Review Article

A comprehensive review of disclosures in academic journals regarding the synthesis of Rasagiline and its closely related compounds along with major biological activity advancements

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ABSTRACT

This review article was primarily focused to unwind the prior art disclosures about the synthetic strategies adopted for the preparation of Rasagiline and its closely related scaffolds. Additionally, some of the major biological activity advancements of Rasagiline and its derivatives were also given the priority. It was observed that, propargyl part/ indane part/ or both of Rasagiline was extended through numerous synthetic pathways to achieve enhanced biological activity. Additionally, numerous resolution routes were also executed to isolate the intended product with high chiral purity. Hence, this review contribution can be a good platform for the worldwide researchers to design new routes to synthesize Rasagiline and its structurally close resemblance derivatives.

Key words: Rasagiline, indane moiety, propargyl moiety, mesylation, resolution, synthesis, isolation.

An overview of the drug information, medical use and (MAO-B) inhibition. Rasagiline R is a propargylamine based. Rasagiline ***R*** is a propargylamine based drug prescribed for the treatment of idiopathic Parkinson's disease [1, 2]. It has been marketed around the globe with the trade names as AZIPRON®, AZILECT® tablets, having the active pharmaceutical ingredient Rasagiline (as mesylate) along with other associated excipients [3]. It is a renowned irreversible inhibitor of monoamine oxidase-*B* (MAO-B) [4-6]. Rasagiline mesylate ***RM*** has the IUPAC nomenclature as 1*H*-inden-1-amine,2,3-dihydro-*N*-2-propynyl-(1*R*)-methanesulfonate with an empirical of $(C_{12}H_{13}N)CH_4SO_3$ and molecular weight (MW: 267.34 g/mol). It is a white to off-white powder, freely soluble in water or ethyl alcohol and sparingly soluble in iso-propyl alcohol [7, 8]. The compound AGN-1135 (*N*-2-propynyl-l-indanamine-hydrochloride) was reported to be an irreversible MAO-B inhibitor with selectivity in the rat *in-vivo* [9, 10].

Systematic exfoliation of past disclosures

Numerous synthetic routes were disclosed in various patent publications to isolate ***R*** and its associated compounds.

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A recent review article was published with details of all those patent disclosures towards the synthetic aspects of ***R***/***RM***/***RH*** and its closely related compounds (salts/impurities/forms) [11]. This work was selective towards the prior art disclosures in academic journals about the synthesis and biological activity studies towards ***R*** and its closely related compounds. **Youdim MBH** and coworkers had disclosed a commercial synthetic route to isolate ***R*** and its mono-fluorinated derivatives along with an extensive biological application studies as Patent applications in United States Patent and Trade Mark Office [12, 13]. **Lawson WB & Rao GJS**, had reported the resolution and configurations studies of 1-aminoindan or 2,3-dihydro-1*H*-inden-1-amine **1** using *L*-malic acid or 2-hydroxybutanedioic acid **2** in absolute ethanol to obtain its optical isomers [14] or the same can be achieved by the formation of diastereomeric salts [15].

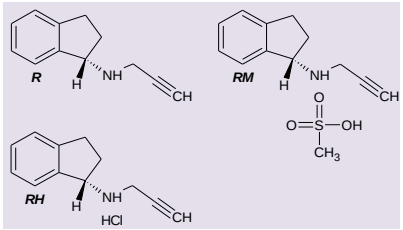

Figure 1: Rasagilne *R*-form and its popular salts.

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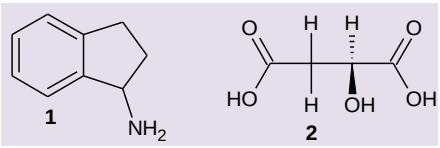


Figure 2: Key starting material 1 and the resolving agent 2

Maruyama W & coworkers had reported the anti-apoptotic function of ***R*** and (1*S*)-*N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine **3**. This initiative had established the role of these compounds to suppress the activation of caspases and DNA fragmentation [16, 17].

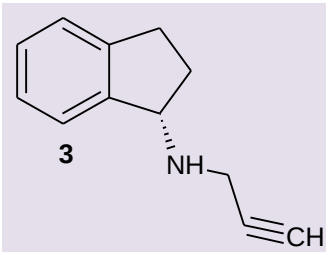


Figure 3: Structure of Rasagiline *S*-form

Youdim MBH & coworkers had demonstrated the role of ***R*** as a selective and potent inhibitor of mitochondrial MAO-B. Additionally the work reports the metabolite/s of ***R*** (metabolite is **1**) and *N*-methyl-*N*-(1-phenylpropan-2-yl)prop-2-yn-1-amine; selegiline **4** (metabolites are 1-phenylpropan-2-amine **5** and *N*-methyl-1-phenylpropan-2-amine **6** [18].

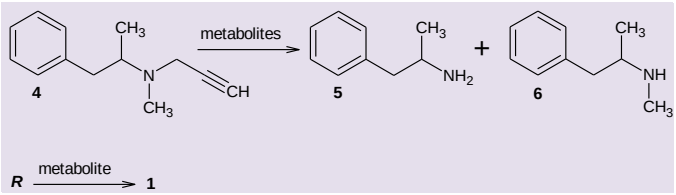


Figure 4: Structure of Rasagiline & Selegiline metabolites

Youdim MBH & coworkers had demonstrated the molecular basis of neuroprotective activities of ***R*** and three other related compounds {((3*R*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-5-yl ethyl (methyl) carbamate **7**, (3*S*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-5-yl ethyl (methyl) carbamate **8** and 3-[(1*R*)-1-(dimethylamino) ethyl]-2, 3-dihydro-1*H*-inden-5-yl ethyl (methyl) carbamate **9**; rivastigmine} [19]. **Akao Y** & coworkers had illustrated the anti-apoptotic potential of ***R*** [20].

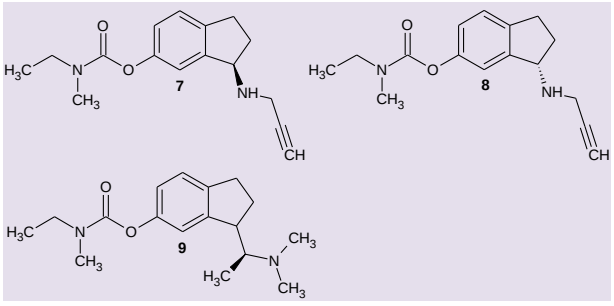


Figure 5: Rasagiline related compounds as per [18]

Maruyama W & coworkers had illustrated the anti-apoptotic capabilities of four aliphatic compounds like {(2*R*)-*N*-methyl-*N*-(prop-2-yn-1-yl)heptan-2-amine **10**, (2*S*)-*N*-methyl-*N*-(prop-2-yn-1-yl)heptan-2-amine **11**, (2*R*)-*N*-(prop-2-yn-1-yl)heptan-2-amine **12** and 3-[(2*R*)-heptan-2-ylamino]propanoic acid **13**} [21]. This work was influenced by the initiatives from **Yu PH** & coworkers [22] and **Berry MD** & **Boulton AA** [23].

