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Investigation and structural elucidation of a process related impurity in candesartan cilexetil by LC/ESI-ITMS and NMR

Bhanu Raman[a,*], Brajesh A. Sharma[a,b], Ganesh Mahale[b], Dharmendra Singh[b], Ashok Kumar[b]

[a] Department of Chemistry, K. J. Somaiya College of Science and Commerce, Vidyavihar (E), Mumbai 400077, India
[b] Ipca Laboratories Ltd., Chemical Research Division, Kandivli Industrial Estate, Kandivli (W), Mumbai 400067, India

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ABSTRACT

Four impurities were detected in candesartan cilexetil bulk drug samples by HPLC and LC/MS. These impurities were marked as CDC-I, II, III and IV. One of the impurities CDC-II was unknown and has not been reported previously. An optimized method using liquid chromatography coupled with electrospray ionization ion trap mass spectrometry (LC/ESI-ITMS) in positive ion mode has been developed to carry out structural identification of unknown impurity. Based on mass spectrometric data and synthetic specifics the structure of CDC-II was proposed as 2-ethoxy-1-[[2′-(1-ethyl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid ethyl ester. The impurity was isolated by semi-preparative HPLC and structure was confirmed by NMR spectroscopy. The plausible mechanism for the formation of impurities is also discussed.

1. Introduction

Impurity profile of an active pharmaceutical ingredients (APIs) and evaluation of their toxicity effect is necessary step in developing a safe and effective drug and is essential for medical safety reasons [1]. In spite of strict regulatory requirements regarding the purity of drugs, the presence of both process-related and degradation product cannot be completely eliminated. Therefore, the principle knowledge needed for any drug is that of its impurity and degradation products. Typically process-related impurities are unwanted chemicals that remain with the APIs and could be generated at any of the synthetic steps or contamination of any un-reacted molecule involved in the process development.

The isolation and further characterization of impurities by various spectroscopic techniques is a tedious and time consuming procedure. Liquid chromatography in combination with multistage mass spectrometry (HPLC/MS^n) is useful for it's capability to afford both molecular mass and sub-structural information. Chromatographic techniques coupled with ion trap instruments with MS and MS^n capabilities are widely used mass spectrometric tools for the online structural elucidation of drug impurities, metabolites, proteins, peptides, terpenes, flavones, and carbohydrates [2].

Candesartan cilexetil (CDC), 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate, is an ester pro-drug that is hydrolysed during absorption from the gastrointestinal tract to the active form candesartan (2-ethoxy-1-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid). Candesartan (CD) is a potent, long-acting, selective AT_1 subtype anginotensin II receptor antagonists (AIIRAs), which blocks the ability of angiotensin II to raise blood pressure by constricting or squeezing arteries and veins and ultimately leads to a reduction in blood pressure. Consequently it reduces the work of the heart and is useful in patients with heart failure [3–5].

A liquid chromatography method for CDC-desethyl impurity determination is reported [4]. Stenhoff et al. has reported bio-analytical method for drug, pro-drug and metabolite determination in human plasma and urine [5]. Ferreiros et al. reported LC–DAD/MS/MS method for detection of impurities formed by base catalysis hydrolysis and transesterification during solid phase extraction [6]. Rao et al. has reported stability indicating method for CDC methyl ester, CDC ethyl ester, hydroxyl CDC, 1*N*-ethyl CDC and 2*N*-ethyl CDC impurities in bulk drug [7]. Identification, isolation and structural elucidation of desethyl CDC, 1*N*-ethyl CDC, 2*N*-ethyl CDC, 1*N*-ethyl oxo CDC and 2*N*-ethyl oxo CDC impurities in formulations has been reported by Mohan et al. [8]. Stress degradation and impurity profile studies using chromatographic and spectroscopic techniques such as LC, LC–MS/TOF, FTIR and NMR have also been reported [9–11].

The present paper deals with process related impurity of CDC. During process development studies of CDC, four impurities in the bulk drug samples were detected by in-house HPLC method, out of

* Corresponding author. Tel.: +91 02221025919; fax: +91 02221024918.
E-mail address: drbhanuraman@rediffmail.com (B. Raman).

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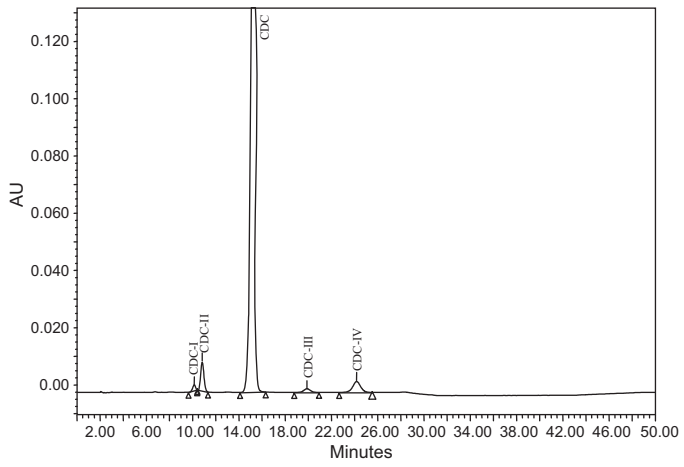


