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ORIGINAL ARTICLE

Synthesis and characterization of critical process related impurities of an asthma drug – Zafirlukast ☆

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KEYWORDS

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Abstract Zafirlukast is an oral leukotriene receptor antagonist (LTRA) for the treatment of pulmonary disorders such as asthma. During the process development of zafirlukast, eight process related impurities were observed at a level of 0.1–0.15 area percent. Synthesis and characterization of these impurities and investigation of the root cause of their formation is described.

1. Introduction

Zafirlukast (Fig. 1, Accolate) is a synthetic and selective peptide leukotriene receptor antagonist (LTRA) that has been approved for the prophylactic treatment of asthma. The CYP 3A4 isozyme is responsible for metabolism of many drugs (Phipatanakul et al., 2000). Zafirlukast inhibits the activity of cytochrome isozyme CYP 3A4, CYP 2C9 and blocks the action of the cysteinyl leukotriene on the CysLT1 receptors thus reducing constriction of the airways, build-up of mucus in the lungs and inflammation of the breathing passages. Structurally, zafirlukast is similar to 3-methylindole because it contains *N*-methylindole moiety that has a 3-alkyl substituent on the indole ring.

Impurity removal is a critical and important task in pharmaceutical process research, where the final product meets stringent purity requirements. The presence of impurities in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug product. International Conference on Harmonization (ICH) guidelines (2006) recommend identifying and characterizing all impurities present in APIs at a level of 0.10%. These impurities are required in pure form to understand the impurity profile and development of an accurate analytical method (Krishnaiah et al., 2009) during the research and development phase.

An improved and scalable process was developed for zafirlukast in our group (Goverdhan et al., 2009a; Raghupathi

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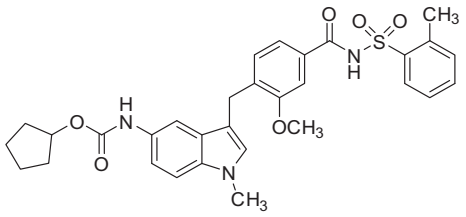

Fig. 1 Structure of zafirlukast 1.

Reddy et al., 2009; Srinivas et al., 2004). At the time of development, eight process related impurities were observed in the reaction mass at a level of 0.1–5.0 area percent. After the work up process to isolate the product, some of the impurities especially impurity G and H were completely washed out. Out of eight, three impurities (A–C) (Goverdhan et al., 2009b) were identified and characterized, however their synthesis and the cause for their formation were not known and three impurities (C–E) were disclosed in our previous publication (Goverdhan et al., 2009a). Herein, we report the complete impurity profile for zafirlukast made using our process, including identification, characterization of unknown impurities (D–H) and detailed experimental procedures for the synthesis of all impurities (A–H).

2. Results and discussion

Zafirlukast **1** was synthesized by following the known synthetic sequence (Scheme 1). During the process development, eight unknown impurities were detected in crude level at significant levels (0.10–1.5%). On the basis of LC–MS data and chemistry involved in the process, tentative structures were proposed for unknown impurities (Fig. 2).

From the synthetic sequence (Scheme 1), it is expected that impurities A and B were derived from coupling of acid **8** with *meta* and *para* isomers present in the starting sulfonamide **11**. Synthesis of these impurities were accomplished from acid **8**, sulfonamides **12** and **13** by using dicyclohexylcarbodiimide (DCC)/*N*,*N*-dimethylaminopyridine (DMAP) coupling reaction as shown in Scheme 2. These two impurities were characterized and confirmed by ^{1}H NMR, mass and IR spectral data (Goverdhan et al., 2009b).

Impurity C is likely to arise due to small amount of compound **15** present in the penultimate **8**. Compound **15** could not be purged from acid **8**. During the hydrolysis of ester **7** in aqueous methanol, considerable amount of acid **15**[1] was formed along with acid **8**. The formation of **15** is explained by transesterification of carbamicester **8**, wherein the cyclopentyl group was substituted with methyl group by nucleophillic attack of methoxide group at carbonyl carbon of carbamate during the hydrolysis step.

Impurity C was independently synthesized from readily available amine **6** (Scheme 3). Amine group in compound **6** was protected as its methyl carbamate **14** using methylchloroformate and *N*-methylmorpholine (NMM) in toluene. Alkaline hydrolysis of methyl ester **14** with LiOH·H_2O in aq. methanol gave the acid **15**, which was treated with sulfonamide **11** under peptide coupling conditions using DCC/DMAP to afford impurity C. Impurity C was confirmed by ^{1}H NMR, mass and IR spectral data (Goverdhan et al., 2009b).

Impurity D is a process related impurity resulting from contamination of **5** with **17** (Jiang et al., 2001; Ancell et al., 2004). Compound **17** contains the same functional groups as **5**, which led to the formation of impurity D along with zafirlukast in the same way. Impurity D was synthesized independently from dibromo compound **16** by utilizing same reaction conditions (Scheme 4).

Benzylic bromination of compound **3** with NBS in chloroform under refluxing conditions furnished dibromo compound **16**. Dialkylated compound **17** was synthesized from **16** and **10** using cuprous oxide in 1,4-dioxane at 95–100 °C. Nitro group in compound **17** was reduced in the presence of Raney Ni to furnish diamine **18**. The carbamate **19** was prepared from the diamine by utilizing the known procedure with cyclopentyl chloroformate and NMM in toluene. By employing LiOH hydrolysis conditions, ester **19** was converted to acid **20**, which was then coupled with sulfonamide under DCC coupling conditions to afford impurity D.

Similar to impurity D, the origin of impurity E again pointed to the presence of **21** (Jiang et al., 2001; Ancell et al., 2004), in the compound **5** (contamination of **5** with **21**). Dialkylated compound **21** was formed along with **5** during the Friedel–Crafts alkylation. Since compound **21** also contains the same functional groups as **5**, impurity E was formed in a similar manner during the synthesis of zafirlukast[2] (Scheme 5).

A mixture of **5** and **21** was produced during the alkylation reaction of **4** with **10** using cuprous oxide in 1,4-dioxane. Nitro compound **21** was separated from **5** by using silica gel column chromatography. Impurity E was synthesized independently from compound **21** by a four step reaction sequence viz, alkylation, nitro reduction, carbamate formation, ester hydrolysis and amide coupling reactions.

Synthesis of zafirlukast involves the condensation of **8** with **11** by using the DCC coupling reaction. Impurity F might be formed via degradation of compound **1** to impurity **26** (Savidge et al., 1998) under basic conditions [by applying the forced degradation of **1,** in basic condition the same impurity **26** was observed] followed by reaction with readily available acid **8** under same reaction conditions.

Synthesis of impurity F began from compound **6**. Hydrolysis of compound **6** with LiOH in aq. methanol furnished amino acid **25**. Finally synthesis of impurity F was achieved from compound **25** by sequential amide bond formations with sulfonamide **11** followed by acid **8** in the presence of DCC/DMAP in dichloromethane. Impurity F was confirmed by comparing HPLC retention time with the pure sample (Scheme 6).

[1] During the hydrolysis of ester **7** in aqueous methanol, considerable amount of acids **15** and **25** were formed along with acid **8**. Compound **25** reacts with **11** in presence of DCC/DMAP to form compound **26**, it is potential metabolite and synthetic manner depicted in Scheme 6.

