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## SYNTHESIS AND CHARACTERIZATION OF POTENTIAL IMPURITIES OF RASAGILINE MESYLATE: AN ANTI-PARKINSON'S DRUG

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### ABSTRACT

Rasagiline mesylate is prepared by different synthetic approaches. Almost in all the approaches, three major impurities (N, N-di-(2-propynyl)-indanylamine; N-allyl indanylamine and N-propylindanylamine) are observed in the API. The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. In this publication, a description of these impurities and their origins in Rasagiline process are presented along with synthesis and spectral characterization.

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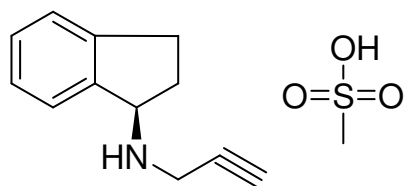
### Key Words

Rasagiline mesylate,  
Impurities, N,  
N-di-(2-propynyl)-indanylamine,  
N-allyl indanylamine,  
N-propylindanylamine

## INTRODUCTION

Mathur, A., Rasagiline mesylate (1) is an active pharmaceutical substance with an empirical formula of  $C_{12}H_{13}N$ ,  $CH_4O_3S$  and a molecular weight of 267.34. Rasagiline mesylate is the international common accepted name for R-(+)-N-propargyl-1-aminoindan mesylate, which is represented in figure 1.

**Figure 1:** Chemical structure of Rasagiline mesylate (1)



Human cells contain two forms of monoamine oxidase (MAO) type A and type B. Both are found in the brain, but MAO type B is far more prevalent and is responsible for the breakdown of dopamine after its release into the synapse. Parkinson's disease is characterized by the death of cells that use dopamine to transmit their signals, which result in a decrease in synaptic signal strength and concomitant symptomology. By inhibiting the breakdown of dopamine in the synapse, Rasagiline mesylate (1) permits the signaling neurons to re-absorb more of it for re-use later, somewhat compensating for the diminished quantities. Rasagiline mesylate is an irreversible inhibitor of monoamine oxidase<sup>1</sup> used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases<sup>2</sup>. It is selective for MAO type B over type A by a factor of fourteen<sup>3</sup>.

Laboratory studies shown that Rasagiline has invitro and invivo neuroprotective effects. But its neuroprotective effect in Parkinson's disease patients is unknown at present. These studies shown that MAO type B metabolizes an opioid-related chemical called MPTP (not an opioid itself), into a neurotoxin called MPP+ that in turn creates free radicals. There is an uncertainty because the mechanism of cell death in human Parkinson's disease may or may not involve the actions of free radicals, but there is suggestive evidence that the drug slows disease progression. The ADAGIO study found that early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent.

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (*i.e.* the identity as well as the quantity of impurity in the pharmaceuticals), is now receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the European Pharmacopoeia (EP), British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations.

The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances<sup>4</sup>, products<sup>5</sup> and residual solvents<sup>6</sup>. There is a good significant demand for the impurity-reference standards along with the API reference standards for both regulatory authorities and pharmaceutical companies. A number of recent articles<sup>7-9</sup> have described a designed approach and guidance for isolating and identifying process-related impurities and degradation products using mass spectrometry, Nuclear Magnetic Resonance (NMR). High-performance liquid chromatography (HPLC), Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS), and tandem mass spectrometry for pharmaceutical substances.

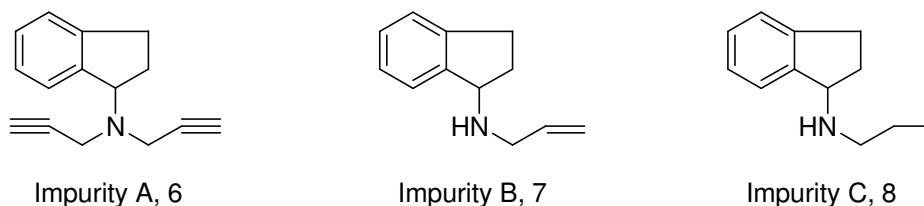
The procedure of impurity profiling, begins with the detection of the impurities using the thin-layer chromatography, high-performance liquid chromatography or gas chromatography. Procurement of standard impurity samples from the synthetic organic chemists which include, last intermediate of the synthesis, products of predictable side reaction, degradation products if any, etc.

