Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2020, 9 (4): 575-588

(International Peer Reviewed Journal)

Degradation Study of Valsartan: Isolation and Structural Elucidation of Novel Degradants

K.V.K. Mohan.P[1,2], S.S.K. Chakravarthy Kotha[1], Raju Doddipalla[1], Vijay Bommuluri[1], Chidananda Swamy Rumalla[1]*, Raghu Babu Korupolu[2], Deviprasad Rendedula[1] and Muralidharan Kaliyaperumal[1]

1. Department of Medicinal Chemistry, GVK Biosciences Pvt. Ltd, IDA Nacharam, Hyderabad-500076, Telangana, **INDIA**
2. Department of Engineering Chemistry, Andhra University, Visakhapatnam-530003, A.P., **INDIA**

Email: rchidanandaswamy@gmail.com, pulletikurthikrishnamohan@gmail.com

Accepted on 1st June, 2020

ABSTRACT

To describe the stability of Valsartan under stress conditions and to identify the degradation products. Valsartan was subjected to hydrolytic, oxidative, thermal and photolytic stress conditions as per ICH guidelines. The drug showed degradation only in peroxide condition, while it was stable to other stress conditions. Two degradation products (DP) were formed, identification of the DP's was performed by using mass spectrometry coupled to ultra-performance liquid chromatography (UPLC-MS) and were separated on a C18 column by using Autopurification mass spectrometer (APMS) system by using gradient elution. The structures were established by 1D and 2D NMR spectroscopic studies and HRMS. The products were identified as N-((2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamide (DP-1), N-pentanoyl-N-(tetrazolo[1,5-f]phenanthridin-6-ylmethyl)-L-valine (DP-2). Both the degradants are novel.

High Lights:

- Valsartan was subjected to force degradation under acidic, basic, oxidative, photolytic and thermal conditions as per ICH guidelines.
- In Acid and base degradation no degradants were formed.
- In Oxidative degradation two degradant products were formed.

Keywords: Valsartan, degradation products, HRMS, ^{1}H NMR, ^{13}C NMR, gCOSY, ^{1}H-^{13}C gHSQC, ^{1}H-^{13}C gHMBC, ^{1}H-^{15}N gHSQC and ^{1}H-^{15}N gHMBC.

INTRODUCTION

Valsartan is a white fine powder. Its chemical formula is $C_{24}H_{29}N_5O_3$, its exact mass is 435.22. It is soluble in Acetonitrile and water. Valsartan sold under the trade name Diovan. Valsartan is used to treat high blood pressure, heart failure, and diabetic kidney disease [**1**], it is taking orally. Valsartan is available as a combination of drugs like valsartan/amlodipine, valsartan/hydrochlorothiazide, valsartan/amlodipine/hydrochlorothiazide or valsartan/sacubitril [**1-4**]. Valsartan was patented in the year 1990, and came into medical use in 1996 [**5**] and is available as a generic medication [**6**]. In

2016, valsartan was the 92nd most prescribed medication in the United States, with more than eight million prescriptions [7, 8]. Valsartan is used to treat high blood pressure, heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack [9, 10]. It also states the drug should not be used in people with kidney disease [10]. Valsartan is used to slow the worsening and the development of end-stage kidney disease [11]. Valsartan falls in Food and Drug Administration (FDA) pregnancy category D and includes a black box warning for fetal toxicity [10, 12]. Use in pregnancy may harm the baby and use when breastfeeding is not recommended [12]. The U.S. labeling makes no recommendation regarding continuation or discontinuation of valsartan for breast-feeding mothers [11]. The Canadian labeling does not recommend use by nursing women [13]. It is an angiotensin II receptor antagonist and works by blocking the effects of angiotensin II [1] which include constricting blood vessels and activating aldosterone, to reduce blood pressure [14]. Every drug has to meet the stability guidelines of International Council for Harmonization (ICH) and other regulatory authorities for structural conformation of degradation products (DPs) [15-17]. Common side effects include feeling tired, dizziness, high blood potassium, diarrhea, and joint pain. Other serious side effects may include kidney problems, low blood pressure, and angioedema.

MATERIALS AND METHODS

Chemicals and reagents: Valsartan drug substance was a kind gift sample from a manufacturing unit in Hyderabad. Solvents and buffers used for analysis were HPLC grade Acetonitrile (Merck), Formic acid (Merck), Dimethyl sulfoxide-d_6 containing 0.03% (v/v) TMS (Cambridge isotope limited), Sodium Hydroxide (Rankem), Hydrochloric Acid (Finar), Hydrogen Peroxide (Finar) and water used was Milli-Q grade.

Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS): Waters Acquity UPLC with single quadrupole mass spectrometer (SQD2) was used. Column used was Acquity BEH C18, 2.1mm × 50 mm, 1.7µ; Mobile phase A: 0.1% formic acid (Aq); Mobile phase B: Acetonitrile; T/% of B: 0.0/3, 0.4/3, 2.5/98, 3.4/98, 3.5/3, 4.0/3; Diluent: Acetonitrile, water (50:50); Column Temp: 35°C. Masslynx 4.1 software controlled the whole system.

Auto purification mass spectrometer (APMS): Auto purification mass spectrometer is a combination of water Binary gradient pump 2545, Waters PDA detector module 2996, and Sample manager 2767 with open bed fraction collector. Column: XBridge-C18 (250 X 19mm) 5µ, mobile phase A: 10mM Ammonium Bicarbonate (Aq); mobile phase B: Acetonitrile: T% of B: 0.0/25, 1.0/25, 11.0/40, 11.1/100, 13.0/100, 13.1/25, 15.0/25. Sample prepared in Acetonitrile.

Nuclear Magnetic Resonance spectroscopy: NMR analysis of API, oxidative degradation products of Valsartan was taken on Agilent MR400MHz NMR instrument equipped with 5mm ONE NMR probe with Z- gradient shim system which has the sensitivities of 480:1 and 225:1 for 1H and 13C nuclei respectively and also equipped with auto sampler with 100 samples hold capacity. All the NMR analysis has been performed at 298K probe temperature with fine automatic tuning and matching for the frequency of respective nuclei. The ^{1}H and ^{13}C chemical shifts are reported on δ scale in ppm, relative to tetra methyl silane (TMS) as internal standard. The spectra were set to δ 0.00 ppm in ^{1}H NMR (TMS) and δ 39.50 ppm in ^{13}C NMR (DMSO-d_6).

Key parameters used for NMR analysis:

One dimensional (1D) analysis: 1H NMR data acquired and processed with following parameters like spectral width (SW) =17.95 ppm, relaxation delay time (D1) =1 sec, number of scans (NT) =16, number of data points (NP) =64k, 90° pulse width (PW90) =7.4µ sec, acquisition time (AT) =4.0 sec, operating spectrometer frequency (SF) =399.63MHz and line broadening (LB) =0.5Hz. 13C NMR data acquired and processed with following parameters like spectral width (SW) =248.8 ppm, relaxation delay (D1) =3sec, number of scans (NT) =4000, data points (NP) =64k, 90° pulse width

(PW90) =7.6µsec, acquisition time (AT) =1.31sec line broadening (LB) =2.0Hz spectrometer frequency (SF) =100.48MHz parameters.

Two-dimensional (2D) analysis: homonuclear ^{1}H-^{1}H gDQCOSY experiment has been performed to know the proton-proton correlations with following parameters (SW) =18.00 ppm in both F1 & F2 projections, relaxation delay time (D1) =1sec, number of scans (NT) =16, number of data points (NP) =1078(F2) & 400(F1), dummy scans (SS) =32. 1H-13C gHSQC was done to know the ^{1}Jcorrelations between proton-carbon with (SW) =18.00 ppm (F1) and (SW1) = 240.0 ppm (F2), relaxation delay time (D1) =1sec, number of scans (NT) =16, number of data points (NP) =1078(F2) & 400(F1), dummy scans (SS) =32 And gHMBC has been performed to reveal the exact structure of degradation product(s) with (SW) =18.00 ppm (F1) and (SW1) = 240.0 ppm (F2), relaxation delay time (D1) =1sec, number of scans (NT) =16, number of data points (NP) =1078(F2) & 400(F1), dummy scans (SS) =32 parameters.

