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Research Article

PROCESS DEVELOPMENT FOR SYNTHESIZING CEFPODOXIME PROXETIL

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ABSTRACT

Cephalosporins are the highly used Broad spectrum antibiotics, belong to β-lactam class . It was discovered by Brotzu in fungus Cephalosporium *Acremonium* which produces a chemical which show antimicrobial activity. Abraham isolated the three types of cephalosporin antibiotics cephalosporin P, cephalosporin N, cephalosporin C.7-ACA is widely used as the substrate for synthesizing cephalosporin antibiotics. Modification of the 7-ACA side-chains resulted in the development of useful antibiotic agents, and the first agent is Cephalothin (cefalotin) was launched by. Eli Lilly Company in 1964. Cephalosporins resemble penicillin in that they have a β-lactam structure, but the five-member thiazolidine ring characteristic of the penicillin is replaced by a six-member dihydrothiazine ring. The bactericidal action of beta lactam antibiotics is directly attributable to their ability to react with PBP's. The research work relates to an improved and cost effective process for the industrial manufacture of Cefpodoxime Proxetil. More specifically it relates to preparation of products of good quality with high yield and the products are removed and the same can be recycled using simple industrial and viable method. It can be possible with by using intermediate MAEM to synthesize Cefpodoxime proxetil. The drug is registered in USP and belongs to 3rd generation drug. There are many patents which gives the procedure of Synthesis of Cefpodoxime Proxetil. These synthesis procedures have taken as standard procedure for pursuing the project work. At present, MAEM is highly used intermediate to synthesis cephalosporin antibiotics. In this project work modification has done for synthesizing of cephalosporin antibiotics by utilizing MAEM as intermediate and other chemicals like different Lewis acid, and solvent as alternate of intermediate, chemicals and solvents which are given in patents to synthesize cephalosporin antibiotics .Resulting yield has improved via making small time synthesis reaction .This is helpful for the commercial purpose. The Reaction monitoring were done by HPLC and identification of final product were done by MASS, I.R, NMR and then comparing with the well known literature. Recovery of the side product and byproduct (mercaptobenzothiazole) were achieved to allow a greener process and utilizes for synthesis of other familiar drugs.

Keywords: Cepfodoxime proxetil, NMR, Thin layer chromatography, High performance liquid chromatography, Mercaptobenzothiazole

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1. INTRODUCTION:

Since some years ago the synthesis of antibiotics is a branch of pharmaceutical chemistry to which some investments have been made in order to develop new compounds with antimicrobial activity. In 1945, Brotzu discovered the fungus *Cephalosporium Acremonium* which produce a chemical which show antimicrobial activity. In 1948 Abraham at the Sir William Dunn School of Pathology at the University of Oxford and his colleagues have been supplied cultures of the fungus and were isolated three principal antibiotic components :i) Cephalosporin P, (a steroid antibiotic that resembles fusidic acid) with minimal antibacterial activity. ii) Cephalosporin N, later discovered to be identical with synnematin N (a penicillin derivative now called penicillin N.iii) Cephalosporin C it was isolated in 1952 from a mold of the genus Cephalosporium[1].

A decade later the nucleus (7-aminocephalosporanic acid) was isolated and used as the basis for a series of synthetic derivatives, including Cephalothin, cephaloridine and Cephaloglycin. (a cephem containing ring now called nucleus of cephalosporin drugs). He noticed that these cultures produced substances that were effective against *Salmonella Typhi*, the cause of typhoid fever, which had beta-lactamase. The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA), was derived from cephalosporin C and proved to be analogous to the penicillin nucleus 6-aminopenicillanic

acid, but it was not sufficiently potent for clinical use. Modification of the 7-ACA side-chains resulted in the development of useful antibiotic agents, and the first agent is Cephalothin (cefalotin) was launched by. Eli Lilly Company in 1964.

The Cephalosporins are a class of β-lactam antibiotics originally derived from Acremonium, which was previously known as "Cephalosporium". Together with cephamycins they constitute a subgroup of β-lactam antibiotics called cephem. [2,3] Cephalosporins are among the most important antibiotics. Cephalosporins resemble penicillin in that they have a β-lactam structure, but the five-member thiazolidine ring characteristic of the penicillin is replaced by a six-member dihydrothiazine ring .The dihydrothiazine ring of the cephalosporin provides the molecule with the ability to resist bacterial enzymes; the antibacterial activity emanates from the β-lactam ring shared by penicillin and Cephalosporins. [4]

Modifications at position 7 of the cephalosporin nucleus generally affect the antibacterial spectrum, and substitutions at position 3 of the dihydrothiazine ring alter the pharmacokinetics and metabolic parameters of the drug. In an effort to obtain derivatives possessing a broader antibacterial spectrum, greater stability towards lactamases and improved pharmacological properties, modifications of the cephem basic skeleton is required. In cephalosporin nucleus there are two positions available for chemical manipulation, C3 and C7. A wide variety of amine acylation methods have been used for the production of C7- acylamino derivatives by the use of acyl chlorides, mixed anhydrides, active esters, and carbodiimides to improve pharmacodynamic property . To improve the chemical reactivity of 7-ACA, the solubility in organic solvents is increased by conversion of the carboxylic acid at C4 of 7-ACA into an ester such as tert-butyl dimethylsilyl, benzhydry1,p-nitrobenzyl, o-p-methoxybenzyl to improve pharmacokinetic property .

