% v/v ethyl acetate and hexanes.

Yield: 13.5 g; Yellow liquid; IR (KBr): 3378, 3080, 2945, 2740, 2326, 1695, 1643, 1598, 1472, 1434 cm^{-1}; Mass (m/z): 243 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 2.61 (*m*, 2H), 4.15 (*t*, 2H), 5.16& 5.19 (*ABq*, 2H), 5.89 (*m*, 1H), 6.54,6.69& 6.84 (*t*, 1H), 7.32 (*d*, 1H), 7.45 (*d*, 1H), 7.49 (*s*, 1H), 9.93 (*s*, 1H).

a) **Preparation of 4-Difluoromethoxy-3-(but-3-en-1-yloxy)benzoic acid:**

To a cooled solution of 4-Difluoromethoxy-3-(but-3-en-1-yloxy)benzaldehyde **(**12 g, 0.0496 mol) in methanol (120 ml) was added 50% w/v aqueous potassium hydroxide solution (14.4 ml) at 0-5°C. The reaction mass was stirred for 5 min at this temperature and ~30% aqueous hydrogen peroxide (25.31 ml, 0.22 mol) was added slowly over a period of 15 min. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction for about 5 hrs. Thereafter, the reaction mass was cooled and water (360 ml) was added at 0-5°C. A solution of ~35% concentrated hydrochloric acid (12 ml) was added to the reaction solution during which product precipitated out. The obtained product was filtered, washed with water and dried at 40-45°C.

Yield: 11.8 g; White Crystalline Solid; M.P.:111-113°C; IR (KBr): 1692, 1644, 1607, 1511, 1470, 1446, 1384, 1275, 1230 1205 cm^{-1}; Mass (m/z): 257 $[M-H]^-$; ^1H NMR (500 MHz, $CDCl_3$): 12.61 (*m*, 2H), 4.15 (*t*, 2H), 5.15& 5.20 (*ABq*, 2H), 5.90 (*m*, 1H), 6.53,6.66 & 6.83 (*t*, 1H), 7.23 (*d*, 1H), 7.69 (*s*, 1H), 7.73 (*d*, 1H).

b)Preparation of 3-(But-3-en-1-yloxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-benzamide [impurity-V]:

To a solution of 4-Difluoromethoxy-3-(but-3-en-1-yloxy)benzoic acid **(**3 g, 0.012 mol) in toluene (30 ml) was added *N*,*N*-Dimethylformamide (0.2 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (2.07 g, 0.012 mol) was added slowly over a period of 10 min at 70-80°C. The reaction mass was stirred at this temperature for completion of the reaction for about 3 hrs. Thionyl chloride was distilled out at 40-50°C to get an oily residue. In another flask a mixture of **8** (3.78 g, 0.023 mol) and potassium *tert*-butoxide (2.6 g, 0.023 mol) in *N*,*N*-Dimethylformamide (20 ml) was stirred at 10-15°C for 45 min. Thereafter, the reaction mass was cooled to 0-5°C and a solution of above prepared 4-Difluoromethoxy-3-(but-3-en-1-yloxy)benzoylchloride in *N*,*N*-Dimethylformamide (10 ml) was added slowly over a period of 15 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction for ~1 hr. Thereafter, the reaction mixture was cooled and quenched with water (30 ml). It was acidified with conc. hydrochloric acid (p^H adjusted to 2). The product which precipitates out was filtered, washed with water (30 ml) and dried to afford crude product. The obtained crude product was stirred in aqueous sodium hydroxide solution (p^H adjusted to 9-10) for purification to obtain pure compound.

