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Novel Process for Preparation of Tetrabenazine and Deutetrabenazine

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ABSTRACT:

A novel process for the synthesis of tetrabenazine **1** and deutetrabenazine **2,** two well-known drugs used for the treatment of chorea associated with Huntington's disease have been developed. All reaction parameters were optimized through a series of reactions and by using DoE techniques. The newly developed methods are industrially scalable and comprise of cheap, commercially available raw materials and hence are highly efficient. The added advantage is that the developed processes evade the use of genotoxic alkylating agents and therefore could be considered as safe and viable alternatives to the existing methods.

KEYWORDS:

Tetrabenazine, Deutetrabenazine, Deuterated methanol (MeOH-D_4), Mitsunobu reaction.

INTRODUCTION:

Tetrabenazine **1** was invented by Hoffmann-La-Roche, Nutley, NJ.[1] It was also known as Ro 1-9569, Nitoman and Xenazine. It is a benzoquinolizine derivative with the chemical name 1, 3, 4, 6, 7, 11b-hexahydro-9, 10-dimethoxy-3-(2-methylprpopyl)- 2H –benzo [α] quinolizin-2-one (Figure 1). Initially it was developed as an antipsychotic agent.[2] Despite of 50 years of medicinal

background, the U.S. Food and Drug Administration (USFDA) approved Tetrabenazine **1** on August 15, 2008, for the treatment of chorea associated with Huntington's disease.[3]

Deutetrabenazine **2** (trade name-*Austedo*) is a stable, non-radioactive deuterium analog of an approved drug, tetrabenazine, in which six hydrogen atoms at the 9 and 10-methoxy (-OCH_3) substituents of tetrabenazine **1** are replaced by deuterium (Figure 1). Deutetrabenazine was found effective for the treatment of chorea associated with Huntington disease due to improved pharmacokinetic properties when compared to the non-deuterated drug, tetrabenazine. Deutetrabenazine was originally developed by Auspex Pharmaceuticals. In 2015, Teva acquired Auspex Pharmaceuticals and submitted a New Drug Application (NDA) in the United States for the treatment of Huntington's disease. On April 03, 2017 Teva pharmaceutical received approval from the U.S. Food and Drug Administration (USFDA) to market Deutetrabenazine as the first deuterated drug for the treatment of chorea associated with Huntington disease.[4] Both tetrabenazine **1** and deutetrabenazine **2** are racemic mixtures (Figure 1).

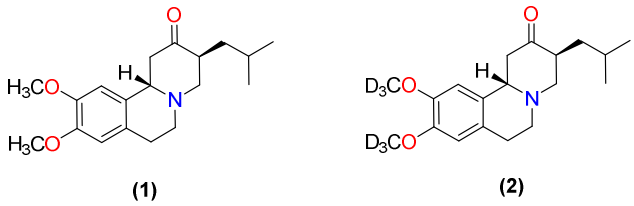


Figure 1. Chemical structures of **1** and **2**

The First synthesis of tetrabenazine **1** was reported by Hoffmann-La-Roche Inc, New Jersey in 1960,[5] whereas the first synthesis of deutetrabenazine **2** was reported by Auspex Pharmaceuticals, La Jolla, CA (US) in 2009.[6] Hoffmann-La-Roche Inc. provided a process for preparation of tetrabenazine **1** which comprises the condensation of 6,7-dimethoxy-3,4-dihydroisoquinoline with 3-methylene-5-methyl-2-hexanone in an alkaline medium. Wellcome Foundation Limited, England, described a new methodology for preparation of tetrabenazine **1**

which involved the reaction of 3, 4-dihydro-6,7-dimethoxyisoquinoline with (2-acetyl-4-methylpentyl)-trimethylammonium iodide in alcohol.[7] This methodology has advantages such as noticeably higher yield (65%), the use of less solvent and avoids the use of mercuric acetate. Auspex Pharmaceuticals developed a process for the preparation of deutetrabenazine by reacting d_6-6,7-Dimethoxy-3,4-dihydroisoquinoline and (2-acetyl-4-methyl-pentyl)-trimethylammonium iodide in ethanol. The product was isolated by column chromatography in yield of 35%. This process utilized genotoxic d_3-Iodomethane and tedious technique of column chromatography resulting in low yields hence it was not feasible for industry.[8] In another approach, Auspex Pharmaceuticals described the process for preparation of deutetrabenazine by the reaction of d_6-6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride and (2-acetyl-4-methyl-pentyl)-trimethyl-ammonium iodide in methanol-water. This process also involved the use of expensive and genotoxic d_3-Iodomethane.[9]

Deutetrabenazine **2** undergoes extensive and rapid metabolism after oral dosing, to the major circulating active metabolite **3**. The active metabolite **3** is then further metabolized by CYP2D6 to form 10-O-Desmethyl **4** and 9-O-Desmethyl **5** metabolites (Figure 2).