For the complete NMR analysis 10 mg of sample has been dissolved in Deuterated DMSO-D6 (Cambridge Isotope Laboratories, Inc.; D, 99.9% + 0.03% V/V TMS as internal reference standard) solvent.

High Resolution Mass Spectrometry (HRMS): Samples were analysed on Thermo Q Exactive orbitrap MS with ESI ion source; instrument parameters: Spray Voltage: 3500 V; Aux gas heater Temperature: 440°C; Capillary Temperature: 270°C. Sheath gas flow rate: 53; Aux gas flow rate: 14; Sweep gas flow rate: 3. Reserpine (monoisotopic mass: 608.2734 Da) was used to check the accuracy of the Mass system. Dionex ultimate 3000 LC was controlled by Chromeleon software, Mass data was acquired by using Xcalibur software.

Degradation Behaviour of Valsartan: No degradation products were found in Acidic, Basic, thermal and photolytic conditions for Valsartan API. The drug was found to be labile to hydrogen peroxide a total of 17% degradation was found DP-1 with 13.36% and DP-2 with 4.23% respectively. Degradation details were shown in table 1. Acid, base, oxidative, thermal and photolytic degradation chromatograms were shown in figure 1.

Table 1. Valsartan force degradation studies

S. No.	Conditions	DP-1	DP-2	`API
1	Valsartan API	--	--	99.86%
2	Acid (0.1N HCl)	--	--	99.82%
3	Base (0.1N NaOH)	--	--	99.92%
4	Oxidation (5% H_2O_2)	13.36%	4.23%	82.41%
5	Thermal (120°C for 48 h)	--	--	99.76%
6	Photolytic (285nm for 48 h)	--	--	99.96%

RESULTS AND DISCUSSION

The degradants were formed after 24h of heating at 60°C. The resultant oxidative degradation solution was diluted with acetonitrile, water and taken for LCMS analysis. Two degradants were formed. In acid and base conditions no degradation were observed. The solution was neutralized with sodium thiosulfate further diluted with acetonitrile, water and taken for purification.

Isolation of oxidative degradation products: Both the degradation products formed in oxidative degradation were isolated as per the procedure Auto Purification Mass spectrometer (APMS). Two fraction peaks were pooled separately, freezed and lyophilized. By using HRMS, 1D, 2D NMR the structure of the degradation products were elucidated. Both the degradants were found to be novel. All the three structures Valsartan, and degradation products has been given in the figure 2, the degradation products are labelled as DP-1, DP-2.

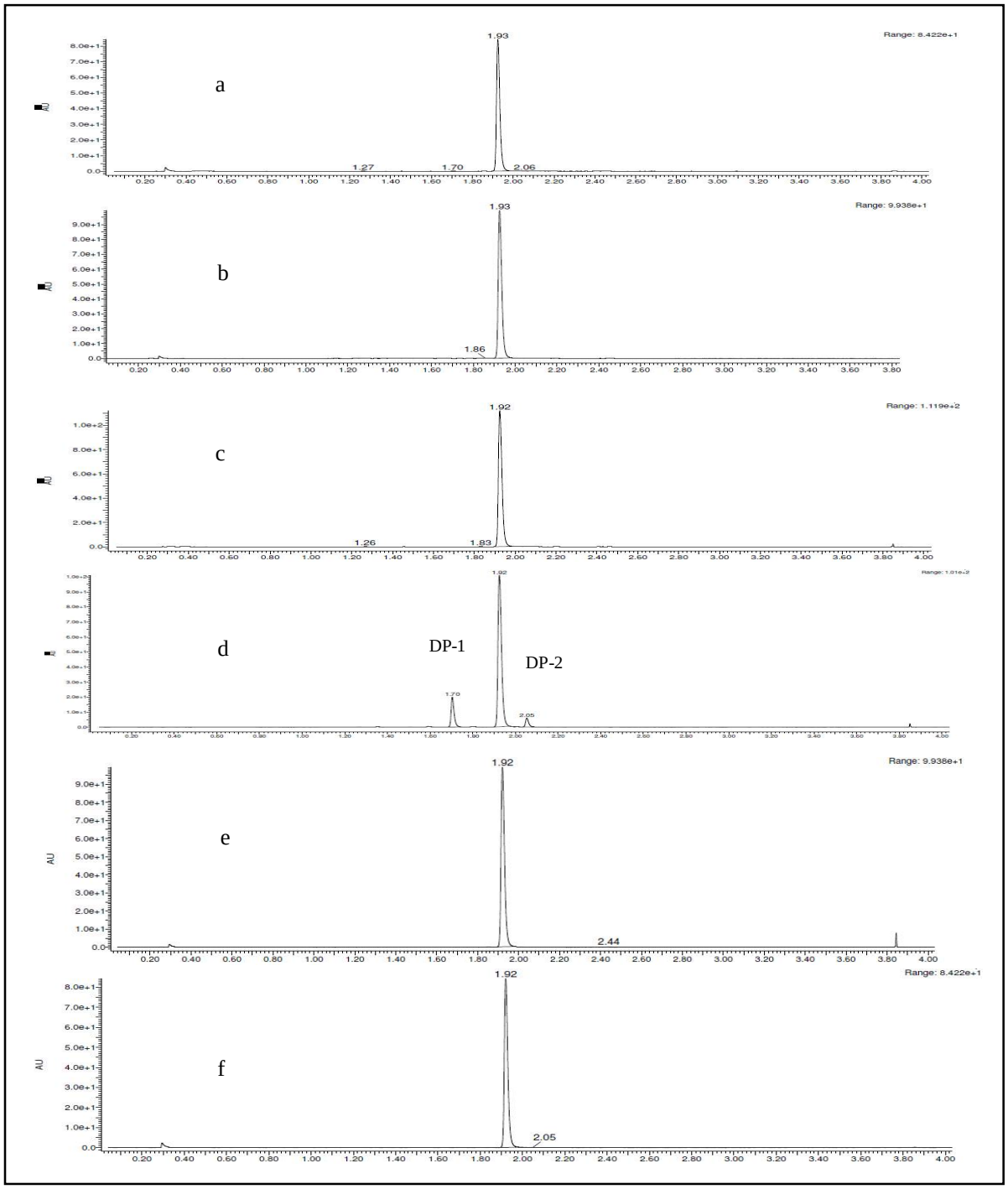


Figure 1. LCMS chromatograms of Valsartan and Valsartan degradant products (a) Valsartan (API), (b) Acid degradation, (c) Alkaline degradation, (d) Oxidative degradation, (e) Thermal degradation and (f) Photolytic degradation.

Structure elucidation of Valsartan: The HRMS of Valsartan showed a protonated molecular ion peak at *m/z* 436.2346 $[M+H]^+$ corresponding to molecular formula $C_{24}H_{30}N_5O_3$ as shown in figure.4(a). Proton NMR spectrum of API has been showed 8 aromatic protons at 6.96 to 7.6 7 ppm and 19 aliphatic protons at 0.69 to 4.62 ppm. API compound protons and carbons has shown splitting at room temperature and got merged into single set of signals at higher temperature, this is due to the presence of tertiary amide near to chiral center and formed rotamers. In addition to this two labile protons, i.e tetrazole ring -NH and carboxylic acid protons were under gone chemical exchange with

