Review Article

An overview of prior patents for the sequential progress in the synthetic approaches of Rasagiline, its salts, crystallographic forms and impurities

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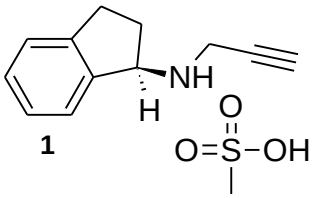
ABSTRACT

This review work was intended to provide the essential details disclosed in prior patents on the synthesis of Rasagiline, its salts (as crystalline or amorphous forms) and a few impurities. Quite a high number of patents were published in various patent trademark offices around the world regarding the synthesis of Rasagiline. Among them, the patents which fall under the similar family are excluded to prevent the possible duplication of the information. The remaining distinct patents were carefully reviewed and the particulars are grouped in chronological order. Moreover, this initiative can provide an essential backyard for the global researchers and the organizations to get the details on the methodological flourish of Rasagiline. More importantly, the work forms a firm basis for to invent/innovate a few more new strategies to commercialize Rasagiline in its pharmaceutically suitable and stable forms. Additionally, researchers can avail the information about the organizations which are behind the continuous process improvement on various aspects of Rasagiline.

Key words: Rasagiline base, Rasagiline mesylate, Propargylation, *N*-alkylation, Racemization.

The popular drug, Rasagiline is an irreversible inhibitor of monoamine oxidase. It is used widely as a monotherapy during the initial stages of Parkinson's disease or as an adjunct therapy in more advanced scenarios [1, 2].



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Rasagiline mesylate ($C_{13}H_{17}NO_3S$) **1** has the IUPAC name: [(1*R*)-*N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine methanesulfonate] with a CAS registry number: 161735-79-1 and a molecular weight: 267.34 g/mol. It is commercially marketed under the brand/trade name Azilect®. Rasagiline is a renowned propargylamine derivative with a good clinical efficacy. Interestingly, *R*-(+)-enantiomer is therapeutically active and hence gained a wide clinical importance to treat Parkinson's disease, memory disorders and dementia of the Alzheimer type (DAT), depression, and hyperactive syndrome in children [3]. The *S*-(-)-enantiomer of Rasagiline has a bit of neuroprotective properties but the potency of *R*-(+)-enantiomer over the monoamineoxidase enzyme (MAO-B) is around 1000-fold higher. However, the racemic Rasagiline hydrochloride was discovered in 1970s and was effectively used to treat hypertension [4]. After achieving the resolution of enantiomers, it was found that *R*-(+)-enantiomer was an active MAO-B inhibitor with a reasonably high degree of selectivity. Meanwhile, *S*-(-)-enantiomer had showed relatively very low MAO-B inhibitory activity [5].

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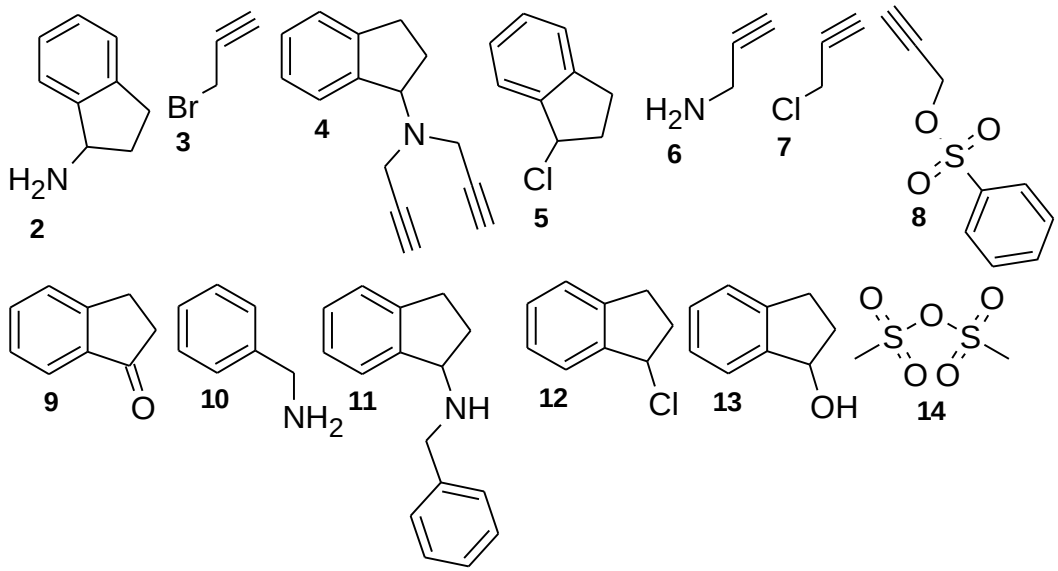
Literature review

A chronological flow was maintained in this review initiative to tabulate all the essential process centric details disclosed in the prior patents regarding the synthesis, racemization, purification, impurity profiling, various stable salts of Rasagiline and its crystallograhic forms.



Huebner CF., in 1966, had reported the condensation of 1-amino-indane **2** with propargyl bromide **3** in the presence of sodium carbonate and acetone to isolate 1-(*N*,*N*-dipropargyl-amino)-indane hydrochloride **4** with a melting point of 160-163ºC (yield: 11.82%, recrystallized from ethyl alcohol). Furthermore, the condensation of 1-chloro-indane **5** with propargylamine **6** was achieved in isopropyl alcohol to isolate the racemic Rasagiline hydrochloride with a melting point of 178-179ºC (yield: 22.27%, recrystallized from ethyl alcohol) [6].

Maurice WG, *et al*., in 1968 & 1970, had demonstrated synthesis and applications of *N*-substituted 1-aminoindanes. The condensation of **5** with **6** was executed in the presence of sodium iodide in ethyl alcohol to isolate the racemic Rasagiline hydrochloride with a melting point of 185-187ºC (recrystallized from isopropyl alcohol). It was believed that, *N*,*N*-di(1-indanyl)-propargyl amine hydrochloride (dimer) had formed as an intermediate [4,7].

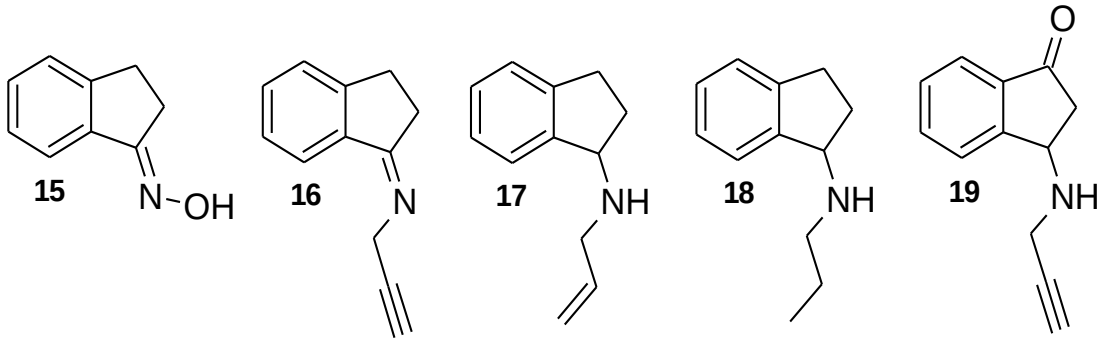
Youdim MBH, *et al*., in 1991, 1995 & 1996, had illustrated the synthesis and effective resolution of the racemic Rasagiline base. Rasagiline base was prepared by treating **2** with propargyl chloride 7 in the presence of potassium carbonate and acetonitrile. The isolated Rasagiline base was treated with ethereal hydrochloride (HCl gas purged to diethyl ether) to isolate the Rasagiline hydrochloride with a melting point of 182-184ºC (yield: 46.82%, recrystallized from isopropyl alcohol).The racemic mixture of Rasagiline base was resolved in a preparative HPLC (high performance liquid chromatography) column and converted to *S*-(-)-enantiomer hydrochloride with a melting point of 182-184ºC (isolated from diethyl ether). Similarly, *R*-(+)-enantiomer hydrochloride was isolated with a melting point of 179-181ºC (isolated from diethyl ether). Moreover, the work extends to report the reaction of *R*-(-)-enantiomer of **2** with **7** in the presence of potassium carbonate and acetonitrile to isolate *R*-(+)-enantiomer of Rasagiline hydrochloride with a melting point of 183-185ºC (yield: 35.18%, recrystallized from isopropyl alcohol). Under the similar context, *S*-(+)-enantiomer of **2** was reacted with **7** to get *S*-(-)-enantiomer of Rasagiline hydrochloride with a melting point of 183-185ºC (recrystallized from isopropyl alcohol). Furthermore, *R*-(+)-Rasagiline base was treated with *L*-tartaric acid to isolate *R*-(+)-di-Rasagiline tartarate with a melting point of 175-177ºC (yield: 46.59%, isolated from methyl alcohol). In an illustration, propargyl benzenesulfonate **8** was reacted with racemic **2** in the presence of aqueous sodium hydroxide in toluene to isolate *R*-(+)-di-Rasagiline tartarate. It was treated with methanesulfonic acid in isopropyl alcohol to isolate **1** with a melting point of 157ºC. [5,8-11].

Gutman AL, *et al*., in 2002, had reported the condensation of 2,3-dihydro-1*H*-1-indanone **9** with benzylamine **10** in the presence of acetic acid and benzene to form the important imine intermediate. It was reduced using sodium borohydride in ethyl alcohol and treated with sodium hydroxide solution to isolate the racemic *N*-benzyl-2,3-dihydro-1*H*-inden-1-amine **11** with a boiling point of 125-135ºC (yield: 82%, purity: 95.9% by gas chromatography-

GC). In an alternate pathway, that involved the condensation of 1-chloro-2,3-dihydro-1*H*-indene **12** with **10** in acetonitrile to isolate racemic **11** with a boiling point of 125-135ºC (yield: 64%) [12]. It was resolved under the influence of *R,R*-tartaric acid in water to isolate the crude salt. It was recrystallized from water to isolate the *R,R*-tartarate salt of **11** with a melting point of 135-144ºC (yield: 32%). *S*-isomer of **11** was recovered and resolved using potassium-*t*-butoxide in dimethylsulfoxide to isolate **11** (yield: 80%). *R,R*-tartarate salt of **11** was reduced using palladium-carbon in water to isolate *R*-isomer of **2** with a boiling point of 130-140ºC (yield: 72%). This can also be treated with **3** or **7** to isolate Rasagiline base as per the past disclosures [12].

