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Identification, Synthesis and Characterization of Impurities of (S)-Mitiglinide Calcium Dihydrate

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(S)-Mitiglinide Calcium dihydrate (**1**), an important potent hypoglycemic agent. During laboratory optimization and later in bulk synthesis the formation of various impurities was observed. The method of preparation of most of these impurities is not available in literature. We describe herein the formation, synthesis, preparation and characterization of these impurities.

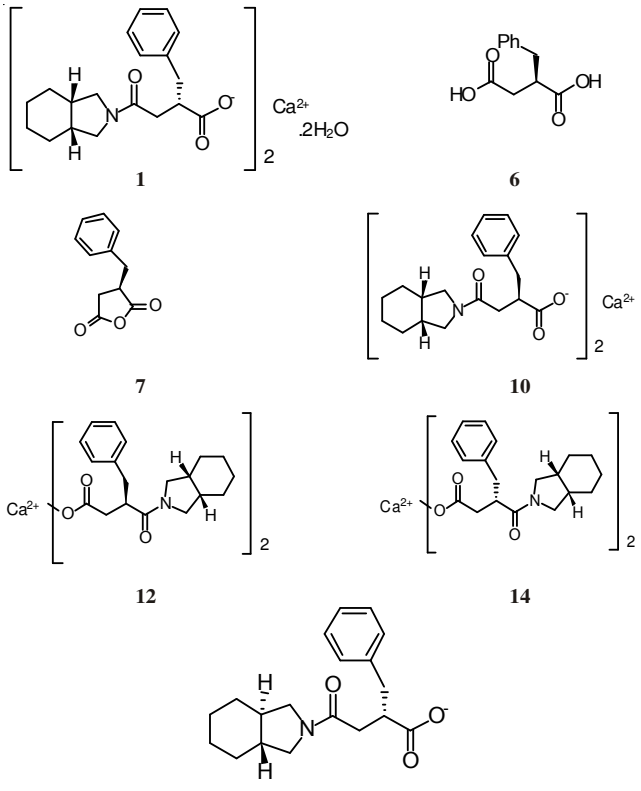
Keywords: Mitiglinide Calcium, Regio isomer, Impurities, Hypoglycemic agent.

INTRODUCTION

(S)-Mitiglinide calcium dihydrate (**1**), calcium (2S)-2-benzyl-4-[(3aR,7aS)-octahydro-2*H*-isoindol-2-yl]-4-oxobutanoate hydrate (1:2:2), a novel hypoglycemic agent with a chemical structure different from that of the sulfonylureas. Mitiglinide inhibits the ATP-sensitive potassium channels in pancreatic β-cells and stimulates insulin release. The configuration of the stereogenic C-atom in the succinyl moiety is very important for the activity of compound and the absolute (S)-configuration is necessary for insulin secretory effect[1-5]. It is useful for the treatment of type-2 diabetes.

(S)-Mitiglinide calcium dihydrate is designated chemically as calcium (2S)-2-benzyl-4-[(3aR,7aS)-octahydro-2*H*-isoindol-2-yl]-4-oxobutanoate hydrate (1:2:2). Its literature synthesis[6] (**Scheme-I**) involves dehydration of (S)-2-benzyl-succinic acid (**2**) with acetic anhydride in the presence of dichloromethane gives corresponding anhydride (**3**). Reaction of (**3**) with *cis*-octahydroisondole (**8**) in presence of toluene affords (S)-mitiglinide (**4**) which on treatment with anhydrous calcium chloride in presence of sodium hydroxide and water gives (S)-mitiglinide calcium dihydrate (**1**).

During laboratory optimization of mitiglinide calcium dihydrate (**1**), many process related impurities were detected by HPLC analysis and their structure tentatively assigned as **6-16** on the basis of their LC-MS data. The guidelines recommended by ICH state that the acceptable levels for a known and unknown compound (impurity) in the drug should be less than 0.15 and 0.10 %, respectively in an API[7]. In order to quantify and limit the impurities in the final drug substance, it is necessary to have standard for the impurities. However, no synthetic details have been reported and the impurities are not commercially available. In this context, the present study describes identification, synthesis and characterization of impurities of (S)-mitiglinide calcium dihydrate.



