Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(3):91-100
(http://derpharmachemica.com/archive.html)

Synthesis and characterization of Novel Related Substances of Lumefantrine, an anti-malarial drug

***[b]Madhuresh Kumar Sethi,*[a] Anantavena Rani Gonuguntla, [a]Siva Lakshmi Devi Arikatla, [a]Suryanarayana Mulukutla, [b]Rajakrishna Yerramalla, [b]Jaganmohanarao Bontalakoti, [b]Lakshminarayana Vemula and [b]Jayaprakash Thirunavukarasu**

[a]Department of Analytical Development & [b]Department of Research and Development, Mylan Laboratories ltd, Plot No. 31, 32, 33 & 34A, ANRICH Industrial Estate, Bollaram Village, Jinnaram Mandal, Medak Dt-502 325, Andhra Pradesh, India

---

ABSTRACT

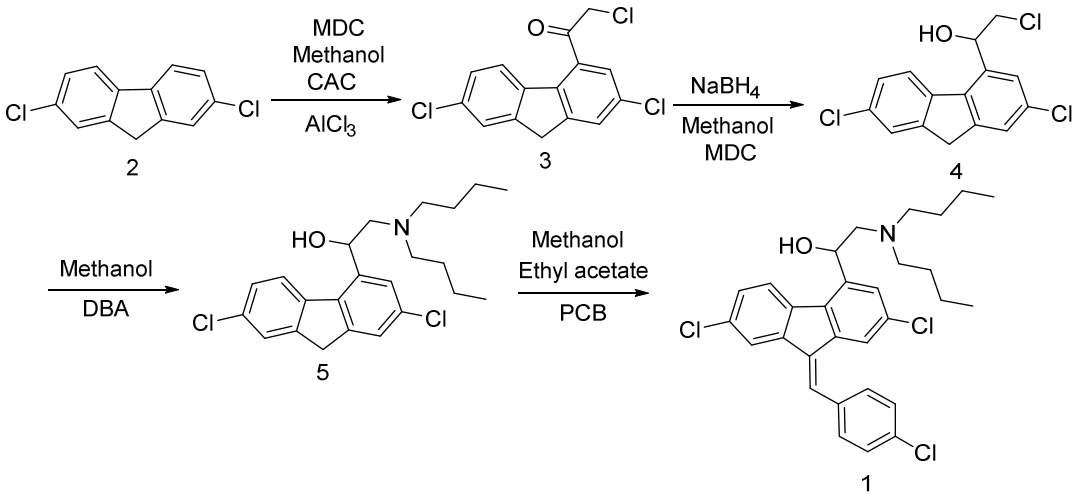
*Structural characterization related substances of Lumefantrine using IR, NMR data (^{1}H & ^{13}C NMR & MS). During the process development of Lumefantrine, a known antimalarial drug, six related substances were identified. All the six impurities were subsequently synthesized and characterized by IR, NMR and MS spectral data. The six related substances are known as 1-[(9Z)-2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]-2-(diethylamino)ethanol **6**, 2-(butylamino)-1-[(9Z)-2,7-dichloro-9-(4-chloro benzylidene)-9H-fluoren-4-yl]ethanol **7**, 2,7-dichloro-4-[2-(dibutyl amino)-1-hydroxyethyl]-9H-fluoren-9-one **8**, 1-[(9Z)-9-benzylidene-2,7-dichloro-9H-fluoren-4-yl]-2-(dibutylamino) ethanol **9**, 2-(dibutylamino)-1-[(9Z)-2,7-dichloro-9-(3-chlorobenzylidene)-9H-fluoren-4-yl]ethanol **10**, and 2-(dibutylamino)-1-[(9Z)-2,7-dichloro-9-(2-chlorobenzylidene)-9H-fluoren-4-yl]ethanol **11**. The present work describes the formation, synthesis and characterization of these impurities. By controlling these new six process related substances will make this high doses anti-malarial drug safer for human use*

Keywords: Lumefantrine, antimalarial, related substances, impurities, synthesis, and characterization

---

INTRODUCTION

Lumefantrine is an antimalarial drug chemically known as 2-(dibutylamino)-1-[(9Z)-2, 7-dichloro-9-(4-chlorobenzylidene)-9H-floren-4-yl] ethanol, which is used in the prevention and treatment of Malaria in worm blooded animals. Lumefantrine is using the combination of β-Artemether in the treatment of Malaria. Lumefantrine is an important drug substance and to obtain information on product profile, a comprehensive study was undertaken on the impurities generated during the process development (Scheme 1).[1-7]

