Synthesis of new molecules based on 1-pyrindane ring as a new strategy in the neurodegenerative diseases treatment

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Abstract: Neurodegenerative diseases are one of the major causes of death in aged population all over the world. The Alzheimer's disease (AD) is the most common amongst these, followed by the Parkinson's disease (PD). The existing therapies (**selegiline** and **rasagiline**, propargylaminic drugs usually used in PD treatment as monoamine oxidase-B inhibitors) are still very far from doctor and patient's expectations. In this way, the drawing of new therapeutical neuroprotective agents is a great challenge, in order to improve the effectiveness of the existing drugs, or to introduce new alternative therapies. In this work, we describe the synthesis of new propargylic derivatives based on 1-pyrindane ring as a new strategy in the treatment of neurodegenerative diseases. The synthesis was done in due to provide enough number of new compounds endowed with molecular diversity in the pentacyclic ring from 6,7-dihydro-5H-cyclopenta[b]pyridine, commercially available, and 2-bromo-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine, easily obtained after bromination of the product of the Sakurai-Midorikawa cyclization between cyclopentanone and ethyl acetoacetate in the presence of ammonium acetate. Classic synthetic methodologies were used, in order to prepare different chemical precursors which will enhance the chemical diversity. In a first step, racemic mixtures was obtained, the enantiomeric pure compounds can be achieved through chemical or enzymatic resolution of the racemates or through enantioselective synthetic processes.

Keywords: neuroprotection, pyrindanes, rasagiline agonists

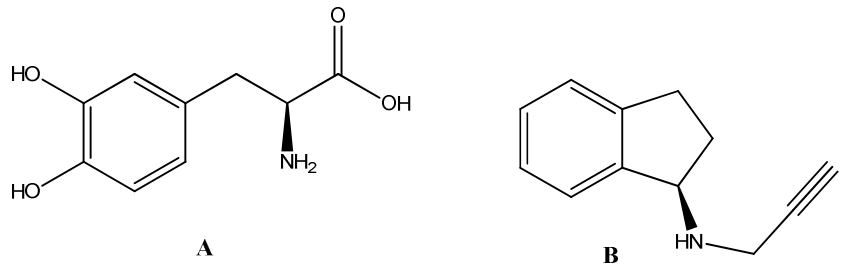
1. Introduction[1-5]

The technological advances of the last century brought an improvement in the life quality of people worldwide. In the field of medicine, this advance resulted in a significant increasing of life expectancy, which also brought health problems related to the aging of mankind. Among these problems are neurodegenerative diseases that, together with cardiovascular diseases and cancer are a first scale problem in developed countries and a major cause of morbidity and mortality in population. Parkinson's disease (PD) and Alzheimer's (AD) are progressive neurodegenerative disorders, which are traditionally considered as diseases of different identity. However, numerous clinical review papers demonstrate that DP, frequently associated to dementia, is accompanied by neuropathologic characteristics of AD.

So far, no drug has shown neuroprotective properties enough to slow the PD. Levodopa (Figure 1), a dopamine precursor, used for over 30 years to treat this disease, contributes to the symptoms reduction. Moreover, carbidopa and benzerazide (specific DOPA descarboxylase inhibitors), in a joint action, prevent levodopa degradation before it reaches the brain. Besides the development of new technology to improve levodopa action, were introduced alternative treatments for PD, as dopamine agonists (for example, ropinirole) and MAO-B inhibitors such as selegiline and rasagiline, which may be used alone or in combination with levodopa.

Rasagiline, *R*(+)-*N*-propargyl-1-aminoindane, is the result of researches that attempted to produce a selective inhibitor of MAO-B that did not provide toxic metabolites such as amphetamine and methamphetamine resulting from the selegiline metabolism. In this compound, (R) isomer of a racemic mixture, the propargyl group is responsible for the potent inhibitory activity against MAO-B and the neuroprotective properties. Its enantiomer is a weak inhibitor of MAO, however, has the same rasagiline's neuroprotective capabilities.

The two-way action of rasagiline - selective inhibition and neuroprotection - has encouraged the synthesis of new analogues which will be submitted to assays aiming to measure their inhibitory capacity against the MAO-A MAO-B, acetyl and butyrylcholinesterase (AChE and BChE), which will establish the therapeutic potential against the PD and AD, and in the near future may be useful in combating these diseases.



