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Identification, Synthesis, and Characterization of Potential Process Related Compounds of Rivastigmine Tartrate

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ABSTRACT

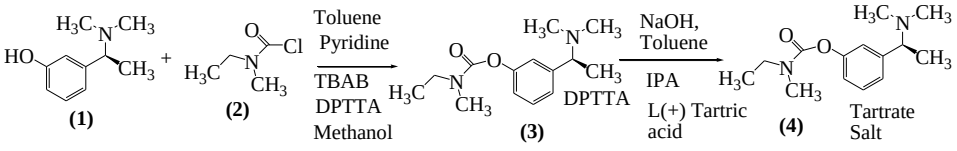
Seven potential process related compounds (impurities) were detected during the impurity profile study of drug substance, rivastigmine tartarate (4). Simple HPLC and MS methods were used for the detection of these process impurities. Based on the spectral data and synthesis the structures of these impurities were characterized as -(S)-3-(1-(Dimethylamino) ethyl) phenyl dimethyl carbamate (6); (S)-3-(1-(dimethylamino) ethyl) phenyl diethyl carbamate (8); (1-Ethyl-3-(1-(3-hydroxyphenyl) ethyl)-1,3-dimethylurea (11); (S)-3-(1-(Dimethylamino) ethyl) phenyl ethylcarbamate (12); 3-Acetyl phenyl ethyl (methyl) carbamate (13); (S)-N,N-dimethyl-1-(3-(4-nitro phenoxy) phenyl) ethanamine (15) and 3-Nitrophenyl ethyl (methyl) carbamate (17). The seven synthesized impurities were co-injected with rivastigmine sample to confirm the retention time in HPLC. The structures of these compounds were established on the basis of spectral data (IR, [1]HNMR, [13]CMR and MS).

Keywords: Rivastigmine tartrate, Process related compounds, Synthesis, Identification

INTRODUCTION

Rivastigmine tartarate (4), chemically known as (*S*)-3-[1-(Dimethylamino) ethyl] phenyl *N*-ethyl-*N*- methylcarbamate tartarate, is approved under the trade name Exelon. Rivastigmine is the first USFDA approved drug in the form of capsules and patches for the treatment of mild to moderate dementia of the Alzheimer's [1-4]. It was developed by Marta Weinstock-Rosin of the department of Pharmacology at the Hebrew University of Jerusalem [5]. Rivastigmine has demonstrated significant treatment effects on the cognitive (thinking and memory), functional (activities of daily living) and behavioral problems commonly associated with Alzheimer's [6]and Parkinson's disease dementias [6,7]. During the analysis of different laboratory batches of rivastigmine, seven unknown impurities with area percentage ranging from 0.02%-0.15% was detected by a simple HPLC method.

As per International Conference on Harmonisation (ICH) guidelines, it is necessary to identify and characterize the impurities which are present at 0.1% level [8-12]. Several methods are reported in the literature for the preparation of rivastigmine [13], but the related compound synthesis was not discussed. This impurity profile study is very important for process development chemist to understand the formation of potential impurities during the synthesis of drug substance. In the present work two USP and five process related impurities of rivastigmine tartrate were synthesized and characterized using spectroscopic techniques. The general route of synthesis of rivastigmine tartrate is outlined in Scheme 1.



Scheme 1: Synthesis of rivastigmine tartrate

EXPERIMENTAL SECTION

General procedures

^{1}NMR and ^{13}CMR spectra were recorded on a Bruker Advance 300 Spectrometer. Chemical shifts are reported in ppm downfield from Tetramethylsilane (TMS) as internal standard. Electrospray ionization (ESI) mass spectra were performed on Thermo Finnigan LCQ Classic Mass Spectrometer. IR spectrometer-8400 (SHIMADZU) used. Uncorrected melting points were determined on electrothermal melting point apparatus. Analytical HPLC were run with symmetry C18, 250 × 4.6 mm column at 290 nm. Solvents and reagents were used without any pretreatment.