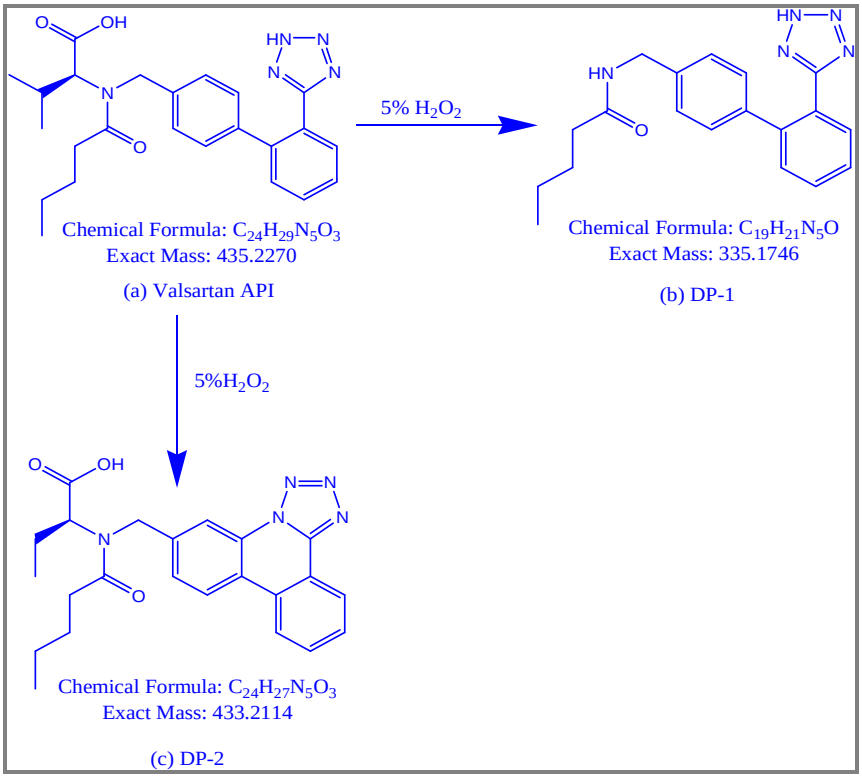
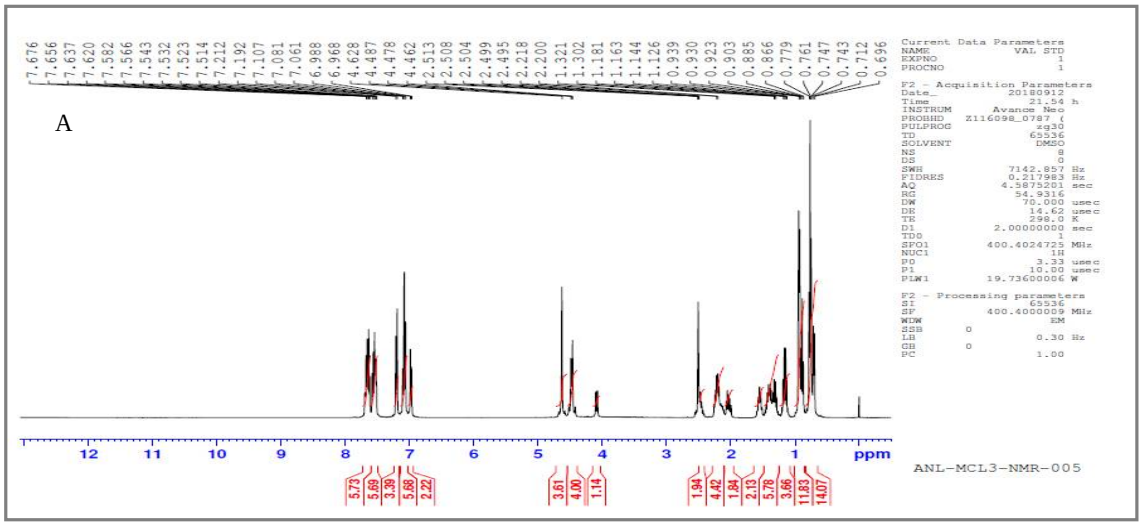


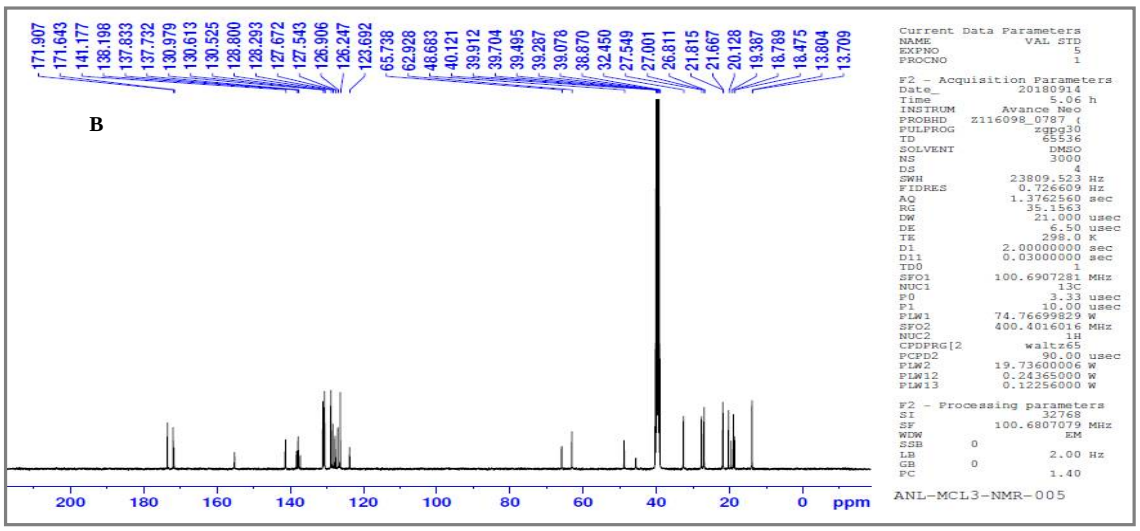
Figure 2. (a) Valsartan API, (b) DP-1, (c) DP-2.

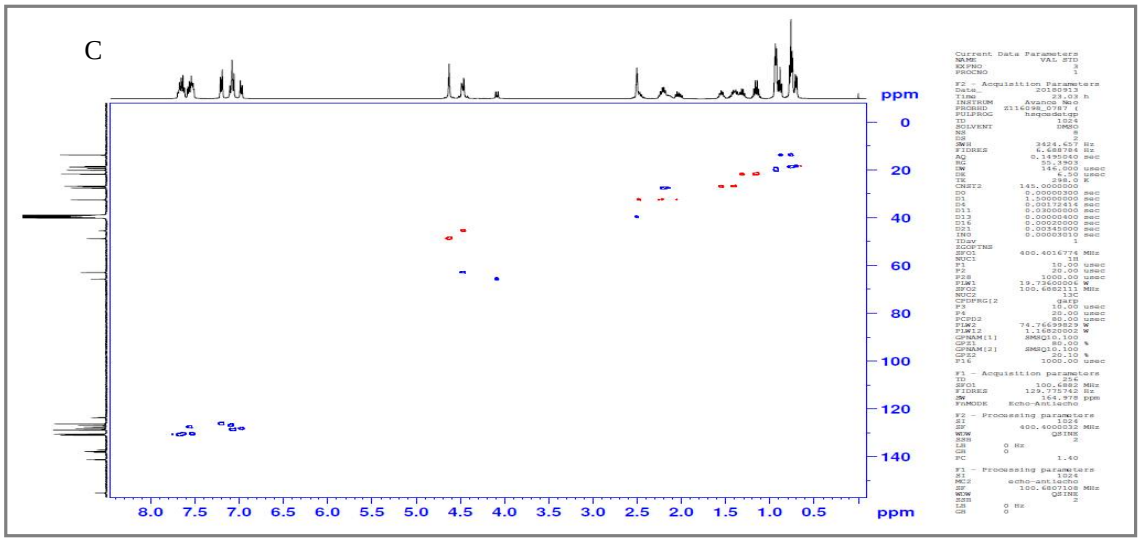
Table 2. Valsartan assignments of ^{1}H and ^{13}C NMR signals

Atom No	Type of Atom	1H Chemical Shift (PPM) Coupling Const(J)	13C Chemical Shift (PPM)
1	C	-	137.83 and 138.19
2,6	CH	7.1 and 7.19(d, 8.0Hz, 2H)	126.24 and 126.90
3,5	CH	6.96 and 7.06(d, 8.0Hz, 2H)	128.29 and 128.80
4	C	-	137.16 and 137.73
7	C	-	141.31 and 141.17
8	CH	7.52(m, 1H)	130.52
9	CH	7.68(m, 1H)	130.97
10	CH	7.56(m, 1H)	127.57 and 127.67
11	CH	7.62(m, 1H)	130.61
12	C	-	123.56 and 123.69
13	C	-	155.13
14	N	-	-
15	N	-	-
16	N	-	-
17	N	-	-
18	CH_2	4.47 and 4.62(m, 2H)	45.44 and 48.68)
19	N	-	-
20	C	-	173.46
21	O	-	-
22	CH2	2.05,2.21 and 2.49 (m, 2H)	32.45
23	CH2	1.41 and 1.55 (m, 2H)	26.81 and 27.00
24	CH2	1.14 and 1.30 (m, 2H)	21.66 and 21.81
25	CH3	0.76 and 0.88 (t, 7.6Hz, 3H)	13.7 and 13.8
26	CH	4.07 and 4.46(d, 10.4Hz, 1H)	62.92 and 65.73
27	CH	2.18 (m, 1H)	27.54
28	C	-	171.64 and 171.90
29	O	-	-
30	OH	not observed	-
31,32	CH_3	0.69, 0.74 and 0.93 (d, 6.4Hz, 6H)	18.47, 18.78, 19.38 and 20.12

moisture of the NMR solvent and is showing broad signal, and also tetrazole -NH exhibiting tautomeric nature in the ring. The assignments of ^{1}H and ^{13}C NMR signals are made and are shown in table 2, 1D NMR and 2D NMR spectra shown in figure 3.







