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Synthesis and spectral characterization of potential impurities of tiaprofenic acid

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ABSTRACT

During the process development of tiaprofenic acid (1). Two impurities A&C with respect to tiaprofenic acid were detected by in-house method of simple reverse phase high-performance liquid chromatography (HPLC). Two impurities A&C have been prepared. The ^{1}H and ^{13}C NMR data of impurities A&C were reported in this paper for the first time. Based on the spectral data, the structure of these impurities A&C were characterized as (5-Ethylthiophen-2-yl)phenylmethanone and (2RS)-2-(5-benzoylthiophen-3-yl) propanoic acid. The synthesis, characterization of these impurities were discussed.

KEYWORDS

Tiaprofenic acid;
Impurities;
Degradation;
Characterization and synthesis.

INTRODUCTION

Tiaprofenic acid, chemically know as (2RS)-2-(5-Benzoylthiophen-2-yl)propanoic acid with an empirical formula of $C_{14}H_{12}O_3S$ and a molecular weight of 260.3. Tiaprofenic acid is a non-steroidal anti-inflammatory drug (NSAID) of the arylpropionic acid (profen) class, used to treat pain, especially arthritic pain. The typical adult dose is 300 mg twice daily. It is not recommended in children. It is sparingly metabolised in the liver to two inactive metabolites. Most of the drug is eliminated unchanged in the urine. Renal disease impairs excretion, and it should be used with caution in renal disease. Long-term use of tiaprofenic acid is associated with severe cystitis, roughly 100 times more commonly than other NSAIDs[1]. It is contraindicated in patients with cystitis and urinary tract infections. The presence of impurities or its related compounds in a drug substance can have a significant impact on the quality and safety of the drug product. During the process development of tiaprofenic acid, two impurities[3] were observed in the range of 0.05-0.15% level along with the main product peak in the HPLC analysis. As per the general guidelines recommended by ICH to qualify the drug substance, the amount of acceptable level for a known and unknown related compound (impurity) should be less than 0.15 and 0.10%respectively, In order to meet the stringent regulatory requirements, the impurities present in the drug substance must be identified and characterized. Hence, a comprehensive study was undertaken to synthesize and characterize these two impurities of tiaprofenic acid. In this article, we report modified synthesis of impurity C of known method[2]. The new synthesis, characterization of impurity A was discussed. The ^{1}H and ^{13}C NMR data of impurities A and C were reported in this paper for the first time.

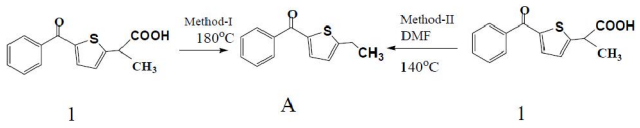

Figure 1 : Synthesis of impurity-A.

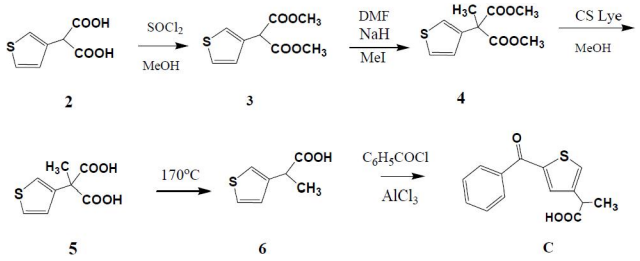

Figure 2 : Synthesis of impurity-C.

EXPERIMENTAL

Samples and chemicals

The investigated samples of tiaprofenic acid impurities A and C were synthesized after identification by in-house HPLC method. HPLC grade acetonitrile and acetic acid were obtained from Merck, Mumbai, India. AR grade sodumdihyrogen phosphate, phosphoric acid and triethylamine were obtained from SD fine chemicals limited, Mumbai, india. Water use for the preparation of mobile phase was purified using Millipore milli-Q plus (Milford, MA, USA) purification system. Chloroform-d and dimethylsulfoxide-d6 were purchased form Aldrich Chemicals co., USA.