RESULTS AND DISCUSSION

Rivastigmine tartarate (4) was prepared from (S)-3-(1-(dimethyl amino) ethyl) phenol (1) by following the known method (Scheme 1). A typical HPLC chromatogram of a laboratory batch of rivastigmine (Figure 1) was recorded as described in the experimental section and the target impurities under study were marked as imp-A (6), Retention Time (RT): 7.695 min), imp-B (8) (RT): 28.124 min), imp-C (11) (RT): 30.535 min), imp-D (12) (RT): 16.370 min), imp-E (13) (RT):41.556 min), imp-F (15) (RT): 109.767 min) and imp-G (17) (RT): 44.075 min). The spectroscopic data of impurity-A to impurity-G were compared with those of rivastigmine tartarate.

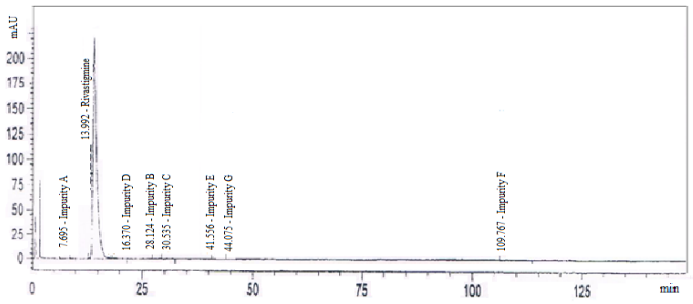
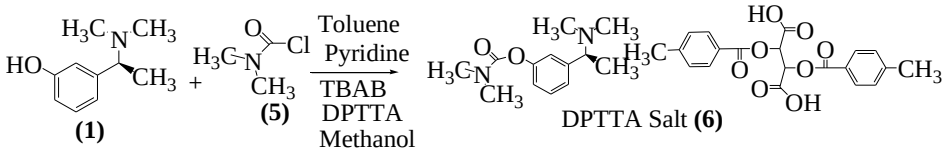


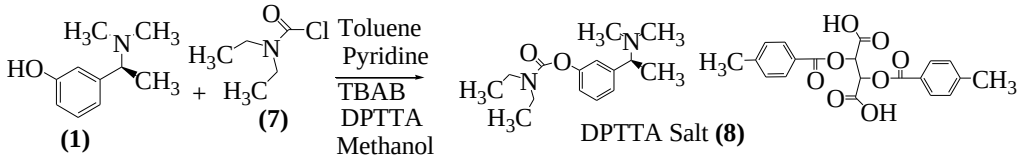
Figure 1: HPLC chromatogram of rivastigmine tartrate sample spiked with seven impurities

Formation of related compounds

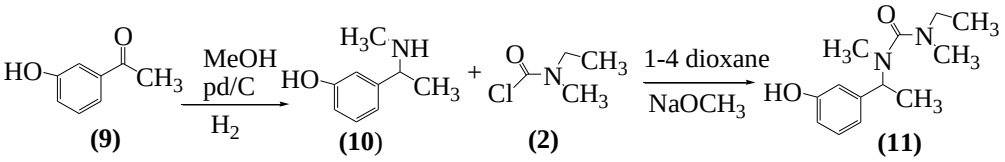
(S)-3-(1-(Dimethylamino) ethyl) phenol (1) reacted with dimethylcarbamic chloride (5) in the presence of toluene with Tetrabutylammonium Bromide (TBAB) and pyridine leads to formation of Impurity-A (Scheme 2). In the same way phenol (1) is reacted with diethylcarbamic chloride (7) to get the Impurity-B (Scheme 3). Impurity-Cis prepared by reacting compound (10) with ethyl (methyl) carbamic chloride (2) in presence of dioxane and$NaOCH_3$ (Scheme 4). [Phenol (10) is prepared from compound (9) by hydrogenation using liq.$NH_3$and pd/c]. In the same fashion phenol (1) is reacted with acetic acid, Carbonyldiimidazole (CDI) and ethylamine leads to formation of (12) Impurity-D (Scheme 5). 1-(3-hydroxyphenyl) ethanone (9) reacted with ethyl (methyl) carbamic chloride (2) in 1,4 dioxane with $NaOCH_3$ leads to formation of (13) Impurity-E (Scheme 6). Impurity-F (15) is prepared upon reaction of phenol (1) with 1-fluoro-4-nitrobenzene (14) in Dimethyl Formamide (DMF) with potassium carbonate. Scheme 7 and finally 3-nitrophenol (16) reacted with ethyl (methyl) carbamic chloride (2) in toluene with TBAB and pyridine leads to formation of (17) Impurity-G (Scheme 8).