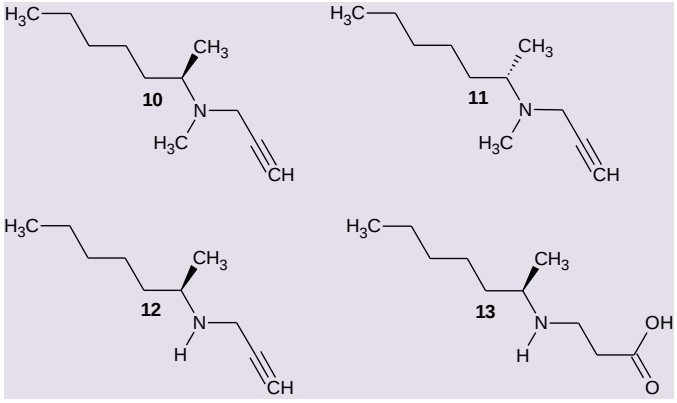


Figure 6: Aliphatic amines as per [21]

Sterling J & coworkers had reported the synthesis, characterization and biological activity studies (against Alzheimer's disease) of carbamate derivatives of *N*-propargylaminoindans and *N*-propargylphenethylamines. The work had established the fact that, *N*-methylation of propargylamine enhanced the MAO-A & B inhibitory activities and decreased the AChE inhibitory activity [24]. **Maruyama W** & coworkers had illustrated the anti-apoptotic action determination of ***R*** and its derivatives like **7**, **8**, **9**, (3*R*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-5-ol **14** and 2,3-dihydro-1*H*-inden-5-yl ethyl(methyl)carbamate **15**. The experimental outcomes suggested that, anti-apoptotic-neuroprotective activity was found to reside in the propargylamine extension and certainly not in the carbamate moiety. In the context, both **7** & **8** were found to be as effective as ***R*** to protect dopaminergic SH-SY5Y cells against apoptosis induced by the peroxynitrite donor. The donated compounds used for the experimentation were prepared by Teva Pharmaceuticals (Netanya, Israel) [25].

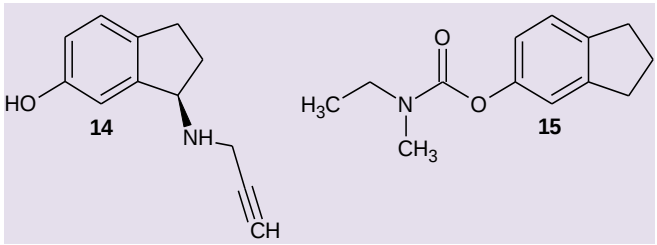


Figure 7: Rasagiline related compounds as per [25]

Yogev-Falach M and coworkers had demonstrated the use of **7** & **8** for the treatment of Alzheimer's disease [26]. **Guillon J** & coworkers had demonstrated the multi-step synthesis, configurational studies and the preliminary reports for MAO-B inhibition by some novel *N*-propargyl-3-pyrrol-1-ylindanamine derivatives [27]. **Binda C** & coworkers had reported the complexation, binding mode studies and high-resolution crystal structure details of four compounds such as

R, **3**, **13** and (1*R*)-*N*-methyl-*N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine **16** with MAO-B inhibition studies [28].

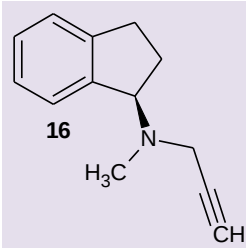


Figure 8: Rasagiline related compound as per [28].

Hubálek F & coworkers had illustrated the spectroscopic and the kinetics of inhibitory activity of five compounds such as ***R***, **3**, **11**, **13** & **16**. The study outcome suggests that, MAO-B and MAO-A are more selective towards ***R*** than *S*-enatiomer **3** by 2500-fold and 17-fold, respectively [29]. **Waibel S** & coworkers had reported the clinical combination of ***R*** and riluzole to enhance neuroprotective treatment strategies of amyotrophic lateral sclerosis (ALS) [30]. **Bar-Am O** & coworkers had illustrated the *in-vivo* regulation of protein kinase-C by ***R*** and its derivatives **7** & **8** [31]. **Parkinson Study Group** had established the importance of ***R*** based on clinical trials to treat Parkinson's disease [32, 33]. **Rascol O** & coworkers had reported the clinical study details of ***R*** in comparison with the catecol-*O*-methytransferase inhibitor, entacapone, for the treatment of Parkinson's disease [34]. **Youdim MBH** & coworkers had compiled a comprehensive review article on the pharmacological activity of ***R*** and the fundamental molecular mechanism behind its neuroprotective and neurorescue activities [35].

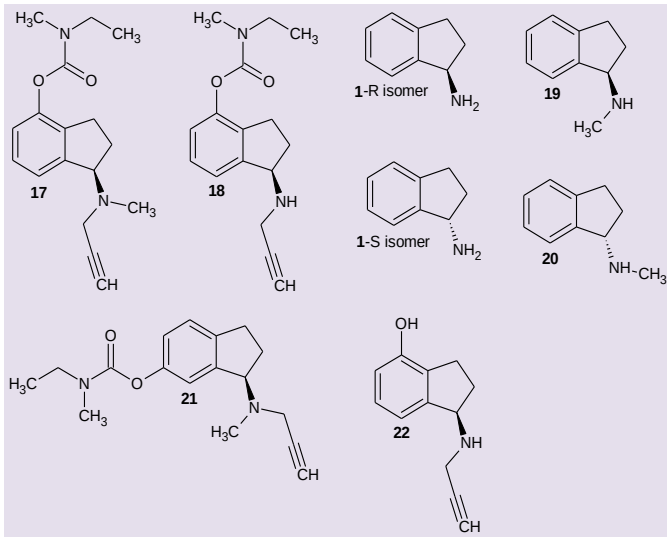
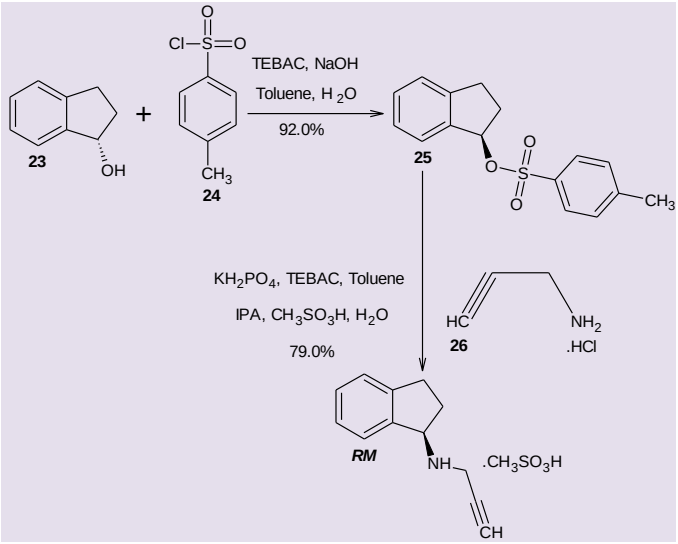


