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RESEARCH ARTICLE

Identification and Characterization of Prasugrel Degradation Products by GC/MS, FTIR and ^{1}H NMR

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ABSTRACT:
The objective of the present work was to separate, identify and characterize the degradation products of Prasugrel hydrochloride under hydrolytic and oxidative stress conditions according to the International Conference on Harmonization (ICH) guideline Q1A (R2). The drug degraded under acidic, basic, and oxidative stress. Five degradation products were formed, which were separated using preparative TLC. Mass fragmentation pathway of the drug was first established with the help of GC/MS studies. The degradation products were subjected to FTIR and 1H NMR studies. The obtained mass spectral data were employed to characterize the degradation products and assign structures. The degradation products were identified as 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2(3H)-one, 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4H)-one, 2-acetoxy-5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine 5-oxide, 1-cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione and 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate.

KEYWORDS: Stress studies, Prasugrel hydrochloride, GC/MS, FTIR, 1H NMR, degradation Products.

INTRODUCTION:
Prasugrel chemically is 5-[2-cyclopropyl-1-(2-fluoro-phenyl)-2-oxoethyl]-4,5,6,7-tetra hydrothieno [3,2-c] pyridin-2-yl acetate (Fig. 1). Its empirical formula is $C_{20}H_{20}FNO_3S$ and its molecular weight is 373.442 g/mol.

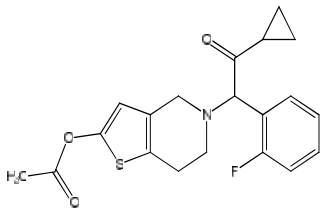

Fig. 1: Chemical Structure of Prasugrel

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Prasugrel is a member of the thienopyridine class of ADP receptor inhibitors, like ticlopidine and Clopidogrel[1]. These agents reduce the aggregation ("clumping") of platelets by irreversibly binding to P2Y12 receptors. Prasugrel inhibits adenosine diphosphate–induced platelet aggregation more rapidly, more consistently, and to a greater extent than do standard and higher doses of Clopidogrel in healthy volunteers and in patients with coronary artery disease[2-4]. A pharmacodynamic study suggests that acute coronary syndrome (ACS) patients can be safely switched from Clopidogrel to Prasugrel and that doing so results in a further reduction in platelet function after one week[5]. When patients receive a loading dose of Prasugrel prior to switching from Clopidogrel, the reduction in platelet function occurs within two hours [6]. Literature survey revealed that many analytical methods like UV [7], LC-MS [8-12], HPTLC [13-16] and HPLC [16-18] were reported for the analysis of Prasugrel. Also, literature survey revealed

that three impurities of Prasugrel hydrochloride have been already identified [19], (Fig. 2). Other articles studied the identification, synthesis and characterization of related substances of Prasugrel hydrochloride [20, 21].Though these methods already exist in the literature, none of the methods carried out studies to isolate and characterize degradation products of Prasugrel hydrochloride formed by hydrolysis or oxidation under stress condition according to ICH.

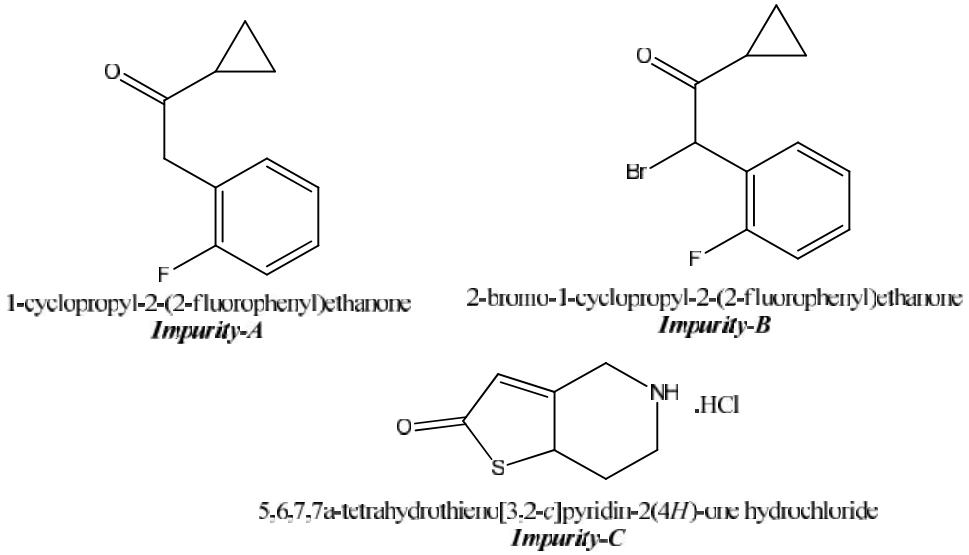


Fig. 2: Chemical Structure of impurities of Prasugrel hydrochloride

An attempt was made towards isolation and characterization of degradation products. Therefore, an endeavor of the present study was to degrade the drug under hydrolytic and oxidation conditions, to isolate the products on preparative TLC and to characterize the major products by GC/MS, FTIR and ^{1}H NMR studies.

MATERIALS AND METHODS:

Chemical and Reagents:

Prasugrel hydrochloride was obtained as gift sample from Medico laboratories (Homs, Syria) and was used without further purification. Analytical reagent grade hydrogen peroxide (H_2O_2). Sodium hydroxide (NaOH) was purchased from HiMedia (Mumbai, India). Hydrochloric acid (HCl), Methanol, Dichloromethan, acetonitrile, n-hexan, and tetrahydrofuran were supplied by Merck.

Instrumentation:

GC/MS:

GC/MS analyses were performed on Shimadzu – GC/MS-QP2010 Plus device equipped with RTX-5 column®, Restek Corporation (30.0 m × 0.32 mm; film thickness 0.50 µm) fused silica capillary column (5% diphenyl polysiloxane, 95% dimethyl polysiloxane). Carrier gas was He, and gas flow rate 1.64 ml/min. Mass spectra were obtained by electron impact (EI) ionization at 70 eV with an emission current of 400 mA. The scan time was 1 s and the scan range was m/z 29–600. The ion source temperature was maintained at 280 ºC. The identity confirmed by fragmentation pattern and by Nist and Wiley mass spectral libraries. The temperature program was as follows of the column was 100°C; 25°C/min. until 200°C and 8°C/min. until 300˚ C, holding for 5.5 min.

