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An Improved Economical Process for Preparation of Apremilast and Identified their Impurities

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The object of the present study is to provide an improved and commercially viable process for the preparation of apremilast, which is simple, cost effective and non-hazardous. In this process avoided the usage of acetic anhydride and high temperature. In this method, an alternative process using protected 3-aminophthalic acid (**2**) with acetyl chloride in the presence of triethanolamine as catalyst in dichloromethane solvent at 0 to 5 °C for 1 h. then followed by condensed with compound **3** to get the final compound **4**. Besides, there were two unknown impurities like 3-(amino-1,3-dioxoisoindolin-2-yl)phthalic acid (**5**) and 4-aminoisobenzofuran-1,3-dione (**6**) identified by HPLC. A thorough study has been under taken to synthesize and characterize these unknown impurities. This improved process has a number of industrial advantages, such as economical material cost and relatively high yield. The structure of the synthesized compounds was elucidated by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses.

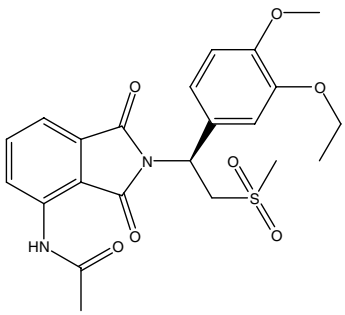
Keywords: 3-Amino phthalic acid, Triethanolamine, DCC, Acetyl chloride.

INTRODUCTION

Apremilast [(+)-*N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]acetamide] is an oral agent that inhibits the activity of phosphodiesterase type 4 (PDE4) and the production of multiple pro-inflammatory cytokines and chemokines *in vitro*, including tumour necrosis factor (TNF)-α, interleukin (IL)-8, IL-12, IL-23, CXCL9, CXCL10 and interferon-γ [1,2]. Apremilast has demonstrated anti-inflammatory effects *in vitro* and has shown efficacy in a pre-clinical mouse model for psoriasis [2].

cAMP is a pivotal second messenger that is well known to regulate inflammatory responses [3]. The sole means of degrading cAMP is through the activity of the large superfamily of phosphodiesterases (PDE) [4]. The four PDE4 genes (A, B, C and D) exhibit distinct target and regulatory properties [5]. Each of these genes can produce multiple protein products due to mRNA splice variants, resulting in approximately 19 different PDE4 proteins that fall into either short or long isoform categories. Apremilast is a novel PDE4 inhibitor with TNF-α inhibitory activity [1] currently under clinical investigation for the treatment of psoriasis and other inflammatory conditions [6-8].

Previously, the synthesis of apremilast [9] was accomplished by 3-aminophthalic acid (**1**) reacted with acetic anhydride which was further condensed with compound **3** (**Scheme-II**), however, this process suffered from the high temperature and acetic anhydride which is used as precursor in the manufacturing of illicit narcotic drugs and psychotic substances. Herein, we reported, a new process for producing apremilast **I**. In this process, an alternative process using protected 3-aminophthalic acid (**2**) with acetyl chloride in the presence of triethanolamine as catalyst in dichloromethane solvent at 0 to 5 °C for 1 h. then followed by condensed with compound **3** to get the final compound **4** (**Scheme-I**). Besides, there were two unknown impurities like 3-(amino-1,3-dioxoisoindolin-2-yl)phthalic acid (**5**) and 4-aminoisobenzofuran-1,3-dione (**6**) identified by HPLC. A thorough study has been under taken to synthesize and characterize these unknown impurities. This improved process has a number of industrial advantages, such as economical material cost and relatively high yield.



Structure of apremilast

EXPERIMENTAL

3-Aminophthalic acid and other reagents and solvents were obtained from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in DMSO-d_6; chemical shift data were reported in δ (ppm) from the internal standard TMS. The IR spectra were recorded on KBr pellets on a Perkin Elmer FTIR spectrophotometer. The reaction monitoring and purity (area percentage) were analyzed by high-performance liquid chromatography (HPLC) at λ = 210 nm using Inertsil NH_2 column (250 mm × 4.6 mm, 5 µm) at 1.0 mL/min flow. The purity of trifluoroacetic acid was analyzed by gas chromatography Agilent 7890A and a HP-FFAP capillary column (capillary dimension = 30 m × 320 µm × 0.25 µm), oven temperature = 60-200 °C, ramp = 15 °C/min, detector heater = 250 °C; N_2 flow = 25 mL/min, H_2 flow = 30 mL/min and air flow = 400 mL/min.

