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# Isolation and characterization of degradation impurities in docetaxel drug substance and its formulation

Dinesh Kumar*, Rajesh Singh Tomar, Santosh Kumar Deolia, Moloy Mitra, Rama Mukherjee, Anand C. Burman

*Analytical Laboratory-I, Dabur Research Foundation, 22, Site-IV, Sahibabad, Ghaziabad, Uttar Pradesh 201010, India*

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**Abstract**

The degradation of docetaxel drug substance and its injection formulation has been investigated. The majority of impurities were observed in a base degradation study and all five degradation products were characterized. These impurities were isolated, enriched and were subjected to mass and NMR spectral studies. Based on the spectral data, these were characterized as 10-deacetyl baccatin III, 7-epi-10-deacetyl baccatin III, 7-epi-10-oxo-10-deacetyl baccatin III, 7-epi docetaxel and 7-epi-10-oxo-docetaxel, respectively. The last two impurities were also detected in the stability study of docetaxel formulation.

Out of these degradation impurities two substances have been previously identified while the other three previously unreported.


*Keywords:* Docetaxel; Degradation impurity; Identification; Chromatography; HPLC; Spectroscopy; Characterization

## 1. Introduction

Docetaxel is an anticancer agent of the taxoid family. An analogue of Paclitaxel, docetaxel was obtained by semi-synthesis from 10-deacetyl baccatin III, extracted from the needles of the European yew tree *Taxus baccata* L. [1,2]. In less than a decade, docetaxel has progressed from initial studies in anthracycline-refractory metastatic breast cancer to several large, phase III randomized trials, evaluating its efficacy as adjuvant, neoadjuvant, and first-line therapy for metastatic breast cancer, non-small cell lung cancer (NSCLC), gastric and ovarian cancer [3]. A simple and sensitive method of high performance liquid chromatography coupled with electrospray ionization mass spectrometry (HPLC/ESI-MS/MS) was developed to resolve and identify docetaxel degradation impurities. The epimerization of taxane-related compounds (e.g., Taxol) is known [4,5] and might be expected here also.

The present study describes the degradation, isolation and characterization of impurities of docetaxel. These impurities were isolated using preparative LC and characterized by using NMR and LC–MS/MS spectral data. The degradation impurity, 10-deacetyl baccatin III and 7-epi docetaxel were known previously [6], while other three degradation impurities were found to be previously unreported. The monitoring of these impurities is important for pharmaceutical drug development and quality control of drug substance and its formulation.

## 2. Experimental

### 2.1. Chemicals

The chemicals and reagents were used for the analysis and purification purpose of docetaxel and degradation impurities: acetonitrile (HPLC grade), dichloromethane (LR grade), highly pure Milli Q water was used with the help of Millipore Milli-Q plus purification system, docetaxel drug substance, docetaxel injection: this also contains mainly Tween 80 and docetaxel.

### 2.2. Analytical conditions

The chromatographic separation was performed on Agilent HPLC system consisting of an Agilent Technologies 1100 Series

* Corresponding author. Tel.: +91 120 4378405; fax: +91 120 4376902.
*E-mail address:* dineshk@dabur.com (D. Kumar).

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quaternary solvent delivery module, UV detector and auto sampler. The data was processed using Chemstation software (LC-3D rev. A.09.03 [1417]). The HPLC method was developed for the analysis of docetaxel and its degradation impurities. The analytical condition used were, C18 column (YMC pack ODS-A, 150 mm × 4.6 mm i.d., 5 μm particle size), column oven temperature 35 °C, with a flow rate of 1.2 ml/min, the gradient condition was developed using % Solvent A (mixture of 60:40, v/v of Milli Q water and acetonitrile) and Solvent B (acetonitrile) and the detection was performed at 230 nm. The impurities were eluted according to the step gradient by changing the % of (Solvent B) at different times, *T* (min)/% Solvent B = 0/0, 26/0, 66/83, 67/100, 71/100, 72/0 and 80/0.

The HPLC chromatograms were integrated for the detected impurity peaks, while peaks arising out of blank, diluent and placebo (Tween 80 in the case of the formulation) were auto inhibited.

### 2.3. Forced degradation of docetaxel drug substance

Forced degradation studies were performed on the docetaxel drug substance with the intention of achieving high stress conditions of heat, acid, base and peroxide to ensure maximum degradation.

#### 2.3.1. Thermal degradation

Twelve milligrams of docetaxel drug substance was subjected to thermal degradation at 105 °C for about 20 h.