The possibilities of spectroscopic techniques in drug impurity profiling without chromatographic separation are also worth mentioning. Spectra obtained by using high-resolution, highly sensitive NMR spectrometers and mass spectrometers with APCI/ESI facilities are suitable to provide a fingerprint picture regarding the purity of the sample.

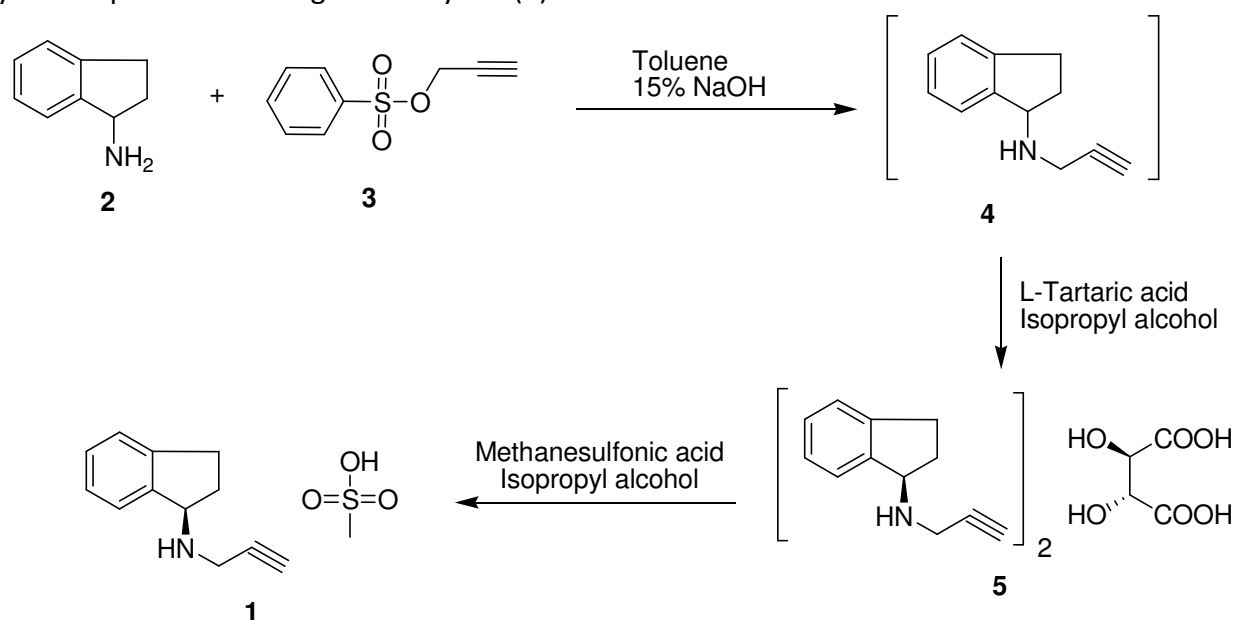
The important step in the impurity profiling is the synthesis of the material (impurity standard) with the proposed structure. The retention and spectral matching of the synthesized material with the impurity in question is useful for analytical method development and validation.

There are many synthetic methods known in the literature for the synthesis of Rasagiline mesylate<sup>10</sup>.

**Figure 2:** Chemical structure of Rasagiline impurities



**Scheme 1:** Synthetic process of Rasagiline mesylate (1)



Impurity A is a process impurity and is well controlled by maintaining proper reaction conditions. The main source for Impurity B and C was one of the key raw materials, propargyl benzene sulfonate. Impurity B and C formation was diminished by controlling the impurity levels in that key raw material.

### Sources of Impurities

#### Impurity A

Impurity A was a process impurity and found as a major impurity during the synthesis of Rasagiline mesylate (1).

Commercial synthetic process (Scheme 1) of Rasagiline mesylate (1) was reported by Moussa and co-workers<sup>11</sup>. In all the above synthetic approaches, three impurities (Figure 2) are observed as a major impurities and they are designated as Impurity A (N, N-di-(2-propynyl)-indanylamine, 6), Impurity B (N-allyl indanylamine, 7) and Impurity C (N-propylindanylamine, 8).

