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Investigation of Alcaftadine using a Double Oxidation Process by Eliminating Column Chromatography

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Alcaftadine is an active pharmaceutical ingredient (API) used as an ophthalmic solution for the prevention of itching associated with allergic conjunctivitis. The originally reported synthesis uses a time-consuming column chromatography technique for the isolation of hydroxymethylated product alcohol (**10**). A simple yet effective double oxidation strategy is developed using oxidation grade manganese dioxide to avoid tedious chromatographic purification. Firstly, a partial oxidation of hydroxymethylated crude mass (mixture of compounds **9**, **10** and **16**) was carried out using a limited amount of MnO_2 to get rid of critical diol impurity (**16**) and to allow crystallization of alcohol (**10**) crude, followed by its second oxidation using additional MnO_2 to provide alcaftadine *via* a scale-up friendly process. This synthetic approach has been proven to be cost effective and commercially viable. Various impurities formed during the process were also identified and eliminated to obtain ICH guideline purity of alcaftadine API. The process was validated in plant scale and US DMF was filed to manufacture alcaftadine API.

Keywords: Synthesis, Alcaftadine, Oxidation, Column chromatography.

INTRODUCTION

Alcaftadine is chemically known as 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5*H*-imidazo[2,1-*b*][3]benzazepine-3-carboxaldehyde. It belongs to the benzazepines category of heterocyclic compounds. Benzazepines are organic molecules represented by a benzene ring fused to an azepine ring *i.e.* unsaturated seven-membered heterocyclic compounds with one nitrogen atom replacing a carbon atom. Alcaftadine was developed by Janssen Pharmaceuticals [1] as a 0.25% ophthalmic solution for prevention of itching associated with allergic conjunctivitis [2,3]. It was approved in the United States in 2010 under trade name Lastacaft. Alcaftadine ophthalmic drops are used to prevent itching of eye caused by a condition known as allergic conjunctivitis "pink eye". It works by preventing the effects of certain inflammatory substances, which are produced by cells in the eyes and sometimes cause allergic reactions [4,5].

Alcaftadine demonstrated greater efficacy than ketotifen [6] and olopatadine [7] to treat allergic conjunctivitis and hence it will have big market shares in coming years [8,9]. A literature survey revealed various process patents [10-19] and novel polymorphs were reported for alcaftadine by Friedrich [20] and MSN Labs [21].

EXPERIMENTAL

All chemicals and solvents were either purchased from Avra Synthesis, Vishnupriya Chemicals (oxidation grade MnO_2) and Aquila organics, all from India. ^{1}H NMR was performed on 300 MHz FT-NMR (Bruker) using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. MS was performed on a Quattro Micro API Mass Spectrometer 0-800 Da in Auto spec. IR was recorded on Perkin Elmer spectrum 100 FT-IR. High performance liquid chromatography (HPLC) was performed on Shimadzu LC solution by using X-terra RP-18 (250 × 4.6 mm, 5.0 µ), Mobile Phase-A; 0.1% TEA in water, adjusted to pH 9.0 with H_3PO_4 mobile phase-B; water:acetonitrile: isopropyl alcohol (25:70:5) v/v, conc.: 1.0 mg/mL. All compounds were confirmed either by ^{1}H NMR and MS or by comparing with reported data from literature.

1-(Ethoxycarbonyl)piperidine-4-carboxylic acid (KSM-I) (14): Added sodium hydroxide flakes (34.68 Kg) to purified water (750 mL) into a reactor at 20-30 ºC under stirring by providing external cooling. Add isonipecotic acid (**13**) (56 kg) to above solution. Dropwise added ethyl chloroformate (56.92 kg) to reaction mass at 5-20 ºC under stirring in 4-6 h. Heated the reaction mass to 20-30 ºC and maintained for 3 h till HPLC complies. The reaction mass was acidified to pH 1-2 by addition of conc. HCl. Added toluene (168 L) to the above reaction mass and stirred for 1 h at 25-30 ºC. Concentrated the combined organic layer (toluene layer) under vacuum at > 70 ºC. Charged the cyclohexane (280 L) to above reaction mass at 50-60 ºC and then cooled the reaction mixture at 25-30 ºC for 1 h. Filter-off the isolated solid at 25-30 ºC and washed solid product with cyclohexane (56 L). Dried the white solid at 50-55 ºC in vacuum for 8-12 h to get KSM-I (**14**) (74.14 kg, 85%). ^{1}H NMR and mass spectral data were matched with reported values [22].

1-(2-Phenylethyl)-1*H*-imidazole (KSM-II) (3): Added 2-phenylethylalcohol (**12**) (40 kg) to toluene (400 L) into a reactor at 25-30 ºC under constatnt stirring. Cooled the reaction mass to 0-10 ºC and then addded triethyl amine (40.54 kg) to the above solution at 0-10 ºC followed by methane sulfonyl chloride (42 kg) over a period of 1-3 h at 0-10 ºC under stirring. Purified water (203 L) was added at 0-25 ºC since the reaction is exothermic in nature and then separated the organic and aqueous layers. To organic layer, added imidazole (**2**) (27.5 kg), anhydrous K_2CO_3 powder (55.37 kg) and tetrabutylammonium bromide (6.51 kg) at 25-30 ºC and then heated the contents at 105-110 ºC for 1 h under constant stirring till HPLC complies. Added toluene (203 L) at 25-30 ºC to the above reaction mass and then separate the organic and aqueous layers. Combined two organic layers, added purified water (101 L) and stirred for 15 min at 25-30 ºC and again separate the organic and aqueous layers. Solvent was distilled off under vacuum below 65 ºC and liquid KSM-II (**3**) (38.32 kg, 68%) was unloaded into a drum. ^{1}H NMR and mass spectral data were matched with reported values [23-28].