1 **6** **7** **10** **12** **14** **16**

Mitiglinide calcium dihydrate (**1**) and process related impurities

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz Avance NMR spectrometer; the chemical shifts were reported ppm relative to either residual solvent or tetramethylsilane. The FT-IR spectra were recorded on Perkin-Elmer Spectrum one FT-IR spectrometer and only prominent peaks are reported. Mass spectra were recorded on a Agilent 1100 series LC-MSD-TRAP-SL system. HPLC analysis was carried out on Waters Alliance 2487 or Waters Alliance 2695 systems. All the reagents used were of LR grade and used without further purification. All the anhydrous reactions were carried out under a nitrogen atmosphere. Silica gel (120-200 mesh) was used for column chromatography.

General experimental procedure

(2R)-2-Benzylbutanedioic acid (or) (R)-2-benzylsuccinic acid (6): To a solution of (R, S)-2-benzylsuccinic acid (60 g, 288 mmol) **5** in ethanol (720 mL) was added (S)-α-methylbenzylamine (35 g, 289 mmol) at 28-30 °C and the mixture was stirred for 5 h at 28-30 °C. The salt was filtered and then washed with ethanol (60 mL). The wet material was dried at 40-45 °C for 5 h. The dried material was suspend in ethanol (100 mL) then mixture was heated to 55-60 °C and stirred for 2 h then cooled to 28-30 °C. The salt was filtered and then washed with ethanol (20 mL). Dry the wet material under vacuum at 40-45 °C.To the suspension of the dried salt in dichloromethane was added water. The pH was adjusted to 13 with 10 % sodium hydroxide solution (2.5 g in 25 mL) and stirred for 10 min. The layers were separated and the aqueous layer was washed with dichloromethane. The aqueous layer pH was adjusted to 1-2 with 2N HCl (12 mL) and stirred for 3 h at 28-30 °C. Dry the product under vacuum for 5-6 h at 50-55 °C to afford (R)-2-benzylsuccinic acid **6** (8 g, 26.6 % yield). IR (KBr, ν_{max}, cm^{-1}): 3032, 2953, 2918, 1712, 1603, 1497, 1457, 1450, 1433, 1295, 1241, 945, 872, 761, 705. ^{1}H NMR (DMSO-d_6): δ 12.23 (br, s, 2H) 7.17-7.32 (m, 2H), 7.17-7.32 (m, 2H), 7.17-7.32 (m, 1H), 2.85-2.94 (m, 1H), 2.85-2.94 (m, 1H), 2.69-2.77 (m, 1H), 2.38-2.46 (dd, *J* = 16.8 and 8.7, 1H), 2.20-2.27 (dd, *J* = 16.8 and 4.2, 1H). ^{13}C NMR: 175.13, 172.89, 138.72, 128.93, 128.28, 126.32, 42.44, 36.89. ESI-MS: *m/z* 231 ($[M + Na]^+$, $C_{11}H_{12}O_4$ calcd. 208), *m/z* 207 ($[M-H]^-$).