#### 2.3.2. Acid stressed degradation

Twelve milligrams of docetaxel was dissolved in 25 ml with 1:1 mixture of water and acetonitrile, 1 ml of 0.1N HCl solution was added and kept for about 4.0 h at room temperature.

#### 2.3.3. Base stressed degradation

Twelve milligrams of docetaxel was dissolved in 25 ml with 1:1 mixtures of water and acetonitrile, 0.2 ml of 0.1N NaOH solution was added and kept for about 4.0 h at room temperature.

#### 2.3.4. Peroxide stressed degradation

Twelve milligrams of docetaxel was dissolved in 25 ml with 1:1 mixture of water and acetonitrile, 1 ml of 3% hydrogen peroxide solution was added and kept for 8.0 h at room temperature.

The degradation samples were analyzed by HPLC as described in Section 2.2.

#### 2.3.5. Results of forced degradation study

In the forced degradation study, five major degradation impurities were detected in various stressed conditions. These degradation impurities were labeled as Impurities I, II, III, IV and V (Fig. 1).

In the acid stressed condition the resultant degradation was a single major degradation impurity (Impurity IV), which is known to be 7-epi docetaxel. In the thermal stressed condition, one major impurity was observed, which was the same as that observed under acid stressed conditions.

In the peroxide stressed condition docetaxel degradation was not observed. The major docetaxel degradation was observed in the base stressed condition. In the base degradation of docetaxel, five major impurities were observed and of these five impurities, three impurities (Impurities II, III and V) were found to be unknown and the remaining two (Impurities I and IV) have been reported previously. Isolation attempts were made to enrich these unknown impurities.

### 2.4. Isolation of impurities

Degradation impurities were isolated from base stressed docetaxel drug substance (Fig. 1) and stability samples of docetaxel injection using preparative LC. The preparative LC system used was a Shimadzu chromatograph equipped with LC-8A solvent delivery module, SCL-8A system controller, SIL-8A auto injector, SPD-6A UV/Vis detector, FCV 100B fraction collector and data recorder C-R6A chromatopac. For the isolation, an Inertsil ODS-3 column with dimension of 250 mm × 20 mm, packed with 8 μm particle size was used. The gradient condition was developed using Milli Q water and acetonitrile with a flow rate of 35 ml/min and the detection was performed at 230 nm. The gradient programme was used by changing the % of acetonitrile at different times, *T* (min)/% acetonitrile = 0/20, 20/50, 50/50, 60/60, 70/80, 75/20 and 90/20. For isolation, about 1.5 g of docetaxel was used for the base degradation. Ten runs were performed using 150 mg in each loading on to the preparative LC column for the isolation of impurities. The major peaks were isolated separately. All isolated fractions were pooled together for individual impurities having purity more than 95%. All isolated and final pooled fractions were analyzed by analytical HPLC. For confirmation Impurities IV and V were also isolated from the stability sample of docetaxel injection. After isolation, the extraction of degradation impurities was performed individually with dichloromethane. The solvent evaporation was performed under high vacuum using a Buchi rotavapor R-124 equipped with vacuum system B-178 and water bath B-480.

Finally, about 20–30 mg of each impurity was obtained in solid form.

### 2.5. LC–MS/MS analysis

Electrospray ionization and tandem mass spectrometry experiments were performed using a triple quadrupole mass spectrometer (MDS Sciex model API 4000). The positive ion electrospray data were obtained by switching the capillary voltage between +5000 and −4500 V, respectively. Collision potential (30 V) and nitrogen gas was used in the collision cell for MS–MS studies.

### 2.6. NMR spectroscopy

The NMR experiments were performed on Bruker spectrometers operating at 300 and 400 MHz in $CDCl_3$. The $^1H$ chemical

shift values were reported on the $\delta$ scale in ppm, relative to TMS ($\delta = 0.00$) as internal standard. Standard pulse sequences provided by Bruker were used for homonuclear correlation spectra (COSY 45) experiments.