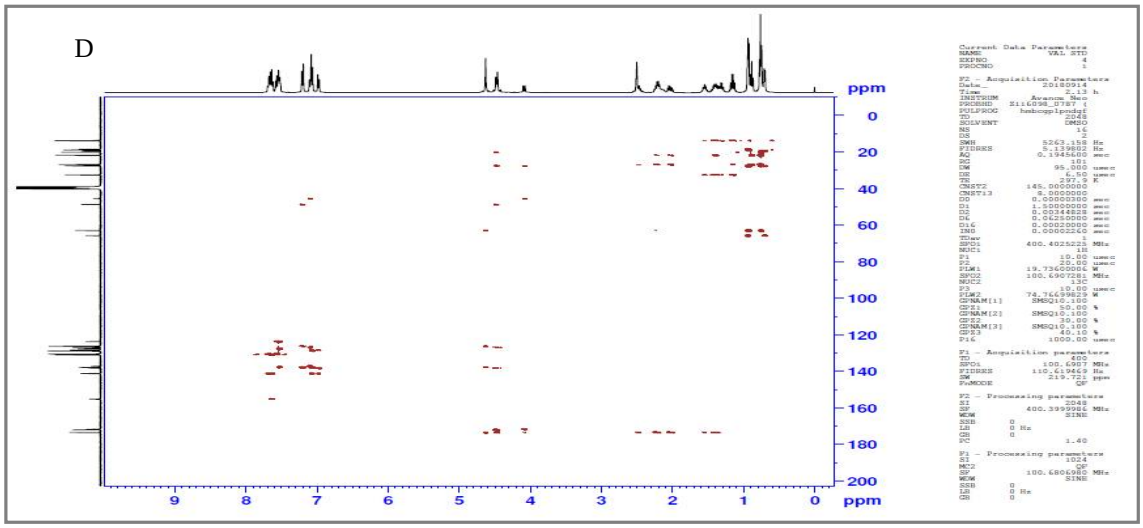


Figure 3. NMR spectrum of Valsartan (A) ^{1}H NMR (B) ^{13}C NMR (C) HSQC (D) ^{1}H-^{13}C HMBC.

Structure elucidation of DP-1: Valsartan on treatment with Hydrogen peroxide, DP-1 has been formed and its preliminary confirmation by LCMS and the HRMS data has showed a protonated molecular ion peak at *m/z* 336.1819 $[M+H]^+$ corresponding to molecular formula $C_{19}H_{22}N_5O$ as shown in figure 4(b). The precise structure of DP-1 was further confirmed by NMR studies and its full characterization details has been given in table 3, the presence of NH proton as triplet in proton NMR at 8.29 ppm confirms the secondary amide. The absence of Isopropyl group and acid peak in proton NMR and also the absence of carboxylic acid group carbon in carbon NMR indicate that the 3-methyl butanoic acid group has been cleaved from parent API (Valsartan). This has been further verified by gradient ^{1}H-^{13}C HMBC data (Figure 6) where the key correlations from –NH triplet and H18 is showing to only one carbon i.e. at 172.11 ppm around carbonyl region, indicates absence of 3-methyl butanoic acid group and presence of valeryl group, this further confirmed by the key correlations form H22 and H23. These important correlations are shown in structure (Figure 5) with arrow marks. Two doublet signal pattern at 7.03 ppm and 7.12 ppm indicates the presence of 1, 4 di-substituted benzene ring. Two doublet signals at 7.45 and 7.56 ppm and two triplet pattern signals at 7.49 and 7.59 ppm confirms the presence of 1, 2 di-substituted benzene ring. All the 1D and 2D data validated for Valsartan DP-1 as shown in figure 7.

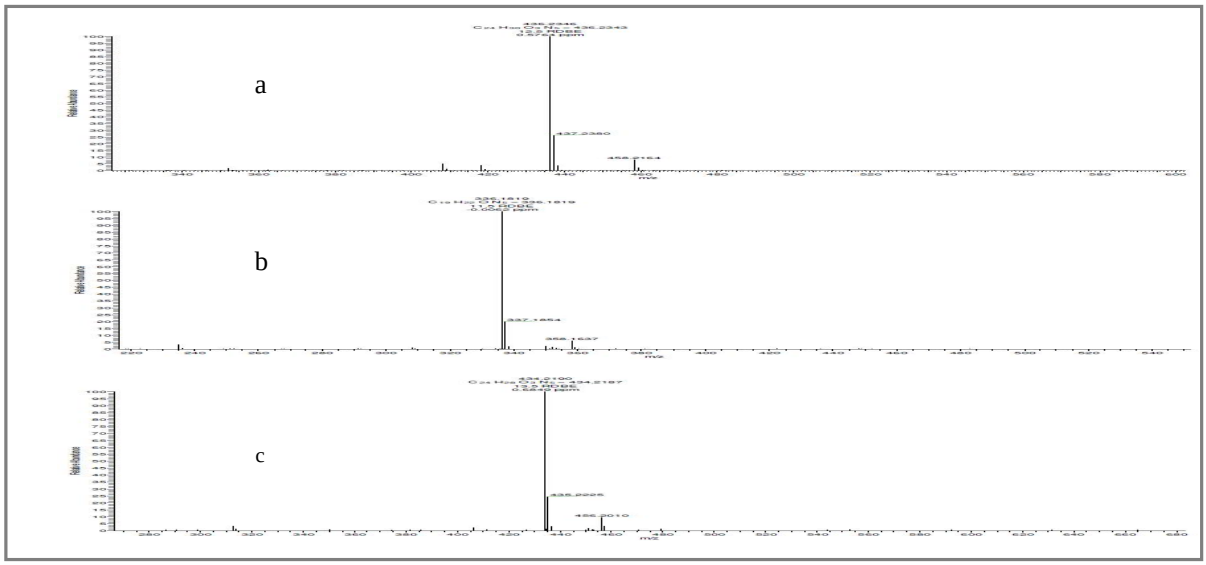


Figure 4. HRMS spectrum of (a) Valsartan, (b) DP-1 (c) DP-2.

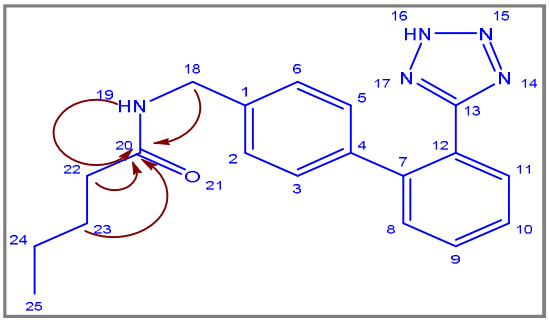


Figure 5. Structure of DP-1, shown with key correlations by arrow marks.