Figure 9: Rasagiline related compounds as per [36].

Binda C & coworkers had illustrated the binding of R and its related compounds to human MAOs. The work had established the crystallographic analysis of complexes and the kinetics of inhibition process. The compounds used for the studies are ***R***, **1**-*R* isomer, **1**-*S* isomer, (1*R*)-1-[methyl(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-4-yl ethyl(methyl)carbamate **17**, (1*R*)-1-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-4-yl ethyl(methyl)carbamate **18**, (1*R*)-*N*-methyl-2,3-dihydro-1*H*-inden-1-amine **19**, (1*S*)-*N*-methyl-2,3-dihydro-1*H*-inden-1-amine **20**, (3*R*)-3-[methyl(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-5-yl ethyl(methyl)carbamate **21** and (1*R*)-1-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-4-ol **22**. All the compounds used for the tests were received from Teva Pharmaceuticals [36].

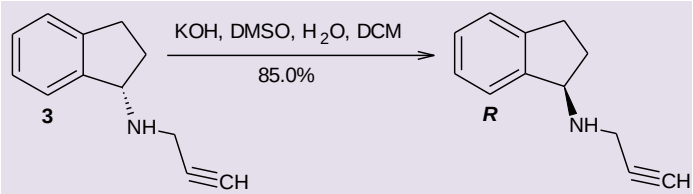
Youdim MBH & coworkers had reported a collective review contribution on the therapeutic potential of MAO inhibitors, which includes many molecules along with ***R*** and its related compounds [37]. **Oldfield V** & coworkers had prepared a review article covering all the disclosures of ***R*** towards its effectiveness to treat Parkinson's disease [38]. **Gallagher DA** & **Schrag A** had compiled a review work covering the newer pharmacological treatments on the quality of patients with Parkinson's disease. In that coverage, ***R*** had improved HR-QOL as monotherapy in early Parkinson's disease (based on one study). Meanwhile, it was not completely in more advanced state of the disease (based on one study) [39]. To improve the yield and purity of ***RM***, **Tatendra RK** & coworkers had reported a new process to manufacture ***RM*** using (1*S*)-2,3-dihydro-1*H*-inden-1-ol **23**. The condensation of **23** with 4-methylbenzenesulfonyl chloride **24** was achieved in the presence of triethylbenzylammonium chloride (TEBAC), sodium hydroxide solution and toluene to isolate (1*R*)-2,3-dihydro-1*H*-inden-1-yl 4-methylbenzenesulfonate **25**. It was treated with prop-2-yn-1-amine hydrochloride **26** (to be made free base by the addition of ammonia solution) under the catalytic impact of di-potassium hydrogen phosphate (KH_2PO_4) and TEBAC in toluene to get the residue (crude ***R***). To the residue, added isopropyl alcohol and treated with methanesulfonic acid (CH_3SO_3H) to isolate ***RM***. This process was efficient to manufacture enatiomerically pure ***RM*** in reasonably high yield [40].



Scheme 1: Route of synthesis to isolate *RM* from 23 as per [40].

Numerous synthetic routes were reported in prior arts for the isolation of ***R*** and its salts but the recovery and

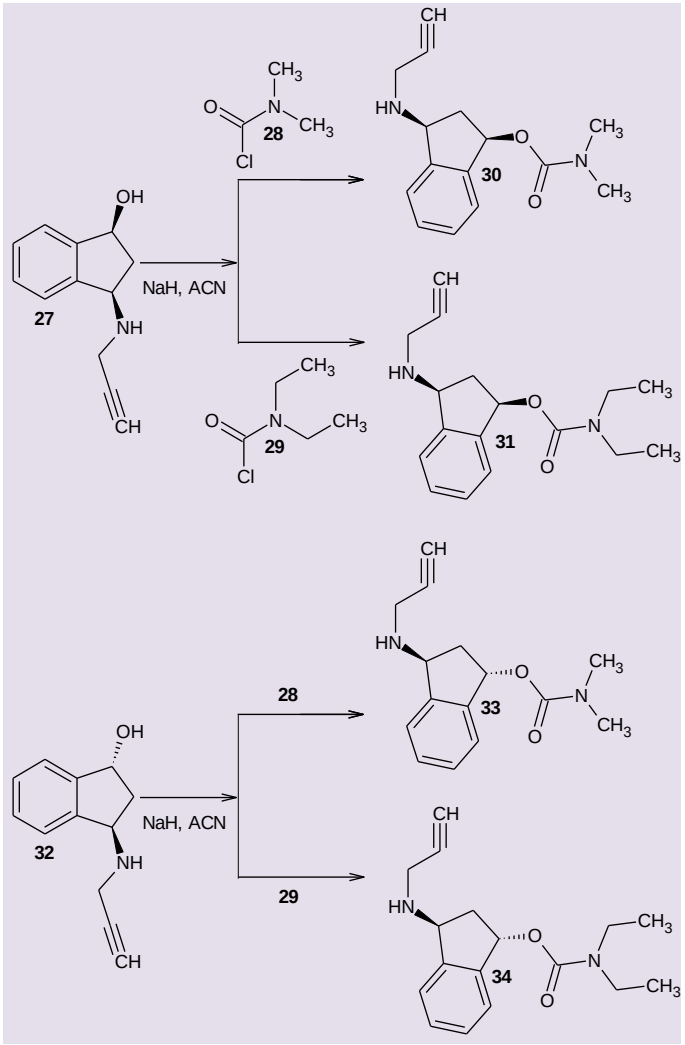
reconversion of unwanted enatiomer **3** was not attempted. In this context, **Kapubalu SK** & coworkers had reported an efficient one-pot racemization of **3** with high conversion rate and purity. The reported process involves the addition of potassium hydroxide and *N*,*N*-dimethylsulfoxide (DMSO) to the residue comprising the unwanted **3** and heated to 80^0C. It was maintained at the same temperature under agitation for 2 h and then cooled, quenched to water and extracted with dichloromethane (DCM). Upon solvent distillation, light brown colored oily mass of ***R*** was isolated. This work had adopted the process optimization strategy to finalize the above mentioned base, solvent and temperature for the efficient racemization [41]. This sort of racemization was attempted for the first time since the process to isolate the racemic mixture of ***R*** (free base or as hydrochloride salt) and other related compounds were reported by **Gittos MW** & coworkers [42, 43].



