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Review Article

A Synthetic Approach to Parkinson's Disease Drugs: Pramipexole and Rotigotine

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Abstract

In recent years, there has been numerous notable changes in Parkinson's disease medication. Researchers have produced new medications and gained a firm understanding of how to employ existing treatments. This has made a major impact on the lives of those suffering from the condition. Parkinson's medicine is used to treat the symptoms by compensating for the brain's loss of dopamine. Medication, particularly in the early stages of Parkinson's disease, can significantly lessen symptoms. This review displays one of the main categories of the antiparkinson agents, as it focuses on the synthetic methodology of two important dopaminergic medications namely; pramipexole and rotigotine.

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Introduction

A neurodegenerative condition with a typical appearance between the ages of 55 and 65 is Parkinson's disease (PD). Both motor and non-motor symptoms gradually worsen, which has a significant impact on a person's life. There is no known cure for Parkinson's disease, although several treatments have been established to aid control its symptoms [1]. There are various PD subtypes. Every one of them has its own unique set of factors and symptoms**.** Early-stage symptoms include resting tremor, bradykinesia, postural and muscle deformities and speech difficulties [2]. Late-stage motor characteristics are among the other symptoms in PD [3]. Common non-motor symptoms have been disregarded in preference of motor symptoms, which are the conventional key indicators of PD [4,5]. Non-motor symptoms can occur at any stage of Parkinson's disease, making them possible early biomarkers for the disease even though they are most frequently studied in more severe stages [6,7]. These symptoms can significantly lower quality of life, so traditional non-motor treatments concentrate on improving accessibility. New treatments are being developed, but more research is still required because PD treatments largely emphasise motor symptoms [8]. Dopamine levels in the caudate nucleus and putamen have decreased, according to biochemical studies; PD is generally regarded as a disease of the neuronal system, which primarily affects the nigrostriatal dopaminergic system (Figure 1) [9]:

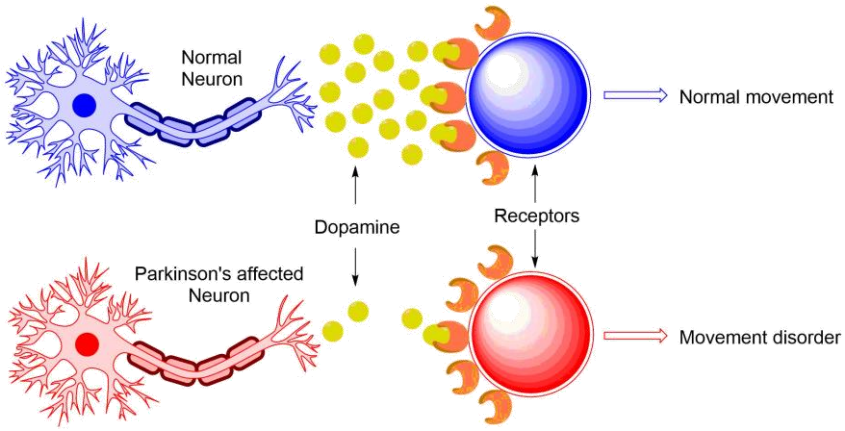


Figure 1. Comparison between dopamine levels and their effects on movement in the normal neuron (blue) and Parkinson’s affected neuron (red)

Two major pathological processes that are the foundation of this disease's diagnosis are the early, selective degeneration of dopamine neurons and the build-up of Lewy bodies, which are made of misfolded a-synuclein and accumulate in various body systems of Parkinson's patients [1]. Communication with neurons in the basal ganglia is aided by the release of the neurotransmitter dopamine by neurons of the substantia nigra. This allows for fine tuning of an organism's motions. Gradual degeneration of substantia nigra neurons reduces the amount of dopamine accessible for neurotransmission in the corpus striatum [10]. Dopamine agonists are commonly used as the initial therapy alternatives rather than L-DOPA because early-onset has a slower disease progression and is more likely to acquire L-DOPA-related dyskinesia. L-DOPA may not always need to be avoided when treating early-onset PD, according to recent research [11]. Though the specific origin of Parkinson's disease has not been determined, advances in treatment have been made. There are four categories of antiparkinson drugs: dopaminergic

medications, monoamine oxidase inhibitors (MAOIs), catechol O-methyltransferase inhibitors (COMT) and anticholinergics. This review will highlight two of these drugs from the viewpoint of synthetic methodologies.