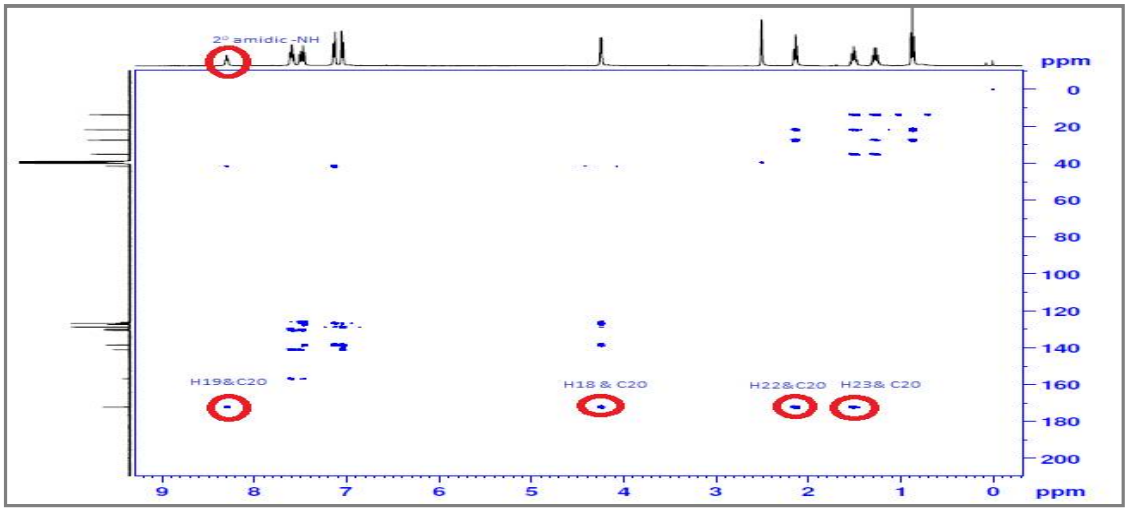
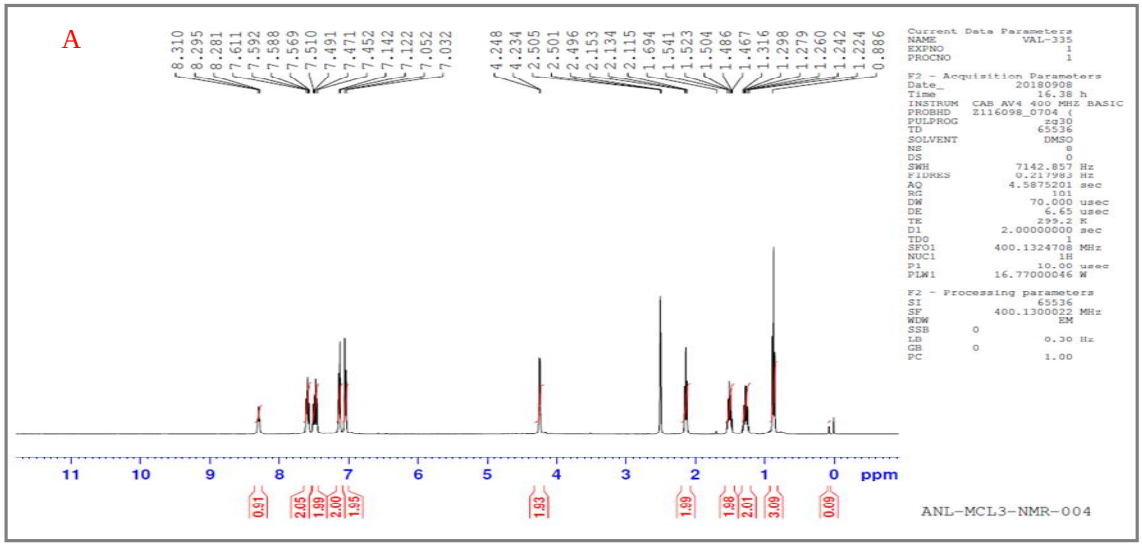
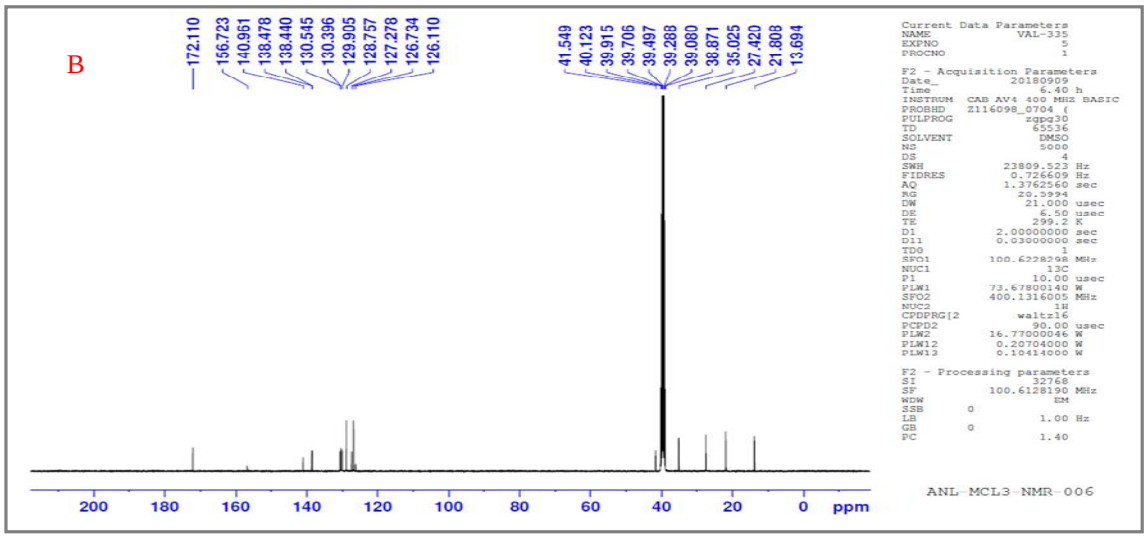


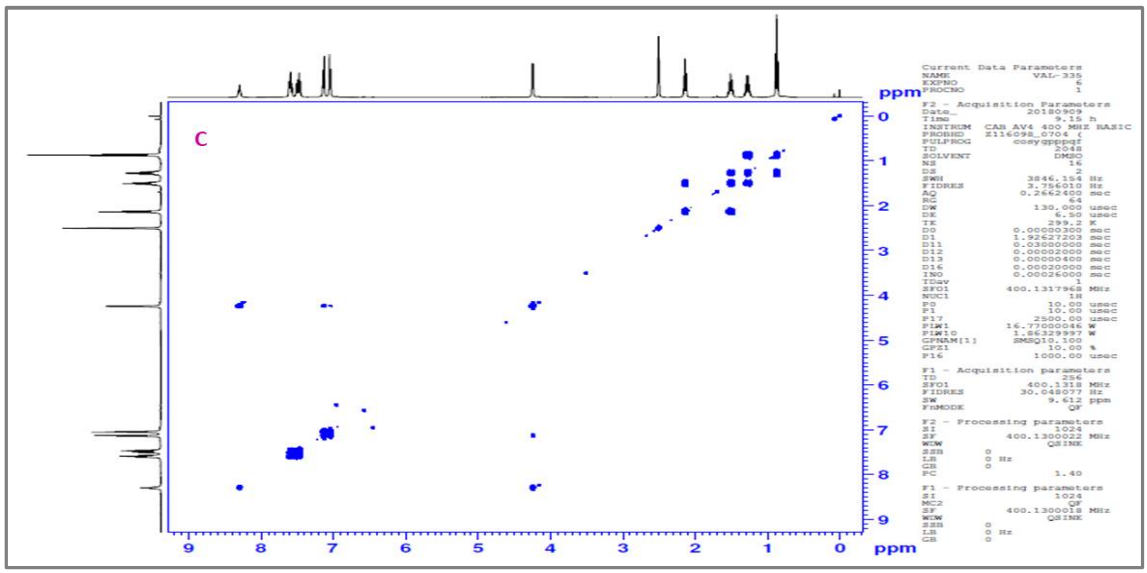
Figure 6. DP-1 NMR correlation spectrum of HMBC.