Scheme 2: Disclosed resolution pathway of 3 to form *R* as per [41].

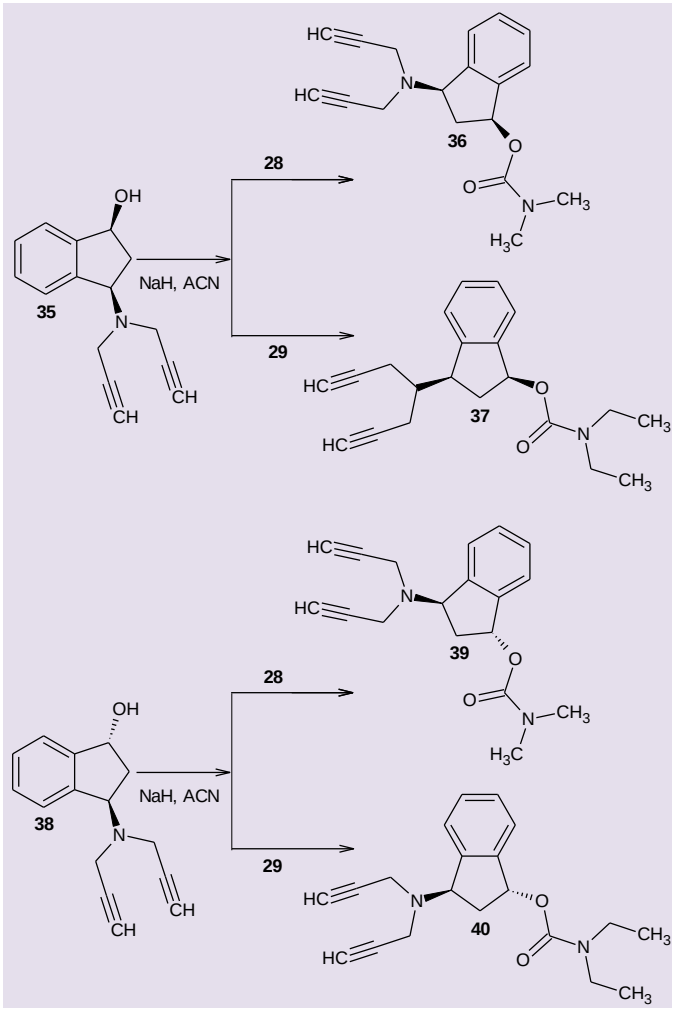
Alonso N & coworkers had demonstrated the synthesis, characterization and the interesting neuroprotective effects of some novel carbamate derivatives of ***R***. As per the disclosure, (1*S*,3*R*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-ol **27** or (1*R*,3*R*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-ol **32** or (1*S*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-ol 35 or (1*R*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-ol **38** in acetonitrile was treated with dimethylcarbamic chloride **28** or diethylcarbamic chloride **29** in the presence of sodium hydride (NaH) to isolate eight carbamate derivatives of ***R***. The novel compounds isolated are (1*R*,3*S*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-yl dimethylcarbamate **30**, (1*R*,3*S*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-yl diethylcarbamate **31**, (1*S*,3*S*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-yl dimethylcarbamate **33**, (1*S*,3*S*)-3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-yl diethylcarbamate **34**, (1*S*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl dimethylcarbamate **36**, (1*S*,3*S*)-3-(hepta-1,6-diyn-4-yl)-2,3-dihydro-1*H*-inden-1-yl diethylcarbamate **37**, (1*R*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl dimethylcarbamate **39** and (1*R*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl diethylcarbamate **40**. These compounds were tested for the high-throughput screening of multitarget drugs in chemical neurosciences.

Three compounds (**34**, **36** & **39**) had exhibited reasonably high neuroprotective effects [44]. This work was inspired from **González-Díaz H** & coworkers, since they disclosed the synthesis, characterization and assay of MAO-B inhibitors. They synthesized 3-hydroxy, acetate or benzoate derivatives mono/di-propargyls starting from benzaldehyde [45]. The same team (**Luan F** & coworkers) had extended their work towards the study of 1,3-derivatives of ***R*** which are potentially useful in neurodegenerative diseases. The derivatives were synthesized from benzaldehyde through the multistep pathway, they are **27**, **32**, **35**, **38**, (1*S*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl acetate **41**, (1*R*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl acetate **42**, (1*S*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl benzoate **43** and (1*R*,3*R*)-3-[di(prop-2-yn-1-yl)amino]-2,3-dihydro-1*H*-inden-1-yl benzoate **44** [46].



Scheme 3a: Synthesis of Rasagilne related compounds as per [44-46].

Rodríguez-Borges J & coworkers had reported the synthesis and characterization of novel propargylated 1-pyrindane derivatives. The isolated compounds having close structural resemblance to ***R*** are 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide **45**, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl acetate **46**, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol **47**, 7-(prop-2-yn-1-yloxy)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine **48**, 5,6-dihydro-7*H*-cyclopenta[*b*]pyridin-7-one **49**, *N*-(prop-2-yn-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-amine **50** and *N*,*N*-di(prop-2-yn-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-amine **51** [47].



Scheme 3b: Synthesis of Rasagiline related compounds as per [44-46].

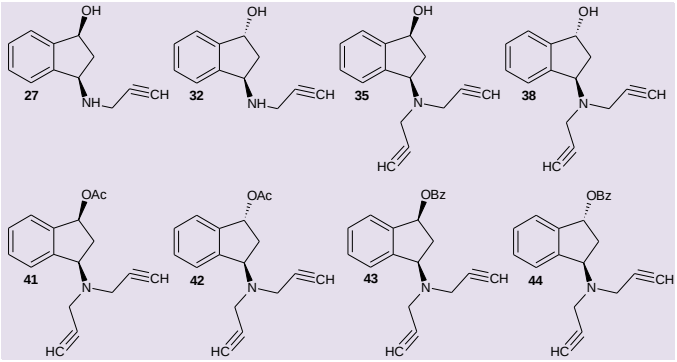


Figure 10: Rasagiline related compounds as per [44-46].