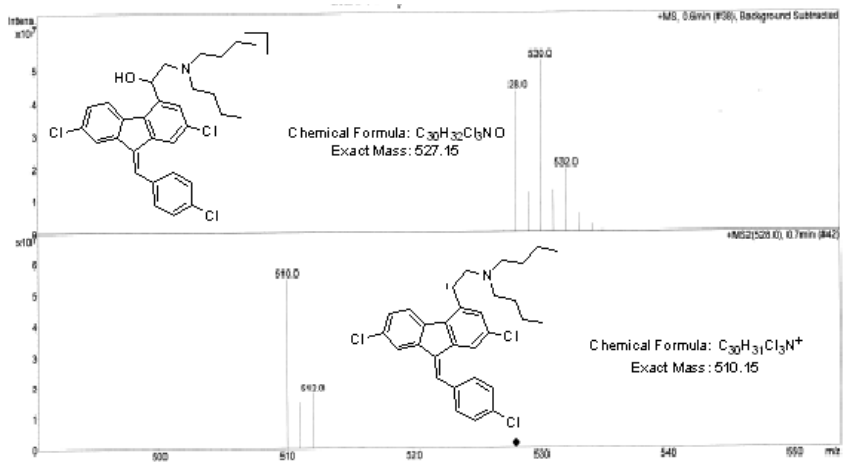


Scheme 1. Reported synthetic scheme for Lumefantrine

MATERIALS AND METHODS

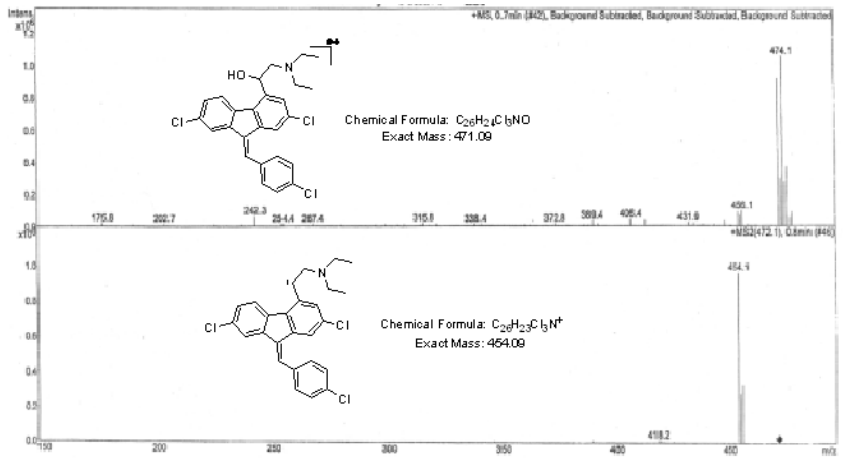
General. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz respectively on *Bruker 300 MHz Advance NMR spectrometer*. The ^{1}H and ^{13}C chemical shifts are reported on δ scale in ppm, relative to TMS (δ 0.00ppm) and $CDCl_3$ (77.00ppm) as internal standards respectively. Some of the impurities also recorded in DMSO-d_6 at 300 MHz and 75 MHz respectively. The ^{1}H and ^{13}C chemical shifts are reported on δ scale in ppm, relative to TMS (δ 0.00ppm) and DMSO-d_6 (δ 39.50ppm) as internal standards respectively. The FT-IR spectra were recorded in the solid state as KBr dispersion using a *Perkin Elmer Spectrum One Spectrometer*. The Mass spectral data was recorded on an *Agilent 1100 Series LC-MSD-TRAP-SL system* and *Perkin-Elmer Clarus GC-MS system*. The percentage of Carbon, Hydrogen and Nitrogen was determined by using *Thermo Finnigan Flash EA1112 Elemental analyzer*.

Preparation of 2-(dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(4-chlorobenzylidene)-9H-floren-4-yl] ethanol (Lumefantrine) 1. To a stirred solution of NaOH (1.97 g 0.0492 mol) in methanol (100 ml) there was added 1-(2, 7-dichloro-9 H-fluren-4-yl)-2-(dibutyl amino) ethanol (10 g, 0.0246 mol) and para chloro benzaldehyde (5.24 g 0.0372). The suspension obtained was stirred at reflux temperature till the absence of starting material by TLC. After confirming the product formation reaction mixture was cooled to room temperature and further stirred at same temperature for overnight. The precipitated solids were filtered and washed with methanol and dried under vacuum at 50°C to get desired compound. (Purity by HPLC: 99%). IR (cm^{-1}): 3408, 3092, 2953, 2928, 2870, 2840, 1634, 1589, 1487, 1465, 1443, 1400, 1365, 1308, 1268, 1241, 1207, 1173, 1156, 1085, 1071, 1014, 980, 933, 874, 839, 815, 806, 770; ^{1}H NMR ($CDCl_3$, δ ppm): 7.75 (d, 1H, CH, *J* 1.5 Hz), 7.68 (d, 1H, CH, *J* 1.5 Hz), 7.60-7.63 (m, 1H, CH), 7.32-7.35 (dd, 1H, CH, *J* 1.7,8.3 Hz), 7.45-7.50 (m, 1H, CH), 5.35-5.39 (dd, 1H, CH, *J* 3.0,9.9 Hz), 2.41-2.74 (m, 1H, CH_2Ha), 2.86-2.92 (m, 1H, CH_2Hb), 2.41-2.74 (m, 4H, CH_2), 1.25-1.56 (m, 8H, CH_2), 0.97 (t, 1H, CH, *J* 7.2 Hz), 7.60-7.63 (m, 1H, CH), 7.45-7.50 (m, 4H, CH), 4.54 (broad, 1H, OH), ^{13}C NMR ($CDCl_3$, δ ppm): 138.2, 141.5, 120.6, 133.2, 126.3, 135.0, 135.0, 136.4, 123.9, 128.3, 132.8, 123.0, 139.8, 65.5, 60.0, 53.5, 29.1, 20.6, 14.0, 127.6, 134.7, 130.5, 129.1, 133.2; MS: m/z: 528 $[M+H]^+$; Analysis calcd. for $C_{30}H_{32}Cl_3NO$: C, 68.12; H, 6.10; N, 2.65% Found: C, 68.38; H, 6.14; N, 2.63 %.