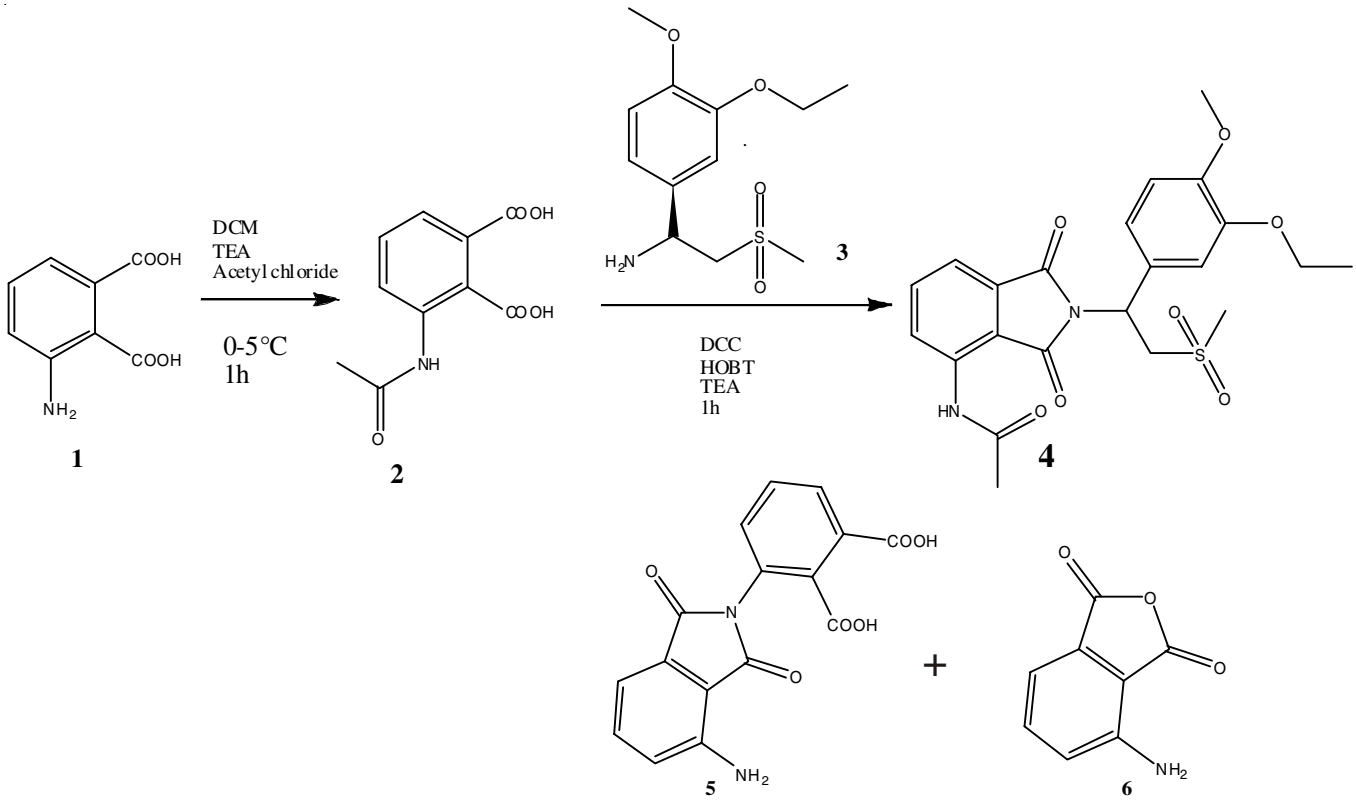
Preparation of acetamidophthalic acid (2): A 3-neck round bottom flask was charged with compound 3-aminophthalic acid (**1**) (5.0 g) and dichloromethane (25 mL) and added triethanolamine (1.0 mol). To this reaction mixture acetyl chloride (2.0 mol) was added slowly at 0-5 °C temperature and stirred for 1 h (the reaction was monitored by TLC), solid separated filtered then washed with cold dichloromethane and dried under vacuum.

Chromatographic purity: 98.5 %; yield: 5.2 g; m.p.: 178-180 °C; ^{1}H NMR (400 Hz, DMSO-d_6): 2.01 (s, 3H, CH_3); 7.44-7.57 (m, 2H, Ar-H); 7.50-7.57 (dd, 1H, Ar-H); 9.59 (br, 1H, NH); 13.91 (br, s, 2H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz):26.2, 127.3, 128.2, 128.9, 135.6, 140.5, 144.4, 168.2, 169.5, 170.4. Mass (*m/z*): 224 (M+1), Anal. calcd. for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.79; H, 4.02; N, 6.24.