Yield: 3.4 g; White Crystalline Solid; M.P.:142-144°C; IR (KBr): 3439, 3258, 1650, 1601, 1557, 11545, 1505, 1483, 1402, 1388, 1306, 1275, 1213, 1152 cm^{-1}; Mass (m/z): m/z; 403 $[M+H]^+$, 405 $[M+H+2]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*: 2.54 (*m*, 2H), 4.19 (*t*, 2H), 5.10 & 5.18 (*Abs*, 2H), 5.91 (*m*, 1H), 7.03,7.18& 7.33 (*t*, 1H), 7.36 (*d*, 1H), 7.66 (*d*, 1H), 7.74 (*s*, 1H), 8.77 (*s*, 2H), 10.66 (*brs*, 1H).

(b) Preparation of 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)-N-(pyridin-4-yl)benzamide [Roflumilast impurity-VI] :

To a solution of 4-Difluoromethoxy-3-cyclopropylmethoxybenzoic acid **(**5 g, 0.02 mol) in toluene (50 ml) was added *N*,*N*-Dimethylformamide (0.5 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (3.5 g, 0.03 mol) was added slowly over a period of 20 min at 70-80°C. The reaction mass was stirred at this temperature for completion of the reaction which takes about 2 hrs. Thionyl chloride was distilled out at 40-50°C to get an oily residue. In another flask, a mixture of 4-Amino pyridine (3.6 g, 0.04 mol) and sodium *tert*-butoxide (3.7 g, 0.09 mol) in *N*,*N*-Dimethylformamide (20 ml) was stirred at 10-15°C for 45 min. Thereafter, the reaction mass was cooled to 0-5°C and added a solution of above prepared 4-Difluoromethoxy-3-Cyclopropylmethoxybenzoyl chloride in *N*,*N*-Dimethylformamide (10 ml) slowly over a period of 15 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction, which takes about 1 hr. Thereafter, the reaction mixture was cooled, quenched with water (50 ml) and ethyl acetate (50 ml) was added. It was stirred for 15 min and layers were separated. The ethyl acetate layer was washed with 2*N* aqueous hydrochloric acid (20 ml) followed by 0.2% sodium hydroxide solution (20 ml) and finally with 5% aqueous sodium chloride solution (25 ml). The ethyl acetate layer was concentrated and the product was isolated by column chromatography using 10% v/v ethyl acetate and hexanes.

Yield: 2.1 g; White crystalline solid; M.P.:120-122°C; IR (KBr): 3225, 3153, 1689, 1592, 1512, 1425, 1407, 1390, 1333, 1278 cm^{-1}; Mass (m/z): 335 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*; 0.36 & 0.65 (2*m*, 4H), 1.28 (*m*, 1H), 3.91 (*d*, 2H), 6.47, 6.72 & 6.97 (*t*, 1H), 7.21 (*d*, 1H), 7.36 (*d*, 1H), 7.52 (*s*, 1H), 7.62 (*d*, 2H), 8.46 (brs, 1H), 8.53 (*d*, 2H).

(c) *N*-(3-Chloropyridin-4-yl)-3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamide [Roflumilast impurity-VII]:

To a solution of 4-Difluoromethoxy-3-cyclopropylmethoxybenzoic acid **(**6 g, 0.02326 mol) in toluene (60 ml) was added *N*,*N*-Dimethylformamide (0.5 ml) at 20-30°C. The resultant reaction mixture was heated to 70-80°C and thionyl chloride (4.15 g, 0.035mol) was added slowly over a period of 20 min at 70-80°C. The reaction mixture was stirred at this temperature for completion of the reaction which takes about 2 hrs. Thionyl chloride was distilled out at 40-50°C to get an oily residue. In another flask, a mixture of 4-Amino-3-chloro pyridine (5.93 g, 0.047 mol) and potassium *tert*-butoxide (5.17 g, 0.05 mol) in *N*,*N*-Dimethylformamide (30 ml) was stirred at 10-15°C for 45 min. Thereafter, the reaction mass was cooled to 0-5°C and a solution of above prepared 4-Difluoromethoxy-3-

cyclopropylmethoxybenzoyl chloride in *N,N*-Dimethylformamide (30 ml) was added slowly over a period of 15 min at 0-5°C. The reaction temperature was raised to 20-30°C and stirred at this temperature for completion of the reaction which takes about 1 hr. Thereafter, the reaction mixture was cooled and quenched with water (60 ml). Ethyl acetate (60 ml) was added to it. It was stirred for 15 min and layers were separated. The ethyl acetate layer was washed with 2*N* aqueous hydrochloric acid (30 ml) followed by 0.2% w/v sodium hydroxide solution (30 ml) and finally with 5% aqueous sodium chloride solution (25 ml). The ethyl acetate layer was concentrated and the crude product was purified by using isopropanol.