^{1}H NMR Spectroscopy:

About 10 mg of the tested substances were each dissolved in 0.6 mL of Chloroform-d and were immediately analyzed by NMR spectroscopy. The one-dimensional NMR measurements were performed on a Bruker Avance III NMR spectrometer (Bruker, Rheinstetten, Germany) with 400 MHz for ^{1}H, employing the manufacturer's pulse programs. The ^{1}H chemical shift values were reported on the scale in ppm. Standard Bruker pulse sequences were applied by running ACD/Labs (ACD/NMR Processor Academic Edition) software version 12.01.

IR Spectroscopy:

The IR spectrum was recorded in the solid state as a KBr disk, using the FT-IR (Bruker, alpha) spectrophotometer, the wave length resolution was set to 4 cm^{-1}, the IR spectrum was collected in a range of 400–4000 cm^{-1}, with Bruker Opus 5.5 software.

Preparative TLC Method:

A mixture of (n-hexan:tetrahydrofuran)(1:1 v/v) was used as a mobile phase for the separation of degradation products in acidic and basic media, while acetonitrile

was used as a mobile phase for the separation of degradation products in oxidative medium. Glass TLC plates 20X20 cm, coated with (SIL. G. UV_{254}) were purchased from Macherey-Nagel GmbH and Co. KG, Germany.

Preparation of degradation samples of Prasugrel hydrochloride:

Acid and base degradation:

Accurately weighed 100 mg of Prasugrel hydrochloride was dissolved in 90 ml of methanol. The drug was subjected to accelerated degradation under acidic and basic conditions by adding 10 ml of 1 N HCl and 10 ml 1 N NaOH, respectively, and refluxed at 60 °C for a period of 2 and 1 h, respectively. The accelerated degradation in acidic and basic media was performed in the dark in order to exclude the possible degradation effect of light on the drug.

Peroxide degradation:

Accurately weighed 100 mg of Prasugrel hydrochloride was dissolved in 90 ml of methanol. Subsequently, 10 ml of hydrogen peroxide 30.0% v/v was added and the solution was heated in boiling water bath for 1 hour till the removal of excess hydrogen peroxide.

Data analysis:

structure formulae were generated and processed by ChemBio Draw Ultra 12.0 Software.

RESULTS AND DISCUSSION:

Isolation of degradation product(s) by preparative TLC:

The resultant solutions were subjected to preparative TLC, the bands were visualized using UV_{254} lamp, and the desired band was scratched with a spatula, extracted with the mobile phase which was finally evaporated, then the resulted solid was subjected to spectroscopic experiments.

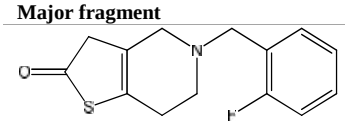
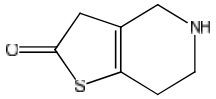
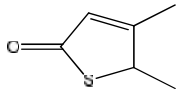
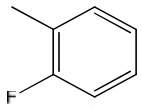
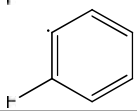
Characterization of the degradation product:

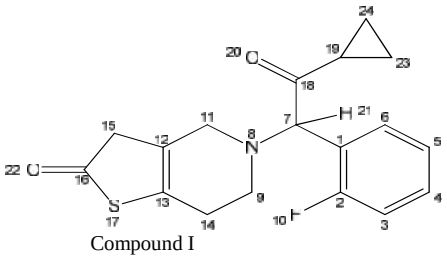
Characterization of the compounds was performed using analytical data obtained from GC/MS, IR and ^{1}H NMR spectrum experiments.

Elucidation of the structures of degradation products resulted from hydrolytic stress conditions (compound I and tautomer):

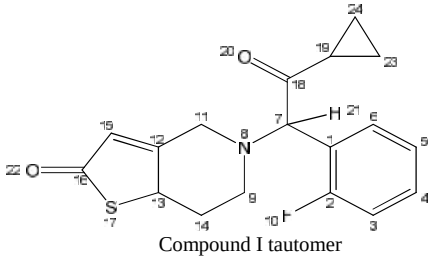
According to TLC analysis, it was found that there were two degradation products (compound I and tautomer). The MS, IR, and ^{1}H NMR spectra of compound I and tautomer were recorded. The major Mass fragments obtained by GC/MS analysis are given in (table 1).

Table 1: The Mass fragment of compound I and tautomer

Major fragment	*m/z*
	263/264
	155/156
	128/129
	110/111
	95/96



Compound I



Compound I tautomer

Fig. 3: Structure of compound I and tautomer

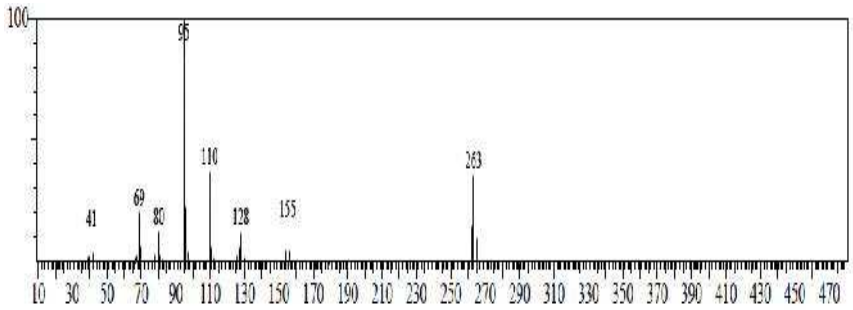


Fig. 4: Mass spectrum of compound I and tautomer

As shown in (Fig. 4) and (table 1) that the main fragment of the compound I was *m/z*: 95/96 which correspond to fluoro-phenyl fragment and m/z: 155/156 refers to 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2(3H)-one. FTIR spectra of compound I and tautomer are shown in (Fig. 5), (Fig. 6) and (table 2).