Pramipexole

(*S*)-N^6-propyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole-2,6-diamine

In terms of clinical usage, pramipexole serves as one of the most commonly prescribed dopamine agonists for the management of Parkinson's disease, and it may be taken alone or in combination with other medications. The non-ergoline aminobenzothiazole compound, Pramipexole, agitates only the dopamine D2-like receptor subclass, which consists of the D2, D3, and D4 receptor variants. Pramipexole is a distinct chemical in terms of its medicinal possibilities since it prefers D3 [12,13]. The D3 receptor focus holds significance for Parkinson's disease motor and psychological symptoms, bipolar and unipolar depression and restless leg syndrome. Pramipexole is primarily prescribed to treat the signs and symptoms of idiopathic Parkinson's disease, as well as the mild to severe indications of primary restless leg syndrome [14–16]. Pramipexole is administered as an early mono-therapy to individuals who have early Parkinson's disease and as an adjuvant therapy with levodopa in patients who have advanced Parkinson's disease [17]. Among the main therapeutic options for people with idiopathic RLS is Pramipexole because it is a long-acting dopamine agonist [18].

Chemically, the synthesis of pramipexole (**1**) and its hydrochloride salt **2** was primarily reported in a European patent in 1989 [19].

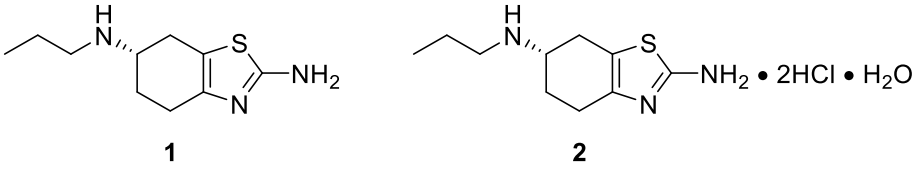
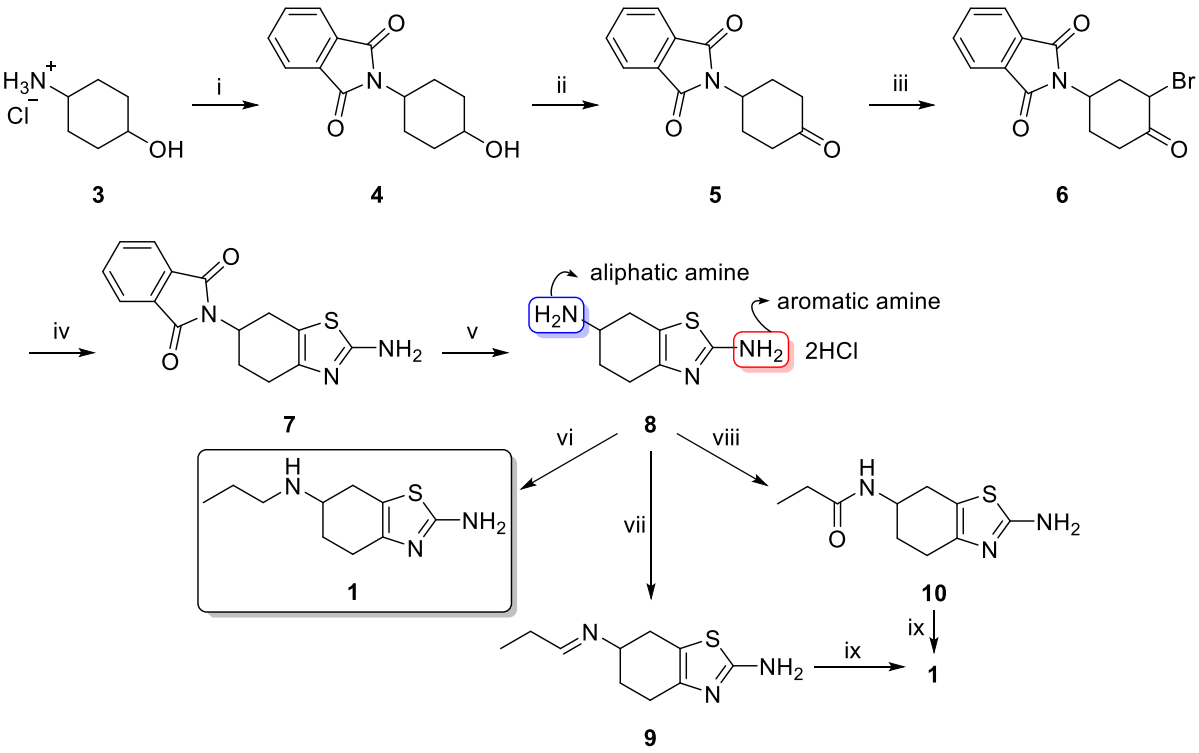