Fig. 1. Typical HPLC chromatogram of CDC (RT 15.5) with impurities; CDC-I (RT 10.1), CDC-II (RT 10.9), CDC-IIl (RT 19.9) and CDC-IV (RT 24.2).

which one was found to be unknown and has not reported before. In view of the fact that the impurity levels were above the acceptable limits of 0.1%, a comprehensive study was carried out using a suitable spectrometric and spectroscopic techniques.

2. Experimental

2.1. Materials and reagents

CDC bulk drug samples were obtained from Chemical Research Division Ipca Laboratories Ltd. (Mumbai, India). HPLC grade acetonitirile was purchased from Merck Ltd. (Mumbai, India) and analytical reagent grade trifluroacetic acid (TFA) was purchased from Lancaster, England. De-ionized water prepared using miliQ plus purification system (Millipore, Bradford, USA) was used throughout the studies. Potassium bromide (FTIR grade), DMSO-d_6, $CDCl_3$ and D_2O were purchased from Merck KGaA (Darmstadt, Germany).

2.2. Synthesis of reference material

2.2.1. Synthesis of CDC-I

In a round bottom flask 1-[(2′-cyanobiphenyl-4-yl)methyl]-2-ethoxy-1H-benzimidazole-7-carboxylic acid ethyl ester (10 g), tributyltin chloride (23 gm), sodium azide (4.5 g), diisopropyl ethyl amine (2.1 g) was taken in xylene (50 mL). This mixture was heated to reflux for 18–20 h. After work up, the isolated CDC-I was purified by conventional column chromatography using (2:1, *v*/*v*) hexane and ethyl acetate as eluent. The obtained material was analyzed and found to have purity 97% (by area normalization).

2.2.2. Synthesis of CDC-III and CDC-IV

CDC (5.0 g) was taken in acetone (25 mL) followed by potassium carbonate (1.7 g) and diethylsulfate (1.3 g). The mixture was heated and stirred for 3–4 h. The mixture was then cooled and quenched with water. The solid was filtered and washed with cold water. The obtained material was analyzed and has found to have CDC-III (25%) and CDC-IV (20%). The above solid material was subjected to conventional column chromatography using (2:1, *v*/*v*) hexane and ethyl acetate as eluent. The appropriate fractions were collected separately for CDC-III and CDC-IV. The combined fractions were evaporated and impurities were re-crystallized from ethyl acetate.

2.3. Liquid chromatography mass spectrometry

The LC part was consisted of an 1100 series HPLC (Agilent Technologies, Waldbronn, Germany) equipped with quaternary gradient pump, degasser and auto sampler. A Kromasil cyano column (250 mm × 4.6 mm i.d., 5 μm particles akzo nobel, Sweden) was used for chromatographic separations. The mobile phase composed of water adjusted to pH 3.0 with TFA (A) and acetonitrile (B) in a gradient mode (T_{min}/A:B; T_0/50:50; T_{25}/50:50; T_{28}/15:85; T_{40}/20:80; T_{45}/50:50). The flow rate was set to 1.0 mL/min with UV detector wavelength fixed at 210 nm. The sample solution (500 ppm) was prepared in mixture of acetonitrile:water (80:20, *v*/*v*) and 20 μL was injected. The ESI-MS and MS/MS analysis was carried out on LCQ-Advantage (Thermo Finnigan, San Jose, USA) ion trap mass spectrometer. The source voltage was kept at 3.0 kV and capillary temperature at 250 °C. Nitrogen was used as both sheath and auxiliary gas. Mass range was kept at *m*/*z* 100–800. MS/MS studies were carried out by maintaining normalized collision energy at 35% with the mass range *m*/*z* 100–800.

The EI-MS studies were carried out on PolarisQ (Thermo Finnigan, San Jose, USA) mass spectrometer with ionization electron beam energy of 70 eV. The sample was introduced in the source with the help of direct inlet probe.

2.4. Semi-preparative HPLC

The unknown impurity was isolated from using Waters Autopurification system consisting of 2525 binary gradient pump, a 2487 UV detector and 2767 sample manager (Waters, Milford, USA). A Kromasil cyano column (150 mm × 21.2 mm i.d., 5 μm particles akzo nobel, Sweden) was used for preparative isolation. A mixture of water (pH adjusted to 3.0 ± 0.1 with TFA) and acetonitrile in the ratio of (60:40, *v*/*v*) was used as mobile phase. The flow rate was maintained at 20 mL/min. The sample solution of 20 mg/mL was prepared by using mixture of acetonitrile and water (80:20, *v*/*v*) as a diluent. The injection volume was 10.0 mL and the UV detection was monitored at 210 nm. The crude samples of CDC containing CDC-II in the range of 1.0–10.0% (area normalization) were subjected to semi-preparative isolation. The impurity was eluted at about 12.6 min. The fractions were collected manually between retention times 12.4 min and 13.0 min. The purity of the isolated fractions was checked by analytical HPLC method described in Section 2.2. The fraction showing the presence of impurity above 95% were mixed together and concentrated to dryness under high vacuum. The HPLC purity of the isolated impurity was found to be above 97%. This isolated solid impurity was used for spectral characterization without any further purification.