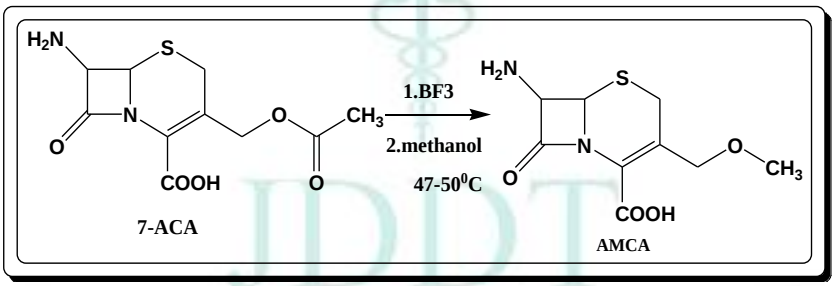
The cephalosporin nucleus can be modified to gain different properties. Cephalosporins are sometimes grouped into "generations" by their antimicrobial properties. The first Cephalosporins were designated first-generation Cephalosporins, whereas, later, more extended-spectrum Cephalosporins were classified as second-generation Cephalosporins. Each newer generation of Cephalosporins has significantly greater Gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against Gram-positive organisms. Fourth-generation Cephalosporins, however, have true broad-spectrum activity.5

2. MATERIALS & METHODS:

2.1 Experimental Part

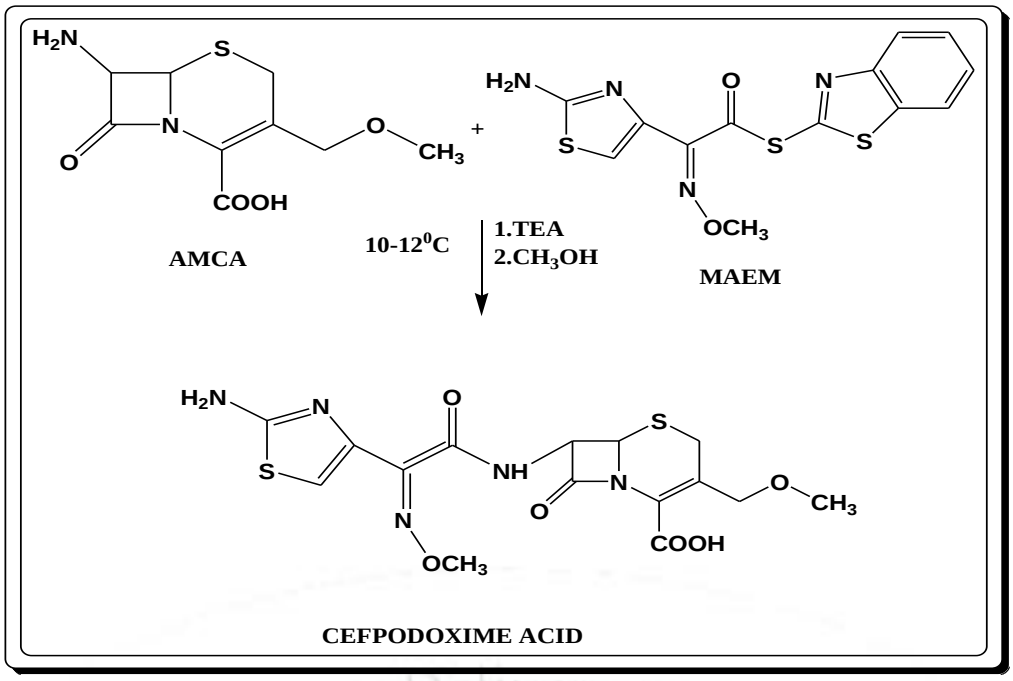
Synthetic Preparation of Cefpodoxime Proxetil