## 3. Results and discussion

Representative HPLC chromatograms of the forced degradation study are shown in Fig. 1. The targeted impurities for

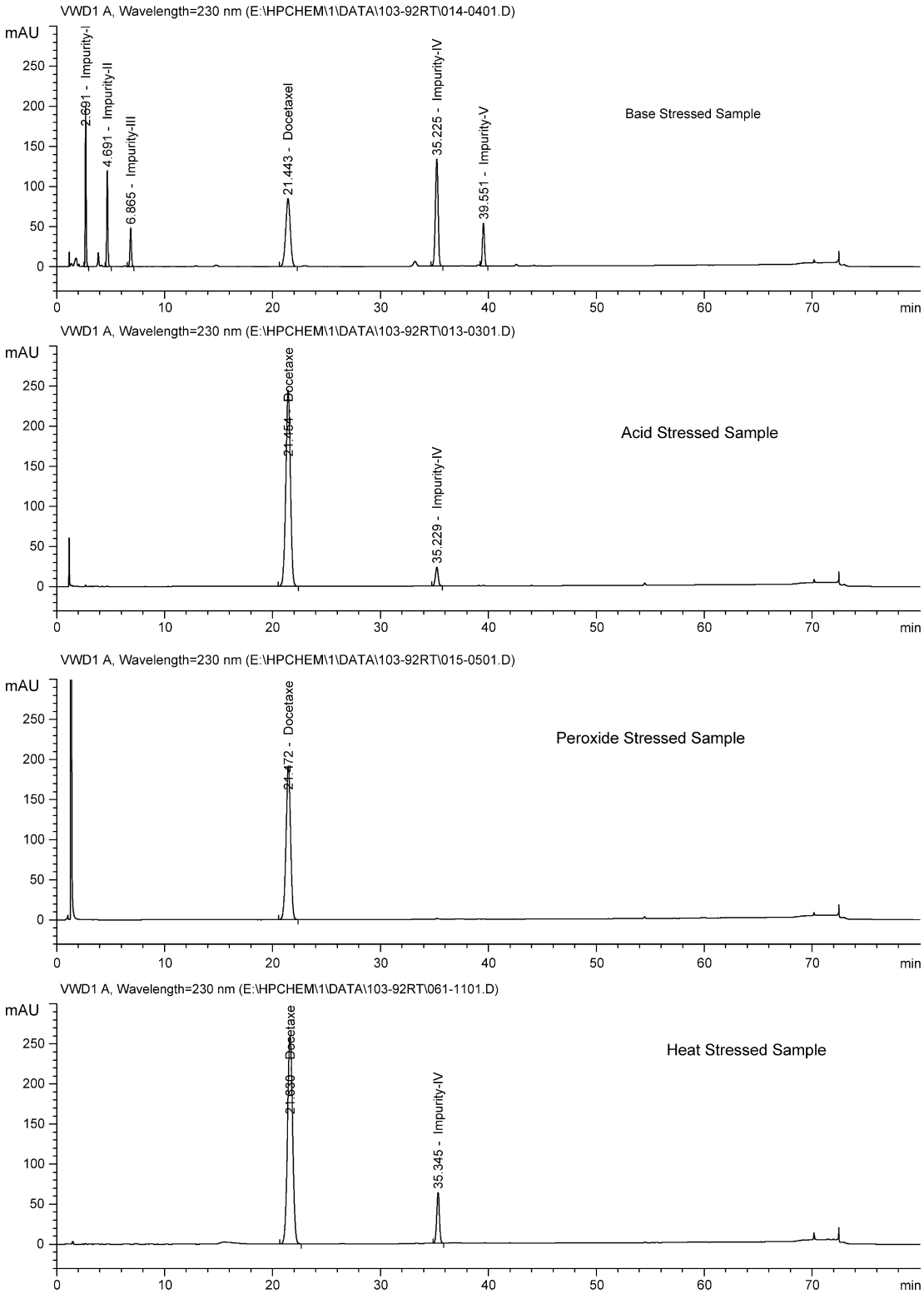



Fig. 1. HPLC chromatograms of docetaxel forced degradation studies.

Table 1
Name, structure and molecular weight of the docetaxel and degradation impurities