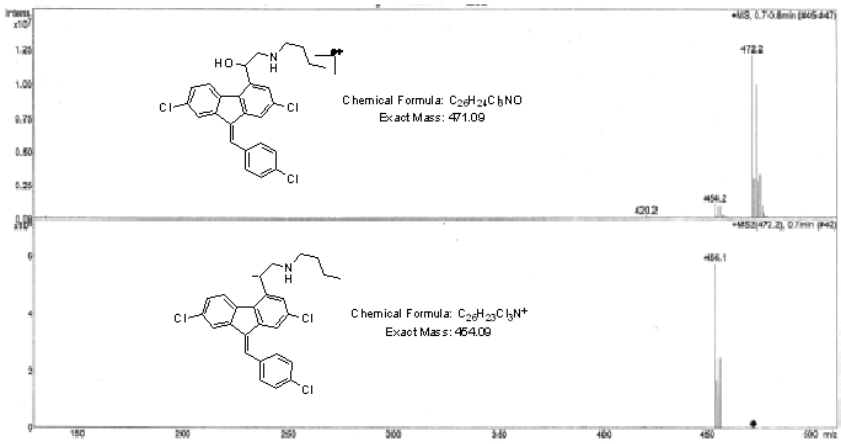
1-[(9*Z*)-2, 7-dichloro-9-(4-chlorobenzylidene)-9*H*-fluoren-4-yl]-2-(diethylamino) ethanol 6.

(Diethyl amine Impurity). To a stirred solution of p-chlorobenzaldehyde (5.22 g 0.0371 mol) in methanol (50 ml) there was added 1-(2,7-dichloro-9 H-fluren-4-yl)-2-(diethyl amino)ethanol (10 g, 0.0286 mol). The suspension was heat to 50-60^{0}C and sodium hydroxide (2.3 g 0.0575) solution in methanol (100ml). The suspension obtained was stirred at reflux temperature till the absence of starting material by TLC. The reaction mass was cooled to room temperature and stirred overnight, recovered material by filtration and washed with methanol and dried under vacuum at 50^{0}C to get desired compound. (Purity by HPLC: 99%). IR (cm^{-1}): 3412, 3080, 2970, 2932, 2831, 1630, 1591, 1489, 1462, 1443, 1407, 1373, 1327, 1262, 1239, 1200, 1162, 1109, 1090, 934, 885, 871, 860, 808, 747; ^{1}H NMR ($CDCl_3$, δ ppm): 7.75 (d, 1H, CH, *J* 1.8 Hz), 7.68 (d, 1H, CH, *J* 1.8 Hz), 7.60-7.66 (m, 1H, CH), 7.33-7.37 (dd, 1H, CH, *J* 1.8,8.4 Hz), 7.44-7.54 (m, 1H, CH), 5.36-5.40 (dd, 1H, CH, *J* 3.3,10.2 Hz), 2.39-2.47 (dd, 1H, CH_2Ha, *J* 10.2,12.9 Hz), 2.89-2.93 (dd, 1H, CH_2Hb, *J* 3.6,12.9 Hz), 2.60-2.84 (m, 4H, CH_2), 1.10 (t, 4H, CH_2, *J* 7.1 Hz), 7.60-7.75, (m, 1H, CH), 7.44-7.54 (m, 4H, CH), 4.59 (broad, 1H, OH), ^{13}C NMR ($CDCl_3$, δ ppm): 138.2, 141.5, 126.3, 134.1, 120.6, 134.9, 134.9, 136.4, 123.9, 128.4, 132.8, 122.9, 139.9, 65.3, 58.8, 46.6, 11.8, 127.6, 134.6, 130.5, 129.0, 133.1; MS: m/z: 472 $[M+H]^+$.

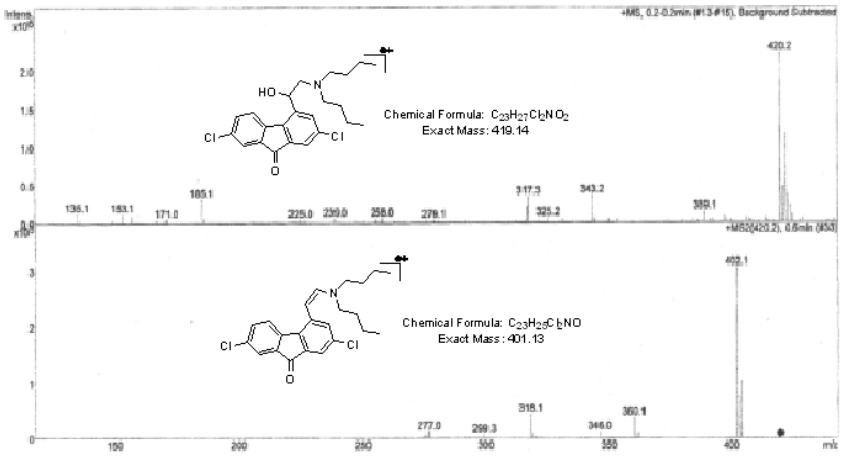


2-(butylamino)-1-[(9*Z*)-2,7-dichloro-9-(4-chloro benzylidene)-9*H*-fluoren-4-yl]ethanol 7 (Desbutyl Lumefantrine). To a stirred solution of p-chlorobenzaldehyde (5.22 g 0.0371 mol) in methanol (50 ml) there was added 2-(butylamino)-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol (10 g, 0.0286 mol). The suspension was heat to 50-60^{0}C and sodium hydroxide (2.3 g 0.0575) solution in methanol (100ml). The suspension obtained was stirred at reflux temperature till the absence of starting material by TLC. The reaction mass was cooled to room temperature and stirred overnight, recovered material by filtration and washed with methanol and dried under vacuum at 50^{0}C to get desired compound. (Purity by HPLC: 91%). IR (cm^{-1}): 3433, 3320, 2958, 2926, 2862, 2834, 1673, 1629, 1590, 1489, 1439, 1432, 1408, 1268, 1102, 1088, 1015, 931, 879, 867, 835, 773; ^{1}H NMR ($CDCl_3$, δ ppm): 7.65-7.76 (m,