Figure 2. Structures of pramipexole and its hydrochloride salt

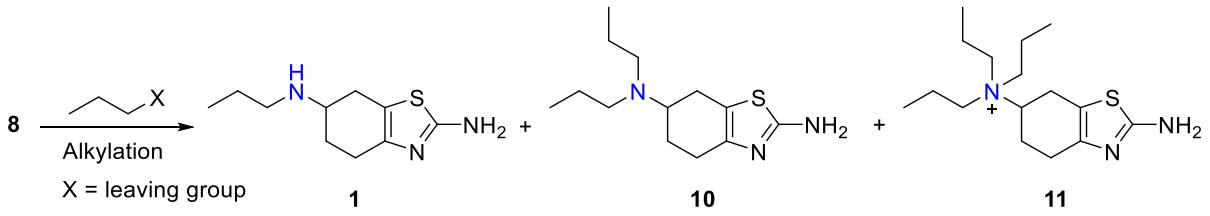
According to the aforementioned reference, the synthesis started with 4-aminocyclohexanol hydrochloride (**3**) through the protection of the amine group with phthalic anhydride in the aid of *N*,*N*-diisopropylethylamine DIPEA in toluene at reflux for 36 hours to produce compound **4** [20]. This was then oxidized with chromic acid which was formed *in situ* from potassium dichromate and sulfuric acid in chloroform and small amounts of water at 30 °C for three hours to produce ketone **5** [21] which was brominated at α-position by 36%HBr in glacial acetic acid at room temperature for two hours to give the α-bromoketone **6** [22]. Compound **6** underwent Hantzsch thiazole synthesis with thiourea and NaOH in ethanol at reflux for two hours follow by the treatment with HCl to afford aminobenzothiazole derivative **7** [23]. Then, hydrazine hydrate in ethanol at reflux for two hours were utilized to generate the diaminobenzothiazole **8** [20]. Depending on the differences in the basicity between aliphatic and aromatic amine [24] and to get the carbon skeleton of compound **8**, the alkylation of the aliphatic amine was achieved into three pathways: (vi) direct alkylation with *n*-propyl bromide to get compound **2**; (vii) imine formation with propionaldehyde to produce compound **9** followed by reduction with $LiAlH_4$ in dry THF; and (viii) acylation with propionyl chloride to afford compound **10** and followed by reduction using former conditions (Scheme 1):



Reagents and conditions: (i) Phthalic anhydride, DIPEA, toluene, reflux, 36 h; (ii) potassium dichromate, H_2SO_4, $CHCl_3$ / water, 30 °C, 3 h; (iii) 36% HBr / glacial HOAc, r.t., 2 h; (iv) thiourea, EtOH, NaOH, reflux, 5 h; (v) hydrazine hydrate, EtOH, reflux, 2 h, then HCl; (vi) *n*-propyl bromide, K_2CO_3, MeOH, reflux, 72 h; (vii) propanal, K_2CO_3, MeOH, 50 °C, 2 h; (viii) propionyl chloride, pyridine, DMAP, –10 °C–r.t.; 10 h; (ix) $LiAlH_4$, dry THF, reflux, 1 h.

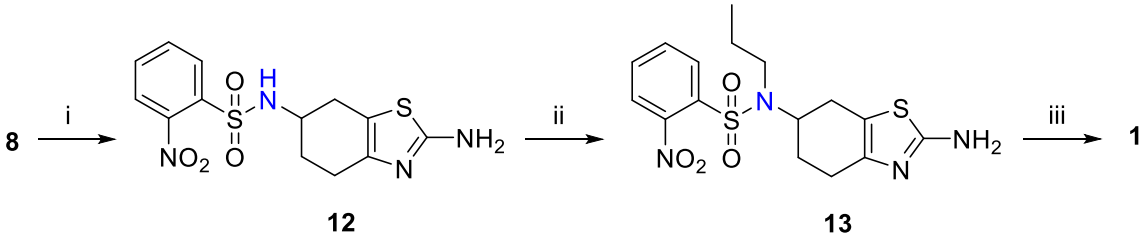
Scheme 1. Synthetic routes of pramipexole (1) from aminocyclohexanol (3)

In addition to the ambiguous details about the synthetic protocol, there were side products related to the enantiopurity of the desired isomer [25], which in turn resulted in low isolation of the preferred product yield. Another disadvantage arose from the alkylation pathway (i) is the peralkylation of the aliphatic amine to produce the tertiary **11** amine or the quaternary ammonium salt **12** (Scheme 2) [26], that could generate pharmacologically inactive compounds due to the absence of the proton on the aliphatic amine.



Scheme 2. The possible products of the alkylation of compound 8

Another selective route of the alkylation of diamine **8** utilizing Fukuyama protocol was reported [27]. The treatment of compound **8** with 2-nitrobenzenesulfonyl chloride in THF at 0°C to r.t. in the aid of triethylamine TEA afforded the sulfonamide derivative **12** which subsequently reacted with *n*-propyl bromide in the presence of excess of K_2CO_3 in DMF at 60°C overnight to yield *N*-propyl sulfonamide derivative **13** [28]. This was eventually deprotected through the reaction with thioglycolic acid in the assistance of potassium carbonate or lithium hydroxide in DMF at r.t. overnight to obtain compound **1** (Scheme 3):



Reagents and conditions: (i) 2-Nitrobenzenesulfonyl chloride, TEA, THF, 0 °C-r.t.; (ii) *n*-propyl bromide, K_2CO_3, DMF, 60°C, overnight; (iii) thioglycolic acid, K_2CO_3 or LiOH, DMF, r.t., overnight.