[2] As per available reported synthetic schemes preparation of **1** involves Friedel–Crafts alkylation between **4** and **10** in the presence of Lewis acid. In Friedel–Craft's alkylation poly (di) substituted indole derivatives of **17** and **21** were formed and it was detected at significant levels (10.0–15.0%) area percent in preparation of **7**. Impurities **18** and **22** were detected at significant level (0.20–0.30%) after isolation of the **6**.

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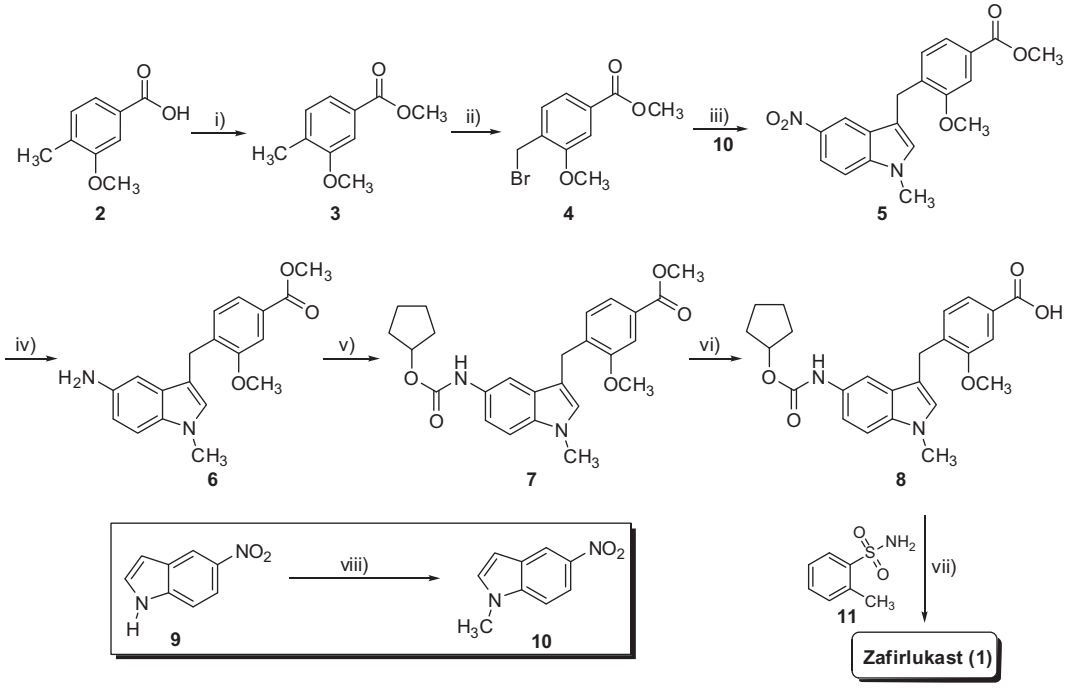


Scheme 1 Synthesis of zafirlukast: (i) $SOCl_2$, methanol; (ii) 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), 2,2′-azobisisobutyronitrile (AIBN), cyclohexane, reflux; (iii) compound **10**, Cu_2O, 1,4-dioxane, EtOAc, MeOH; (iv) Raney Ni, H_2, EtOAc; (v) cyclopentyl chloroformate, NMM, toluene, MeOH; (vi) $LiOH{\cdot}H_2O$, aq. methanol; (vii) compound **11**, DCC, DMAP, dichloromethane, acetonitrile; (viii) dimethyl sulfate, NaOH.

Formation of impurities G and H could be explained on the basis of the mechanism involved in the DCC/DMAP coupling reaction. The acid **8** reacts with the DCC to produce impurity H through key intermediates *O*-acylisourea **27** and impurity G. The reaction pathway involves the rearrangement of the *O*-acylisourea **27** to the stable *N*-acylurea (impurity G) followed by its hydrolysis that gives the impurity H (Scheme 7).

Impurity G was synthesized independently by carrying out owing the DCC coupling in the presence of diisopropylethylamine (DIPEA) instead of DMAP (Scheme 8).

Similarly impurity H was also prepared in parallel from compound **8** and cyclohexyl amine using standard amide coupling conditions (Scheme 8). The molecular formula and structure of impurity H was confirmed by HRMS, in which the exact mass of $[M+H]^+$ (m/z) 504.2873) was determined by positive ESI HRMS (calcd for $C_{30}H_{37}N_3O_4$: 504.2862).

3. Conclusions

In conclusion, the structures of impurities and their root cause of formation during the synthesis of the zafirlukast were identified. The requirements to synthesize and confirm the structures of proposed impurities of zafirlukast have been fulfilled.

4. Experimental section

The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and DMSO-d_6 using 50 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989A LC–MS spectrometer. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus. The thermal analysis was carried out on TA Q1000. The thermo gram was recorded from 40 to 250 °C under the nitrogen flow of 50 mL/min at a heating rate of 10 °C/min. The solvents and reagents were used without further purification.

5. High performance liquid chromatography (HPLC)

A Waters Model Alliance 2690-separation module equipped with a waters 996-photo diode array detector was used. The analysis was carried out on zodiac 100, C18 columns, 250 mm × 4.6 mm, 5 μm particle size with a mobile phase consisting of (A) (degassed buffer) 7.27 g of KH_2PO_4 1.0 g of 1-decanesulphonicacid sodium salt in 1000 mL of milli-Q water and pH adjusted to 4.0 with diluted phosphoric acid (1.0 g in 10.0 mL water) and methanol in the ratio of 85:15. (B) Acetonitrile, methanol, and water in the ratio of 850:100:50, sample dissolved in diluent (acetonitrile:water in the ratio of 8:2) and injection load was 20 μl, program gradient elution (T (min)/A (v/v)/B (v/v) = 0/60/40, 5/60/40, 17/38/62, 33/38/62, 35/40/60, 45/26/74, 55/26/74, 60/14/86, 65/7/93, 75/60/40, 85/60/40) was used with UV detection at 220 nm at a flow rate of 0.8 mL/min. The column temperature was maintained at 27 °C. The data was recorded using Waters Millennium software. This LC method was able to detect all the isomers and impurities ranged from 0.05% to 0.10% in the presence of parent compound.

