Synthesis of New Propargylated 1-Pyrindane Derivatives as Rasagiline Analogues

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Supplementary Data

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6,7-dihydro-5H-cyclopentapyridine-N-oxide (5). 3-chloroperbenzoic acid (3.84 g; 17.1 mmol) was slowly added to a solution of 4 (2.04 g, 17.1 mmol) in DCM. The mixture was stirred at room temp. for 2 hours. The solvent was evaporated under reduced pressure and the crude purified by chromatographic column (ethyl acetate) giving 2.30 g of a white solid (η=99%). $^1$H NMR (CDCl$_3$, 400 MHz), δ(ppm): 2.12 (2H, q, J=7.6 Hz, CH$_2$); 2.96 (2H, t, J=7.6 Hz, CH$_2$); 3.11 (2H, t, J=8.0 Hz, CH$_2$), 6.99-7.06 (2H, m, Harom), 7.98 (1H, d, J=7.2 Hz, Harom). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (ppm): 22.84 (CH$_2$), 30.34 (CH$_2$) 32.40 (CH$_2$), 123.45 (C$_{para}$), 124.71 (C$_{meta}$), 138.04 (C$_{ortho}$), 143.10 (C$_{ipso}$ e 153.89 (C$_{ipso}$). ESI-MS: calculated for [C$_8$H$_9$NO + H$^+$] (M + H$^+$) 136.07, obtained 136.27; Rf = 0.05 (ethyl acetate); m.p. = 121-123 ºC

6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate (6). A solutioin of 5 (1.66 g, 12.3 mmol) in acetic anhydride (15.0 mL) was heated to 100ºC for 2 hours. The anhydride excess was evaporated under reduced pressure. Column chromatography purification using ethyl acetate as eluent gave 1.57 g of an orange oil (η=72%). $^1$H NMR (CDCl$_3$, 400 MHz), δ(ppm): 2.03-2.10 (1H, m), 2.12 (3H, s, OC(O)CH$_3$), 2.60-2.69 (1H, m), 2.85-2.93 (1H, m), 3.07 (1H, ddd, $J_1$=5.1 Hz, $J_2$=8.9 Hz, $J_3$=14.6 Hz), 6.13 (1H, dd, $J_1$=5.0 Hz, $J_2$=7.4 Hz), 7.19 (1H, dd, $J_1$=4.9 Hz, $J_2$=7.7 Hz, Harom), 7.60 (1H, dd, $J_1$=1.1 Hz, $J_2$=7.7 Hz, Harom), 8.55 (1H, d, J=4.9 Hz, Harom). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (ppm): 22.11 (OCOCH$_3$), 28.64 (CH$_2$), 31.66 (CH$_2$), 78.08 (CH), 124.27 (C$_{meta}$), 134.10 (C$_{ipso}$), 138.35 (C$_{para}$), 149.68 (C$_{ortho}$), 161.30 (C$_{ipso}$), 171.72 (OCOCH$_3$). ESI-MS: calculated for [C$_{10}$H$_{11}$NO$_2$ + H$^+$] (M + H$^+$) 178.08, obtained 178.10; Rf = 0.44 (ethyl acetate).
6,7-dihydro-5H-ciclopenta[b]pyridin-7-ol (7). A solution of KOH (0.25, 4.54 mmol) in ethanol (5.00 mL) was added to a solution of 6 (0.80 g, 4.54 mmol) in ethanol (2.00 mL). After stirring for 1 hour at r.t., the mixture was extracted with DCM and the organic layer washed with brine. The combined organic layers were dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude purified by column chromatography (ethyl acetate) to afford 0.55 g (η=90%) of a light brown solid. 