High-performance liquid chromatography (HPLC)

An in house LC isocratic method was developed for the separation of all possible related substances (impurities) of Tiaprofenic acid. *SHIMADZU* make HPLC system equipped with 436 pumps and UV detector was used for better separation and quantification of impurities. The preparation of mobile phases of water, glacial acetic acid, n-Hexane and methylene dichloride Mobile phase was prepared in the ration of 0.25:20:500:500. Water silica, 250X4.6 mm, 5µm particle size column was used with a time isocratic program. This LC method was able to separate all the process-related substances with good resolution.

Mass spectrometry

The electrospray ionization and MS-MS studies were performed on a triple quadruple mass spectrometer PE sciex model API 3000. The positive and negative electrospray MS data was obtained by switching the capillary voltage between +5000 and – 4500 V respectively. The MS-MS data was generated with the collision energy remping from 30 to 60 V in nitrogen atmosphere.

NMR spectroscopy

The ^{1}H, ^{13}C, DEPT and 2D experiments for tiaprofenic acid impurities A and C were done on Varian mercury plus 400 MHz FT NMR spectrometer. The solvents used for solifenacin succinate, impurity-1-4 were in $CDCl_3$. The ^{1}H chemical shift values were reported on δ scale in ppm, relative to TMS (δ=0.00 ppm) and in the ^{13}C NMR the chemical shift values wre reported relative to $CDCl_3$ (δ=77.00 ppm)) as internal standard. DEPT spectra revealed the presence of methyl and methane groups as positive peaks and methylene as negative peaks.

FT-IR spectroscopy

The IR spectra were recorded in the solid state as KBr dispersion medium using PerkinElmer 1600 series FT-IR spectrophotometer.

SYNTHESIS OF IMPURITIES

Preparation of (5-ethyl thiophene-2yl)phenyl methanone (6) or impurity A

(a) Method-I

Tiaprofenic acid (10 gm, 0.038 mol) was suspended in round bottomed flask and heated to 170-180°C in oil bath until the solid melts and release of carbon dioxide. The reaction mixture was cooled to 20-25^{0}C, diluted with water (200 ml) and extracted with methylene dichloride (2 X 100ml). The dichloromethane layer was then evaporated under reduced pressure and cooled to room temperature to get reddish oil. (6.2gr, 72%)

(b) Method-II

Tiaprofenic acid (10 gm, 0.038 mol) was suspended in DMF (40ml) at 25-35° C. Heated to 140-150°C and maintained for 3 hr. Reaction was monitored by HPLC. The reaction mixture was cooled to 20-25^{0}C, diluted with water (200 ml) and extracted with methylene dichloride (2 X 100ml). The dichloromethane layer was then evaporated under reduced pressure and cooled to room temperature to get reddish oil.(7gr, 84%)

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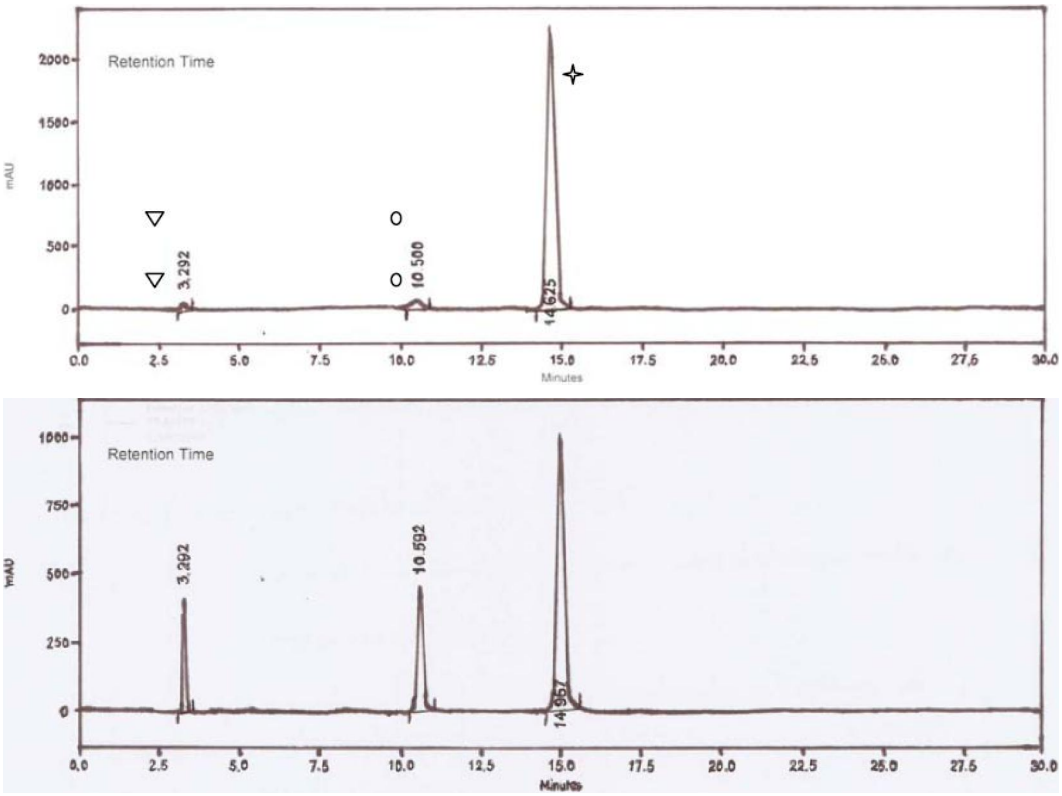