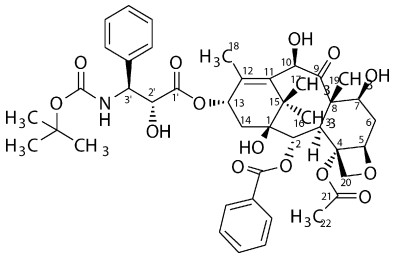
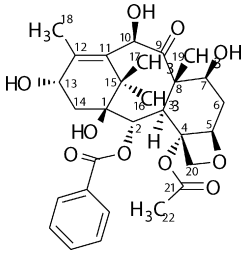
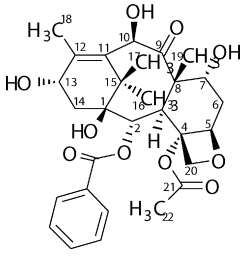
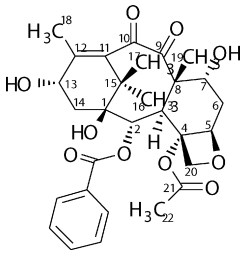
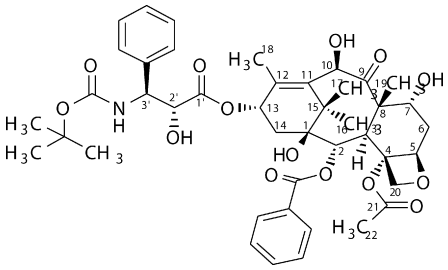
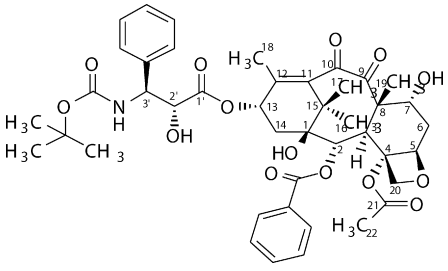
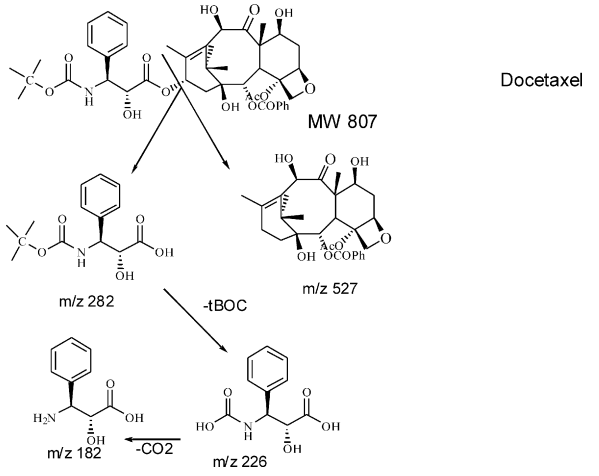
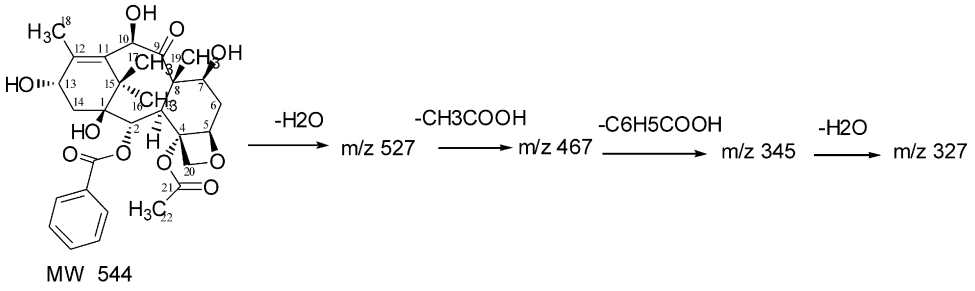
| Name | Structure | Molecular weight |
|---|---|---|
| Docetaxel |  | 807 |
| (Impurity I) 10-deacetyl baccatin III |  | 544 |
| (Impurity II) 7-epi-10-deacetyl baccatin III |  | 544 |
| (Impurity III) 7-epi-10-oxo-10-deacetyl baccatin III |  | 542 |
| (Impurity IV) 7-epi docetaxel |  | 807 |
| (Impurity V) 7-epi-10-oxo-docetaxel |  | 805 |

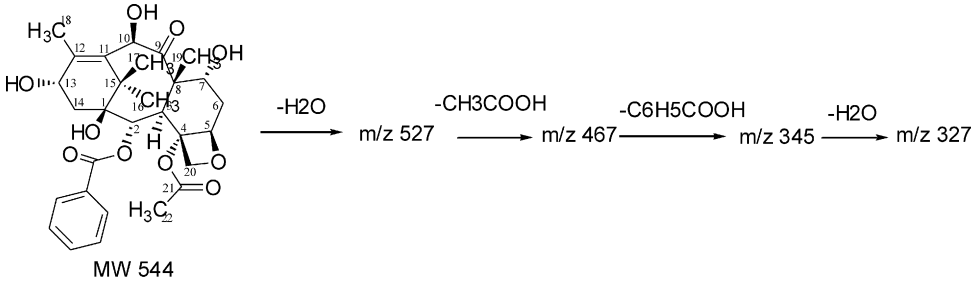
Table 2
Fragmentation pathways of docetaxel and degradation impurity



