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Research Article

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Synthesis of Atenolol Impurities

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ABSTRACT

The aim of this research was to synthesis impurities of Atenolol viz. 2-(4-Hydroxy phenyl acetamide(Impurity A) , 2-[4-[[(2RS)oxiran-2-yl]methoxy]phenyl] acetamide (Impurity C) and 2-[4-[(2RS)-3-chloro-2-hydroxypropxy] phenyl]acetamide (Impurity D) by very conventional method[1].

Keywords: Atenolol, Impurities, Reduction, Synthesis.

INTRODUCTION

Atenolol is Chemically 2-[4-(2RS)-2-hydroxy-3-[(1-methylethylethyl) amino]propoxy] phenyl]acetamide. Atenolol is a beta-adrenaceptor antagonist commonly known as beta blocker. Beta blockers are competitive inhibitors and interfere with the action of stimulating hormones on beta adrenergic receptors in nervous system. Atenolol works by competing for receptor site on cardiac muscle. This slows down the strength of heart's contractions and reduces its oxygen requirements and the volume of blood it has to pump. Hypertension may be treated with this drug because of its ability to increase the diameter of the blood vessels[5-7]. Synthesis of related Substance of Atenolol is official in IP, USP, BP and EP.

EXPERIMENTAL SECTION

Purity of compound was monitored on silica gel 60 F_{254} purchased from Merck and solvents were procured from Aldrich Chemical Co. Ltd. Elemental analysis was performed using HPLC analysis.

General procedure for synthesis of Impurity:
Synthesis Atenolol impurity A (2-(4-hydroxyphenyl) acetamide)
32 mL of methylene di chloride was charged in a glass reactor, gradually 38 g of aluminium chloride was added to it under stirring at room temperature. Reaction mass was chilled to 10°C , mixture of phenol and MDC (15 g phenol + 8 g MDC) was added to reaction mass maintaining temperature below 15°C. Reaction mass was stirred for 30 min and chilled to -5 to 0°C , gradually acetyl chloride addition was done at -5 to 0°C and reaction mass was maintained for 2 hrs at -5 to 0°C, reaction completion was checked on TLC (Sample preparation- 1 mL of reaction mass was quenched in ice water +HCl mixture, white solid which precipitated out was dissolved in methanol). If TLC does not comply, reaction mass was maintained for 30 min more , but if TLC complies then reaction mass was quenched in mixture of ice water and HCl below 25°C, reaction mass was stirred for 30 min, filtered and dried to obtain 15 g of p- hydroxy acetophenone (white solid)[8]

Isopropyl alcohol 1134 mL, 500 g of p- hydroxy acetophenone and 150 g of sulphur was added in 2 L autoclave under stirring at room temperature. Ammonia gas 150 g was purged in reaction mass at room temperature under stirring. Reaction mass was heated gradually to 160- 165°C under 30-32 kg/cm^2 and was maintained for 10 hrs. Reaction mass was cooled to 70°C and 3-5 kg/cm^2 and transferred to S/S reactor with NaOH scrubber to scrub H_2S gas evolved during reaction.

IPA was distilled off atmospherically (approximately 70% of the volume obtained) , reaction mass was cooled to room temperature and filtered to get 466 g of Crude Impurity A (p- Hydroxy phenyl acetamide crude).

Purification of impurity A

15 g of impurity A and 150 mL of water was taken in reactor and was heated to 90 to 95°C and stirred for 30 min for complete dissolution. 0.5 g of charcoal and 1.0 g of Sodium Hydro Sulphite (Hydrous) was added and stirred for 30 min. Reaction mass was filtered hot. Clear filtrate obtained was cooled to room temperature and than chilled to 0-5°C, filtered to obtain 11 g of Impurity A [3].