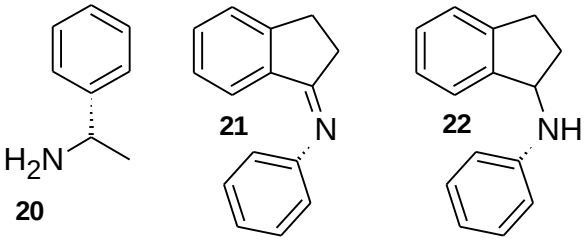
***Lee TB**, et al*., in 2006, had demonstrated the condensation of *S*-1-indanol **13** with **6** in the presence of methanesulfonyl anhydride **14** and triethylamine in dichloromethane to isolate the *R*-Rasagiline base (yield: 68%, as brown liquid) [13].

***Anton F**, et al*., in 2007 & 2009, had illustrated the reaction of **2** with **8** in the presence of aqueous sodium hydroxide in toluene to isolate Rasagiline base through the extraction method (yield: 66.71%, as brown oil). It was treated with *L*-tartaric acid in isopropyl alcohol to isolate *R*-Rasagiline tartarate with a melting point of 176.3-176.8ºC (yield: 28.8%, *S*-isomer: approx. 4%). With the use of similar key reagents, an additional two illustrations were reported. They are, direct and prolonged precipitation methods to isolate Rasagiline tartarate with the melting points in the range of 160.8-163.2ºC having the *S*-isomer content to about 4-16%. The work had even disclosed a few other precipitation methods such as, Rasagiline sulfate isolation, recrystallization of Rasagiline salts from solvents/water and salt inter-conversions etc [14, 15].



Luo JH., in 2007, had reported the reduction of 2,3-dihydro-1*H*-1-indanone oxime **15** using alumino-nickel catalyst in the presence of sodium hydroxide solution and ethyl alcohol to isolate **2** (yield: 80.11%, as oily mass). In another experiment, **9** was treated with oxammonium hydrochloride in the presence of sodium hydroxide solution and ethyl alcohol. Later to the reaction mixture added alumino-nickel catalyst and worked up to isolate the hydrochloride of **2** with a melting point of 208.4-209.5ºC (yield: 76.68%, purity: 98.64% by HPLC, as white crystals). It was treated with **8** in the presence of sodium hydroxide solution and toluene to isolate the racemic Rasagiline base (yield: 79.07%, purity: 93.08% by HPLC, as brown oily mass). In another instance, **15** was dissolved in ethyl alcohol and treated with sodium hydroxide solution. To the reaction mixture added alumino-nickel catalyst for the reduction and later added **8** to isolate the racemic Rasagiline base (yield: 64.89%, purity: 90.45% by HPLC, as brown oily mass). In another example, **9** was treated with oxammonium hydrochloride in the presence of sodium hydroxide solution and ethyl alcohol. To it, added alumino-nickel catalyst for the reduction and then added **8** to isolate racemic Rasagiline base (yield: 62.3%, purity: 92.03% by HPLC, as pale brown oily mass). In a few separate experiments, racemic Rasagiline base was treated with *L*-tartarate in isopropyl alcohol to get the crude solid, which was recrystallized in isopropyl alcohol to isolate *R*-di-(Rasagiline) tartarate with the melting points in the range of 174.2-177ºC (yield range: 20-26%, purity range: 97.46-98.54% by HPLC, as white puffy crystals). It was treated with methanesulfonic acid in isopropyl alcohol to isolate **1** with a melting point of 155-155.8ºC (purity: 99.85% by HPLC, as white crystals) [16].

Feng Q., in 2007, had demonstrated a simple process to isolate the reacemic Rasagiline base by reacting **9** in ethyl alcohol with **6** in the presence of sodium borohydride/palladium-carbon. Around six illustrations were reported with a slight modulated reaction conditions and isolation procedures with good yield (60.19-73.10%) [17].



Zongxuan S, *et al*., in 2008, had illustrated the condensation of **9** in isopropyl acetate with *S*-(-)-1-phenylethylamine **20** in the presence of *p*-toluene-sulfonic acid monohydrate to form (1*Z*)-*N*-phenyl-2,3-dihydro-1*H*-inden-1-imine **21** (82.5%). It was reduced under the impact of Raney-nickel in isopropyl acetate to isolate *N*-phenyl-2,3-dihydro-1*H*-inden-1-amine **22** (yield: 88%). It was dissolved in tetrahydrofuran and treated with phosphorus pentachloride in the presence of triethylamine and then treated with oxammonium hydrochloride to isolate *R*-isomer of **2** (as free base or its hydrochloride salt, yield: 70-90%). Hydrochloride salt of **2** in acetonitrile was treated with **3** in the presence of potassium carbonate followed by the addition of methanesulfonic acid in diethyl ether to obtain **1** with a melting point of 156-158ºC [18].

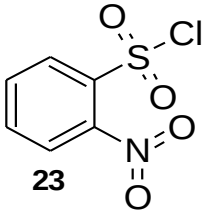
Bosch ILJ, *et al*., in 2009, had reported a few reactions of *R*-isomer of **2** in toluene with **8** in the presence of sodium hydroxide solution to get *R*-Rasagiline base (yield: 67.82-72.49%). It was treated with methanesulfonic acid in toluene or acetonitrile to isolate the crude **1** (yield: 85.54-97.39%, purity: 79.65-93.32% by HPLC). Furthermore, a double recrystallization of crude **1** was done from acetonitrile and then the solid obtained was suspended in acetonitrile/water mixture to get **1** (overall yield: 22-33%, purity: 99-100% by HPLC). They had reported the recrystallization of **1** in isopropyl alcohol, but the final product and the filtrate had isopropyl mesylate traces as an impurity (by GC analysis) [19].

Frenkel A, *et al*., in 2009, had demonstrated the isolation of crystalline solid *R*-Rasagiline base (yield: 70-90%) from its mesylate or tartarate by a few methods like splitting, extraction, water crystallization, melt crystallization, quenching to water, reverse quenching, seeding crystallization etc. Under the usual conditions, *R*-Rasagiline base would be used in its crude form as an oily liquid. The work had reported the isolation of the solid form of *R*-Rasagiline base by various crystallization approaches with a melting point of 15-20ºC (isolated from toluene), 38.2-38.4ºC (isolated from water), 39.0-39.2ºC (isolated from isopropyl alcohol), 40.8ºC (isolated from isopropyl alcohol/water by seeded emulsion) and 41.3ºC (isolated from isopropyl alcohol/water by seeding crystallization) [20-22].

Gore V, *et al*., in 2009, had disclosed a process to get enantiomerically pure *R*-isomer of **2** by treating racemic **2** with 2,3,4,6-di-*O*-isopropylidene-2-keto-*L*-gulonic acid monohydrate in methyl alcohol to isolate the crude salt. It was dissolved in aqueous methyl alcohol and crystallized to isolate the salt. Pure *R*-isomer of **2** (yield: 40-42%, chiral purity: 96-97% by HPLC, as light green oily liquid) was isolated by salt breaking method in the presence of sodium carbonate solution and extracting the free base to dichloromethane [23]. The reported work was much superior to the past disclosed resolving techniques [12,24].

Frenkel A & Koltai T., in 2009, had illustrated a process to manufacture of Rasagiline tannate. Rasagiline base was treated with tannic acid solution to obtain the first mixture. A partial removal of the liquid from the first mixture and the addition of a polar water soluble solvent (ethyl alcohol) had resulted in the formation of second mixture. Furthermore, liquid/solvent was removed completely at ambient temperature to isolate the tannate salt. The isolated Rasagiline tannate had the water content of below 10% and the Rasagiline content was got varied around in the range of 3-64%. The work had disclosed the cleavage of **1** to isolate Rasagiline base as an oily mass and its crystallization to isolate in the solid form with a melting point of 39-39.3ºC. It was then treated with tannic acid solution in various methods to isolate the tannate salt. An improved Rasagiline tannate salt formation was observed in polar solvents than in non-polar solvents (ethyl acetate and hexane) [25].

Caigu H & Huimin H., in 2009, had reported the process to isolate the crystal *form-I* of **1**. It was prepared by taking **1** in (ethyl acetate/ethyl alcohol) or (acetone/ethyl alcohol) or acetonitrile or isopropyl alcohol. The isolated solid had exhibited a prominent DSC endotherm at 157-157.5ºC [26]. ***Stephen BDW***., in 2009, had reported the synthetic pathway to isolate the crystal *form-I* of **1**. The work had employed various solvents to dissolve **1** and isolate the crystal *form-I* at 25-70ºC [27]. ***Patil NS***, *et al*., in 2009, had demonstrated a process to prepare **1** with 90 volume-percent of the particles (*D*-90) with a size of about (600-1500 microns) and (255-1500 microns). It was prepared from **1** or Rasagiline base using the suitable solvents [28].