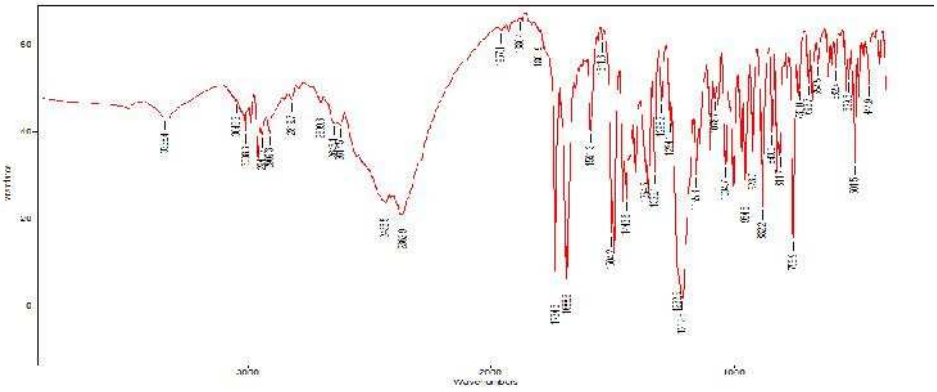


Fig. 5: IR spectrum of compound I

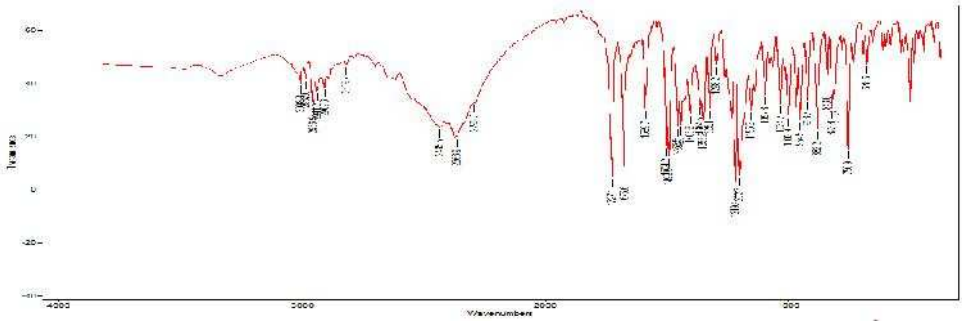


Fig. 6: IR spectrum of compound I tautomer

Table 2: Bands and assignments of compound I and tautomer

Compound I frequency cm^{-1}	Tautomer Frequency cm^{-1}	Assignment
3008, 2941, 2909	2956, 2942	C–H Stretch (aromatic)
2435, 2362	2436, 2364	C-S-C stretch
1734, 1688	1727, 1675	C=O ketone
1591, 1504	1589	C–C stretch (in–ring) aromatic
1232, 1212, 1155	1219, 1202	C–N stretch, Pyridine ring

As shown in (Fig. 5), (Fig. 6) and (table 2), the main functional groups of compound I and tautomer appeared clearly; the absence of ester group compared to Prasugrel hydrochloride, the presence of aromaticity at 3008, 2941, 2909 cm^{-1} for compound I and at 2956, 2942 cm^{-1} for compound I tautomer, the presence of two groups of ketone at 1734 and 1688 cm^{-1} for compound I but for compound I tautomer the two ketone groups at 1727 and 1675 cm^{-1} are shifted to lower wave number, this shift could be explained by the conjugation at the atoms number 9,12,13,23. ^{1}H NMR of compound I and tautomer (400 MHz, Chloroform-d) are shown in (fig. 7) and (fig. 8).

Table 3: ^{1}H NMR Chemical shift assignment for compound I

Chemical shift (ppm)	Multiplicity	No. of protons	Proton position
1.02	quin, J=7.85 Hz	4 H	23, 24
1.50	quin, J=7.80 Hz	1 H	19
2.48	dd, J=14.75, 10.25, 4.00 Hz	1 H	14
2.85	m	1H	14
2.62-2.67	m	1 H	9
2.88- 2.92	m	1 H	9
2.94 - 3.13	dd	2 H	11
3.27	d, J=16.60 Hz	2 H	15
5.10	s	1 H	21
7.04 - 7.17	m	2 H	4, 5
7.33 - 7.44	m	1 H	6
7.51 - 7.61	m	1 H	3