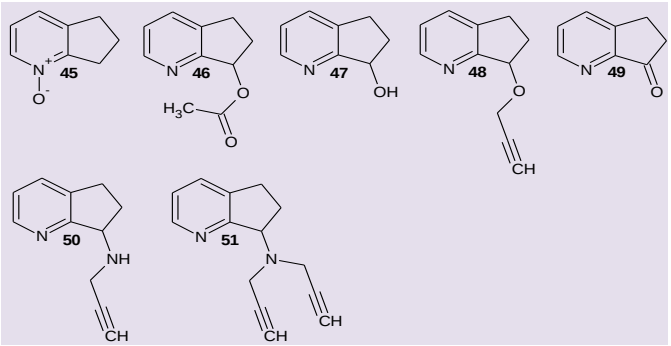
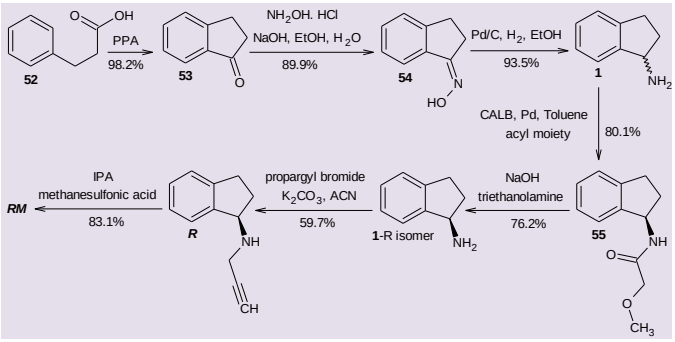


Figure 11: Rasagiline related compounds as disclosed by [47].

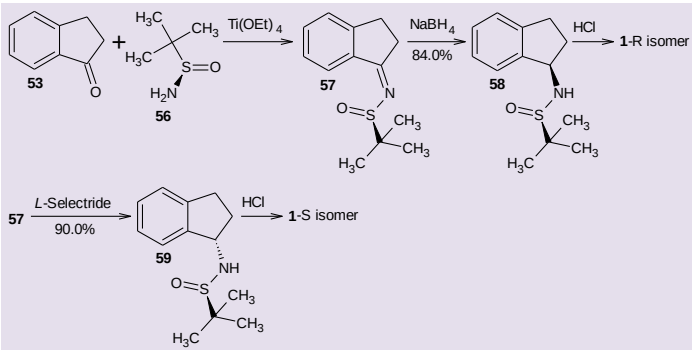
Ma G & coworkers had illustrated the novel seven-step synthetic route to prepare ***RM*** via kinetic resolution (KR) or dynamic kinetic resolution (DKR), catalyzed by Candida antarctica lipase B (CALB) and palladium-nanocatalyst. 3-Phenylpropanoic acid **52** was treated with poly phosphoric acid (PPA) to isolate 2,3-dihydro-1*H*-inden-1-one **53**. It was treated with hydroxylamine hydrochloride (NH_2OH. HCl) in alkaline medium to get (1*E*,*Z*)-*N*-hydroxy-2,3-dihydro-1*H*-inden-1-imine **54**. It was reduced under the impact of Pd/C to get **1**. It was condensed with isopropyl 2-methoxyacetate and racemized under special conditions to isolate *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]-2-methoxyacetamide **55** and then **1**-*R* isomer. It was condensed with propargyl bromide in the presence of potassium carbonate (K_2CO_3) and acetonitrile to form ***R***. It was treated with methanesulfonic acid in isopropyl alcohol to get ***RM*** (overall yield: 25.0%) with an excellent enantioselectivity [48]. The reported process was much superior to the previous disclosures. The racemization of **1** is much superior to the disclosures by **Colyer JT** & coworkers. As per the disclosure, numerous *N*-tert-butanesulfinyl imines were reduced in the presence of sodium borohydride ($NaBH_4$) in tetrahydrofuran and water to obtain the corresponding secondary sulfinamides in high yield and diastereoselectivity. By the use of *L*-Selectride instead of $NaBH_4$ the stereoselectivity was effectively reversed to provide the opposite diastereomer product in high yield and selectivity. The condensation of **53** with 2-methylpropane-2-sulfinamide **56** was achieved in the presence of titanium(*IV*)ethoxide {$Ti(OEt)_4$} to isolate *N*-[(1*E*,*Z*)-2,3-dihydro-1*H*-inden-1-ylidene]-2-methylpropane-2-sulfinamide **57**. It was reduced by $NaBH_4$ to isolate *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]-2-methylpropane-2-sulfinamide **58**. The use of *L*-Selectride for the reduction of **57** had resulted in the formation of *N*-[(1*S*)-2,3-dihydro-1*H*-inden-1-yl]-2-methylpropane-2-sulfinamide **59**. Both **58** and **59** distinctly can be brought under the influence of hydrochloric acid to isolate respective **1**-*R* isomer and **1**-*S* isomer [49].

Numerous synthetic pathways were disclosed to prepare ***RM*** through the formation of **1**-*R* isomer or ***R***. The adopted methodologies includes many patents, a few sectorial pathways are; the resolution driven chiral acids [41, 50], hydrosilylation by the use of chiral rhodium and ruthenium catalysts [51-53], asymmetric synthesis using chiral moieties [49, 54-57], biocatalyst based deracemization with cyclohexylamine oxidase (CHAO) [58], kinetic or dynamic kinetic enzymatic resolution [48, 59-62] and configuration inversion [40]. To overcome the past chemistry and process related issues, **Fonseca T de S** & coworkers had reported a lipase driven chemoenzymatic route to prepare ***RM***. The reduction of **53** under the impact of $NaBH_4$ in methanol gave (*R*,*S*) 2,3-dihydro-1*H*-inden-1-ol **60**. It was acetylated and hydrolyzed in the presence of lipase in hexane to obtain **23**. Further reaction of **23** gave (1*R*)-1-azido-2,3-dihydro-1*H*-indene **62**, it was then converted to **1**-*R* isomer. Addition of