Table 3. Valsartan DP-1 assignments of ^{1}H and ^{13}C NMR signals

Atom No	Type of Atom	1H Chemical Shift (PPM) Coupling Const(J)	13C Chemical Shift (PPM)
1	C	-	138.47
2,6	CH	7.12(d, 8.Hz, 2H)	126.73
3,5	CH	7.03(d, 8.0Hz, 2H)	128.75
4	C	-	138.44
7	C	-	140.96
8	CH	7.45(d, 7.6Hz, 1H)	130.39
9	CH	7.59(t, 7.6Hz, 1H)	130.54
10	CH	7.49(t, 7.6Hz, 1H)	127.27
11	CH	7.56(d, 7.6Hz, 1H)	129.9
12	C	-	126.11
13	C	-	156.72
14	N	-	-
15	N	-	-
16	N	-	-
17	N	-	-
18	CH2	4.23(d, 5.6Hz, 2H)	41.54
19	NH	8.29(t, 5.6Hz, 1H)	-
20	C	-	172.11
21	O	-	-
22	CH2	2.13(t, 7.6H, 2H)	35.02
23	CH2	1.50(m, 2H)	27.42
24	CH2	1.27(m, 2H)	21.8
25	CH3	0.86(t, 7.2Hz, 3H)	13.69


A
8.310
8.295
8.281
7.611
7.592
7.588
7.569
7.510
7.491
7.471
7.452
7.142
7.122
7.052
7.032
4.248
4.234
2.505
2.501
2.496
2.153
2.134
2.115
1.694
1.541
1.523
1.504
1.486
1.467
1.316
1.298
1.279
1.260
1.242
1.224
0.886
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.51
2.05
1.99
2.00
1.95
1.83
1.99
1.68
2.01
3.09
0.09
ANL-MCL3-NMR-004


B
172.110
156.723
140.961
138.478
138.440
130.545
130.396
129.905
128.757
127.278
126.734
126.110
41.549
40.123
39.915
39.706
39.497
39.288
39.080
38.871
35.025
27.420
21.808
13.694
200 180 160 140 120 100 80 60 40 20 0 ppm
ANL-MCL3-NMR-006


C
ppm
0 1 2 3 4 5 6 7 8 9
9 8 7 6 5 4 3 2 1 0 ppm

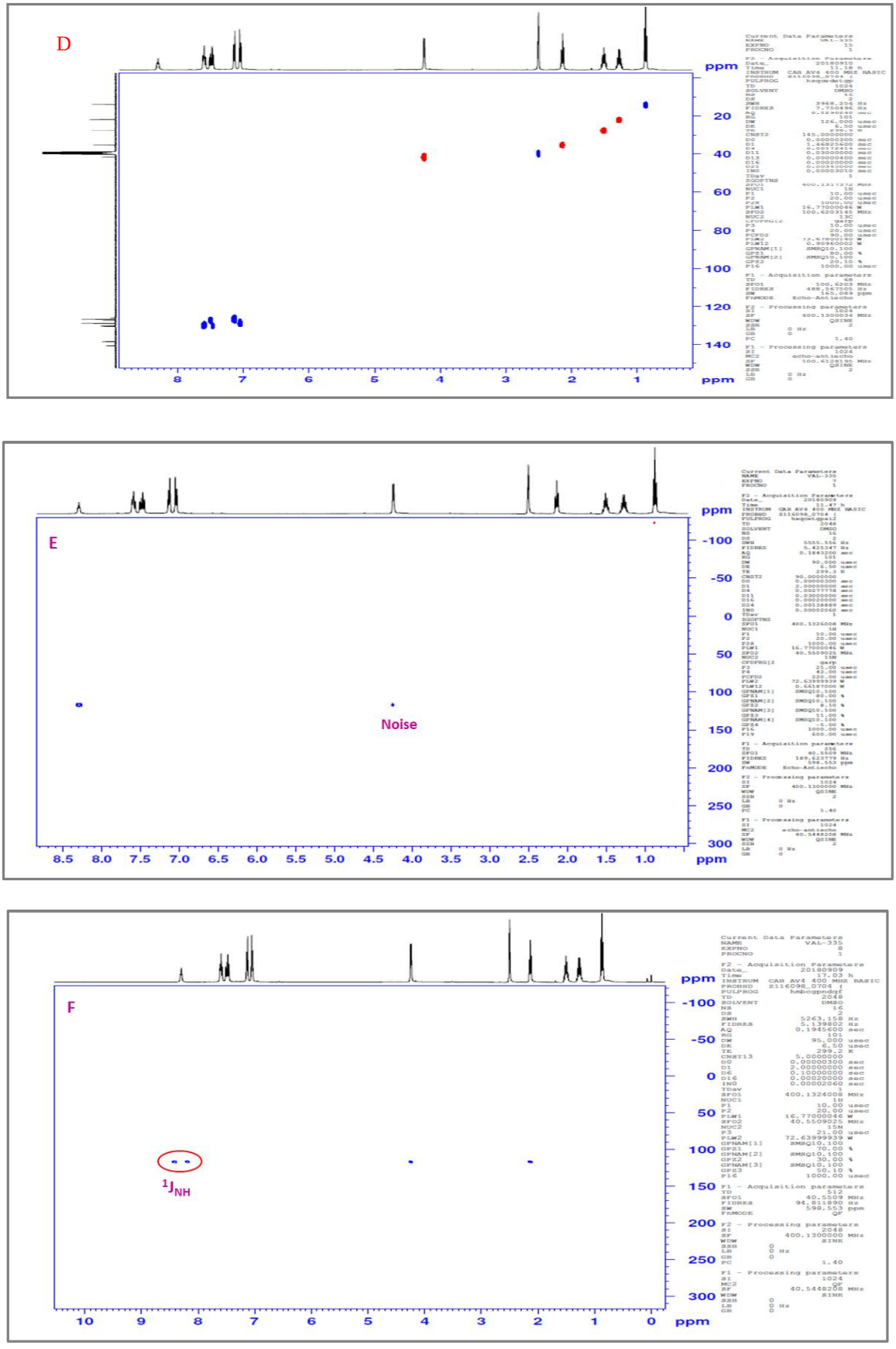


Figure 7. NMR spectra of DP-1 (A) ^{1}H NMR (B) ^{13}C NMR (C) COSY (D) gHSQC (E) ^{15}N gHSQC (F) ^{15}N gHMBC.

Structure elucidation of DP-2: Valsartan on treatment with Hydrogen peroxide, DP-2 has been formed and its preliminary confirmation by LCMS and the HRMS data has showed a protonated molecular ion peak at *m/z* 434.2190 $[M+H]^+$ corresponding to molecular formula $C_{24}H_{28}N_5O_3$ as shown in figure 4(c). The precise structure of DP-2 was further confirmed by NMR studies and its full characterization details have been given in table 4. On comparison of DP-2 data with Valsartan API NMR data it is understood that one of the aromatic proton is showing less in DP-2 and 1, 4 di-substituted benzene ring splitting pattern was not observed in proton as well as carbon NMR data. In the proton NMR, due to rotameric nature of the impurity, all the protons were split in to two sets whereas peaks got merged and was showing as single set of signals at higher temperature 90°C. It is also observed that H6 was showing as singlet. In gradient ^{1}H-^{13}C HMBC data (Figure 8), H18 is showing ^{3}J key correlations with C6, C2, C20, C26 and ^{2}J correlation with C1 shown as arrow marks in the structure. Another key correlation was observed between H2, H6 and H8 protons to C4 carbon (Figure 9). In addition to ^{1}H-^{13}C HMBC data, gradient ^{1}H-^{15}N HMBC data also showed that there is a clear correlation for one of the Nitrogen at 237 from H6 proton. These key points suggesting that the tetrazole ring Nitrogen has involved in cyclisation with adjacent 1,4-di-substituted benzene ring and formed newly six-membered cyclic structure as shown in the DP-2 structure and the assignments of DP-2 chemical shifts are shown in table 4. All the 1D and 2D data validated for Valsartan DP-2 as shown in figure 10.