(R)-Benzylsuccinic anhydride (or) (3R)-3-benzyldihydrofuran-2,5-dione (7): To a suspension of (R)-2-benzylsuccinic acid 6 (25 g, 120 mmol) in dichloromethane (125 mL) was added acetic anhydride (61.2 g, 599 mmol) at 25-30 °C. The reaction mass was heated to 45-48 °C, the reaction mixture was stirred at 45-48 °C and the progress of the reaction was monitored by analytical TLC. After 3 h, TLC revealed the completion of the reaction, then distilled out solvent completely under vacuum at 50-55 °C. To the residue was added diisopropylether (100 mL) and stirred for 1 h at 25-30 °C. The white product formed was filtered and washed with diisopropylether (50 mL). the wet material was dried under vacuum at 40-45 °C to afford (R)-benzylsuccinic anhydride **7** (21 g, 92 % yield). IR (KBr, ν_{max}, cm^{-1}): 3085, 3065, 3027, 2979, 2931, 2875, 1870, 1844, 1771, 1602, 1494, 1456, 1412, 1299, 1289, 1250, 1237, 1214, 1081, 1060, 930, 889, 878, 848, 753. ^{1}H NMR (DMSO-d_6): δ 7.21-7.34 (m, 2H), 7.21-7.34 (m, 2H), 7.21-7.34 (m, 1H), 3.51-3.62 (m, 1H), 3.10-3.16 (dd, *J* = 13.8 and 4.8, 1H), 2.85-2.99 (m, 1H), 2.72-2.80 (dd, *J* = 18.3 and 6.6, 1H). ^{13}C NMR : 174.59, 171.39, 137.86, 128.79, 128.56, 126.66, 41.79, 34.91, 33.54. ESI-MS: *m/z* 191 ($[M + H]^+$, $C_{11}H_{10}O_3$ calcd. 190), *m/z* 189 ($[M-H]^-$).

Calcium *bis*{(2R)-2-benzyl-4-[(3aR,7aS)-octahydro-2*H*-isoindol-2-yl]-4-oxobutanoate} (or) (R)-mitiglinide calcium (10): To a suspension of (R)-benzylsuccinic anhydride **7** (15 g, 78.9 mmol) in toluene (150 mL), was heated to 45-47 °C and added *cis*-octahydroisoindole **8** (11.8 g, 94.6 mmol). The reaction mixture was stirred for 0.5 h, analytical HPLC revealed the absence of the starting material and the formation of regioisomer along with (R)-mitiglinide. The reaction mixture was cooled to room temperature and stirred for 1 h. Filtered the unwanted regioisomer and washed with toluene (15 mL). To the toluene filtrate added sodium hydroxide solution (2.85 g in 75 mL water) and stirred for 15 min. The layers were separated and the organic layer was extracted with water (15 mL). The combined aqueous layer was mixed with ethanol (150 mL) and slowly added calcium chloride solution (6.6 g in 210 mL water) at room temperature. The white precipitate was filtered, washed with purified water (30 mL) and dried. The dried (R)-mitiglinide calcium crude was recrystallized from 95 % ethanol to afford pure (R)-mitiglinide calcium **10** (9 g , 34.3 % yield). IR (KBr, ν_{max}, cm^{-1}) : 3060, 3026, 2926, 2853, 1621, 1562, 1447, 1435, 1336, 1282, 1200, 1186, 1074, 755, 746, 703. ^{1}H NMR (DMSO-d_6): δ 7.13-7.20 (m, 4H), 7.13-7.20 (m, 4H), 7.13-7.20 (m, 2H), 2.96-3.24 (m, 2H), 2.96-3.24 (m, 8H), 2.74-2.78 (m, 2H), 2.60-2.69 (m, 2H), 2.50-2.55 (m, 2H), 2.04-2.12 (m, 2H), 2.04-2.12 (m, 4H), 1.27-1.46 (m, 8H), 1.27-1.46 (m, 8H). ^{13}C NMR: 181.67, 171.10, 141.11, 129.12, 127.87, 125.49, 49.35, 49.22, 44.56, 37.38, 36.76, 35.33, 35.20, 25.43, 25.11, 22.45, 22.17. ESI-MS: *m/z* 316 ($[M + H]^+$, $C_{38}H_{48}N_2O_6Ca$, calcd. 315), *m/z* 314 ($[M-H]^-$).