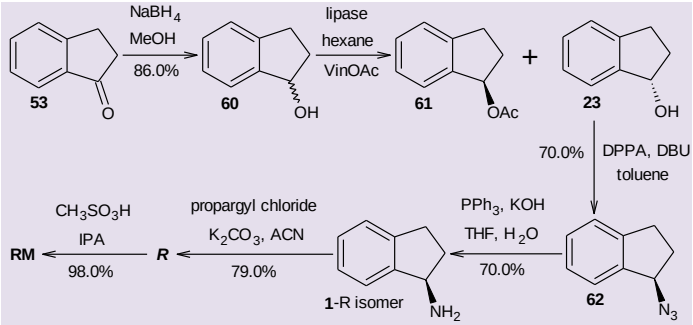
propargyl chloride to **1**-*R* isoler in the presence of K_2CO_3 and acetonitrile gave ***R***. It was treated with methanesulfonic acid in isopropyl alcohol resulted in formation of ***RM***. The disclosed biocatalytic process was very effective to impart *R*-configuration by lipase-mediated kinetic resolution [63]. This work was more inspired by the initiatives earlier by **Fernández R** & coworkers [64] and **Lin FL** & coworkers [65]. A review article by **Carvalho ACL de M** & coworkers had covered all the disclosures from 2007-2015 regarding the lipase mediated synthesis of drug molecules [66].



Scheme 3a: Disclosed route of synthesis to obtain *RM* from 52 as per [48].



Scheme 3b: Disclosed route of synthesis to isolate pure isomeric forms if 1 as per [49].



Scheme 4: Disclosed route of synthesis to isolate RM from 53 as per [63].

Sousa CAD & coworkers had reported the chemical/enzymatic resolution driven synthetic route to prepare enantiomerically pure propargyl ethers {(7*R*)-7-(prop-2-yn-1-yloxy)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine} **63** and {(7*S*)-7-(prop-2-yn-1-yloxy)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine} **64**. The importance of chiral center in ***R*** for the biological activity had influenced the isolation of these enatiomers in pure form [67]. The same team had earlier disclosed the synthesis of racemic mixture of the present disclosed compounds [47].

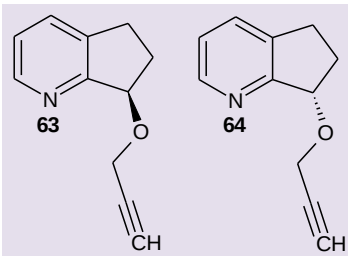


Figure 12: Rasagiline related compounds as per [67].

Rizzo-Aguiar F & coworkers had demonstrated the synthesis and characterization of some analogues of ***R***. The isolated compounds had 1-pyrindane moiety at C-7 position to have the respective propargyl **48** and isobutyl **67** ethers, propargyl **50**, n-propyl **68**, isopropyl **69** and cyclopropyl **70** amines and *N*,*N*-dimethyl **65** and diethylcarbamoyl **66** derivatives [68].

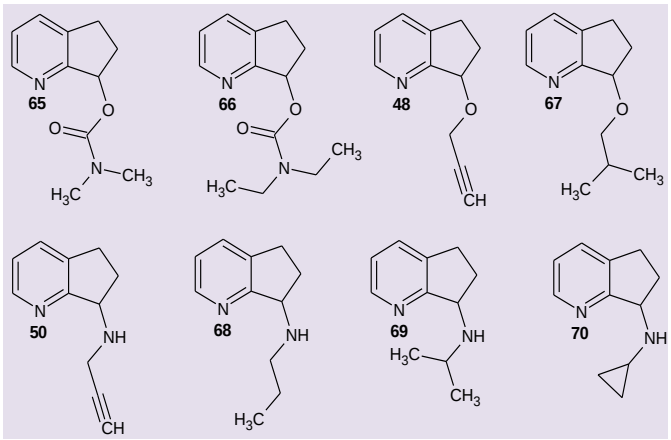
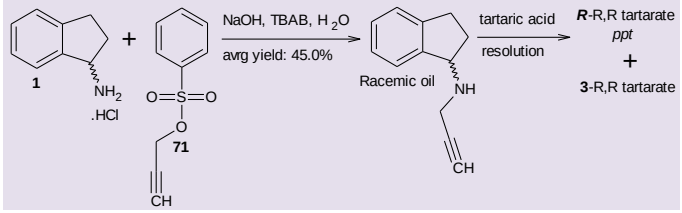


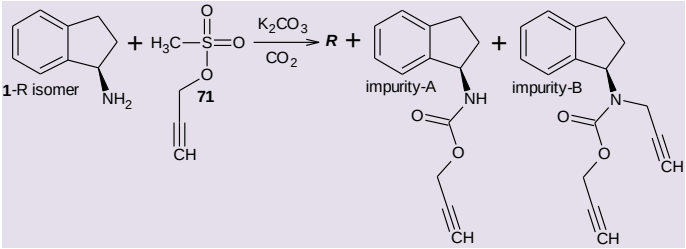
Figure 13: Rasagiline related compounds disclosed as per [70].

Aguilar N & coworkers had reported the synthesis of the *R*,*R*-tartrate salt of ***R*** using simple, abundant and inexpensive chemicals. It was developed with an aim for the practice at routine lab sessions (4 h) of undergraduates. The work involves the condensation of 1 with propargyl benzenesulfonate 71 under alkaline medium in the presence of phase transfer catalyst to obtain the racemic oil of drug. The crude oily mass was dissolved in methanol/isopropyl alcohol and treated with *R*,*R* tartaric acid to isolate the solid ***R***-*R*,*R* tartarate and the other diasteriomer **3**-*R*,*R* tartarate will be in the mother liquor [69].



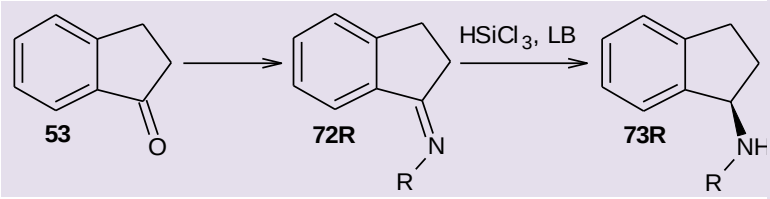
Scheme 5: Simple route of Rasagiline synthesis from 1 as per [69].

An extended work of the past disclosure [70], **Sun Y** & coworkers had disclosed the identification, characterization and synthesis prop-2-yn-1-yl (1*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamate (impurity-A) and prop-2-yn-1-yl (1*R*)-2,3-dihydro-1*H*-inden-1-yl(prop-2-yn-1-yl)carbamate (impurity-B) of ***R***. It was prepared and isolated by the reaction of **1**-*R* isomer with prop-2-yn-1-yl methanesulfonate **71** [71].



