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Design, synthesis and biotest of a bicyclo[3.3.1]nonane analogue of 2-amino-5,6-dihydro-4*H*-1,3-thiazine

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Experimental

Solvents for extraction and chromatography were of technical grade and distilled from indicated drying agents: light petroleum (P_2O_5); ethyl acetate (K_2CO_3); methylene chloride and chloroform (P_2O_5); diethyl ether (sodium, benzophenone). Flash and column chromatography were performed on silica gel Acros (40–60 μm). Reaction control was carried out by TLC on Silufol plates. If otherwise was not stated ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O at 400 and 100 MHz, respectively. Chemical shifts in ^{1}H NMR spectra were assigned using the double resonance technique (NMDR). Spectra are referenced to residual chloroform (δ 7.26 ppm ^{1}H; δ 77.0 ppm ^{13}C). Chemical shifts are given in ppm (δ). Elemental analysis of synthesized compounds was performed on a CNH analyzer Carlo-Erba ER-20. Electrospray (ESI) mass spectra data were recorded on an Agilent LC/MSD 1100 SL mass spectrometer [electrospray ionization at atmosphere pressure, positive ion mode, ion trap mass analyzer, solution flow rate of 10 μl min^{-1}, drying gas (N_2) temperature of 120 °C, nebulizer voltage of 5500 V, capillary voltage of 0–300 V]. IR spectra were measured on a Thermo Nicolet IR200 apparatus in KBr plates. Melting points were measured in block with sealed capillaries.

3-(Chloromethyl)piperidine hydrochloride **5** was prepared as described[1] in 82% yield. Mp 158–160 °C (lit.[1] mp 153–155 °C). ^{1}H NMR (*δ*, $CDCl_3$): 2.01 (m, 4H, $H^4 + H^5$), 2.49 (s, 1H, H^3), 2.80 (m, 2H, H^6), 3.48 (m, 2H, H^2), 3.56 (m, 2H, CH_2Cl), 9.59 (br s, 1H, N^+H), 9.78 (br s, 1H, N^+H). ^{13}C NMR (*δ*, $CDCl_3$): 21.54(C^5), 26.41(C^4), 35.07(C^3), 44.02 (C^6), 46.57(CH_2Cl), 46.68(C^2).

N-*{[3-(Chloromethyl)piperidin-1-yl]carbonothioyl}benzamide* **6**. Benzoyl chloride (0.112 g, 0,8 mmol) was added to a stirred solution of ammonium thiocyanate (0.068 g, 0.9 mmol) in dry acetone under Ar atmosphere. The mixture was refluxed for 10 min, and then 3-(chloromethyl)piperidine hydrochloride **5** (0.129 g, 0.7 mmol) and triethylamine (0.22 ml, 1.6 mmol) were added slowly. After 6 h of reflux the solvent was evaporated, the residue was diluted with water (10 ml) and extracted with diethyl ether (4x20 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated. The resulting red oil was purified by silica gel chromatography (EtOAc–light petroleum, 1:7) to give **6** as yellowish oil (0.116 g, 52%). For *ca*. 1:1 mixture of two diastereoisomers: ^{1}H NMR (*δ*, $CDCl_3$): 1.51–1.98 (m, 4H, $H^4 + H^5$), 2.22 (m, 1H, H^3), 3.16–3.57 (m, 4H, $H^2 + H^6$), 3.95 (m, 1H, CHCl), 4.91 (m, 1H, CHCl), 7.45–7.53 (m, 2H, *m*-H^{Ar}), 7.56–7.63 (m, 1H, *p*-H^{Ar}), 7.84 (d, 2H, *o*-H^{Ar}), 8.63 (br s, 1H, $N\underline{H}$). ^{13}C NMR (*δ*, $CDCl_3$): 23.69, 24.28 (C^5); 27.54, 28.01 (C^4); 37.83, 38.40 (C^3); 46.76 (CH_2Cl); 52.26, 52.58

(C^2); 54.84, 54.97 (C^6); 127.70, 127.89 (C^{2Ar}); 128.91, 129.15 (C^{3Ar}); 132.43, 133.06 (C^{4Ar}); 131.55, 133.76 (C^{1Ar}); 163.41 (C=O); 179.08, 179.13 (C=S). MS (ESI): 296 (M^+).

