Supporting Information

Ca^{2+} sensing receptor cleavage by calpain partially accounts for altered vascular reactivity in mice fed a high fat diet

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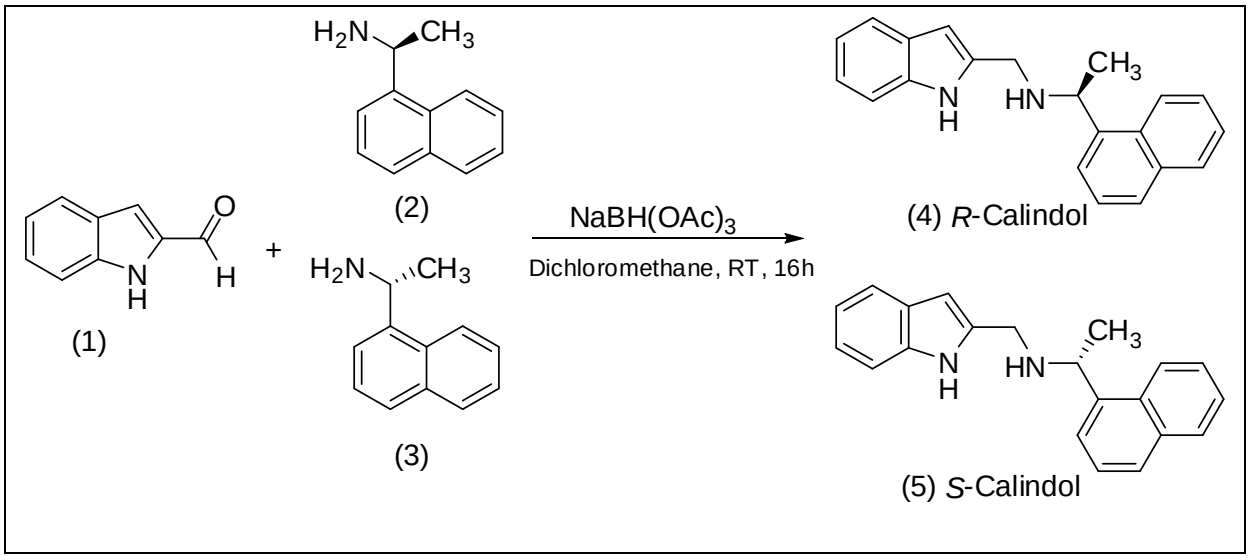
Synthesis of (*R*)-Calindol and (*S*)-Calindol



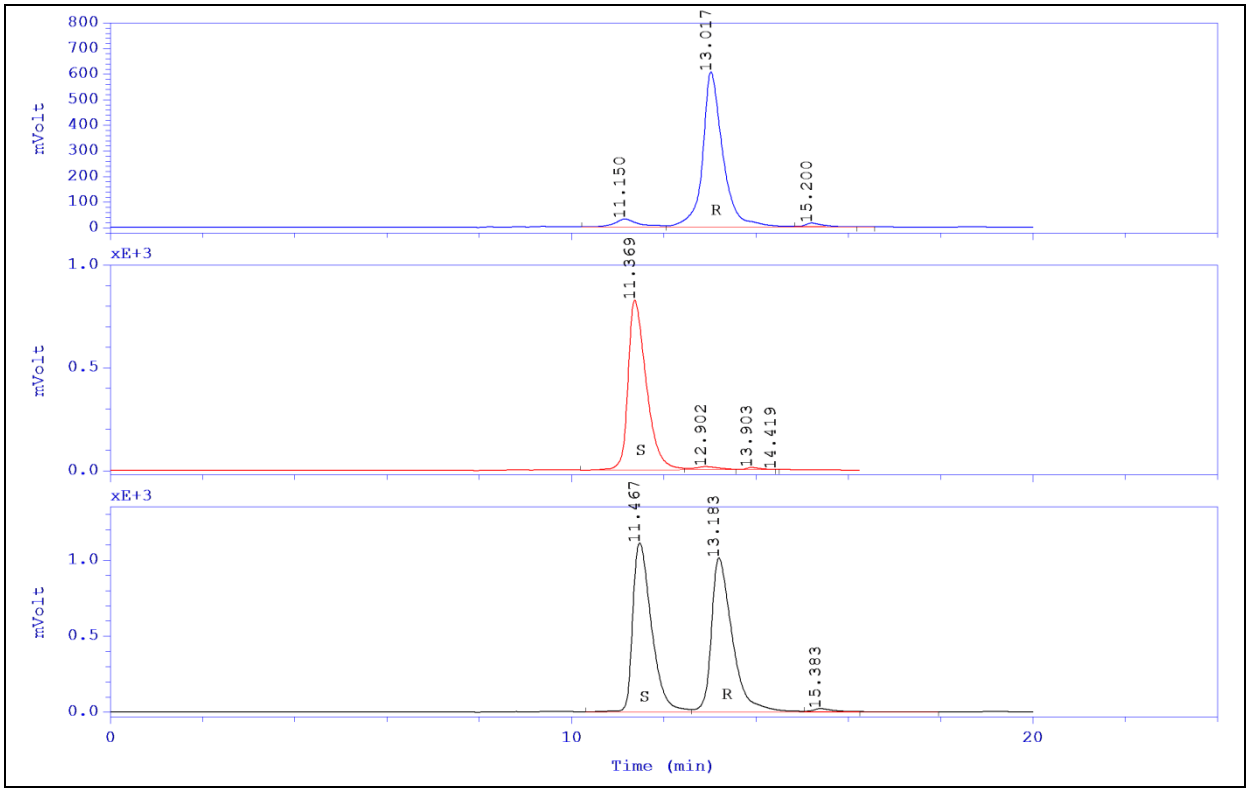
(*R*)-Calindol (HCl) (4): Indol-2-carbaldehyde (500 mg, 3.34 mmol), (*R*)-(+)-1-(1-naphthyl)ethylamine (98%ee) (1eq, 3.34 mmol, 572 mg) and $NaBH(OAc)_3$ (1.6eq, 5.34 mmol, 1.15 g) were stirred at RT in 10 mL dichloromethane overnight under argon.[1] The reaction was quenched upon addition of saturated $NaHCO_3$ and extracted three times with ethyl acetate (EtOAc). Collected organic layers were dried over $MgSO_4$, evaporated to dryness and submitted to column chromatography (hexane/EtOAc 1/1). The pure product was isolated in 91% yield dissolved in Et_2O and precipitated as HCl salt with isopropanole solution of HCl. The enantiomeric purity of the synthesized compound **4** was verified using HPLC (98% *ee*) and specific rotation was determined in MeOH. TLC (hexane:EtOAc, 1:1, v/v):R_f=0.17; $C_{21}H_{20}N_2$, M_r=300.4; **ESI-MS** m/z: 301.5 $[M+H]^+$; **^{1}H NMR** (250 MHz, DMSO-d^6): δ 10.92 (s, 1H, N*H)*, 8.13-7.06 (m, 11H, Ar*H*), 6.23 (s, 1H, Ar*H*), 4.63 (q, 1H, *J*=6.8 Hz, -C*H*-CH_3), 3.71 (m, 2H,CH_2-NH), 2.69 (bs, 1H, N*H*), 1.44 (d, 3H, *J*=6.6 Hz); **^{13}C NMR** (125MHz, DMSO-d^6): δ 148.3, 138.9, 136.2, 134.1, 133.5, 133.4, 128.3, 126.3, 126.2, 126.1, 126.0, 125.7, 125.6, 125.4, 125.2 123.9, 119.7, 110.9, 99.4, 52.2, 44.3, 23.2 ; $[\alpha]^{20°C}_D$=+15,6 ° g $ml^{-1}dm^{-1}$ [MeOH]; Elemental Analysis (Calcd., found for $C_{21}H_{21}N_2Cl$): C (74.88, 75.11), H (6.28, 6.32), N (8.32, 8.28) (M_r =336.9).