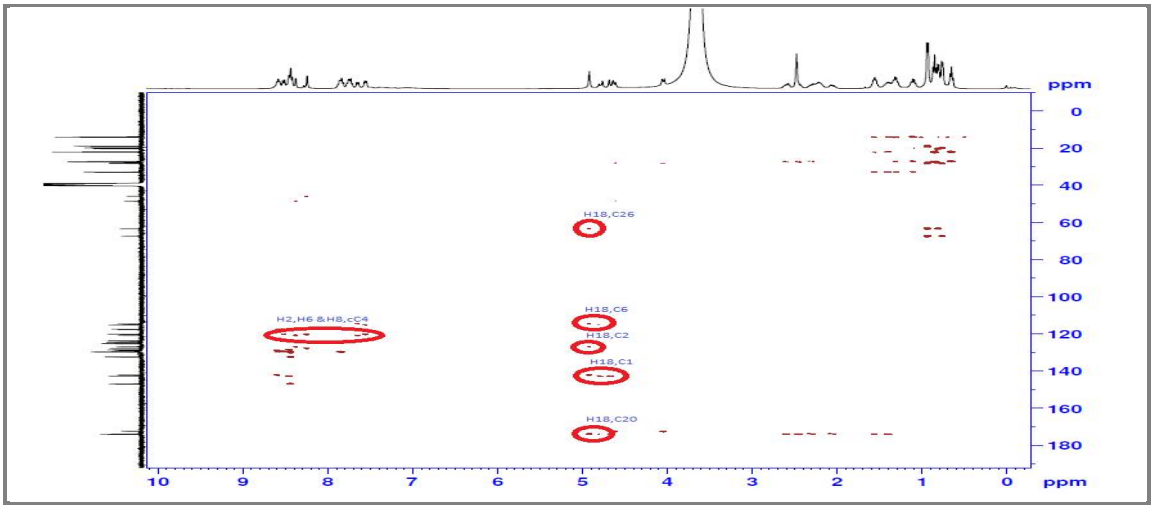


Figure 8. Key correlations shown in the ^{1}H-^{13}C HMBC spectrum of DP-2.

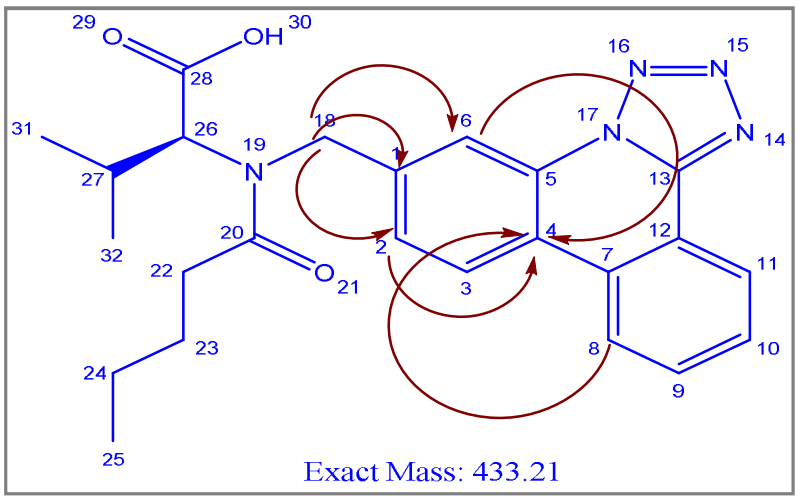
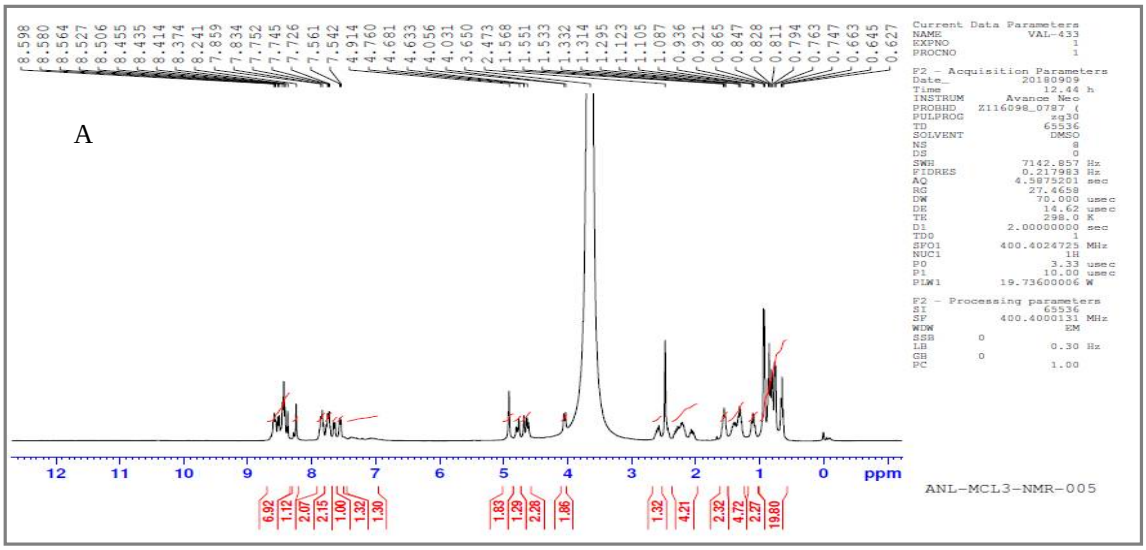
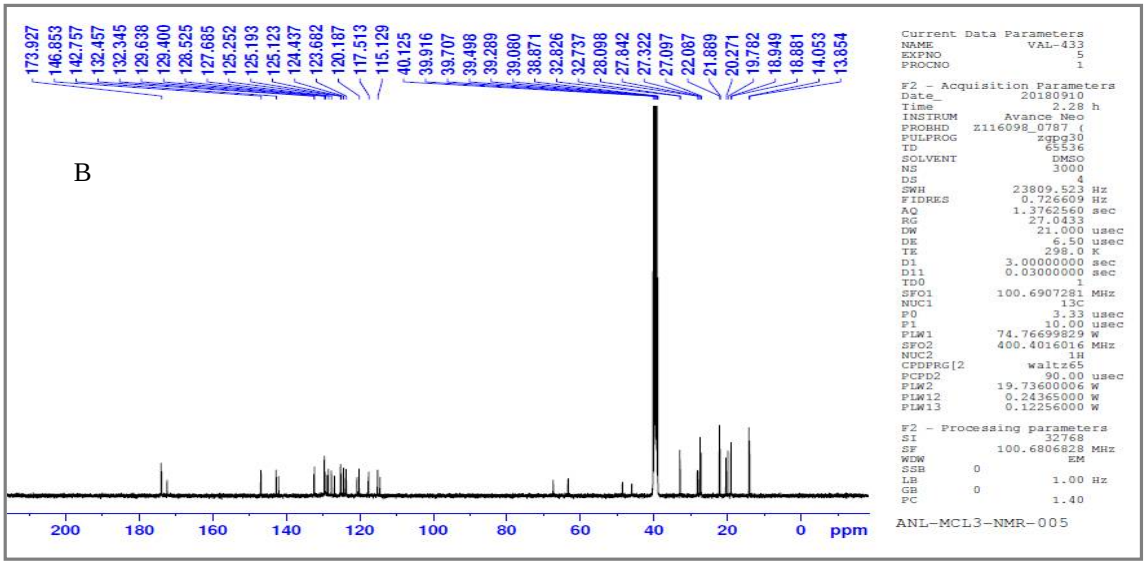
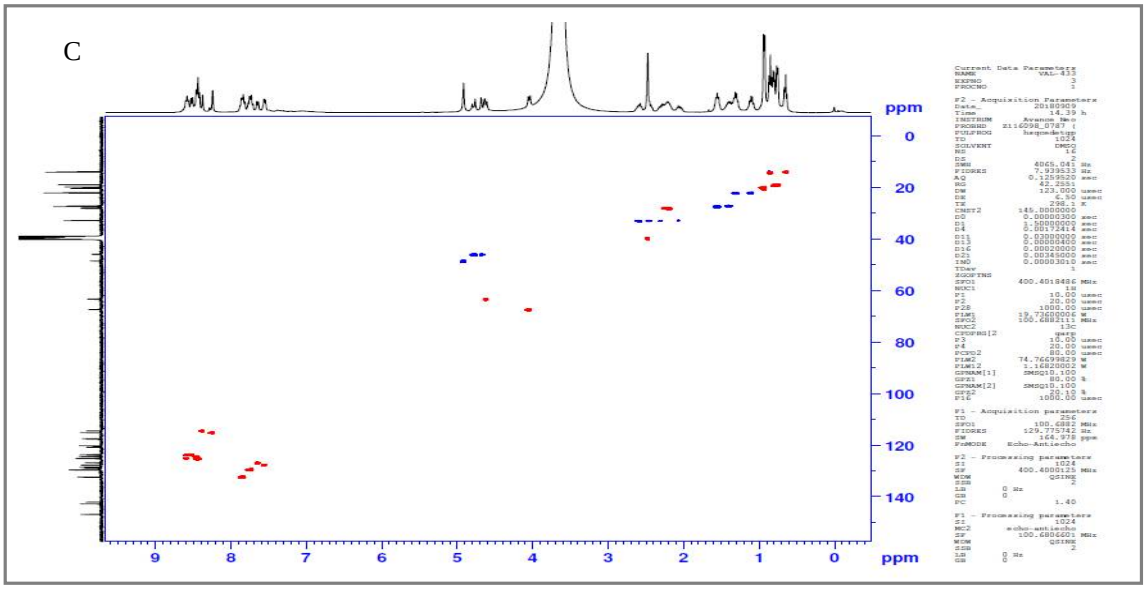


Figure 9. Structure of DP-2, shown with key correlations by arrow marks.