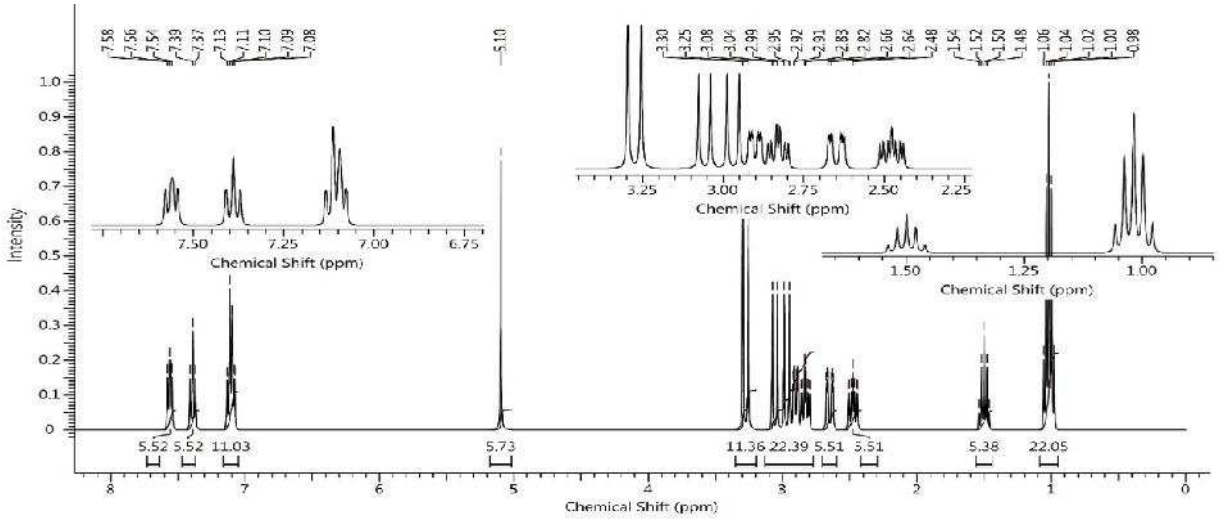


Fig. 7: ^{1}H NMR spectrum of compound I

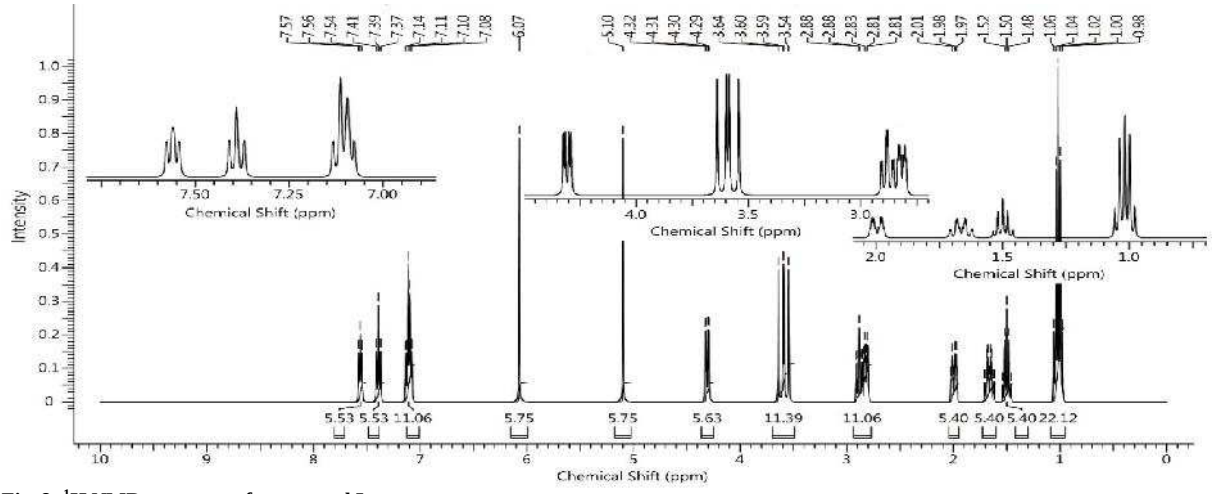


Fig. 8: ^{1}H NMR spectrum of compound I tautomer

Table 4: ^{1}H NMR Chemical shift assignment for compound I tautomer

Chemical shift (ppm)	Multiplicity	No. of protons	Proton position
1.02	quin J=7.90 Hz	4 H	23, 24
1.50	quin, J=7.70 Hz	1 H	19
1.97-2.02	m	1 H	14
2.83-2.91	m	1 H	14
1.62-1.71	m	1 H	9
2.84-2.91	m	1 H	9
3.46 - 3.72	m	2 H	11
4.31	dd, J=10.10, 3.70 Hz	1 H	13
5.10	s	1 H	21
6.07	s	1 H	15
7.01 - 7.19	m	2 H	4, 5
7.31 - 7.45	(m,)	1 H	6
7.56	td, J=6.65, 0.90 Hz	1 H	3

According to these data it was inferred that the acetyl group of Prasugrel hydrochloride was not present in compound I and tautomer. The degradation product was formed by hydrolysis of ester group of Prasugrel hydrochloride to form acetic acid and compound I (and tautomer). On the basis of these data it was concluded that compound I was 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2(3H)-one and its tautomer was 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4H)-one, as shown in (Fig. 3).

Elucidation of the Structure of Degradation Products resulted from oxidative stress conditions:

According to TLC experiments, it was found that there were three spots which indicate to three degradation products (compound III, IV and V). The MS, IR, and ^{1}H NMR spectra of compound III were recorded. The major Mass fragments for compound III are given in (Table 5).

The compound III was formed by oxidation of Prasugrel hydrochloride to form N-Oxide product. GC/MS analysis of compound III revealed a molecular ion peak at *m/z* :95/96 and 245/247 and the fragmentation pattern also confirmed the structure given in (Fig. 9).

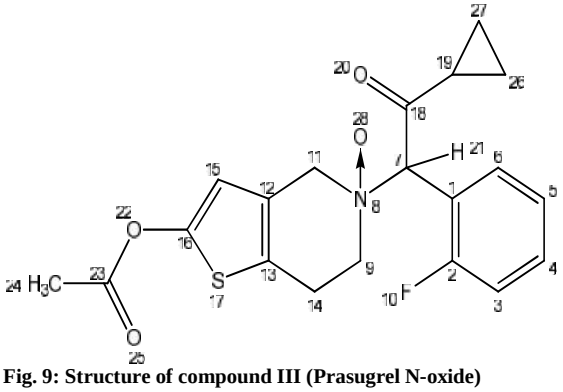


Fig. 9: Structure of compound III (Prasugrel N-oxide)

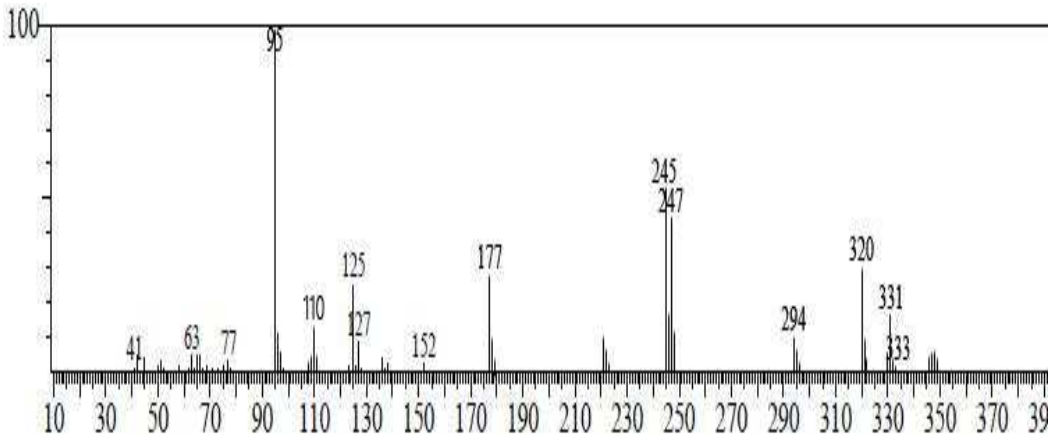


Fig. 10: Mass of compound III

IR spectrum and bands and assignments of compound III are also shown in (fig. 11) and (table 6); respectively.