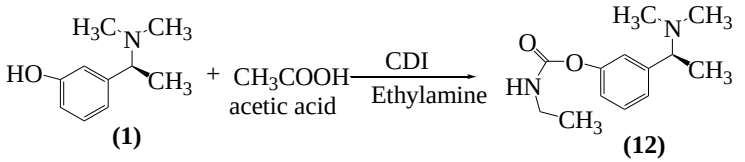
Scheme 2: Synthesis of rivatigmine impurity-A



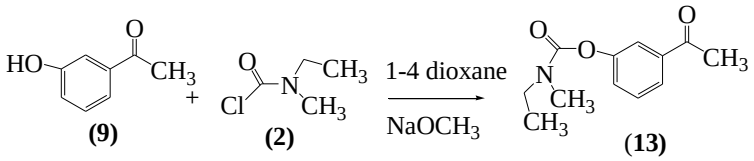
Scheme 3: Synthesis of rivatigmine impurity-B



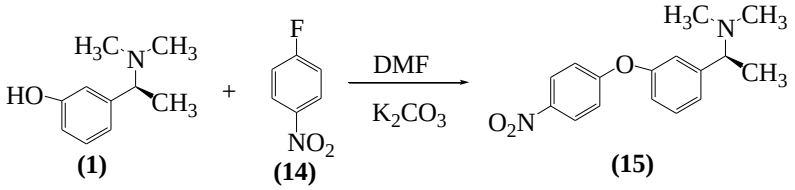
Scheme 4: Synthesis of rivatigmine impurity-C



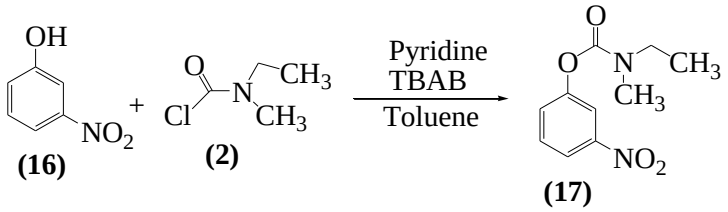
Scheme 5: Synthesis of rivatigmine impurity-D



Scheme 6: Synthesis of rivatigmine impurity-E



Scheme 7: Synthesis of rivatigmine impurity-F



Scheme 8: Synthesis of rivatigmine impurity-G

Synthesis of impurity-A

(*S)-3-(1-(dimethylamino) ethyl) phenyl dimethylcarbamate, (+)-Di-p-toluoyl-D-tartaric acid monohydrate (DPTTA) salt (6)*

(S)-3-(1-(Dimethylamino) ethyl) phenol (1) (l5.0 g, 30.2 mmol) was taken in toluene (50 ml) at 25-30°C. Pyridine (5 ml), TBAB (0.5g,63.21 mmol) and added dimethylcarbamic chloride (5) (3.90 g, 36.31 mmol)at 25-30°C. Heated the reaction mass to 110-115°C. Reaction progress checked by TLC. Cooled reaction mass to 0-5°C. Reaction mass pH adjusted to 9.0-10.0 with aqueous sodium hydroxide, product extracted into toluene and concentrated under vacuum to get oily mass. To the oily mass, methanol (35 ml), water (7 ml) and DPTTA 5.0 g, 33.0 mmol) added and heated to reflux temperature. Cool to 10-15°C, filtered, washed with methanol (7 ml) and dried to afford 6.5 g, white crystalline powder, mp. 151-153°C; HPLC purity 99.732%; IR (KBr, cm^{-1}) 3039.91 (aromatic–C-H Stretching); 2951.19 (aliphatic–C-H Stretching); 2719.72 (Broad –OH,-NH Stretching); 1724.42 (C=O Stretching); 1608.69, 1481.38 (C=C Stretching); 1338.64 (–C-H Bending); 1269.20 (-C-O Stretching); ^{1}HNMR (DMSO-d_6δ ppm): 1.414-1.436 ppm (d, J=6.6,3H); 2.334ppm (s, 6H); 2.397 ppm (s, 6H); 2.880 ppm (s, 3H); 3.014 ppm (s, 3H); 3.999-4.064 ppm (q, 2H); 5.643 ppm (s, 2H); 7.083-7.108 ppm (d, J=7.5, 1H); 7.1772 ppm (s, 1H); 7.225-7.251 ppm (d, 1H); 7.275-7.302 ppm (d, J=8.1, 4H); 7.342-7.394 (t, J=7.8, 1H); 7.787-7.814 ppm (d, J=8.1, 4H). MS m/z 236 $[M+H]^+$, 237; ^{13}C NMR (DEPT) (MeOH, δ ppm): 156.470, 152.848, 145.660, 138.774, 130.109, 129.904, 129.178, 126.276, 125.730, 122.104, 121.696, 66.748, 43.298, 36.819, 36.662, 21.558 and 20.323.