First step of Rasagiline synthesis involves the condensation of racemic 1-aminoindan (2) with propargyl benzene sulfonate (3) in the presence of 15% aqueous NaOH in toluene and consequences racemic Rasagiline (4). After formation of compound 4, it further condenses with compound 3 due to basic reaction conditions and affords impurity A.

#### Impurity B

Impurity B is a process impurity. Propargyl benzene sulfonate (3) was one of the key starting material and it

is synthesized by the condensation of prop-2-yn-1-ol with para toluene sulfonyl chloride. Prop-2-yl-1-ol contains traces of prop-2-en-1-ol as an impurity. This prop-2-en-1-ol transform as allyl benzene sulfonate in propargyl benzene sulfonate. Allyl benzenesulfonate participates in the condensation reaction and leads to impurity B.

### Impurity C

Impurity C is a process impurity. Propargyl benzene sulfonate (3) was one of the key starting material and it is prepared by the reaction of prop-2-yn-1-ol with para toluene sulfonyl chloride. Prop-2-yl-1-ol contains traces of 1-propanol as an impurity. 1-Propanol also participates in the reaction and produces propyl benzene sulfonate impurity in propargyl benzene sulfonate. Propyl benzene sulfonate participates in the subsequent reactions and crops impurity C.

There is no synthetic approach available for the impurities A, B and C in the literature as on date. This made us to provide a feasible synthetic approach for the synthesis of impurity A, B and C to cater the needs of the pharmaceutical industry.

Present paper describes simple and facile synthesis for impurity A, B and C. This may serve as standards for impurity profiling in the drug development.

### MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One),  $^1\text{H}$  (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using  $\text{DMSO-}d_6$  as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up. All the solvents and reagents used were of commercial grade.

**Synthesis of N, N-di-(2-propynyl)-indanylamine (Impurity A, 6):** To a stirring solution of 1-aminoindan (2) (10 g, 0.075 mol), propargyl benzene sulfonate (3) (36.8 g, 0.1875 mol) in toluene (40 mL), added 15% sodium hydroxide solution (20 mL) slowly at below 20°C.

Raised the mass temperature to 28°C and further heated to 40°C. Reaction mass was maintained at the same temperature for 8 hours and progress of the reaction was monitored by in-process TLC (mobile phase: ethyl acetate: n-hexane – 3:2). Charged toluene (15 mL) and water (35 mL) and agitated the mass for 10 minutes. Separated the toluene layer and again added water (25 mL). Adjusted the mass pH to 9 with 10% sodium hydroxide solution (20 mL) and separated toluene layer was washed with water (20 mL). Distilled off solvent completely under reduced pressure to afford impurity A as a light brown colour residue.

Yield: 72.9%; M. F.  $\text{C}_{15}\text{H}_{15}\text{N}$ ; M. Wt. 209.29; IR (KBr,  $\text{cm}^{-1}$ ): 3315 (C-H str in  $\text{C}\equiv\text{CH}$ ), 3012 (aromatic C-H str), 1602 and 1435 (aromatic C-C vib), 2922 (C-H str in  $-\text{CH}_2-$ ), 2134 ( $\text{C}\equiv\text{C}$  str), 1325 (C-N str);  $^1\text{H}$ NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  1.8 (s, 2H,  $\text{C}\equiv\text{CH}$ ), 2.0 – 2.2 (m, 2H,  $-\text{CH}_2-$ ), 2.8-2.95 (m, 2H,  $-\text{CH}_2-$ ), 3.1 (s, 4H,  $-\text{CH}_2-$ ), 4.0 (m, 1H,  $-\text{CH}-$ ), 7.20 (m, 4H, ArH);  $^{13}\text{C}$ NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  26.6, 28.2, 42.4, 68.7, 70.9, 78.9, 126.0, 128.6, 140.2, 144.4; MS  $m/z$  (%) = 210.32 (M+1); Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}$ : C - 86.08, H - 7.22, N - 6.69; Found: C - 86.06, H - 7.23, N - 6.71.