A B

Figure 1: Levodopa (A) and Rasagiline's (B) sctrutures

2. Methods and Experimental Procedures

All reagents were purchased from Fluka and/or Aldrich and were used as received, without further purification or distillation. The solvents were purified and dried according to the procedures described in Vogel, A.I., *A textbook of practical Organic Chemistry*, 2ª ed., Longmans, Green & Co., London, **1951**.

All compounds gave satisfactory ^{1}H-NMR (400 MHz), and ESI-MS spectral data.

General procedure for *N*-oxidation, with mCPBA - 2a (C_8H_9NO) – mCPBA (3.84 g; 17.1 mmol) was slowly added to a solution of **1a** (2.04 g, 17.1 mmol) in DCM (30 mL). The mixture was stirred at r.t. for 3 hours. The solvent was evaporated under reduced pressure and the crude purified by chromatographic column with AcOEt giving 2a (Rf 0.05; 2.30 g; 99%; mp 121-123 ºC) as a white solid. ^{1}H-RMN (CDCl3): δ = 8.01 (d, 1H, J 6.4 Hz); 7.09 (d, 1H, J 7.2 Hz); 7.04 (app t, 1H, J 6.4 Hz, J 7.4 Hz); 3.13 (t, 2H, J 7.6 Hz); 2.99 (t, 2H, J 7.6 Hz); 2.14 (qt, 2H, J 7.6 Hz). ESI-MS: calculated (M + H$^+$) 136.07, obtained 136.27. **2b** ($C_9H_{10}NOBr$) – Following the same procedure as above, with **1b** (1.03 g; 4.86 mmol) and mCPBA (0.88 g; 5.10 mmol). Flash chromatography with AcOEt afforded 2b (Rf 0.2, 1.0 g, 91%). 1H- RMN ($CDCl_3$): δ = 7.28 (s, 1H); 3.22 (t, 2H, J 8.0 Hz); 2.90 (t, 2H, J 8.0 Hz); 2.22 (s, 3H); 2.20 (qt, 2H). ESI-MS: calculated (M + H$^+$) for ^{79}Br 228,10; obtained for ^{79}Br 228.44, calculated for ^{81}Br 230,10; obtained for ^{81}Br 230.23.

Procedure for attainment of acetyl derivatives – 3a ($C_{10}H_{11}NO_2$) – A solution of 2a (1.66 g; 12.3 mmol) in Ac_2O (15 mL) was heated at 100 ºC. The mixture was stirred for 3 h, then the volume was reduced under reduced pressure. The crude was chromatographed in silica gel with AcOEt affording 3a (Rf 0.44, 1.57g, 75%) as a intense orange oil. ^{1}H-RMN ($CDCl_3$): δ = 8.50 (d, 1H, J 4.8 Hz); 7.57 (d, 1H, J 7.6 Hz); 7.18 (dd, 1H, J 7.6 Hz, J 4.8 Hz); 6.10 (dd, 1H, J 7.6 Hz, J 5,2 Hz); 3,04 (ddd, 1H, J 16,4 Hz, J 9,2 Hz, J 5,2 Hz); 2.89-2.82 (m, 1H); 2.65-2.57 (m , 1H); 2.08 (s, 3H); 2.06-1,99 (m, 1H). ESI-MS: calculated (M + H$^+$) 178.08, obtained 178.00. **3b** ($C_{11}H_{12}NO_2Br$) – From **2b** (1.0 g; 4.38 mmol) with Ac_2O (10 mL). Flash chromatography with AcOEt afforded **3b** (Rf 0.55; 0.83 g; 70%). ^{1}H-RMN ($CDCl_3$): δ = 7.23 (s, 1H); 6.01 (dd, 1H, J 7.6 Hz, J 4.4 Hz); 2.93 (ddd, 1H, J 16.0 Hz, J 8.8 Hz, J 5.2 Hz); 2.75 (ddd, J 16.4 Hz, J 8.4 Hz, J 5.2 Hz); 2.67-2.58 (m, 1H); 2.27 (s, 3H); 2.10 (s, 3H), 2.06-2.03 (m, 1H). ESI-MS: calculated (M + H$^+$) for ^{79}Br 270.14; obtained for ^{79}Br 270.06, calculated for ^{81}Br 272.14; obtained for ^{81}Br 271.91.