[1-(2-Phenylethyl)-1*H*-imidazole-2-yl](piperidin-4-yl)-methanone dihydrobromide (stage-I) (6): To KSM-I (**14**) (71.54 kg), added toluene (35 L) into a reactor at 25-30 ºC and stirred under N_2 atmosphere followed by the addition of DMF (2.135 L) to the reaction mass under stirring. Added thionyl chloride (63.52 kg) slowly to reaction mass at 25-45 ºC (highly exothermic) over 3-6 h, heated the reaction mass at 50-55 ºC and stirred for 2 h till HPLC complies. Distilled off the content under vacuum below 50 ºC and cooled the residue at 5-10 ºC. Separately prepared a solution of acetonitrile (175 L) and KSM-II (**3**) (35 kg) in another reactor and to this slowly added to the reaction mass at 0-20 ºC, followed by the addition of triethyl amine (41.11 kg) at 0-20 ºC. Maintained the reaction mass at 10-20 ºC for 3-5 h till HPLC complies and then added ethyl acetate (105 L) to purified water (175 L) and finally added this solution to a above reaction mass at below 35 °C (reverse quenching). Separated the organic and aqueous layers, the organic layer was distilled off below 55 ºC under vacuum to get stage-I_a crude. Cool the stage-I_a crude at 25-30 ºC, added 50% aq. HBr (232 L) and then stirred for 1 h. Heated the reaction mass at 85-90 ºC for 12 h till HPLC complies and then distilled off the reaction mass below 70 ºC. Cool the content at 40-50 ºC, added isopropyl alcohol (235 L), heated at 65-70 ºC for 1 h (free solid observed) and then cooled to 25-30 ºC for 12 h. Filtered-off the solid material and washed with isopropyl alcohol (23.5 L) and filtered under suction pump. Dried the material in hot air oven at 60-65 ºC for 8 h to get white solid of stage-I (**6**) (73.08 kg, 80.8%). m.p.: > 250 ºC, (Lit. [1] > 250 ºC); MS (m.f.: $C_{17}H_{21}N_3O{\cdot}2HBr$): Expected mass: 283.36; Observed mass: 284.23 (M+1). ^{1}H NMR (DMSO-d_6, δ ppm): 8.71 (bs, 1H), 8.51 (bs, 1H), 7.62 (d, 1H), 7.36-7.02 (m, 6H), 5.96 (bs, 3H), 4.63-4.58 (m, 2H), 3.85-3.76 (m, 1H), 3.35-3.30 (m, 2H), 3.06-2.96 (m, 4H), 1.98-1.94 (d, 2H), 1.76-1.67 (m, 2H). FT-IR (KBr, ν_{max}, cm^{-1}): 3085, 2958, 1699, 1499, 1277.

11-Piperidin-4-ylidene-6,11-dihydro-5*H*-imidazo[2,1-*b*]-[3]benzazepine (stage-II) (15): Added stage-I (**6**) (60 kg) in purified water (180 L) at 25-30 ºC and then adjusted the solution at pH 9-10 using aq. NaOH solution (NaOH flakes 12 kg in 60 L of water) under stirring. Now, added CH_2Cl_2 (180 L) to the reaction mass, stirred for 0.5 h, separate both layers and extract aqueous layer with CH_2Cl_2 twice (2 × 120 L). Combined the organic layers and dichloromethane was distilled off under vacuum at below 40 ºC to get crude free base. Trifluoromethane-sulfonic acid (180 kg) was added to crude mass at 25-30 ºC and the temperature of reaction mixture was raised up to 140-150 ºC, stirred for 8-10 h till HPLC complies and then cooled at 25-30 ºC. The pH of the reaction mass was adjusted to 9-10 with aq. NaOH solution by reverse quenching. The reaction mixture was extracted with CH_2Cl_2 (2 × 180 L). The CH_2Cl_2 layer was distilled to get sticky reaction mass, co-distilled with acetone (17.5 L). To a reaction mass, charge acetone (30 L) and stirred for 15 min at 25-30 ºC. Cooled the contents at 0-5 ºC for 2 h. Filtered the isolated compound and washed with chilled acetone (7.5 L) and dry under vacuum at 45-50 ºC for 12 h to get white solid of stage-II (**15**) (21.15 kg, 59.6%). m.p.: 170.93 ºC. ^{1}H NMR (DMSO-d_6, δ ppm): 8.61 (s, 2H), 7.38-7.41 (m, 1H), 7.33-7.23 (m, 4H), 7.18-7.15 (m, 1H), 7.07 (s, 1H), 6.93 (s, 1H), 4.41-4.35 (m, 1H),3.98-3.89 (m, 1H), 3.50-3.39 (m, 1H), 3.34-3.09 (m, 3H), 3.03-2.91 (m, 4H), 2.53-2.49 (m, 1H), 2.37-2.30 (m, 1H). MS (m.f.: $C_{17}H_{19}N_3$): Expected mass: 265.35; Observed mass: 266.15 (M+1). FT-IR (KBr, ν_{max}, cm^{-1}): 3432, 1645, 1466, 1434.