1H, CH), 7.65-7.76 (m, 1H, CH), 7.54-7.62 (m, 1H, CH), 7.28-7.37 (m, 1H, CH), 7.39-7.50 (m, 1H, CH), 5.40 (d, 1H, CH, *J* 6.9 Hz), 2.57-2.79 (m, 1H, CH_2Ha), 3.07-3.12 (m, 1H, CH_2Ha), 2.57-2.79 (m, 2H, CH_2), 1.25-1.56 (m, 2H, CH_2), 1.25-1.56 (m, 2H, CH_2), 0.94 (t, 3H, CH_3, *J* 7.2 Hz), 7.54-7.62 (m, 1H, CH), 7.39-7.50 (m, 4H, CH), ^{13}C NMR ($CDCl_3$, δ ppm): 138.24, 141.47, 119.35, 133.03, 126.12, 134.93, 134.72, 136.25, 124.12, 128.81, 132.36, 123.73, 139.92, 68.00, 54.51, 49.22, 32.26, 20.34, 13.93, 127.79, 133.51, 130.52, 129.30, 132.91; MS: m/z: 472 $[M+H]^+$.

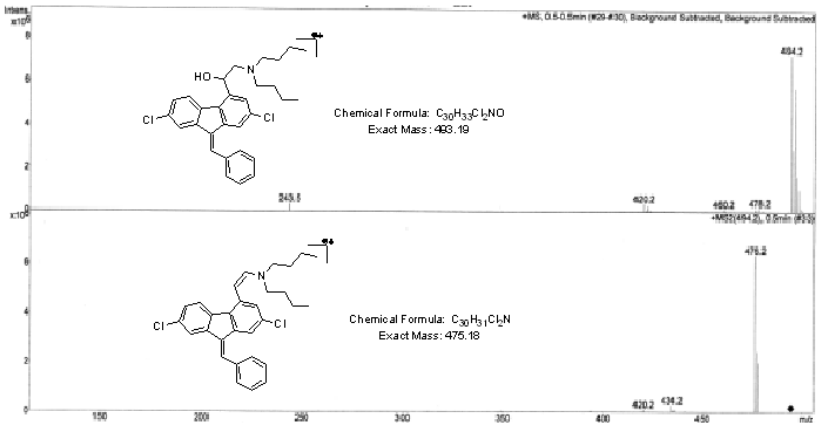


2, 7-dichloro-4-[2-(dibutylamino)-1-hydroxyethyl]-9*H*-fluoren-9-one 8 (Keto impurity). To a stirred of 1-(2,7-dichloro-9 H-fluren-4-yl)-2-(dibutylamino) ethanol (5 g, 0.0123) and methanol (100 ml) there was added sodium hydroxide (1.25 g, 0.0312) and stirred at room temperature , after confirming the absence of starting material concentrated the reaction mass to obtain the desired compound. (Purity by HPLC: 97%). IR (cm^{-1}): 3430, 2966, 2938, 2878, 1726, 1664, 1598, 1437, 1204, 1184, 1132, 1109, 829, 802, 784, 741, 724; ^{1}H NMR (DMSO-d_6, δ ppm): 7.75 (d, 1H, CH, J 1.5 Hz), 7.68 (d, 1H, CH, J 1.5 Hz),7.96-7.99 (m, 1H, CH), 7.74-7.76 (m, 1H, CH), 7.74-7.76 (m, 1H, CH), 5.58 (broad, 1H, CH), 3.12-3.36 (m, 2H, CH_2), 3.12-3.36 (m, 4H, CH_2), 1.66 (broad, 4H, CH_2), 1.28-1.41 (m, 4H, CH_2), 0.88-0.96 (m, 6H, CH_3), 6.76 (d, 1H, CH, J 3.6 Hz), ^{13}C NMR (DMSO-d_6, δ ppm): 190.2, 135.9, 124.2, 134.4, 133.5, 134.4, 141.1, 139.8, 123.7, 134.8, 135.4, 126.9, 138.5, 64.6, 56.3, 51.9, 53.4, 24.7, 19.4, 13.6; MS: m/z: 420 $[M+H]^+$.

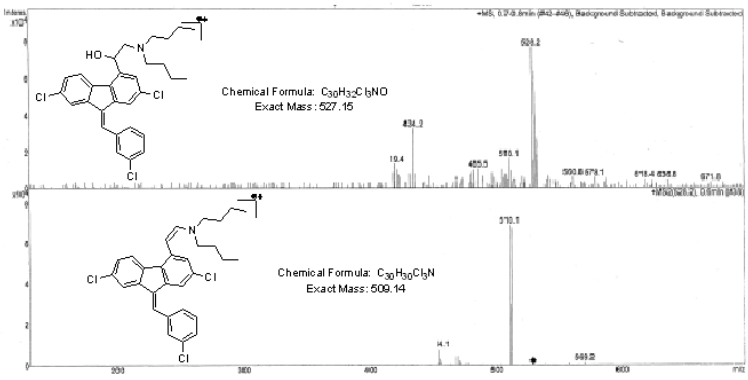


1-[(9Z)-9-benzylidene-2, 7-dichloro-9H-fluoren-4-yl]-2-(dibutylamino) ethanol 9 (Benzylidine impurity). To a stirred solution of Sodium hydroxide (0.98 g, 0.0246 mol) in methanol (100 ml) there was added benzaldehyde (1.68 g 0.0159 mol) and stirred for 30 minutes. Added 2-Dibutylamino-1-(2, 7-dichloro-9H-fluren-4-yl)-ethanol (5 g, 0.0123 mole) and heated to reflux temperature of reaction mixture. Continued the reflux till the absence of starting material. After confirming the product formation reaction mixture was cooled to room temperature and further stirred at same temperature for overnight. The precipitated solids were filtered and washed with methanol. (4.44 g,