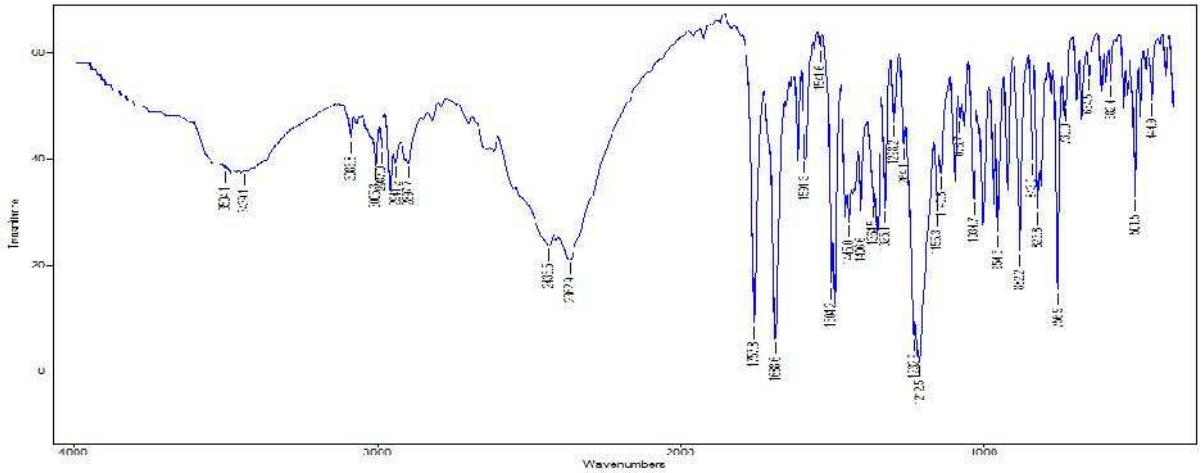


Fig. 11: IR spectrum of compound III

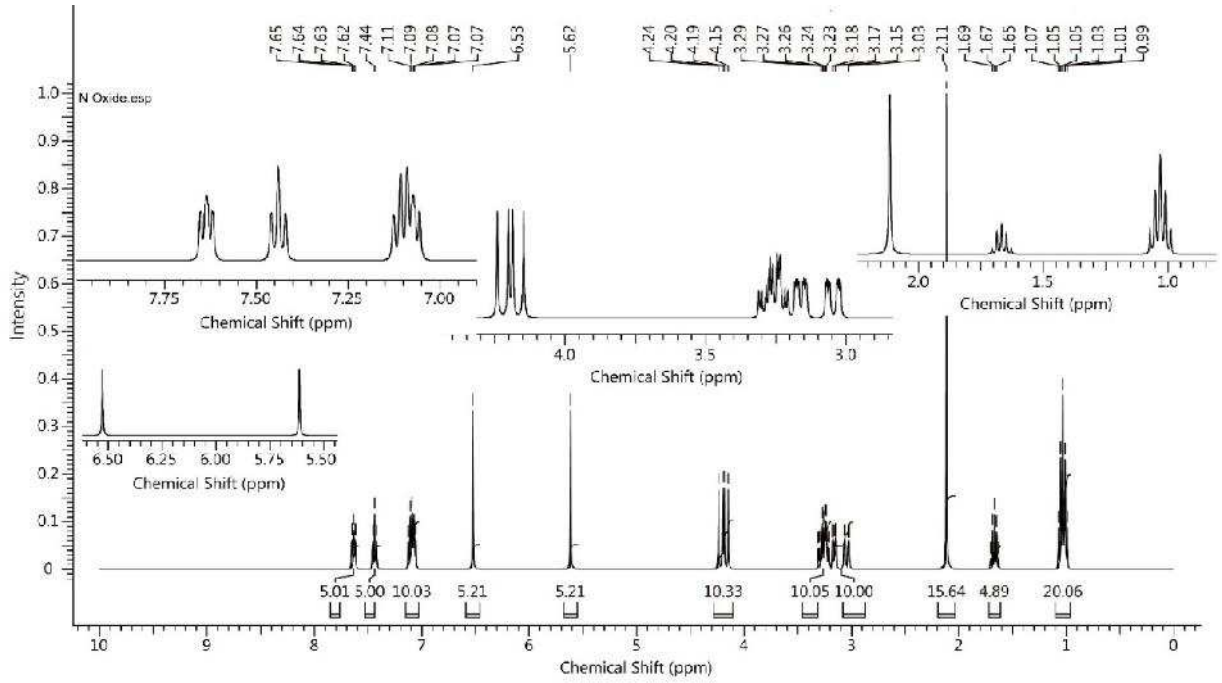


Fig. 12: ^{1}H NMR spectrum of compound III

As shown in (Fig. 11) and (table 6), the main functional groups of compound III appeared clearly; the presence of the aromatic C-H stretch at 3005, 2941, 2897cm^{-1}, the presence of C-S-C stretch at 2435cm^{-1} , the presence of ketone groups C=O, C=O at 1757, 1688 cm^{-1}; respectively. ^{1}H NMR of compound III (400 MHz, Chloroform-d) is shown in (Fig. 12).

Table (5): The Mass fragment of compound III

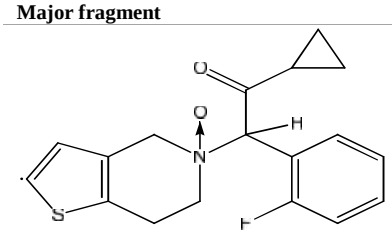
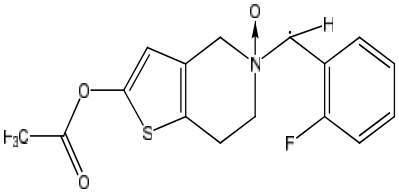
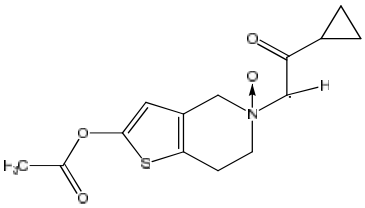
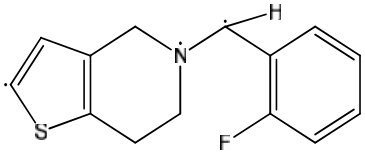
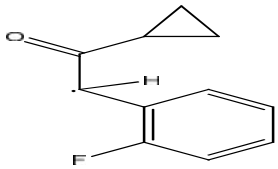
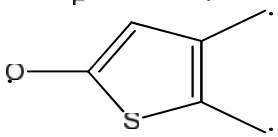
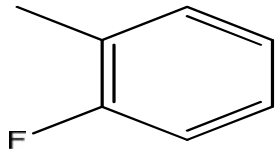
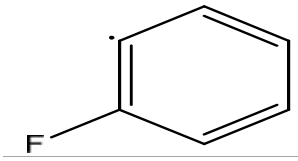
Major fragment	*m/z*
	331/333
	320/321
	294/295
	245/246
	177/178
	125/126
	110/111
	95/96