11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-imidazo[2,1-*b*][3]benzazepine(stage-III) (9): Added formic acid (8.58 L) to a stage-II (**15**) (14.3 kg) at 25-30 ºC under stirring followed by the addition of 37% formaldehyde (2.43 kg) solution. The reaction mass was heated at 75-80 ºC and stirred for 1 h till HPLC complies. Cooled the reaction mass to 25-30 ºC, adjusted the pH 12.0-12.5 with aq. NaOH solution followed by the addition of CH_2Cl_2 (71.5 L) and stirred for 30 min. Separated the aqueous and organic layer, extract aqueous layer with CH_2Cl_2 twice (2 × 43 L). Combined all the organic layers and distilled off the solvent completely under vacuum at below 50 ºC and co-distilled with acetone (7 L). Cooled the residue to 25-30 ºC, added acetone (14 L) and stirred for 1 h

at 25-30 ºC. Filtered the isolated compound and washed thoroughly with chilled acetone (7 L). Charged the wet compound and THF (20 L) to a clean reactor and heated the contents at 60-65 ºC and then cooled the contents at 25-30 °C followed by 0-5 ºC with stirring for 1 h. Filtered the isolated compound again, washed with chilled THF (3.5 L), mixed with ethyl acetate (49 L) to above wet compound and then heated at the reaction mass at 70-75 ºC for 1 h. Added the activated carbon (0.186 kg), stirred for 1 h 70-75 ºC, filtered the carbon and washed the carbon bed with ethyl acetate (4.9 L). Distilled off the ethyl acetate until 1.5 volumes of ethyl acetate remains, filtered and washed with chilled ethyl acetate (4.9 L). Dried the compound under vacuum at 55-60 ºC for 12 h to get white solid of stage-III (9.55 kg, 63.4%) m.p.: 153.5 ºC (Lit. 154.5 ºC [1]); ^{1}H NMR (DMSO-d_6, δ ppm): 7.37-7.34 (m, 1H), 7.28-7.06 (m, 2H), 7.01-7.00 (d, 1H), 6.88 (d, 1H), 4.40-4.35 (m, 1H), 3.88-3.96 (m, 1H), 3.39-3.32 (m, 1H), 2.99-2.93 (m, 1H), 2.74-2.49 (m, 4H), 2.33-2.20 (m, 1H), 2.18-2.14 (m, 1H), 2.10 (m, 3H), 2.04-2.00 (m, 2H). MS (m.f.: $C_{18}H_{21}N_3$); Expected mass: 279.37; Observed mass: 280.17 (M+1). FT-IR (KBr, ν_{max}, cm^{-1}): 3465, 2780, 1644, 1423, 1377.

6,11-Dihydro-11-(1-methyl-4-piperidinylidene)-5*H*-imidazo[2,1-*b*][3]benzazepine-3-carboxaldehyde (alcaftadine) (stage-V) (11)

Step-A: Stage-III (**9**) (1.5 kg), acetic acid (0.75 L) and 37% aq. HCHO (8.1 kg) and anhydrous potassium acetate (0.19 kg) were mixed at 25-30 ºC, heated the reaction mass at 95-100 ºC under stirring and maintained for 10-l5 h at 95-100 ºC. The progress of the reaction was monitored by HPLC for > 65% of stage-IV (**10**) conversion. Reaction mass was cooled to 25-30 ºC and CH_2Cl_2 (15 L) was added. The pH of reaction mass was adjusted to 11-12 with aq. NaOH solution and stirred for 10-15 min. The organic layer was separated and washed successfully with brine solution. The organic layer was concentrated below 60 ºC to obtain a residue. The residue was co-distilled with chloroform (3 L) and concentrated below 60 ºC to obtain a crude residue.

Step-B: The crude residue of step-A was dissolved in chloroform (16.5 L) and MnO_2 (4.69 kg) was added at 25-30 ºC. Reaction mass was heated at 55-65 ºC and maintained for 8-10 h. The progress of reaction was monitored by HPLC till diol (**16**) is below 1.3%. The reaction mass was cooled at 25-30 ºC, filtered through hyflow bed and washed with CH_2Cl_2 (5.63 L). The washings of CH_2Cl_2 and $CHCl_3$ filtrate was combined and concentrated below 60 ºC to obtain a residue. The residue was co-distilled with acetonitrile (3 L) and cooled to 25-30 ºC. Added acetonitrile (1.5 L) to the residue and stirred for 1 h at 25-30 ºC. The solid isolated was filtered and washed with acetonitrile (0.75 L) to get wet solid.

Step-C: Step-B wet solid was dissolved in $CHCl_3$ (12.75 L) followed by the addition of MnO_2 (3.1 kg) at 25-30 ºC under stirring. The reaction mass was heated to 45-50 ºC and maintained at the same temperature for 1 h. Progress of reaction was monitored by HPLC. After the completion of reaction, reaction mixture was cooled to 25-30 ºC; filtered through hyflow bed and washed with CH_2Cl_2 (5.63 L). The washings of CH_2Cl_2 and $CHCl_3$ filtrate were combined, concentrated below 60 ºC to obtain a residue and then co-distilled with acetonitrile (2 L). To the above content, acetonitrile (3 L) was added at 25-30 ºC under stirring and then raised the temperature of the reaction mixture and maintained at 70-80 ºC for 1 h. The content was cooled at 10-15 ºC and left for 1 h. The free solid obtained was filtered and washed with chilled acetonitrile (0.75 L).