Yield: 2.3 g; White Crystalline Solid; M.P.: 89-90°C; IR (KBr): 3316, 1660, 1603, 1582, 1508, 1461, 1406, 1394, 1315, 1292, 1270 cm^{-1}; Mass (m/z): 369 $[(MH)^+]$, 371 $[(MH+2)^+]$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*; 0.37 & 0.59 (2*m*, 4H), 1.28 (*m*, 1H), 3.99 (*d*, 2H), 7.08, 7.23 &7.38 (*t*, 1H), 7.35 (*d*, 1H), 7.61 (*d*, 1H), 7.68 (*s*, 1H), 7.82 (*d*, 1H), 8.52 (*d*, 1H), 8.69 (*s*, 1H), 10.15 (*brs*, 1H).

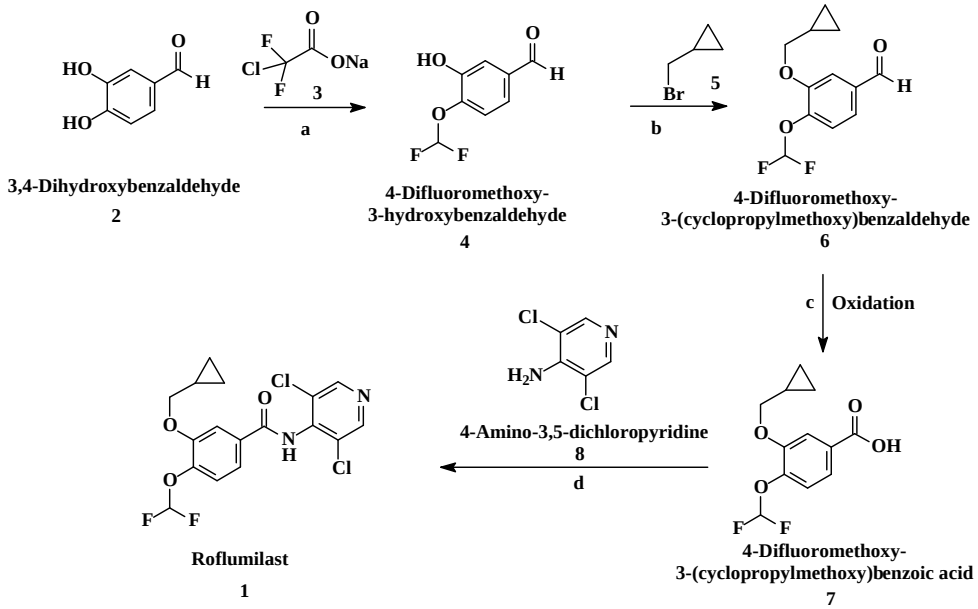
(d) 3,5-Dichloro-4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamido]pyridine-1-oxide [Roflumilast impurity-VIII] :

To a solution of **1** (7 g, 0.0173 mol) in chloroform (210 ml) was added *m*-Chloroperbenzoic acid (5.84 g, 0.07 mol) at 20-30°C. The resultant reaction mixture was stirred at 20-30°C temperature for completion of reaction which takes about 30 hrs. Thereafter, the reaction mass was cooled to 20-30°C. The reaction mass was filtered and washed with acetonitrile (20 ml). The combined filtrate was distilled and the product was isolated by column chromatography using 5% v/v ethyl acetate and hexanes.