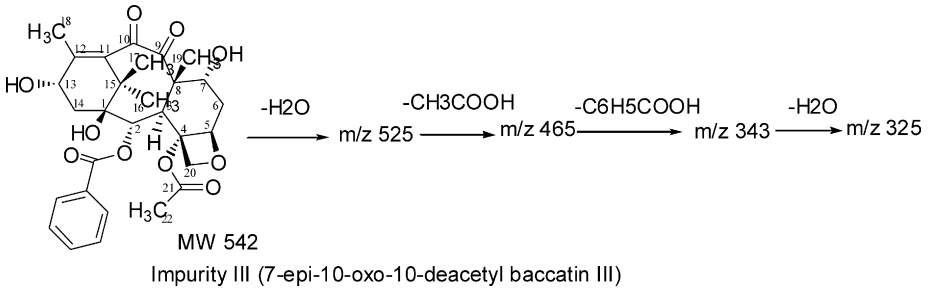

MW 544

Impurity I (10-deacetyl baccatin III)




MW 544

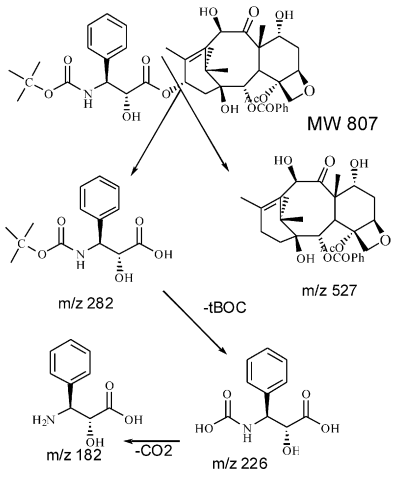
Impurity II (7-epi-10-deacetyl baccatin III)



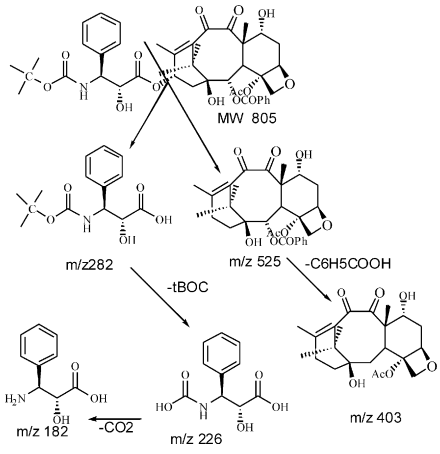

MW 542

Impurity III (7-epi-10-oxo-10-deacetyl baccatin III)

Table 2 (*Continued*)




Impurity IV (7-epi docetaxel)




Impurity V (7-epi-10-oxo-docetaxel)

isolation and characterization were Impurities I, II, III, IV and V. The structures and molecular weights of docetaxel and the identified impurities are given in Table 1.

### 3.1. Structure elucidation of docetaxel Impurity I

This impurity was formed in base stressed docetaxel sample and identified as 10-deacetyl baccatin III, which was a starting material for docetaxel. The ESI mass spectrum of Impurity I showed an ammonium adduct $[M + NH_4]^+$ at (*m/z* 562) and a protonated molecular ion $[M + H]^+$ at *m/z* 545, indicating that the Impurity I has molecular mass less than that of docetaxel by 263 Da. The fragmentation patterns of the molecular ion at *m/z* 545 were obtained as: *m/z* at 527, 345 and 327 amu. These fragments ions are in agreement with the fragmentation pathway of the proposed structure of 10-deacetyl baccatin III as detailed in Table 2. Further confirmation was given by the HPLC retention time and the $^1$H NMR spectrum (Table 3) comparison of Impurity I with 10-deacetyl baccatin III standard substance. In the $^1$H NMR spectrum of docetaxel Impurity I, the chemical shift value of side chain signals were found to be absent. On the basis of spectral data, Impurity I was confirmed as 10-deacetyl baccatin III.