Step-D: The wet solid obtained in step-C was taken into a clean reactor and acetonitrile (1.58 L) was charged and heated at 70-80 ºC for 1 h under stirring. Distilled water (0.07-0.23 L) was slowly added to the contents till formation of a clear solution at 70-80 ºC. Activated charcoal (0.15 kg) was added to the solution and heated at 70-80 ºC for 1 h. The contents were filtered through hyflow bed at 70-80 ºC and washed the bed with hot acetonitrile (0.5 L). The filtrate and washings were combined, again heated at 70-80 ºC for 1 h and then slowly cooled at 10-15 ºC in 2-4 h. The obtained solid was filtered and washed with chilled acetonitrile (0.25 L).

Step-E: The wet solid obtained in step-D was refluxed with ethyl acetate (4.5 L) at 75-80 ºC for 1 h under stirring and clear solution obtained was passed through 0.6 µm filter into other reactor of clean room, washed the line with hot ethyl acetate (1.5 L) and then the contents were cooled to 0-5 ºC. Then *n*-heptane (8 L) was added and stirred for 1 h at 0-5 ºC. The obtained solid was filtered, washed with chilled *n*-heptane (2 L) and dried in vacuum at 55-60 ºC for 10-12 h to get pure alcaftadine API (0.33 kg, 20%). m.p.: 170.8 ºC (Lit [1]: 171.6 ºC). ^{1}H NMR ($CDCl_3$, δ ppm): 9.63 (s, 1H), 7.77 (s, 1H), 7.29-7.18 (m, 4H), 4.78-4.70 (m, 1H), 4.38-4.28 (m, 1H), 3.63-3.52 (m, 1H), 3.00-2.93 (m, 1H), 2.89-2.78 (m, 3H), 2.68-2.63 (m, 1H), 2.50-2.36 (m, 2H), 2.29 (s, 3H), 2.26-2.20 (m, 1H), 2.18-2.07 (m, 1H). MS (m.f.: $C_{19}H_{21}N_3O$); Expected mass: 307.39; Observed mass: 308.23 (M+1). FT-IR (KBr, ν_{max}, cm^{-1}): 3314, 2783, 1666, 1425, 1277.

(11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[*d*]imidazo[1,2-*a*]azepin-3-yl)methanol (stage-IV) (10): ^{1}H NMR ($CDCl_3$, δ ppm): 7.39-7.36 (m, 1H), 7.27-7.23 (m, 1H), 7.10-7.07 (m, 1H), 6.80 (s, 1H), 4.96 (s, 1H), 4.38-4.34 (m, 3H), 3.96-3.86 (m, 1H), 3.44-3.33 (m, 2H), 3.04-2.99 (m, 1H), 2.81-2.62 (m, 4H), 2.51-2.21 (m, 7H). MS (m.f.: $C_{19}H_{23}N_3O$); Expected mass: 309.41; Observed mass: 310.15 (M+1). FT-IR (KBr, ν_{max}, cm^{-1}): 3241, 2788, 1639, 1418, 1271.

(11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[*d*]imidazo[1,2-*a*]azepine-2,3-diyl)dimethanol (Diol) (16): ^{1}H NMR ($CDCl_3$, δ ppm): 7.26-7.09 (m, 4H), 4.52-4.49 (m, 4H), 4.43-4.35 (m, 1H), 4.05-3.96 (m, 1H), 3.58-3.48 (m, 2H), 2.94-2.89 (m, 1H), 2.84-2.65 (m, 4H), 2.42-2.21 (m, 5H), 2.05-1.97 (m, 2H). MS (m.f.: $C_{20}H_{25}N_3O_2$); Expected mass: 339.14; Observed mass: 340.14 (M+1). FT-IR (KBr, ν_{max}, cm^{-1}): 3274, 2790, 1641, 1425, 1280.