Synthesis of impurity-B

(S)-3-(1-(Dimethylamino) ethyl) phenyl diethylcarbamate DPTTA salt (8)

(S)-3-(1-(dimethylamino) ethyl) phenol **(1)** (5.0 g, 30.2 mmol) was taken in toluene (50 ml), pyridine (5 ml), TBAB, (0.5 g, 63.21 mmol) and added diethylcarbamic chloride **(7)** (4.92 g, 36.3 mmol) at 25-30°C. Slowly heated the reaction mass to 110-115°C. Reaction progress checked by TLC. Cooled reaction mass to 0-5°C. Reaction mass pH adjusted to 9.0-10.0 with aqueous sodium hydroxide, product extracted into toluene and concentrated under vacuum to get oily mass. To the oily mass, methanol (35 ml), water (7 ml) and DPTTA (5.45 g, 36.3 mmol) added and heated to reflux temperature. Cool to 10-15°C, filtered, washed with methanol (8 ml) and dried to afford 6.8 g, white crystalline powder, mp. 154-156°C HPLC purity 99.252%; IR (KBr, cm^{-1}) 2978.19 (aromatic –C-H stretching); 2931.90 (aliphatic–C-H stretching); 2715.86 (Broad –OH,-NH stretching); 1720.56 (C=O stretching); 1608.69, 1473.66 (C=C stretching); 1415.80 (–C-H bending); 1269.20 (-C-O Stretching); ^{1}H NMR (DMSO-d_6δ ppm): 1.045-1.173 ppm (m, 6H); 1.386-1.448 ppm (m, 3H); 2.330 ppm (s, 6H); 2.421 ppm (s, 6H); 3.218-3.389 ppm (m, 4H); 4.146-4.211 ppm (m, 2H); 5.665 ppm (s, 2H); 7.088-7.361 ppm (m, 8H); 7.826-7.853 ppm (d, J=8.1, 4H). MS m/z 264 $[M+H]^+$, 265; ^{13}CNMR (DEPT) (MeOH, δ ppm): 156.771, 154.462, 151.714, 148.803, 148.230, 142.983, 142.316, 137.526, 136.977, 129.204, 129.135, 128.666, 127.947, 125.043, 124.700,124.628, 124.208, 121.197, 121.09, 65.558, 45.570, 44.311, 42.251, 42.103, 41.859, 41.717, 41.563, 20.824, 20.343, 18.484, 18.195, 13.333, 12.796, 12.444, 12.307 and 11.837.

Synthesis of impurity-C

(1-ethyl-3-(1-(3-hydroxyphenyl) ethyl)-1, 3-dimethylurea (11)