Yield: 6 g; White Crystalline Solid; M.P.:175-177°C; IR (KBr): 3239, 3058, 3003, 1660, 1598, 1538, 1510, 1478, 1451, 1430, 1421, 1357, 1310, 1288 cm^{-1}; Mass (m/z): 419 $[(MH)^+]$, 421 $[(MH+2)^+]$, 423 $[(MH+4)^+]$; ^1H NMR (500 MHz, $CDCl_3$): *δ(ppm)*; 0.37 & 0.59 (2*m*, 4H), 1.27 (*m*, 1H), 3.98 (*d*, 2H), 7.07, 7.22& 7.37 (*t*, 1H), 7.35 (*d*, 1H), 7.64 (*d*, 1H), 7.69 (*s*, 1H), 8.73 (*s*, 2H), 10.49 (*brs*, 1H).

RESULTS AND DISCUSSION

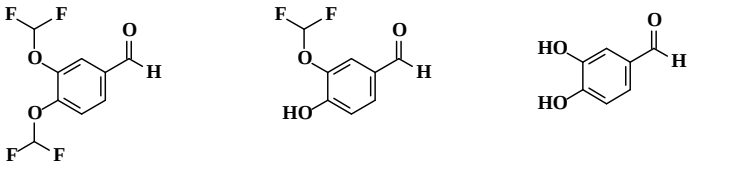
Based on the literature study [6-9], it is understood that most of the synthetic routes of Roflumilast involves the use of three main starting raw materials namely, 3,4-dihydroxybenzaldehyde (**2**), Cyclopropyl methyl bromide (**5**) and 4-Amino-3,5-dichloropyridine (**8**) following the synthetic scheme depicted below (Scheme -1).



Reaction conditions: (a) N,N-Dimethylformamide, K_2CO_3, 90-100°C; (b) Acetonitrile, K_2CO_3, 80-85°C; (c) Methanol, H_2O_2, Aqueous KOH; (d) (i). $SOCl_2$, N,N-Dimethylformamide, Toluene, (ii) Tetrahydrofuran, NaH.

Scheme-1: Synthetic Scheme for Roflumilast Synthesis

In the above route of synthesis, 4-Difluoromethoxy-3-hydroxybenzaldehyde (**4**) is prepared by reaction of 3,4-dihydroxybenzaldehyde (**2**) with Sodium chlorodifluoroacetate (**3**) in the presence of base such as potassium carbonate in *N,N*-Dimethylformamide at temperature of 90-100°C. During the above synthesis, the following impurities may generate contaminating the product.



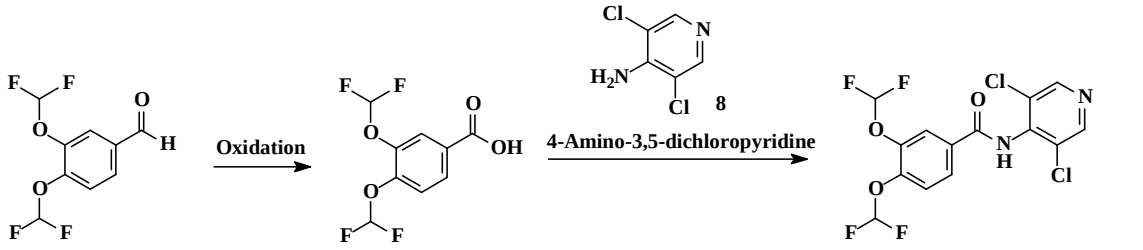
3,4-Di(difluoromethoxy)benzaldehyde
9

3-Difluoromethoxy-4-hydroxybenzaldehyde
10

3,4-Dihydroxybenzaldehyde
2

Figure - 1

Out of the above impurities, 3,4-Di(difluoromethoxy)benzaldehyde (**9**) may carry through the synthesis resulting in the formation of *N*-(3,5-Dichloropyridin-4-yl)-3,4-bis(difluoromethoxy)benzamide *(*Roflumilast impurity-I*)*, as depicted in scheme 2.