Yield: 72%, Purity by HPLC: 94%). IR (cm^{-1}): 3433, 2956, 2930, 2861, 1633, 1493, 1442, 1407, 1325, 1266, 1209, 1179, 1154, 1108, 1074, 1029, 884, 856, 816, 771, 758, 696; ^{1}H NMR ($CDCl_3$, δ ppm): 7.41-7.55 (m, 1H, CH), 7.66-7.77 (m, 1H, CH), 7.60-7.63 (dd, 1H, CH, *J* 2.7,8.4 Hz), 7.66-7.77 (m, 1H, CH), 5.36-5.40 (dd, 1H, CH, *J* 3.0,9.9 Hz), 2.41-2.74 (m, 1H, CH_2Ha), 2.87-2.93 (dd, 1H, CH_2Hb, J 3.5,13.1 Hz), 2.41-2.74 (m, 4H, CH_2), 1.24-1.56 (m, 4H, CH_2), 1.24-1.56 (m, 4H, CH_2), 0.97 (t, 6H, CH_3, *J* 7.2 Hz), 7.66-7.77 (m, 1H, CH), 7.41-7.55 (m, 5H, CH); ^{13}C NMR ($CDCl_3$, δ ppm): 139.7, 141.6, 119.2, 133.0, 124.4, 135.4, 133.5, 136.3, 123.0, 129.4, 132.1, 120.5, 138.4, 65.5, 59.8, 53.3, 29.0, 20.5, 14.0, 125.7, 134.4, 129.0, 128.7, 128.3; MS: m/z: 494 $[M+H]^+$.

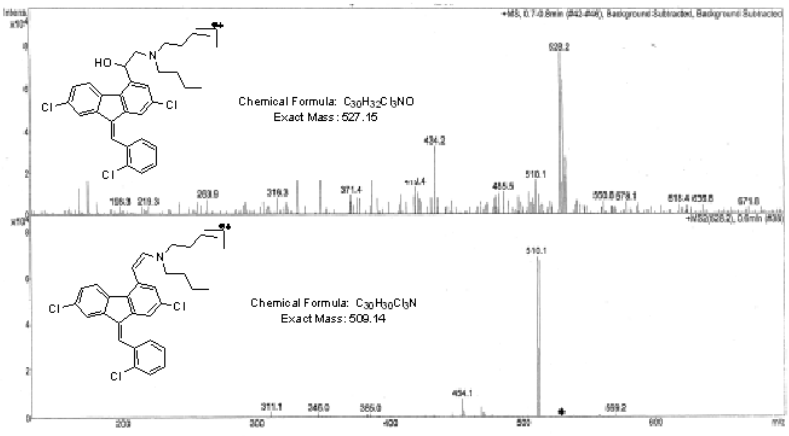


2-(Dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(3-chlorobenzylidene)-9*H*-fluoren-4-yl] ethanol 10 (Meta-Chloro impurity). To a stirred solution of Sodium hydroxide (0.98 g, 0.0246 mol) in methanol (100 ml) there was added meta chloro benzaldehyde (2.24 g 0.0319 mol) and stirred for 30 minutes. Added 2-Dibutylamino-1-(2, 7-dichloro-9H-fluren-4-yl)-ethanol (5 g, 0.0123 mole) and heated to reflux temperature of reaction mixture. Continued the reflux till the absence of starting material. After confirming the product formation reaction mixture was cooled to room temperature and further stirred at same temperature for overnight. The precipitated solids were filtered and washed with methanol. (5.8 g, Yield: 89 %, Purity by HPLC: 93%). IR (cm^{-1}): 3392, 2956, 2930, 2861, 1591, 1563, 1468, 1441, 1406, 1326, 1267, 1209, 1154, 1108, 1077, 895, 882, 817, 786, 770, 687; ^{1}H NMR ($CDCl_3$, δ ppm): 7.73-7.75 (dd, 1H, CH, *J* 1.7,5.3 Hz), 7.65-7.68 (dd, 1H, CH, *J* 1.8,7.8 Hz), 7.60-7.64 (m, 1H, CH), 7.29-7.51 (m, 1H, CH), 7.29-7.51 (m, 1H, CH), 5.37 (d, 1H, CH, *J* 9.0 Hz), 2.43-2.75 (m, 1H, CH_2Ha), 2.75-2.92 (dd, 1H, CH_2Hb, *J* 3.5,12.8 Hz), 2.43-2.75 (m, 4H, CH_2), 1.26-1.53 (m, 4H, CH_2), 1.26-1.53 (m, 4H, CH_2), 0.97 (t, 6H, CH_3, *J* 7.1 Hz), 7.60-7.64 (m, 1H, CH), 7.29-7.51 (m, 1H, CH), 7.29-7.51 (m, 3H, CH), 3.20-4.50 (broad, 1H, OH), ^{13}C NMR ($CDCl_3$, δ ppm): 138.8, 141.3, 119.4, 134.9, 124.6, 137.7, 135.6, 138.3, 123.9, 127.3, 132.4, 123.3, 139.9, 65.8, 60.0, 53.5, 29.1, 20.6, 14.0, 126.2, 136.6, 133.8, 129.0, 128.8, 127.2, 130.1; MS: m/z: 528 $[M+H]^+$.