2.5. NMR spectroscopy

The ^1H, ^{13}C and 2D NMR (DQF, HMBC, HSQC and NOESY) measurements of the isolated impurities and CDC were performed on a AVANCE 400 (Bruker, Fallanden, Switzerland) instrument at 300 K. DEPT spectral editing was used to identify the presence of methyl and methine groups as positive peaks while the methylenes as negative peaks. The exchangeable protons were identified by D_2O exchange experiment. The ^1H and ^{13}C chemical shift values were reported on the δ scale in ppm relative to $CDCl_3$ (7.28 ppm) and (77.0 ppm) respectively for CDC and DMSO-d_6 (2.49 ppm) and (39.5 ppm) respectively for CDC-II.

3. Results and discussion

3.1. Detection of impurities by LC/UV and LC/ESI-MS

A typical chromatogram highlighting the retention times (RTs) for impurities (CDC-I, CDC-II, CDC-III and CDC-VI) and CDC is shown in Fig. 1. Mass spectral data showed $[M+H]^+$ peaks at *m*/*z* 469, 497, 639 and 639 for CDC-I, II, III & VI, while $[M+Na]^+$ molecular ion peaks at *m*/*z* 491, 519, 661 and 661 respectively.

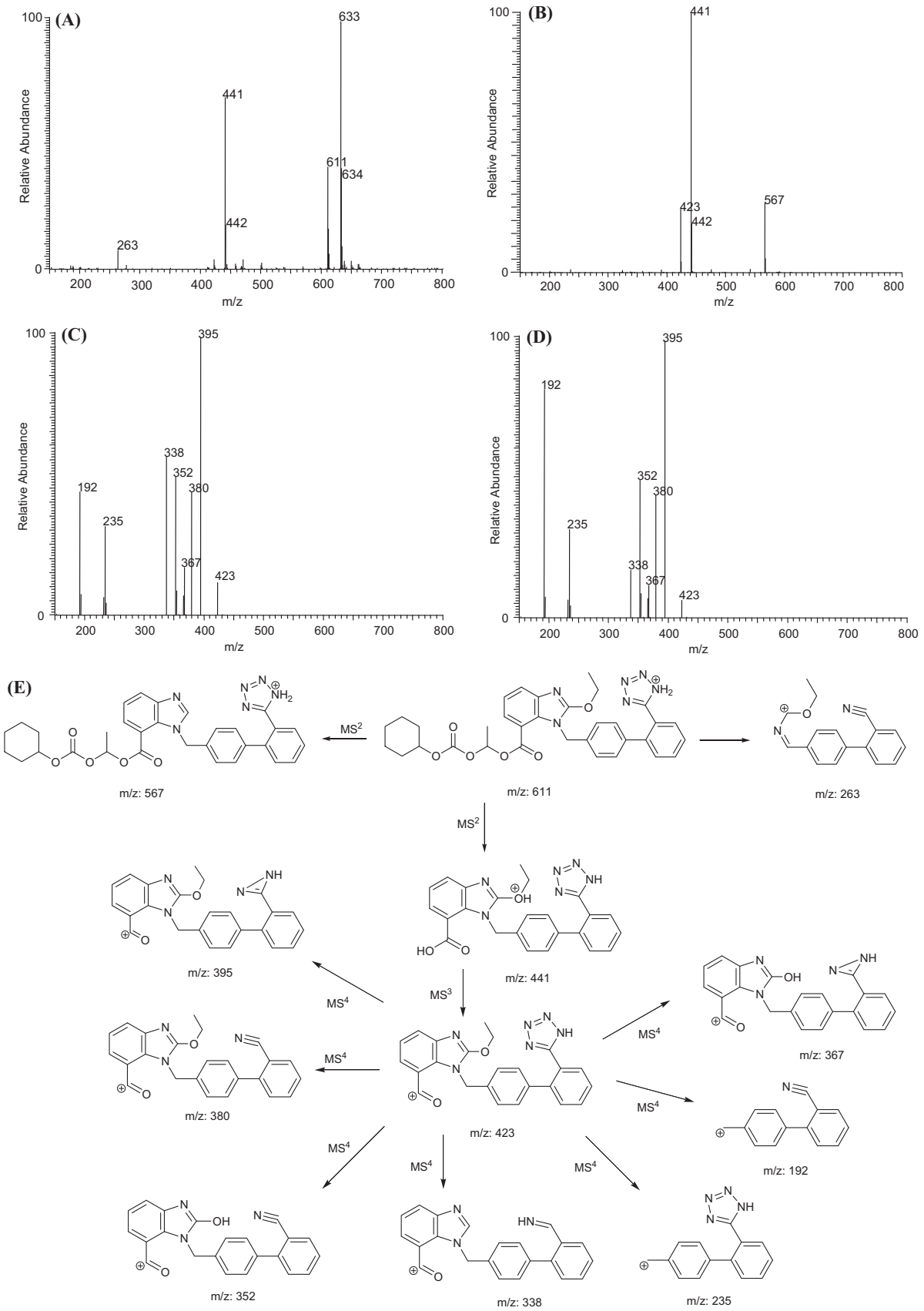


Fig. 2. Mass spectral data of CDC: (A) mass spectrum of CDC showing $[M+Na]^+$ (at *m*/*z* 633) and $[M+H]^+$ (at *m*/*z* 611), (B) MS/MS spectrum of product ion peak at *m*/*z* 611, (C) MS^3 of product ion peak at *m*/*z* 441, (D) MS^4 of product ion peak at *m*/*z* 423 and (E) possible fragmentation mechanism of CDC.