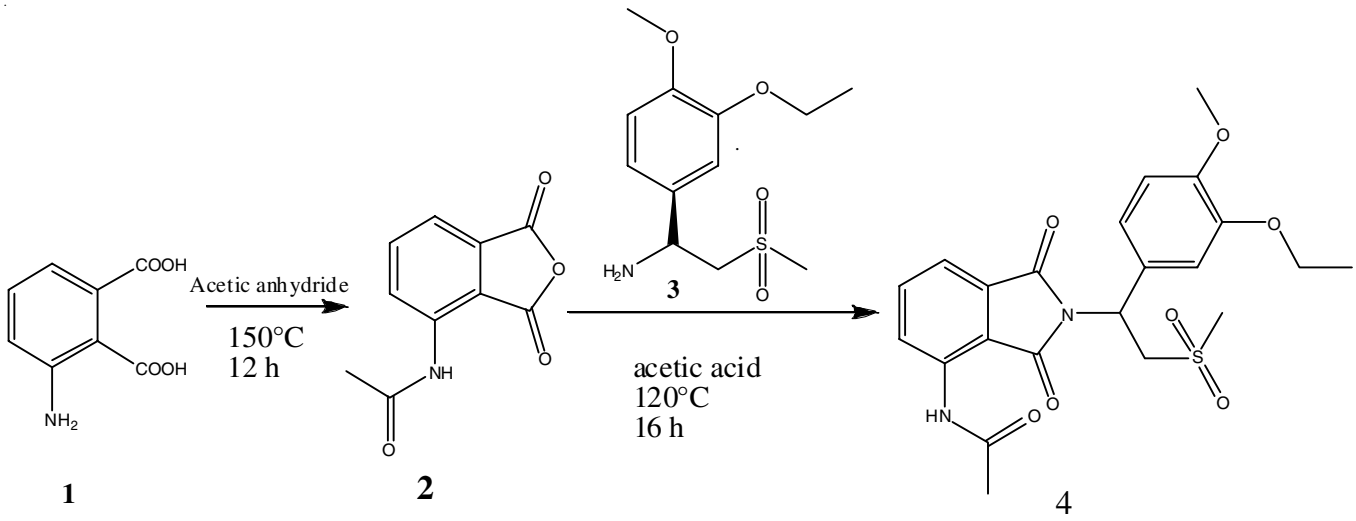
Preparation of apremilast (4): Compound N-acetyl-3-aminophthalic acid (**2**) (5 g) was dissolved in dichloromethane (25 mL) and added 1,3-ethoxy-4-methoxyphenyl)-2-methylsutfonylethylamine (**3**) [10] (1.0 mol). To this added slowly DCC (1.0 mol), HOBT (1.0 mol) and TEA (1.0 mol) at room temperature than stirring was continued for 1 h. After completion of the reaction, filtered the salts and the dichloromethane layer was washed with 5 % $NaHCO_3$ than followed by water. The dichloromethane solvent was removed under reduced pressure added methanol (5 vol) and heated to refluxed for 1 h, cooled the reaction mixture solid separated, filtered and then dried to give the compound apremilast **(4)** with good yield and purity.

Chromatographic purity: 99.6 %; yield: 4.2 g; m.p.: 216.0-218 0 °C; ^{1}H NMR (DMSO-d_6) 1.28-1.32 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.96-4.00 (q, 2H, CH_2), 4.08-4.12 (dd, 1H, CHH), 4.28-4.37 (dd, 1H, CHH), 5.73-5.78 (dd, 1H, NCH), 6.90-6.98 (m, 2H, Ar), 7.08 (s, 1H, Ar), 7.53-7.56 (d, 1H, Ar-H), 7.74-7.93 (t, 1H, Ar-H), 8.4-8.44 (d, 1H, Ar-H), 9.63 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) 14.8, 24.4, 41.0, 47.5, 53.0, 55.7, 63.8, 111.4, 112.2, 112.2, 123.3, 124.9, 124.6, 129.7, 132.8, 145.0, 147.8, 148.8, 167.0, 167.8, 169.6; Mass (*m/z*): 461 (M+1), 462 (M+2); Anal. calcd. for $C_{22}H_{24}NO_7S$: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.16; H, 5.20; N, 5.98.

Preparation of 3-(amino-1,3-dioxoisoindolin-2-yl)-phthalic acid (5): To a stirred solution of 3-aminophthalic acid **(1)** (0.1 mol) along with water (20 mL) charged into reaction



Scheme-I



Scheme-II

flask. Heated, the reaction mixture at 70 °C up to 0.5 h, then cooled to room temperature. filtered and dried.