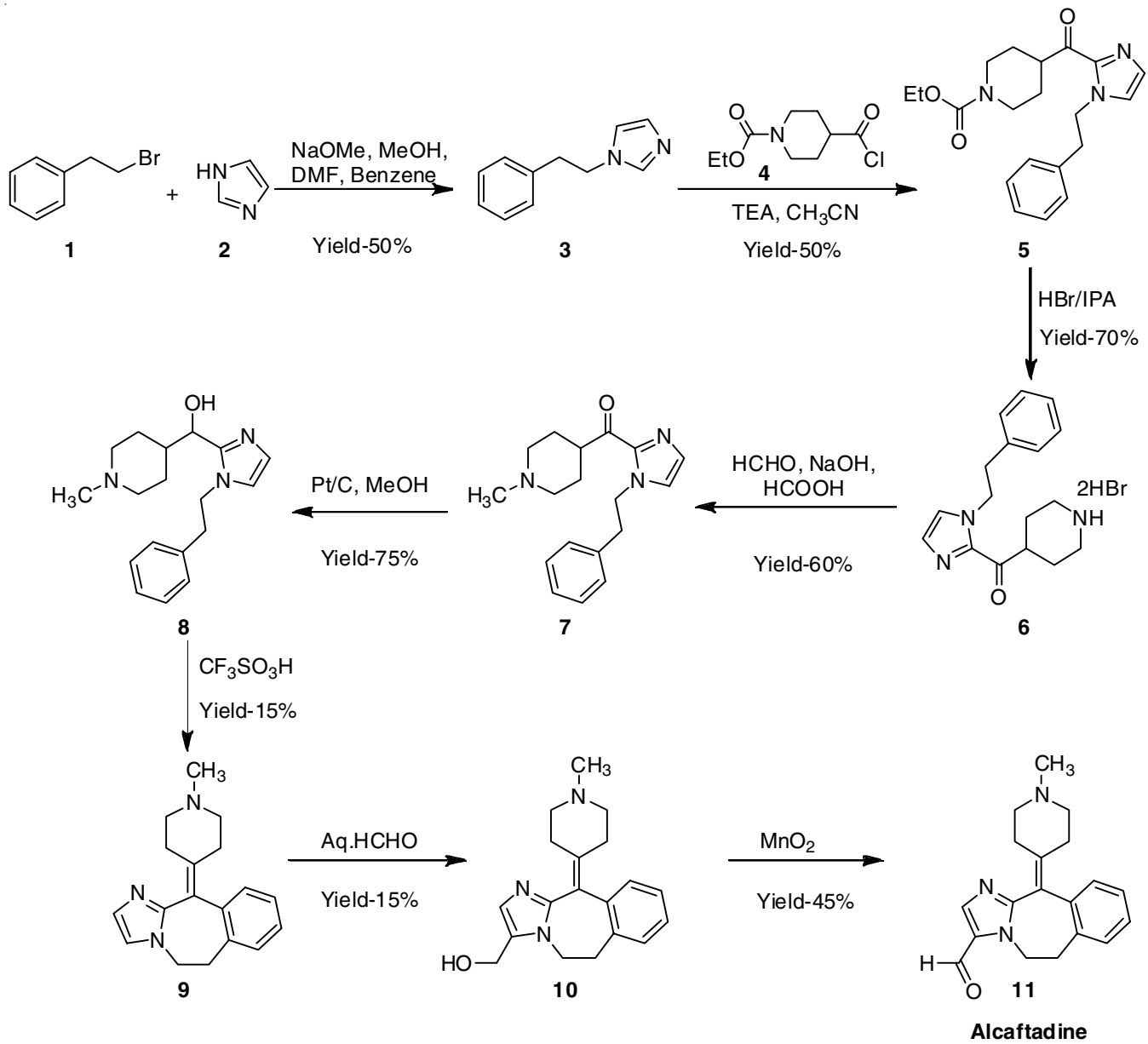
11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[*d*]imidazo[1,2-*a*]azepine-2,3-dicarbaldehyde (dialdehyde) (18): ^{1}H NMR ($CDCl_3$, δ ppm):10.20 (s, 1H), 10.07 (s, 1H), 7.42-7.40 (m, 1H), 7.35-7.26 (m, 2H),7.18-7.15 (m, 1H), 4.72-4.67 (m, 1H), 4.33-4.24 (m, 1H), 3.58-3.43 (m, 1H), 3.12-3.05 (m, 1H), 2.91-2.80 (m, 4H), 2.50-2.40 (m, 5H). MS (m.f.: $C_{20}H_{21}N_3O_2$); Expected mass: 335.41; Observed mass: 336.11 (M+1). FT-IR (KBr, ν_{max}, cm^{-1}): 3409, 2939, 1661, 1453, 1285.

RESULTS AND DISCUSSION

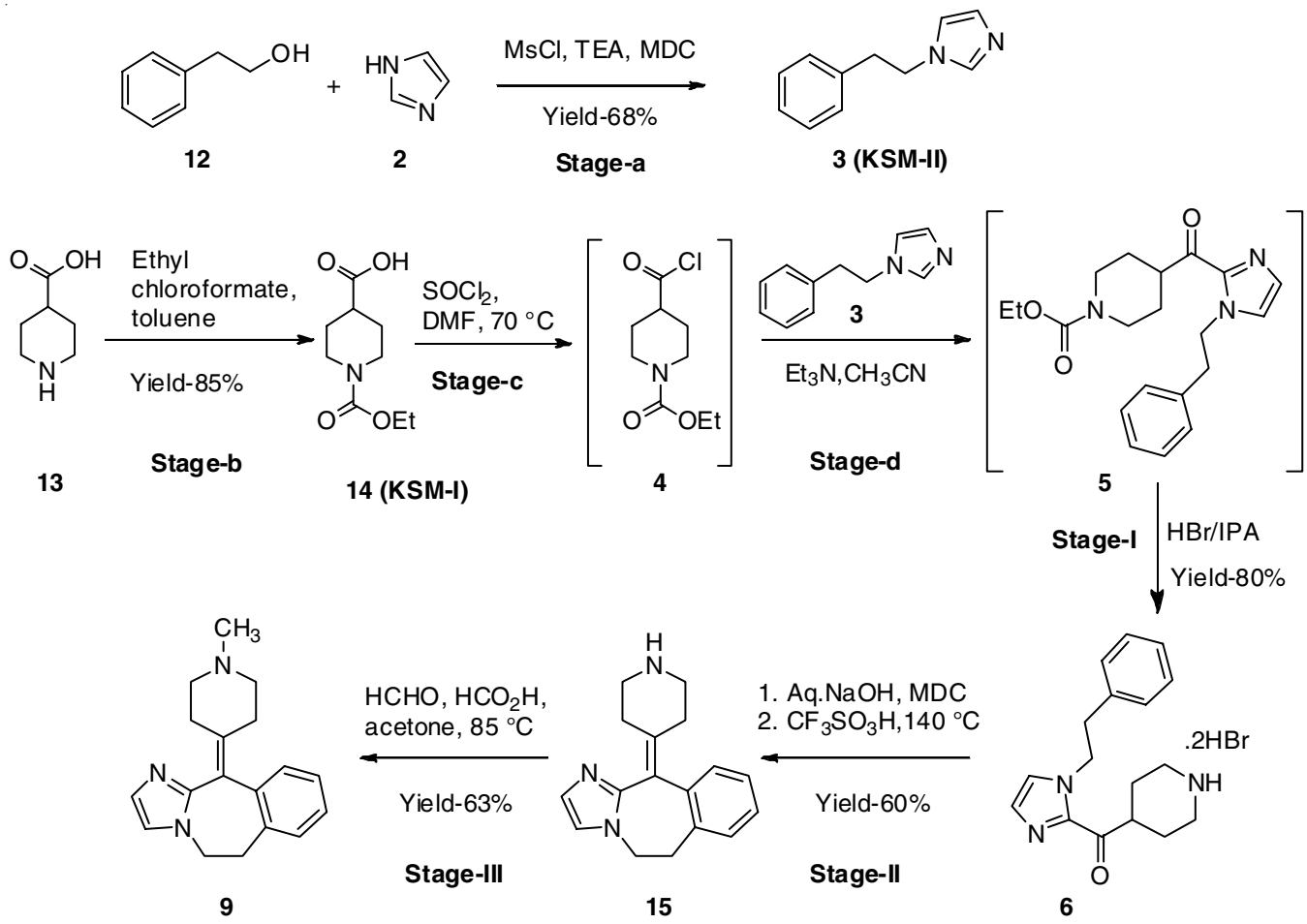
Synthesis of alcaftadine as reported in patent US5468743 is depicted in **Scheme-I**. Major drawbacks of this process are the numbers of steps (eight), use of highly carcinogenic benzene as a solvent in the first step, low yields of the penultimate and pre-penultimate intermediates and purification of using column chromatography. The process also involves the use of expensive platinum catalyst. Hence, it was considered worthwhile to look for a cost effective and easy-to-scale process of alcaftadine with modification of the existing route of synthesis (ROS) and reaction conditions to attain comparatively better yield.