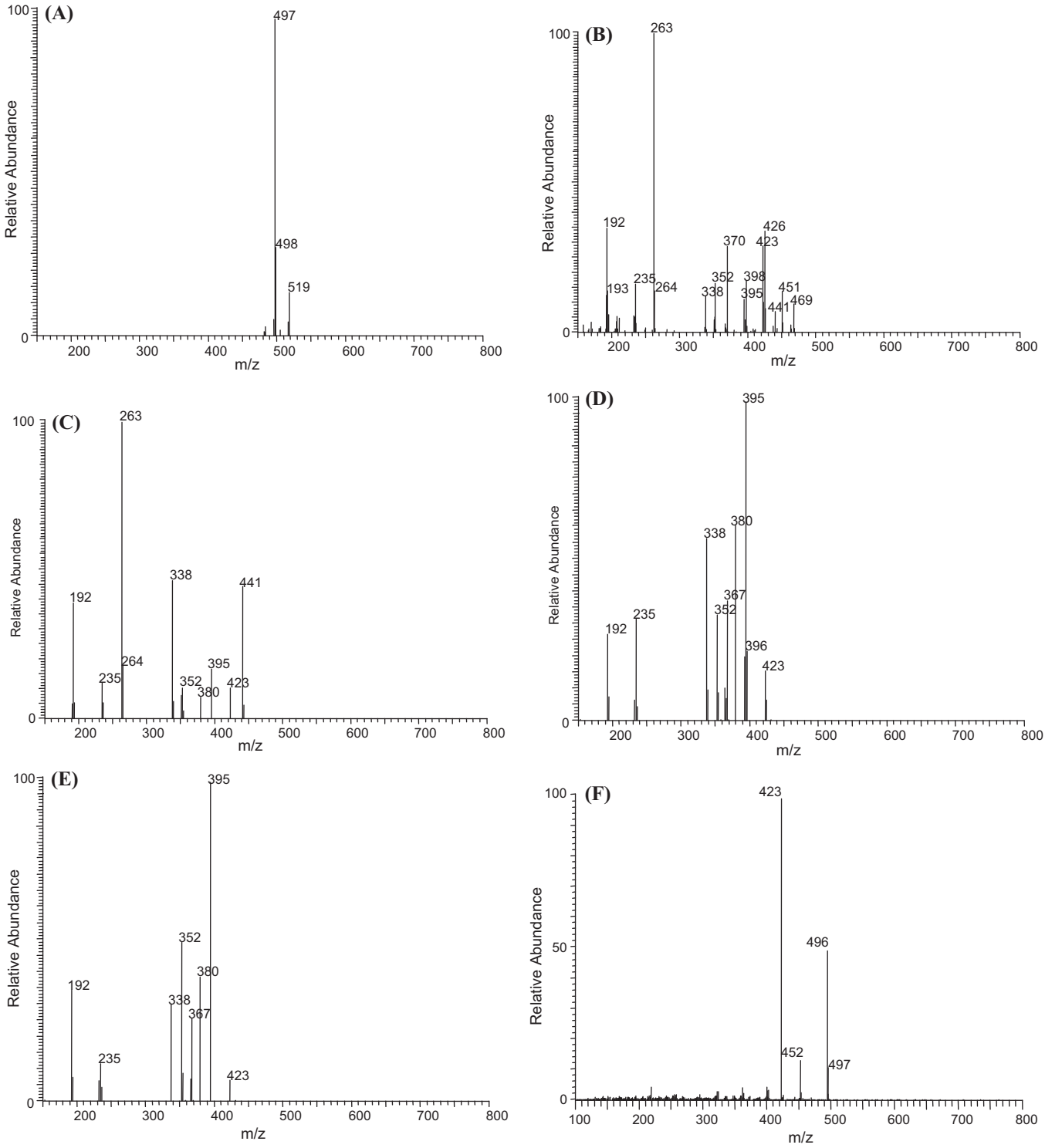


Fig. 3. Mass spectral data of CDC-II: (A) mass spectrum of CDC-II showing $[M+Na]^+$ (at *m/z* 519) and $[M+H]^+$ (at *m/z* 497), (B) MS/MS spectrum of product ion peak at *m/z* 497, (C) MS^3 spectrum of product ion peak at *m/z* 469, (D) MS^4 spectrum of product ion peak at *m/z* 441, (E) MS^5 spectrum of product ion peak at *m/z* 423 (F) EI-MS spectrum of CDC-II and (G) possible fragmentation mechanism of CDC-II.

Based on synthetic specifics and previously known reported possible impurities [4–10] three of these impurities were identified as (2-ethoxy-1-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid ethyl ester) (CDC-I) [7,11], 1-[[(cyclohexy- loxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1-ethyl-1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate (CDC-III) [8,10] and 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1- [[2′-(2-ethyl-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate (CDC-VI) [8,10]. The presence of these impurities was further confirmed by co-injecting the reference material with the test sample. However the mass spectral data obtained for impurity CDC-II was not matching with any of the known reported impurities.