### 3.2. Structure elucidation of docetaxel Impurity II

Docetaxel Impurity II was formed in base stressed docetaxel sample and found to be novel. The ESI mass spectrum of Impurity II gave an ammonium adduct $[M + NH_4]^+$ at (*m/z* 562) and a protonated molecular ion $[M + H]^+$ at *m/z* 545, which is the same as 10-deacetyl baccatin III. The fragmentation pattern was also found to be same as the10-deacetyl baccatin III fragmentation. A significant difference was observed in the $^1$H NMR spectrum (Table 3) and HPLC retention time of Impurity II with respect to 10-deacetyl baccatin III. This indicates that the impurity II could be an isomer of 10-deacetyl baccatin III. The $^1$H NMR spectrum of docetaxel degradation Impurity II showed significantly changes in the $^1$H chemical shifts of the protons at C6, C7 and C10. The COSY 45 correlations in Impurity II were compared with those of 10-deacetyl baccatin III, in that the C6

Table 3
$^1$H NMR data of docetaxel and docetaxel degradation impurities

| Docetaxel | | Impurity IV (7-epi docetaxel) | | Impurity V (7-epi-10-oxo docetaxel) | | Impurity I (10-deacetyl baccatin III) | | Impurity II (7-epi-10-deacetyl baccatin III) | | Impurity III (7-epi-10-oxo-10-deacetyl baccatin III) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| δ (ppm) | Assignments | δ (ppm) | Assignments | δ (ppm) | Assignments | δ (ppm) | Assignments | δ (ppm) | Assignments | δ (ppm) | Assignments |
| 1.13 | (s, 3H, $C_{17}CH_3$) | 1.10 | (s, 3H, $C_{17}CH_3$) | 1.14 | (s, 3H, $C_{17}CH_3$) | 1.10 | (s, 6H, $C_{17}CH_3$ and $C_{16}CH_3$) | 1.07 | (s, 3H, $C_{17}CH_3$) | 1.09 | (s, 3H, $C_{17}CH_3$) |
| 1.24 | (s, 3H, $C_{16}CH_3$) | 1.24 | (s, 3H, $C_{16}CH_3$) | 1.24 | (s, 3H, $C_{16}CH_3$) | – | – | 1.08 | (s, 3H, $C_{16}CH_3$) | 1.10 | (s, 3H, $C_{16}CH_3$) |
| 1.34 | (s, 9H, *t*BOC) | 1.32 | (s, 9H, *t*BOC) | 1.33 | (s, 9H, *t*BOC) | – | – | – | – | – | – |
| 1.76 | (s,3H, $C_{19}CH_3$) | 1.72 | (s, 3H, $C_{19}CH_3$) | 1.73 | (s, 3H, $C_{19}CH_3$) | 1.75 | (s, 3H, $C_{19}CH_3$) | 1.71 | (s, 3H, $C_{19}CH_3$) | 1.71 | (s, 3H, $C_{19}CH_3$) |
| 1.85 | (bs, 3H, $C_{18}CH_3$) | 1.80 | (bs, 3H, $C_{18}CH_3$) | 1.81 | (bs, 3H, $C_{18}CH_3$) | 2.08 | (bs, 3H, $C_{18}CH_3$) | 1.98 | (bs, 3H, $C_{18}CH_3$) | 1.96 | (bs, 3H, $C_{18}CH_3$) |
| 1.80 and 2.59 | (m, 2H, $C_6CH_2$) | 2.35 | (m, 2H, $C_6CH_2$) | 2.38 | (m, 2H, $C_6CH_2$) | 1.79 and 2.60 | (m, 2H, $C_6CH_2$) | 2.34 | (m, 2H, $C_6CH_2$) | 2.33 | (m, 2H, $C_6CH_2$) |