✧ Tiaprofinic acid; O IMP-C; ▽ IMP-A

Figure : (3a) A typical analytical LC chromatogram of a laboratory batch of tiaprofenic acid bulk drug; (b) The LC chromatogram of co injection of the synthetic standard A and C impurities with tiaprofenic acid.

Preparation of (5-ethyl thiophene-2yl)phenyl methanone (6) or impurity C

(a) Preparation of diethyl-2-(3-thienyl)malonate 3

3-Thiophene malonic acid 2(50 g) was charged with 200 mL methanol into round bottom flask and Cooled to 0-5oC. Thionyl chloride (100 g) was added at 0-5oC for 1 hr and and maintained at RT for 1 hr. Reaction was monitored by TLC. The methanol was then evaporated under reduced pressure and diluted with ethyl acetate. The ethyl acetate layer was washed with sodium bicarbonate solution and water. The ethyl acetate layer was then evaporated under reduced pressure and cooled to room temperature to get reddish oil. (52 gr, 84%)

(b) Preparation of 2-methyl-2-(3-thienyl)methyl malonate 4

Sodium hydride (10 g) was charged with 150 ml N,N- dimethylforamide into round bottom flask and cooled to 0-5°C. Diethyl-2-(3-thienyl)malonate 3(50 g) in DMF (30 ml) was added at RT for 30 min and and maintained at RT for 30 min. Methyl iodide (g) was added at RT for 30 min and and maintained at RT for 4 hr. Reaction was monitored by TLC. The reaction mass was quenched with water and extracted with methylene dichloride. The solvent was then evaporated under reduced pressure to provide 42.6 g (79.9%) oily residue.

^{1}H NMR (300 MHz, $CDCl_3$) : 1.8 (s, 3H); 3.72 (s, 3H) ; 3.76 (s,3H) ; 7.06 (d, 1H); 7.20 (m, 2H).

Preparation of 2-methyl-2-(3-thienyl)malonic acid 5 and 2-(3-thienyl)propionic acid 6

2-methyl-2-(3-thienyl)methyl malonate 4 (30 g), methanol and CS lye were charged into round bottom flask and maintained at RT for 4 hrs. The separated solid was collected by filteration, washed with 50ml of methanol, and dried at 80°C for 1 hr to give 36 g of sodium salt of 5. Water was added to the salt and acidified with con HCl, and stirred at RT for 1 hr. The separated solid was collected by filteration, washed with 100ml of methanol, and dried at 80°C for 1 hr to give 24.6 g of crude 2-methyl-2-(3-thienyl)malonic acid 5. The crude 2-methyl-2-(3-thienyl)malonic acid 5 was heated at 170-180°C in oil bath until the solid melts.

The mixture is cooled and vacuum distilled to afford 10.2 g (50%) of 2-(3-thienyl)propionic acid 6.