1-(3-hydroxyphenyl) ethanone (9) (15.22 g, 39.20 mmol) was taken in methanol (120 ml) at 25-30°C. Added 1.52 g (5% Pd/C) and applied 4-6 kg/cm^2 hydrogen pressure at 55-60°C. Reaction progress checked by TLC. Cooled reaction mass to 25-30°C, filtered through high-low and concentrate to afford compound (10) (13.40 g). Compound (10) (5.0 g, 33.07 mmol) was taken in dioxane (25 ml), added sodium methoxide (3.5 g, 66.11 mmol) and added ethyl methylcarbamic chloride (2) (4.02 g, 33.07 mmol) at 25-30°C. Reaction progress checked by TLC. Cooled reaction mass to 25-30°C and pH adjusted to 7.0-8.0 with 10% acetic acid solution, product extracted into dioxane and concentrated under vacuum to get oily mass. Column purification done to afford 1.6 g white crystalline powder, mp. 137-140°C with HPLC purity 98.80%; IR (KBr, cm^{-1}) 3317.67 (aromatic–OH); 2974.33 (aliphatic–C-H stretching); 1720.56 (C=O stretching); 1585.54, 1543.10 (C=C stretching); 1338.64 (–C-H bending); ^{1}HNMR (DMSO-d_6δ ppm): 1.057-1.105 ppm (t, J=7.2, 3H); 1.406-1.429 ppm (d, J=6.9, 3H); 2.436 ppm (s, 3H); 2.715 ppm (s, 3H); 3.044-3.173 ppm (m, 2H); 4.910-4.980 ppm (q, 1H); 6.628-6.659 ppm (dd, J=9.3, 1H); 6.704-6.728 ppm (m, J=7.2, 2H); 7.102-7.156 ppm (t, J=8.1, 1H); 9.334 ppm (broad singlet, 1H). MS m/z 236 $[M+H]^+$, 237; ^{13}C NMR (DEPT) ($CDCl_3$, δ ppm): 164.791, 157.453, 143.343, 129.551, 117.952, 114.251, 114.053, 54.392, 44.974, 35.801, 31.065, 16.627 and 12.843.

Synthesis of impurity-D

(S)-3-(1-(dimethylamino) ethyl) phenyl ethylcarbamate (12)

(S)-3-(1-(dimethylamino) ethyl) phenol (1) (5.0 g, 30.26 mmol) was taken in acetic acid (20 ml). Added CDI (9.81 g, 60.5 mmol) and 40% ethylamine (6.82 g, 60.51 mmol) at 25-30°C. Reaction progress checked by TLC. Added water (25 ml) and methylene chloride (25 ml). Stir for 10 min and separated organic layer and concentrated under vacuum to get oily mass. Column purification done to afford 1.8 g white crystalline powder, mp. 111-113°C, HPLC purity 89.90%; IR (KBr, cm^{-1}) 3302.24 (-NH stretching); 2974.33 (aliphatic–C-H stretching); 1674.27 (C=O stretching); 1531.53,1489.10 (C= stretching); 1338.94 (–C-H bending); 1226.77, 1203.62, 1180.47 (-C-O stretching); ^{1}HNMR (DMSO-d_6δ ppm): 1.073-1.121 ppm (t, J=7.2, 3H); 1.604-1.627 ppm (d, J=6.9, 3H); 2.645 ppm (broad peak, 6H); 3.064-3.155 ppm (quintet, 2H); 4.486-4.558 ppm (q, 1H); 7.193-7.219 ppm (d, J=7.8, 1H); 7.310 (s, 1H); 7.345-7.370 ppm (d, J=7.5, 1H); 7.460-7.512 ppm (t, J=7.8, 1H); 7.808-7.841 ppm (t, J=9.9, 1H); 10.094 (broad peak, 1H). MS m/z 236 $[M+H]^+$, 237; ^{13}C NMR (DEPT) ($CDCl_3$, δ ppm): 153.903, 151.284, 136.187, 129.820, 125.381, 122.928, 122.366, 64.101, 35.306, 15.921 and 14.825.

Synthesis of impurity-E

3-acetylphenyl ethyl (methyl) carbamate (13)

1-(3-hydroxyphenyl) ethanone (9) (5.0 g, 36.72 mmol) was taken in dioxane (25 ml), sodium methoxide (3.96 g,73.33 mmol) and added ethyl methylcarbamic chloride (2) (5.36g, 44.09 mmol) at 25-30°C. Heated the reaction mass to 60-65°C and reaction progress checked by TLC. Cooled reaction mass to 10-15°C. pH adjusted to 7.00-8.00 by adding 10% acetic acid solution. Separated dioxane layer and concentrated under vacuum to afford6.58 g yellowish oily mass. HPLC purity 99.339%; IR (KBr, cm^{-1}) 3068.75 (aromatic –C-H stretching); 2972.31 (aliphatic–C-H stretching); 1718.58 (C=O stretching); 1587.42, 1477.47 (C=C stretching); ^{1}HNMR (DMSO-d_6δ ppm):) 1.087-1.111, 1.175-1.222 ppm (t, 3H); 2.583 ppm (s, 3H); 2.909, 3.041 ppm (s,3H); 3.287-3.313,3.407-3.476 ppm (q, 2H); 7.380-7.417 ppm (m, 1H); 7.512-7.564 ppm (t, J=7.8, 1H); 7.647ppm (s, 1H); 7.797-7.831 ppm (m, 1H). MS m/z 221 $[M+H]^+$, 222, $(M+NH_4)^+$, 239; ^{13}C NMR (DEPT) (DMSO, δ ppm):197.683, 153.885, 151.950, 138.476, 130.082, 127.222, 125.480, 121.709, 43.979, 34.368, 27.260 and 13.494.