Table 6: Bands and assignments of compound III

Frequency cm^{-1}	Assignment
3439	-COO- (ester)
3005, 2941, 2897	C-H stretch (aromatic)
2435, 2362	C-S-C stretch
1757, 1688	C=O, C=O

Table 7: ^{1}H NMR Chemical shift assignment for compound III

Chemical shift (ppm)	Multiplicity	No. of protons	Proton position
0.95 - 1.12	m	4 H	26, 27
1.67	quin, *J*=7.80 Hz	1 H	19
2.11	s	3 H	24
2.99 - 3.19	m	2 H	14
3.19 - 3.34	m	2 H	9
4.10 - 4.30	m	2 H	11
5.62	s	1 H	7
6.53	s	1 H	15
6.99 - 7.17	m	2 H	4, 5
7.44	t, *J*=7.50 Hz	1 H	6
7.55 - 7.70	m	1 H	3

On the basis of these data it was concluded that the compound III was 2-acetoxy-5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine 5-oxide, (Fig. 9). The MS, IR, and ^{1}H NMR spectra of compound IV were recorded. The major Mass fragments for compound IV is given in (table 8).

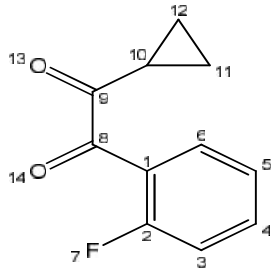


Fig. 13: Structure of compound IV (1-cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione)

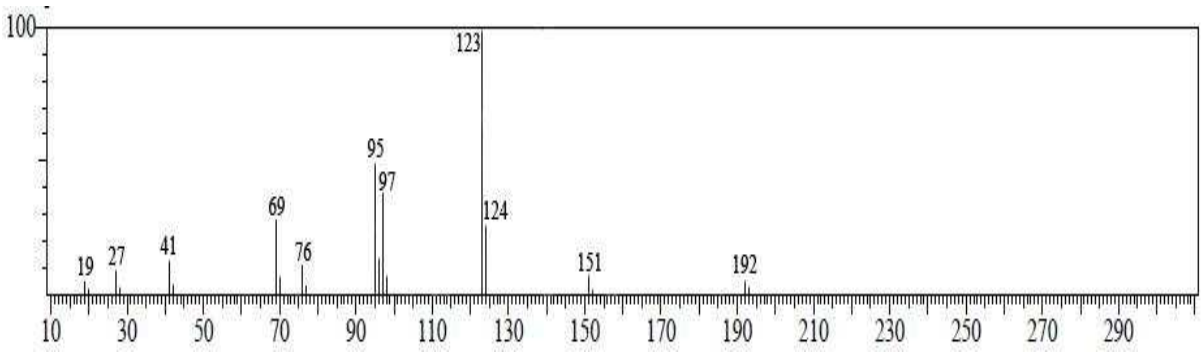


Fig. 14: Mass spectrum of compound IV

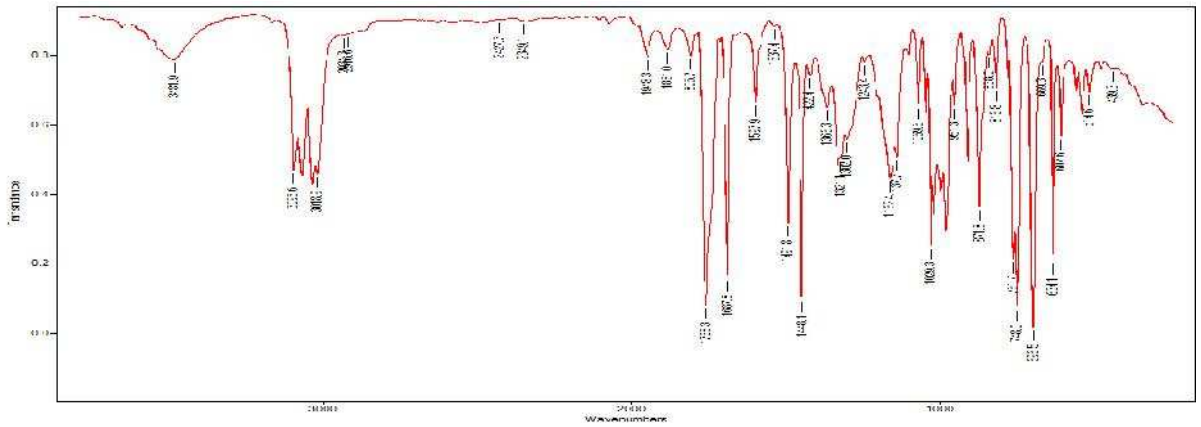
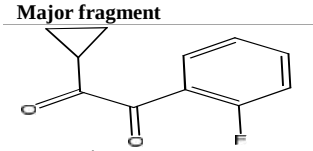
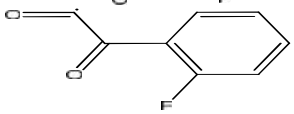
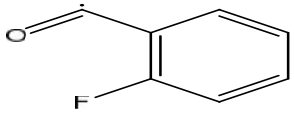
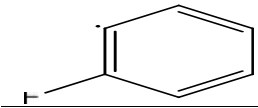


Fig. 15: IR spectrum of compound IV

GC/MS analysis of compound IV revealed a molecular ion peak at *m/z*: 192/193 corresponding to the molecular weight of the suggested compound, and the main fragment was 123/124 which is 2-fluorobenzaldehyde. The fragmentation pattern which is shown in (table 8) also confirmed the structure given in (Fig. 13).