1. Prepration of 7-amino 3-methoxy,3-cephem-4-carboxylic acid from 7-amino cephalosporanic acid.



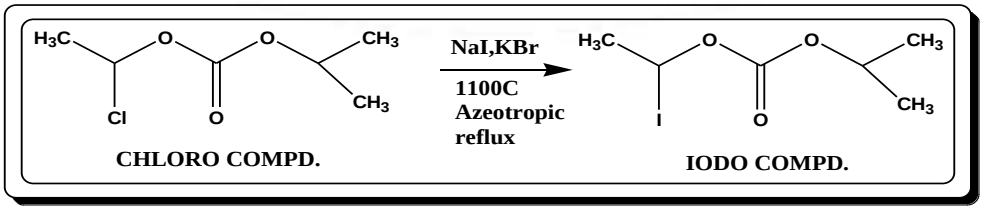
- Charged sulfolane 32g in dry four neck round bottom flask and checked moisture.
- Cooled down to 10^0c and purged 95g boron triflouride gas at 10 to 25^0c.
- After purging BF_3 added methanol 70 gm at 25 to 45^0c.
- Charged 25 gm 7-ACA at 45 to 46^0c.
- Raised the temp. to 47 to 50^0c & stirred the reaction mass till Rx completion.(Rx is monitered by HPLC Method). Its Rx monitoring is shown below.
- After Rx completion poured the Rx mass in to prechilled mixture of 500ml DM water+250 ml MDC+25g NaCl.
- Stirred,settled and separated the aqueous layer.
- Took aqueous layer and charged 900ml MDC.Again sepaerate the aqueous layer & charged again MDC In aqueous layer.
- Stirred,settled and separated out it.
- Collect total organic layer,adjust pH 7.0 to 7.2 with 20% NaOH sol'n
- Stirred the mass 15 min. again left for seperation.
- Collect both aqueous layer & charged 0.5g EDTA at 15-20^0c.
- Adjust the pH 1.0 to 1.2 with TEA at 15 to 20^0c.
- Stirred the Rx mass 30-40 min. at 15-20^0c.
- Again TEA added in mixture to adjust the final pH 2.92 to 3.10.
- Again stiirred for few min.at room temp.
- Filtered it & washed with 100ml water & 100 ml methanol.
- Dry it by vaccum pump & proceed in next stage.

2. Preparation of Cefpodoxime Acid(crude) from 7-AMCA.



- Charged Methanol 110 ml and wet 7 – AMCA at RT
- Cool down to 10^0c , charged MAEM 23 gm at 10^0c and flush with 10 m MeOH.
- Added TEA 7.5 gm slowly In 30 to 45 min. at 10 – 12^0c
- Stirred reaction mix at 10-12^0c till reaction completion.
- After reaction completion charged 560 ml DM water and adjusted pH 5.4 to 5.5 with 5% sulphuric acid.
- Cooled down to 5^0c and stirred 20 min.
- Filtered and washed MBT with 50 ml DM water.
- Took clear filtrate and charged 2.5 gm carbon , 0.5 gm hydro and 0.25 gm EDTA.
- Stirred 30 min. at 20 -25^0c.
- Filtered and washed carbon bed with 50 ml DM water.
- Took clear filterate and added 5% sulphuric acid up to haziness at 25 – 30^0c.
- Stirred 30 min. at 25 – 30^0c.
- Finally adjusted pH 2.5 with 5% sulphuric acid.
- Cooled down to 0 – 5^0c. and stirred 60 min at 0 -5^0c.
- Filtered and washed with –(a) 50 ml DM water
  - (b) 2*90 ml Acetone.
- Sucked properly and unloaded the wet material.
- Dried in the TD at 45 to 50^0c till moisture content less than 1.2% w/w.

3. Preparation of Side Chain Of Cefpodoxime Proxitil



- Charged toluene 280 ml at 25^0c.
- Charged sodium idide 25.344 gm , potassium bromide 0.225 gm and crown ether 2.8 gm at 25C.
- Raised the temp. up to 110^0c for azeotropic reflux. Stirred till m.c.≤0.05% at 110^0c.
- Charged chloro 25 gm compound at 100 -103^0c.
- Stirred reaction mix at 103 -105^0c till reaction completion (chloro ≤ 10.0%)
- After reaction completion , cooled down to the reaction mix to 25 – 30^0c.
- Charged sodium thio sulphate solution (8.44 gm in 56.32 ml DM water).
- Stirred 15 min. settled and seperated organic layer.
- Took organic layer and washed with sodium chloride solution (7.80 gm NaCL in 56.32 ml DM water).
- Took organic layer and dried over 16.89 gm sodium sulphate.
- Took organic layer and distilled out toluene under vaccum at 35 – 40^0c.

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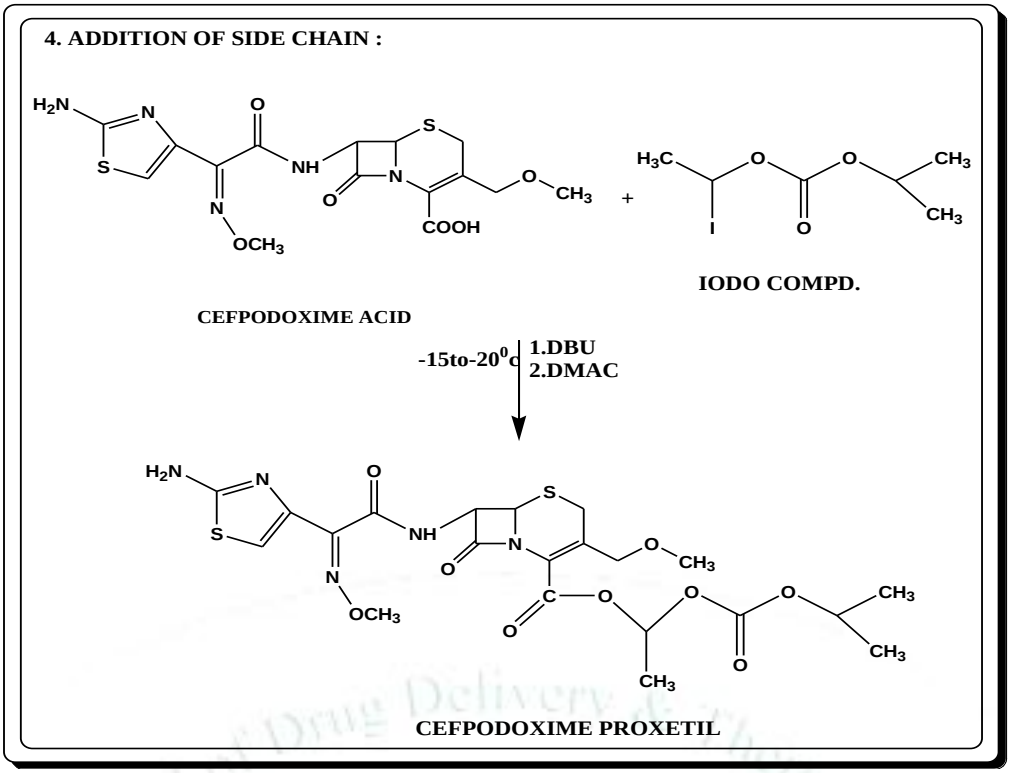
4. Prepration Of Cefpodoxime Proxetil From Cefpodoxime Acid.