The Neuland ROS for stage-III product **9** is shown in **Scheme-II**. The key starting material-I (KSM-I) (**14**) was synthesized from piperidine-4-carboxylic acid (**13**) and ethyl chloroformate with ~85% yield. KSM-II (**3**) was prepared from 2-phenylethanol (**2**) by mesylation followed by reaction with imidazole (**2**) with ~68% yield. KSM-I (**14**) was then reacted with SO_2Cl_2 in DMF to generate the corresponding acid chloride, to which was slowly added KSM-II (**3**) in acetonitrile in presence of triethyl amine. After completion of the reaction, water was charged and product mixture was extracted with ethyl acetate. The ethyl acetate layer was concentrated to obtain a residue (**5**). To the residue, aq. HBr was added and the mixture was refluxed to hydrolyze the carbamate. Water was distilled from the reaction mass, isopropyl alcohol added to it and the mixture heated at 70 ºC; then cooled to 25 ºC and finally filtered to afford stage-I product **6** with ~80% yield and HPLC purity > 95% area.

Dihydrobromide **6** was converted to the free base with aqueous NaOH solution. The crude free base was cyclized to seven-membered ring using trifluoromethanesulfonic acid (triflic acid) at 140-150 ºC for 10 h. The reaction mixture was quenched using aqueous NaOH solution. Work-up using



Scheme-I



Scheme-II

CH_2Cl_2, followed by distillation of solvent and isolation in acetone yielded stage-II product **15** with ~60% yield and HPLC purity > 95% area.

Compound **15** was methylated using formic acid and formaldehyde at 80 ºC for 1-2 h *via* Eschweiler-Clark protocol. After completion of reaction, the pH was adjusted to ~12 with aqueous NaOH solution. The product mixture containing **9** was extracted into CH_2Cl_2, the solution was then concentrated and the residual solid was isolated in acetone. The crude compound was purified with ethyl acetate at reflux temperature, the solvent then distilled off partially and cooled to 15-20 ºC to generate a solid. The suspension was filtered and isolated solid was dried to yield stage-III (**9**) with ~63% yield and HPLC purity > 98% area.

Conversion of compound **9** to alcaftadine proceeded through stage-IV (**10**), formed by hydroxymethylation reaction using potassium acetate, acetic acid and formaldehyde at 100 ºC (**Scheme-III**). However, the stage-IV product (**10**) was further reacted during the same reaction condition to give diol impurity **16**. This impurity was the reason to purify compound **10** using column chromatography in the original synthesis since recrystallization conditions were not working for compound **10** purification.

Process optimization of hydroxymethylation reaction was investigated using potassium acetate (0.35 mol), acetic acid (0.5 V) in formaldehyde solution (5 V) at 100 °C by using HPLC (Fig. 1). After 15 h, a in-process sample of HPLC revealed stage-IV (**10**) (~70% area), stage-III (**9**) (~15% area) and diol (**16**) (~15% area). Further after 20 h, the HPLC results are as follows: stage-IV (**10**) (~65% area); stage-III (**9**) (~10% area) and diol (**16**) (~25% area). Hence, it was concluded that under these conditions, the maximum conversion of stage-III (**9**) to stage-IV (**10**) is ~70% area by HPLC. When reaction was heated for a longer time or by adding extra reagent, it resulted in a decrease in stage-IV (**10**) to ~65% area, stage-III (**9**) to ~10% area and an increase in diol (**16**) to ~25% area by HPLC.