Specification

Appearance : White colure crystalline powder
Melting point : 174-176°C
Solubility : 1 g of impurity A is soluble in 10 mL of 2.5% solution of Sodium Hydroxide
2.5 g of impurity A is soluble in 10 mL of anhydrous methanol

Synthesis Atenolol impurity C
2-[4-[[(2RS)-Oxrain-2-yl]methoxy]phenyl]acetamide

2.5 g of caustic flakes was dissolved in 100 mL of water in reactor under stirring, 10 g of impurity A was added to it at room temperature. Clarity of the solution was checked , reaction mass was chilled to 15- 20°C and then drop wise 8.5 g of 1-chloro-2,3-epoxy-propane was added to reaction mass maintaining temperature 15 to 20°C , after complete addition, temperature of reaction mass was raised to 25°C and stirred for 5-6 hrs. Solid obtained was filtered and washed with water till neutral pH of washing, solid was dried at 100°C to obtain 13.5 g of crude Impurity C i.e. 2-[4-[[(2RS)-Oxrain-2-yl]methoxy]phenyl]acetamide

Purification

13.5 g of crude Impurity C was dissolved in 67.5 mL of methanol by heating reaction mass to 40-45°C. Complete dissolution was checked and to it 0.25 g of activated carbon was added, reaction mass was stirred for 30 min and filtered hot. Clear filtrate was concentrated to 80 % of its total volume, reaction mass was cooled to room temperature and than chilled to -5 to 0 °C, filtered and dried to obtained 10.5 g of white colored pure impurity C.

Specification

Appearance : White powder
Melting Range : 162 to 164°C
Soluble : Clear solution observed in DMF (1g in 10 mL DMF)
Soluble in Methanol

Synthesis of Impurity D
2-[4-[(2Rs)-3-chloro-2-hydroxypropoxy]phenyl]acetamide.

100 mL of methanol was taken in glass reactor, 10 g of Impurity C was charged at room temperature and heated to 40-45°C for Complete dissolution, 3.0 mL of conc. HCl was added gradually drop wise and refluxed at 60 to 65°C for 6 hrs. Completion of Reaction was checked on TLC. After TLC complies, reaction mass was concentrated to ¼ of its volume, cooled to room temperature and than chilled to 5-10°C, filtered and dried to obtain 8 g of crude impurity D (sticky white solid)

Purification:

2.5 g of crude impurity D was charged in 25 mL of Methanol in reactor, heated to 40 to 45°C for complete dissolution, filtered through filter paper and concentrated to ½ of its volume cooled to room temperature, chilled to 5-10°C, filtered to get 2.0 g of pure impurity D (White solid)

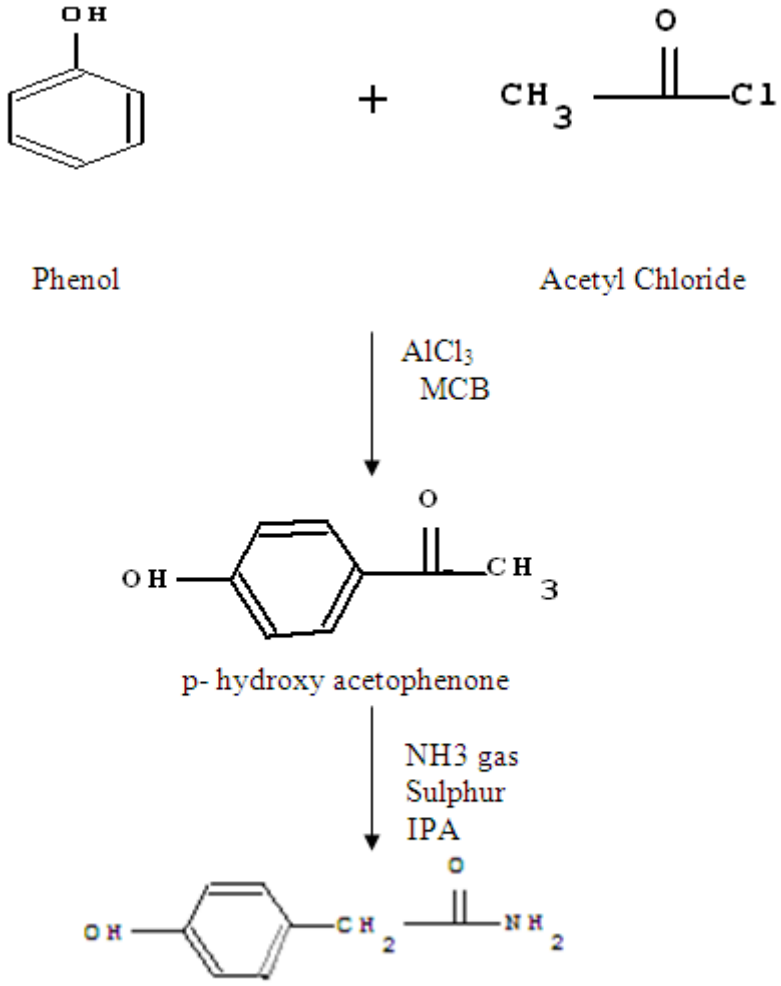
Specification

Appearance : White powder
Melting Range : 118 -122°C
Soluble : Clear solution observed in Methanol.