| 2.27 | (m, 2H, $C_{14}CH_2$) | 2.30 | (m, 2H, $C_{14}CH_2$) | 2.27 | (m, 4H, $C_{14}CH_2$) | 2.27 | (m, 2H, $C_{14}CH_2$) | 2.30 | (m, 2H, $C_{14}CH_2$) | 2.29 | (m, 2H, $C_{14}CH_2$) |
| 2.37 | (s, 3H, $OCH_3$) | 2.49 | (s, 3H, $OCH_3$) | 2.50 | (s, 3H, $OCH_3$) | 2.29 | (s, 3H, $OCH_3$) | 2.37 | (s, 3H, $OCH_3$) | 2.38 | (s, 3H, $OCH_3$) |
| 4.24 | (m, 1H, $C_7H$) | 3.67 | (m, 1H, $C_7H$) | 3.86 | (m, 1H, $C_7H$) | 4.27 | (dd, 1H, $C_7H$) | 3.67 | (m, 1H, $C_7H$) | 3.85 | (m, 1H, $C_7H$) |
| 3.91 | (d, 1H, $C_3H$) | 3.93 | (d,1H, $C_3H$) | 4.03 | (d, 1H, $C_3H$) | 4.01 | (d, 1H, $C_3H$) | 4.05 | (d, 1H, $C_3H$) | 4.11 | (d, 1H, $C_3H$) |
| 4.25 | (s, 2H, $C_{20}CH_2$) | 4.39 | (s, 2H, $C_{20}CH_2$ | 4.38 | (dd, 2H, $C_{20}CH_2$) | 4.25 | (s, 2H, $C_{20}CH_2$) | 4.39 | (s, 2H, $C_{20}CH_2$) | 4.37 | (dd, 2H, $C_{20}CH_2$) |
| 4.61 | (bs, 1H, $C_2H$) | 4.62 | (bs, 1H, $C_2H$) | 4.65 | (bs, 1H, $C_2H$) | | | | | | |
| 4.94 | (dd, 1H, $C_5H$) | 4.91 | (dd, 1H, $C_5H$) | 4.91 | (dd, 1H, $C_5H$) | 4.98 | (dd, 1H, $C_5H$) | 4.94 | (m, 1H, $C_5H$) | 4.93 | (m, 1H, $C_5H$) |
| 5.25 | (d, 1H, $C_3H$) | 5.28 | (d, 1H, $C_3H$) | 5.27 | (d, 1H, $C_3H$) | – | – | – | – | – | – |
| 5.44 | (d, 1H, NH) | 5.41 | (d, 1H, NH) | 5.37 | (d, 1H, NH) | – | – | – | – | – | – |
| 5.21 | (s, 1H, $C_{10}H$) | 5.45 | (s, 1H, $C_{10}H$) | – | – | 5.25 | (s, 1H, $C_{10}H$) | 5.49 | (s, 1H, $C_{10}H$) | – | – |
| 5.68 | (d, 1H, $C_2H$) | 5.74 | (d, 1H, $C_2H$) | 5.87 | (d, 1H, $C_2H$) | 5.64 | (d, 1H, $C_2H$) | 5.71 | (d, 1H, $C_2H$) | 5.83 | (d, 1H, $C_2H$) |
| 6.21 | (t, 1H, $C_{13}H$) | 6.27 | (t, 1H, $C_{13}H$) | 6.23 | (t, 1H, $C_{13}H$) | 4.85 | (t, 1H, $C_{13}H$) | 4.88 | (t, 1H, $C_{13}H$) | 4.93 | (t, 1H, $C_{13}H$) |
| 7.29–7.42 | (m, 5H, side chain Ar-H) | 7.36 | (m, 5H, side chain Ar-H) | 7.38 | (m, 5H, side chain Ar-H) | – | – | – | – | – | – |
| 7.50 | (t, 2H, OBZAr-H) | 7.51 | (t, 2H, OBZAr-H) | 7.53 | (t, 2H, OBZAr-H) | 7.48 | (t, 2H, OBZAr-H) | 7.50 | (t, 2H, OBZAr-H) | 7.52 | (t, 2H, OBZAr-H) |
| 7.62 | (t, 1H, OBZAr-H) | 7.62 | (t, 1H, OBZAr-H) | 7.64 | (m, 1H, OBZAr-H) | 7.60 | (t, 1H, OBZAr-H) | 6.62 | (t, 1H, OBZAr-H) | 7.65 | (t, 1H, OBZAr-H) |
| 8.11 | (d, 2H, OBZAr-H) | 8.13 | (d, 2H, OBZAr-H) | 8.15 | (d, 2H, OBZAr-H) | 8.11 | (d, 2H, OBZAr-H) | 8.12 | (d, 2H, OBZAr-H) | 8.14 | (d, 2H, OBZAr-H) |