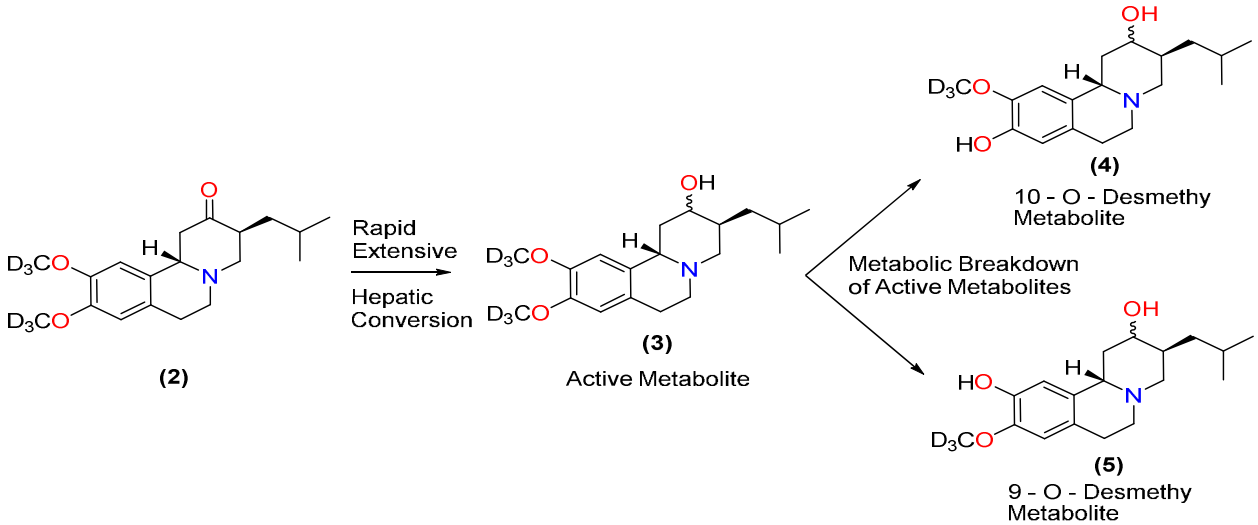


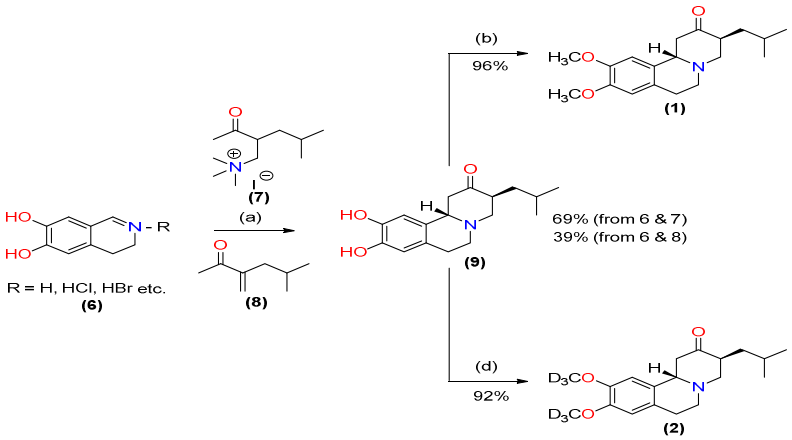
Figure 2. Metabolic Pathway of **2**

RESULTS AND DISCUSSIONS:

Considering the limitations of the reported procedures of **1** and **2**, it is indispensable to develop a new method for the synthesis of **1** and **2** which should overcome the drawbacks associated with previously reported procedures. The present invention accentuates the use of commercially available methanol and deuterated methanol (MeOH-D_4) for methylation for the synthesis of **1** and **2,** respectively by having advantages over use of genotoxic reagent d_3-Iodomethane [10] and necessity of tedious technique of column chromatography from previously developed methods. The newly developed methods provided tetrabenazine **1** in 96% yield whereas deutetrabenazine **2** was obtained in 92% yield.

The synthesis of **1** and **2** started with a common starting material, 6,7-dihydroxy-3,4-dihydroisoquinoline **6** reacted with 2-acetyl-4-methylpentyl)-trimethylammonium iodide **7** or 3-methylene-5-methyl-2-hexanone **8** in methanol-water as a solvent and a potassium carbonate as a base at temperature 65-70°C to obtain key intermediate **9** with HPLC purity >98.5%. The key intermediate **9** was then treated with methanol to obtain **1 in** 96% yield while treatment of **9** with deuterated methanol to synthesize **2** was obtained in 92% yield by using well known Mitsunobu reaction conditions (Scheme 1).

Scheme 1. Improved novel synthesis of **1** and **2**



Reagents and conditions: (a) MeOH/H_2O, K_2CO_3, IPA; (b) TPP, DIAD,CH_3OH; (c) EtOAc/n-Heptane; (d) TPP, DIAD,CD_3OD;

The reaction condition optimization for preparation of the key intermediate **9** was initially carried out in the laboratory by traditional experimental techniques. The details of reaction optimization conditions are depicted in Table S1 (refer SI), including solvents and potassium carbonate (K_2CO_3) as a base. These primary experimental results indicated that methanol-water solvent combination, by using potassium carbonate as a base gave the best conversion of 70% area by HPLC (entry 1, Table S1).

After initial screening of solvent for preparation of compound **9**, various bases were screened to obtain the best yield. The details of various bases are depicted in Table S2 (refer SI). The results of optimized experiments, indicated that potassium carbonate (K_2CO_3) in combination with methanol-water gave the best conversion to afford **9** in 70% area by HPLC (entry 1, Table S2).

For further optimization, we used design of experiment (DoE) tool for preparation of compound **9** (Table S3) (refer SI). In this study we mainly targeted for optimal quantity of **7** due to its high cost. Specifically for this study, we coded compound **7** as DTTSC and compound **9** as DTR-I. After initial laboratory optimization, we found that **7** (DTTSC) is the main cost center and used as 1.21 mole equivalent, against its theoretical requirement of 1.0 mole equivalent for the complete conversion to compound **9** (DTR-I). The reaction was comparatively slow at low temperature along with the formation of impurity. Yields were found to be significantly low while using bases such as TEA, DIPEA, DBU, NaOH, KOH and Na_2CO_3. The yield obtained was 0.9 w/w (62%) against the theoretical yield of 1.45 w/w (100%). To overcome above mentioned issues, we decided to carry out design of experiment (DoE) with 04 number of experimental factors, (2^{4-1}) fraction factorial design for analysis and 2-center point.