Scheme 3. Alternative approach for the alkylation of the diamine 8

It was found that the most active form of aminothiazole-containing dopaminergic are (*S*)-enantiomers such as compound **1**. However, (*R*)-enantiomers can be available as a by-product during the synthesis or oxidation of the final drug. Hu *et al*. [29], assigned and synthesized the possible impurities found in the active pharmaceutical ingredient (API) and those found in the tablet. These impurities are ketone derivatives **14**, hydroxy compounds **15**, dialkylated compounds **16** dimers **17**, and (*R*)-enantiomers **18** of compound **1** or compound **2** (Figure 3).

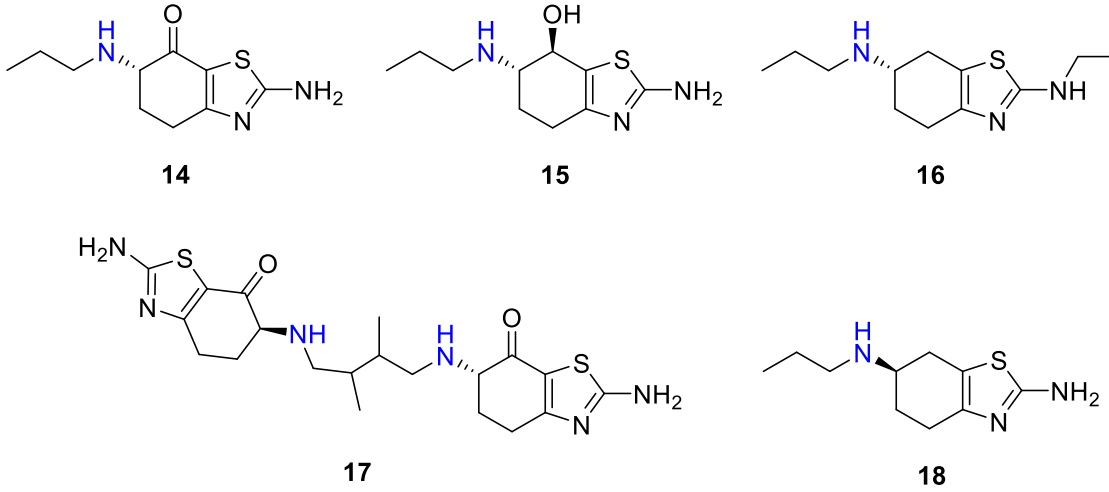
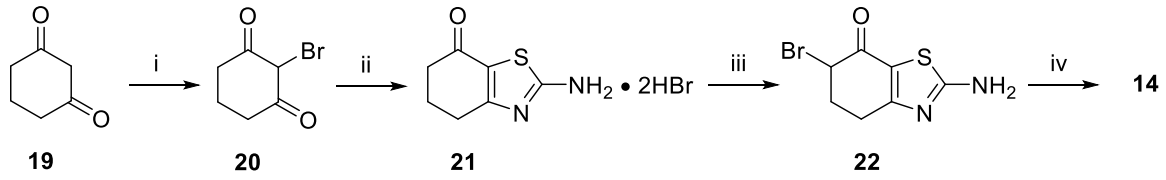


Figure 3. Impurities of compound 1 or compound 2 found in the active pharmaceutical ingredient (API) and the tablet.

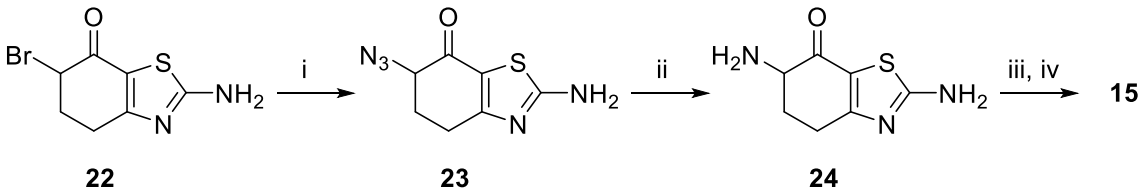
For example, compound **14** has been synthesized starting from 1,3-cyclohexanedione (**19**) which was experienced bromination to produce 2-bromo-1,3-cyclohexanedione (**20**) [30]. This was cyclized with thiourea followed by α-bromination and substituted reaction to achieve the target compound **14** (Scheme 4):



Reagents and conditions: (i) Bromination; (ii) cyclization; (iii) bromination; (iv) substitution with *n*-propyl amine