A
ANL-MCL3-NMR-005


B
ANL-MCL3-NMR-005


C

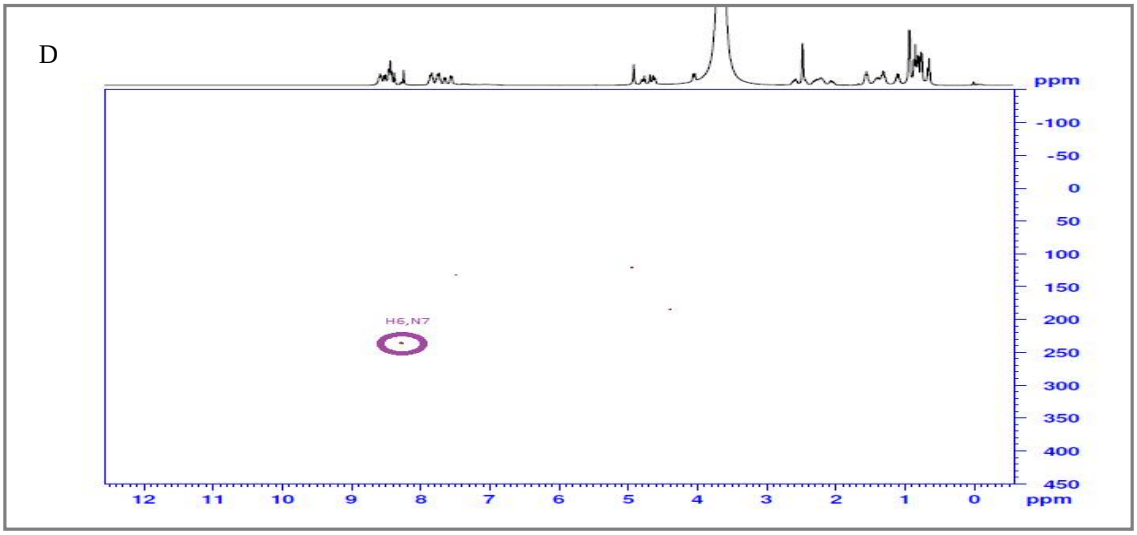


Figure 10. NMR spectra of DP-2 (A) ^{1}H NMR (B) ^{13}C NMR (C) ^{1}H-^{13}C-HSQC (D) ^{15}N HMBC .

Table 4. Valsartan DP-2 assignments of ^{1}H and ^{13}C NMR signals

Atom No	Type of Atom	1H Chemical Shift (PPM) Coupling Const(J)	13 C Chemical Shift (PPM)
1	C	-	142.08 and 142.75
2	CH	7.54 and 7.63(d, 8.4Hz, 1H)	126.84 and 127.68
3	CH	8.45 and 8.58(m, 2H)	124.43 and 125.12
4	C	-	120.18 and 120.75
5	C	-	128.52 and 128.86
6	CH	8.24, 8.37(s, 1H)	114.43 and 115.12
7	C	-	129.63
8	CH	8.52 and 8.58(m, 1H)	123.68 and 123.82
9	CH	7.83(m, 1H)	132.34 and 132.45
10	CH	7.72(m, 1H)	125.19 and 125.25
11	CH	8.43(m, 1H)	125.19 and 125.25
12	C	-	117.51 and 117.65
13	C	-	146.85 and 146.94
14	N	-	-
15	N		-
16	N	-	-
17	N	-	-
18	CH2	4.68, 4.76 and 4.91(m, 2H)	45.90 and 48.48
19	N	-	-
20	C	-	173.92 and 174.07
21	O	-	-
22	CH2	2.06, 2.29 and 2.42(m, 2H)	32.73 and 32.82
23	CH2	1.39 and 1.55(m, 2H)	27.09 and 27.32
24	CH2	1.10 and 1.27(m, 2H)	21.88 and 22.08
25	CH3	0.64 and 0.84(t, 7.2Hz, 3H)	13.85 and 14.05
26	CH	4.03 and 4.63(d, 10Hz, 1H)	63.27 and 67.34
27	CH	2.20(m, 1H)	27.84 and 28.09
28	C	-	172.37 and 172.48
29	O	-	-
30	OH	Not observed	-
31,32	CH3	0.74, 0.79 and 0.92(d, 6.0Hz, 6H)	18.88, 18.94, 19.78 and 20.27

APPLICATION

By this approach we can easily identify and characterize the degradation products of Valsartan by using LCMS, HRMS and NMR.

CONCLUSION

Two degradation products were identified during oxidative degradation of Valsartan and were unambiguously characterized by HRMS and NMR techniques.

ACKNOWLEDGEMENT

The authors wish to thank the management of GVK Biosciences Pvt. Ltd. for supporting this work.

REFERENCES

[1]. Valsartan Monograph for Professionals, Drugs.com. American Society of Health-System Pharmacists. Retrieved 3 March **2019**.
[2]. Sacubitril and Valsartan Monograph for Professionals, Drugs.com. 7 November 2019, Retrieved 12 February **2020**.
[3]. Entresto- sacubitril and valsartan tablet, film coated. DailyMed. 1 September 2019. Retrieved 12 February, **2020**.
[4]. L. Fala, Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure, Ah and Db. **2015**, 8 (6), 330–334. PMC 4636283. PMID 26557227.
[5]. J. Fischer, C. R. Ganellin, Analogue-based Drug Discovery, John Wiley and Sons, **2006**. p. 470. ISBN 9783527607495.
[6]. British national formulary: BNF 76 (76 ed.). Pharmaceutical Press, **2018**, p. 179.
[7]. NADAC as of 2019-02-27, Centers for Medicare and Medicaid Services. Retrieved 3 March, **2019**.
[8]. The Top 300 of 2019. Clincalc.com. Retrieved 22 December, **2018**.
[9]. H. Randa, Chapter 26, Renin and Angiotensin, L. L. In Brunton, B. Chabner, B. C. Knollmann (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics (12th ed.). New York: McGraw-Hill. **2011**. ISBN 978-0-07-162442-8.
[10]. Diovan- valsartan tablet, DailyMed. 12 June 2019. Retrieved 12 February, **2020**.
[11]. S. E. Inzucchi, R. M. Bergenstal, J. B. Buse, M. Diamant, E. Ferrannini, M. Nauck, Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes, Diabetes Care, **2015**, 38 (1), 140–9.
[12]. Valsartan Pregnancy and Breastfeeding Warnings, Drugs.com. Retrieved 3 March, 2019.
[13]. Diovan Product Monograph, Health Canada Drug Product Database. Novartis Pharmaceuticals Canada Inc. Retrieved 5 November, **2015**.
[14]. B. G. Katzung, A. J. Trevor, Chapter 11. Basic and Clinical Pharmacology (13 ed.). McGraw-Hill Education, **2015**, ISBN 978-0071825054.
[15]. ICH, Stability testing of new drug substances and products Q1A (R2), in: International Conference on Harmonization, IFPMA, Geneva, **2003**.
[16]. WHO, Draft Stability Testing of Active Pharmaceutical Ingredients and Pharmaceutical Products, World Health Organization, Geneva, **2007**.
[17]. CPMP, Note for Guidance on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products, Committee for Proprietary Medicinal Products, EMEA, London, **2002**.