In continuation of above experimental factors we have kept few factors constant such as stirring speed (RPM), stirring time, same source of all raw materials, sequence of addition of reagents,

calibrated measuring cylinders, mole equivalent of dihydroxy isoquinoline compound **6**, solvent volume ratio methanol (4.5) : water (1.5) total 6.0 volume and fixed experimental batch size.

Based on above criteria, design for optimal conversion for compound **9** (DTR-I) is depicted in Table S4 (refer SI). These reactions were performed in METTLER TOLEDO's EasyMax-102 parallel synthesizer. Reaction conditions and its monitoring results are depicted in Table S5 (refer SI).

From pareto charts (Figure 3), we observed that, water volume, interaction of **7** (DTTSC) mole equivalent with water volume, **7** (DTTSC) mole equivalent, reaction temperature, interaction of **7** (DTTSC) mole equivalent with reaction temperature are the most important factors for the best conversion of compound **6** to compound **9** (DTR-I). Mole equivalent of potassium carbonate has less impact on conversion of compound **6** to compound **9** (DTR-I).

Based on main effect and interaction plots (Figure 4), it was found that, **7** (DTTSC) mole equivalent, water ratio and temperature played an important role for conversion while potassium carbonate (K_2CO_3) mole equivalent was found to have no significance.

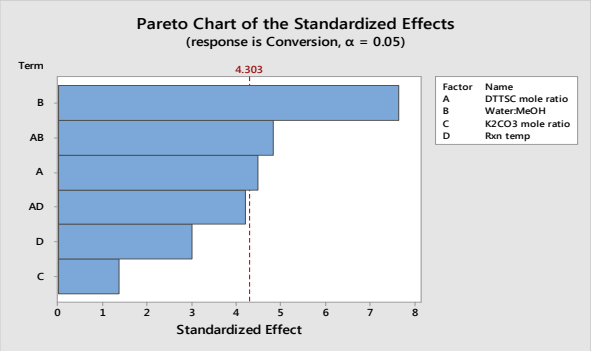


Figure 3. Pareto chart of the standardized effects for conversion of **9**

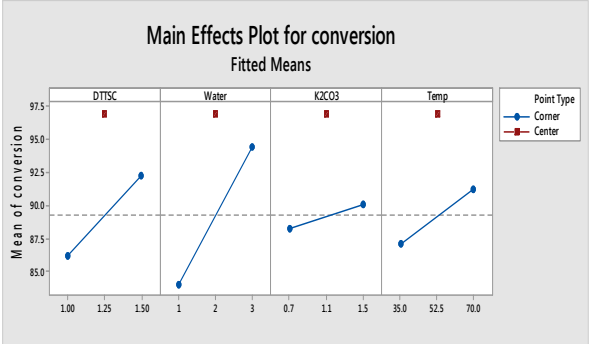


Figure 4. Main effect plot for conversion of **9**

For conversion of **6** to **9**, the interaction plot (Figure 5) shows that **7** (DTTSC) mole equivalent and reaction temperature has an interaction.

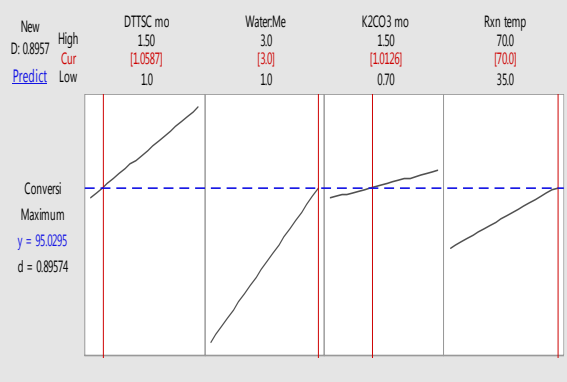


Figure 5. Interaction plot for conversion of **9**

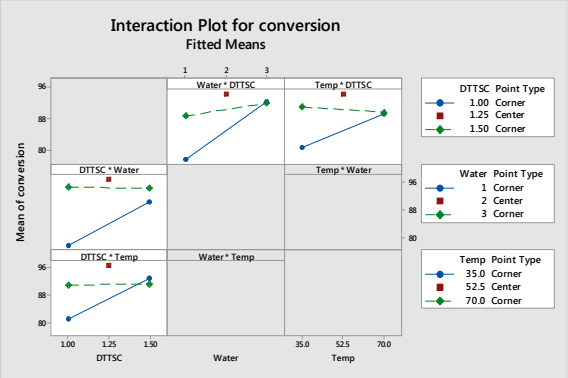


Figure 6. Optimized reaction conditions plot for conversion of **9**

Based on DoE study, the optimized reaction condition was 1.05 mole equivalent of **7** (DTTSC), methanol (3): water (3) volume ratio, 1.0 mole equivalent of potassium carbonate and 65-70°C reaction temperature for 6-10 hrs. (Figure 6). This optimized conditions gave more than 95% conversion of **6** to obtain compound **9** (DTR-I).

We developed a novel synthetic strategy for preparation of **1** and **2** by using Mitsunobu reaction conditions. We used methanol as a source of methyl for **1** and deuterated methanol as a source of deuterated methyl for **2**, in conjunction with cheap and commercially available reagents like triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD). The Mitsunobu reaction is an organic reaction used to convert a primary or secondary alcohol into a variety of compounds using diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP).[11,12]

Synthesis of **1** was carried out by reacting compound **9** with methanol in presence of diisopropyl azodicarboxylate (DIAD) and triphenyl phosphine (TPP). The reaction was carried out at 25-30°C. Tetrabenazine **1** was isolated by using techniques like filtration, evaporation, concentration etc. Tetrabenazine **1** obtained by this process was free of triphenyl phosphine (TPP) and triphenyl phosphine oxide (TPPO) impurities.