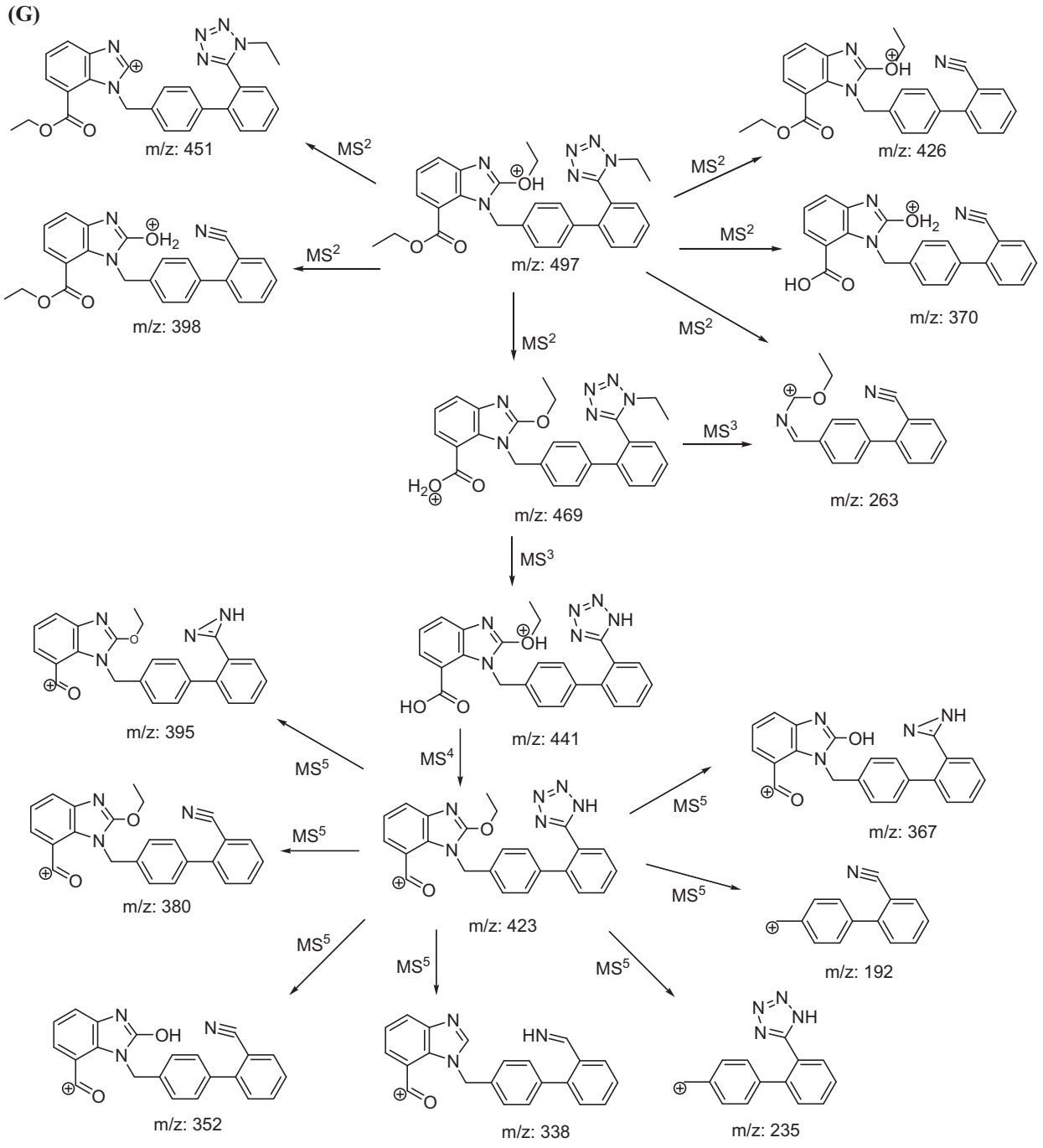


Fig. 3. *Continued.*

3.2. Mass spectrometric investigation of impurity

In order to understand the mass spectral behavior of unknown related substances, a detailed study of the fragmentation pattern up to MS^5 level of the main drug component was undertaken. Mass spectra were recorded in both positive and negative ion modes. As the analytes showed good responses in positive ion ESI-MS as $[M+Na]^+$ ions, this mode was preferred for MS^n experiments. The positive ion ESI-MS spectrum of CDC exhibited a molecular ion peak at *m*/*z* 611 and base peak of $[M+Na]^+$ ion at *m*/*z* 633 (Fig. 2A).

The MS/MS spectrum of the *m*/*z* 611 ion showed product ion peaks at *m*/*z* 567, 441 and 423 (Fig. 2B). MS^3 of *m*/*z* 567 gave product ion peak at *m*/*z* 441. After that the MS^n studies gave the same fragments as given for CDC by Mehta et al. [9]. MS^3 of *m*/*z* 441 directly obtained from *m*/*z* 611 gave product ion peaks at *m*/*z* 423, 395, 380, 367, 352, 338, 238 and 192 (Fig. 2C). MS^4 of ion peak at *m*/*z* 423 (Fig. 2D) produced similar fragmentation pattern as MS^3 of *m*/*z* 441. Loss of ethoxy group is explanation to the formation of product ion peak at *m*/*z* 567 (611–46 Da) from benzimidazole ring. As shown, the major fragment of *m*/*z* 441 is formed due to the loss of cilexetil moiety (611–170 Da) from precursor ion peak. The ion further fragmented into *m*/*z* 423 with the loss of water molecule (441–18 Da). The plausible fragmentation pathway of other fragments are clearly depicted (Fig. 2E).

The ESI-MS spectrum of CDC-II showed molecular ion peak at *m*/*z* 497 and $[M+Na]^+$ ion at *m*/*z* 519 (Fig. 3A). The EI-MS spectrum showed molecular ion peak at $[M]^+$ at *m*/*z* 496 (Fig. 3F). Taking together, ESI-MS and EI-MS spectral data the molecular weight of