Synthesis of impurity-F

(S)-N,N-dimethyl-1-(3-(4-nitrophenoxy) phenyl) ethanamine (15)

(S)-3-(1-(dimethylamino) ethyl) phenol (1) (5.0 g, 30.26 mmol) was taken in DMF (25 ml), potassium carbonate (6.41 g, 60.48 mmol) and added 1-fluoro-4- nitrobenzene (14) (5.12 g, 36.29 mmol) at 25-30°C. Heated the reaction mass to 60-65°C and reaction progress checked by TLC. Cooled reaction mass to 25-30°C added water (250 ml) and methylene chloride (25 ml), stirred and separated organic layer. Organic layer washed with saturated sodium chloride (25 ml) and separated layers. Concentrated organic layer under vacuum to afford 7.28 g yellowish oily mass. HPLC purity 84.118%; IR (KBr, cm^{-1}) 3080.32 (aromatic–C-H stretching); 2976.16 (aliphatic–C-H stretching); 1577.77, 1483.26 (C=C stretching); 1344.38 (-C-O-C stretching); ^{1}HNMR (DMSO-d_6δ ppm): 1.249-1.271 ppm (d, J=6.6, 3H); 2.088 ppm (s, 6H); 3.283-3.344 ppm (q, 1H); 7.040-7.125 ppm (m, 4H); 7.210-7.236 ppm (d, J=7.8, 1H); 7.412-7.463 ppm (t, J=7.6, 1H); 8.241-8.353 ppm (d, 2H); MS m/z 286 $[M+H]^+$, 287; ^{13}C NMR (DEPT) (DMSO, δ ppm): 162.992, 154.172, 147.060, 142.167, 130.173, 126.228, 124.482, 119.117, 118.744, 117.253, 64.158, 42.498 and 19.545.

Synthesis of impurity-G

3-nitrophenyl ethyl (methyl) carbamate (17)

3-nitrophenol (16) (5.0 g, 35.94 mmol) was taken in toluene (50 ml) at 25-30°C. Pyridine (5 ml), TBAB (0.5 g, 1.55 mmol) added ethyl methylcarbamic chloride (2) (3.90 g, 32.08 mmol) at 25-30°C. Heated the reaction mass to 110-115°C and reaction progress checked by TLC. Cooled reaction mass to 0-5°C, pH adjusted to 9.0-10.0 with aqueous sodium hydroxide, separated toluene layer and washed with water (25 ml) and separated layers and concentrated under vacuum to afford 7.2 g yellowish oily mass. HPLC purity 99.441%; IR (KBr, cm^{-1}) 3097.68 (aromatic –C-H stretching); 2974.23 (aliphatic–C-H stretching); 1720.50 (C= stretching); 1529.55,1454.33 (C=C stretching); ^{1}HNMR (DMSO-d_6δ ppm): 1.095-1.142,1.178-1.225 ppm (t, 3H); 2.922,3.048 ppm (s, 3H); 2.296-3.369, 3.413-3.484 ppm (s, 2H); 7.615-7.654 ppm; (m, 1H); 7.663-7.716 ppm (t, 1H); 8.021 ppm (s, 1H); 8.077-8.115 ppm (m, 1H). MS m/z 224 $[M+H]^+$, 225, $(M+NH4)^+$ 242, $(M+Na)^+$ 247; ^{13}C NMR (DEPT) (DMSO, δ ppm): 152.917, 151.600, 148.127, 130.479, 128.843, 120.032, 117.076, 43.627, 33.991 and 12.995.

CONCLUSION

In summary, seven potential impurities of rivastigmine tartrate (8) were synthesized by new and easy work up method. This information would be immensely useful for process chemists working in this area. Synthesis of these potential process impurities of rivastigmine tartrate **(8)** were demonstrated and used as HPLC analytical standards.

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