- Charged DMAC 150ml at 20-25^{0}c.
- Charged CPDA 30g at 20-25^{0}c.
- Stirred till clarity at RT.
- Cooled it to -5 to -10^{0}c.
- Add DBU 10.67 gm at -5 to -10^{0}c.stirred 10 to 20 min.
- Cooled it to -15 to -20^{0}c.Added side chain 21gm at-15 to -20^{0}c.
- Stirred Rx mass at -15 to -20^{0}c till Rx completion.
- After Rx completion poured reaction mix.into(6.3g sodium thiosulphate+840ml DM water+285 ml ethyl acetate)sol'n.
- Stirred 15 min. settle and separate the layer.
- Took aqueous layer and extracted with 190ml ethyl acetate.
- Combined both ethyl acetate layer and washed with(192ml DM water+1.52g hydro+9g NaCl+1.86g sodium thio sulphate) solution two times.
- Took ethyl acetate layer , charged 4.5 gm carbon and 0.352 gm EDTA at 20 – 25^{0}c.
- Stirred 30 min. at 20 – 25^{0}c. filtered and washed carbon bed with 61 ml ethyl acetate.
- Took clear filtrate and distilled out ethyl acetate under vaccum at 30 -35^{0}c till 45.17 ml remains in RBF.
- Charged 45.17ml methanol and distilled out ethyl acetate and methanol mix. Under vaccum till 45ml remain in RBF.
- Repeated above step.
- Charged 113.99 ml methanol and 17 ml(1:1HCL) Sol'n.
- Stirred 10 min. at 20 -25^{0}c.
- Dispersed reaction mix into 750 ml DM water and maintained the pH 4 – 4.1 by 5% ammonia solution at 25 – 28^{0}c.
- Stirred 30 min. at 25 -28^{0}c
- Cooled down to 10 – 15^{0}c.
- Stirred 60 min. 10 -15^{0}c.
- Filtered and washed with 150 ml DM water three times.
- Unloded and dried in hot air oven till M.C.≤2.0%.

3. RESULTS AND DISCUSSION:

3.1. Physical Parameters6, 7

The Physical appearances and odors of following compound are:

Table: 1

Compound	Appearances	Color	Odors
Cefpodoxime Proxetil	Crystalline Powder	White to lightish brown	Having a faint odor

3.2 Solubility Parameters 8,9

The solubility of synthesized compound is as follows:

Table: 2

Compound	Solubility
Cefpodoxime Proxetil	Very slightly soluble in water, Soluble in acetonitrile and in methanol. Freely soluble in dehydrated alcohol Slightly soluble in ether.

3.3 Determination of Melting Point Range:

Melting points of the newly synthesized compounds were determined by open capillary method using the melting point apparatus. The melting points of synthesized compounds are given in

Table 3:

Compound	Melting point (^{0}c)
Cefpodoxime Proxetil	111-114

3.4 HPLC Parameters of Compounds [10, 11]

The retention times of following compounds are as follows:

Table: 4

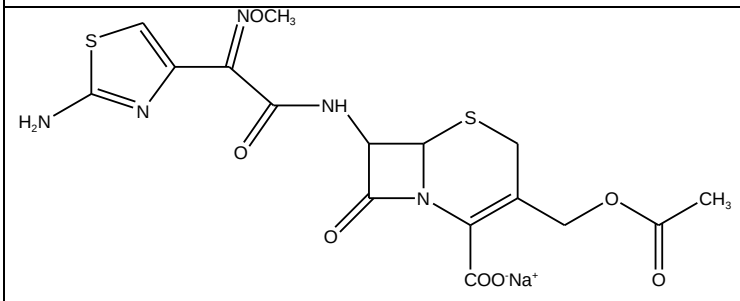
s.no	Compounds	Retention Time
1	7-ACA	6.26-6.30
2	AMCA	3.80-3.90
3	ADCA	3.23-3.27
4	Chloro Compd.	8.51-8.55
5	Iodo Compd.	10.50-10.55
6	MAEM	16.70-16.75
7	CPDA	7.92-7.83
8	CPPN-A CPPN-B	10.78-10.80 9.73-9.80
9	Cefpodoxime proxetil	12.31-12.35