^{1}H NMR (300 MHz, $CDCl_3$) 6 : 1.37 (t, 3H); 2.92 (m, 2H) ; 3.70-4.0 (m,3H) ; 6.85 (d, 1H); 7.45 (m, 3H) ; 7.57 (t, 1H) ; 7.82 (d, 2H).

(5-ethyl thiophene-2yl)phenyl methanone or Impurity C

$AlCl_3$(20 g, 146 mmol) was charged with 150 ml Methylene dichloride into round bottom flask and cooled to 0-5°C. Benzoyl chloride (11.3g 80.4 mmol) was added at 0-5°C for 20 min and and maintained at 0-5°C for 30 min. 2-(3-thienyl)propionic acid 6(10.9 g, 70 mmol) in 25 ml methylene dichloride was added at 10-15°C for 20 min and maintained at 15-20°C for 3 hr. The reaction mass was diluted with methylene dichloride and quenched with mixture of water and Con HCl. The separated organic layer was washed with water and extracted with dilute solution of sodium bicarbonate followed by acidification of the aqueous layer with con HCl and extraction with methylene dichloride. The solvent was dried then evaporated under reduced pressure to provide a residue (10 g, HPLC purity 96.4%). The residue was on long standing to afford low melting solid.

RESULTS AND DISCUSSIONS

Detection of impurities A and C

A typical analytical LC chromatogram of a laboratory batch of tiaprofenic acid bulk drug recorded using the LC method as described in section 2.2 is shown in Figure 3a. The target impurities under study are marked as IMP-A, and IMP-C are recorded using the LC method as described in section 2.2 is shown in Figure 3b.

Structure elucidation of (5-ethyl thiophene-2yl)phenyl methanone or impurity A

Sample was analyzed by HPLC and its purity was found to be 98.14%, molecular weight of is impurity A is 216. The protonated molecular ion at m/z 217 (M+1) confirms the mass as 216 corresponding to molecular formula of $C_{13}H_{12}OS$. IR spectrum displayed characteristic absorptions at 3110. 3072.,2936, & 1735 cm-1 corresponding to aromatic >CH and carbonyl stretching. The peaks at 1518.65 & 1432.52 cm^{-1} in IR spectrum is indicative of >C=C< ring stretching.

^{1}H NMR (300 MHz, $CDCl_3$) : 1.37 (t, 3H); 2.92 (m, 2H) ; 6.85 (d, 1H); 7.45 (m, 3H) ; 7.57 (t, 1H) ; 7.82 (d, 2H).

^{13}C NMR (70 MHz, $CDCl_3$) : 15.5, 24.0, 124.8, 128.3, 129.0, 131.9, 135.4, 138.3, 140.9, 157.9, 187.9.

Structure elucidation of 2-(5-benzoylthiophen-3-yl)propanoic acid or impurity C

Sample was analyzed by HPLC and its purity was found to be 97.8%, molecular weight of is impurity C is 260.3. The protonated molecular ion at m/z 261.8 (M+1) confirms the mass as 260.3 corresponding to molecular formula of $C_{14}H_{12}O_3S$. IR spectrum displayed characteristic absorptions at 3110. 3072.,2936, 1735,1728 cm-1 corresponding to aromatic >CH and two carbonyl stretching. The peaks at 1518.65 & 1432.52 cm^{-1} in IR spectrum is indicative of >C=C< ring stretching.

^{1}H NMR (300 MHz, $CDCl_3$) : 1.42 (d, 3H); 3.85 (m, 1H) ; 7.62 (d, 2H) ; 7.65-7.75 (m, 4H); 7.82 (s, 1H); 12.5 (brs, 1H)

^{13}C NMR (70 MHz, $CDCl_3$) : 15.5, 24.0, 124.8, 128.26, 128.3, 129.0, 129.0, 131.9, 135.4, 138.3, 140.9, 157.9, 187.9

CONCLUSION

This research paper describes the synthesis, and structure elucidation of process related impurities in tiaprofenic acid. The impurities were separated by reverse phase chromatographic technique. The synthesized impurities were characterized using spectroscopic techniques. To the best of our knowledge, impurity A had not been isolated or synthesized as pure substance until now. The new synthesis, characterization of impurity A was discussed. The ^{1}H and ^{13}C NMR data of impurity A and impurity C were reported in this paper for the first time.

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