**1H NMR (CDCl₃, 400 MHz), δ(ppm):** 2.05-2.14 (1H, m), 2.52-2.61 (1H, m), 2.80-2.88 (1H, m), 3.07 (1H, ddd, J₁=4.3 Hz, J₂=8.9 Hz, J₃=13.2 Hz), 4.76 (1H, bs, -OH), 5.28 (1H, app t, J= 6.00 Hz), 7.16 (1H, dd, J₁=5.0 Hz, J₂=7.6 Hz, Harom), 7.59 (1H, dd, J₁=0.6 Hz, J₂=7.6 Hz, Harom), 8.43 (1H, d, J=4.9 Hz, Harom). 

**13C NMR (CDCl₃, 100 MHz) δ (ppm):** 28.41 (CH₂), 33.65 (CH₂), 74.83 (CH-OH), 123.57 (Cmeta), 134.44 (Cipso), 137.54 (Cpara), 148.45 (Cortho) e 166.04 (Cipso). 

**ESI-MS:** calculated for [C₈H₉NO + H]⁺ (M + H⁺) 136.07, obtained 136.07; Rf = 0.16 (ethyl acetate); m.p. = 80-83 ºC

7-(prop-2-yn-1-yloxy)-6,7-dihydro-5H-cyclopena[b]pyridine (±1). To a solution of 7 (1.22 g; 9.03 mmol) in DCM, potassium tert-butoxide (1.01 g; 9.03 mmol) in DMF and propargyl chloride (0.98 mL; 13.50 mmol) were added. The system was stirred under argon atmosphere overnight and at r.t.. A saturated solution of NaHCO₃ was added and the organic layer separated. The aqueous phase was extracted with DCM and the organic layers washed with brine and dried over anhydrous Na₂SO₄. After solvent evaporation, chromatographic purification yielded 0.80 g (η=50%) of a dark oil. 

**1H NMR (CDCl₃, 400 MHz), δ(ppm):** 2.09-2.16 (1H, m), 2.32-2.39 (1H, m), 2.42 (1H, t, J=2.4 Hz, OCH₂CCH), 2.77 (1H, ddd, J₁=4.6 Hz, J₂=8.7 Hz, J₃=13.3 Hz), 3.00-3.08 (1H, m), 4.38 (1H, dd, J₁=2.4 Hz, J₂=15.6 Hz, OCHHCCCH), 4.46 (1H, dd, J₁=2.4 Hz, J₂=15.7 Hz OCHHCCCH) 4.98 (1H, dd, J₁= 3.7 Hz, J₂= 7.0), 7.10 (1H, dd, J₁=4.9 Hz,
$J_2 = 7.6$ Hz, Harom), 7.51 (1H, dd, $J_1 = 0.6$ Hz, $J_2 = 7.6$ Hz, Harom), 8.39 (1H, d, $J = 4.9$ Hz, Harom). $^{13}$C NMR (CDCl$_3$, 100 MHz), δ(ppm): 28.78 (CH$_2$), 31.66 (CH$_2$), 57.45 (OCH$_2$CCH), 75.14 (OCH$_2$CCH), 81.08 (OCH$_2$CCH), 81.84 (CH), 124.01 (C$_{meta}$), 133.97 (C$_{para}$), 138.21 (C$_{ipso}$), 148.94 (C$_{ortho}$), 163.40 (C$_{ipso}$). HR-ESI-MS: calculated for [C$_{11}$H$_{11}$NO + H]$^+$ (M + H$^+$) 174.0913, obtained 174.0917; $Rf = 0.65$ (ethyl acetate).