Spectra Analysis

3.5 I.R of the synthesized compound:

The functional groups of synthesized compounds can be concluded from the value of I.R spectra, it is also an identification source of the compound:

Table: 5

COMPOUND	Common Value	Interpretation
	-1745 stretch -1600Asym. 1400 symm. -1690-1640 3350&3180 1740-1715	-β-lactam amide -showsalt formation -Oxime peak -Primary amine -Ester peak

3.6 Interpretation of Mass Spectra of Following Synthesizes Compound:

Table: 6

Compound	Molecular Weight	Base Peak	Molecular ion peak
Cefpodoxime Proxetil	557.60	558.1	558.1

3.7 Interpretation of NMR Spectra of following Synthesizes Compound:[12]

- ***Cefpodoxime proxetil:***

H-NMR (DMSO-d6): 9.62 (m, 1H, NHCO), 7.25 (s, 2H, NH2), 6.87 and 6.81 (2q, 1H, OCH(CH3)O), 6.74 (s, 1H, thiazole), 5.85 (m, 1H, H-7), 5.20 (m, 1H, H-6),

4.82 (m, 1H, OCH (CH3)), 4.15 (s, 2H, CH3OCH2), 3.83 (s, 3H, NOCH3), 3.65 and

3.52 AB, q, 2H, H-2), 3.20(s, 3H, CH2OCH3), 1.49 (d, 3H, CH3CH), 1.25 (m, 6H, (CH3)2).

These all described data confirms the synthesized drugs.

5.8 Yield of Following Synthesized Products

The theoretical yield & practical yield are calculated on the basis of substrate i.e In case of CPPN and Cefotaxime, 7-ACA is taken as substrate and &7-ADCA is taken as substrate for Cefetamet. All value of yield are calculates in reference of 50 g substrate.

Table: 7

Compound	Theoretical yield	Practical yield	%yield
Cefpodoxime Proxetil	102.45gm	86.96gm	84.89

CONCLUSION:

The use of MAEM as starting material for preparing cefpodoxime Proxetil, allowed to obtain better yields for the synthesis of these antibiotics. Previous esterification of the chloroacetylated derivative followed by cleavage of the chloroacetyl protective group, allowed to eliminate the drawbacks of the classic pathways of synthesis, especially the final purification of cefpodoxime Proxetil by column chromatography. Moreover, the utilization of MAEM allows diminish the production cost of the final product. The reaction time has been reduced by lowering the time for acylation. The overall yield has been increased to 91% with good. Recovery of the byproduct (mercaptobenzothiazole) was achieved to allow a greener process.

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Table 1.1: List of Chemicals Used In Isolation Process

Chemical Name	Grade	Company
ACETONE	B (For Synthesis)	SPECTROCHEM
TEA	A (For Synthesis)	Qualigens Fine Chemicals, Mumbai
BSA	A (For Synthesis)	ALDRICH
ETHYL ACETATE	A (For Synthesis)	SPECTROCHEM
SULFOLANE	A (For Synthesis)	S.D Fine Chemicals, Mumbai
METHANOL	B (For Synthesis)	SPECTROCHEM
7ACA		SANDOZ
SULPHURIC ACID	B (For Synthesis)	SPECTROCHEM
MDC	B (For Synthesis)	SPECTROCHEM
THF	B (For Synthesis)	SPECTROCHEM
EDTA	B (For Synthesis)	SPECTROCHEM
MAEM		SANDOZ
CARBON	A	SPECTROCHEM
SODIUM IODIDE	A (For Synthesis)	MERCK
POTASSIUM BROMIDE	B (For Synthesis)	MERCK
SODIUM THIOSULPHATE	B (For Synthesis)	ALDRICH
TOLUENE	A (For Synthesis)	SPECTROCHEM
CROWN ETHER	A (For Synthesis)	ALDRICH
CHLORO COMPD.	B (For Synthesis)	SPECTROCHEM
SODIUM SULPHATE	B (For Synthesis)	SPECTROCHEM
AMMONIA	B (For Synthesis)	SPECTROCHEM
SODIUM HYDROXIDE	B (For Synthesis)	Qualigens Fine Chemicals, Mumbai
DMAC	B (For Synthesis)	SPECTROCHEM
Hydrochloric Acid		Central Drug House (p)ltd. New Delhi
Ortho-phosphoric acid	A (HPLC grade)	ALDRICH
7-ADCA	A (HPLC grade)	SANDOZ
Sodium ethyl Hexonate	B (For Synthesis)	Central Drug House (p)ltd. New Delhi
Dimethyl formamide	A (For Synthesis)	SPECTROCHEM