Ethyl {[3-(chloromethyl)piperidin-1-yl]carbonothioyl}carbamate **7.** Sodium thiocyanate (0.34 g, 4.2 mmol) was added to a stirred solution of ethyl chloroformate (0.38 g, 3.5 mmol) in ethyl acetate at room temperature under Ar atmosphere. In 2 h the solvent and volatile reagents were evaporated under reduced pressure at temperature below 30 ºC. The residue was diluted with ethyl acetate and triethylamine (0.4 ml, 2.8 mmol) and compound **5 (**0.489 g, 2.8 mmol) were added. After 2 h at room temperature the mixture was washed with water (5x5 ml), dried over Na_2SO_4 and concentrated. The resulting mass was purified by silica gel chromatography (EtOAc–light petroleum, 1:7) to give **6** as a colorless oil (0.193 g, 25%). ^{1}H NMR (*δ*, $CDCl_3$): 1.25 (t, 3H, ^3J 7.1 Hz, Me), 1.47 (m, 1H, J_{gem} 10.9 Hz, H^5), 1.67 (m, 1H, J_{gem} 10.9 Hz, H^5), 1.81 (m, 1H, J_{gem} 13.1 Hz, H^4), 1.93 (m, 1H, J_{gem} 13.1 Hz, $^3J_{4,3}$ 4.5 Hz, H^4), 2.16 (m, 1H, $^3J_{3,4}$ 4.5 Hz, H^3), 3.21 (t, 2H, *J* 11.1 Hz, H^6), 3.47 (m, 2H, H^2), 4.07 (m, 1H, CHCl), 4.14 (q, 2H, ^3J 7.1 Hz, J_{gem} 14.3 Hz, $C\underline{H_2}Me$), 4.75 (br s, 1H, CHCl), 7.62 (s, 1H, NH). ^{13}C NMR (*δ*, $CDCl_3$): 14.31 (Me), 24.06, 27.82, 37.98, 46.76 (CH_2Cl), 52.37 (C^2), 54.93 (C^6), 62.49 ($\underline{C}H_2Me$), 150.60(C=O), 179.63(C=S). MS (ESI): 264 (M^+).

1,3-Diazabicyclo[3.3.1]nonane-2-thione **8**. Thiourea derivative **7** (0.193 g, 0.7 mmol) in saturated aqueous solution of $NaHCO_3$ with ethanol (1:1, 10 ml) was refluxed during 1 day. The mixture was concentrated to 5 ml and extracted with ethyl acetate (3x20 ml). Combined organic fractions were dried over Na_2SO_4, evaporated and subjected to silica gel chromatography (EtOAc–light petroleum, 1:5) to yield compound **8** as a white solid (0,028 g, 23%). ^{1}H NMR (*δ*, $CDCl_3$): 1.52 (m, 1H), 1.66–1.75 (m, 3H), 1.95 (m, $^3J_{5,9}$ 4.3 Hz, 1H, H^5), 3.18–3.26 (m, J_{9gem} 14.1 Hz, J_{8gem} 12.6 Hz, 4H, $H^8 + H^9 + H^4$), 3.46 (dd, 1H, J_{gem} 12.6 Hz, $^3J_{8,7}$ 8.8 Hz, H^8), 4.25 (dd, 1H, J_{gem} 14.1 Hz, $^3J_{9,5}$ 4.3 Hz, H^9), 7.4 (br s, 1H, NH). ^{13}C NMR (*δ*, $CDCl_3$): 21.14 (C^7), 27.88 (C^6), 29.14 (C^5), 49.12 (C^4), 50.97 (C^8), 56.48 (C^9), 195.65 (C=S). IR (KBr): 3192 (NH), 1226 (C=S) cm^{-1}. MS (ESI): 156 (M^+).

3-(Bromomethyl)piperidine hydrobromide **9** was prepared according to a method described[2] in 65% yield. Mp 180–182 °C. ^{1}H NMR (*δ*, D_2O): 1.32 (m, 1H, J_{gem} 11.6 Hz, H^5), 1.67 (m, 1H, J_{gem} 11.6 Hz, H^5), 1.84–1.91 (m, 2H, C^4H_2), 2.09 (m, 1H, C^3H), 2.73 (m, 1H, J_{gem} 12.6 Hz, H^6), 2.89 (m, 1H, J_{gem} 12.6 Hz, H^6), 3.28–3.34 (m, 2H, J_{gem} 12.6 Hz, H^2; J_{gem} 12.4 Hz, CHBr), 3.40–3.49 (m, 2H, J_{gem} 12.6 Hz, H^2; J_{gem} 12.4 Hz, CHBr). ^{13}C NMR (δ, D_2O): 21.37 (C^5), 26.79 (C^4), 35.02 (C^3), 35.21 (CH_2Br), 43.98 (C^6), 47.33 (C^2). MS (ESI): 178 ($[M - HBr]^+$, 100), 180 $[M - HBr + 2]^+$, 100).