In a similar manner, preparation of **2** was carried out by reacting compound **9** with deuterated methanol in presence of diisopropyl azodicarboxylate (DIAD) and triphenyl phosphine (TPP).

Since deuterated methanol was found as a major cost contributing factor, we thought of optimizing its mole equivalent ratio in initial laboratory experiments. The detailed results are depicted in Table S6 (refer SI). These experimental results indicated that 10.0 mole equivalent of deuterated methanol gave the best conversion of 84% area by HPLC (entry 2 of Table S6).

Optimization of reaction conditions for preparation of 2 was also carried out with the help of DoE tool. Specifically for this study, we coded compound **9** as DTR-I. Based on initial laboratory optimization data, we found that deuterated methanol is the main cost center and used as 10.0 mole equivalent, against its theoretical requirement of 2.0 moles for maximum conversion of compound **9** (DTR-I) to afford **2**. In this DoE study, we decided to carry out design of experiment (DoE) with 03 number of experimental factors, (2^3) full factorial design for analysis and 2 center point. The details of experimental factors for **2** are depicted in Table S7 (refer SI).

Along with above mentioned variable experimental factors, we kept a few factors constant such as stirring speed (RPM), stirring time, same source of raw materials, sequence of addition of reagents, calibrated measuring cylinders, mole equivalent of compound **9** (DTR-I), dichloromethane volume and fixed experimental batch size.

Based on above criteria, the design for optimal quantity of deuterated methanol and maximum conversion for **2** is depicted in Table S8 (refer SI).

Above mentioned reactions are performed in METTLER TOLEDO's EasyMax-102 parallel synthesizer. Reaction conditions and its monitoring results are depicted in Table S9 (refer SI). From pareto charts (Figure 7), we observed that for maximum conversion of compound **9** (DTR-

I) to compound **2**, deuterated methanol mole equivalent plays a significant role. The mole equivalent of deuterated methanol in combination with triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) was also found to be significant. It was found that temperature does not play significant role in the conversion of **9** to compound **2.**

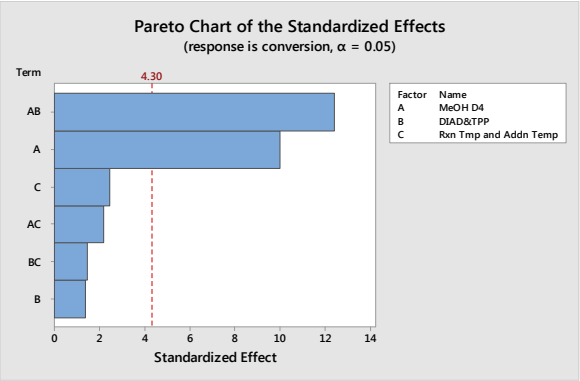


Figure 7. Pareto chart of the standardized effects for conversion of **9** to **2**

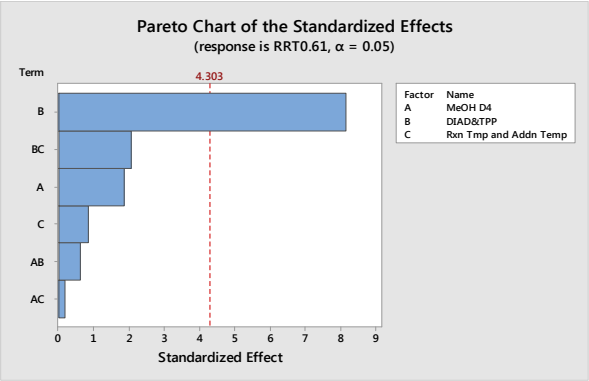


Figure 8. Pareto chart of the standardized effects for **4**

As displayed in Figure 8, formation of impurity **4** is highly dependent on mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD). Deuterated methanol mole equivalent plays a moderate role. The importance of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) mole equivalents in combination with reaction temperature in the formation of impurity **4** was also found to be a moderate contributor.

Like **4**, formation of impurity **5** is highly dependent on mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) (Figure 9). Deuterated methanol mole equivalent plays a moderate role as well as triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) mole equivalents with the combination of reaction temperatures also have moderate influence for the formation of **5**.

As per main effect plot for conversion of **2** (Figure 10), reaction conversion is highly dependent on mole equivalent of deuterated methanol, conversion increases sharply with deuterated

methanol mole equivalent. Whereas increase in mole equivalents of triphenyl phosphine (TPP), diisopropyl

azodicarboxylate (DIAD) with reaction temperature provided less conversion.

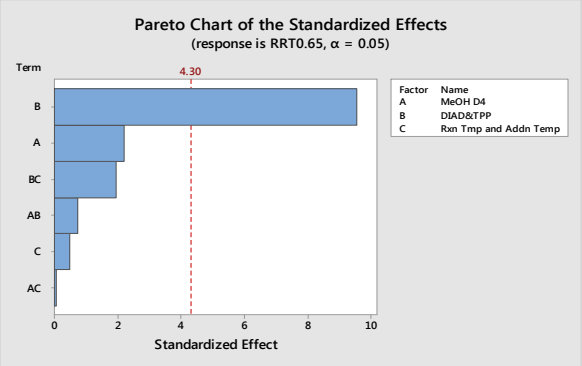


Figure 9. Pareto chart of the standardized effects for **5**

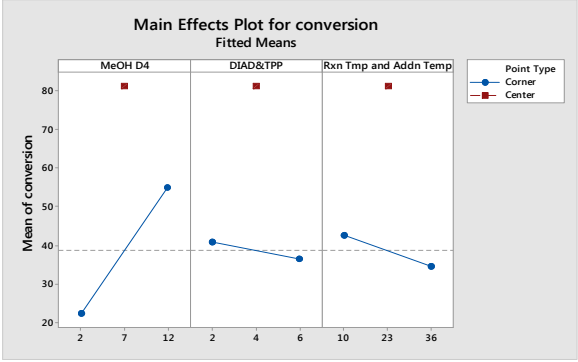


Figure 10. Main effect plot for conversion of **2**

The interaction plot (Figure 11) indicates that mole equivalents of deuterated methanol have strong interaction with mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) for maximum conversion of **2**. However there was very less impact of mole equivalents of deuterated methanol with reaction temperature as well as mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) with reaction temperature on conversion of **2**.