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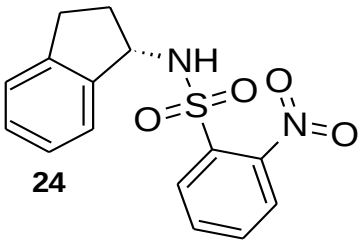

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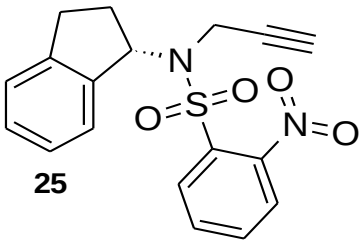

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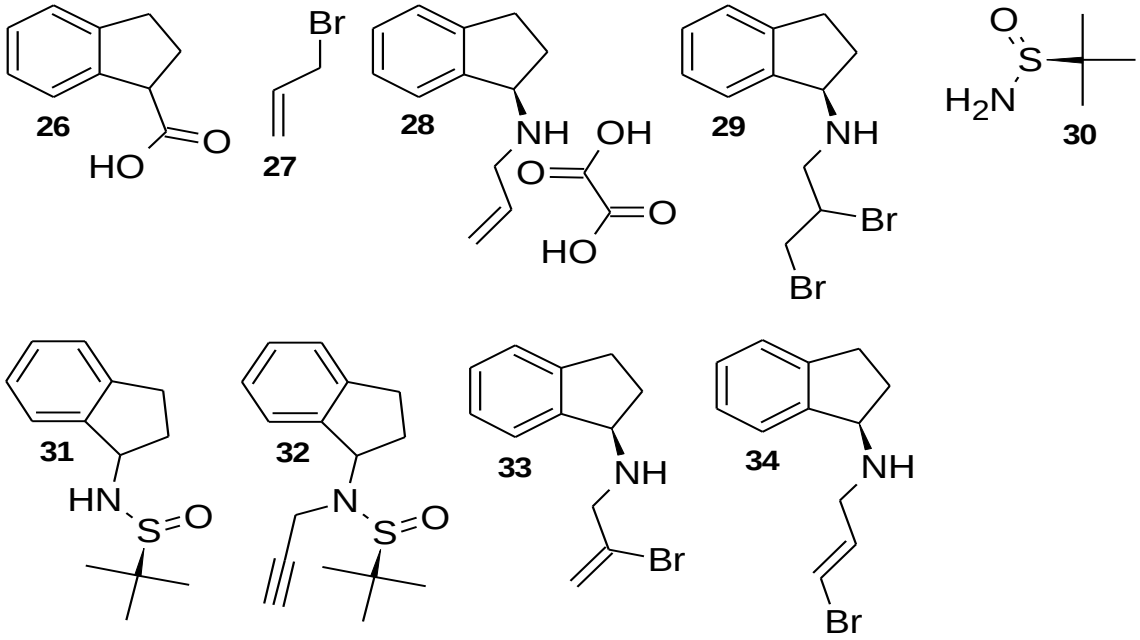
***Qiandong L**, et al.*, in 2009, had demonstrated the condensation of *R*-isomer of **2** in dichloromethane with *O*-nitro-benzene-sulfonyl chloride **23** in the presence of triethylamine to isolate *R-N*-(2-nitro) benzenesulfonyl-1-indenamine **24** (yield: 95%, as white solid). It was dissolved in toluene and treated with **3** in the presence of sodium hydroxide and catalytic amount of tetrabutylammonium bromide to get *R-N*-propargyl-*N*-(2-nitro)-benzenesulfonyl-1-indenamine **25** (yield: 81%, as pale yellow solid). *N*,*N*-dimethylformamide, lithium hydroxide monohydrate and mercapto-propionic acid were added to **25** to isolate *R*-Rasagiline base (yield: 96%, as yellow oily liquid). The work had also reported the use of racemic **2** for the above steps to get racemic Rasagiline base, which was treated with *L*-tartaric acid in isopropyl alcohol to isolate the salt. It was dissociated further to isolate the *R*-Rasagiline base (as yellow brown oil) [29].

Huang C & He H, in 2009, had disclosed the preparation of *form-I* of **1** from various solvents like isopropyl alcohol, ethyl alcohol, acetone, ethyl acetate and acetonitrile. The crystal *form-I* had showed the characteristic endothermic peak at about 157.07ºC [30].

***Cherukupally P**, et al.*, in 2010, had illustrated the reaction of **9** in methyl alcohol with **6** to isolate hydrochloride salt of (1*Z*)-*N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-imine **16**. It was then reduced using sodium borohydride in methyl alcohol to get the crude racemic Rasagiline base. It was treated with isopropyl alcohol/HCl (18%) to get the racemic Rasagiline hydrochloride. Moreover, the salt cleavage had resulted in the formation of Rasagiline base. The work also had reported the use of a few suitable reducing agents like Raney nickel, palladium on carbon, and platinum dioxide; lithium aluminium hydride; sodium borohydride; sodium cyanoborohydride; sodium borohydride in acidic conditions; and sodium bis(2-methoxyethoxy)-aluminum hydride (vitride®) to isolate **16** in reasonably high yields. A few suitable chiral resolving agents were used like *L*-(+)-tartaric acid and (-)-di-*p*-toluoyltartaric acid (DPTTA) to isolate the required *R*-isomer. With the use of these reagents, enantiomerically pure salts of Rasagiline (hydrochloride/tartarate/mesylate) were prepared with good yields. Furthermore, the work provides a process for the preparation of **1** having D_{90} below 6 µm. It was done by adding the solution of **1** in isopropyl alcohol to chilled methyl-*t*-butyl ether. The work involved the isolation of Rasagiline & its salts which are significantly free from the critical impurities like *N*,*N*-di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine **4**, *N*-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-amine **17**, *N*-propyl-2,3-dihydro-1*H*-inden-1-amine **18** & 3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-one **19** [31].



***Marras G**, et al.*, in 2010, had disclosed a multi-step process starting from (±)-2, 3-dihydro-l*H*-indene-l-carboxylic acid **26** to isolate *R*-Rasagiline base (as light green oily mass). The process had involved a series of reaction steps like Curtius rearrangement, resolution, hydrolysis, de-protection etc to isolate the intended product [32].

***Allegrini P**, et al.*, in 2010, had illustrated the condensation of **6** and **9** in the presence of sodium borohydride in tetrahydrofuran to isolate the racemic Rasagiline base (yield: 91%). It was treated with *L*-(+)-tartaric acid in ethyl alcohol to get *R*-Rasagiline tartarate. It was cleaved under nitrogen atmosphere using sodium bicarbonate solution and ethyl acetate to isolate *R*-

Rasagiline base (as an oily liquid). It was taken in isopropyl alcohol and treated with methanesulfonic acid to isolate **1** (yield: 89% from its tartarate salt). The work was extended further to provide the procedure to isolate the crystalline form of *R*-Rasagiline base with a melting of 40-41ºC [33].

Phull MS, *et al*., in 2010, had reported a multi-step process to isolate **1**. In an example, **9** was reacted with allyl bromide **27** in the presence of potassium carbonate in acetonitrile and then treated with oxalic acid to obtain *R*-(-)-*N*-allyl-1-aminoindan oxalate **28**. It was de-oxalated and then brominated (by bromine) in dichloromethane to isolate *R*-(-)-*N*-(2,3-dibromo-propyl)-1-aminoindan **29**. It was hydrolyzed using potassium hydroxide solution in ethyl alcohol to isolate *R*-Rasagiline oxalate. Under the similar conditions, racemic **29** was synthesized and hydrolyzed. It was then treated with *L*-tartaric acid to isolate the crude solid. It was then de-tartarated by treating with sodium hydroxide solution and mesylated by the addition of methanesulfonic acid in isopropyl alcohol to obtain **1** (purity: 99.8%, chiral purity: 99.5%). The resolving process can be adapted to racemic **28** using *L*-tartaric acid or it can be effectively implemented to racemic **29** using *L*-tartaric acid. The work had provided an improved process by eliminating the drawbacks of past disclosures [34].

Stahl HP., in 2010, had demonstrated the preparation, solubility profile, and hygroscopicity details of two new salts of Rasagiline. Rasagiline base was taken in isopropyl alcohol and ethanedisulfonic acid was added to isolate Rasagiline edisilate with a melting point of 201ºC (yield: 56.3%). Under the similar conditions, Rasagiline base was treated with oxalic acid in isopropyl alcohol to obtain Rasagiline oxalate with a melting point of 204ºC (yield: 93.1%) [35].

Frenkel A, *et al*., in 2010, had reported the isolation of mono-Rasagiline citrate, di-Rasagiline citrate or tri-Rasagiline citrate or a mixture of all them. These salts or salt mixtures were prepared by treating Rasagiline base (solid) with citric acid in ethyl alcohol or a few other solvents/water [36].

Stephen BDW, *et al*., in 2010, had illustrated a few more Rasagiline salts such as tartrate with a melting point of 176.2-177.3ºC, maleate with a melting point of 87.2-87.8ºC, sulphate with a melting point of 159.4-161.1ºC, hydrochloride with a melting point of 177.0-180.0ºC, tosylate with a melting point of 129.3-129.9ºC, fumarate with a melting point of 125.4-126.2ºC, phosphate with a melting point of 109.5-110.4ºC, acetate with a melting point of 69.2-69.7ºC, besylate, tannate, benzoate, galactarate, gluconate, glucuronate, succinate, hetartarate etc from Rasagiline base using various suitable solvents/water. Some of those salts were isolated in their crystalline forms (*form I/II*) and a few salts in their amorphous form [37].

Thomas T, *et al*., in 2011, had reported the preparation and advantages of a few salts of Rasagiline such as gluconate, *L*-aspartate, citrate, *DL*-lactate, saccharinate, docusate, lauryl sulphate, 4-dodecylbenzenesulfonate, linoleate, pentanoate, propanoate, acetate, decanoate, octanoate, hexanoate and oleate. These salts were prepared from Rasagiline base using appropriate solvents [38].

Patil NS, *et al*., in 2011, had demonstrated the isolation of a few Rasagiline salts. The salts reported are maleate (*form-II*), mandelate (*form-I*) and salicylate (*form-I*), surprisingly these salts had good purity and had exhibited an adequate stability, good flowability and a good dissolution properties [39].

Dongwei C, *et al*., in 2011, had illustrated a multi-step process to isolate **1**. The reaction of **9** with *t*-butyl-sulfinamide **30** was carried out under the catalytic impact of isopropyl titanate in tetrahydrofuran to get *N*-(2,3-dihydro-1*H*-inden-1-yl)-2-methylpropane-2-sulfinamide **31** (yield: 59%). It was dissolved in dimethyl formamide and reacted with sodium-*t*-butoxide. To the reaction mass, **7** was added to isolate *N*-(2,3-dihydro-1*H*-inden-1-yl)-2-methyl-*N*-(prop-2-yn-1-yl)propane-2-sulfinamide **32** (yield: 51% from **9**). The solution of methanesulfonic acid in diethyl ether was added to the solution of **32** in methyl alcohol to isolate the enantiomerically pure **1** with a melting point of 156-158ºC (yield: 46% from **9**, as white crystals, isolated from methyl-*t*-butyl ether) [40].