5H-cyclopenta[b]pyridin-7(6H)-one (9). A solution of DMSO (1.28 mL; 18.0 mmol) anhydrous DCM was added dropwise to a cooled solution (-78 ºC) of (COCl)$_2$ (0.79 mL; 9.01 mmol) in anhydrous DCM. 15 minutes later, a solution of 7 (1.22 g; 9.01 mmol) and Et$_3$N (5 mL, 36.0 mmol) were added dropwise. The system was stirred under argon atmosphere for 24 hours. After addition of 40.0 mL of water, the organic layer was separated. The aqueous phase was extracted with DCM and the organic layers washed with NaHCO$_3$ and brine, and dried over anhydrous Na$_2$SO$_4$. The chromatographically purified crude gave 0.84 g ($\eta = 70\%$) of a greenish solid. $^1$H NMR (CDCl$_3$, 400 MHz), δ(ppm): 2.76-2.79 (2H, m); 3.19 (2H, tapp, $J = 6.0$ Hz); 7.46 (1H, dd, $J_1 = 4.5$ Hz, $J_2 = 7.8$ Hz, Harom), 7.90 (1H, dd, $J_1 = 1.4$ Hz, $J_2 = 7.9$ Hz, Harom), 8.78 (1H, d, $J = 4.5$ Hz, Harom). $^{13}$C NMR (CDCl$_3$, 100 MHz), δ(ppm): 24.41 (CH$_2$), 35.81 (CH$_2$), 128.24 (C$_{meta}$), 136.27 (C$_{para}$), 150.41 (C$_{ipso}$), 151.66 (C$_{ortho}$) 155.01 (C$_{ipso}$), 206.20 (C=O). ESI-MS: calculated for [C$_8$H$_7$NO + H]$^+$ (M + H$^+$) 134.06, obtained 134.07; $Rf = 0.30$ (ethyl acetate); m.p. = 98-101 ºC.

N-(prop-2-yn-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-amine (2). Method A – To an ice bath cooled solution of 7 (0.11 g, 0.81 mmol) and Et$_3$N (0.25 mL, 1.80 mmol) in dry DCM, methanesulfonyl chloride (0.15 mL, 1.90 mmol) was added under argon atmosphere. After 3 hours, saturated aqueous solution of NaHCO$_3$ was added, and the
organic layers washed with brine and dried over anhydrous Na$_2$SO$_4$. The removal of solvent affords a dark brown crude which was used in the next step without further purification. To a solution of this crude (0.08 g; 0.46 mmol) in anhydrous DCM, propargylamine (0.04 mL; 0.58 mmol) and DMAP (catalytic amount) were added under argon atmosphere. After 2 hours, the solvent was removed under reduced pressure and the obtained crude was purified by column chromatography. The joined aliquots afforded 0.01 g ($\eta = 14\%$) of a dark oil. **Method B** – To a solution of 9 (0.17 g; 1.26 mmol) and NaBH(OAc)$_3$ (0.54 g; 2.52 mmol) in DCE propargylamine (0.12 mL; 1.89 mmol) was added at r.t. under argon atmosphere. 24 hours after, TLC control determined the end of the reaction and the mixture was extracted with DCM, washed with brine and dried with anhydrous Na$_2$SO$_4$. The crude purification by chromatographic column gave 0.16 g ($\eta=72\%$) of a dark oil. **$^1$H NMR (CDCl$_3$, 400 MHz)** $\delta$(ppm): 1.87-2.03 (m + bs, 1H + NH); 2.26 (1H, t, $J$=2.4 Hz, NHCHHCCCH), 2.45-2.53 (1H, m); 2.84-2.92 (1H, m); 2.91 (1H, ddd, $J_1$=3.8 Hz, $J_2$=8.8 Hz, $J_3$=12.7 Hz); 3.58 (1H, dd, $J_1$=2.3 Hz, $J_2$=17.0 Hz, NHCHHCCCH); 3.72 (1H, dd, $J_1$=2.4 Hz, $J_2$=17.0 Hz, NHCHHCCCH), 4.42 (1H, t, $J$=7.0 Hz); 7.12 (1H, dd, $J_1$= 5.0 Hz, $J_2$=6.9 Hz, Harom); 7.55 (1H, d, $J$=7.6 Hz, Harom); 8.42 (1H, d, $J$=4.9 Hz, Harom). **$^{13}$C NMR (CDCl$_3$, 100 MHz), $\delta$(ppm):** 28.16 (CH$_2$), 31.29 (CH$_2$), 36.53 (NHCH$_2$CCH), 61.15 (CH), 71.53 (NHCH$_2$CCH), 82.07 (NHCH$_2$CCH), 122.29 (Cmeta), 132.71 (Cipso), 136.62 (Cpara), 147.82 (Crotho) e 164.49 (Cipso). **HR-ESI-MS:** calculated for [C$_{11}$H$_{12}$N$_2$ + H]$^+$ (M + H$^+$) 173.1073, obtained 173.1072; R$_f$ = 0.22 (DCM/MeOH – 19:1).