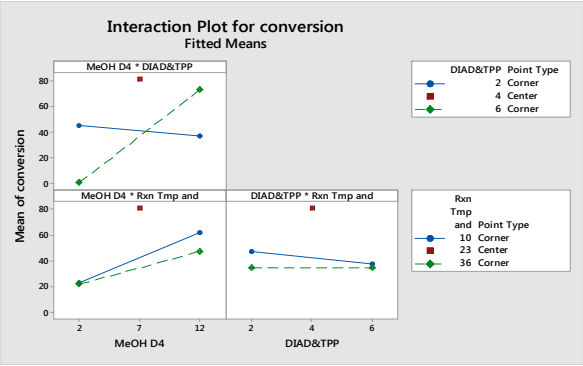


Figure 11. Interaction plot for conversion of **2**

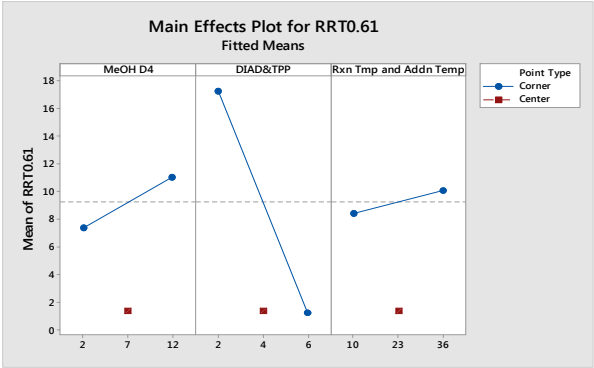


Figure 12. Main effect plot for formation of **4**

Based on main effect plot for formation of **4** (Figure 12), it was concluded that formation of **4** was highly dependent on mole equivalents of deuterated methanol, triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD). The level of impurity **4** increases with the increase in deuterated methanol mole equivalent and decreases sharply with the increase in mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD). Whereas formation of **4** gradually increases with increase in reaction temperature.

The interaction plot for **4** (Figure 13) indicates that there was strong interaction of mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) with reaction temperature. Whereas the mole equivalent of deuterated methanol, triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) with reaction temperature has no interaction with each other.

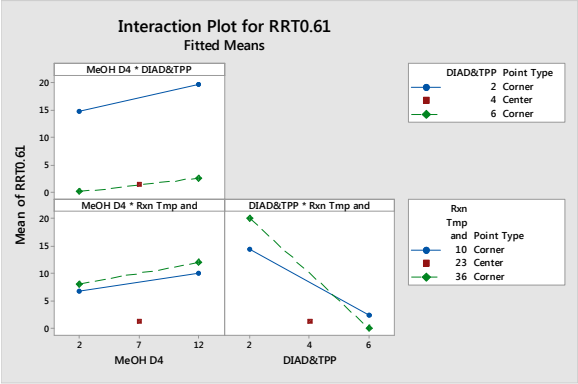


Figure 13. Interaction plot for formation of **4**

Main effect plot for formation of impurity **5** (RRT 0.65) (Figure 14) show that formation of **5** was highly dependent on mole equivalents of deuterated methanol, triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD). The level of impurity **5** increases with the increase in deuterated methanol mole equivalents. Formation of **5** decreases sharply with the increase in mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD).

Formation of **5** was gradually increased with increase in reaction temperature but reaction temperature has little to no effect in comparison.

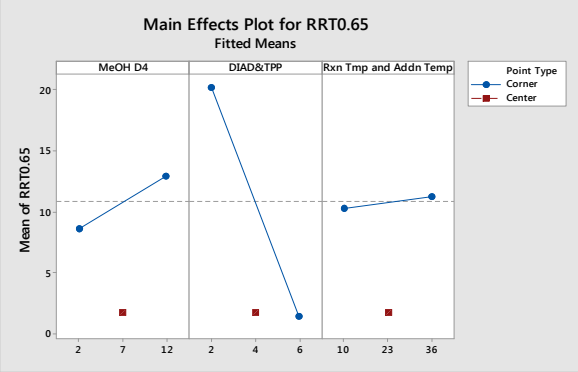


Figure 14. Main effect plot for formation of **5**

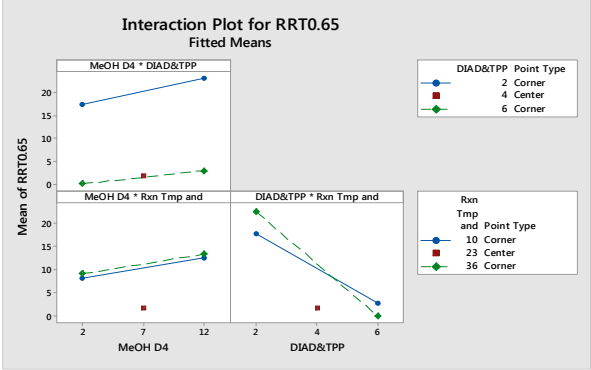


Figure 15. Interaction plot for formation of **5**

The interaction plot for impurity **5** (Figure 15) indicates that there was a strong interaction of mole equivalents of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) with reaction temperature. Whereas mole equivalent of deuterated methanol, triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD) with reaction temperature has no interaction with each other.