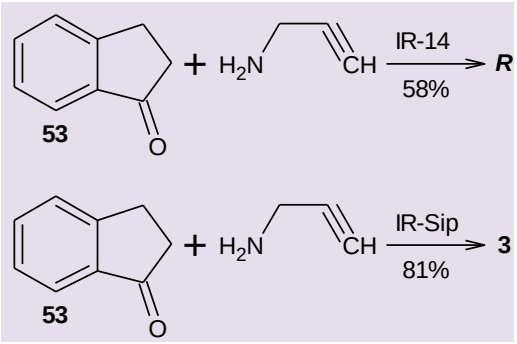
Scheme 6: Disclosed route of synthesis to isolate Rasagiline impurities from 1-*R* isomer as per [71].

Brenna D & coworkers had illustrated the flow process to isolate **1**-*R* isomer from **53** via imine formation **72R** and its stereo-selective metal free reduction **73R** [72].



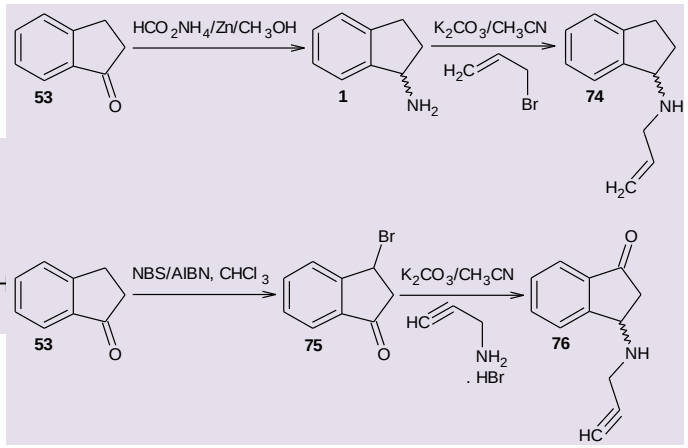
Scheme 7: Preparation of 1-*R* isomer from 53 as per [72].

Matzel P & coworkers had reported the synthesis of ***R***, **3** and other compounds (selegiline and pramipexole) in a single step asymmetric synthesis by reductive amination in the presence of imine reductases (IRs). This method is an efficient route for the synthesis of pharmaceutically active scaffolds comprising chiral secondary and tertiary amines [73].

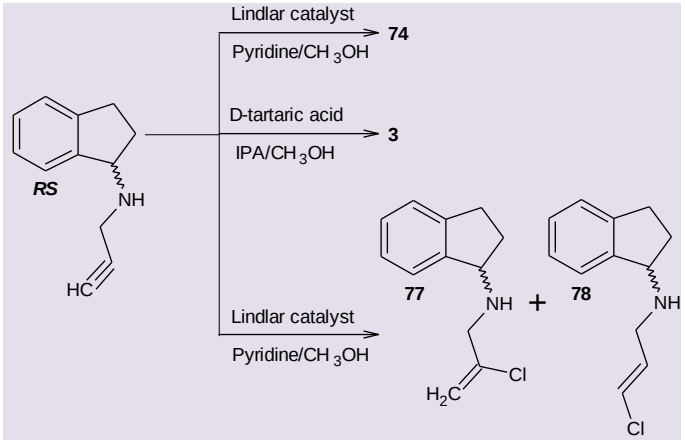


Scheme 8: Synthesis of Rasagiline & its *S*-isomer from 53 as per [73].

Raju NM & coworkers had reported the synthesis and structural elucidation of some major impurities of ***R***. Treatment of **53** with ammonium formate (HCO_2NH_4) and reduction from zinc dust gave **1**. The addition of 3-bromoprop-1-ene to **1** in the presence of potassium carbonate in acetonitrile had resulted in the formation of *N*-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-amine **74** (low yield and purity). In another example, **53** in chloroform was treated with *N*-bromo succinamide in the presence azobisisobutyronitrile to get 3-bromo-2,3-dihydro-1*H*-inden-1-one **75**. It was condensed with prop-2-yn-1-amine hydrobromide in the presence of potassium carbonate in acetonitrile to obtain 3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-one **76**. In another demonstration, ***RS*** was treated with Lindlar's catalyst in the presence of pyridine to isolate **74** (good yield and purity). Similarly, the treatment of ***RS*** with D-tartaric acid in alcohol medium resulted in the isolation of **3**. In line to the context, treatment of ***RS*** with concentrated hydrochloric acid gave two products like *N*-(2-chloroprop-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-amine **77** and *N*-[(2*E*,*Z*)-3-chloroprop-2-en-1-yl]-2,3-dihydro-1*H*-inden-1-amine **78** [74].



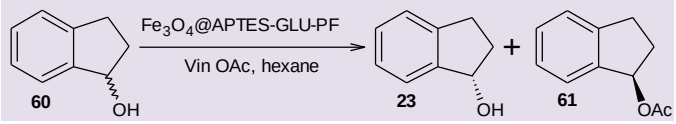
Scheme 9a: Synthesis of Rasagiline related compounds as per [74].



Scheme 9b: Synthesis of Rasagiline related compounds as per [74].

Sun H & coworkers had reported a review article about the use of various biocatalysts like reductases, oxidases, hydrolases, lyases, isomerases and transaminases for the preparation of active pharmaceutical ingredients including ***R*** [75]. This work includes the details furnished in the previous disclosure regarding the chemo-enzymatic pathway to synthesize ***R*** [63]. **Albarrán-Velo J** & coworkers had

contributed a review article regarding the use of bio-catalysts for the stereo-selective asymmetric synthesis of active pharmaceutical ingredients [76]. This work had highlighted some of the past initiatives [66, 67, 73] towards the synthesis of ***R*** via bio-catalysm pathway. **Galvão WS** & coworkers had reported the kinetic resolution of secondary alcohols (including **60** to isolate the intermediate for ***R*** synthesis) using nano-hydrid bio-catalysts [77].



Scheme 10: Resolution pathway to isolate 23 and 61 from 60 as per [77].

Xiao X & coworkers had demonstrated the design, synthesis and biological activity estimation of several derivatives of ***R*** having various linkers like -OCH_2-, -SCH_2-, -OCH_2CH_2-, -OCH_2CH_2O-, -$OCH_2CH_2CH_2O$- etc. This work had established **79** (D14) as the promising derivative with a similar inhibitory activity as ***R*** with an improved iso-form selectivity [78].