Chi-Hsiang Y & ***Tsung-Ting C***., in 2011, had reported the condensation of **9** with **6** in methyl-*t*-butyl ether using *p*-toluene sulfonic acid to form the intermediate **16**. It was effectively reduced using 20% di-isobutyl-aluminum-hydride (DIBAL-H) in hexane to isolate the racemic Rasagiline base (yield: 81%). It was treated with *S*-(+)-mandelic acid in methyl-*t*-butyl ether to isolate *R*-Rasagiline mandelate (yield: 45%). De-salting it with 2% sodium hydroxide solution gave *R*-Rasagiline base (yield: 90%). It was treated with methanesulfonic acid in isopropyl alcohol to isolate **1** (yield: 80%) [41].

Gore V, *et al*., in 2011, had illustrated the condensation of *R*-isomer of **2** with **8** under the influence of 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) in tetrahydrofuran to get *R*-Rasagiline base (yield: 80-82%,

purity: 64.33% by HPLC, as yellow oily mass). It was treated with methanesulfonic acid in isopropyl alcohol to isolate **1** (yield: 47%, purity: 99.84%, chiral purity: 100% by HPLC) [42].

Thanedar AA, *et al*., in 2011, had demonstrated a comparative example to condense racemic **2** in acetonitrile with **7** in the presence of potassium carbonate to isolate racemic Rasagiline base (yield: 101%, purity: 72.33% by HPLC, as oily residue). It was done as per the previous disclosure [10]. In another example, **9** in ethyl alcohol was reacted with **6** in the presence of titanium (*IV*) iso-propoxide to form the respective titanium complex. It was reduced by sodium borohydride and performed acid-base isolation to get racemic Rasagiline base (yield: 22.57%, purity: 98% by HPLC). It was resolved using *L*-(+)-tartaric acid in isopropyl alcohol to isolate the crude salt. It was recrystallized from methyl alcohol to isolate *R*-Rasagiline tartarate (recovery: 80%, purity: 99.89% by HPLC). It was de-salted and treated with methanesulfonic acid in acetone to isolate **1** (yield: 72.12%, purity: 99.97% by HPLC). A direct conversion process of tartarate salt to **1** (yield: 88.14%, purity: 99.5%, chiral purity: 99.9% by HPLC) was also reported [43].

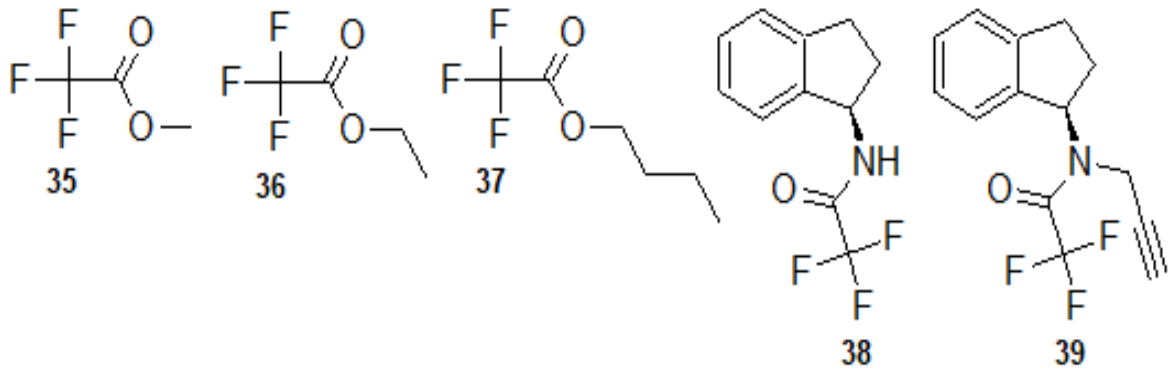
Selic L., in 2011, had disclosed the preparation of a few salts of Rasagiline and those are exclusively used to resolve racemic Rasagiline base. The major salts reported are Rasagiline-*L*-mandelate, Rasagiline-*D*-mandelate, Rasagiline-*R*-mandelate (yield: 33%, with a melting point of 107-111^{o}C), *R*-Rasagiline-(+)-camphor-10-sulfonate (yield: 27%, with a melting point of 167-170^{o}C), Rasagiline orotate, Rasagiline cinnamate, Rasagiline-1-hydroxy-2-naftoate, Rasagiline fumarate, Rasagiline benzoate and Rasagiline-(-)-camphor-10-sulfonate. The work also had disclosed the recrystallization methods of those salts along with an efficient analysis method [44].

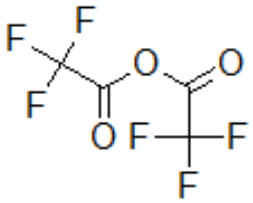
Zope SS, *et al*., in 2011, had demonstrated the synthesis of some Rasagiline salts like, *R*-Rasagiline phosphate (purity: 99.96%), *R*-Rasagiline benzoate (yield: 78%, purity: 99.94%), *R*-Rasagiline mandelate (yield: 61%, purity: 99.89%) and *R*-Rasagiline oxalate (purity: 99.9%) from *R*-Rasagiline free base in isopropyl alcohol [45].

Sun J, *et al*., in 2011, had reported a method to prepare *R*-Rasagiline base starting from racemic **2** as the raw material through enzyme-catalyzed asymmetric acylation reaction, hydrolysis and *N*-propargylation reactions. The *R*-isomer of **2** in isopropyl ether was reacted with **8** in the presence of sodium carbonate solution to isolate the desired propargylated product (yield: 82.5%, as yellow oily liquid) [46].

Dwivedi SD, *et al*., in 2011, had illustrated the synthesis of many salts of Rasagiline from its base using the suitable solvents. The salts reported are *R*-Rasagiline hydrobromide *form-I*, amorphous Rasagiline hydrobromide, *R*-Rasagiline hydrogen phosphate, **1** from *R*-rasagiline hydrobromide *form-I*, *form-I* of **1**, *R*-Rasagiline 1,2-edisylate *form-II*, crystalline *R*-Rasagiline-2-napsylate, *R*-Rasagiline-1,5-dinapsylate *form-I*, *R*-Rasagiline 1,5-dinapsylate *form-II*, crystalline *R*-Rasagiline-l-napsylatate, *R*-Rasagiline ascorbate, amorphous Rasagiline ascorbate [47].

Sathe DG, *et al*., in 2011, had demonstrated the reaction of *R*-(-)-isomer of **2** hydrochloride with **8** in the presence of sodium hydroxide solution and tetra-butyl-ammonium-bromide to get the crude *R*-Rasagiline base (yield: 60%, as *an* oily mass). It was subjected to column chromatography to isolate *R*-Rasagiline base (recovery: 90%). The un-reacted *R*-(-)-isomer of **2** was recovered by the basification and extraction processes. *R*-Rasagiline base was treated with methanesulfonic acid in isopropyl alcohol to isolate **1** (yield: 83%). The work was extended further to provide the preparation methods of Rasagiline hydrochloride, *form-I* and *form-II*, Rasagiline hydrobromide, Rasagiline palmitate. Furthermore, the work reported the route to synthesize and isolate the impurities like **33** (impurity A) and **34** (impurity B) [48].





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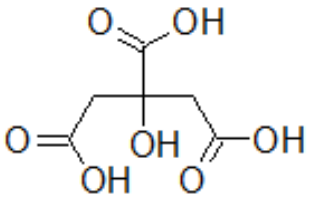

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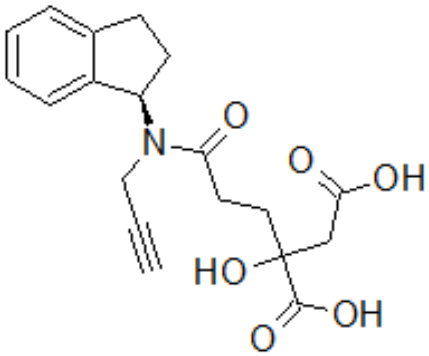

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Elffrink WWJ, in 2011, had disclosed the techniques to synthesize a few crystallographic forms of Rasagiline hydrochloride like *form-I* (as per the past disclosures), *form-II* and *form-III* (by the use of an inert solvent for a sufficient time to attain the conversion) [49].

Bohumil D., in 2012, had illustrated the resolution of racemic **2** in methanol using *L*-(+)-aspartic acid, *L*-(-)-malic acid and (2*R*, 3R)-tartaric acid. The work had reported the conversion of *S*-isomer of **2** to its *R*-isomer (yield: 94%, purity: 96% by HPLC) in the presence of potassium-*tert*-butoxide in dimethyl sulfoxide. It also extends to report the condensation of *R*-isomer of **2** hydrochloride with **3** in the presence of sodium hydroxide solution under the toluene medium to form Rasagiline base (not isolated). To the Rasagiline base dissolved in toluene, added methanesulfonic acid in isopropyl alcohol to isolate **1** (purity: 99.86%, chiral purity: 100%, by HPLC) [50].

Liu G, *et al*, in 2012, had reported the condensation of *R*-isomer of **2** with methyl trifluoroacetate **35** in methyl alcohol to isolate *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]-2,2,2-trifluoroacetamide **38** (yield: 96%, purity: 99.5% by HPLC). Similarly, ethyl trifluoroacetate **36** in ethyl alcohol was used to isolate **38** (yield: 98%, purity: 99.7% by HPLC). Additionally, butyl-trifluoroacetate **37** in pentyl alcohol or tetrahydrofuran was used to get **38** (yield: 94%, purity: 99.2% by HPLC). In the next step, **38** was treated with **7** in the presence of *N*,*N*-dimethylformamide and sodium hydroxide solution to obtain *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]-2,2,2-trifluoro-*N*-(prop-2-yn-1-yl)acetamide **39** (yield: 86%, purity: 99.1% by HPLC). A slight process modification was done to condense **3** to with **38** to obtain **39** (yield: 90%, purity: 99.7% by HPLC). A few different reagents and solvents were used to condense **3** or **7** with **38** to isolate **39** with good optical purity. Hydrolysis of **39** under the suitable alkaline conditions had resulted in the formation of *R*-Rasagiline base (yield: 86-96%, purity: 99.8-99.3%). It was treated with methanesulfonic acid in diethyl ether to get **1** (yield: 82%, purity: 99.3%) [51].