Scheme 4. Synthesis of compound 14

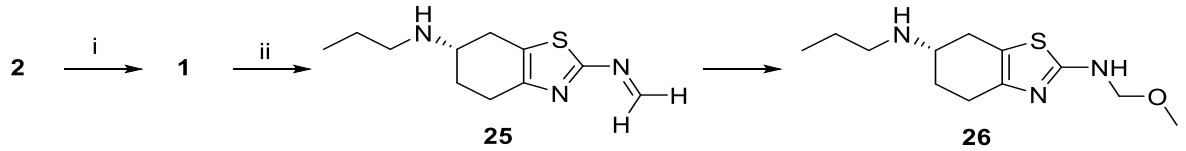
The replacement of bromide of adduct **22** by sodium azide afforded azido derivative **23**. This was reduced by the catalytic hydrogenation to obtain diamine **24** which was reacted with propionaldehyde and selectively reduce by $NaBH_4$ to give compound **15** (Scheme 5):



Reagents and conditions: (i) NaN_3; (ii) H_2, Pd/C; (iii) propionaldehyde (iv) $NaBH_4$

Scheme 5. Synthesis of hydroxy derivative 15

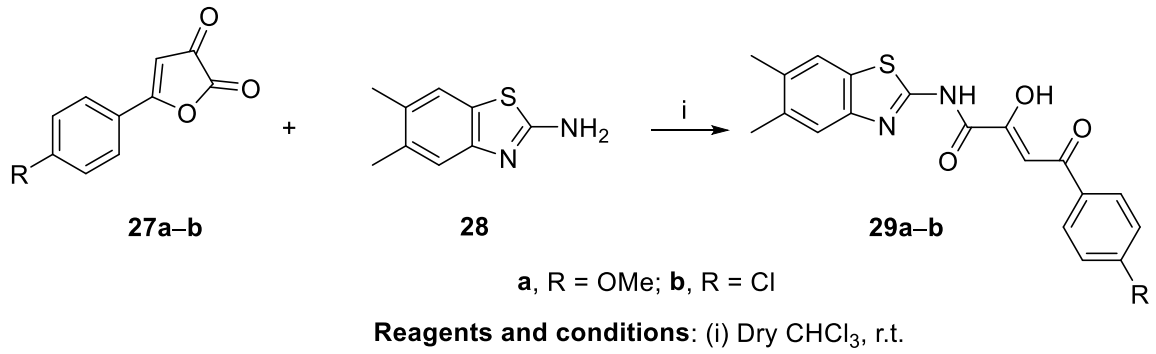
Al-Rifai *et al*. [31] identified another impurity **26** resulting from the degradation of pramipexole hydrochloride salt **2**. This impurity has a relative retention time of 0.88 compared to compound **2** in HPLC. In this study, the derivative **26** was synthesized (Scheme 6) and fully characterized and its degradation route had also been suggested. In the synthetic pathway, the free amine **1** was liberated from the hydrochloride salt **2** by the treatment with alkaline solution which was then treated with formaldehyde to give the corresponding imine **25**. This subsequently converted to derivative **26** when the reaction last for ten hours in methanol.



Reagents and conditions: (i) 2.0 N NaOH; (ii) formaldehyde, AcOH, MeOH, r.t., 10 h

Scheme 6. Synthesis of the impurity 26

It is worth to mention that pramipexole derivatives exhibit an antibacterial activity. Pulina *et al*. [32], synthesized a library of 4-aryl-*N*-(5,6-R-benzo[*d*]thiazol-2-yl)-2-hydroxy-4-oxobut-2-enamides from the reaction of 5-arylfuran-2,3-diones with 5,6-R-benzo[*d*]thiazole-2-amines in dry chloroform at ambient temperature. The antibacterial and the analgesic activities of the synthesized derivatives have been screened and two of these derivatives **29a** and **29b** (Scheme 7) demonstrated potent antibacterial activity against *S. aureus* and *E. coli* and analgesic activity compared to various controls.



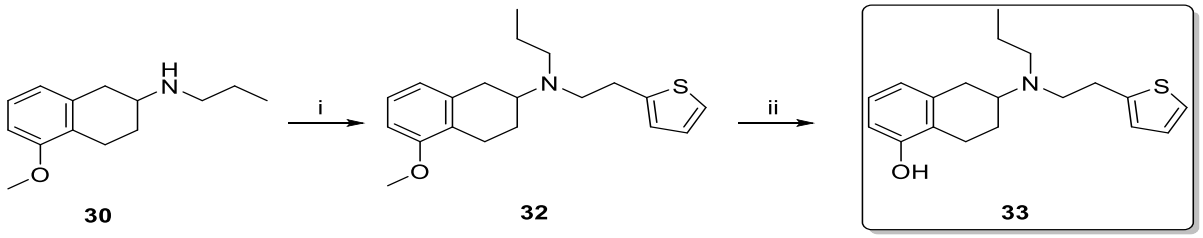
Scheme 7. Synthesis of pramipexole derivatives 29a and 29b