5.1. General procedure for DCC/DMAP amide coupling

To a stirred mixture of acid (1 mmol), DMAP (1 mmol), sulfonamide/amine (1.16 mmol) in dichloromethane (10.0 volumes to the acid) was added DCC (1.08 mmol) and

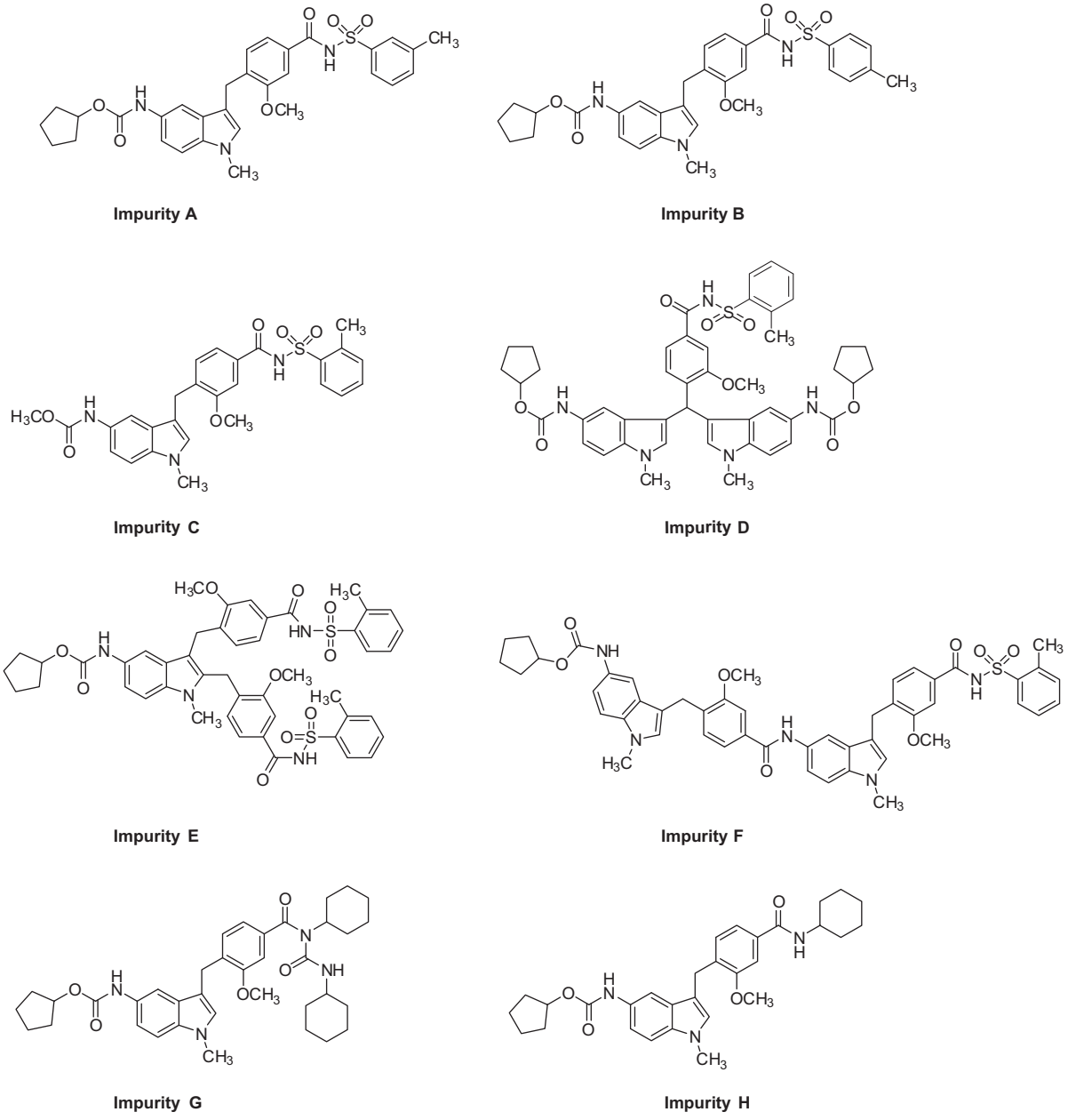
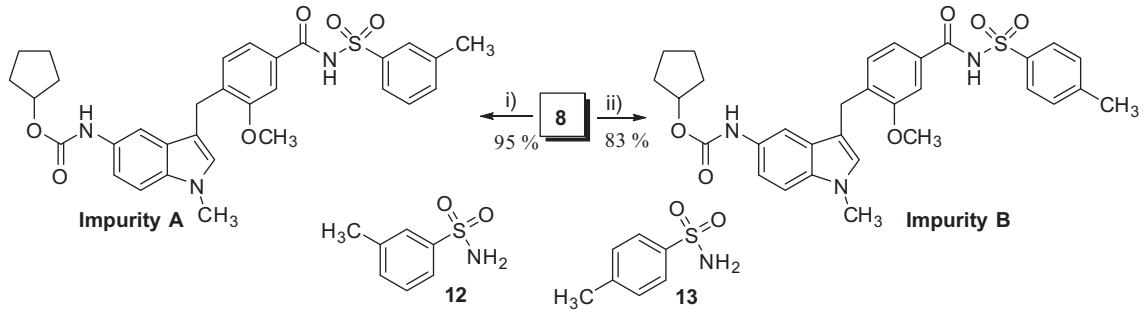


Fig. 2 Structures of zafirlukast impurities A–H.



Scheme 2 Synthesis of impurities A and B: (i) compound **12**, DCC, DMAP, dichloromethane; (ii) compound **13**, DCC, DMAP, dichloromethane.

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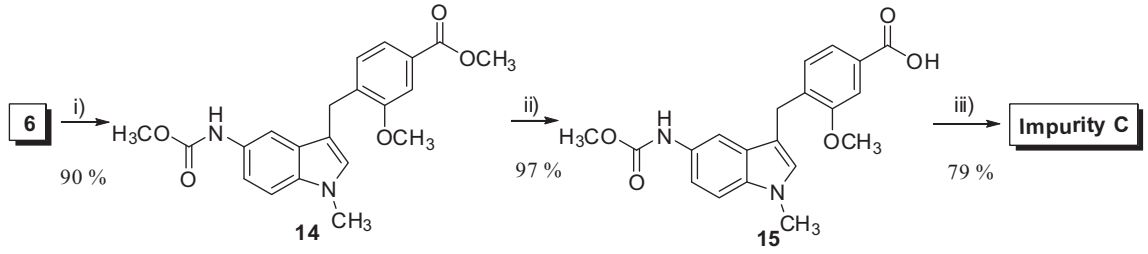
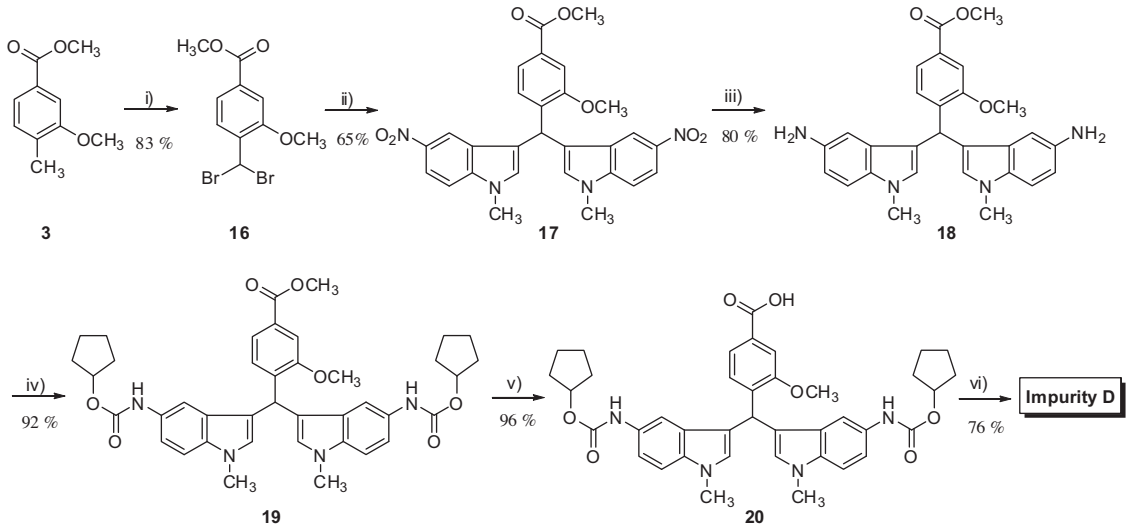
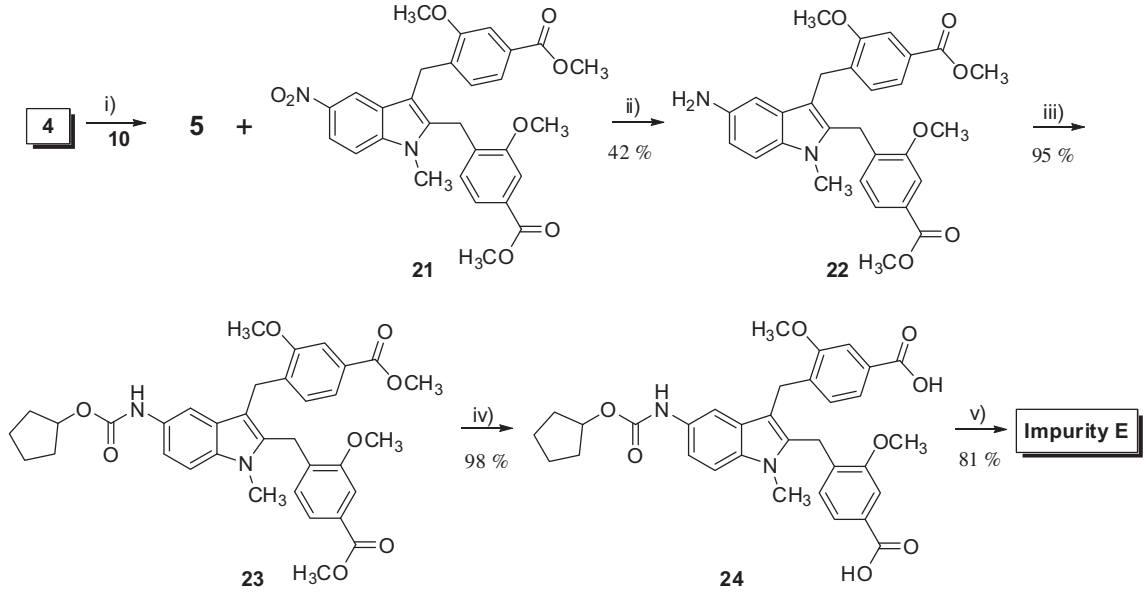