Analysis of Related Substance by HPLC Method:

Instrumentation:
A high performance liquid chromatograph system, with LC solutions data handling system (Thermo)

Route of Synthesis
Impurity A



(Impurity A) 2-(4-hydroxyphenyl)acetamide
/ Para hydroxyl phenyl acetamide

Analytical Column: A stainless steel column 150 mm long, 4.6 mm internal diameters filled with octadecylsilane chemically bonded to porous silica particles of 5 µm diameter (Use Inertsil C 18, 5 µ, 150 mm x 4.6 mm).[4]

Pump mode : Isocratic
Wavelength : 226 nm
Flow rate : 1mL per minute
Injection volume : 10 µl
Run time : 30 min.

Reagents:
1. Sodium HeptaSulphonate
2. Tetra butyl ammonium hydrogen sulphate
3. Tetrahydrofuran
4. Methanol
5. Potassium dihydrogen phosphate
6. Phosphoric acid
7. HPLC grade Water

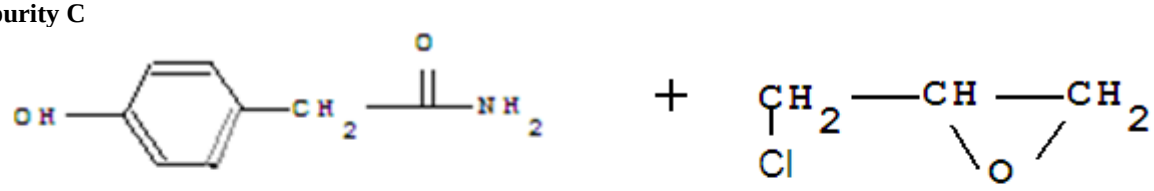
Preparation of Mobile Phase:

Mobile phase : Weighed accurately 1.0 g of Sodium heptasulphonate R and 0.4 g of tetra butyl ammonium hydrogen sulphate into a clean dry 1000 mL glass beaker. Added 20 volume of tetrahydrofuran, 180 volume of Methanol and 800 volume of 3.4 g/l solution of potassium dihydrogen phosphate R, Adjusted pH to 3.0 with phosphoric acid R, and filtered through 0.45µm membrane filter paper and degassed before use.[2]

Preparation of solutions:

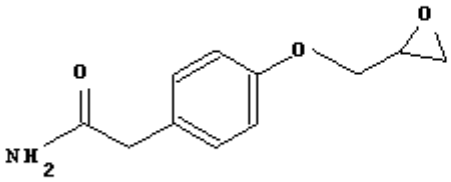
Ts 1 : Atenolol 100 ppm solution
Ts 2 : Impurity A 100 ppm solution
Ts 3 : Impurity C 100 ppm solution
Ts 4 : Impurity D 100 ppm solution
Ts 5 : Specificity (Atenolol 100 ppm + Imp A 100 ppm +Imp C 100 ppm + Imp D 100 ppm)

Impurity C



Impurity A
2-(4-hydroxyphenyl)acetamide

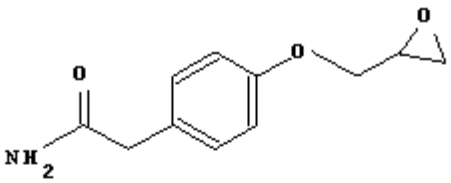
1-Chloro-2,3-epoxy-propane



Impurity C

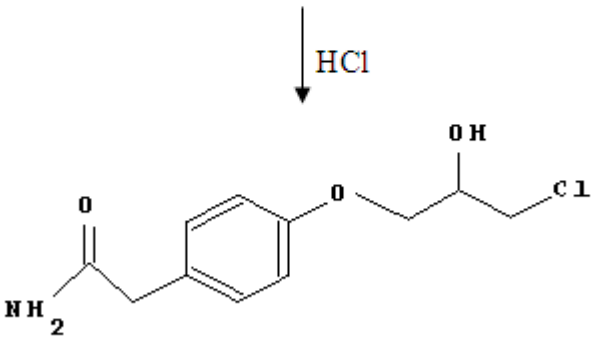
2-[4-[[(2RS)-Oxrain-2-yl]methoxy]phenyl]acetamide