Oemer R, *et al*, in 2012, had demonstrated a high yield method for the synthesis of **1** by the alkylation of **39**. The trifluoroacetyl protection had enabled to carry out an alkylation of **38** with a high yield and purity under very mild conditions with a wide range of reaction conditions and reagent selection. *R*-isomer of **2** hydrochloride was treated with trifluoroacetic anhydride **40** in the presence of pyridine and dichloromethane to isolate **38** (yield: 95%, purity: 99.5% by HPLC). It was alkylated with **3** in the presence of cesium carbonate in acetonitrile to isolate **39** (purity: 97.8% by HPLC) and then hydrolyzed in the presence of potassium hydroxide solution and methyl alcohol to get *R*-Rasagiline base (purity: 99.5% by HPLC). It was taken in isopropyl alcohol and added methanesulfonic acid to get **1** (yield: 88%, purity: 100% by HPLC, as white crystals) [52].

Yao Q & Chen Z, in 2012, had illustrated the condensation of **9** with **6** in the presence of *p*-toluenesulfonic acid in methyl-*t*-butyl ether to form **16**. It was dissolved in-*situ* in toluene and added 20% di-isobutylaluminum hydride solution (DIBAL-H dissolved in n-hexane) and worked up to isolate racemic Rasagiline base (yield: 81%). It was resolved by converting to its mandelate salt (yield: 45%) to isolate the required *R*-isomer. It was subjected to de-saltation (yield: 90%) using sodium hydroxide solution and then treated with methanesulfonic acid in isopropyl alcohol to obtain **1** (yield: 80%) [53].

Tang L, *et al*., in 2012, had reported the treatment of **15** in aqueous ethyl alcohol with aluminium-amalgum to isolate racemic **2** (purity: 98.9-99.9%). It was condensed with **8** in the presence of sodium hydroxide solution and dichloromethane to form racemic Rasagiline base. It was resolved by the formation of tartarate salt in isopropyl alcohol to isolate *R*-Rasagiline tartarate with a melting

point of 174.9-176.3ºC (yield: 41.05%). It was dissolved in isopropyl alcohol and treated with methanesulfonic acid to obtain **1** with a melting point of 150.1-151ºC (yield: 81%) [54].

Nagarajan K, *et al*., in 2012, had demonstrated a process to isolate **1** with a particle size of about 255-590 microns. It was achieved by the crystallization from isopropyl alcohol and the disclosed method was devoid of routine comminution techniques to control the particle size of **1** [55].

Dwivedi SD, *et al*., in 2011, had illustrated the process to isolate *R*-Rasagiline besylate *form-I* with the larger particle size by treating Rasagiline base with benzene sulfonic acid solution in ethyl acetate. Similarly, a few other salts were also prepared like *R*-Rasagiline hydrobromide *form-I* and its larger particle size, amorphous Rasagiline hydrobromide, *R*-Rasagiline hydrogen phosphate *form-I* and *form-I* of **1**. The reaction of **9** in methyl alcohol with hydroxylamine hydrochloride was carried out in the presence of sodium hydroxide solution to obtain **15**. It was reduced under the catalytic impact of Raney-nickel (with 5 Kg of hydrogen pressure) in the presence of ammoniacal methyl alcohol to get racemic **2**. It was treated with **7** in the presence of potassium carbonate and sodium hydroxide using the solvent dimethyl formamide to isolate the racemic Rasagiline base (as yellow oil). The isolated base was resolved using *L*-(+)-tartaric acid and desalted to isolate *R*-Rasagiline base (as oil) and then converted to required salt forms [56].

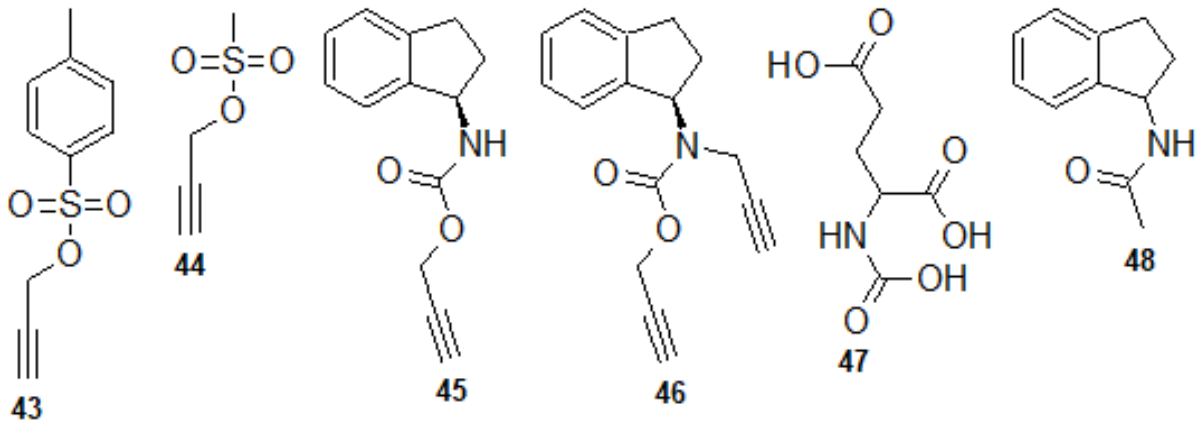
Zhang R, *et al*., in 2012, had disclosed the condensation of *R*-isomer of **2** in acetonitrile with propargyl methanesulfonate **44** to isolate **1** with a melting point of 156-158ºC (yield: 97.8%). The isolation of **1** in different scales as above was reported via one-pot processes (yield: 85-92%) along with a few comparative examples as per the past disclosures [57].

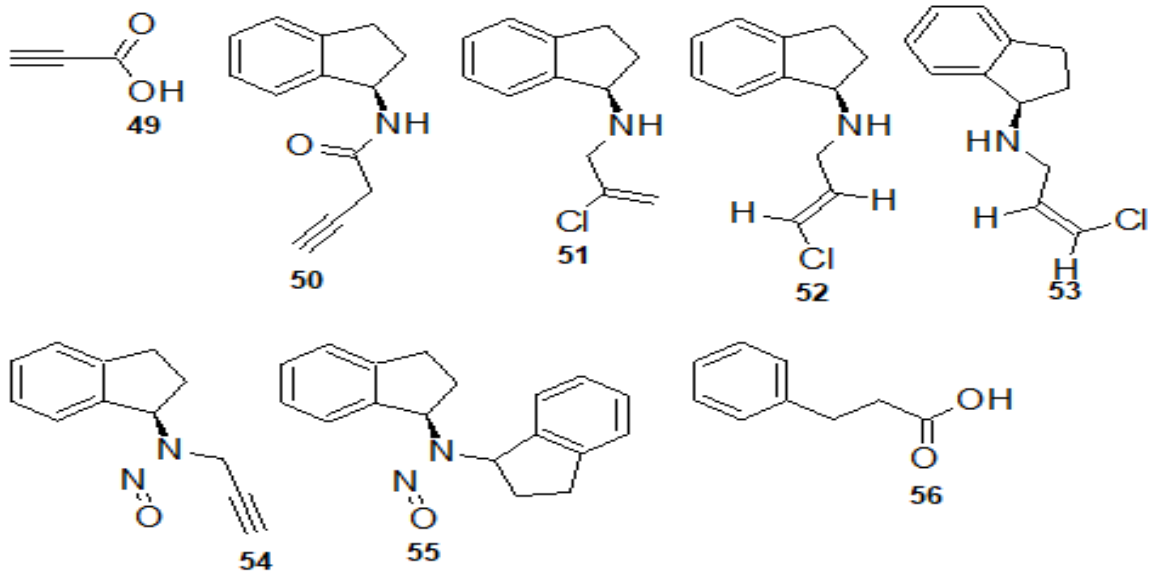
Bahar E, *et al*., 2012, had demonstrated the synthesis and applications of deuterated Rasagiline, its salts. The work was primarily focused on the varied metabolic profile of deuterated forms of Rasagiline than the protonated forms. To substantiate it, phase-I bio-trasformations of deuterated Rasagiline was conducted with encouraging results [58].

Ulanenko K, *et al*., in 2013, had reported the synthesis of 2-(2-((2, 3-dihydro-li/-inden-l-yl)(prop-2-ynyl)amino)-2-oxoethyl)-2-hydroxysucckiic acid **42** from citric acid **41**. In the first step, **41** was esterified to form trimethyl citrate. It was then converted to 1, 2-dimethyl citrate by a selective stearically controlled saponification. In the next step, an amidation reaction was conducted between *R*-Rasagiline base and 1, 2-dimethyl citramide and finally the esters were hydrolyzed to isolate **42** (yield: 3.5%) [59].

Santosh VP, *et al*., in 2013, had reported the condensation of *R-(-)*-isomer of **2** hydrochloride in acetonitrile with **7** in the presence of potassium carbonate to isolate crude base. It was purified by the selective pH adjustment and selective extraction to suitable solvents to isolate *R*-Rasagiline base (purity: 99.82% by HPLC, as oily mass). It was treated with methanesulfonic acid in isopropyl alcohol to obtain **1** (purity: 99.99% by HPLC). An optional isolation of free base was reported by converting in-*situ* to **1** with good purity. This work avoids the tedious and time-consuming column chromatographic purification method & the solvent recrystallization techniques to get pure free base, instead had incorporated a simple workup techniques to get the *R*-Rasagiline base with high purity. [60].

Gade SR, *et al*., in 2013, had demonstrated the treatment of Rasagiline base with *L*-(+)-tartaric acid in methyl alcohol to isolate Rasagiline hemi-tartarate (yield: 70-75%, purity: 99.91-99.98% by HPLC) [61].





***Sun Y**, et al*., in 2014, had demonstrated a one-pot synthetic process to condense *R*-(-)-isomer of **2** in acetonitrile or *N*,*N*-dimethyl formamide with propargyl-*p*-toluenesulfonate **43** or **44** in the presence of sodium carbonate or potassium carbonate or triethylamine to form an intermediate. It was not isolated, but immediately treated with methanesulfonic acid to isolate the crude solid. It was recrystallized in isopropyl alcohol to isolate **1** with a melting point of 156-157°C (yield: approximately 40-50%, purity: more than 99.5% by HPLC). The work was extended further to isolate a few impurities like prop-2-yn-1-yl (1*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamate **45** and prop-2-yn-1-yl-(1*R*)-2,3-dihydro-1*H*-inden-1-yl-(prop-2-yn-1-yl)carbamate **46** from the filtrate by the column chromatography technique [62].