Procedure for hydrolysis with KOH – 4a (C_8H_8NOH) – To a solution of 3a (0.80 g; 4.45 mmol) in EtOH (2 mL), was added a solution of KOH (0.25 g; 4.45 mmol) in EtOH (5 mL). The mixture was stirred for 1 h at rt, then DCM (50 mL) and water (50 mL) were added. The resulting misture was extracted with DCM (2x50 mL) and the pooled organic layers were

washed with brine (50 mL). Removal of solvent left a crude that after chromatographed in slica gel with AcOEt afforded 4a (Rf 0.2; 0.55 g, 90%, mp 80-83 °C) as a light brown oil. ^{1}H-RMN ($CDCl_3$): δ = 8.38 (s, 1H); 7.56 (d, 1H, J 7.6 Hz); 7.13 (dd, 1H, J 7.6 Hz, J 5.2 Hz); 5.26-5.22 (m, 1H); 3.98 (sl, 1H); 3.08-3.00 (m, 1H); 2.85-2.76 (m, 1H); 2.58-2.48 (m, 1H); 2.11-2.01 (m, 1H). ESI-MS: calculated (M + H^+) 136.07, obtained 136.07. **4b** ($C_{11}H_{12}NO_2Br$) – From **3b** (0.30 g; 1.11 mmol) with KOH (0.16 g; 2.79 mmol). Flash chromatography with AcOEt afforded **4b** (Rf 0.4; 0.204 g; 80%). ^{1}H-RMN ($CDCl_3$): δ = 7.17 (s, 1H); 5.18 (dd, 1H, J 7.4 Hz, J 5.8 Hz); 3.29 (sl, 1H); 2.92 (ddd, 1H, J 16.4 Hz, J 9.2 Hz, J3 4.0 Hz); 2.71-2.64 (m, 1H); 2.57-2.48 (m, 1H); 2.25 (s, 3H); 2.07-2.02 (m, 1H).

Procedure for Swern's oxidation – 5a (C_8H_7NO) – To a cooled (-78 °C) solution of $(COCl)_2$ (0.79 mL; 9.01 mmol) in dry DCM (20 mL) was added a solution of DMSO (1.28 mL; 18.0 mmol) in dri DCM (5 mL). The mixture was stirred for 15 min under argon atmosphere, then a solution of **4a** (1.22 g; 9.01 mmol) in Et_3N (5.0 mL; 36.0 mmol) was added dropwise. After 24 h, the system was cooled (ice bath) and water (40 mL) was added. The resulting mixture was extracted with DCM (2x50 mL) and the pooled organic layers was washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), and dried over Na_2SO_4. The purified (DCM/MeOH 19:1) crude gave 5a (Rf 0.45; 0.48 g; 40%; mp 98-101 °C) as a greenish solid. ^{1}H-RMN ($CDCl_3$): δ = 8.78 (d, 1H, J 4.5 Hz); 7.90 (d, 1H, J 7.4 Hz); 7.46 (dd, 1H, J 7.8 Hz, J 4.5 Hz); 3.19 (app t, 2H, J 6.0 Hz); 2.76-2.79 (m, 2H).