Calcium *bis*{(3R)-3-benzyl-4-[(3aR,7aS)-octahydro-2*H*-isoindol-2-yl]-4-oxobutanoate} (or) (R)-mitiglinide calcium regioisomer (12): To a suspension of (R)-benzylsuccinic anhydride **7** (15 g, 78.9 mmol) in toluene (150 mL) was heated to 45- 47 °C and added *cis*-Octahydroisoindole (**8**) (11.8 g, 94.6 mmol) at 45-47 °C. The reaction mixture was stirred for 0.5 h, whereupon TLC revealed the absence of starting material. The reaction mixture was cooled to room temperature and stirred for 1 h at 25-30 °C. Filtered the product and washed with toluene (15 mL) and dried at 40-45 °C to obtained (R)-mitiglinide regioisomer **11**. To the dried material suspended in purified water (25 mL) added sodium hydroxide solution (2.80 in 50 mL water) at 25-30 °C. To the clear solution of the reaction mass was added calcium chloride solution (6.6 g in 210 mL water) for 45 min at 25-30 °C. The white precipitate was filtered and washed with water (30 mL) and dried. The dried (R)-mitiglinide regioisomer was recrystallized from 95 % ethanol (270 mL) to afford pure (R)-mitiglinide calcium regioisomer **12** (6.5 g, 24.7 % yield). IR (KBr, ν_{max}, cm^{-1}): 3061, 3027, 2926, 2856, 1621, 1600, 1549, 1464, 1409, 1336, 1311, 1244, 1231, 1185, 1074, 770, 744, 702. ^{1}H NMR (DMSO-d_6): δ 7.11-7.25 (m, 4H), 7.11-7.25 (m, 4H), 7.17-7.25 (m, 2H), 3.35-3.53 (m, 2H), 2.95- 3.12 (m, 2H), 2.95-3.12 (m, 4H), 2.54-2.81 (m, 4H), 2.54-2.81 (m, 2H), 2.27-2.41 (m, 2H), 1.88-2.13 (m, 2H), 1.88-2.13 (m, 4H), 0.61-

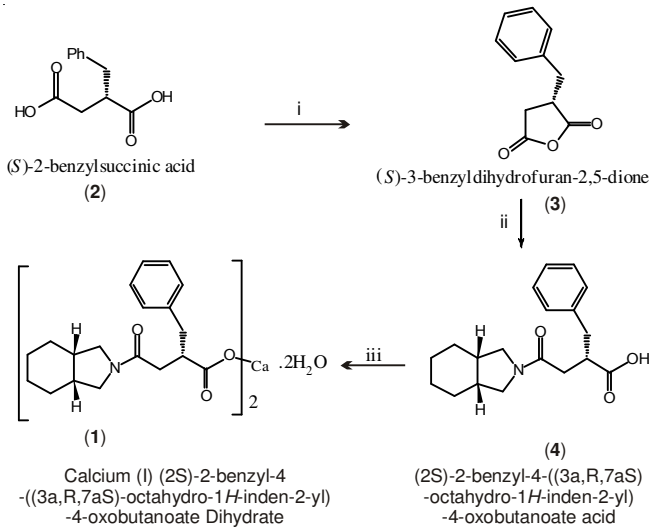
1.14 (m, 8H), 0.61-1.41(m, 8H). ^{13}C NMR: 178.80, 173.45, 140.26, 128.87, 128.01, 125.78, 49.98, 48.88, 42.54, 40.42, 38.94, 36.36, 35.22, 25.29, 24.66, 22.93, 21.19. ESI-MS: *m/z* 316 ([M + H]$^+$, $C_{38}H_{48}N_2O_6Ca$, calcd. 315), *m/z* 314 ([M-H]$^-$).