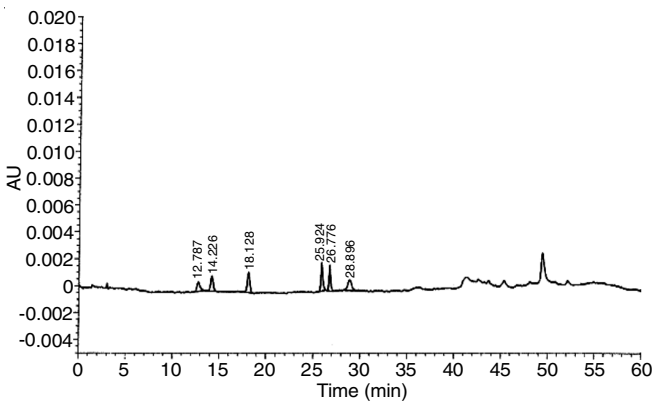
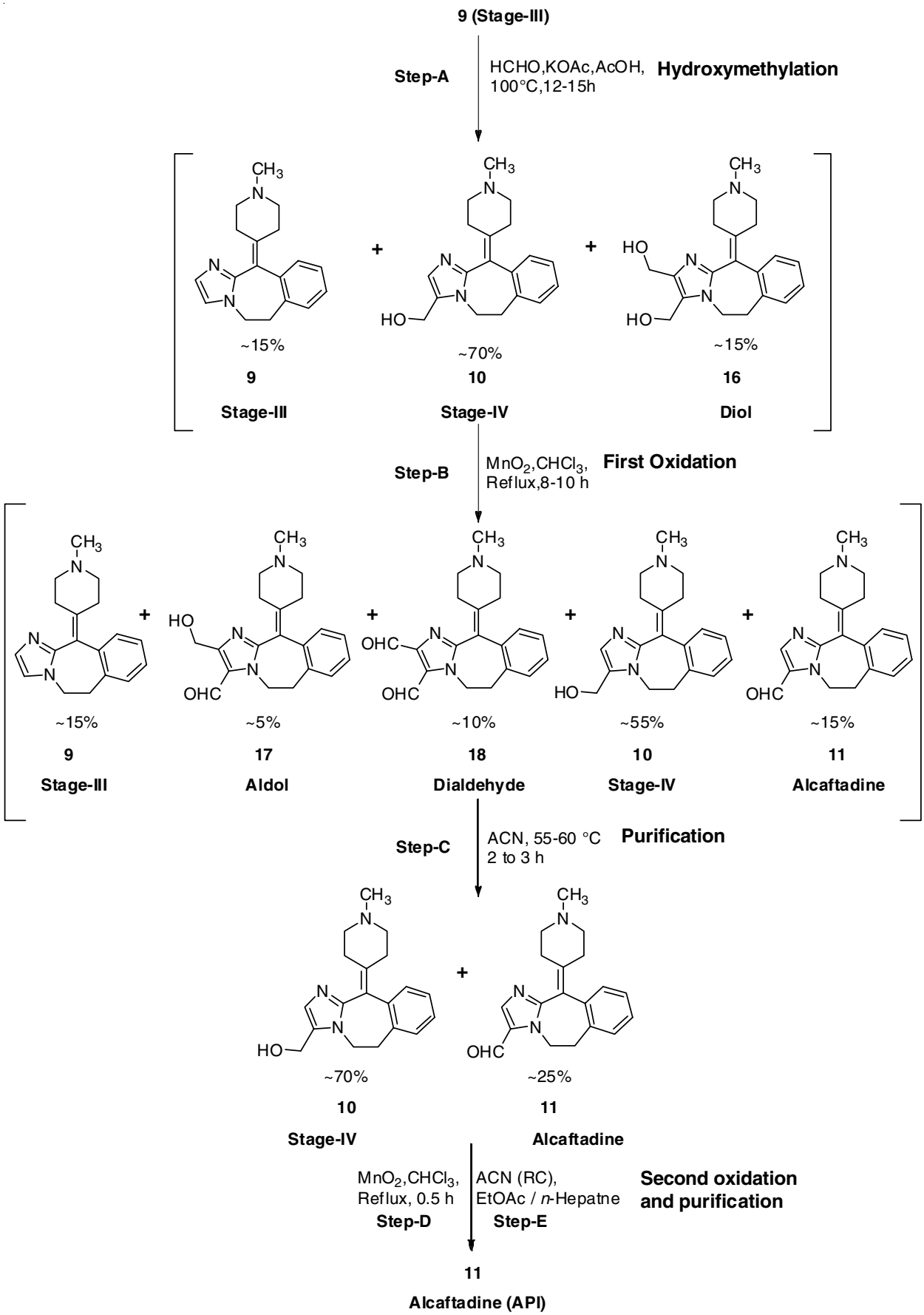


Fig. 1. Typical HPLC chromatogram with system suitability solution


9 (Stage-III)
Step-A
HCHO,KOAc,AcOH,
100°C,12-15h
Hydroxymethylation
~15%
9
Stage-III
~70%
10
Stage-IV
~15%
16
Diol
Step-B
MnO_2,$CHCl_3$,
Reflux,8-10 h
First Oxidation
~15%
9
Stage-III
~5%
17
Aldol
~10%
18
Dialdehyde
~55%
10
Stage-IV
~15%
11
Alcaftadine
Step-C
ACN, 55-60 °C
2 to 3 h
Purification
~70%
10
Stage-IV
~25%
11
Alcaftadine
MnO_2,$CHCl_3$,
Reflux, 0.5 h
Step-D
ACN (RC),
EtOAc / *n*-Hepatne
Step-E
Second oxidation
and purification
11
Alcaftadine (API)

Scheme-III

It was important to remove the diol impurity and unreacted stage-III (**9**) from the reaction mixture. The original way was recrystallization but after attempting various solvents or their combinations, the best yield achieved for stage-IV (**10**) by acetone (1 V) crystallization process was ~16% area having diol (**16**) ~2% area and stage-III (**9**) ~1% area by HPLC. All other solvents used resulted in the generation of a sticky reaction mixture. The second option tried to purify stage-IV (**10**) was silica gel (neutralized with triethylamine) column chromatography. However, the volume of solvents required was very high and it was neither reproducible nor feasible at scale production. Hence, it was considered worthwhile to look for an alternative way to remove stage-III (**9**) and diol impurity from the crude stage-IV (**10**) reaction mass.