Impurity D



Impurity C

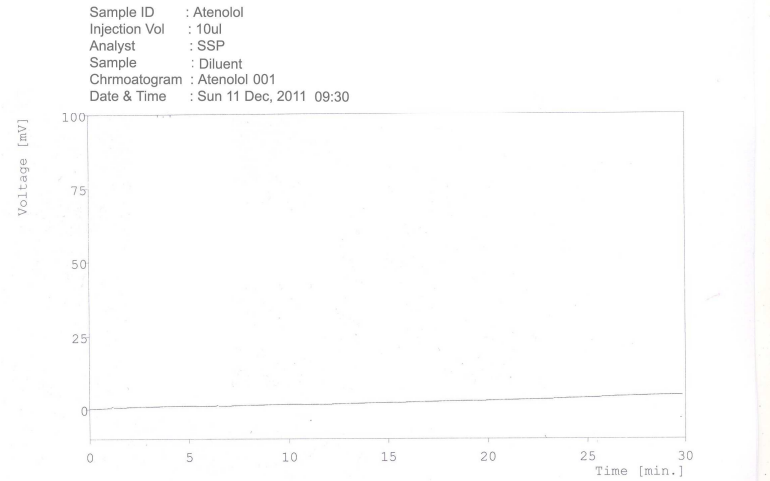
2-[4-[[(2RS)-Oxrain-2-yl]methoxy]phenyl]acetamide



Impurity D

2-[4-[(2Rs)-3-chloro-2-hydroxypropoxy]phenyl]acetamide

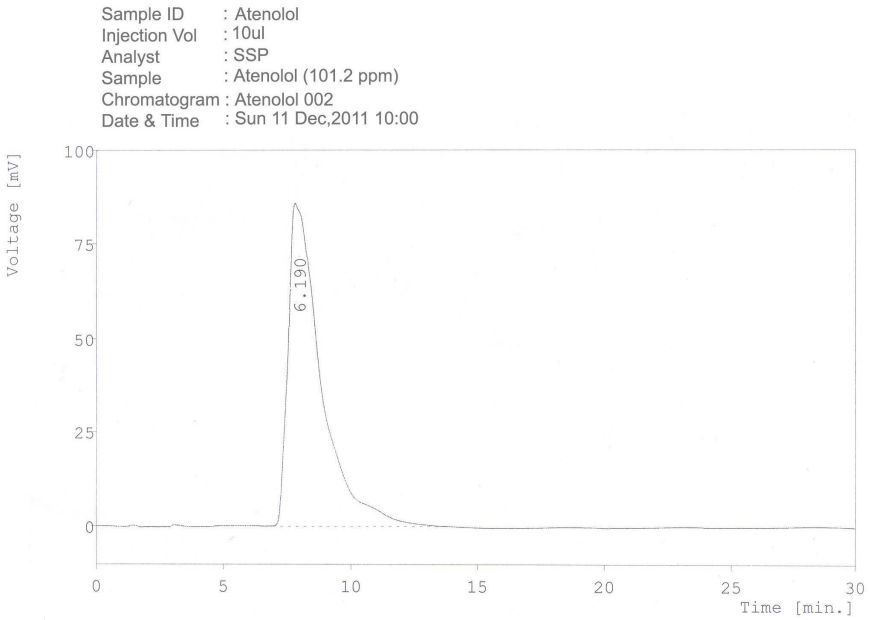
Graphs 1 Diluent



Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	0.000	000.000	000.000	000.000	000.000	000.000
-	Total	000.000	000.000			