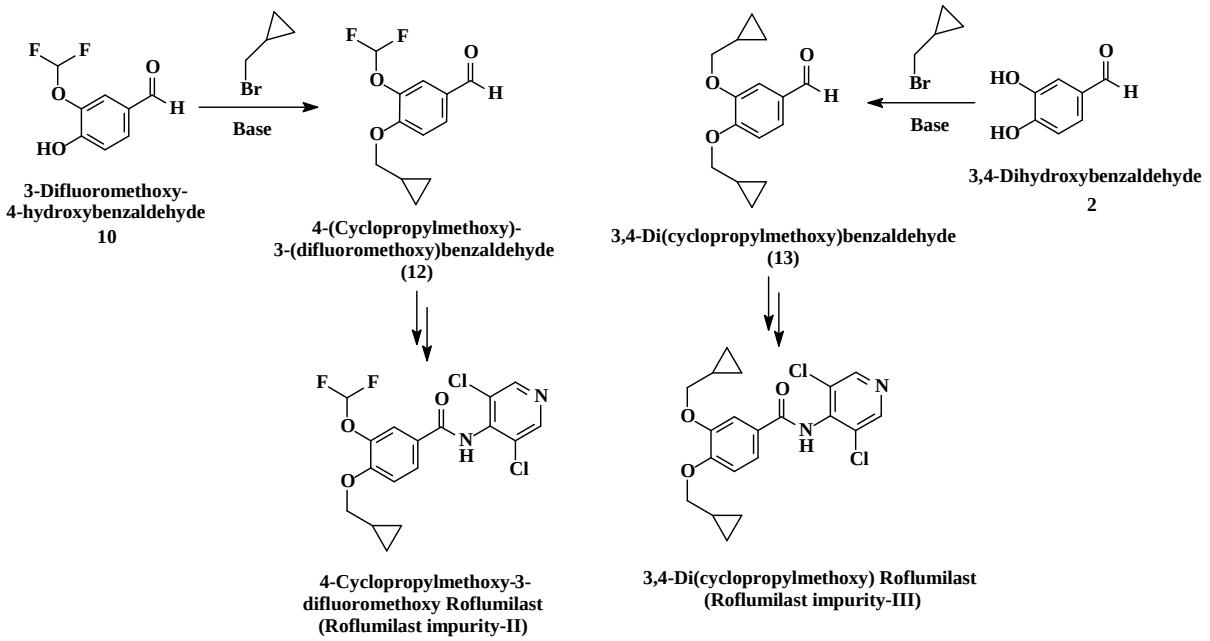
3,4-Di(difluoromethoxy)benzaldehyde
9

3,4-Di(difluoromethoxy)benzoic acid
11

3,4-Di(difluoromethoxy)Roflumilast
(Roflumilast Impurity I)

Scheme - 2

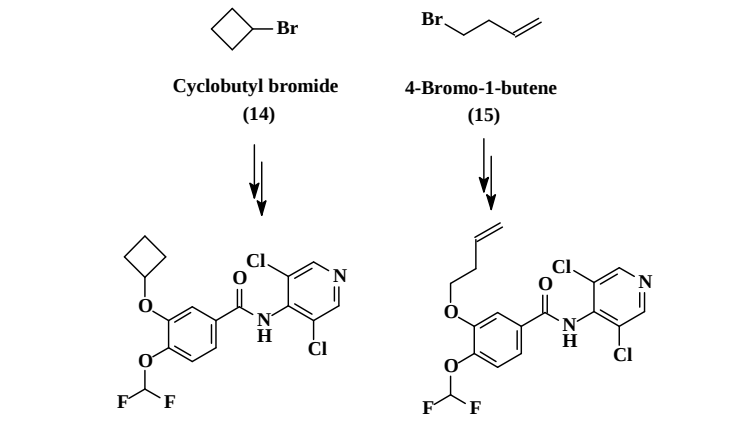
The remaining two impurities, 3-Difluoromethoxy-4-hydroxybenzaldehyde (**10**) and the unreacted starting material 3,4-Dihydroxybenzaldehyde (**2**) would react with Cyclopropylmethyl bromide (**5**) resulting in the formation of below two impurities, namely, 4-(Cyclopropylmethoxy)-3-(difluoromethoxy)benzaldehyde (**12**), and 3,4-Di(difluoromethoxy)benzaldehyde (**13**).