Rotigotine

(*S*)-6-(propyl(2-(thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol

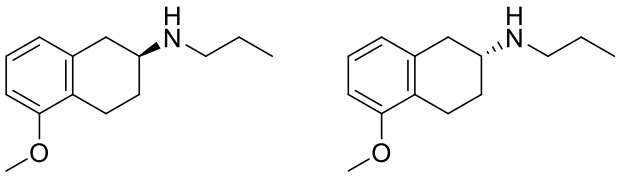
Rotigotine seems to be a recently approved non-ergoline medicine that operates as a dopamine agonist to manage Parkinson's disease and restless legs syndrome. It was produced by Aderis Pharmaceuticals and leased to UCB S.A. in 2006. It has been used in Europe since 2007 [33]. Rotigotine generally prefers D2 and D3 receptors, and a relative more powerful D1 receptor component would be necessary in a hypothesized higher standard of rotigotine if opposed to apomorphine and dopamine itself [34].

The synthesis of rotigotine (**33**) was initially describe in 1985 by Horn *et al*. [35] in two steps by the reaction of 2-(*N*-*n*-propylamino)-5-methoxytetralin (**30**) with 2-thiopheneacetic acid (**31**) in the presence of trimethylaminoborohydride in dry xylene at reflux for 18 h under inert atmosphere to afford 2-(*N*-*n*-propyl-*N*-2-thienylethylamino)-5-methoxytetralin (**32**) which was treated with boron tribromide in dichloromethane at room temperature for 90 min to produce compound **33** in 55% yield (Scheme 8):



Scheme 8. First synthesis of rotigotine (**33**)

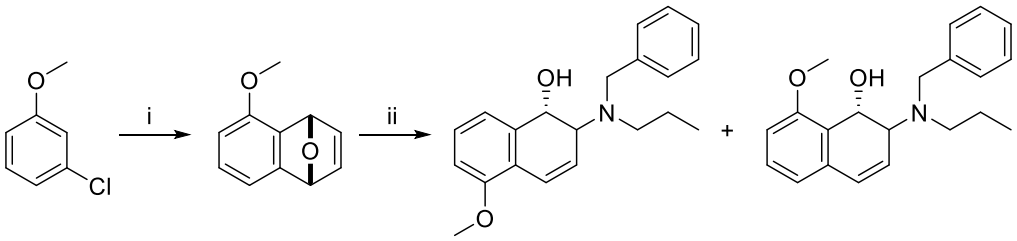
However, the synthesis and separation of the racemic amines **30a** and **30b** (Figure 4) are crucial to achieve compound **33**. Most of the reported literatures describe this aim as the maximum theoretical yield of these synthons did not exceed 50% [36].



30a **30b**

Figure 4. Structure of chiral amines 30a and 30b

Thus, the attention has been drawn to synthesize **38a** precursors or their derivatives and separate them to obtain the highest active compound. Webster *et al*. [37], reported the synthesis of rotigotine (**33**) starting from (1*R*,4*S*)-5-methoxy-1,4-dihydro-1,4-epoxynaphthalene (**36**) in a multi-steps protocol. At the beginning, oxabicyclic alkene **36** was synthesized from the reaction of 3-chloro-methoxybenzene (**34**) with furan (**35**) in the presence of diisopropylamine and *n*-BuLi in THF at −10 °C for four hours. Then, the rhodium(I) salt-assisted ring-opening reaction of compound **36** with *N*-*n*-propyl-benzylamine (**37**) in the aid of catalytic amounts of (2*R*)-1-[(1*R*)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(diphenylphosphino)ferrocene **(*S*,*R*)-PPF-Pt-Bu$_2$** in tetrahydrofuran at 60 °C for 120 h produced approximately equimolar amounts of easily separable tertiary amines **38a** and **38b** in 50% and 44% yield respectively (Scheme 9). Noteworthy, both of these isomers undergo similar reaction, however, we will state the reactions of compound **38a** as it will eventually lead to rotigotine (**33**).