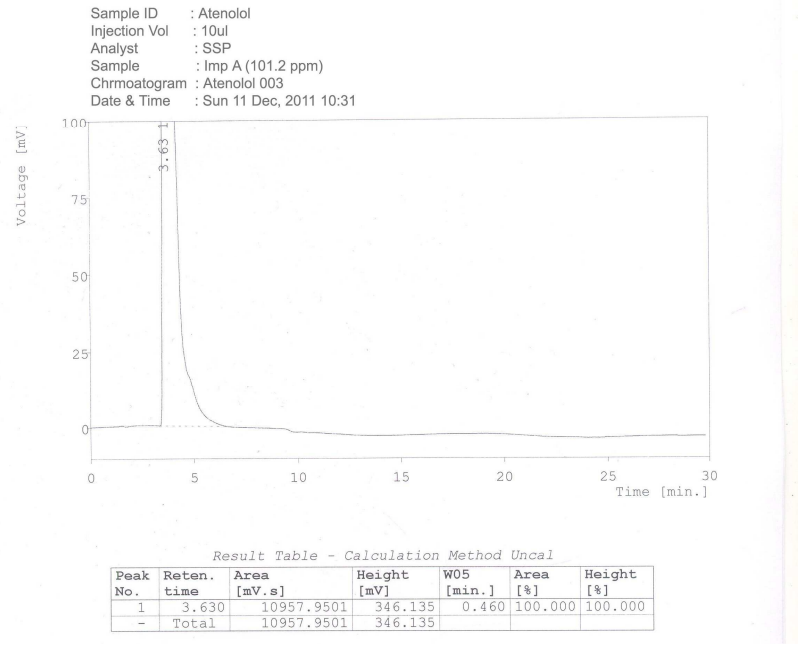
Graphs 2 Atenolol



Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	6.190	7728.6332	85.680	1.240	100.000	100.000
-	Total	7728.6332	85.680			

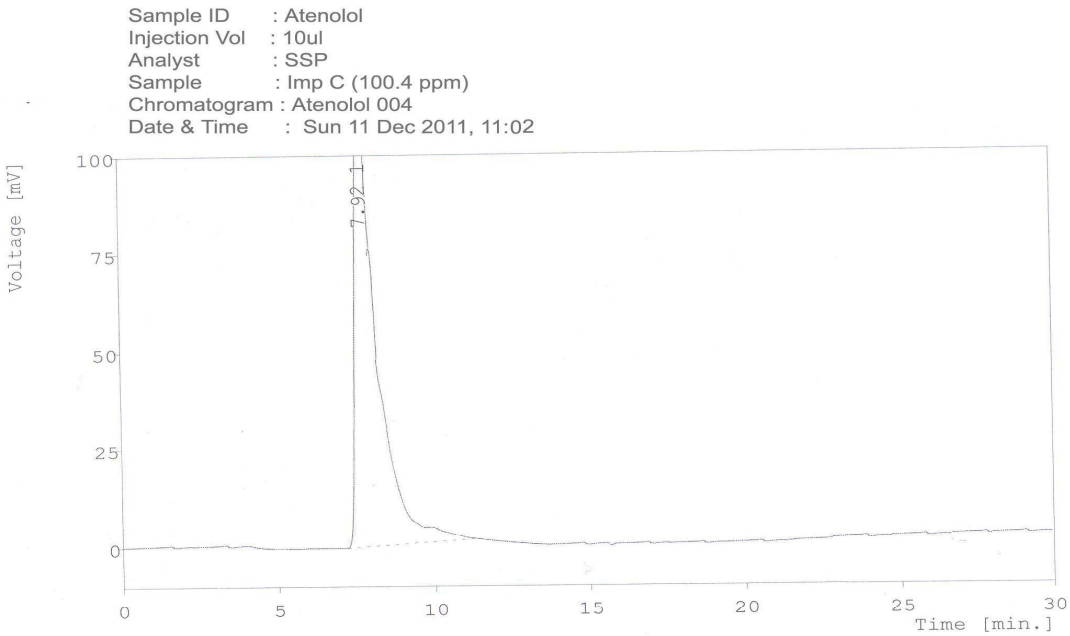
Graphs 3 Impurity A



Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	3.630	10957.9501	346.135	0.460	100.000	100.000
-	Total	10957.9501	346.135			