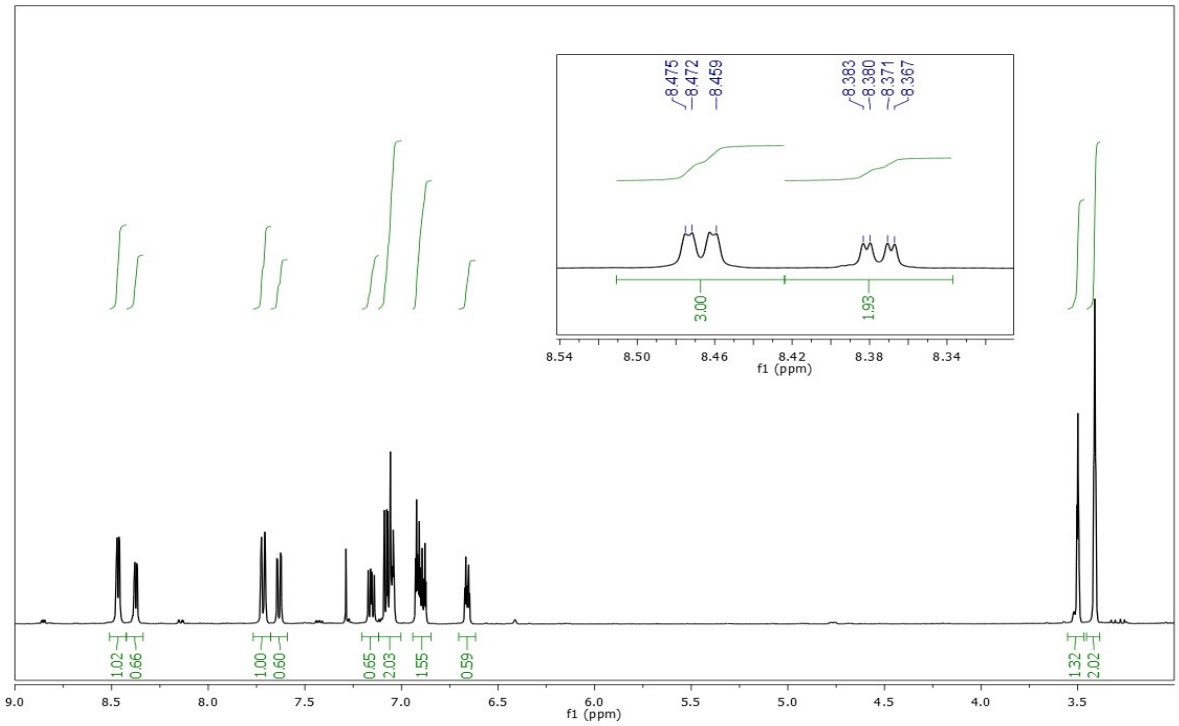
Procedure for oxidation with PCC – 5b (C_9H_8NOBr) – To a solution of 4b (0.33 g; 1.45 mmol) in dry DCM (30 mL) was added PCC (0.94 g; 4.34 mmol). The mixture was stirred for 2 h then filtered through celite and silica. The removal of solvent left a dark brown crude that after chromatographed witn hexane/AcOEt 1:1 afforded 5b (Rf 0.34, m 0.04 g, 12%) as white crystalline solid. ^{1}H-RMN ($CDCl_3$): δ = 7.44 (s, 1H); 3.01-2.98 (m, 2H); 2.76-2.74 (m, 2H); 2.38 (s, 3H).

Procedure for *O*-allylation – 6a ($C_{11}H_{11}NO$) – To a solution of **4a** (1.22 g; 9.03 mmol) in dry DCM (30 mL), a solution of KOtBu (1.01 g; 9.03 mmol) in DMF (5 mL) and propargyl chloride (0.98 mL; 1.5 eq.) were added. The system was stirred in argon atmosphere overnight. The reaction was stopped with a saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with DCM (3x50 mL) and the pooled organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After chromatographic purification, with AcOEt, **6a** was isolated (Rf 0.65, 0,16g, 10%) as a dark oil. ^{1}H RMN ($CDCl_3$): δ = 8.39 (d, J 4.9 Hz, 1H); 7.51 (dd, J 7.6 Hz, J 0.6 Hz, 1H); 7.10 (dd, J 7.6Hz, J 4.9 Hz, 1H); 4.98 (dd, J 7.0 Hz, J 3.7 Hz, 1H); 4.46 (dd, J 15.7 Hz, J 2.4 Hz, 1H); 4.38 (dd, J 15.6 Hz, J 2.4 Hz, 1H); 3.00-3.08 (m, 1H); 2.77 (ddd, J 13.3Hz, J 8.7 Hz, J 4.6 Hz, 1H); 2.42 (t, J 2.4 Hz, 1H); 2.32-2.39 (m, 1H); 2.09-2.16 (m, 1H).