Table 8: The Mass fragment of compound IV

Major fragment	*m/z*
	192/193
	151/152
	123/124
	95/97

IR spectrum and bands and assignments of compound IV are also shown in (Fig. 15) and (table 9); respectively.

Table 9: Bands and assignments of compound IV

Frequency cm^{-1}	Assignment
3095, 3018	C-H stretch (aromatic)
1758, 1687	C=O, C=O di-ketone
1448,1491	C–C stretch (in–ring) aromatics
748, 696, 634	C-H bend

As shown in (Fig. 15) and (table 9), the main functional groups of compound IV appeared clearly; the presence of aromatic C-H stretch 3095 and 3018 cm^{-1}, the presence of di-ketone at 1758 and 1687 cm^{-1} respectively . ^{1}H NMR of compound IV (400 MHz, Chloroform-d) is shown in (Fig. 16).

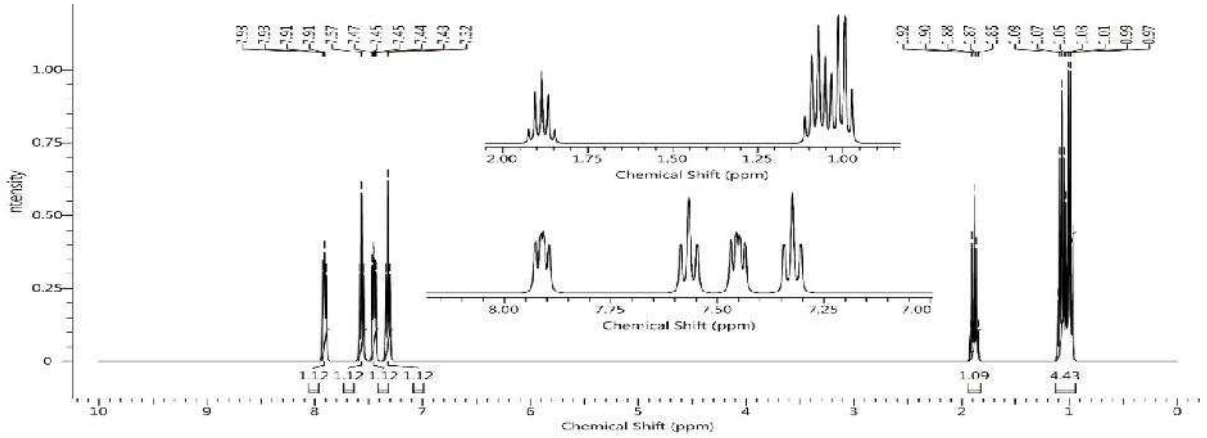


Fig. 16: ^{1}H NMR spectrum of compound IV

Table 10: ^{1}H NMR Chemical shift assignment for compound IV

Chemical shift (ppm)	Multiplicity	No. of protons	Proton position
0.93 - 1.14	m	4 H	11, 12
1.88	quin, *J*=7.75 Hz	1 H	10
7.26 - 7.38	m	1 H	5
7.39 - 7.50	m	1 H	6
7.51 - 7.62	m	1 H	4
7.91	td, *J*=6.50, 1.00 Hz	1 H	3

On the basis of these data it was concluded that compound IV: 1-cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione (Fig. 13). The MS, IR, and NMR spectra of compound V were recorded. The major Mass fragments for compound IV is given in (table 11).

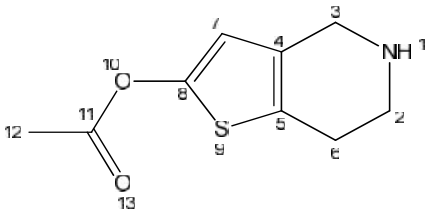


Fig. 17: Structure of compound V (4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate)

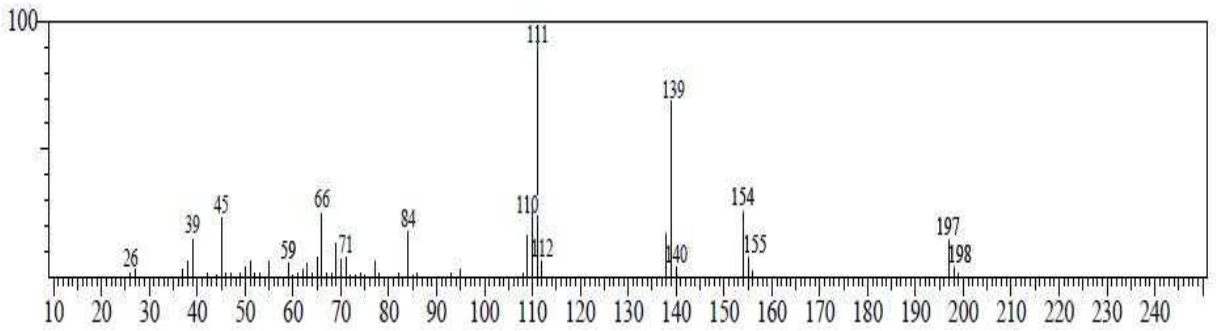
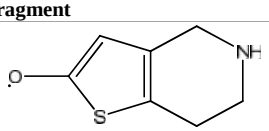
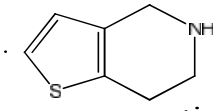
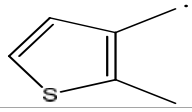


Fig. 18: Mass spectrum of compound V

GC/MS analysis of compound IV revealed a molecular ion peak at *m/z*: 197/198 corresponding to the molecular weight of the suggested compound, and the main fragment was 111/112 which correspond to 2,3-dimethylthiophene. The fragmentation pattern which is shown in (table 11) also confirmed the structure given in (Fig. 17).

Table (11): The Mass fragment of compound V

Major fragment	*m/z*
	154/155
	139/140
	111/112

IR spectrum and bands and assignments of compound V are also shown in (Fig. 19) and (table 12); respectively.

As shown in (Fig. 19) and (table 12), the main functional groups of compound V appeared clearly; the presence of aromatic C-H stretch 3082, 3015 and 2933 cm^{-1}, the presence of C=O at 1703 cm^{-1}. ^{1}H NMR of compound V (400 MHz, Chloroform-d) is shown in (Fig. 20).