### Synthesis of allyl 4-methylbenzenesulfonate (9):

Charged 47% sodium hydroxide solution (15 mL) and water (20 mL) into a RBF and started agitation at 25°C. Allyl alcohol solution (10 g, 0.17 mol dissolved in 10 mL toluene) slowly added over a period of 30-40 minutes at 15-20°C. Added triethylbenzylammonium chloride (0.5 g, 0.05% w/w) followed by p-toluene sulfonyl chloride solution (42.4 g, 0.20 mol in 50 mL toluene) slowly at the same temperature. Mass temperature raised to 26°C and reaction progress was monitored by in-process TLC (mobile phase: ethyl acetate: n-hexane – 1:1. Separated the toluene layer and washed with saturated sodium bicarbonate solution (25 mL) followed by water (2 X 20 mL). Distilled off solvent completely under reduced pressure to afford allyl 4-methylbenzenesulfonate (9) as a light yellow colour residue.

Yield: 88.4%; M. F.  $\text{C}_{10}\text{H}_{12}\text{O}_3\text{S}$ ; M. Wt. 212.27; IR (KBr,  $\text{cm}^{-1}$ ): 3052 (C-H str in  $\text{C}=\text{CH}_2$ ), 3014 (aromatic C-H str), 1604 and 1475 (aromatic C-C vib), 2945 (C-H str in  $-\text{CH}_3$ ), 1078 (S=O str);  $^1\text{H}$ NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  2.3 (s, 3H,  $-\text{CH}_3$ ), 4.2 (d, 2H,  $-\text{CH}_2-$ ), 5.2 (m, 2H,  $\text{C}=\text{CH}_2$ ), 5.9

(m, 1H, -CH=), 7.40 (d, 2H, ArH), 7.90 (d, 2H, ArH); <sup>13</sup>CNMR (300 MHz, DMSO-d<sub>6</sub>): δ 24.1, 65.6, 116.8, 127.5, 130.0, 133.2, 137.9, 144.3; MS *m/z* (%) = 213.32 (M+1); Anal. Calcd for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>S: C - 56.58, H - 5.70; Found: C - 56.60, H - 5.69.

#### Synthesis of N-allyl indanylamine (Impurity B, 7) from 2 and 9:

Charged toluene (60 mL) into a fresh RBF and started stirring at 25-30°C. Charged 1-aminoindan (2) (12 g, 0.09 mol) and allyl 4-methylbenzenesulfonate (9) (19.1 g, 0.09 mol) slowly under stirring at the same temperature. Mass was feeded with 10% sodium hydroxide solution (26 mL) slowly at below 15°C. Reaction mass temperature raised to 20°C and maintained at the same temperature for 15 hours and progress of the reaction was monitored by in-process TLC (mobile phase: ethyl acetate: n-hexane - 3:2). Charged water (35 mL) and agitated the mass for 10 minutes. Separated the toluene layer and washed with water (2 X 30 mL). Distilled off solvent completely under reduced pressure to afford impurity B as a brown colour residue.

Yield: 73.6%; M. F. C<sub>12</sub>H<sub>15</sub>N; M. Wt. 173.25; IR (KBr, cm<sup>-1</sup>): 3038 (C-H str in C=CH<sub>2</sub>), 3022 (aromatic C-H str), 1598 and 1465 (aromatic C-C vib), 2930 (C-H str in -CH<sub>2</sub>-), 1670 (C=C str), 1321 (C-N str), 3364 (N-H str); <sup>1</sup>HNMR (300 MHz, DMSO-d<sub>6</sub>): δ 2.2 (s, 1H, -NH), 2.0-2.2 (m, 2H, -CH<sub>2</sub>-), 2.8-2.9 (m, 2H, -CH<sub>2</sub>-), 3.4 (m, 2H, -CH<sub>2</sub>-), 4.0 (m, 1H, -CH-), 5.2 (m, 2H, =CH<sub>2</sub>), 5.9 (m, 1H, -CH=), 7.2 (m, 4H, ArH); <sup>13</sup>CNMR (300 MHz, DMSO-d<sub>6</sub>): δ 28.1, 30.4, 49.6, 63.2, 116.0, 126.0, 129.1, 134.3, 139.7, 143.8; MS *m/z* (%) = 174.65 (M+1); Anal. Calcd for C<sub>12</sub>H<sub>15</sub>N: C - 83.19, H - 8.73, N - 8.08; Found: C - 83.20, H - 8.76, N - 8.04.