Scheme 3 Synthesis of impurity C: (i) Methyl chlorolormate, NMM, toluene; (ii) $LiOH{\cdot}H_2O$, aq. methanol; (iii) compound **11**, DCC, DMAP, dichloromethane.



Scheme 4 Synthesis of impurity D: (i) NBS, AIBN, $CHC1_3$; (ii) compound **10**, Cu_2O, 1,4-dioxane; (iii) Raney Ni, H_2, EtOAc; (iv) cyclopentyl chloroformate, NMM, toluene; (v) $LiOH{\cdot}H_2O$, aq. methanol; (vi) compound **11**, DCC, DMAP, dichloromethane.



Scheme 5 Synthesis of impurity E: (i) Cu_2O, 1,4-dioxane, EtOAc, MeOH; (ii) Raney Ni, H_2, EtOAc; (iii) cyclopentyl chloroformate, NMM, toluene; (iv) $LiOH{\cdot}H_2O$, aq. methanol; (v) compound **11**, DCC, DMAP, dichloromethane.

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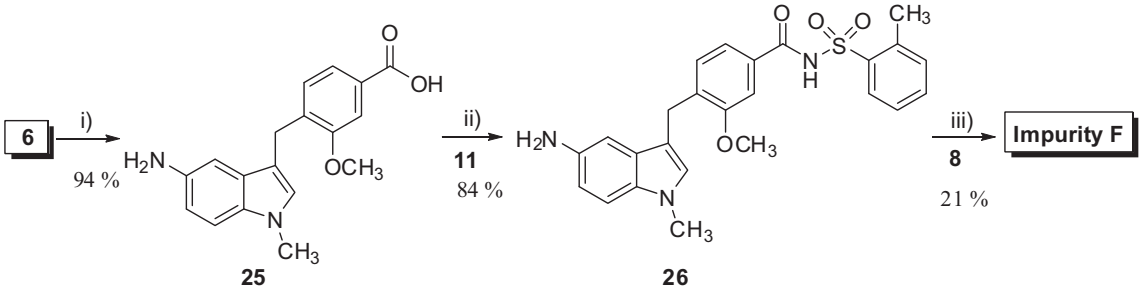
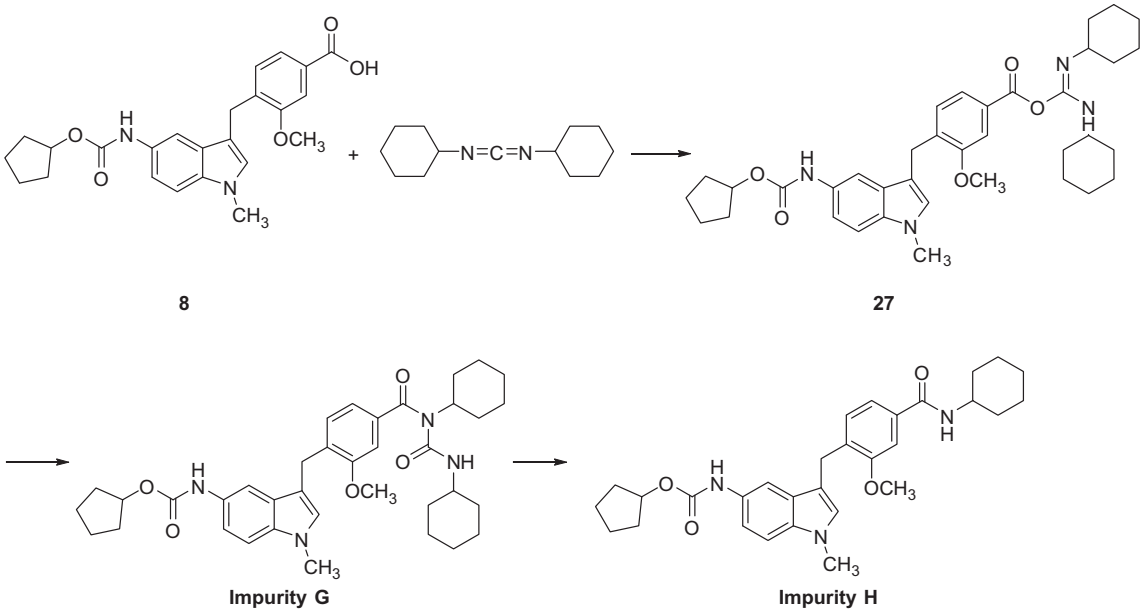
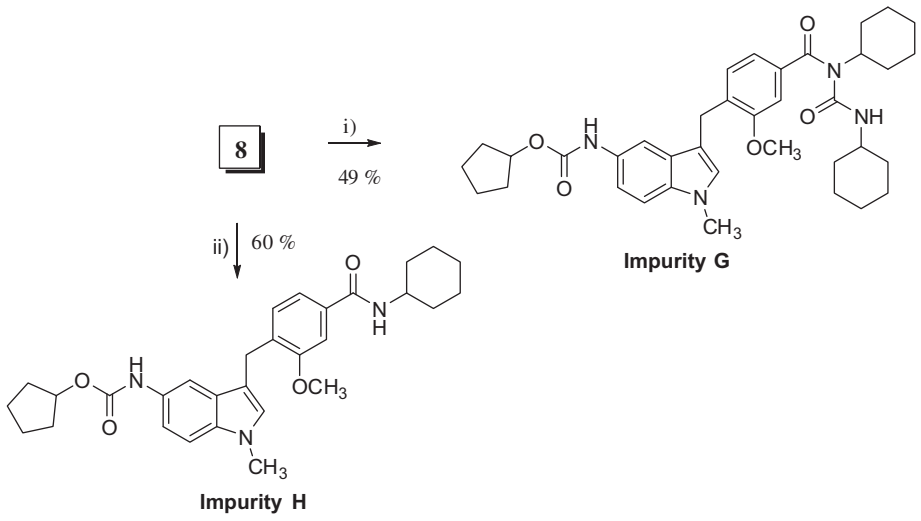