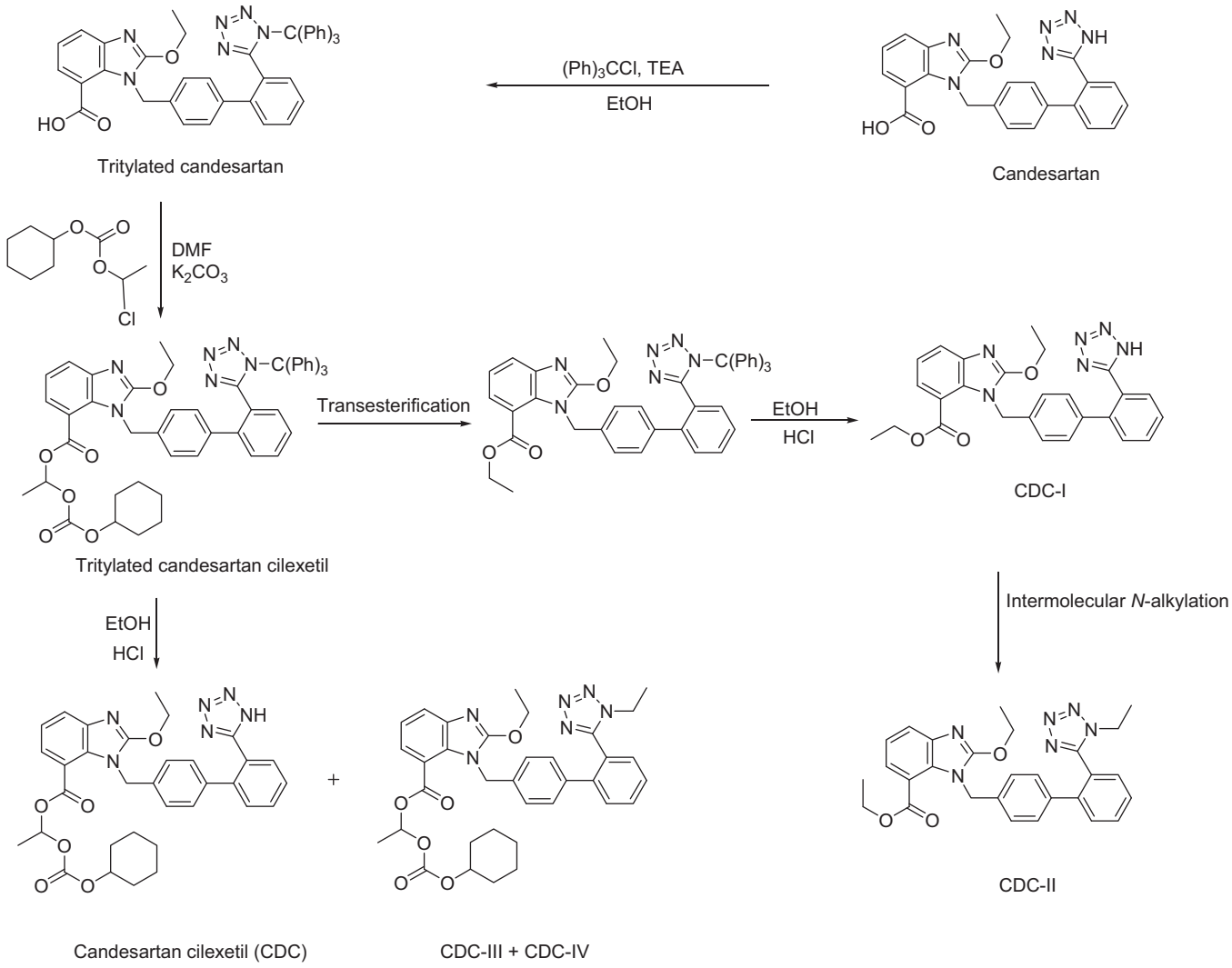


Fig. 4. Plausible mechanism of formation of CDC-II.

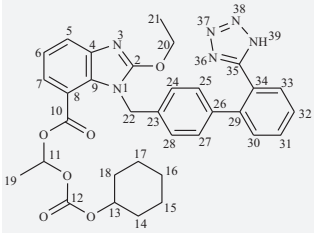
CDC-II is confirmed as 496. The higher order ESI-MS fragmentation spectra (MS^2, MS^3, MS^4 and MS^5) of CDC-II were discernible and easy to compare with that of CDC. The MS/MS spectrum of ion peak at *m*/*z* 497 gave product ion peaks *m*/*z* 469, 451, 426, 423, 395, 370, 352, 263, 235 and 192 (Fig. 3B). MS^3 of major product ion peaks were carried out to understand the fragmentation pathway. Product ion peak at *m*/*z* 451, 441, 398, 395, 380,370, 352, 338, 263, 235 and 192 were obtained by MS^3 analysis of precursor ion peak at *m*/*z* 469 (Fig. 3C). MS^4 of major product ion peaks were carried out, however for comparison and structural elucidation the only ion peak at *m*/*z* 441 was found close to CDC fragmentation pattern. Hence detailed analysis of ion peak at *m*/*z* 441 was carried out. Product ion peak at *m*/*z* 423, 395, 380, 367, 352, 338, 238 and 192 were obtained by this analysis (Fig. 3D). The fragment ion at *m*/*z* 423 obtained from *m*/*z* 441 was subjected to MS^5 analysis. The obtained spectra gave similar fragmentation pattern as of MS^4 of *m*/*z* 441 (Fig. 3E). Arranging the fragments sequentially it is derived that the product ion peak at *m*/*z* 469 (497–28 Da) and *m*/*z* 441 (469–28 Da) are formed possibly due to the loss of two ethyl group from impurity molecule. Fragment ion peaks obtained from MS^4 of *m*/*z* 441 were similar to fragments obtained from MS^3 of *m*/*z* 441 of CDC. Consequently it is