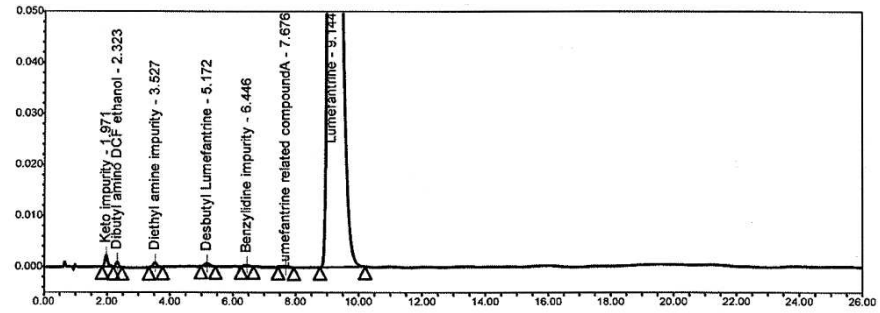
2-(dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(2-chlorobenzylidene)-9*H*-fluoren-4-yl] ethanol 11 (Ortho Chloro impurity). To a stirred solution of Sodium hydroxide (0.98 g, 0.0246 mol) in methanol (100 ml) there was added

ortho chloro benzaldehyde (2.24 g 0.0159 mol) and stirred for 30 minutes. Added 2-Dibutylamino-1-(2, 7-dichloro-9H-fluren-4-yl)-ethanol (5 g, 0.0123 mole) and heated to reflux temperature of reaction mixture. Continued the reflux till the absence of starting material. After confirming the product formation reaction mixture was cooled to room temperature and further stirred at same temperature for overnight. The precipitated solids were filtered and washed with methanol. (5.6 g, Yield: 85 %, Purity by HPLC: 95%). IR (cm^{-1}): 3392, 3084, 3015, 2956, 2931, 2861, 1590, 1470, 1440, 1407, 1326, 1265, 1215, 1156, 1109, 1075, 1054, 881, 851, 817, 760; ^{1}H NMR ($CDCl_3$, δ ppm): 7.54-7.82 (m, 1H, CH), 7.54-7.82, (m, 1H, CH), 7.54-7.82 (m, 1H, CH), 7.21-7.43 (m, 1H, CH), 7.21-7.43 (m, 1H, CH), 5.38 (d, 1H, CH, *J* 8.1 Hz), 2.42-2.75 (m, 1H, CH), 2.87-2.92 (dd, 1H, CH, *J* 3.2,13.1 Hz), 2.42-2.75 (m, 4H, CH_2), 1.22-1.53 (m, 4H, CH_2), 1.22-1.53 (m, 4H, CH_2), 0.97 (t, 6H, CH_3, *J* 7.2 Hz), 7.54-7.82 (m, 1H, CH), 7.21-7.43 (m, 4H, CH), 3.05-4.35 (broad, 1H, OH); ^{13}C NMR ($CDCl_3$, δ ppm): 138.8, 141.2, 119.7, 134.1, 126.0, 135.6, 134.4, 138.5, 123.9, 128.7, 132.3, 123.9, 139.9, 65.6, 60.0, 53.5, 29.1, 20.6, 14.0, 126.2, 135.6, 133.2, 130.2, 130.0, 126.8, 131.0; MS: m/z 528 $[M+H]^+$.



RESULTS AND DISCUSSION

During the process development of Lumefantrine, HPLC analysis of Lumefantrine revealed six related substances or impurities ranging from 0.01-0.15%. According to ICH (International conference on Harmonization) guidelines the amount of acceptable level for known & unknown impurities in final drug must be less than 0.15% and 0.10% respectively. [8, 9] In order to meet the regulatory requirements, the impurities need to be identified and characterized. Hence, samples of Lumefantrine were initially analyzed by LCMS to provide parent ions at m/z 528, 494, 528, 528, 420, 472, 472 and 406 for related six impurities of Lumefantrine **1**, and thus provide for a basis for initial identification. To confirm their proposed structures and complete their characterization, all impurities individually synthesized and characterized by their respective IR, NMR and MS spectral data. The structure of these related substances were assigned as 2-chloro-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol **4**, 1-[(9*Z*)-2,7-dichloro-9-(4-chlorobenzylidene)-9*H*-fluoren-4-yl]-2-(diethylamino)ethanol **6**, 2-(butylamino)-1-[(9*Z*)-2,7-dichloro-9-(4-chloro benzylidene)-9*H*-fluoren-4-yl]ethanol **7**, 2-(dibutylamino)-1-(2,7-dichloro-9*H*-fluoren-4-yl)ethanol 5, 2,7-dichloro-4-[2-(dibutylamino)-1-hydroxyethyl]-9*H*-fluoren-9-one **8**, 1-[(9Z)-9-benzylidene-2,7-dichloro-9H-fluoren-4-yl]-2-(dibutylamino)ethanol **9**, 2-(dibutylamino)-1-[(9*Z*)-2,7-dichloro-9-(3-chlorobenzylidene)-9*H*-fluoren-4-yl]ethanol **10**, 2-(dibutylamino)-1-[(9*Z*)-2,7-dichloro-9-(2-chlorobenzylidene)-9*H*-fluoren-4-yl]ethanol **11** respectively.