![Diagram](image)

$N,N$-di(prop-2-yn-1-yl)-6,7-dihydro-5$H$-cyclopenta[b]pyridin-7-amine (±3). To a solution of 2 (0.12g; 0.72 mmol) in anhydrous DCM, propargyl chloride (52.0 $\mu$L; 0.72 mmol) and DMAP as catalyst were added. The system reacted for 24 hours at r.t.. After addition of water, the mixture was extracted with DCM and the organic layers washed
with brine and dried over anhydrous Na₂SO₄. After purification by flash chromatography, 0.10 g (η=57%) of a dark brown oil was obtained. **¹H NMR (CDCl₃, 400 MHz)** δ(ppm): 2.22 (2H, t, J=2.4 Hz, 2 x NHCH₂CCH) 2.23-2.40 (2H, m), 2.77-2.85 (1H, m); 3.01 (1H, ddd, J₁=5.1 Hz, J₂=8.6 Hz, J₃=13.7 Hz); 3.70 (2H, dd, J₁=2.4 Hz, J₂=16.9 Hz, 2 x NHCH₂CCH); 3.83 (2H, dd, J₁=2.4 Hz, J₂=16.9 Hz, 2 x NHCH₂CCH); 4.44 (1H, t, J=6.7 Hz); 7.11 (1H, dd, J₁=4.9 Hz, J₂=7.6 Hz, Harom); 7.52 (1H, dd, J₁=1.3 Hz, J₂=7.6, Harom); 8.45 (1H, d, J=4.2 Hz, Harom). **¹³C NMR (CDCl₃, 100 MHz)** δ(ppm): 28.05 (CH₂), 29.01 (CH₂), 40.71 (2 x NHCH₂CCH), 66.83 (CH), 73.60 (NHCH₂CCH), 80.94 (NHCH₂CCH), 123.21 (Cmeta), 133.52 (Cpara), 138.21 (Cipso), 148.79 (Cortho) 164.17 (Cipso). **HR-ESI-MS:** calculated for [C₁₄H₁₄N₂ + H]⁺ (M + H⁺) 211.1230, obtained 211.1224; Rf = 0.75 (DCM/MeOH – 9:1).
Figure 1: $^1$H-NMR spectrum of compound 5.

Figure 2: $^{13}$C-NMR spectrum of compound 5.
Figure 3: $^1$H-NMR spectrum of compound 6.

Figure 4: $^{13}$C-NMR spectrum of compound 6.
Figure 5: $^1$H-NMR spectrum of compound 7.

Figure 6: $^{13}$C-NMR spectrum of compound 7.
Figure 7: $^1$H-NMR spectrum of compound 1.

Figure 8: $^{13}$C-NMR spectrum of compound 1.
**Figure 9**: $^1$H-NMR spectrum of compound 9.

**Figure 10**: $^{13}$C-NMR spectrum of compound 9.
Figure 11: $^1$H-NMR spectrum of compound 2.

Figure 12: $^{13}$C-NMR spectrum of compound 2.
Figure 13: $^1$H-NMR spectrum of compound 3.

Figure 14: $^{13}$C-NMR spectrum of compound 3.
Figure 15: HR-ESI-FIA-TOF spectrum of compound 1.
Figure 16: HR-ESI-FIA-TOF spectrum of compound 2.
Figure 17: HR-ESI-FIA-TOF spectrum of compound 3.