To get rid of triphenyl phosphine (TPP) and triphenyl phosphine oxide (TPPO) impurities compound **2** further recrystallized from mixture of ethyl acetate and n-heptane. Compound **2** was obtained with HPLC purity >99.5%.

In the synthesis of **1** and **2**, Mitsunobu reaction was carried out by using triphenylphosphine (TPP), diisoproyl azodicaboxylate (DIAD) in tetrahydrofuran. In this reaction triphenylphosphine oxide (TPPO) was formed as a by-product and it was removed selectively during work-up operation to obtain a highly pure deutetrabenazine **2** which was free from triphenylphosphine (TPP) and triphenylphosphine oxide (TPPO) impurities.

We filed a patent application for this innovation in April 2016, [13] published in October 2017.[14]

CONCLUSION

An efficient, robust, industrially viable and cost effective process was developed for the synthesis of tetrabenazine and deutetrabenazine which are used to treat chorea associated with Huntington's disease. New methodologies have been developed for O-methylation by using methanol and deuterated methanol for the synthesis of tetrabenazine and deutetrabenazine respectively by using Mitsunobu reaction conditions. Advantage of this novel process for the preparation of tetrabenazine include the utilization of inexpensive and commercially available methanol and avoiding the use of genotoxic iodomethane. Also this novel process for the preparation of deutetrabenazine does not involve use of tedious technique of column chromatography and genotoxic d_3-Iodomethane.

EXPERIMENTAL SECTION

Materials and Methods. 6,7-dihydroxy-3,4-dihydroisoquinoline hydrochloride **6** and (2-acetyl-4-methyl-pentyl)-trimethylammonium iodide **7** were purchased from M/s. Aktinos Healthcare Private Limited, According to the suppliers the purity of 6,7-dihydroxy-3,4-dihydroisoquinoline hydrochloride **6** and (2-acetyl-4-methyl-pentyl)-trimethylammonium iodide **7** were >99%. Deuterated Methanol (MeOH-D_4) were purchased from Cambridge Isotope Laboratories Inc. with >99.5% isotopic enrichment by ^{1}HNMR. Diisopropyl azodicarboxylate (DIAD) was procured from Spectrochem. Other reagents were purchased from Globe chemie, Avra, & Finar. Solvents like methanol, dichloromethane, toluene and isopropyl alcohol were procured from commercial sources and also used without further purification. ^{1}HNMR spectra were recorded on a Bruker 500 Ultra shield at 500 MHz (^{1}H) deuterated chloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-d_6) without usage of an internal standard. Chemical shifts are reported in ppm. Mass spectra were recorded on Acquity UPLC PDA detector using electron spray ionization (ESI). FTIR spectra were recorded on PerkinElmer precisely spectrum 400 FT-

IR/FT-NIR Spectrometer. HPLC chromatograms were recorded on a LC-2010 CHT liquid chromatograph SHIMADZU or Ultimate 300 Auto sampler DIONEX.

Large Scale Preparation of Dihydroxy Isoquinoline compound 9. In stainless steel cylindrical shape reactor, a slurry of methanol (12 lit.), 6,7-dihydroxy-3,4-dihydroisoquinoline hydrochloride **6** (4.0 kg.) and water (12 lit.) was stirred and (2-acetyl-4-methyl-pentyl)-trimethylammonium iodide **7** (6.6 kg.) was added to it. The reaction mass was stirred at room temperature and potassium carbonate (2.8 kg.) was added in five equal lots. The reaction mass was heated to 65-70°C and was stirred for 30 hours. The reaction mass was cooled to room temperature and water (12 lit.) was added to it and stirred for 4 hours. The solid was filtered and washed with water, the solid was taken in isopropanol (10 lit.) and the mixture was heated to 75-80°C for 15-30 min. The reaction mass was cooled, the solid was filtered and washed with isopropanol and dried under vacuum till constant weight to give product **9** (4.0 kg., 69%). HPLC purity: 98.50%; Mp 191.1-191.5°C; FTIR (In KBr): 3442, 2959, 2456, 1714, 1276, 872, cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6) δ 8.70 (s, 2H) , 6.45 (d, 2H, *J* = 11.2 Hz.), 3.35 (d, 1H, *J* = 9.6 Hz.), 3.20 (dd, 1H, *J* = 11.6, 6.0 Hz.) 3.08 - 3.55 (m, 1H), 2.85 - 2.80 (m, 1H), 2.66 -2.40 (m, 5H), 2.22 (t, 1H, *J* = 12.0 Hz.), 1.65 - 1.57 (m, 2H), 0.92 - 0.83 (m, 7H); ESI-MS (*m/z*) 290.3 $[M + H]^+$.