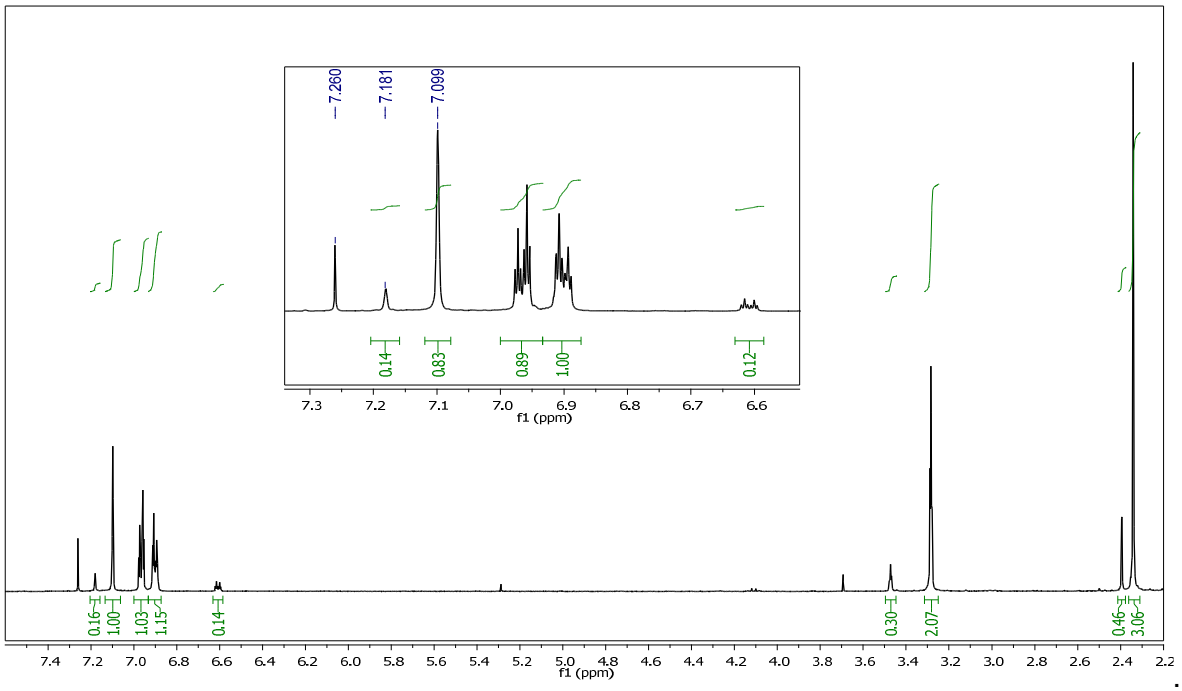
Procedure for reductive amination – 7a ($C_{11}H_{12}N_2$) – To a solution of 5a (0.17 g; 1.26 mmol) and $NaBH(OAc)_3$ (0.54 g; 2.52 mmol) in dry DCE (50 mL), propargylamine (0.12 mL; 1.89 mmol) was added. The mixture was stirred under argon atmosphere for 24 h at rt. TLC control determined the end of the reaction and the mixture was extracted with DCM (3x50 mL), the pooled organic layers were washed with brine (50 mL) and dried with Na_2SO_4. The crude was chromatographed in slica gel with DCM/MeOH 19:1 and 7a (Rf 0.22; 0.14g; 62%) was isolated as a dark oil. **^{1}H RMN ($CDCl_3$):** δ = 8.42 (d, *J* 4.9 Hz, 1H); 7.43 (d, *J* 7.6 Hz, 1H); 7.00 (dd, J 6.9 Hz, *J* 5.0 Hz, 1H); 4.31 (t, *J* 7.0 Hz, 1H); 3.61 (dd, *J* 2.4 Hz, J 17.0 Hz, 1H), 3.47 (dd, *J* 17.0 Hz, *J* 2.3 Hz, 1H); 2.91 (ddd, *J* 12.7 Hz, *J* 8.8 Hz, *J* 3.8 Hz, 1H); 2.72-2.80 (m, 1H); 2.45 (bs, 1H); 2.33-2.42 (m, 1H); 2.19 (t, *J* = 2.4, 1H), 1.75-1.84 (m, 1H).

Procedure for *N*-allylation – 8a ($C_{14}H_{14}N_2$) – To a solution of 7a (0.12 g; 0.72 mmol) in dry DCM (10 mL), propargyl chloride (52 μL; 0.72 mL) and DMAP (catalyst) were added. The mixture was stirred under argon atmosphere for 24 h. Then, saturated aqueous NaHCO3 solution (50 mL) was added. The resulting mixture was extracted with DCM (2x50 mL) and the pooled organic layers was washed with water (50 mL) and brine (50 mL), and dried over Na2SO4. The solvent removal left a crude that after chromatographed in silica gel with DCM/MeOH 9:1 afforded 8a (Rf 0.75; 0.03 g; 17%) as a dark brown oil. ^{1}H RMN ($CDCl_3$): δ = 8.45 (d, *J* 4.2 Hz, 1H); 7.52 (dd, *J* 7.6 Hz, *J* 1.3 Hz, 1H); 7.11 (dd, *J* 7.6 Hz, *J* 4.9 Hz, 1H); 4.44 (t, *J* 6.7 Hz, 1H); 3.83 (dd, *J* 16.9 Hz, *J* 2.4 Hz, 2H); 3.70 (dd, *J* 16.9 Hz, *J* 2.4 Hz, 2H); 3.01 (ddd, *J* 13.7 Hz, *J* 8.6 Hz, *J* 5.1 Hz, 1H); 2.77-2.85 (m, 1H); 2.23-2.40 (m, 2H), 2.22 (t, *J* 2.4 Hz, 2H).