methylene proton was observed at 2.34 ppm, the C7 methine proton was observed at 3.67 ppm and the C10 methine proton observed at 5.49 ppm, while in 10-decaetyl baccatin III, the C6 methylene proton is observed at 2.60 ppm, the C7 methine proton is observed at 4.27 ppm and the C10 methine proton is observed at 5.25 ppm. All spectral data supports the epimerization of 10-deacetyl baccatin III at the C7 position. Hence, Impurity II was confirmed as 7-epi-10-deacetyl baccatin III.

### 3.3. Structure elucidation of docetaxel Impurity III

Docetaxel Impurity III was also formed in the base stressed docetaxel sample and found not to be reported previously. From the ESI mass spectrum of Impurity III, the ammonium adduct $[M + NH_4]^+$ (*m/z* 560), is the base peak and a protonated molecular ion $[M + H]^+$ is seen at *m/z* 543, indicating that the Impurity III has a molecular mass less than that of docetaxel (265 Da) and less than that of 10-deacetyl baccatin III (by 2 Da). The fragmentation pathway of the protonated molecular ion at *m/z* 543 was obtained as: *m/z* at 525, 465, 343 and 325. These fragment ions are in agreement with the fragmentation pattern of the proposed structure as given in Table 2.

The $^1$H NMR spectrum (Table 3) showed the absence of the C10 methine proton signal, which was present in 10-deacetyl baccatin III at 5.25 ppm. The $^1$H NMR spectrum of docetaxel degradation Impurity III showed significant changes in the $^1$H chemical shifts of the protons at C6 and C7. The COSY 45 correlations in Impurity III were compared with those of 10-deacetyl baccatin III, in that the C6 methylene proton observed at 2.33 ppm and the C7 methine proton was observed at 3.85 ppm while in 10-decaetyl baccatin III, the C6 methylene proton is observed at 2.60 ppm and the C7 methine proton is observed at 4.27 ppm. All spectral data indicates epimerization of 10-deacetyl baccatin III at the C7 position as well as the oxo formation of 10-deacetyl baccatin III at the C10 position. Thus, Impurity III was confirmed as 7-epi-10-oxo-10-deacetyl baccatin III.

### 3.4. Structure elucidation of docetaxel Impurity IV

Impurity IV was formed in acid stress, base stress and heat stress conditions. This was also formed in the stability samples of docetaxel injection. The ESI mass spectrum of degradation Impurity IV showed a protonated molecular ion $[M + H]^+$ at *m/z* 808, which is same as docetaxel but the HPLC retention time of Impurity IV differs from docetaxel. This indicates that Impurity IV could be an isomer of docetaxel. The fragmentation pathway of the protonated molecular ion at *m/z* 808 was obtained as: *m/z* at 527, 282, 226 and 182. These fragment ions are in agreement with the fragmentation pattern of the proposed structure as given in Table 2. The $^1$H NMR spectrum of Impurity IV (Table 3) showed significant changes in the $^1$H chemical shifts of the protons at the C7 and C6 position, which indicates a change in the stereochemistry at C7 position. The $^1$H chemical shift values of the C6 methylene proton, C7 methine proton and C10 methine proton of Impurity IV were visible in its $^1$H NMR spectrum and have also confirmed by a COSY 45 NMR spectrum to be at 2.35, 3.67 and 5.45 ppm, respectively, while in the $^1$H NMR spectrum of docetaxel these showed $^1$H proton chemical shift values of C6 (2.59 ppm), C7 (4.24 ppm) and C10 (5.21 ppm). All these spectral data suggest the epimerization of docetaxel at the C7 position. Hence, Impurity IV was confirmed as 7-epi docetaxel, which is already a known impurity.

### 3.5. Structure elucidation of docetaxel degradation Impurity V

Impurity V was detected in the stability samples of docetaxel injection and also formed in the base stressed condition. The ESI mass spectrum of Impurity V gave a protonated molecular ion $[M + H]^+$ at *m/z* 806, indicating that Impurity V has a molecular mass less than that of docetaxel (by 2 Da). The fragmentation pathway of the protonated molecular ion 806 was obtained as: *m/z* at 525, 403, 226 and 182. These fragment ions are in agreement with the fragmentation pattern of the proposed structure as given in Table 2. The $^1$H NMR spectrum of Impurity V (Table 3) showed a significant change in the $^1$H chemical shifts value of the proton at the C7 and C6 positions, which indicates a change in the stereochemistry at the C7 position. Another significant difference is observed in the $^1$H NMR spectrum at the C10 position. The C10 methine proton signal was found to be absent in Impurity V while in docetaxel, the C10 methine proton signal is observed at 5.21 ppm. The COSY 45 NMR spectral correlations for this Impurity V were compared with those of docetaxel. In impurity V, the C6 methylene protons are observed at 2.38 ppm and the C7 methine proton is observed at 3.86 ppm while in docetaxel, the C6 methylene protons are observed at 2.59 ppm and C7 methine proton is observed at 4.24 ppm. All of these spectral data confirm that the docetaxel degradation Impurity V is 7-epi-10-oxo-docetaxel.

## 4. Conclusion

The major five degradation impurities of docetaxel were isolated from base stressed and formulated stability sample of docetaxel using preparative LC and characterized using NMR spectroscopic and MS techniques. Of these five degradation impurities, two impurities were previously known impurities 10-deacetyl baccatin III and 7-epi docetaxel, while other three degradation impurities were found to be novel and were characterized as 7-epi-10-deacetyl baccatin III, 7-epi-10-oxo-10-deacetyl baccatin III and 7-epi-10-oxo docetaxel.

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