Table 13: ^{1}H NMR Chemical shift assignment for compound V

Chemical shift (ppm)	Multiplicity	No. of protons	Proton position
2.10	s	3 H	12
2.65 - 2.85	m	2 H	6
2.86 - 3.01	m	2 H	2
3.42	dd, J=13.40, 4.60 Hz	2 H	3
6.81	s	1 H	7

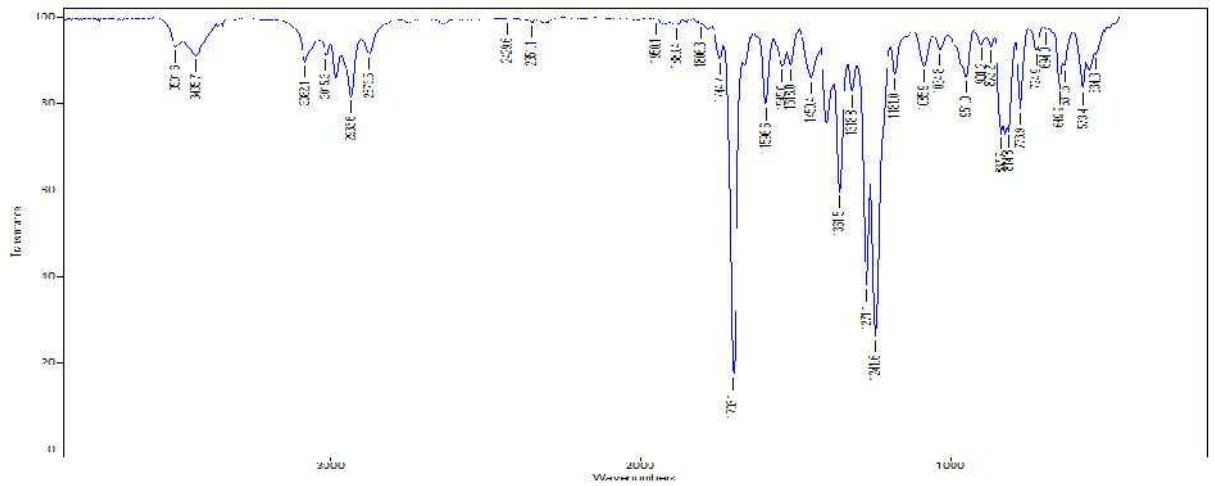


Fig. 19: IR spectrum of compound V

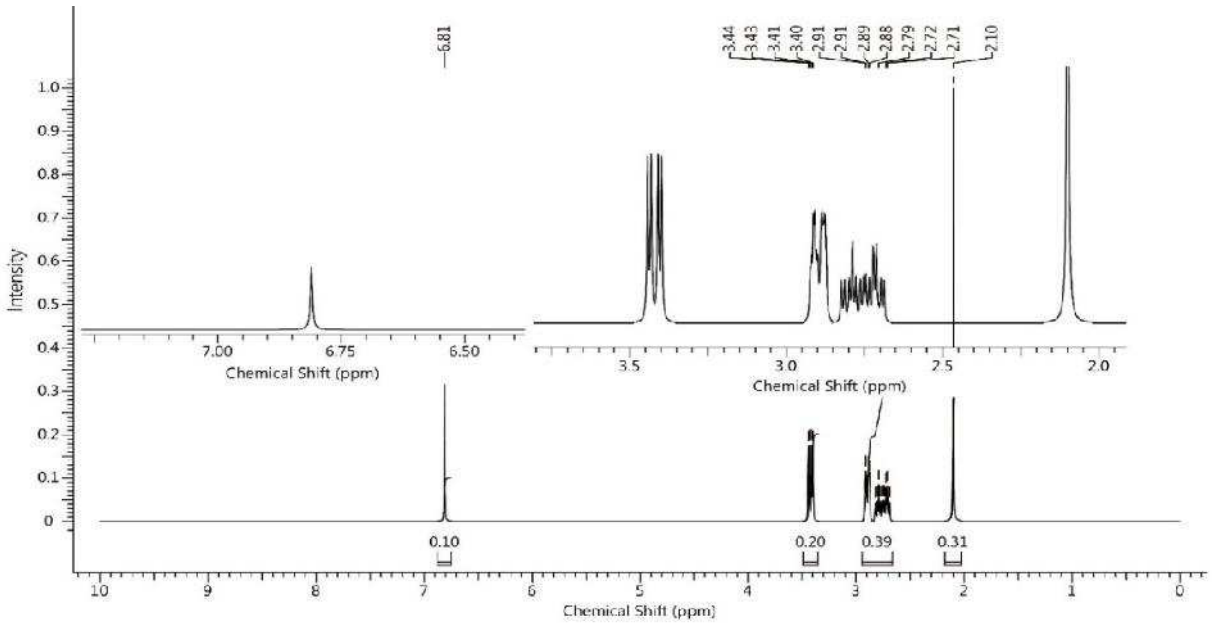


Fig. 20: ^{1}H NMR spectrum of compound V

On the basis of these data it was concluded that compound V was 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate (Fig. 17).

CONCLUSIONS:

The hydrolytic and oxidative degradation products of Prasugrel hydrochloride were isolated by preparative TLC and characterized using spectroscopic techniques namely GC/MS, IR and ^{1}H NMR. The degradation products were identified as 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2(3H)-one and 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4H)-one in acidic and basic media, 2-acetoxy-5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine 5-oxide, 1-cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione and 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate in oxidative medium.

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CONFLICT OF INTEREST:

There is no conflict of interest to declare.

LIST OF ABBREVIATIONS:

GC/MS: Gas Chromatography/Mass Spectrometry
FTIR: Fourier transforms infrared spectroscopy
NMR: Nuclear magnetic resonance
ICH: International Conference on Harmonization

TLC: Thin Layer Chromatography
HPTLC: High Performance Thin Layer Chromatography
ADP: Adenosine Diphosphate
ACS: Acute Coronary Syndrome
LC/MS: Liquid Chromatography/ Mass Spectrometry
RP-HPLC: Reversed Phase High Performance Liquid Chromatography
EI: Electron Impact

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