N-*[3-Thia-1-azabicyclo[3.3.1]non-2-ylidene]benzamide* **10** was prepared according to the procedure described for **6** from of ammonium thiocyanate (1.072 g, 14.1 mmol), benzoyl chloride (1,34 ml, 10.5 mmol), bromide **9** (2 g, 7.75 mmol) and triethylamine (1.10 ml, 7.91 mmol). The product was purified by silica gel chromatography (EtOAc–light petroleum, 1:3) to give **10** as a white solid (0.401 g, 20%). Mp 114–116 ^{0}C. ^{1}H NMRDR (*δ*, $CDCl_3$): 1.59–1.80 (m, 2H, C^6),1.81 (m, J_{gem} 13.1 Hz, 1H, H^7), 1.96 (m, J_{gem} 13.1 Hz, 1H, H^7), 2.74 (m, J_{gem} 12.6 Hz, , 1H, H^8), 2.80 (m, 1H, H^5), 3.25 (m, J_{gem} 12.6 Hz, , 1H, H^8), 3.32 (m, 2H, H^4), 3.60 (d, J_{gem} 13.1 Hz, 1H, H^9), 4.59 (dd, J_{gem} 13.1 Hz, *J* 4.5 Hz, 1H, H^9), 7.44 (m, J_{m-o} 7.8 Hz, 2H, H^{m-Ar}), 7.52 (d, J_{p-o} 7.5 Hz, 1H, H^{p-Ar}), 8.19 (dd, J_{o-m} 7.8 Hz, J_{o-p} 7.5 Hz, 2H, H^{o-Ar}). ^{13}C NMR (*δ*, $CDCl_3$): 22.39, 29.41, 31.54, 34.37, 53.02, 56.88, 128.11, 129.65, 132.07, 136.24, 175.86, 176.57. MS (ESI):

260 (M+). IR (KBr): 1521 (C=N), 1635 (C=O), 2848 (C–H), 3058 (C–H) cm^{-1}. Found (%): C, 64.89; H, 6.25; N, 10.55; S, 12.10. Calc. for $C_7H_{11}NS_2$: $C_{14}H_{16}N_2SO$ (%): C, 64.58; H, 6.19; N, 10.76; S, 12.32.

3-Thia-1-azabicyclo[3.3.1]nonane-2-thione **11**. A stirred solution of bromide **9** (1.98 g 7.65 mmol) and carbon disulfide (4.03 ml, 66.9 mmol) in DMF (5 ml) was treated with dry potassium carbonate (2.29 g, 16.6 mmol) at room temperature. In 12 h the mixture was concentrated, the residue diluted with water (30 ml) and extracted with ethyl acetate (3x20 ml). Combined organic fractions were dried over Na_2SO_4, evaporated and subjected to silica gel chromatography (EtOAc–light petroleum, 1:5) to yield compound **10** as bright yellow solid (0.476 g, 36%). Mp 65–67 °C. ^{1}H NMRDR (δ, $CDCl_3$): 1.58–1.63 (m, 2H, H^6), 1.80–1.99 (m, 2H, H^7), 2.88 (m, 1H, $^3J_{5,9}$ 10.1 Hz, $^3J_{5,4(9)}$ 2.5 Hz, H^5), 2.96 (dd, 1H, J_{gem} 12.1 Hz, $^3J_{9,5}$ 2.5 Hz, H^9), 3.22 (m, 1H, J_{gem} 12.1 Hz, $^3J_{9,5}$ 10.1 Hz, H^9), 3.48–3.60 (m, 3H, J_{8gem} 12.4 Hz, $H^{8ax} + H^4$), 4.75 (m, 1H, J_{gem} 12.4 Hz, H^{8eq}). ^{13}C NMR (δ, $CDCl_3$): 22.76, 28.15, 32.42 (C^5), 38.80 (C^4), 56.11, 58.86, 210.40 (C=S)._MS (ESI): 173 (M+), 195 (M + Na). IR (KBr): 921, 1004, 1024, 1089, 1120, 1180, 1209, 1228, 1317, 1338, 1353, 1378, 1396, 1446, 1471, 2852, 2919 cm^{-1}. Found (%): C, 48.53; H, 6.35; N, 7.91; S, 37.28. Calc. for $C_7H_{11}NS_2$(%): C, 48.51; H, 6.40; N, 8.08; S, 37.01.