Calcium *bis*{(3S)-3-benzyl-4-[(3aR,7aS)-octahydro-2*H*-isoindol-2-yl]-4-oxobutanoate} (or) (S)-mitiglinide calcium regioisomer (14): To (S)-benzylsuccinic anhydride 3 (15 g, 78 mmol), anhydrous toluene (150 mL) was added and heated to 45-47 °C. Slowly added *cis*-octahydroisoindole (**8**) (11.8 g, 94.6 mmol) for a period of 10-15 min at 45-47 °C, when analytical HPLC showed the absence of starting material and the formation of (S)-regio isomer along with (S)-mitiglinide. The reaction mixture was cooled to 25-30 °C and stirred for 1 h. Filtered the regioisomer and washed with toluene (15 mL), dried at 45-50 °C to afford (S)-mitiglinide regioisomer **13**. To the dried material purified water was added (25 mL) and slowly added sodium hydroxide solution (2.8 g in 50 mL water) at 25-30 °C. To the obtained clear solution calcium chloride solution was added (5.49 g in 175 mL water) at 25-30 °C. The reaction mixture was stirred for 10 h at 25-30 °C. Filtered the white precipitate and washed with water (50 mL). The wet material was dried at 45-50 °C. The dried material was suspended in ethanol (120 mL) was heated to reflux to get clear solution. To the clear solution water was added (6 mL) at 80-85 °C. The reaction mixture was slowly cooled to 25-30 °C and stirred for 4 h at 25-30 °C. The white precipitate was filtered and washed with ethanol (6 mL) and dried under vacuum at 45-50 °C to afford (S)-mitiglinide calcium regioisomer 14 (6.0 g , 23.0 % yield). IR (KBr, ν_{max}, cm^{-1}): 3061, 3027, 2926, 2856 1621, 1601, 1550, 1464, 1416, 1336, 1312, 1231, 1185, 1075, 814, 795, 769, 701. ^{1}H NMR (DMSO-d_6): δ 7.17-7.25 (m, 2H), 7.11-7.25 (m, 4H), 7.11-7.25 (m, 4H), 3.34-3.53 (m, 2H), 2.95-3.18 (m, 4H), 2.95-3.18 (m, 2H), 2.55-2.84 (m, 4H), 2.55-2.84 (m, 2H), 2.27-2.40 (m, 2H), 1.88-2.12 (m, 2H), 1.88-2.12 (m, 2H), 0.62-1.41 (m, 8H), 0.62-1.41 (m, 8H). ESI-MS: *m/z* 316 ([M + H]$^+$, $C_{38}H_{48}N_2O_6Ca$ calcd. 315), *m/z* 338 ([M + Na]$^+$), *m/z* 314 ([M-H]$^-$.

(2S)-2-Benzyl-4-[(3aS,7aS)-octahydro-2*H*-isoindole-2-yl]-4-oxobutanoic acid (16): To a suspension of (S)-benzylsuccinic anhydride **3** (9 g, 78 mmol) in toluene (90 mL) was heated to 45-47 °C and *trans*-octahydroisoindole solution (7 g in 45 mL) was added drop wise at 45-47 °C. The reaction mixture was stirred at 45-47 °C and the progress of the reaction was monitored by analytical TLC. After 0.5 h, TLC revealed the completion of the reaction. The reaction mass was cooled to 25-30 °C and stirred for 1 h. Filtered the material, washed with toluene (5 mL) and dried at 45-50 °C to yield the trans mitiglinide (**16**) (2.0 g, 22 % yield). IR (KBr, ν_{max}, cm^{-1}): 3419, 3082, 3025, 2927, 2872, 2848, 1720, 1607, 1462, 1427, 1417, 1372, 1333, 1268, 1225, 1192, 1173, 748,703. ^{1}H NMR (DMSO-d_6): δ 12.13 (br,s 1H) 7.17-7.31 (m, 2H), 7.17-7.31 (m, 2H), 7.17 -7.31 (m, 1H), 3.44-3.58 (m, 2H), 2.57-2.96 (m, 2H), 2.57-2.96 (m, 2H), 2.57-2.96 (m, 1H), 2.40-2.50 (m, 1H), 2.18-2.27 (m, 1H), 1.71-1.82 (m, 2H), 1.71-1.82 (m, 2H), 1.06-1.46 (m, 2H), 1.06-1.46 (m, 2H), 1.06-1.46 (m, 2H).^{13}C NMR: 175.61, 168.66, 139.14, 128.91, 128.25, 126.22, 51.06, 50.28, 44.17, 42.67, 42.43, 37.16, 34.72, 28.07, 27.95, 25.17, 25.10. ESI-MS: *m/z* 316 ([M + H]$^+$, $C_{19}H_{25}NO_3$, calcd. 315), *m/z* 338 ([M + Na]$^+$).