correlated that the fragment *m*/*z* 423 obtained by MS^4 is due to the loss of water molecule (441–18 Da). This systematic loss is indication for the presence of two additional ethyl groups. Based on synthetic specifics and mass spectral data the plausible structure of the unknown impurity is 2-ethoxy-1-[[2′-(1-ethyl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid ethyl ester. The plausible fragmentation pathway of other fragments are clearly depicted (Fig. 3G).

3.3. Structural confirmation by NMR

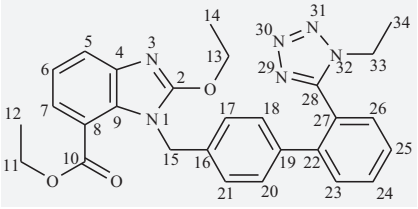
The impurity CDC-II was isolated by semi-preparative HPLC and taken for NMR spectral analysis. In ^1H NMR spectra 17 protons appeared in the upfield region (δ 0.76–5.49 ppm) and 11 in the downfield region (δ 6.85–7.69 ppm). ^1H and ^{13}C spectrum taken together showed two set of additional ethyl group as compared to CDC, concurrently absence of cyclohexyl 1-chloroethylcarbonate (cilexetil) group. This confirms that one set of additional ethyl group in CDC-II is forming ethyl ester after replacing cilexetil group and another set of extra ethyl group is attached to tetrazole moiety as presumed by MS^n fragmentation. Considering existence of annular tautomeric forms [8], 2D NOESY, HMBC and HSQC NMR experiments were carried out. 2D NOESY experiment showed in space correlation of methyl group at H34 and H26. Both NOESY and HMBC predicted that the ethyl group is attached to the N32 of tetrazole group. Complete proton and carbon position assignment compared

Table 1
^{1}H, ^{13}C NMR data of CDC (in $CDCl_3$) and CDC-II (in DMSO-d_6).