Table 1.2: List of Chemicals Used In TLC and HPLC analysis

Si. No.	Name of Chemicals	Grade of chemicals
1	Chloroform	HPLC grade, Merck
2	Toluene	AR grade, Merck
3	Methanol	HPLC grade, Merck
4	Acetonitrile	HPLC grade, Merck
5	Formic acid	AR grade, Merck
6	Glacial acetic acid	AR grade, Merck
7	Acetone	HPLC grade, Merck
8	Ethyl acetate	AR grade, Merck
9	Water for HPLC	HPLC grade, Merck

4.4 NMR SPECTRA OF CEFPODOXIME PROXETIL

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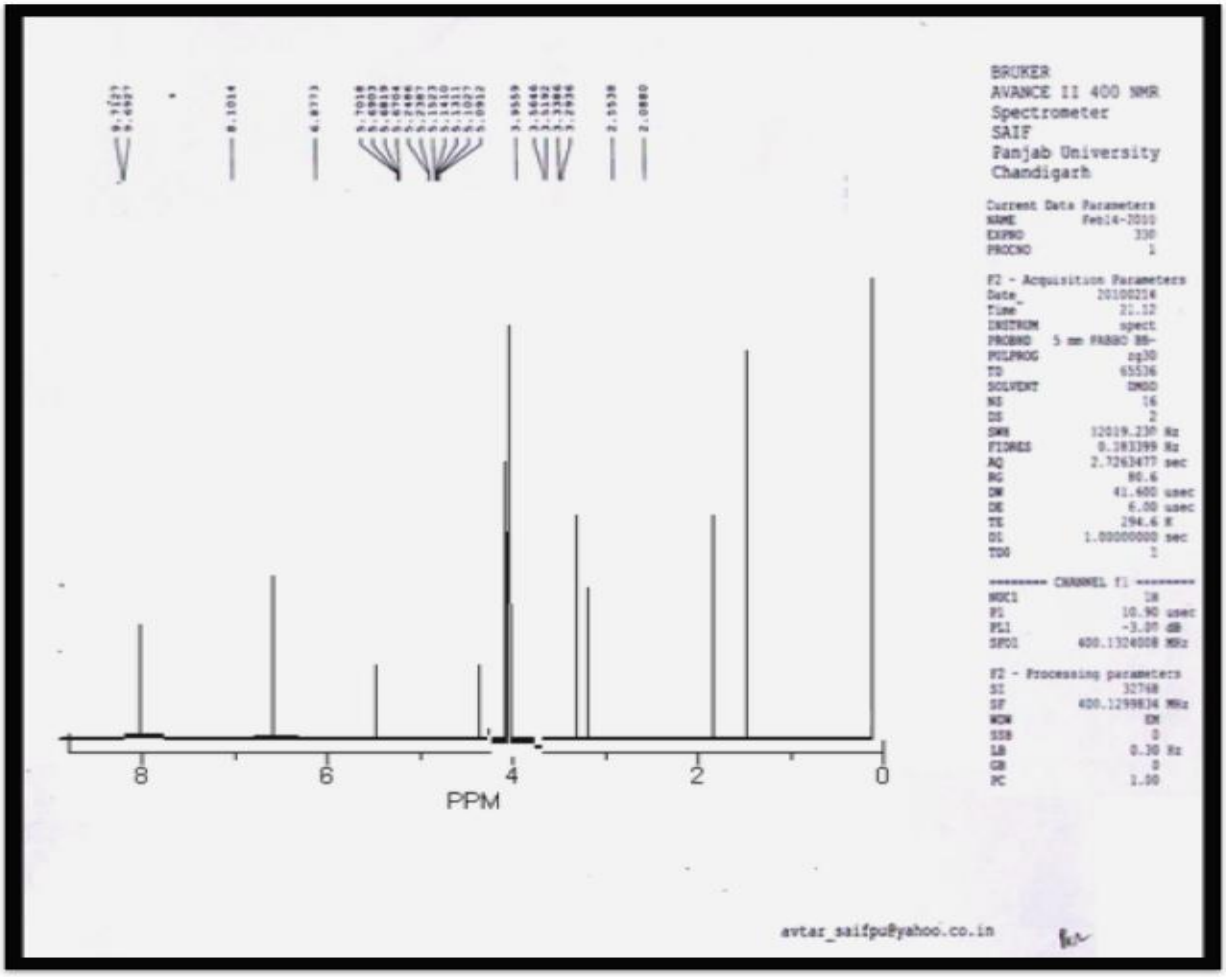
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Panjab University
Chandigarh
PPM
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6
4
2
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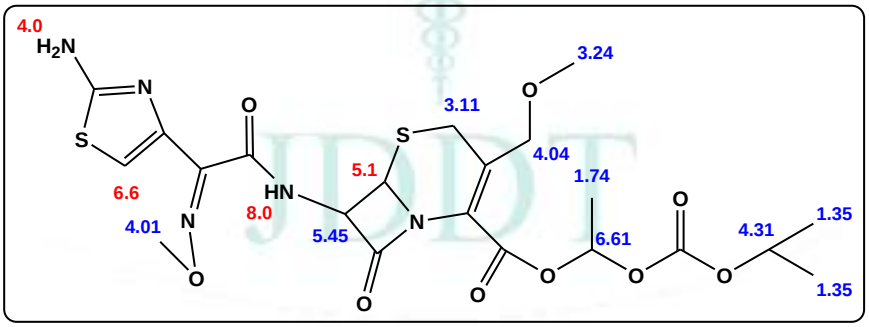
Spectrum