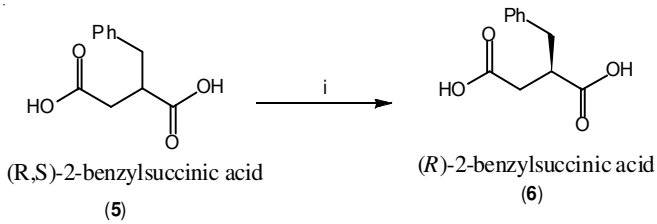
RESULTS AND DISCUSSION

(S)-Mitiglinde calcium dihydrate 1 synthesized is shown in **Scheme-I**. Dehydration of (S)-2-benzylsuccinic acid **2** with acetic anhydride gives corresponding (S)-Benzylsuccinic anhydride **3**. The reaction of **3** with *cis*-octahydroisoindole **8** in the presence of toluene gives (S)-mitiglinide **4**, which upon treatment with anhydrous calcium chloride in presence of sodium hydroxide and water afforded (S)-mitiglinide calcium dihydrate **1**.



Scheme-I: Reagents and conditions: (i) Dichloromethane, acetic anhydride, 40-45 °C; (ii) *cis*-Octahydroisoindole, toluene, 40-45 °C; (iii) NaOH, H_2O, calcium chloride, ethanol

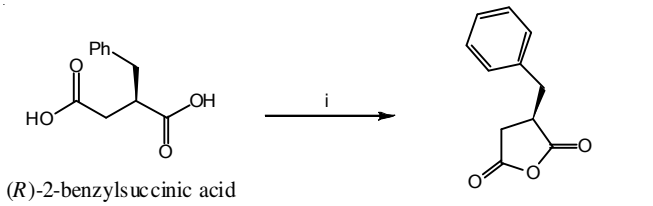
In Laboratory Optimization of (S)-mitiglinide calcium, many process related impurities were identified and their synthesis was undertaken. During the resolution of (R,S)-2-benzylsuccinic acid **5** with (R)-α-methyl benzylamine, formation of 2-4 % of the undesired R-isomer was observed when analyzed by Chiral-HPLC, its corresponding carry over throughout the synthesis leads to contamination of (S)-mitiglinide calcium with (R)-isomer impurity. (R)-2-Benzylsuccinic acid impurity **6** was synthesized by the resolution of (R,S)-2-benzylsuccinic acid **5** with (S)-α-methyl benzylamine in the presence of dichloromethane. The resulting amine salt was liberated by sodium hydroxide in the presence of water and dichloromethane, followed by the aqueous phase acidification to pH 1-2 with ^{1}N HCl to get (R)-2-benzylsuccinic acid **6** (**Scheme-II**).



Scheme-II: Reagents and conditions: (i) (S)-α-Methylbenzylamine,ethanol, Dichloromethane, Conc HCl 25-30 °C

In **Scheme-III**, synthesis of (R)-benzylsuccinic anhydride impurity **7** was prepared by the dehydration of (R)-2-

benzylsuccinic acid (**6**) and acetic anhydride in the presence of dichloromethane.

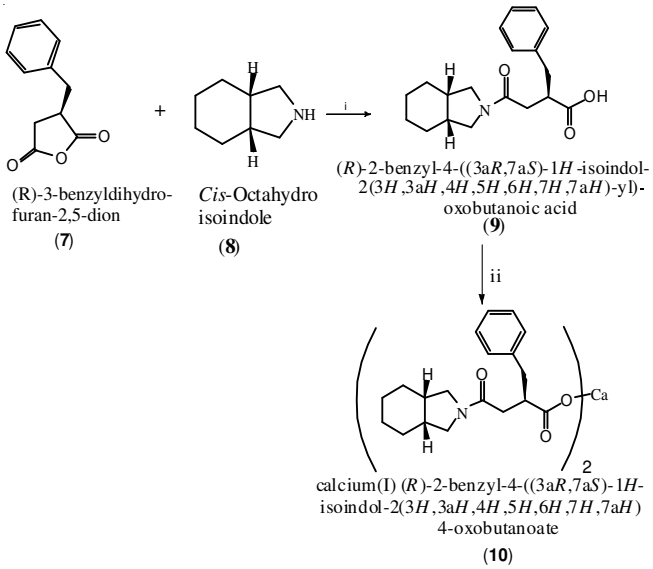


(*R*)-2-benzylsuccinic acid (**6**)