Scheme 6 Synthesis of impurity F: (i) $LiOH{\cdot}H_2O$, aq. methanol; (ii) compound **11**, DCC, DMAP, dichloromethane; (iii) compound **8**, DCC, DMAP, dichloromethane.



Scheme 7 Proposed pathway of formation of impurities G and H.



Scheme 8 Synthesis of impurities G and H: (i) DCC, DIPEA, dichloromethane; (ii) cyclohexyl amine, DCC, DMAP, dichloromethane.

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maintained at 25–35 °C for 3–4 h. Then reaction mass was filtered and the solid was washed with dichloromethane (2.0 volumes to the acid). The filtrate was separated and washed with dil. HCl (2.0 volumes to the acid) followed by water (10.0 volumes to the acid). The solvent was distilled completely under vacuum below 45 °C to obtain solid. The crude compound was re-crystallized from acetonitrile and the wet compound was dried under vacuum at 70–75 °C to furnish amide.

5.2. General procedure for chloroformate coupling

To a solution of amine (1.0 mol) and *N*-methylmorpholine (3.3 mol) in toluene (3.0 volumes to the amine) chloroformate (5.7 mol) was added slowly at 25–35 °C. The resulting reaction mass was maintained at room temperature for 45–60 min. The solvent was distilled from the reaction mass, methanol (3.0 volumes to the amine) was added, the precipitated solid was filtered under vacuum and washed with methanol (0.5 volumes to the amine). The obtained wet solid was dried at 50–55 °C for 2–3 h to afford the carbamate.

5.3. General procedure for LiOH hydrolysis

To a stirred solution of methyl ester (1.0 mol) in methanol (6.0 volumes of the ester), a solution of lithium hydroxide monohydrate (2.5 mol) and water (1.5 volumes to the ester) was added. The resulting reaction mass was heated to reflux (60–65 °C) and maintained under reflux for 2–3 h. The reaction mixture was cooled to 25–35 °C and acidified to pH 1.0–2.0 with conc. HCl. The reaction mixture was kept aside for 1–2 h and the precipitated solid was filtered, washed with water, and dried under vacuum at 70–75 °C to give acid.

5.3.1. {3-[2-Methoxy-4-(toluene-3-sulfonylaminocarbonyl)-benzyl]-1-methyl-1H-indol-5-yl}-acetic acid cyclopentyl ester (Impurity A) (Goverdhan et al., 2009b)

Yield 95% (12.9 g), purity 98.4%, mp 204–210 °C, IR (KBr, ν_{max}, cm^{-1}): 3331, 2933, 1682, 1677, 1586, 1494, 1341, 1241, 1157, 888. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 12.38 (s, 1H), 9.16 (s, 1H), 7.78 (s, 2H), 7.57 (s, 1H), 7.52 (s, 1H), 7.51 (s, 1H), 7.50 (s, 1H), 7.36 (dd, J = 1.6, 8.0 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.16–7.11 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 7.01 (s, 1H), 5.07–5.01 (m, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.62 (s, 3H), 2.40 (s, 3H), 1.90–1.49 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 164.8, 156.5, 153.6, 139.4, 138.7, 135.2, 134.1, 133.1, 130.9, 130.0, 129.2, 128.9, 128.3, 127.6, 127.1, 124.7, 120.6, 114.4, 110.8, 110.0, 109.4, 108.1, 76.1, 55.6, 32.3, 30.6, 24.6, 23.2, 20.8. MS, m/z = 576 [M + H], 593 [M + NH_3] and 598 [M + Na].

5.3.2. {3-[2-Methoxy-4-(toluene-4-sulfonylaminocarbonyl)-benzyl]-1-methyl-1H-indol-5-yl}-acetic acid cyclopentyl ester (Impurity B) (Goverdhan et al., 2009b)

Yield 83% (11.2 g), purity 97.9%, mp 248–252 °C, IR (KBr, ν_{max}, cm^{-1}): 3326, 3090, 2933, 1679, 1627, 1584, 1453, 1342, 1241, 1166, 663. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 12.40 (s, 1H), 9.20 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.61 (bs, 1H), 7.60–7.35 (m, 4H), 7.26 (d, J = 8.2 Hz, 1H), 7.17–7.08 (m, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.01 (s, 1H), 5.07–5.02 (m, 1H), 3.96 (s, 2H), 3.95 (s, 3H), 3.70 (s, 3H), 2.40 (s, 3H), 1.90–1.50 (m, 8H). ^{13}C NMR (100 MHz, DMSO–d_6): δ_C 164.8, 156.5, 153.6, 136.5, 135.1, 133.1, 130.9, 130.1, 129.4, 129.2, 128.3, 127.6, 127.1, 125.5, 120.6, 114.4, 110.8, 109.9, 109.4, 108.1, 76.2, 55.6, 32.3, 30.6, 24.6, 23.2, 21.1. MS, m/z = 576 [M + H] and 593 [M + NH_3].

5.3.3. {3-[2-Methoxy-4-(toluene-2-sulfonylaminocarbonyl)-benzyl]-1-methyl-1H-indol-5-yl}-carbamic acid methyl ester (Impurity C)

Step-1: *3-Methoxy-4(5-methoxycarbonylamino-1-methyl-1H-indol-3-ylmethyl)-benzoic acid methyl ester* (**14**): [Amine **6** (15 g, 0.0462 mol), *N*-methylmorpholine (6 mL, 0.0552 mol) and methyl chloroformate (7 mL 0.093 mol)]; yield 90.3% (15.9 g), purity 99.8%, mp 150–153 °C, IR (KBr, ν_{max}, cm^{-1}): 3389, 2932, 1725, 1705, 1541, 1293, 1238, 761. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 7.56 (s, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 2H), 6.77 (s, 1H), 6.57 (bs, 1H), 4.07 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H). MS, m/z = 383 [M + H] and 405 [M + Na].