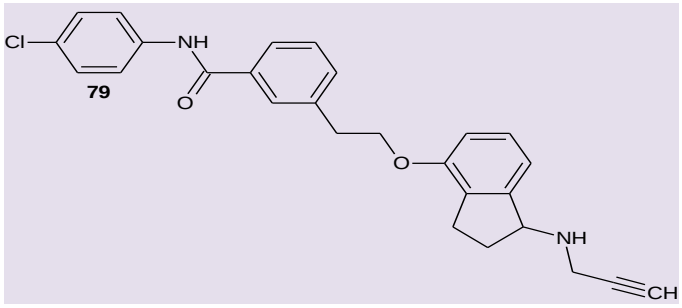
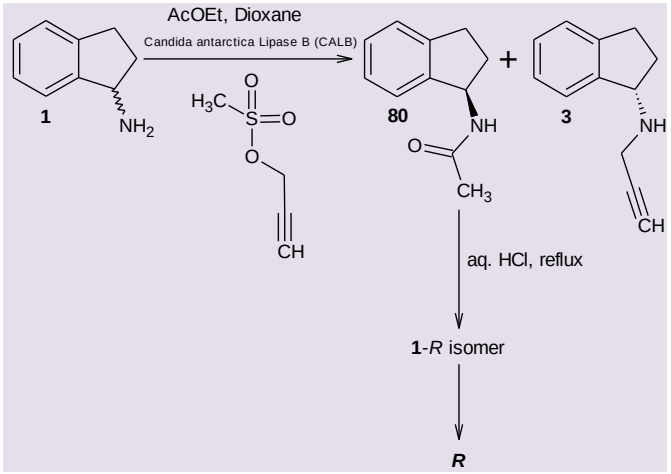


Figure 14: Rasagiline related compound 79 disclosed as per [78].

Pérez-Venegas M & coworkers had the use of Candida antarctica Lipase B (CALB) in the kinetic resolution of racemic chiral amines. This work had contributed to an efficient and easily scalable process to manufacture ***R*** with high chiral purity. This disclosure involves the conversion of **1** to **3** and *N*-[(1*R*)-2,3-dihydro-1*H*-inden-1-yl]acetamide **80** by the use of ethyl acetate and prop-2-yn-1-yl methanesulfonate. Aqueous HCl treatment to **80** and then the reaction with prop-2-yn-1-yl methanesulfonate gave ***R*** [79].

Avila-Ortiz CG & coworkers had reported a review article regarding the utility of mechanochemistry in enantio-selective synthesis. This work had emphasized the role of enzymes for the resolution of amino acids and amines [80], thus covering the past disclosure to prepare ***R*** [79]. **El-Shorbagi A-N** & coworkers had contributed a comprehensive review article on the management of Parkinson's disease (PD), enriched with drug discovery and pharmacological approaches of numerous PD specific drugs [81]. **Guieu B** & coworkers had demonstrated the synthesis, characterization and biological activity studies of racemic trans-Propargylamino-Donepezil **81** [82].



Scheme 11: Synthesis of *R* from 1 as per [79].

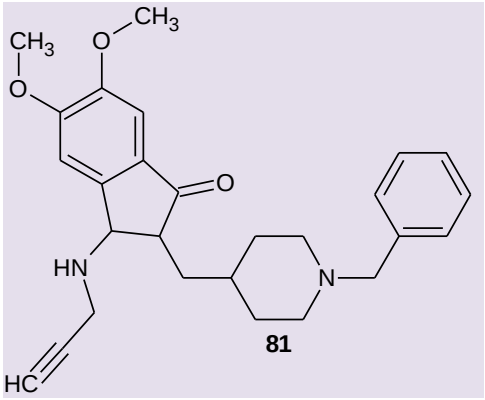
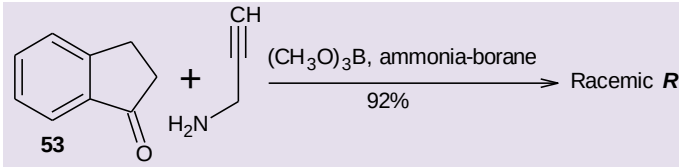


Figure 15: Rasagiline related compound 81 disclosed as per [82].

Li J & coworkers had illustrated the synthesis of chiral helic[1]triptycene[3]arenes and their enantio-selective recognition towards chiral aminoindan groups like **1** *R*-isomer, **1** *S*-isomer, ***R*** and **3** [83]. **Ramachandran PV** & coworkers had reported the synthesis of racemic ***R*** from **53** using the specific catalyst system {$(CH_3O)_3B$ and ammonia-borane} [84].



Scheme 12: Synthesis of racemic Rasagiline from 53 as per [84].

Ying P & coworkers had reported a review article regarding the pathway of liquid-assisted grinding mechanochemistry in the synthesis of active pharmaceutical ingredients. This article had covered the preparation of ***R*** and its *S*-isomer **3** from **1** [85]. **Zhang K** & coworkers had demonstrated the use of AcRedAm through rational design to obtain highly stereo-selective mutants. The best mutant formed could synthesize ***R*** from **53** in moderate yield with high enantiomeric purity [86]. **Dugarte-Dugarte AJ** & coworkers had illustrated the characteristic hydrogen bonding patterns and C-H....π interactions in the structure of ***RM*** was

determined using laboratory and synchrotron X-ray powder diffraction data aided with DFT calculations [87].

Summary

This review contribution was empowered with twelve reaction schemes (**Scheme 1** to **12**) being furnished for a better understanding of the synthetic pathways disclosed by various researchers. Similarly, eighty one compounds (**Figure 1** to **15**) were sequentially numbered to provide a systematic flow for the disclosed compounds related to ***R***. In most of the circumstances, academic journal disclosures are given the priority during the literature survey by excluding the contents published in patents. Hence, an exclusive patent focused contribution was furnished towards the synthesis of ***R*** [11]. This review article was focused mainly on the academic disclosures towards the synthesis of ***R*** and its close resemblance scaffolds.

CONCLUSION

This review article provides a glimpse of disclosed details in prior arts towards the synthesis of Rasagiline and some of its close resemblance scaffolds. This work had given the importance to exfoliate the disclosed information from the academic journals and hence patents are intentionally excluded. This work could serve as a vital template for the researchers around the globe to design the synthesis of scaffolds related to Rasagiline core moiety. In recent times, special emphasis was given by the researchers to adopt green chemistry pathway for the synthesis of Rasagiline with high enantio-selectivity.

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