(*R*)-3-benzyldihydrofuran-2,5-dione (**7**)

Scheme-III: Reagents and conditions: (i) Aceticanhydride, Dichloromethane, 40-45 °C, Diisopropylether

(R)-Mitiglinide calcium impurity[8] **10** is one of the potential impurities aroused during the synthesis due the presence of (R)-2-benzylsuccinic acid (**6**) as one of the impurities in the (S)-2-benzylsuccinic acid (**2**). (R)-mitiglinide calcium was synthesized by the condensation of (R)-2-benzylsuccinic anhydride **7** with *cis*-octahydroisoindole (**8**) in the presence of toluene gives (R)-mitiglinide (**9**), followed by the treatment with anhydrous calcium chloride in the presence NaOH and water, further recrystallization with 95 % aqueous ethanol gives (R)-mitiglinide calcium (**10**) (**Scheme-IV**).



(R)-3-benzyldihydro-furan-2,5-dion (**7**)

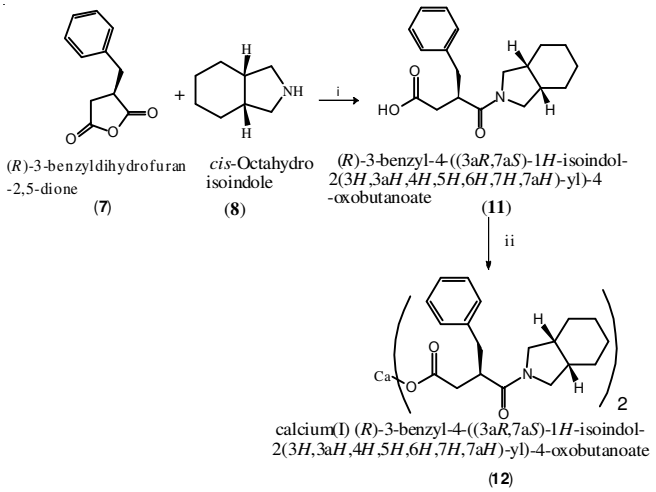
Cis-Octahydro isoindole (**8**)

(*R*)-2-benzyl-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-oxobutanoic acid (**9**)

calcium(I) (*R*)-2-benzyl-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*) 4-oxobutanoate (**10**)

Scheme-IV: Reagents and conditions: (i) Toluene, 40-45 °C (ii) NaOH, H_2O, calcium chloride, ethanol, 25-30 °C

(R)-Mitiglinide calcium regioisomer **12** is one of the potential impurity aroused due the presence of (R)-2-benzyl-succinic acid impurity in (S)-benzylsuccinic anhydride (**3**). During the condensation of (S)-benzylsuccinic anhydride with *cis*-octahydroisoindole (**8**), there is a formation of 0.2-0.3 % (R)-mitiglinide regioisomer was observed by analytical HPLC. (R)-Mitiglinide calcium regioisomer **12** was prepared by the condensation of (R)-benzylsuccinic anhydride **7** with *cis*-octahydroisoindole (**8**) in the presence of toluene gives (R)-mitiglinide regioisomer **11**, followed treatment with anhydrous calcium chloride in the presence of NaOH and water to afforded (R)-mitiglinide calcium regioisomer (**12**) (**Scheme-V**).