4.0
H_2N
N
S
O
6.6
HN
8.0
4.01
N
O
5.1
5.45
N
O
S
3.11
O
3.24
4.04
1.74
6.61
O
O
O
O
4.31
1.35
1.35

Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH	6.6	7.41	thiazole
		-0.85	1 -N from 2-thiophene
		?	1 unknown substituent(s) from 3-thiophene
		?	1 unknown substituent(s) from 3-furan
			-> 1 increment(s) not found
NH2	4.0	4.00	aromatic C-NH
NH	8.0	8.00	sec. amide
CH	5.45	3.08	propiolactam
		2.10	1 alpha -N-C=O from methine
		0.27	1 beta -SR from methine
		?	1 unknown substituent(s)
CH	5.1	3.42	propiolactam
		1.04	1 alpha -SR from methine
		0.62	1 beta -N-C=O from methine
		?	1 unknown substituent(s)
		?	1 -R from N-CHx
			-> 1 increment(s) not found
CH2	3.11	1.37	methylene
		0.63	1 alpha -C=C
		1.11	1 alpha -S-C
CH	6.61	1.50	methine
		0.17	1 alpha -C
		4.94	2 alpha -O-C=O
CH3	1.74	0.86	methyl
		0.44	1 beta -OC(=O)-C=C
		0.44	1 beta -OC(=O)
CH	4.31	1.50	methine
		0.34	2 alpha -C
		2.47	1 alpha -O-C=O
CH3	1.35	0.86	methyl
		0.44	1 beta -OC(=O)
		0.05	1 beta -C
CH3	1.35	0.86	methyl
		0.44	1 beta -OC(=O)
		0.05	1 beta -C
CH2	4.04	1.37	methylene
		0.63	1 alpha -C=C
		2.04	1 alpha -O-C
CH3	3.24	0.86	methyl
		2.38	1 alpha -O-C
CH3	4.01	0.86	methyl
		3.15	1 alpha -O-N=C