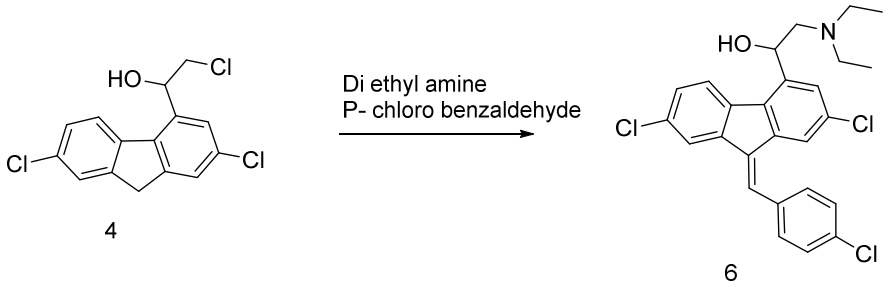
Peak Results

	Name	RT	Area	% Area	RT Ratio
1	Keto impurity	1.97	15287	0.32	0.22
2	Dibutyl amino DCF ethanol	2.32	6823	0.14	0.25
3	Diethyl amine impurity	3.53	8390	0.18	0.39
4	Desbutyl Lumefantrine	5.17	7063	0.15	0.57
5	Benzylidine impurity	6.45	3344	0.07	0.70
6	Lumefantrine related compoundA	7.68	4128	0.09	0.84
7	Lumefantrine	9.14	4739939	99.06	1.00

Fig.1 HPLC chromatogram of Lumefantrine

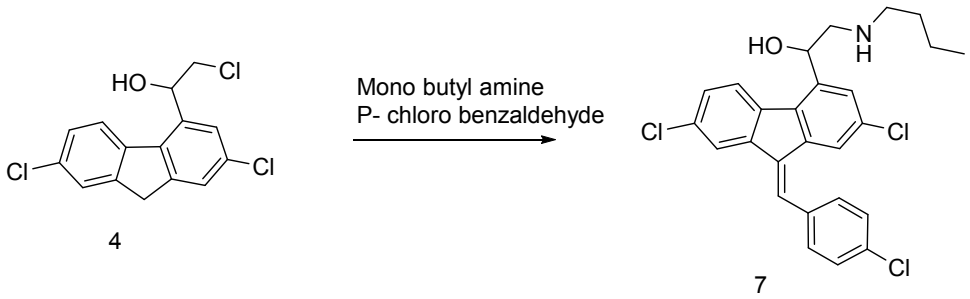
Formation of related compounds

The substance **6** was formed by condensation of 2-chloro-1-(2, 7-dichloro-9H-fluoren-4-yl) ethanol **4** in presence of Diethyl amine and Parachlorobenzaldehyde. The mass spectrum displayed a protonated molecular ion at m/z 472 and the NMR spectrum showed 2.60-2.84ppm m, 1.10ppm t(7.1) corresponding to diethyl protons at and 7.44-7.54 m protons corresponding to Parachlorobenzaldehyde protons. Based on the spectral data the structure was confirmed as 1-[(9*Z*)-2,7-dichloro-9-(4-chlorobenzylidene)-9*H*-fluoren-4-yl]-2-(diethylamino)ethanol **6**.



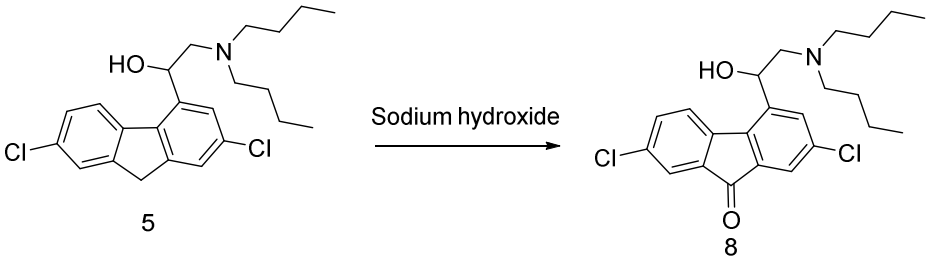
Scheme 2

Related substance **7**, a product which was formed by the condensation of 2-chloro-1-(2, 7-dichloro-9H-fluoren-4-yl) ethanol **4** in presence of monobutyl amine and parachloro benzaldehyde. The mass spectrum displayed a protonated molecular ion at m/z 472 whilst in the IR spectrum showed a broad band appeared at 3433,3320 cm^{-1} corresponding to NH stretching and the NMR spectrum showed 2.57-2.2.79ppm m, 1.25-1.56ppm m, 0.94ppm t(7.2) corresponding to butyl protons. Based on the spectral data, the structure was confirmed as 2-(butylamino)-1-[(9*Z*)-2, 7-dichloro-9-(4-chloro benzylidene)-9*H*-fluoren-4-yl] ethanol **7**.