(*S*)-Calindol (HCl) (5): This compound was synthesized and isolated in the same manner as the compound **4** using (*S*)-(-)-1-(1-naphthyl)ethylamine (98% *ee*). The enantiomeric purity of

the synthesized compound **5** was verified using HPLC (98% *ee*) and specific rotation was determined.

TLC (hexane:EtOAc, 1:1, v/v):R_f=0.17; $C_{21}H_{20}N_2$, M_r=300.4; **ESI-MS** m/z: 301.4 $[M+H]^+$; **^{1}H NMR** (250 MHz, DMSO-*d*^{6}): δ 10.93 (s, 1H, N*H*), 8.17-6.96 (m, 11H, Ar*H*), 6.23 (s, 1H, Ar*H*), 4.61 (q, 1H, *J*=6.5 Hz, -C*H*-CH_3), 3.75 (m, 2H,CH_2-NH), 2.74 (bs, 1H, N*H*), 1.43 (d, 3H, *J*=6.8 Hz); **^{13}C NMR** (125MHz, DMSO-*d*^{6}): δ 147.2, 136.6, 134.2, 134.1, 133.4, 128.3, 126.3, 126.2, 126.1, 126.0, 125.7, 125.6, 125.4, 125.2 123.9, 119.7, 112.0, 102.1, 52.3, 47.3, 24,5; $[\alpha]^{20°C}_D$=-16,2 ° g $ml^{-1}dm^{-1}$ [MeOH]; Elemental Analysis (Calcd., found for $C_{21}H_{21}N_2Cl$): C (74.88, 74.90), H (6.28, 6.18), N (8.32, 8.21); (M_r =336.9).

HPLC Chromatograms of both synthetized compounds



(Isopropyl alcohol /EtOH / MeOH : 1/ 1/ 1, 0.5mL/min,) Top: compound **4**; medium: compound **5**, bottom: mixture of **4** and **5** (1:1) (detailed analytical procedures will be reported elsewhere).

References

1. Abdel-Magid AF,Carson KG, Harris BD, Maryanoff CA, Shah RD. Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. J Org Chem 1996; 61:3849-3862.
2. Ohta Y, Chiba H, Oishi S, Fujii N, Ohno H. Construction of nitrogen heterocycles bearing an aminomethyl group by copper-catalyzed domino three-component coupling−cyclization, J Org Chem 2009;74:7052–7058.
3. Kessler A, Faure H, Petrel C, Ruat M, Dauban P, Dodd RH. N^2-Benzyl-N^1-(1-(1-naphthyl)ethyl)-3-phenylpropane-1,2-diamines and conformationally restrained indole analogues: development of calindol as a new calcimimetic acting at the calcium sensing receptor, Bioorg Med Chem Lett 2004;14:3345–3350.