Graphs 4 Impurity C

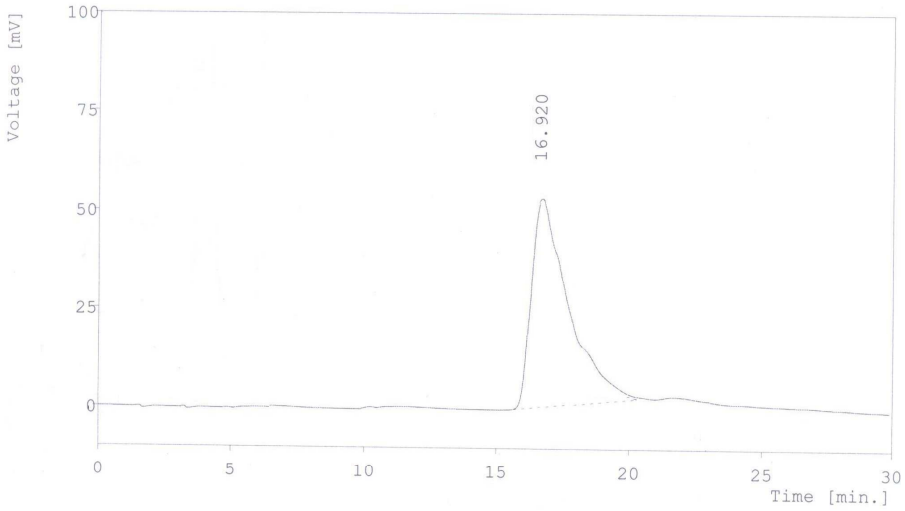


Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	7.920	6836.8317	115.404	0.930	100.000	100.000
-	Total	6836.8317	115.404			

Graphs 5 Impurity D

Sample ID : Atenolol
Injection Vol : 10 ul
Analyst : SSP
Sample : Imp D (100.1 ppm)
Chromatogram : Atenolol 005
Date & Time : Sun 11 Dec, 2011 11: 34

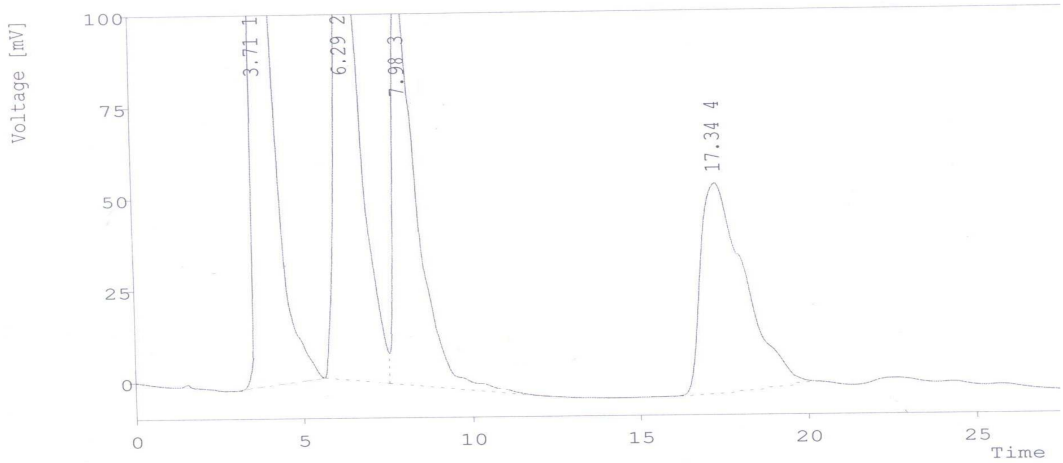


Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	16.920	7118.3969	62.171	2.000	100.000	100.000
-	Total	7118.3969	62.171			

Graphs 6 Specificity

Sample ID : Atenolol
Injection Vol :10ul
Analyst : SSP
Sample : Specificity (Imp A+Atenolol +imp c+ Imp D)
Chromatogram : Atenolol 006
Date & Time : Sun 11 Dec, 2011 12:00



Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	3.710	10464.0374	336.845	0.450	32.923	49.917
2	6.290	7283.0112	168.166	0.700	22.914	24.920
3	7.980	6854.7442	112.528	0.950	21.567	16.675
4	17.340	7181.9296	57.276	2.080	22.596	8.488
-	Total	31783.7224	674.815			

CONCLUSION

Synthesized compound can be used as impurity standard of Atenolol, which can be further studied in various aspects.

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