2-(Methylthio)-3-thionia-1-azabicyclo[3.3.1]non-2-ene iodide **12.** Methyl iodide (0.06 ml, 0.97 mmol) was added to a solution of bicyclic compound **11** (0.10 g, 0.58 mmol) in methylene dichloride (5 ml) under Ar atmosphere. The mixture was stirred for 1 h at room temperature and evaporated. The residue was dissolved in methanol (5 ml) and treated with gaseous ammonia during 2 h. After concentration the reaction mass was purified by silica gel chromatography (EtOAc–light petroleum, 1:3) to give yellow oil (0.16 g, 90%). ^{1}H NMR (δ, $CDCl_3$): 1.44 (m, 1H, J_{gem} 11.5 Hz, H^6), 1.66 (m, 1H, J_{gem} 11.5 Hz, $J_{6,5}$ 3.8 Hz, H^6), 1.77–1.83 (m, 2H, J_{7gem} 13.3 Hz, $J_{7,8}$ 10.3 Hz, $J_{5,6}$ 3.8 Hz, $J_{7,8}$ 3.0 Hz, H^5+H^7), 2.02 (m, 1H, J_{gem} 13.3 Hz, H^7), 2.65 (s, 3H, Me), 3.07 (dd, 1H, J_{gem} 13.7 Hz, $J_{8,7}$ 10.3 Hz, H^8), 3.15 (m, 2H, H^9), 3.25 (m, 1H, J_{gem} 13.7 Hz, $J_{8,7}$ 3.0 Hz, H^8), 4.49 (br s,1H, H^4), 5.31 (br s,1H, H^4). ^{13}C NMR (δ, $CDCl_3$): 9.05, 20.26 (Me), 24.40, 31.35 (C^5), 37.76, 51.57, 56.55, 197.75 ($C=S^+$). MS (ESI): 188 ($M\text{-}I^+$), 315 (M^+).

3-Thia-1-azabicyclo[3.3.1]nonane-2-imine **2.** *Method A*: Benzamide **10** (0.170 g, 0.65 mmol) was refluxed in conc. aqueous HCl (5 ml) for 8 h. The reaction mixture was concentrated, treated with saturated aqueous solution of $NaHCO_3$ (2 ml) and extracted with chloroform (3x10 ml). Combined organic layers were dried over Na_2SO_4, evaporated, recrystallized from isopropanol and subjected to silica gel chromatography (chloroform–methanol, 10:1) to yield crude compound **2** as a white solid (0.023 g, 23%). *Method B*: Thionyl chloride (0.043 ml, 0.60 mmol) was added to a solution of bicyclic compound **11** (0.10 g, 0.58 mmol) in methylene dichloride (5 ml) under Ar atmosphere. The mixture was stirred for 1 h at room temperature and evaporated. The residue was dissolved in methanol (5 ml) and treated with gaseous ammonia during 2 h. After concentration the reaction mass was purified by silica gel chromatography (chloroform–methanol, 10:1) to give compound **2** as a white solid (0.034 g, 38%). ^{1}H NMRDR (δ, $CDCl_3$): 1.36 (m, 1H, H^6), 1.43 (m, J_{gem} 13.5 Hz, $J_{\text{7ax,8ax}}$ 10.6 Hz, $J_{\text{7ax,8eq}}$ 3.9 Hz, 1H, H^{7ax}), 1.71 (m, J_{gem} 13.5 Hz, $J_{7eq,8ax}$ 3.4 Hz, 1H, H^{7eq}), 1.88–1.95 (m, 2H, H^5+H^6), 2.80 (dd, J_{gem} 13.2 Hz, $J_{9,5}$ 9.3 Hz, 1H, H^9), 3.0 (m, J_{gem} 13.2 Hz, $J_{8ax,7ax}$ 10.6 Hz, $J_{8ax,7eq}$ 3.4 Hz, 1H, H^{8ax}), 3.47 (m, 2H, H^4), 3.71 (dt, J_{gem} 13.2 Hz, $J_{8eq,7ax}$ 3.9 Hz,1H, H^{8eq}), 3.92 (d, 1H, J_{gem} 13.2 Hz, 1H, H^9), 4.75

(br s, 1H, NH). ^{13}C NMR (δ, CDCl$_3$): 24.07 (C^7), 28.35 (C^6), 37.97 (C^5), 44.69, 47.05, 47.69, 158.31 (C=NH). MS (ESI): 172 (M+O), 188 (M+2O). Found (%): C, 54.02; H, 7.65; N, 17.89; S, 20.20. Calc. for $C_7H_{12}N_2S$ (%): C, 53.81; H, 7.74; N, 17.93; S, 20.52.

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