Step-2: *3-Methoxy-4(5-methoxycarbonylamino-1-methyl-1H-indol-3-ylmethyl)-benzoic acid* (**15**): Yield 97% (12.6 g), purity 97.5%, mp 128–132 °C, IR (KBr, ν_{max}, cm^{-1}): 3240, 2951, 1707, 1687, 1416, 1279, 779. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 7.53–7.46 (m, 3H), 7.23–7.15 (m, 3H), 6.78 (s, 1H), 6.65 (bs, 1H), 4.08 (s, 2H), 3.94 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H). MS, m/z = 369 [M + H] and 391 [M + Na].

Step-3: *Methyl-1-methyl-3-(4-(O-tolylsulfonylcarbamoyl)-benzyl)-1H-indol-5-ylcarbamate (Impurity C)* (Goverdhan et al., 2009b): Yield 78.8% (11.2 g), purity 98.0%, mp 118–122 °C, IR (KBr, ν_{max}, cm^{-1}): 3569, 3343, 2953, 1697, 1657, 1556, 1430, 1333, 1258, 1167, 757, 591. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 12.56 (s, 1H), 9.28 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.60–7.55 (m, 2H), 7.51 (s, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 7.17–7.10 (m, 1H), 7.08 (d, J = 8.2 Hz, 1H), 7.03 (s, 1H), 3.96 (s, 2H), 3.94 (s, 3H), 3.69 (s, 3H), 3.62 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 164.8, 156.6, 154.3, 137.5, 136.8, 135.2, 133.4, 133.3, 132.3, 130.8, 130.4, 130.0, 129.3, 128.4, 127.1, 126.1, 120.6, 114.5, 110.9, 110.0, 109.5, 108.4, 55.6, 51.3, 32.2, 24.6, 19.5. MS, m/z = 522 [M + H], 539 [M + NH_3], 544 [M + Na].

5.3.4. 4-[Bis-(5-cyclopentyloxycarbonylamino-1-methyl-1H-indol-3-yl)-methyl]-3-methoxy benzoic acid-2-methyl benzene sulfonamide (Impurity D)

Step-1: *4-Dibromomethyl-3-methoxy-benzoic acid methyl ester* (**16**): A solution of benzoate **3** (20 g, 0.11 mol) in chloroform (100 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (40 g, 0.14 mol) followed by 2, 2′-azobis-isobutyronitrile (AIBN) (1.0 g, 0.006 mol) at room temperature. The resultant reaction mass was maintained under reflux (65–75 °C) for 3–4 h. The reaction mass was cooled to 25–35 °C, water (2000 mL) was added and maintained for 45–60 min at 25–35 °C. The organic layer was separated and concentrated under vacuum. The obtained residue was triturated with *n*-hexane (200 mL), the obtained solid was filtered, washed with *n*-hexane (40 mL), and dried under vacuum at 45–50 °C for 3–4 h to afford 24 g (83%) of title compound **16** as off white solid with 95.5% purity. mp 131–134 °C, IR (KBr, ν_{max}, cm^{-1}): 3054, 2952, 1715, 1407, 1298, 740. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 7.91 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 1.4, 8.4 Hz, 1H), 7.50 (s, 1H), 7.11 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H). MS, m/z = 338 [M + H].

Step-2: *4-[Bis-(1-methyl-5-nitro-1H-indol-3-yl)-methyl]-3-methoxy-benzoic acid methyl ester* (**17**): A suspension of **16**

(20 g, 0.06 mol), **10** (10 g, 0.06 mol) and cuprous oxide (24.3 g, 0.17 mol) in 1,4-dioxane (100 mL) was maintained at 95–100 °C for 12–15 h. The reaction mass was filtered through hyflow and washed with acetone (100 mL). The filtrate was concentrated under reduced pressure and the obtained residue was refluxed in a mixture of methanol (90 mL) and ethyl acetate (10 mL) for 60 min. The reaction mixture was cooled to 25–35 °C and maintained for 4 h. The obtained solid was filtered and dried at 40–45 °C to afford 19.5 g (65%) of title compound **17** with 95% HPLC purity. mp 144–149 °C, IR (KBr, ν_{max}, cm^{-1}): 2999, 2950, 2834, 1718, 1619, 1512, 1329, 1289, 1234, 1034. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 8.29 (s, 1H), 8.14−8.07 (m, 2H), 7.74 (dd, J = 1.6, 8.4 Hz, 1H), 7.66 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.67 (s, 1H), 6.41 (s, 1H), 5.30 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.76 (s, 6H). MS, m/z = 529 [M + H].

Step-3: *4-[Bis-(1-methyl-5-amino-1H-indol-3-yl)-methyl]-3-methoxy-benzoic acid methyl ester* (**18**): A suspension of **17** (75 g, 0.15 mol), ethyl acetate (750 mL), water (75.0 mL) and Raney Ni (2.5 mL) was hydrogenated in autoclave by maintaining the reaction under hydrogen pressure (5–6 kgf/cm^2) at 25–35 °C for 3–4 h. After completion of reaction (monitored by TLC), catalyst was filtered through hyflow and washed with ethyl acetate (150 mL). The filtrate was acidified to pH 1–2 with dilute HCl, stirred for 30–45 min and the solid obtained was filtered. The wet compound was basified to pH 7–8 with 10% aqueous sodium carbonate solution at 25–35 °C, and then filtered. The obtained wet compound was stirred in 300 mL of methanol at 25–35 °C for 45 min filtered, washed with methanol (75 mL), and dried at 50–55 °C to afford 53.2 g (80%) of title compound **18** with 96.7% HPLC purity. mp 181–184 °C, IR (KBr, ν_{max}, cm^{-1}): 3401, 3354, 2948, 1712, 1495, 1292, 1233, 760. ^{1}H NMR (200 MHz, DMSO-d_6), δ_H 7.54 (s, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.55−6.38 (m, 6H), 5.97 (s, 1H), 4.45 (s, 4H), 3.85 (s, 3H), 3.83 (s, 3H), 3.38 (s, 6H). MS, m/z = 469 [M + H] and 491 [M + Na].

Step-4: *4-[Bis-(5-cyclopentyloxycarbonylamino-1-methyl-1H-indol-3-yl)-methyl]-3-methoxy-benzoic acid methyl ester* (**19**): [**18** (15 g, 0.03 mol), *N*-methylmorpholine (12 mL, 0.10 mol) and cyclopentyl chloroformate (16 mL, 0.17 mol)]; yield 92% (18.5 g), purity 99.7%, mp 165–170 °C, IR (KBr, ν_{max}, cm^{-1}): 3328, 2956, 1718, 1710, 1492, 1291, 1231, 761. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 7.70–7.32 (m, 4H), 7.23–7.16 (m, 5H), 6.63 (s, 2H), 6.48 (s, 2H), 6.24 (s, 1H), 5.20–5.15 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.66 (s, 6H), 1.92–1.52 (m, 16H). MS, m/z = 715 [M + Na].

Step-5: *4-[Bis-(5-cyclopentyloxycarbonylamino-1-methyl-1H-indol-3-yl)-methyl]-3-methoxy-benzoic acid* (**20**): Yield 96% (14.0 g), purity 98.5%, mp 172–174 °C, IR (KBr, ν_{max}, cm^{-1}): 3312, 2957, 1725, 1697, 1491, 1213, 1037, 798. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 12.78 (bs, 1H), 9.17 (s, 2H), 7.55 (s, 1H), 7.48−7.12 (m, 8H), 6.96−6.68 (m, 1H), 6.65 (s, 1H), 6.13 (s, 1H), 5.06−5.01 (m, 2H), 3.89 (s, 3H), 3.65 (s, 6H), 1.90−1.50 (m, 16H). MS, m/z = 701 [M + Na].