The third option tried was complete oxidation of crude reaction mass *i.e.* stage-IV (**10**) having stage-III (**9**) and diol (**16**). After exploring oxidizing regents like ceric ammonium nitrate (CAN), TEMPO/NaOCl and Dess-Martin Periodinane (DMP), in various solvent combination for oxidation of crude stage-IV (**10**), MnO_2 (oxidation grade)-$CHCl_3$ combination was found to yield a favourable result with no over-oxidation product like acid compound formation. Although $CHCl_3$ is not an ideal solvent from an industrial standpoint (Class-2 limit: 60 ppm), but it was successfully removed from the final API by following EtOAc:*n*-heptane recrystallization. Initially, when we carried out the reaction of crude stage-IV (**10**) in refluxing $CHCl_3$ by using multiple lots of fresh MnO_2, reaction was partially completed, stage-IV (**10**) was ~10% present by HPLC; however, there was no diol impurity. Extra lots of the MnO_2 resulted in no further reaction. A key problem in the reaction was the liberation of water during oxidation reactions, which deactivated the fresh MnO_2. To complete the reaction, large quantity of MnO_2 (35-45 mol) were required, which in turn resulted in loss of yield. Alcaftadine isolated by this process did not have ICH-guideline purity. Attempts to charge the MnO_2 in further small portions, also resulted in very long reaction time (48 h) and unknown impurity formation, which was very difficult to remove.

However, the above experiments gave us an important clue that the diol impurity (**16**) is more reactive than stage-IV alcohol (**10**). Based on this observation, we carried out the oxidation using 15 mol of fresh MnO_2. During the reaction, it was observed that the diol converted to the non-polar dialdehyde compound (**18**) within first 15 min of reaction, as indicated by TLC. It is thought that this non-polar dialdehyde compound (**18**) may be easy to remove from the crude reaction mass by leaching in suitable solvent. The first oxidation reaction monitoring in larger scale showed following profile by HPLC: stage-III (**9**) ~15% area, stage-IV (**10**) ~55% area, diol (**16**) ~1% area, dialdehyde (**18**) ~10% area, aldol (**17**) ~5% area and alcaftadine (**11**) ~15% area (**Scheme-III**). Thus, the first (partial) oxidation reaction got rid of the diol impurity but it left behind three new oxidation products dialdehyde, aldol and Alcaftadine. Now the challenge was to remove dialdehyde (**18**) and aldol (**17**) from the reaction mass by using suitable solvent without much loss of stage-IV (**10**) and alcaftadine (**11**). After completion of the first oxidation reaction, the spent MnO_2 was filtered off and the filtrate was concentrated and co-distilled with acetonitrile to obtain a crude mass. This crude mass on acetonitrile (1 V) slurry at 50-55 ºC for 1h followed by filtration resulted as a pale yellow crystalline solid compound. This solid showed a surprising HPLC profile, stage-IV (**10**) ~70% area and alcaftadine (**11**) ~25% area by HPLC. The spent aceto-nitrile mother liquor contained three undesired compounds stage-III (**9**), dialdehyde (**18**) and aldol (**17**). Thus, three undesired compounds of stage-IV (**10**) reaction were completely removed after first oxidation reaction followed by acetonitrile slurry operation.

The second oxidation reaction of stage-IV (**10**) and alcaftadine (**11**) mixture was carried out in $CHCl_3$ at 45-50 ºC by using MnO_2 (5 mol) for 30 min to get alcaftadine (**11**) with ~98% area by HPLC. TLC showed complete disappearance of stage-IV (**10**). After completion of reaction, the spent MnO_2 was filtered and $CHCl_3$ was concentrated to obtain crude product. This crude compound on acetonitrile recrystallization gave alcaftadine (**11**) technical grade [29]. The technical grade sample was purified by ethyl acetate:*n*-heptane mixture to get pure alcaftadine (API grade) with all kind of impurities (organic, inorganic, residual solvent, heavy metal, GTI) under ICH guidelines. The overall yield obtained in the process over two oxidation steps from stage-III (**9**) to alcaftadine (**11**) was ~20% yield with high quality (HPLC > 99.5% area).

Conclusion

A novel method to remove the diol (**16**) formed during the alcaftadine synthesis is developed by using two oxidation reactions instead of column chromatography. High quality alcaftadine API was achieved with ~20% overall yield from stage-III (**9**) against product patent yield ~6.7%. Synthesis of alcaftadine by double oxidation process is cost effective and commercially viable for scale up. Three process validation batches in plant from stage-I to stage-V (alcaftadine API) were successfully completed by following current process and filed a US DMF (No. 28277) to manufacture alcaftadine API at Neuland Laboratories Ltd.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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