Large Scale Preparation of Tetrabenazine 1. A slurry of tetrahydrofuran (2000 ml), dihydroxy isoquinoline compound **9** (250 g), methanol (276.8 g) and triphenylphosphine (679.9 g) was prepared in a glass line cylindrical shape reactor, in which slowly added a solution of diisopropylazodicarboxylate (DIAD) (524.1 g) in tetrahydrofuran (500 ml) at 25-30° C over the period of 1 to 2 hrs. The reaction mass was stirred for 3-6 hours at 25-30°C. The reaction mass was washed with water and organic layer was concentrated under vacuum. A mixture of water

(2500 ml) and toluene (7500 ml) was added to the concentrated mass and the mixture was stirred. The aqueous layer was separated and the organic layer was washed with 5% aqueous sodium hydrogen sulphate solution (2500 ml, 3 times).The aqueous layers were collected together and the pH was adjusted to 9-11 using aqueous ammonia solution (750 ml).Dichloromethane (2500 ml) was added to it and the organic layer was separated and concentrated under vacuum. Water (1250 ml) was added to the concentrated mass and the mass was stirred for at 25-30°C for 2 hours. The solid was filtered, washed and dried under vacuum to give **1** (262.3 g, 96%); FTIR (In KBr): 2942, 2919, 1701, 1516, 1465, 1370, 1263, 1159, 1010, 860, 749 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.57 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.52 (d, 1H, *J* = 11.2 Hz.), 3.32 (dd, 1H *J* = 11.6, 6.4 Hz.), 3.13 - 3.10 (m, 2H), 2.93 -2.90 (m, 1H), 2.77 - 2.73 (m, 2H), 2.64 - 2.53 (m, 2H), 2.37 (t, 1H, *J* = 11.6 Hz.), 1.83 - 1.80 (m, 1H), 1.69 - 1.66 (m, 1H), 1.08 - 1.04 (m, 1H), 0.94 - 0.91 (m, 6H); ESI-MS (*m/z*) 318.3 $[M + H]^+$.

Purification of Tetrabenazine 1. In a glass line cylindrical shape reactor, a slurry of tetrabenazine **1** (10 g) and ethyl acetate (30 ml) was heated to 65-70°C.The mixture was stirred for 60-90 minutes and filtered through micron filter. The filtrate was cooled to 25-30°C and n-heptane (100 ml) was added to it. The mixture was stirred for about 4 hours at 25-30°C.The solid was filtered, washed with n-heptane and dried under vacuum to give **1** (9.6 g, 96%). HPLC purity: 99.75%; FTIR (In KBr): 2942, 2919, 1701, 1516, 1465, 1370, 1263, 1159, 1010, 860, 749 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d6) δ 6.70(s, 1H), 6.69 (s, 1H), 3.72 (s, 6H), 3.46 (d, 1H, *J* = 10.0 Hz.), 3.24 (dd, 1H, *J* = 11.5, 6.0 Hz.), 3.15 - 3.11 (m, 1H), 2.95 -2.89 (m, 1H),2.85 (dd,1H *J* = 13.0, 3.0 Hz), 2.69 - 2.65 (m, 2H), 2.52 - 2.46 (m, 2H), 2.28 (t, 1H, *J* = 12.0 Hz.), 1.66 - 1.63 (m, 2H), 0.94 - 0.85 (m, 7H); ESI-MS (*m/z*) 318.3 $[M + H]^+$.

Large Scale Preparation of Deutetrabenazine 2. A slurry of dichloromethane (24 lit.), dihydroxy benzoquinoline compound **9** (3.0 kg.), deuterated methanol (MeOH-D_4) (3.75 kg.) and triphenylphosphine (8.16 kg.) was prepared in a glass line cylindrical shape reactor, in which slowly added a solution of diisopropylazodicaboxylate (DIAD) (6.30 kg.) in dichloromethane (6 lit.) at 25-30°C over the period of 1 to 2 hrs. The reaction mass was stirred for 2 hours at 25-30°C. The reaction mass was washed with water and organic layer was concentrated under vacuum. Toluene was added to the residue and the mixture was stirred. The mixture was filtered and the filtrate was washed with 5% aqueous sodium hydrogen sulphate solution (15 lit., 3 times). The aqueous layer was collected together and the pH was adjusted to 9-11 using aqueous ammonia solution. Dichloromethane (30 lit.) was added to it and the organic layer was separated and concentrated under vacuum. Ethyl acetate (30 lit.) was added to the residue, carbon treatment was given and ethyl acetate was removed under vacuum. Isopropanol (6 lit.) was added to the residue and the mixture was heated to 75-80°C for 15-30 minutes. The reaction mass was cooled, the solid was filtered and washed with isopropanol and dried under vacuum to give **2** (3.06 kg, 92%). HPLC purity: 98.82%; FTIR (In KBr): 2942, 2920, 2246, 2067, 1700, 1513, 1269, 1113, 990, 747 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.56 (s, 1H), 3.53 (d, 1H, *J* = 10.5 Hz.), 3.32 - 3.30 (m, 1H), 3.17 - 3.13 (m, 2H), 2.92 (dd, 1H, *J* = 13.5,3.0 Hz), 2.77 - 2.73 (m, 2H), 2.64 -2.53 (m, 2H), 2.37 (t, 1H, *J* = 11.5 Hz.), 1.84 - 1.79 (m, 1H), 1.69 - 1.67 (m, 1H), 1.08-1.04 (m, 1H), 0.94-0.91 (m, 6H); ESI-MS (*m/z*) 324.4 $[M + H]^+$

Large Scale Purification of Deutetrabenazine 2. In a glass line cylindrical shape reactor, a slurry of deutetrabenazine **2** (1.70 kg.) and ethyl acetate (13.6 lit.) was heated to 60-65°C.The mixture was stirred for 60-90 minutes and filtered through micron filter. The filtrate was concentrated under vacuum and isopropanol (1.7 lit.) was added to the residue. The mixture was

heated to 75-80°C for 15-30 minutes and was cooled to 25-30°C.The off-white solid was filtered, washed with isopropanol and dried under vacuum to give **2** (1.53 kg, 90%). HPLC purity: 99.77%; Mp 128.75-129.42°C; FTIR (In KBr): 2942, 2920, 2246, 2067, 1700, 1513, 1269, 1113, 990, 747 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d6) δ 6.69 (s, 2H), 3.46 (d, 1H, *J* = 10.0 Hz.), 3.25 (dd, 1H, *J* = 11.5, 6.0 Hz.), 3.15 - 3.11 (m, 1H), 2.95 -2.89 (m, 1H),2.85 (dd,1H *J* = 13.5, 3.0 Hz), 2.70 - 2.64 (m, 2H), 2.52 - 2.44 (m, 2H), 2.28 (t, 1H, *J* = 11.5 Hz.), 1.66 - 1.63 (m, 2H), 0.93 - 0.85 (m, 7H); ESI-MS (*m/z*) 324.4 $[M + H]^+$; $[\alpha]_D$ – 0.3° [C 0.3, DCM at 25°C].