***Sun Y**, et al*., in 2014, had illustrated the isolation and analysis methods of **45**, **46** and *R*-mesylate of **4**. The LCMS data of isolated impurities are $[M^+H]^+$ 216.1 for **45**, $[M^+H]^+$ 254.1 for **46** and $[M^+H]^+$ 210.1 for mesylate of **4** [63].

***Prudic D**, et al*., in 2015 & 2016, had reported a process for the preparation of optically pure *R*-isomer of **2** by a diastereomeric resolution of racemic **2** using *N*-acetyl-*L*-glutamic acid **47** as an effective resolving agent. The formation of diastereomeric salts of *R*-isomer of **2** with **47** and their use in the synthesis of optically enriched Rasagiline base was also reported. Rasagiline base was treated with methanesulfonic acid in isopropyl alcohol to obtain **1** (yield: 76.6%, purity: 100% by HPLC). The reaction of **9** with hydroxylamine hydrochloride was carried out in ethyl alcohol to get **15** (yield: 91.6%). It was reduced by Raney-nickel in the presence of ammonia enriched methyl alcohol to isolate racemic **2** (yield: 100%) [64, 65].

***Frenkel A**, et al*., in 2015, had reported the synthesis of **19** from *N*-(2,3-dihydro-1*H*-inden-1-yl)acetamide **48**. Impurity **19** was formed during the production of **1** under certain specific conditions. The work was extended further to contribute a commercial process to get **1** with very low content of **19**. Racemic **2** was treated with **8** in the presence of sodium hydroxide solution to isolate racemic Rasagiline base. It was treated with *L*-tartaric acid in isopropyl alcohol to isolate *R*-Rasagiline tartarate, it was then de-salted and treated further with methane sulfonic acid to isolate **1** (with around 0.01-0.02% of **19** content) [66].

***Chen J**, et al*., in 2019, had demonstrated the reaction of *R*-(-)-isomer of **2** with Propynoic acid **49** in dichloromethane under the presence of suitable acid amine coupling agents like dicyclohexylcarbazone/ 4-dimethylaminopyridine to get *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]but-3-ynamide **50** (yield: 97.7%, purity: 96.76% by HPLC). Similarly, the use of 1-hydroxybenzotriazole/ 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in tetrahydrofuran gave **50** (yield: 95.2%, purity: 96.59% by HPLC). The use of (azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium-hexafluorophosphate/ di-isopropylethylamine in 2-methyltetrahydrofuran had resulted in the formation of **50** (yield: 96.8%, purity: 96.84% by HPLC). It was dissolved in toluene/xylene/benzene and treated with diphenylsilane/triphenylsilane/diphenylmethylsilane and di-*o*-chlorophenylboronic acid/ bis-fluorophenylboronic acid to isolate Rasagiline base (yield: 59.4-60.7%, purity: 99.72-99.77% by HPLC). It was diluted in isopropyl alcohol and treated with methanesulfonic acid to obtain **1** (yield: 58.5%, purity: 99.89% by HPLC) [67].

***Li J**, et al*., in 2020, had reported a one-pot synthetic procedure to isolate Rasagiline base by the condensation of

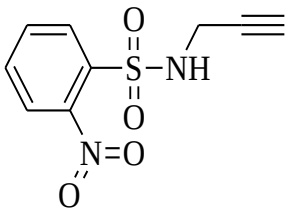
9 with **6** in the presence of a suitable dehydrating agent/s (sodium borohydride, glacial acetic acid and tetra-isopropyl titanate) in tetrahydrofuran to isolate racemic Rasagiline base (yield: 93.6%, purity: 95.67% by HPLC, as red-brown oily liquid). It was resolved by the use of *L*-(+)-tartaric acid to get *R*-Rasagiline tartarate (yield: 39%, purity: 99.46% by HPLC, as off-while solid). It was de-salted and treated with methanesulfonic acid in isopropyl alcohol to get **1** (yield: 87.6%, purity: 99.80% by HPLC) [68].

Ma Y, *et al*., in 2020, had demonstrated the condensation of *R*-(-)-isomer of **2** with **3** in the presence of *N*,*N*-diisopropylethylamine in acetonitrile to isolate *R*-Rasagiline base (yield: 45.3-58%, purity: 91.4-97.54% by HPLC). It was dissolved in isopropyl alcohol and added methanesulfonic acid to isolate **1** (yield: 83.1%, purity: 99.3% by HPLC). The work had even covered the process to recover the un-reacted **2** from the filtrate (recovery: 32%, purity: 81% by HPLC) [69].

Ma Y, *et al*., in 2021, had illustrated the synthesis of a few critical genotoxic impurities like (1*R*)-*N*-(2-chloroprop-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-amine **51** (purity: 84.6% by HPLC, as light yellow oil), (1*R*)-*N*-[(2*E*)-3-chloroprop-2-en-1-yl]-2,3-dihydro-1*H*-inden-1-amine **52** (yield: 89.3% by HPLC, as yellow oil), (1*R*)-*N*-[(2*Z*)-3-chloroprop-2-en-1-yl]-2,3-dihydro-1*H*-inden-1-amine **53** (purity: 88.4% by HPLC, as yellow oil), (1*R*)-*N*-nitroso-*N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine **54** (purity: 88-8.9% by HPLC, red-brown oil) and *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]-*N*-nitroso-2,3-dihydro-1*H*-inden-1-amine **55** (purity: 75-79.8% by HPLC, as brown-black oil). These are the process related impurities of **1**, and are synthesized by the suitable reagents under the favorable reaction conditions. The work had even extended to provide the characterization details of impurities and their detection methods in the finished product [70,71].

Hu A, *et al*., in 2022, had demonstrated an electro-reduction synthetic pathway (a green chemistry approach) to isolate racemic **2** hydrochloride. The reduction of **15** under electrolytic conditions (alkaline) was performed in the presence of an organic solvent to obtain racemic **2** hydrochloride with a melting point of 210-212ºC (yield: 90.6%, as a white solid) [72].

Tang H, *et al*., in 2023, had reported the cyclization of 3-phenylpropanoic acid **56** in the presence of trifluoromethanesulfonic acid and trifluoromethanesulfonic anhydride to isolate **15** (yield: 86.84%, purity: 99.37% by HPLC). It was dissolved in tetrahydrofuran and treated with sodium triacetoxyborohydride and added the solution of **6** in tetrahydrofuran to obtain racemic Rasagiline hydrochloride (yield: 79%, purity: 99.67% by HPLC). It was de-salted and resolved using *L*-tartaric acid in methyl alcohol to isolate *R*-Rasagiline tartarate (yield: 34.38%, purity: 98.83%). It was treated with methanesulfonic acid in isopropyl alcohol to isolate **1** (yield: 94.97%, purity: 100%, chiral purity: 100% by HPLC). The disclosed initiative was proved to be an industrially feasible process involving cyclization, reductive amination, resolution and salification using the readily available starting materials, simple reagents and solvents [73].



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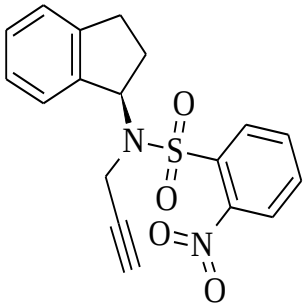

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Wu G, *et al*., in 2023, had illustrated the use of **9** as the starting material to obtain *S*-isomer of **13** (yield: 75.6-82%, purity: 98.3-98.6% by HPLC) in high purity through the asymmetric reduction of a chiral auxiliary and borane intermediate. It was dissolved in tetrahydrofuran and treated with 2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide **57**, triphenylphosphine and di-isopropyl azodicarboxylate under the nitrogen atmosphere to isolate *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide **58** (yield: 81.5-85%, purity: 98-98.8% by HPLC). In this step, a chiral amine was constructed in a simple pathway and the amino group was protected by the nitro sulfonyl group. The reported work successfully avoids the formation of unwanted poly-substituted byproducts. Intermediate **58** was dissolved in dimethylformamide and treated with lithium hydroxide solution. To the mixture, mercaptopropionic acid in dimethyl formamide was added drop-wise and worked-up by pH adjustment to obtain *R*-Rasagiline base (yield: 92%, 97.5% by HPLC). Upon the use of lithium hydroxide solution in dimethyl acetamide and mercapto-acetic acid, **1** was isolated with relatively good purity (yield: 84.4%, purity: 97.1% by HPLC). In another experiment, lithium-bistrimethylsilylamide in *N*-methyl pyrrolidone and thioglycolic acid was used to isolate **1** in reasonably good purity (yield: 77%, purity: 95.8% by HPLC) [74].

Summary

Numerous researchers (inventors) associated to various global organizations (assignees) had contributed to commercialize Rasagiline, its salts and crystallographic forms.

The information regarding the assignee of all the disclosures till date was revealed in **Table 1**. To the context, "Teva Pharma" leads under the category of publication of patents on various aspects of Rasagiline and its close related compounds.