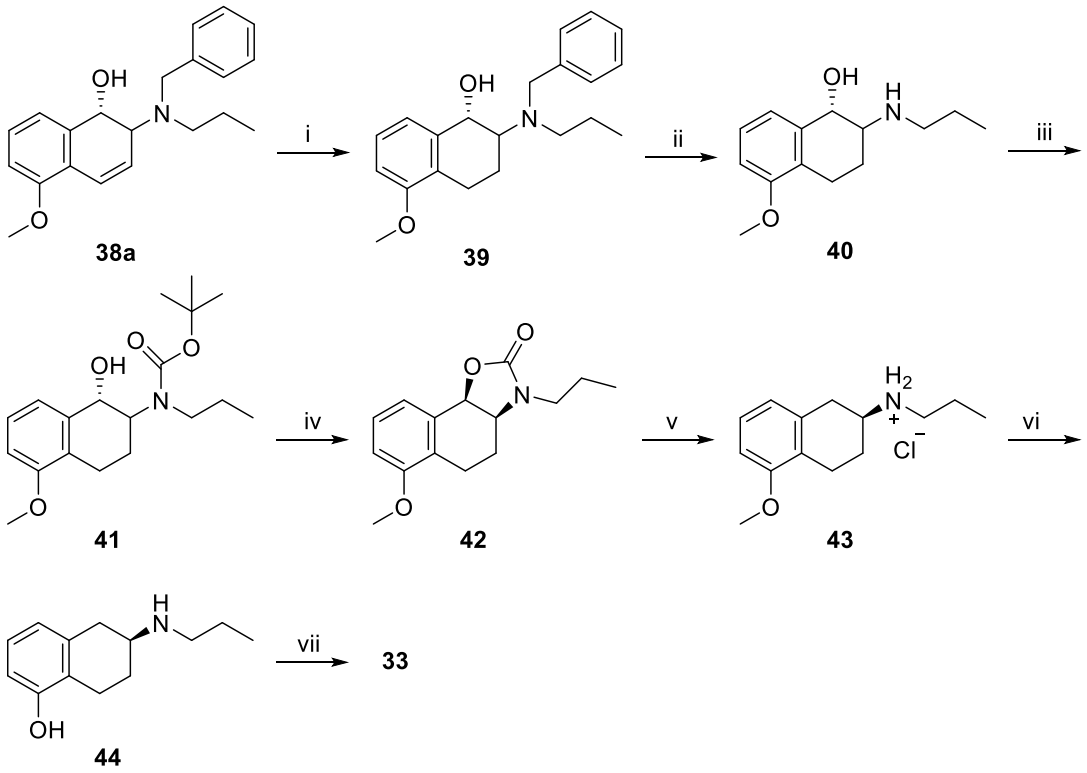


34 **36** **38a** **38b**

Reagents and conditions: (i) **35**, diisopropylamine, *n*-BuLi, THF, –10 °C, 4 h; (ii) **37**, [Rh(cod)$_2$OTf] (1 mol%), (*S*,*R*)-PPF-Pt-Bu$_2$ (1.5 mol%), THF, 60 °C, 120 h.

Scheme 9. Synthesis of compounds 38a and 38b

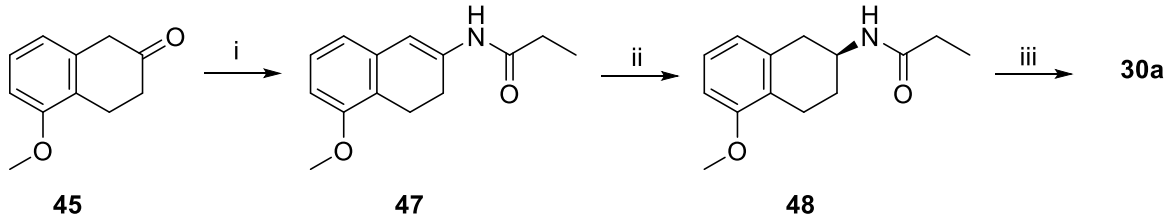
When derivative **38a** is treated with toluenesulfonyl hydrazide and sodium acetate in THF/water mixture at 80 °C for two hours, the double bond of the cyclohexene moiety is selectively reduced to give compound **39** which was catalytically hydrogenated to remove the benzyl group and resulted in secondary amine **40**. This was protected by *tert*-butyloxycarbonyl group (Boc) to give the protected amine **41** that was cyclized in iron-assisted reaction in DCM at room temperature for three hours to produce cyclic carbamate **42**. Another catalytic hydrogenation presence of 2N HCl and ethanol and at about 2.4 bars and room temperature afforded the hydrochloride salt **43** of amine **30a**. The final two steps were the hydrolysis of methoxy group at the aromatic moiety followed by the substitution reaction 2-(thiophen-2-yl) ethyl 4-methylbenzenesulfonate (**45**) to give rotigotine (**33**) (Scheme 10).



Reagents and conditions: (i) toluenesulfonylhydrazide, NaOAc, H_2O/THF, 80 °C, 2 h; (ii) H_2, 10%Pd/C, EtOAc, r.t., 6 h; (iii) Boc_2O, THF, 70 °C, overnight; (iv) $FeCl_3 \cdot 6H_2O$, DCM, r.t., 3 h; (v) H_2 (35 psi), 10%Pd/C, 2N HCl, EtOH, r.t., (vi) BBr_3, DCM, –10 °C–r.t., overnight; (vii) 2-(thiophen-2-yl)ethyl 4-methylbenzenesulfonate (**45**), Na_2CO_3, xylene, 10°C, 24 h.