Step-6: *Dicyclopentyl-3,3′-((2-methoxy-4-(O-tolylsulfonylcarbamoyl)phenyl)methylene)-bis(1-methyl-1H-indole-5,3-diyl)bicarbonate (Impurity D):* Yield 76% (6.5 g), purity 92.1%, mp 161–166 °C, IR (KBr, ν_{max}, cm^{-1}): 3329, 2934, 1693, 1626, 1542, 1335, 1231, 1162, 594. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 12.56 (bs, 1H), 9.15 (s, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.59−7.53 (m, 2H), 7.50−7.38 (m, 4H), 7.26 (d, J = 8.0 Hz, 2H), 7.22−7.16 (m, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.65 (s, 2H), 6.08 (s, 1H), 5.05−4.97 (m, 2H), 3.89 (s, 3H), 3.65 (s, 6H), 2.64 (s, 3H), 1.89−1.48 (m, 16H). MS, m/z = 830 [M−H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8, 157.1, 154.2, 138.6, 137.6, 136.8, 134.6, 133.7, 132.3, 131.4, 130.2, 129.7, 128.9, 127.2, 126.3, 119.5, 116.4, 110.1, 109.2, 55.8, 32.7, 32.2, 31.8, 29.6, 29.3, 23.5, 22.6, 20.3. Anal. Calcd for $C_{46}H_{49}N_5O_8S$: C, 66.41; H, 5.94; N, 8.42. Found: C, 66.35; H, 5.99; N, 8.49.

5.3.5. 4-[[5-Cyclopentyloxycarbonylamino-2-[(3-methoxy benzoic acid-2-methyl benzene sulfonamide-4-yl)-methyl]-1-methyl-1H-indol-3-yl]-methyl]-3-methoxy-benzoic acid-2-methyl benzene sulfonamide (Impurity E)

Step-1*: 3-Methoxy-4-[1-methyl-[2-(4-(3-methoxy benzoic acid methyl ester)-2-yl-methyl)]-5-nitro-1H-indol-3yl methyl] benzoic acid methyl ester* (**21**): This compound was formed as a by-product during the preparation of **5** and it was isolated using column chromatography (*n*-hexane:ethylacetate/8:2), the obtained crude solid was purified in methanol. The obtained wet solid was dried at 45–55 °C under vacuum to afford the 6.0 g of title compound **21** with 97.6% HPLC purity. mp 145–149 °C, IR (KBr, ν_{max}, cm^{-1}): 3080, 2946, 1717, 1610, 1518, 1231, 1034. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 8.52 (s, 1H), 8.09 (dd, J = 2.4, 8.8 Hz, 1H), 7.52 (s, 1H), 7.45 (s, 1H), 7.43−7.39 (m, 2H), 7.29−7.25 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 4.19 (s, 2H), 4.13 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.87 (s, 6H), 3.55 (s, 3H). MS, m/z = 533 [M + H].

Step-2: *Methyl-3-methoxy-4-[1-methyl-[2-(4-(3-methoxy benzoic acid methyl ester)-2-yl-methyl)]-5-amino-1H-indol-3yl methyl] benzoate* (**22**): This compound was prepared in the same way as compound **18**, using compound **21** instead of **17**, compound **21** (10 g, 0.027 mol) and Raney Ni (2.5 mL) under hydrogen pressure (5–6 kgf/cm^2) at 25–35 °C for 3–4 h to afford 2.0 g (42%) of titled compound **22** with 94.9% HPLC purity. mp 164–168 °C, IR (KBr, ν_{max}, cm^{-1}): 3427, 3380, 2946, 1722, 1434, 1291, 1102, 759. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 9.60 (broad, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.41 (s, 1H), 7.35 (s, 1H), 7.35−7.30 (m, 3H), 7.03 (dd, J = 2.0, 8.8 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 4.18 (s, 2H), 3.99 (s, 2H), 3.81 (s, 6H), 3.80 (s, 6H), 3.57 (s, 3H). MS, m/z = 503 [M + H] and 525 [M + Na].

Step-3: *3-Methoxy-4-[1-methyl-[2-(4-(3-methoxy benzoic acid methyl ester)-2-yl-methyl)]-5-(cyclopentyloxycarbonylamino)-1H-indol-3yl methyl] benzoic acid methyl ester* **(23)**: [**22** (15 g, 0.03 mol), *N*-methylmorpholine (12 mL, 0.10 mol) and cyclopentyl chloroformate **9** (16 mL, 0.17 mol)]; yield 95% (17.3 g), purity 93.8%, mp 173–177 °C, IR (KBr, ν_{max}, cm^{-1}): 3273, 2953, 1718, 1694, 1501, 1237, 762. ^{1}H NMR (DMSO-d_6, 400 MHz), δ_H 9.19 (s, 1H), 7.54 (s, 1H), 7.41 (s, 1H), 7.35−7.29 (m, 4H), 7.18−7.10 (m, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 5.06−5.02 (m, 1H), 4.12 (s, 2H), 3.93 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 6H), 3.51 (s, 3H), 1.89−1.50 (m, 8H). MS, m/z = 615 [M + H] and 637 [M + Na].

Step-4: *3-Methoxy-4-[1-methyl-[2-(4-(3-methoxy benzoic acid methyl ester)-2-yl-methyl)]-5-(cyclopentyloxycarbonylamino)-1H-indol-3yl methyl] benzoic acid* (**24**): Yield 98% (14 g), purity 98.5%, mp 162–164 °C, IR (KBr, ν_{max}, cm^{-1}):

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3386, 2962, 1697, 1546, 1413, 1245, 1036, 769. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 9.17 (s, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.32–7.26 (m, 3H), 7.17–7.10 (m, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H), 5.08–5.02 (m, 1H), 4.10 (s, 2H), 3.93 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.49 (s, 3H), 1.92–1.52 (m, 8H). MS, m/z = 585 [M−H].

Step-5: *Cyclopentyl-2,3-bis-(2-methoxy-4-(O-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-ylcarbamate (Impurity E):* Yield 80.6% (12.5 g), purity 91.1%, mp 131–134 °C, IR (KBr, ν_{max}, cm^{-1}): 3327, 2928, 2851, 1625, 1575, 1536, 1311, 1244, 1088, 802, 641. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 12.60 (bs, 2H), 9.17 (s, 1H), 8.02 (dd, J = 2.8, 8.0 Hz, 2H), 7.57 (t, J = 7.2 Hz, 2H), 7.55–7.30 (m, 9H), 7.18–7.10 (m, 2H), 6.91 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 5.06–5.02 (m, 1H), 4.10 (s, 2H), 3.91 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.40 (s, 3H), 2.58 (s, 3H), 2.57 (s, 3H), 1.90–1.52 (m, 8H). MS, m/z = 891 [M−H]. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 164.9, 157.7, 156.6, 153.8, 137.7, 136.9, 135.2, 135.0, 133.6, 133.2, 132.4, 130.5, 130.1, 129.0, 128.4, 127.2, 126.3, 120.8, 120.6, 110.0, 109.8, 109.3, 109.0, 55.8, 55.6, 32.4, 29.7, 24.2, 23.9, 23.3, 19.6. Anal. Calcd for $C_{47}H_{48}N_4O_{10}S_2$: C, 63.21; H, 5.42; N, 6.27. Found: C, 63.16; H, 5.48; N, 6.35.