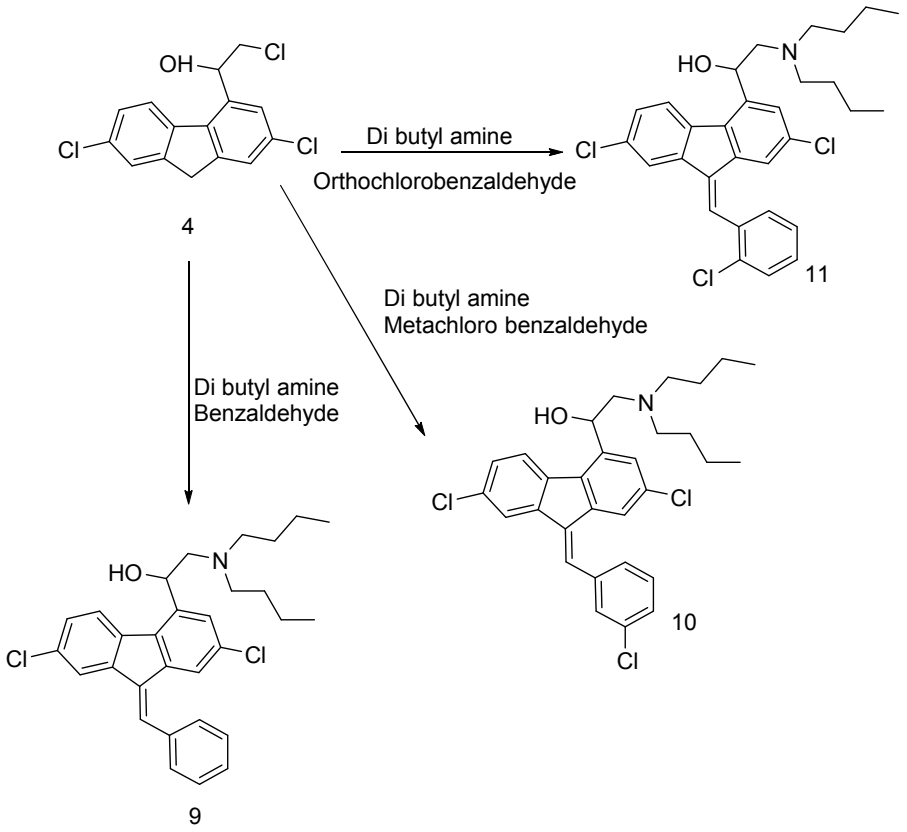
Scheme 3

2, 7-dichloro-4-[2-(dibutylamino)-1-hydroxyethyl]-9*H*-fluoren-9-one **8**, which was the product obtained while doing workup of 2-(dibutylamino)-1-(2, 7-dichloro-9*H*-fluoren-4-yl) ethanol **5** with Sodium hydroxide. The mass spectrum displayed a protonated molecular ion at m/z 420 whilst in the IR spectrum showed a sharp bands at 1726, 1664 cm^{-1} corresponding to carbonyl stretching and the NMR spectrum showed carbonyl carbon at 190.2ppm. Based on the spectral data, the structure was confirmed as 2, 7-dichloro-4-[2-(dibutylamino)-1-hydroxyethyl]-9*H*-fluoren-9-one **8**.



Scheme 4

1-[(9Z)-9-benzylidene-2, 7-dichloro-9H-fluoren-4-yl]-2-(dibutylamino) ethanol **9**, which was the product obtained by the condensation of 2-chloro-1-(2, 7-dichloro-9H-fluoren-4-yl) ethanol **4** in presence of dibutyl amine and benzaldehyde. The mass spectrum displayed a protonated molecular ion at m/z 494 and the NMR spectrum showed a multiplet 7.41-7.55ppm m, corresponding to benzyl protons. 2-(dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(3-chlorobenzylidene)-9*H*-fluoren-4-yl] ethanol **10**, which was product obtained by the condensation of 2-chloro-1-(2, 7-dichloro-9H-fluoren-4-yl) ethanol **4** in presence of dibutyl amine and metachloro benzaldehyde. The mass spectrum displayed a protonated molecular ion at m/z at 528 and the NMR spectrum showed quaternary carbon at 133.2ppm. Based on the spectral data, the structure was confirmed as 2-(dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(3-chlorobenzylidene)-9*H*-fluoren-4-yl] ethanol **10**. 2-(dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(2-chlorobenzylidene)-9*H*-fluoren-4-yl] ethanol **11**, which was product obtained by the condensation of 2-chloro-1-(2, 7-dichloro-9H-fluoren-4-yl) ethanol **4** in presence of Dibutyl amine and Orthochloro benzaldehyde. The mass spectrum displayed a protonated molecular ion at m/z at 528 and the NMR spectrum showed quaternary carbon at 129.0ppm. Based on the spectral data, the structure was confirmed as 2-(dibutylamino)-1-[(9*Z*)-2, 7-dichloro-9-(2-chlorobenzylidene)-9*H*-fluoren-4-yl] ethanol **11**.



Scheme 5

CONCLUSION

In conclusion, we have identified, synthesized and characterized six process related substances or impurities **6, 7, 8, 9, 10 and 11** of Lumefantrine **1** in order to control these related substances in drug product below the levels as advised by ICH. By controlling these new six process related substances will make this high doses anti-malarial drug safer for human use.

Acknowledgements
We thank the management of R&D, Mylan Laboratories ltd., for supporting this work.

REFERENCES

[1] Ulrich Beutler, C Peter.; Fuenfschilling.; and Andreas, Steinkemper.; Novartis Pharma AG; Chemical and Analytical Development: CH-4002 Basel, Switzerland, *Organic Process Research & Development* **2007**, *11, 341-345.*
[2] Boehm, M. Fuenfschilling.; Krieger, P. C.; Kuesters, E. M.; Struber, F.; *Org. Process Res. De*V. **2007**, *11*, 336-340.
[3] (a) Rao, D. R.; Kankan, R. N.; Phull, M. S.; Patent Application CN 1009-3724 20060424, **2005**. (b) Deng, R.; Zhong, J.; Zhao, D.; Wang, J.; Yaoxue, X. **2000**, *35* (1), 22. (c) Allmendinger, Th.; Wernsdorfer, W. H. PCT WO 99/67197.
[4] Perrumattam, J.; Shao, Ch.; Confer, W. L. *Synthesis* **1994**, 1181.
[5] Fuenfschilling, P. C.; Hoehn P.; Mutz J.-P. *Organic Process Res. De*v. **2007**, 11, 13.
[6] Di Nunno, L.; Scilimati, A. *Tetrahedron* **1988**, *44*, 3639.
[7] Pharmacopeial Forum, Vol. 36(2) [Mar.-Apr. **2010**]

[8] International Conference on Harmonization guidelines Q3A (R2) Impurities in New Drug Substances October 25, **2006** (this guideline provides guidance for registration application on the content and qualification of impurities in new drug substances produced by the chemical synthesis).
[9] International Conference on Harmonization guidelines Q3B (R2) Impurities in New Drug Substances 2 June **2006** (Guidance for registration or marketing application on the content and qualification of impurities in new drug product).