Scheme - 3

The above two impurities (**12**, & **13**) may carry through the synthesis resulting in the formation of 4-(Cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-3-(difluoromethoxy)benzamide *(*Roflumilast impurity-II*)* and 3,4-Bis(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)benzamide *(*Roflumilast impurity-III*).*

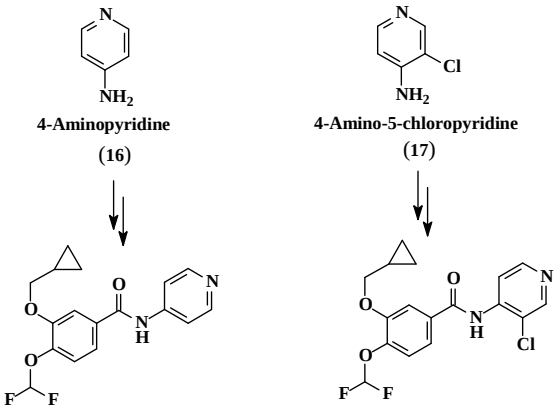
Thereafter, synthesis of second key raw material, Cyclopropyl methyl bromide (**5**) was investigated. It was found that, this raw material contains two major degradation impurities such as, Cyclobutyl bromide (**14**) and 4-Bromo-1-butene (**15**), which may carry through the synthesis giving rise to the corresponding Roflumilast impurities, 3-Cyclobutyl-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide *(*Roflumilast impurity-IV*)* and 3-(But-3-en-1-yloxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide *(*Roflumilast impurity-V*),* as depicted below.



Scheme - 4

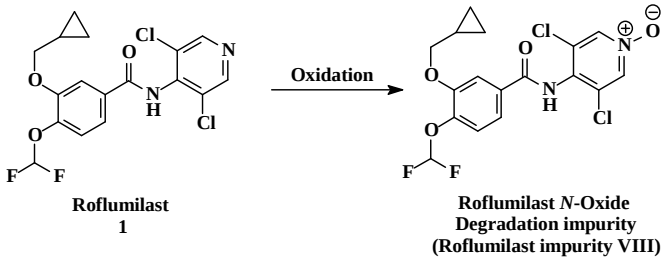
The third key raw material, 4-Amino-3,5-difluoropyridine (**8**) is prepared by reaction of 4-Aminopyridine (**16**) with concentrated hydrochloric acid in the presence of hydrogen peroxide in toluene at 80-85°C. During the above process, the following two impurities namely, unreacted 4-Aminopyridine (**16**) and 4-Amino-5-chloropyridine (**17**)

may generate in 4-Amino-3,5-dichloropyridine, which can undergo subsequent reaction leading to the formation of 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)-*N*-(pyridin-4-yl)benzamide (Roflumilast impurity VI) and *N*-(3-Chloropyridin-4-yl)-3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamide (Roflumilast impurity VII), as depicted below in scheme 5.



Scheme - 5

Apart from the above process related impurities, 3,5-Dichloro-4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzamido]pyridine-1-oxide (Roflumilast impurity VIII) of following chemical structure is an oxidation impurity in Roflumilast drug substance [10].



Scheme - 6

CONCLUSION

Appropriate control of these impurities in the corresponding raw materials, intermediates and in the final drug substance are required while preparing Roflumilast to meet the current regulatory requirements. Individual synthesis of all these above Roflumilast impurities have been described in the experimental section along with their characterization data using IR, ^{1}H NMR and Mass spectroscopy.

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