Procedure for hydrolysis and *in situ* dehydration – 9a' and **9a''** (C_8H_7N) – A solution of **3a** (0.33 g; 2.44 mmol) in concentrated sulfuric acid (1 mL; 18.76 mmol) was heated at 100 ºC for 1 h after that the mixture was poured into an ice cooled 10% NaOH aqueous solution. The pH was correct until 7-8 with $NaHCO_{3(s)}$. The resulting mixture was extracted with Et_2O (3x 50 mL) and the pooled organic layers was washed with saturated aqueous $NaHCO_3$ solution (50 mL), water (50 mL) and brine (50 mL). The removal of solvent left a dark orange oil that was chromatographed in silca gel with AcOEt to afford **9a'** and **9a''** (Rf 0.4; 0.28 g; 83%) as an orange oil consisting of a isomeric mixture (spectrum below). **9a'** ^{1}H RMN ($CDCl_3$): δ = 8.46 (dd, 1H, J 5.0 Hz, J 1.4 Hz); 7.69 (dq, 1H, J 7.6 Hz, J 0.6 Hz); 7.04 (dd, 1H, J 2.0 Hz, J 0.8 Hz); 7.03-7.01 (m, 1H); 6.89 (dt, 1H, J 5.6 Hz, J 2.0 Hz); 3.38 (t, 2H, J 1.8 Hz). **9a''** 1H-RMN ($CDCl_3$): δ = 8.38 (dd, 1H, J 5.0 Hz, J 1.4 Hz); 7.60 (dd, 1H, J 7.6 Hz, J 1.6 Hz); 7.13 (dd, 1H, J 7.6 Hz, J 4.8 Hz); 6.86 (dt, 1H, J 6.0 Hz, J 2.0 Hz); 6.63 (dt, 1H, J 6.0 Hz, J 2.0 Hz); 3.47 (t, 2H, J 1,8 Hz). ESI-MS: calculated ($M + H^+$) 118.15, obtained 118.20.