5.3.6. Cyclopentyl-3-(2-methoxy-4-(3-(2-methoxy-4-(O-tolylsulfonylcarbamoyl)-benzyl)-1-methyl-1H-indol-5-ylcarbamoyl)-benzyl)-1-methyl-1H-indol-5-ylcarbamate (Impurity F)

Step-1*: 4-(5-Amino-1-methyl-1H-indol-3-ylmethyl)-3-methoxybenzoic acid* (**25**): Yield 94% (36.0 g), purity 99.5%, mp 118–120 °C, IR (KBr, ν_{max}, cm^{-1}): 3421, 2929, 2598, 1689, 1411, 1255, 735. ^{1}H NMR (200 MHz, DMSO-d_6), δ_H 12.5 (broad, 1H), 10.16 (broad, 1H), 7.58–7.43 (m, 4H), 7.25 (s, 1H), 7.20–7.11 (m, 2H), 4.02 (s, 2H), 3.96 (s, 3H), 3.78 (s, 3H). MS, m/z = 311 [M + H].

Step-2: *4-((5-Amino-1-methyl-1H-indol-3-yl)-methyl)-3-methoxy-N-(phenylsulfonyl) benzamide* (**26**): Yield 84% (24.3 g), purity 97.2%, mp 108–110 °C, IR (KBr, ν_{max}, cm^{-1}): 3340, 3363, 3327, 2929, 2852, 1627, 1576, 1161, 867, 591. ^{1}H NMR (DMSO-d_6, 200 MHz), δ_H 7.94 (dd, J = 1.6, 8.0 Hz, 1H), 7.49 (s, 1H), 7.45–7.24 (m, 5H), 7.06 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 2.0, 8.8 Hz, 1H), 6.82 (dd, J = 2.0, 8.8 Hz, 1H), 6.96 (s, 1H), 3.91 (s, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 2.55 (s, 3H). MS, m/z = 464 [M + H].

Step-3: *Cyclopentyl-3-(2-methoxy-4-(3-(2-methoxy-4-(O-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-ylcarbamoyl)benzyl)-1-methyl-1H-indol-5-ylcarbamate (Impurity F):* Yield 21% (4.4 g), IR (KBr, ν_{max}, cm^{-1}): 3366, 2959, 1703, 1692, 1490, 1457, 1338, 1237, 1162, 1036, 872, 592. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.58 (s, 1H), 9.96 (s, 1H), 9.22 (s, 1H), 8.0 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.84 (s, 1H), 7.75–7.63 (m, 2H), 7.57–7.35 (m, 7H), 7.27 (d, J = 8.0 Hz, 1H), 7.06–7.05 (m, 4H), 5.09–5.03 (m, 1H), 3.96 (s, 4H), 3.94 (s, 3H), 3.90 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 2.56 (s, 3H), 1.90–1.53 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 164.9, 164.7, 156.4, 153.6, 137.8, 136.7, 135.0, 134.2, 133.8, 133.2, 132.6, 132.2, 130.9, 130.7, 130.3, 129.2, 129.0, 128.5, 128.2, 127.2, 126.9, 126.0, 120.6, 119.4, 116.2, 114.3, 111.4, 111.1, 110.8, 109.5, 109.3, 108.2, 76.1, 55.6, 32.3, 30.6, 24.6, 23.2, 19.5. MS, m/z = 868 [M + H], 890 [M + Na]. HRMS (EI); m/z calcd. for (M + NH$_4$) $C_{49}H_{53}N_6O_8S$: 885.3646; found: 885.3627.

5.3.7. {3-[4-(1,3-Dicyclohexyl-ureidocarbonyl)-2-methoxy-benzyl]-1-methyl-1H-indol-5-yl}-carbamic acid cyclopentyl ester (Impurity G)

To a stirred mixture of benzoic acid **8** (10 g, 0.024 mol), *o*-toluene sulfonamide (4.9 g, 0.026 mol) in dichloromethane (100 mL), DCC (5.5 g, 0.026 mol) was added followed by diisopropylethylamine (3.7 g, 0.028 mol) at 25–35 °C. The reaction mixture was stirred for 4–5 h. After completion of the reaction, the unwanted DCU was filtered and washed with dichloromethane (20 mL). The organic layer was washed with 10% aqueous HCl followed by water (100 mL). The organic layer was distilled under reduced pressure below 45 °C and methanol was added to the residue. The reaction mixture was heated to 60–65 °C, stirred for 10–15 min, cooled to 25–35 °C and stirred for 45 min. The separated solid was filtered and washed with methanol (20 mL) to afford impurity G. yield 49% (7.3 g), mp 98–100 °C; IR (KBr, ν_{max}, cm^{-1}): 3285, 2932, 1714, 1685, 1626, 1535, 1225, 1038, 770. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 9.18 (bs, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.66 (bs, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.16–7.10 (m, 1H), 7.08 (s, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 5.10–5.04 (m, 1H), 4.19–4.09 (m, 1H), 3.89 (s, 2H), 3.83 (s, 3H), 3.67 (s, 3H), 3.13–3.03 (m, 1H), 1.90–1.50 (m, 16H), 1.45–0.90 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 171.5, 157.1, 154.4, 154.0, 135.5, 134.1, 133.0, 129.9, 129.8, 127.9, 127.8, 118.8, 115.2, 112.6, 110.1, 109.2, 108.6, 57.5, 55.5, 50.7, 49.5, 33.9, 32.8, 32.2, 30.7, 26.2, 25.3, 25.0, 24.9, 24.4, 23.6. MS, m/z = 629 [M + H] and 651 [M + Na]. HRMS (EI); m/z calcd. for (M + H) $C_{37}H_{48}N_4O_5$: 629.3703; found: 629.3711.

5.3.8. Cyclopentyl-3-(4-(cyclohexylcarbamoyl)-2-methoxy benzyl)-1-methyl-1H-indol-5-ylcarbamate (impurity H)

Yield 60.4% (7.2 g), mp 175–179 °C IR (KBr, ν_{max}, cm^{-1}): 3325, 3288, 2930, 2851, 1694, 1626, 1573, 1496, 1238, 1041, 783. ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 9.17 (bs, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.60 (bs, 1H), 7.39 (s, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 5.05 (t, J = 6.0 Hz, 1H), 3.92 (s, 2H), 3.89 (s, 3H), 3.80–3.73 (m, 1H), 3.70 (s, 3H), 1.92–1.50 (m, 12H), 1.38–1.02 (m, 6H). ^{13}C NMR (50 MHz, DMSO-d_6), δ_C 165.0, 156.4, 153.6, 133.8, 133.1, 132.2, 130.9, 128.8, 128.1, 127.1, 119.1, 114.3, 111.5, 109.2, 108.2, 76.1, 55.4, 48.2, 33.3, 32.4, 32.3, 25.2, 24.9, 24.5, 23.2.

MS, m/z = 504 [M + H]. HRMS (EI): m/z calcd for (M + H) $C_{30}H_{37}N_3O_4$: 504.2862, found: 504.2873.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jscs.2011.06.002.

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