(*R*)-3-benzyldihydrofuran-2,5-dione (**7**)

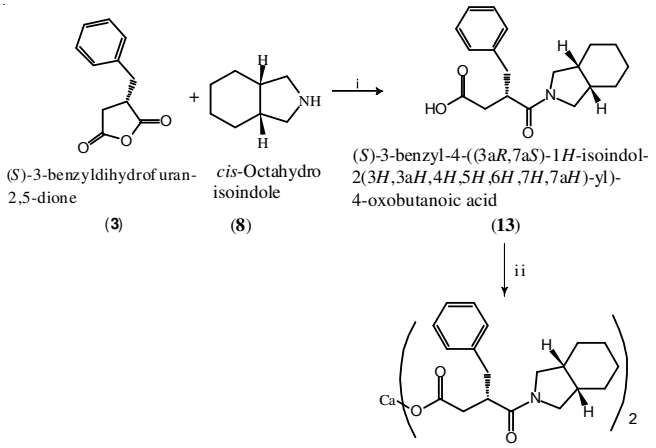
cis-Octahydro isoindole (**8**)

(*R*)-3-benzyl-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-4-oxobutanoate (**11**)

calcium(I) (*R*)-3-benzyl-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-4-oxobutanoate (**12**)

Scheme-V: Reagents and conditions: (i) Toluene, 40-45 °C (ii) NaOH, H_2O, calcium chloride, ethanol, 25-30 °C

During the condensation of (S)-benzylsuccinic anhydride (**3**) with *cis*-octahydroisoindole (**8**) in the presence of toluene, formation of 20-30 % undesired regioisomer was observed when analyzed by HPLC. The (S)-mitiglinide calcium regio-isomer impurity[9] was synthesized by the condensation of (S)-benzylsuccinic anhydride (**3**) and *cis*-octahydroisoindole 8 in the presence of toluene. The resulting unwanted regioisomer **13** was filtered and dried, followed by reaction with anhydrous calcium chloride in the presence of NaOH and water. The obtained crude (S)-mitiglinide calcium regioisomer was further purified with 95 % aqueous ethanol gives (S)-mitiglinide calcium regioisomer (**14**) (**Scheme-VI**).



(*S*)-3-benzyldihydrofuran-2,5-dione (**3**)

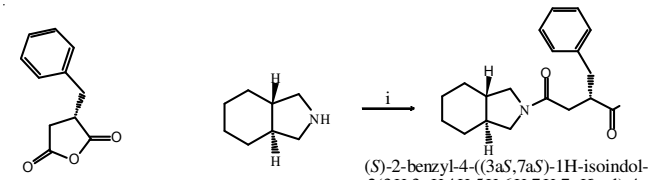
cis-Octahydro isoindole (**8**)

(*S*)-3-benzyl-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-4-oxobutanoic acid (**13**)

calcium(I) (*S*)-3-benzyl-4-((3a*R*,7a*S*)-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-4- (**14**)

Scheme-VI: Reagents and conditions (i) Toluene, 40-45 °C (ii) NaOH, H_2O, calcium chloride, ethanol, 25-30 °C

In some of commercial samples, *cis*-octahydroisoindole (**8**) was founded to be contaminated with traces of *trans*-octahydroisoindole impurity (**15**), although the amount of contamination of *trans*-mitiglinide impurity **16** in (S)-mitiglinide calcium dihydrate (**1**) was never more than 0.15 %. The *trans*-mitiglinide impurity was synthesized by the condensation of (S)-2-benzylsuccinic anhydride **3** with *trans*-octahydroisoindole (**15**) in the presence of toluene to obtain *trans*-mitiglinide impurity **16** (**Scheme-VII**).



(*S*)-3-benzyldihydrofuran-2,5-dione (**3**)

Trans-Octahydro isoindole (**15**)

(*S*)-2-benzyl-4-((3a*S*,7a*S*)-1H-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-4-oxobutanoic acid (**16**)

Scheme-VII: Reagents and conditions: (i) Toluene, 40-45 °C

Conclusion

For better knowledge of the synthetic path way of an active pharmaceutical ingredient (API) it is mandatory to identify all the impurities formed/anticipated. In this context we have synthesized and characterized different potential process related impurities of (S)-mitiglinide calcium dihydrate.

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