MASS SPECTRA OF CEFPODOXIME PROXETIL

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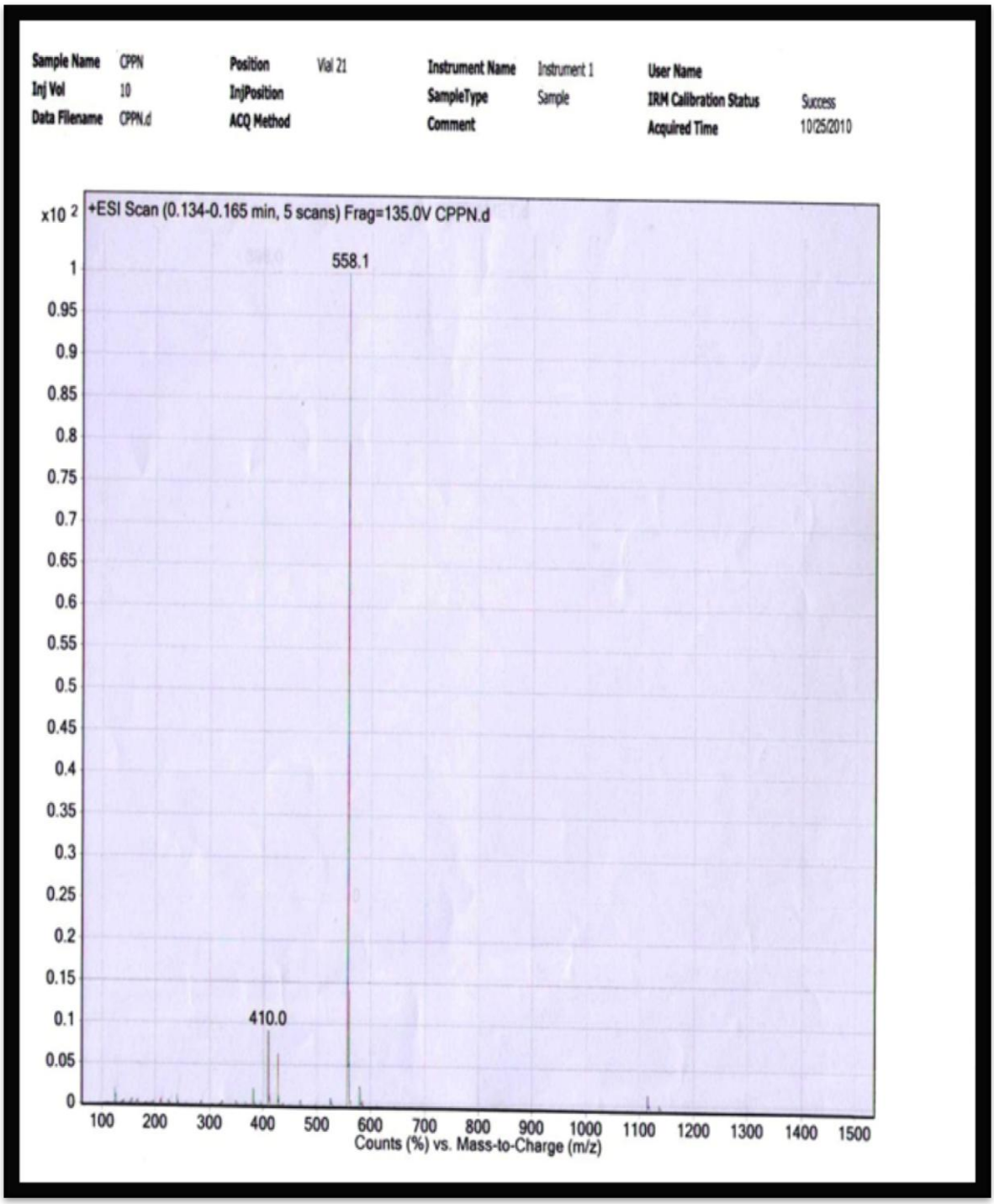
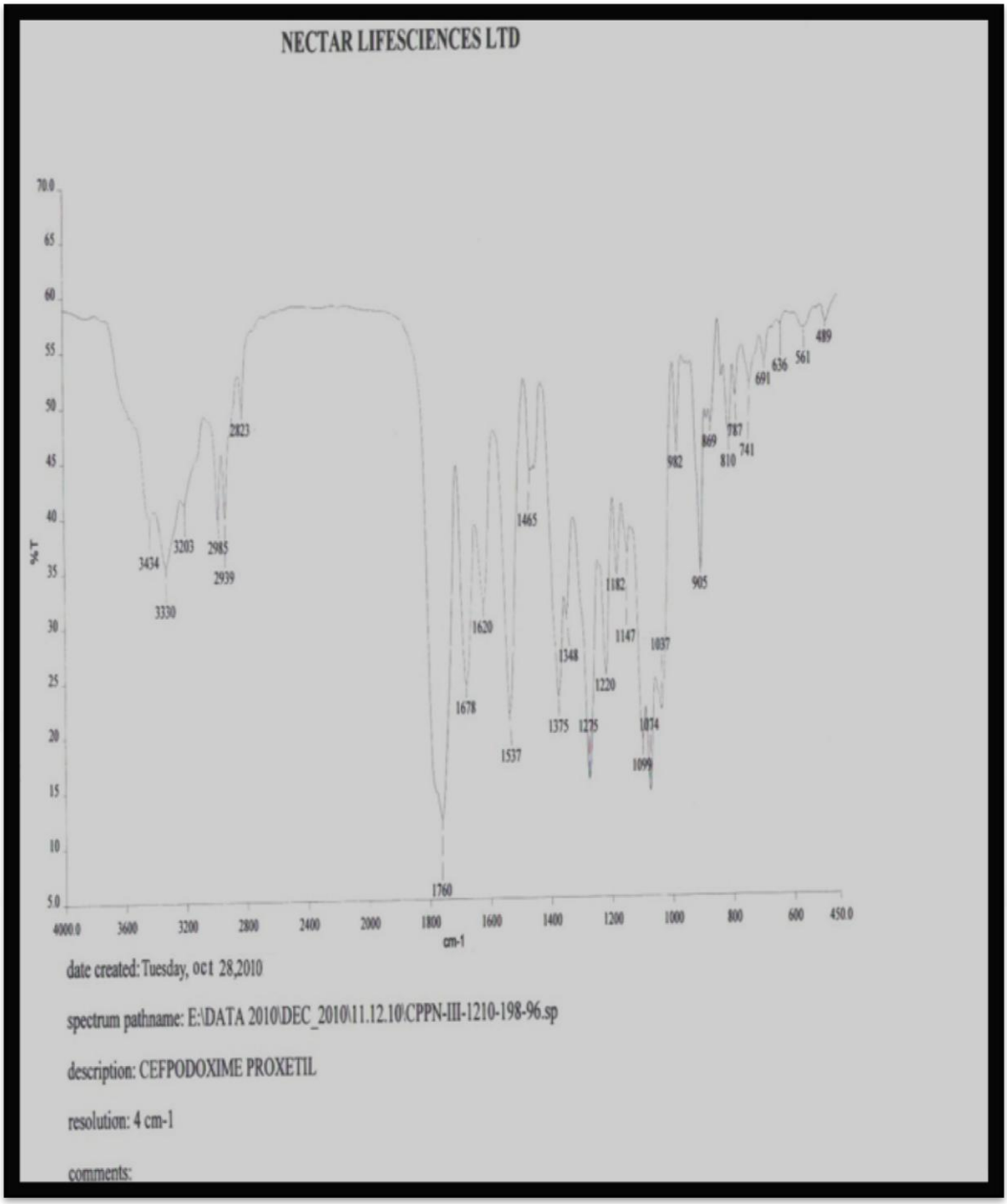


Spectrum

I.R SPECTRA OF CEFPODOXIME PROXETIL



Spectrum-

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