Table 1. **List of organizations/institutions behind the disclosed work (patent/s applied by/assignee)**

Ref. No.	Patent No.	Applicant/s or Assignee Organization/s
[4], [7].	US3513244A DE1443403A1	Aspro Nicholas Ltd
[5], [8], [9], [10].	US5453446A, EP0436492A2, WO9511016A1, US5532415A	Teva Pharma [IL]; Technion Res & Dev foundation [IL]
[6].	US3253037A	Ciba Geigy Corp
[11].	CN1031995C	Orvet Bv [NL]
[12].	WO02068376A1	ISP Finetech Ltd [IL]
[13], [14], [15], [20], [25], [36], [66].	US 2006/0199974A1, US2007/112217A1, US7491847B2, EP2101569B1, US 7547806B2, US7855233B2 EP2939669A1	Teva Pharma [IL]
[16].	CN101062897A	Chongqing Pharm Res Inst Co [CN]
[17].	CN1990455A	Beijing D Venture Pharm Tech [CN]
[18].	CN101260048A	Suzhou Chireach Biomedical Tec [CN]
[19], [27], [37].	US2009292141A1, WO2009118657A2 US20100041920A1	Medichem SA [ES]
[21], [22], [53], [58], [59].	WO2009154777A, WO2009154782A1, WO2012058219A2, WO2012058219A2 WO2013055684A1	Teva Pharma [IL]; Teva Pharma [US]
[23].	CA2723869A1	Generics UK Ltd [GB]
[24].	EP0235590A2	Warner Lambert Co [US]
[26].	CN101486655A	Meide Jiangxi Biotechnology Co [CN]
[28], [39].	WO2009122301A2 WO2011080589A2	Actavis Group Ptc Ehf [IS]
[29].	CN101381314A	Chengdu Healthcare Pharmaceuticals [CN]
[30].	CN101486655A	Meide Jiangxi Biotechnology Co [CN]
[31].	WO2010059913A2	Dr. Reddys Lab Ltd [IN]; Dr. Reddys Lab Inc [US]
[32].	WO2010049379A1	Chemo Iberica SA [ES]
[33].	US2010029987A1	Dipharma Francis S R I [IT]
[34].	EP2231582A1	Cipla Ltd [IN]
[35], [38].	US2010234636A1 WO2011003938A1	Ratiopharm GMBH [DE]
[40].	CN102010353A	Winchem Science and Technology Co Ltd
[41].	US2011218361A1	Everlight USA Inc [US]
[42].	CN102203053A	Generics UK Ltd
[43], [45].	WO2011048612A2, WO2011095985A2	Glenmark Generics Ltd [IN]
[44].	WO2011064216A1	Lek Pharmaceuticals [SI]
[46].	CN102154432A	Bengbu BBCA Medicine Science Dev Co Ltd

[47], [51].	WO2011121607A2, WO2012153349A2	Cadila Healthcare Ltd [IN]
[48].	EP2364967A2	USV Ltd [IN]
[49], [50], [56].	WO2011012140A2 WO2012116752A1 WO2012153349A2	Synthon BV [NL]
[51].	CN102464589A	Chiral Quest Suzhou Co Ltd
[52].	WO2012096635A1	Fargem Farmasoetik Arastirma Gelistirme Merkezi Sanayi Ve Ticaret A S [TR]
[53].	CN102476998A	Taiwan Everlight Chemical Ind Corp
[57].	CN102675122A	Dongguan Daxin Biolog Technology Co Ltd
[55], [50].	US20120321896A1, WO2013054346A2	Alkem Lab Ltd [IN]
[52].	CN102786422A	Topharman Shanghai Co Ltd; Shanghai Inst Materia Medica; Shandong Topharman Medical Raw Material Co Ltd
[61].	EP2610239A1	Dr. Reddys Lab Ltd [IN]
[62], [63].	CN103804200A, CN103864646A	Changzhou No 4 Pharmaceutical Factory Co Ltd
[64], [65].	WO2015070995A, WO2016116607A1	Farma Grs D O O [SI]
[67].	CN109180499A	Shanghai Bocimed Pharmaceutical Co Ltd
[68].	CN110776429A	Qilu Pharmaceutical Co Ltd
[69], [70], [71].	CN111333517A, CN113030283A, CN113045456A	Shanghai Aobo Pharmtech Inc Ltd; Zhejiang Huahai Pharm Co Ltd
[72].	CN114438531A	Univ Hunan
[73].	CN115838333A	Jiangsu Szyy Pharmaceutical Res Institute Co Ltd
[74].	CN115947675A	Boji Medical Technology Co Ltd

CONCLUSION

This work was primarily aimed to cover the disclosures in prior patents for the synthetic approaches on Rasagiline, its salts (in crystalline or amorphous forms) and a few impurities. Numerous patents were published at various patent trademark offices over the years covering many aspects of the drug, Rasagiline. To the context, the patents with attempts/explorings on the synthesis, impurity profiling, salt formation (in crystalline or amorphous form) of Rasagiline were considered, as retrieved from the web search tools/databases like *Google Patents*, *USPTO (*United States Patent and Trademark Office*)* and *Espacenet (*European Patent Office*).* This review work provides the essential information regarding the key starting material/s, reagents and solvents employed to obtain Rasagiline and its salts. The present review initiative can assist global researchers to venture further on the synthetic aspects and reaction optimization studies to isolate Rasagiline and its clinically acceptable salts. Racemization, recovery of *S*-isomer and its effective reuse are the key process bottle-necks either at the initial phase or at the end. An optimized process with the use of commercially viable starting material/s and the use of green solvents/ reagents under mild reaction conditions would favor the large scale manufacturing of Rasagiline and its stable salts.

REFERENCES

1. Akao Y, Maruyama W, Yi H, et al. An anti-Parkinson's disease drug, N-propargyl-1(R)-aminoindan (rasagiline), enhances expression of anti-apoptotic Bcl-2 in human dopaminergic SH-SY5Y cells. Neurosci Lett. 2002;326(2):105–8. Available from: http://dx.doi.org/10.1016/s0304-3940(02)00332-4
2. Oldfield V, Keating GM, Perry CM. Rasagiline: A review of its use in the management of Parkinson??S disease. Drugs. 2007;67(12):1725–47. Available from: http://dx.doi.org/10.2165/00003495-200767120-00006
3. Lakhan SE. From a Parkinson's disease expert: Rasagiline and the Future of Therapy. Mol Neurodegener. 2007;2(1):13. Available from: http://dx.doi.org/10.1186/1750-1326-2-13
4. Maurice WG, John WJ, Leslie FW. Methods of lowering blood pressure in animals by administering secondary and tertiary amines. 1970. Available from: https://worldwide.espacenet.com/patent/search/family/010332675/publication/US3513244A?q=US3513244A

5. Youdim MBH, Finberg JPM, Levy R, et al. Use of the R-enantiomers of N-propargyl 1-aminoindan compounds for treating Parkinson's disease. 1995. Available from: https://worldwide.espacenet.com/patent/search/family/011060756/publication/US5453446A?q=US5453446A
6. Huebner CF. N-2-alkynyl-amino-benzocylo-alkanes. 1966. Available from: https://worldwide.espacenet.com/patent/search/family/027394548/publication/US3253037A?q=US3253037A
7. Maurice WG, John WJ, Langley B et al. Process for the preparation of therapeutically utilizable N-substituted -1-aminoindanes. 1968. Available from: https://worldwide.espacenet.com/patent/search/family/010313839/publication/DE1443403A1?q=pn%3DDE1443403A1
8. Youdim MBH, Finberg JPM, Levy R, et al. R-Enantiomer of *N*-propargyl-1-aminoindan, its preparation and pharmaceutical compositions containing it. 1991. Available from: https://worldwide.espacenet.com/patent/search/family/011060756/publication/EP0436492A2?q=EP0436492A2
9. Youdim MBH, Finberg JPM, Levy R, et al. R-Enantiomer of n-propargyl-1-aminoindan, salts, compositions and uses thereof. 1995. Available from: https://worldwide.espacenet.com/patent/search/family/022487049/publication/WO9511016A1?q=wo9511016
10. Youdim MBH, Finberg JPM, Levy R, et al. R-enantiomer of N-propargyl-1-aminoindan, salts, compositions and uses thereof. 1996. Available from: https://worldwide.espacenet.com/patent/search/family/011060756/publication/US5532415A?q=US5532415A
11. Youdim MBH, Finberg JPM, Levy R, et al. Process for preparation of R-enantiomers of N-Propargyl-1-aminoindan compounds. 1996. Available from: https://worldwide.espacenet.com/patent/search/family/036764609/publication/CN1031995C?q=CN1031995C
12. Gutman AL, Zaltzman I, Ponomarev V, et al. Process for the preparation of rasagiline and its salts. 2002. Available from: https://worldwide.espacenet.com/patent/search/family/011075183/publication/WO02068376A1?q=pn%3DWO02068376A1
13. Lee TB, Ian CL, Eliezer B. Process for the synthesis of enantomeric indanylamine dervatives. 2006. Available from: https://worldwide.espacenet.com/patent/search/family/036794953/publication/US2006199974A1?q=US%202006%2F0199974A1
14. Anton F, Ramy LH, Eduard G et al.. Methods for isolating propargylated aminoindans. 2007. Available from: https://worldwide.espacenet.com/patent/search/family/038067736/publication/US2007112217A1?q=US2007%2F112217A1
15. Anton F, Ramy LH, Eduard G et al. Methods for isolating propargylated aminoindans. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/038067736/publication/US7491847B2?q=pn%3DUS7491847B2
16. Luo JH. Improved process for preparing 2,3-dihydro-1H-indenes-1-amine and derivative thereof. 2007. Available from: https://worldwide.espacenet.com/patent/search/family/038964212/publication/CN101062897A?q=pn%3DCN101062897A
17. Feng Q. Simple and novel process for preparing indenes derivatives. 2007. Available from: https://worldwide.espacenet.com/patent/search/family/038213024/publication/CN1990455A?q=pn%3DCN1990455A
18. Zongxuan S, Yanfei Z, Benliang X, et al. Method for preparing rasagiline. 2008. Available from: https://worldwide.espacenet.com/patent/search/family/039960783/publication/CN101260048A?q=CN101260048
19. Bosch ILJ, Burgarolas MMC, Masllorens LJ. New method for obtaining an aminoindan mesylate derivative. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/041226227/publication/US2009292141A1?q=pn%3DUS2009292141A1
20. Frenkel A, Koltai T. Crystalline solid rasagiline base. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/039536623/publication/EP2101569B1?q=pn%3DEP2101569B1
21. Frenkel A, Ronen BD. Process for preparing and drying solid rasagiline base. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/041431882/publication/WO2009154777A2?q=pn%3DWO2009154777A2
22. Frenkel A. Process for purifying rasagiline base. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/041434361/publication/WO2009154782A1?q=wo2009154782
23. Gore V, Manojkumar B, Sonawane S, et al. A process for the preparation of enantiomerically pure amines. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/040874479/publication/CA2723869A1?q=rasagiline%20mesylate
24. Goel OP. Improved process for the resolution of 1-aminoindanes. 1987. Available from: https://worldwide.espacenet.com/patent/search/family/025242822/publication/EP0235590A2?q=EP235590
25. Frenkel A, Koltai T. Tannate salt of rasagline. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/039536617/publication/US7547806B2?q=pn%3DUS7547806B2
26. Caigu H, Huimin H. Methanesulfonic acid rasagiline crystal form and preparation thereof. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/040889740/publication/CN101486655A?q=cn101486655
27. Stephen BDW. Polymorphic form of an aminoindan mesylate derivative. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/041010318/publication/WO2009118657A2?q=wo2009%2F118657
28. Patil NS, Pagire HS, Neela PK, et al. Rasagiline mesylate particles and process for the preparation thereof. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/041022558/publication/WO2009122301A2?q=wo2009122301
29. Qiandong L, Jian X, Yong Z. Preparation method of (R)-(+)-N-propargyl-1-indan amines. 2009. Available from: https://worldwide.espacenet.com/patent/search/family/040461395/publication/CN101381314A?q=cn101381314
30. Huang C, He H. Methanesulfonic acid rasagiline crystal form and preparation thereof. 2009. Available from: https://