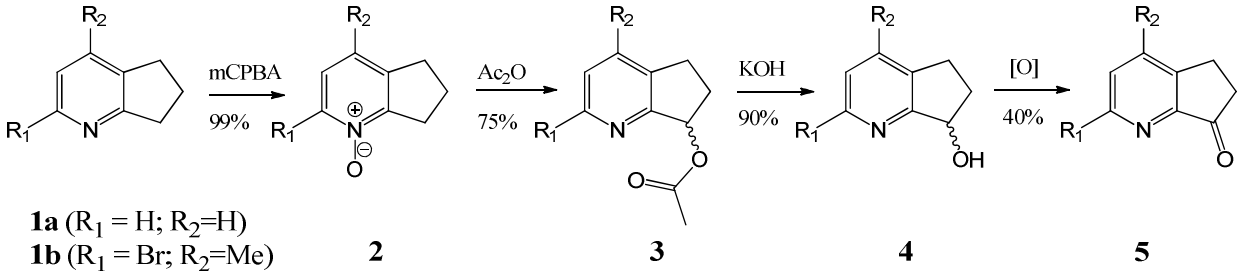


9b' and **9b''** (C_9H_8NBr) – Following the procedure as above, with **3b** (0.58 g; 2.15 mmol) and H_2SO_4 (1 mL; 18.77 mmol). Flash chromatography with hexane/AcOEt 1:1 afforded **9b'** and **9b''** (Rf 0.65; 0.29 g; 64%) as an orange oil consisting of a isomeric mixture (spectrum below). **9b'** ^{1}H RMN ($CDCl_3$): δ = 7.18 (s, 1H); 6.90 (dt, 1H, J 5.6 Hz, J 2.0 Hz); 6.61 (dt, 1H, J 6.0 Hz, J 2.0 Hz); 3.47 (t, 2H, J 2.0 Hz); 2.39 (s, 3H). **9b''** ^{1}H-RMN ($CDCl_3$): δ = 7.10 (s, 1H); 6.96 (dt, 1H, J 5.6 Hz, J 2.0 Hz); 6.90 (dt, 1H, J 6.0 Hz, J 2.0 Hz), 3.28 (t, 2H, J 2.0 Hz); 2.34 (s, 3H). ESI-MS: calculated (M + H^+) for ^{79}Br 210.07; obtained for ^{79}Br 210.20, calculated for ^{81}Br 212.07; obtained for ^{81}Br 212.20



3. Results and Discussion

Starting from commercial available 6,7-dihydrocyclopenta[*b*]pyridine (**1a**) and 2-bromo-4-methyl-6,7-dihydrocyclopenta[*b*]pyridine (**1b**), easily obtained through bromination of Sakurai-Midorikawa cyclization product from cyclopentanone,[6,7] the synthetic rout was designed in order to give compounds possessing *N*- or *O*-propargylamine groups and, attached to different positions at the scaffold. First, racemic propargylic derivatives were obtained than, when the synthetic pathway is optimized, the same methodology will be applied in the enantiomerically pure compounds.

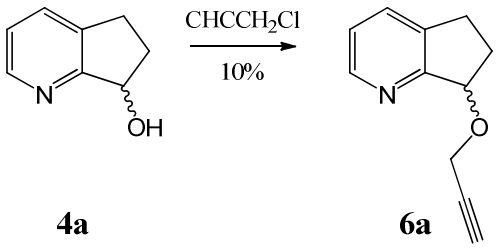


1a (R_1 = H; R_2=H)
1b (R_1 = Br; R_2=Me) **2** **3** **4** **5**

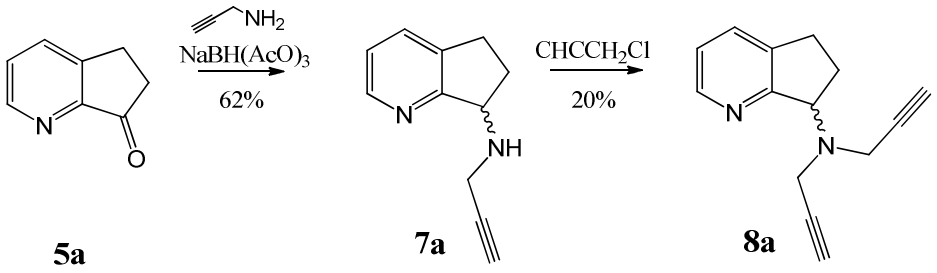
Scheme 1

Scheme 1 shows most common functionalization steps aiming to functionalize this kind of structure.[7] After *N*-oxidation, better yields were obtained using meta-chloroperbenzoyc acid instead of classic AcOH/H_2O_2 system,[7] the reaction with acetic anhydride afforded racemic acetyl derivatives (**3a,b**). The carbonyl group was hydrolyzed whith KOH and, the achieved alcohols were transformed in ketones by Swern's oxidation, these methodologies gained ground to older and classical ones as LiOH/THF/H_2O hydrolysis or LAH ester reduction followed by PDC/PCC oxidation.

From the alcohol **4a**, it was possible to form the derivative **6** through reaction with propargyl chloride and, from the ketone **5a**, a *N*-propargyl derivative (**7**) was obtained by reductive amination, after that, another reaction with propargyl chloride affords the *N*,*N*-bis-propargyl derivative **8** (scheme 2).