Scheme 10. Chiral synthesis of rotigotine (33)

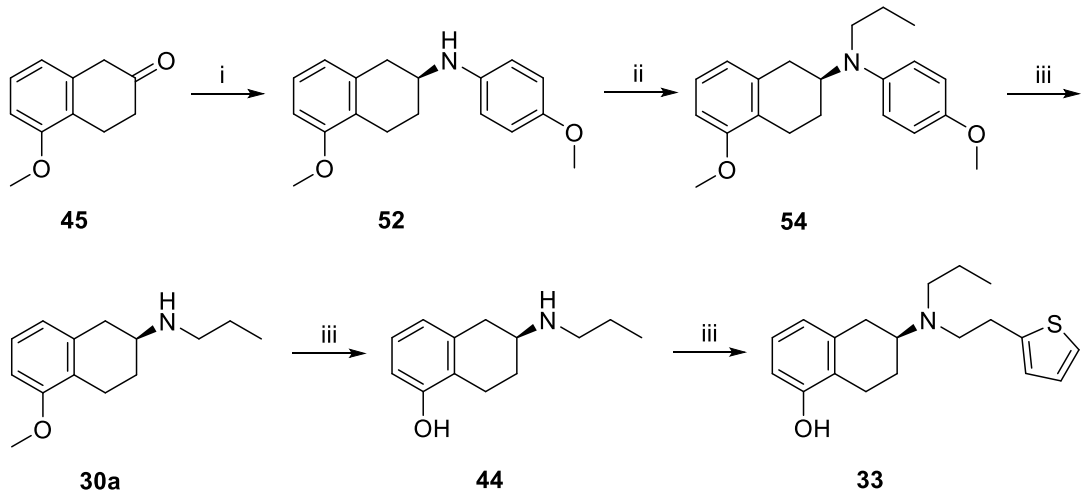
The skeleton of tetralone-based enamides is an alternative protocol to access rotigotine. For this objective, a gram-scale synthesis of enamide **47** was reported [38] through the acid-catalyzed reaction of 5-methoxytetralone (**45**) with propenamide (**46**) in toluene at 110 °C for 24 h. A variety of catalysts and conditions were then screened to achieve the optimum pathway for asymmetric reduction of the double bond on the cyclohexene ring. It was shown that ruthenium-catalyzed that amide **48** can be obtained in 91% enantiomeric excess (*ee*) when ruthenium-catalyzed hydrogenation in methanol at 25 bar and 30 °C for 18 hours was applied. Amide **48** was selectively reduced by sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in THF at reflux to achieve amine **30a** in 97% conversion (Scheme 11):



Reagents and conditions: (i) **46**, toluene, 110 °C, 24 h; (ii) H_2 (25 bar), [RuCl((*R*)-T-BINAP)2(μ-Cl)$_3$][NH_2Me_2], MeOH, 30 °C, 18 h; (iii) Red-Al, THF, reflux

Scheme 11. Asymmetric synthesis of amine 30a from 5-methoxytetralone (45)

Another enantioselective route for the synthesis of rotigotine (**33**) tetralones had been described by Park *et al*. [39]. They converted 5-methoxytetralone (**45**) to secondary amine **52** in 78% yield and 81% *ee* using Hantzsch ester **50** [40] and chiral phosphonic acid catalyst **51** in the aid of molecular sieve in toluene at room temperature for 20 hours. The reductive amination of propionaldehyde (**53**) with amine **52** in the presence of sodium cyanoborohydride in methanol at room temperature gave the tertiary amine **54** which was reacted with cerium ammonium nitrate CAN in a mixture of water/methanol 1:1 at ambient temperature gave the synthon **30a**. The treatment of this precursor with boron tribromide in methylene chloride at –40 °C overnight afforded compound **44**. This was reacted with thiophene derivative **45** in xylene at 140 °C for 24 hours to produce rotigotine (**33**).



Reagents and conditions: (i) **49**, Hantzsch ester **50**, chiral phosphoric acid **51**, 4 Å, toluene, r.t, 20 h; (ii) **53**, $NaBH_3CN$, MeOH, r.t., 12 h; (iii) $(NH4)_2[Ce(NO_3)_6]$, H_2O/MeCN 1:1, r.t., 5 h; (iv) BBr_3, DCM, –40 °C–r.t., overnight; (v) 2-(thiophen-2-yl)ethyl-4-methylbenzenesulfonate (**45**), Na_2CO_3, xylene, 140 °C, 24 h.

Scheme 12. Enantioselective synthesis of rotigotine (33) from 5-methoxytetralone (45)

Conclusion

It seems that the synthesis of pramipexole and rotigotine is easily to be achieved as their structures are accessible via different routes. However, both of them have N-n-propylcyclohexylamine moiety. There are two major challenges in their syntheses. First, the alkylation of the cyclohexylamine residue could result in multiple alkylation and the separation of isomers is rather challenging to get the enantiopure isomer for ligand-receptor binding. To avoid these difficulties, it is recommended to utilize the enantioselective protocols that including using chiral catalysts.

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