#### Synthesis of N-allyl indanylamine (Impurity B, 7) from 4:

Charged 1-aminoindan (15 g, 0.112 mol), 5% palladium on barium sulphate (0.8 g), 0.45 g of quinolone and 100 mL of methanol into a RBF and started stirring at ambient temperature. The flask was placed in a hydrogenation apparatus and the mass was thoroughly purged with nitrogen. The nitrogen was then replaced by hydrogen and the reaction mixture was stirred at ambient temperature and atmospheric pressure until

2.5 L (0.112 mol) of hydrogen was consumed. The flask was flushed with nitrogen and the solution was filtered through a thick celite pad. The filtrate was concentrated under reduced pressure to afford oil. Dissolved the oil in dichloromethane (40 mL) and then washed with saturated sodium bicarbonate solution (10 mL) followed by water (10 mL). Distillation of dichloromethane layer under reduced pressure afforded thick residue. Purification of this residue with column chromatography by eluting with 10% ethyl acetate in n-hexane affords impurity B as a light brown colour residue.

#### Synthesis of N-propylindanylamine (impurity C, 8) from 2 and 10:

Charged 1-aminoindan (25 g, 0.187 mol), 2-Chloro ethanol (16.6 g, 0.206 mol), sodium iodide (2.84 g, 0.019 mol) and 100 mL toluene into RBF and started stirring at 25°C. Reaction mass heated to reflux and maintained under reflux till TLC complies. Reaction completed after 11 hours of reaction maintenance. Reaction progress was monitored by TLC (mobile phase: toluene and methanol in 9:1). Cooled the mass to 30°C and added water. Separated the organic and aqueous layers and washed the toluene layer with water. Distilled off toluene completely to afford yellowish residue. This residue was purified with column chromatography by eluting with 10% ethyl acetate in n-hexane to afford impurity C as a light yellowish residue.

Yield: 78.4%; M. F. C<sub>12</sub>H<sub>17</sub>N; M. Wt. 175.27; IR (KBr, cm<sup>-1</sup>): 2950 (C-H str in -CH<sub>3</sub>), 3036 (aromatic C-H str), 1582 (aromatic C-C vib), 3345 (N-H str); <sup>1</sup>HNMR (300 MHz, DMSO-d<sub>6</sub>): δ 1.0 (t, 3H, -CH<sub>3</sub>), 1.6 (m, 2H, -CH<sub>2</sub>-), 2.0-2.2 (m, 2H, -CH<sub>2</sub>-), 2.6 (t, 2H, -CH<sub>2</sub>-), 2.8-2.9 (m, 2H, -CH<sub>2</sub>-), 4.0 (m, 1H, -CH-), 7.4 (m, 4H, ArH); <sup>13</sup>CNMR (300 MHz, DMSO-d<sub>6</sub>): δ 11.5m 24.0, 28.9, 30.1, 49.6, 63.0, 126.8, 128.9, 140.2, 143.8; MS *m/z* (%) = 176.45 (M+1); Anal. Calcd for C<sub>12</sub>H<sub>17</sub>N: C - 82.23, H - 9.78, N - 7.99; Found: C - 82.26, H - 9.76, N - 7.98.

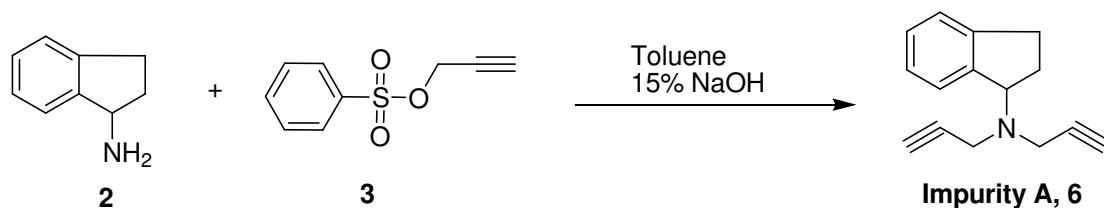
#### Synthesis of N-propylindanylamine (impurity C, 8) from 4:

A solution of 10 g 1-aminoindan, Raney Ni (5% wet, 2 g) and 100 mL toluene was placed in high-pressure hydrogenation apparatus. Stated the agitation at atmospheric pressure and flushed the flask with nitrogen. 2 Kg hydrogen pressure was applied and

maintained at ambient temperature till the hydrogen intake was seized. Stopped the agitation and filtered the mass under nitrogen atmosphere. Filtrate was washed with dilute HCl solution and then with water. Distilled off toluene completely under reduced pressure to afford impurity C as a residue.