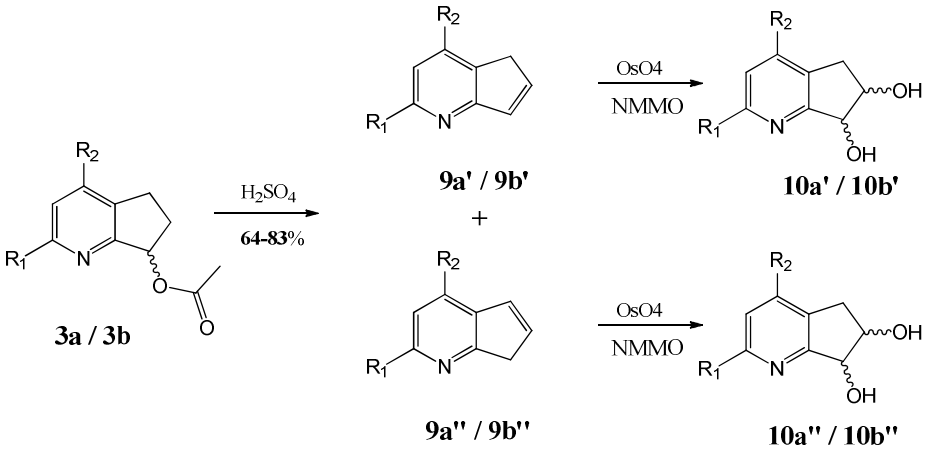


4a **6a**



Scheme 2

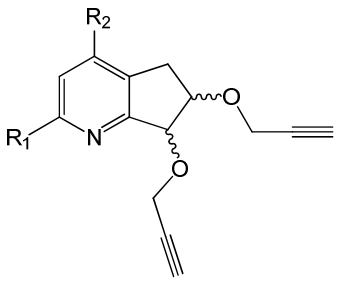
Recent approaches involve vicinal functionalization at the pentacycle of the pyrindane scaffold (scheme 3). This was achieved after acidic hydrolysis with dehydration from 7-acetyl derivatives (**3a** and **3b**) with sulphuric acid.[8] The di-hydroxylation of alkenes **9a** and **9b** was performed with osmium tetroxide without results.



Scheme 3

^{1}H-RMN spectral data show that, in both cases (from **3a** and **3b**), the dehydration affords a pair of isomers which cannot be separated by column chromatography. Yet, time seems to be determinant in the ratio of the isomeric mixtures, after 1 hour **9a** and **9b** were obtained in ratio 3:2 and 13:87, respectively. Some studies suggest that short reaction time promotes the attainment of only one of the isomers, alkenes **9a'** and **9b'**. Complementary assays, with these substrates, are needed to confirm this hypothesis and guarantee the formation of the desired alkenes (Scheme 3).

The diols **10a** and **10b** will be useful at the attainment of desired bis-propargyl derivatives **11a** / **11b** and **12a** / **12b** (figure 2).



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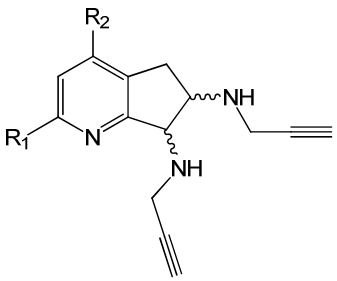

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Figure 2

4. Conclusion

In conclusion, a new class of 1-pyrindane derivatives was synthetized, whose synthesis revealed to be effective and simple.

5. Acknowledgements

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6. References

1. Moussa B.H.Youdim, Mati Fridkin, Hailin Zheng, *Mechanisms of ageing and Development*, **2005**, 126, 317-326.

2. O. Rascol, D. J. Brooks, E. Melamed, W. Oertel, W. Poewe, F. Stocchi, E Tolosa, *Lancet*, **2005**, 365, 947-954.

3. Orit Bar-Am, Orly Weinreb, Tamar Amit and Moussa B.H.Youdim, *Journal of Neurochemistry*, **2010**, 112, 1131-1137.

4. M. Asif, A. Siddiqui e G. L. Plosk. *Rasagiline*. Drugs Aging. 22 (1): 63-91. **2005**

5. D. R. Guay. *Rasagiline (TVP-1012): A new selective monoamine oxidase inhibitor for Parkinson's disease*. Am. J. Geriatr. Pharmacother. 4(4). 330-46. **2006**

6. Sakurai, A.; Midorikawa, H., *Bulletin of the Chemical Society of Japan* **1968,** *41* (1), 165-167.

7. (a) Lyle, M. P. A.; Narine, A. A.; Wilson, P. D., *J. Org. Chem.* **2004,** *69* (15), 5060-5064. (b) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D., *Organic & Biomolecular Chemistry* **2006,** *4* (5), 877-885. (c) Xie, Y.; Huang, H.; Mo, W.; Fan, X.; Shen, Z.; Shen, Z.; Sun, N.; Hu, B.; Hu, X., *Tetrahedron: Asymmetry* **2009,** *20* (12), 1425-1432.

8. Robison, M. M., *Journal of the American Chemical Society* **1958,** *80* (23), 6254-6257.