ASSOCIATED CONTENT

Supporting Information

Experimental details with ^{1}HNMR, FTIR, Mass and HPLC chromatogram.

Reaction optimization Tables S1 to S9.

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Author contribution

All authors contributed to the conceptual development of this process. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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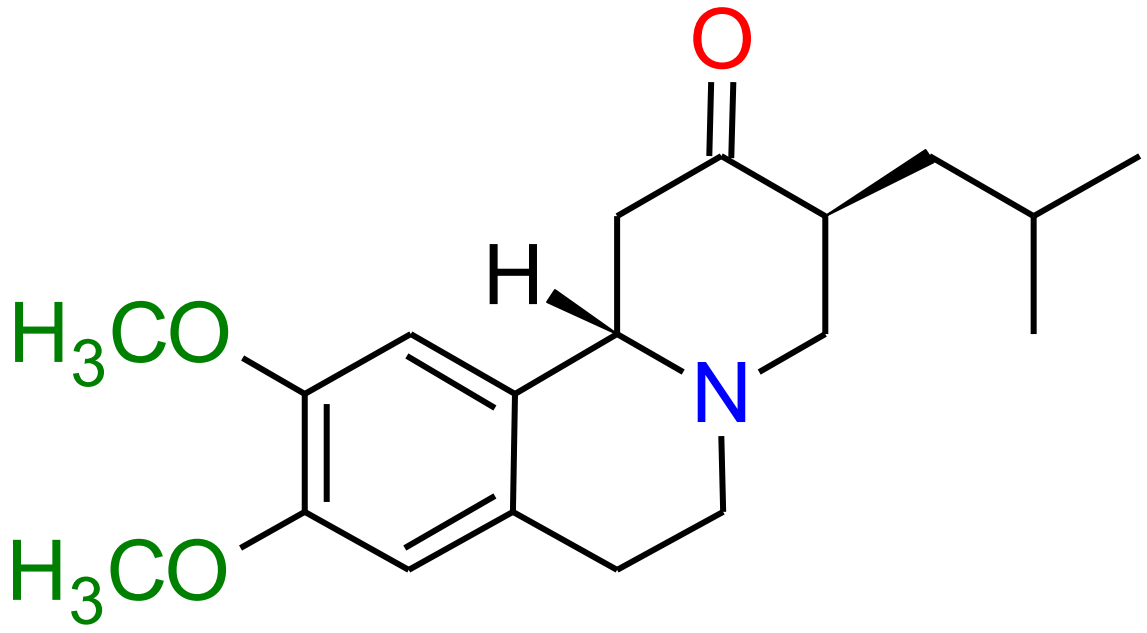

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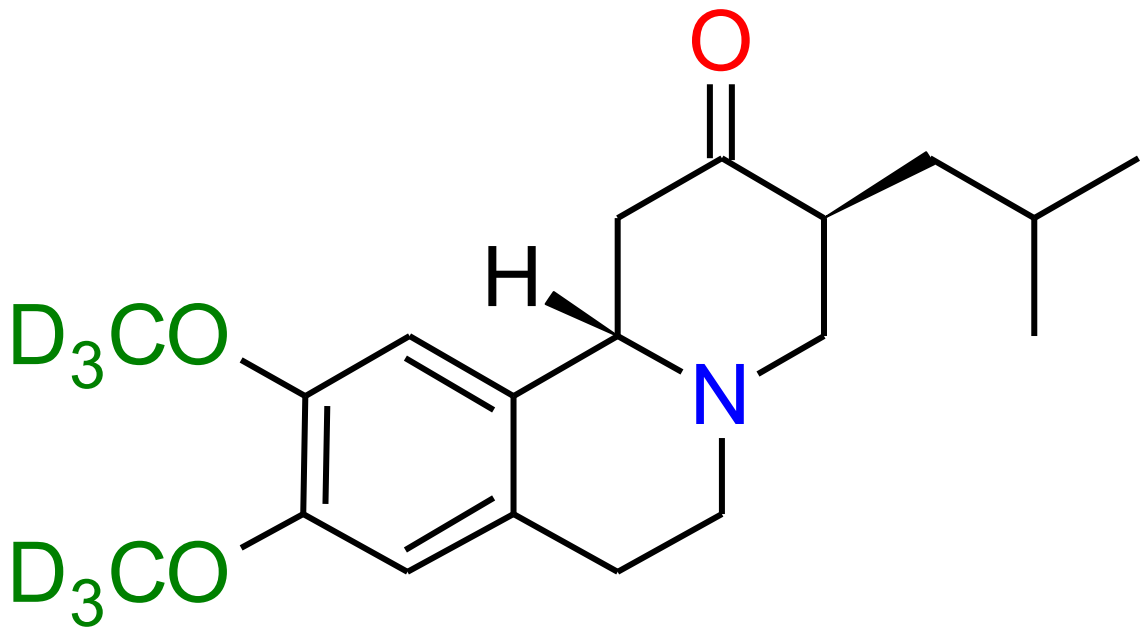

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