## RESULTS AND DISCUSSIONS

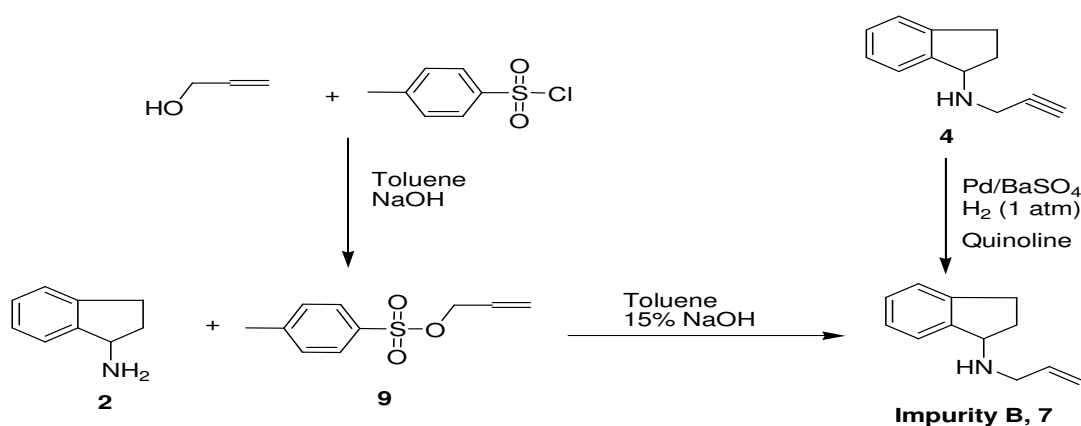
The object of our work was to prepare impurity A, B and C by simple chemical conversions, which serves the **Scheme 2:** Synthetic process of Impurity A



N, N-di(2-propynyl)-indanyamine (Impurity A) of  $C_{15}H_{15}N$  with molecular ion peak at (M+1) showed that m/z is equivalent to molecular weight (209.29) of proposed compound. Hence m/z value confirms the molecular weight of the compound. The IR peak at  $3315\text{ cm}^{-1}$  was suggesting C-H stretching of  $C\equiv C$  and  $2134\text{ cm}^{-1}$  was indicating  $C\equiv C$  stretching. The IR peaks at  $3012\text{ cm}^{-1}$  indicates aromatic C-H stretching. The HNMR peak at  $\delta$  1.8 (s, 2H) indicates the presence of two alkyne protons. The HNMR peak at  $\delta$  7.2 (m, 4H) suggests aromatic ring having four hydrogens.

Literature is well available for the partial reduction of alkynes<sup>12</sup>. Impurity B was a partial reduced product of

**Scheme 3:** Synthetic process of Impurity B



need of Rasagiline mesylate (1) method validations and regular analysis. The synthesis of impurities A, B and C are described in the experimental section.