Yield: 90 %; HPLC purity: 93.05 %; m.p.: > 250 °C; IR (cm^{-1}): 1735, 1699, 3458; ^{1}H NMR (DMSO-d_6): 4.015 (s, 2H, CNH_2), 7.04 (d, 1H, Ar-H), 7.08-7.12 (d, 1H, Ar-H), 7.41-7.54 (t, 1H, Ar-H), 7.65-7.71 (t, 1H, Ar-H), 7.52-7.57 (d, 1H, Ar-H), 7.92-8.02 (d, 1H, Ar-H); Mass (*m/z*): 325 (M-1); Anal. calcd. for $C_{16}H_{10}N_2O_6$: C, 58.90; H, 3.09; N, 8.59; Found: C, 58.82; H, 3.01; N, 8.48.

Preparation of 4-aminoisobenzofuran-1,3-dione (6): To a stirred solution of 3-aminophthalic acid **(1)** (1.0 mol) in acetone along with DCC (1.2 mol) was for 12 h at room temperature then filtered the dicyclohehyl urea salts. The solution was concentrated to get yellow crystals dried under vacuum. This impurity is degradable at room temperature and stable at 0 °C.

Yield: 92 %.; HPLC Purity: 96 %; m.p.: >165 °C, IR (cm^{-1}): 1731, 1692, 3453; ^{1}H NMR (DMSO-d_6):3.9 (s, 2H, CNH_2), 7.07-7.09 (q, 1H, Ar-H), 7.55-7.56 (d, 1H, Ar-H), 7.57-7.59 (d, 1H, Ar-H), Mass (*m/z*): 164 (M+1); Anal. calcd. for $C_8H_7O_4N$:C, 58.89; H, 4.29; N, 8.58; Found C, 58.79; H, 4.27; N, 8.48.

RESULTS AND DISCUSSION

The synthetic route for the preparation of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl sulfonyl ethyl]-4-acedtamido-isoindoline-1,3-dione (apremilast **4**) is outlined in **Scheme-I**. In this, acetyl chloride reacts with 3-aminophthalic acid (**1**) in the presence of TEA as a catalyst in dichloromethane solvent at 0-5 °C temperature to obtain the acetamidophthalic acid (**2**), which is further cyclized with **3** in the presence of DCC, HOBT, TEA and methylene chloride at ambient temperature to get apremilast **4** with good yields and purity (99.6 %). During the synthesis, there were two unknown impurities like 3-(amino-1,3-dioxoisoindolin-2-yl)phthalic acid (**5**) and 4-aminoisobenzofuran-1,3-dione (**6**) identified by HPLC. A thorough study has been under taken to synthesize and characterize these unknown impurities. The structure of the synthesized compounds was elucidated by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses.

Conclusion

An improved process for apremilast has been provided with good quality and high yield. The advantages ensure that the efficient cost effective and industrial convenient process will be employed for commercial production.

REFERENCES

1. H.W. Man, P. Schafer, L.M. Wong, R.T. Patterson, L.G. Corral, H. Raymon, K. Blease, J. Leisten, M.A. Shirley, Y. Tang, D.M. Babusis, R. Chen, D. Stirling and G.W. Muller, *J. Med. Chem.*, **52**, 1522 (2009).
2. P.H. Schafer, A. Parton, A.K. Gandhi, L. Capone, M. Adams, L. Wu, J.B. Bartlett, M.A. Loveland, A. Gilhar, Y.-F. Cheung, G.S. Baillie, M.D. Houslay, H.-W. Man, G.W. Muller and D.I. Stirling, *Br. J. Pharmacol.*, **159**, 842 (2010).
3. K. Tasken and E.M. Aandahl, *Physiol. Rev.*, **84**, 137 (2004).
4. M. Conti and J. Beavo, *Annu. Rev. Biochem.*, **76**, 481 (2007).
5. M.D. Houslay, G.S. Baillie and D.H. Maurice, *Circ. Res.*, **100**, 950 (2007).
6. M. Khobzaoui, H.J. Gutke and M. Burnet, *Curr. Opin. Investig. Drugs*, **6**, 518 (2005).
7. A.B. Gottlieb, B. Strober, J.G. Krueger, P. Rohane, J.B. Zeldis, C.C. Hu and C. Kipnis, *Curr. Med. Res. Opin.*, **24**, 1529 (2008).
8. K. Papp, C. Bolduc, P. Rohane, D. Sutherland, M. Jones and A. Hu, 66th Annual AAD Meeting, San Antonio, Texas, Feb. 1–5 (2008).
9. H.-W. Man, P. Schafer, L.M. Wong, R.T. Patterson, L.G. Corral, H. Raymon, K. Blease, J. Leisten, M.A. Shirley, Y. Tang, D.M. Babusis, R. Chen, D. Stirling and G.W. Muller, *J. Med. Chem.*, **52**, 1522 (2009).
10. G.W. Muller and H.-W. Man, Substituted Phenethylsulfones and Method of Reducing TNFα Levels, US Patent 6,020,358 (2000).