CDC



CDC-II



Position	Integration	δ (ppm)	Multiplicity, J (Hz)[a]	^{13}C (δ in ppm)
1	–	–	–	
2	–	–	–	158.0
3	–	–	–	–
4	–	–	–	140.1
5	1H	6.79	m	121.1
6	1H	6.88	t/7.92	121.2
7	1H	7.45	dd/7.92, 0.91	124.2
8	–	–	–	115.2
9	–	–	–	130.7
10	–	–	–	163.3
11	1H	6.63	q/5.48	91.8
12	–	–	–	152.4
13	1H	4.48	–	77.7
14,18	4H	1.65	m	31.2
15,17	4H	1.16	m	23.5
16	2H	1.65	m	25.0
19	3H	1.27	d/5.48	19.2
20	2H	4.07 & 4.36	m	67.6
21	3H	1.40	t/7.01	14.5
22	2H	5.61	s	46.9
23	–	–	–	136.6
24, 28	2H	6.69	d/8.22	125.3
25, 27	2H	6.81	d/8.22	129.4
26	–	–	–	138.1
29	–	–	–	140.9
30	1H	7.28	m	130.5
31	1H	7.56	m	131.2
32	1H	7.56	m	128.2
33	1H	7.98	m	131.1
34	–	–	–	123.3
35	–	–	–	154.6
36	–	–	–	–
37	–	–	–	–
38	–	–	–	–
39	1H	15.94	brs	–

Position	Integration	δ (ppm)	Multiplicity, J (Hz)[a]	^{13}C (δ in ppm)
1	–	–	–	–
2	–	–	–	158.3
3	–	–	–	–
4	–	–	–	141.6
5	1H	7.66	dd/7.92, 0.91	121.6
6	1H	7.16	t/7.92	120.8
7	1H	7.45	dd/7.92, 0.91	123.1
8	–	–	–	115.7
9	–	–	–	130.9
10	–	–	–	165.6
11	2H	4.14	q/7.31	61.0
12	2H	1.17	t/7.31	13.9
13	2H	4.55	q/7.01	66.6
14	3H	1.35	t/7.01	14.3
15	2H	5.49	s	46.2
16	–	–	–	136.9
17,21	2H	6.85	d/8.22	126.6
18,20	2H	6.97	d/8.22	128.7
19	–	–	–	137.6
22	–	–	–	140.8
23	1H	7.69	m	130.3
24	1H	7.55	m	131.7
25	1H	7.55	m	128.0
26	1H	7.55	m	131.2
27	–	–	–	122.4
28	–	–	–	153.8
29	–	–	–	–
30	–	–	–	–
31	–	–	–	–
32	–	–	–	–
33	2H	3.58	q/7.31	42.1
34	3H	0.76	t/7.31	13.3

s, singlet; d, doublet; m, multiplet; dd, doublet of doublet; t, triplet; brs, broad singlet.
[a] ^{1}H–^{1}H coupling constants.

with CDC is given in Table 1. To the best of our knowledge, this is a novel impurity.

3.4. Synthesis of impurity CDC-II

CDC-I (5.0 g) was taken in acetone (25 mL) followed by potassium carbonate (3.1 g) and diethylsulfate (1.5 g). The mixture was heated and stirred for 4–5 h. The mixture was filtered in hot condition and washed with acetone. The obtained filtrate was subjected to conventional column chromatography using (2:1, *v*/*v*) hexane and ethyl acetate as eluent. The combined fractions were evaporated and impurity CDC-II was obtained as white solid.

3.5. Formation of impurities

During synthesis of CDC, tetrazolyl protected CDC derivative is transesterified followed by deportation [11] at penultimate stage, can undergo the intermolecular *N*-alkylation [10] to yield CDC-II. In another possibility, impurity CDC-III is formed can undergo base catalysed hydrolysis and transesterificaton when extracted from ethanolic solution. Such type of possible transesterfication reactions is explained [6,12]. The possible mechanism of formation of impurity is depicted in Fig. 4.

4. Conclusion

LC/MS and MS^n studies of trace-level (<0.2%) impurities associated with candesartan cilexetil bulk drug were carried out using an ion trap mass spectrometer. The structural elucidation of the impurities was made on the basis of evidence found from MS^n fragmentation. The NMR data in combination with knowledge of the synthetic route confirmed the structure of unknown impurity as 2-ethoxy-1-[[2′-(1-ethyl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid ethyl ester.

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