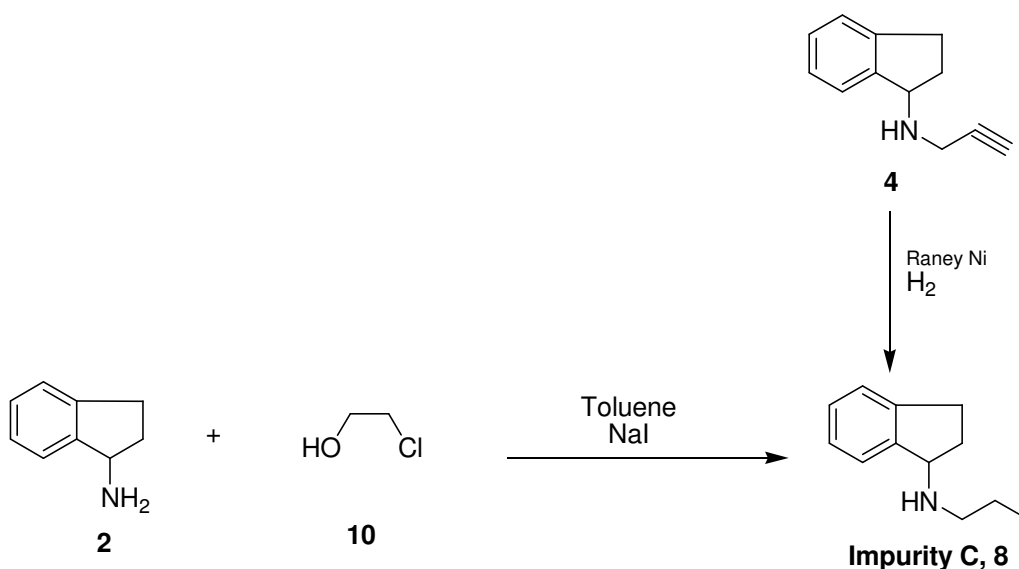
Impurity A was synthesized according to the process described in scheme 2. Impurity A was synthesized with excess equivalents of propargyl benzenesulfonate (2) at  $40^{\circ}\text{C}$ . Reaction was preceded well and completed within 8 hours and obtained impurity A has 99.2% of purity by HPLC (area %). Impurity A was well characterized by spectral analysis.

Rasagiline. According to scheme 3, Impurity B was synthesized in two processes. First process describes the condensation of 1-aminoindan (2) with allyl 4-methylbenzenesulfonate (9) in the presence of base and toluene solvent. Allyl 4-methylbenzenesulfonate (9) was prepared by the condensation of allyl alcohol and p-toluene sulfonyl chloride in basic conditions. Reaction was proceeded very smoothly at ambient temperature and completed within 1 hour of maintenance. Condensation of compound 4 with 9 was critical and improper reaction maintenance caused more impurity formation. Impurity formation was less at  $20^{\circ}\text{C}$  and below temperature.

Second process comprises the partial reduction of N-propargyl-1-aminoindan (4) with Pd/BaSO<sub>4</sub> in the presence of quinolone. Reaction progress should monitor with in-process TLC to avoid the formation of saturated product. After completion of the reaction, hydrogen source should be seized to avoid the further reduction of the product.

N-allyl indanylamine (Impurity B) of C<sub>12</sub>H<sub>15</sub>N with molecular ion peak at (M+1) showed that m/z is equivalent to molecular weight (173.25) of proposed compound. Hence m/z value confirms the molecular weight of the compound. The IR peak at 3038 cm<sup>-1</sup> was suggesting C-H stretching of C=C and 1670 cm<sup>-1</sup>

**Scheme 4:** Synthetic process of Impurity C



In the first process, 1-aminoindan (2) on condensation with 2-chloroethanol with catalytic NaI in toluene solvent resulted Impurity C. In the second process, complete reduction of N-propargyl-1-aminoindan (4) with Raney Ni under hydrogen pressure. Both the reactions were proceed will without resulting any impurities.

N-propylindanylamine (Impurity C) of C<sub>12</sub>H<sub>17</sub>N with molecular ion peak at (M+1) showed that m/z is equivalent to molecular weight (175.27) of proposed compound. Hence m/z value confirms the molecular weight of the compound. The IR peak at 3950 cm<sup>-1</sup> was suggesting C-H stretching of –CH<sub>3</sub> group and 3345 cm<sup>-1</sup> indicating N-H stretching. The HNMR peak at δ 1.0 (t,

indicating C=C stretching. The IR peaks at 3022 cm<sup>-1</sup> indicates aromatic C-H stretching. The HNMR peak at δ 2.2 (s, 1H) indicates the presence of N-H proton. The HNMR peak at δ 5.2 (m, 2H) suggesting =CH<sub>2</sub> protons and peak at δ 5.9 indicating –CH= proton. The HNMR peak at δ 7.2 (m, 4H) suggests aromatic ring having four hydrogens.

Literature is well available for the total reduction of alkynes<sup>13</sup>. Impurity C completely reduced product of Rasagiline. Impurity C was prepared as shown in the scheme 3.

3H) indicates the presence of –CH<sub>3</sub> proton and peak at δ 7.2 (m, 4H) suggests aromatic ring having four hydrogens.

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