worldwide.espacenet.com/patent/search/family/040889740/publication/CN101486655A?q=pn%3DCN101486655A
31. Cherukupally P, Vajrala VR, Adla VK, et al. Preparation of rasagiline and salts thereof. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/042198815/publication/WO2010059913A2?q=wo2010059913
32. Marras G, Rasparini M, Tufaro R, et al. A process for the preparation of (*R*)-1-aminoindanes. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/040445758/publication/WO2010049379A1?q=wo2010049379
33. Allegrini P, Romano BG, Attolino E, et al. Crystalline Form of Rasagiline and Process for the Preparation Thereof. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/041609045/publication/US2010029987A1?q=pn%3DUS2010029987A1
34. Phull MS, Rao DR, Kankan RN. Process for the synthesis of propargylated aminoindan derivatives. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/040469984/publication/EP2231582A1?q=EP2231582
35. Stahl HP. Novel salts of the active substance rasagiline. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/037398781/publication/US2010234636A1?q=pn%3DUS2010234636A1
36. Frenkel A, Safadi M, Koltai T. Citrate salt of Rasagiline. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/042354337/publication/US7855233B2?q=US7855233
37. Stephen BDW, Lopez ED, Velez MB. New salt forms of an aminoindan derivative. 2010. Available from: https://worldwide.espacenet.com/patent/search/family/041056824/publication/US2010041920A1?q=pn%3DUS2010041920A1
38. Thomas T, Christian J, Ramesh GM. Salts of rasagiline and pharmaceutical preparations thereof. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/042634609/publication/WO2011003938A1?q=pn%3DWO2011003938A1
39. Patil NS, Pagire HS, Kumar NP et al. Solid state forms of rasagiline salts. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/044144855/publication/WO2011080589A2?q=pn%3DWO2011080589A2
40. Dongwei C, Jiancheng Q, Xiying W. New method for preparing rasagiline mesylate. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/043840709/publication/CN102010353A?q=CN102010353
41. Chi-Hsiang Y, Tsung-Ting C. Method for producing compound for preparation of anti-parkinson's disease drug. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/044531896/publication/US2011218361A1?q=us2011218361
42. Gore V, Manojkumar B, Sonawane S, et al. An improved process for the preparation of amines. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/041112523/publication/CN102203053A?q=CN102203053
43. Thanedar AA, Deshmukh SA, Zope SS, et al. Processes for the preparation of propargylated aminoindans or a pharmaceutically acceptable salt thereof. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/043900759/publication/WO2011048612A2?q=pn%3DWO2011048612A2
44. Selic L. Novel salts of rasagiline. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/041682528/publication/WO2011064216A1?q=pn%3DWO2011064216A1
45. Zope SS, Deshmukh C, Kelkar LM, et al. Rasagiline salts and processes for the preparation thereof. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/044355887/publication/WO2011095985A2?q=pn%3DWO2011095985A2
46. Sun J, Chen W, Wei Y et al. Method for preparing rasagiline. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/044436103/publication/CN102154432A?q=pn%3DCN102154432A
47. Dwivedi SD, Prasad A, Patel MR. Rasagiline and its pharmaceutically acceptable salts. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/044211868/publication/WO2011121607A2?q=pn%3DWO2011121607A2
48. Sathe DG, Damle SV, Sawant KD, et al. Process for preparation of rasagiline and salts thereof. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/044186155/publication/EP2364967A2?q=pn%3DEP2364967A2
49. Elffrink WWJ. Polymorphs of rasagiline hydrochloride. 2011. Available from: https://worldwide.espacenet.com/patent/search/family/041505731/publication/WO2011012140A2?q=pn%3DWO2011012140A2
50. Bohumil D. Process of resolution of 1-aminoindan. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/044625268/publication/WO2012116752A1?q=pn%3DWO2012116752A1
51. Liu G, Wang Z, Liu J. Preparation methods of rasagiline, mesylate thereof and intermediate of rasagiline. 2012.. Available from: https://worldwide.espacenet.com/patent/search/family/046068753/publication/CN102464589A?q=pn%3DCN102464589A
52. Oemer R, Hasan K, Ilker E, et al. A new method for the synthesis of rasagiline. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/044533280/publication/WO2012096635A1?q=wo2012096635
53. Yao Q, Chen Z. Preparation method of compound for preparing medicine for treating Parkinson's disease. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/046089789/publication/CN102476998A?q=pn%3DCN102476998A
54. Tang L, Yong Z, Yin Y, et al. Process for preparing 2,3-dihydro-1H-indene-1-amine. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/046807747/publication/CN102675122A?q=pn%3DCN102675122A
55. Nagarajan K, Kumar R, Patel DKA et al. Rasagiline mesylate having large particle size and a process for preparation thereof. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/044319928/publication/US2012321896A1?q=pn%3DUS2012321896A1
56. Dwivedi SD, Prasad A, Patel MR. Rasagiline and its pharmaceutically acceptable salts. 2012. Available from:

https://worldwide.espacenet.com/patent/search/family/046939731/publication/WO2012153349A2?q=pn%3DWO2012153349A2
57. Zhang R, Liu Z, Yang X, et al. Method for preparing rasagiline mesylate. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/047152030/publication/CN102786422A?q=pn%3DCN102786422A
58. Bahar E, Frenkel A, Piryatinsky V. Deuterium enriched rasagiline. 2012. Available from: https://worldwide.espacenet.com/patent/search/family/045973513/publication/WO2012058219A2?q=pn%3DWO2012058219A2
59. Ulanenko K, Verba G, Safadi M, et al. Rasagiline citramide. 2013. Available from: https://worldwide.espacenet.com/patent/search/family/048042234/publication/WO2013055684A1?q=pn%3DWO2013055684A1
60. Santosh VP, Prashanth PP, Dharmesh KAP. A process for the preparation of N-propragyl 1-amino indane and pharmaceutically acceptable salts thereof. 2013. Available from: https://worldwide.espacenet.com/patent/search/family/048082617/publication/WO2013054346A2?q=pn%3DWO2013054346A2
61. Gade SR, Adla VK, Vempati C. Preparation of Rasagiline Hemitartrate. 2013. Available from: https://worldwide.espacenet.com/patent/search/family/047559035/publication/EP2610239A1?q=pn%3DEP2610239A1
62. Sun Y, Yan Y, Feng X, et al. Preparation method of rasagiline and analogue thereof. 2014. Available from: https://worldwide.espacenet.com/patent/search/family/050701641/publication/CN103804200A?q=pn%3DCN103804200A
63. Sun Y, Yan Y, Feng X, et al. Preparation and analysis method of impurity of rasagiline mesylate. 2014. Available from: https://worldwide.espacenet.com/patent/search/family/050903722/publication/CN103864646A?q=pn%3DCN103864646A
64. Prudic D, Ruzic M, Kljajic A, et al. Process for the preparation of enatiomerically pure 1-aminoindan. 2015. Available from: https://worldwide.espacenet.com/patent/search/family/051266306/publication/WO2015070995A1?q=pn%3DWO2015070995A1
65. Ruzic M, Kralj D, Klobcar A, et al. Process and intermediates for the racemization of enantiomerically enriched 1-aminoindane. 2016. Available from: https://worldwide.espacenet.com/patent/search/family/055221430/publication/WO2016116607A1?q=pn%3DWO2016116607A
66. Frenkel A, Lidor HR, Bahar E. 3-Keto-*N*-propargyl-1-aminoindan. 2015. Available from: https://worldwide.espacenet.com/patent/search/family/044151964/publication/EP2939669A1?q=pn%3DEP2939669A1
67. Chen J, Yu C, Ying S. Preparation method of rasagiline mesylate and intermediate thereof. 2019. Available from: https://worldwide.espacenet.com/patent/search/family/064937495/publication/CN109180499A?q=pn%3DCN109180499A
68. Li J, Gao Y, Sun C et al. Improved preparation method of rasagiline racemic intermediate. 2020. Available from: https://worldwide.espacenet.com/patent/search/family/069378536/publication/CN110776429A?q=pn%3DCN110776429A
69. Ma Y, Li W, Mu Y, et al. Improved method for preparing rasagiline. 2020. Available from: https://worldwide.espacenet.com/patent/search/family/071177686/publication/CN111333517A?q=pn%3DCN111333517A
70. Ma Y, Mu Y, Li W, et al. Rasagiline genotoxic impurity compound as well as preparation method and application thereof. 2021. Available from: https://worldwide.espacenet.com/patent/search/family/076458044/publication/CN113030283A?q=pn%3DCN113030283A
71. Ma Y, Wei R, Li W, et al. Novel rasagiline impurity compound, and preparation method and application thereof. 2021. Available from: https://worldwide.espacenet.com/patent/search/family/076506016/publication/CN113045456A?q=pn%3DCN113045456A
72. Hu A, Wang M, Yi Y et al. Electrochemical preparation method of rasagiline and Pevonedistat intermediates. 2022. Available from: https://worldwide.espacenet.com/patent/search/family/081362416/publication/CN114438531A?q=pn%3DCN114438531
73. Tang H, Xia C, Wang F, et al. Synthesis method of rasagiline mesylate. 2023. Available from: https://worldwide.espacenet.com/patent/search/family/085574928/publication/CN115838333A?q=CN115838333
74. Wu G, Wang T, Zuo L, et al. Rasagiline intermediate and preparation method and application thereof. 2023. Available from: https://worldwide.espacenet.com/patent/search/family/087288402/publication/CN115947675A?q=pn%3DCN115947675A

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