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New compounds with 4-azatricyclo[4.3.1.1^{3,8}]undecane framework

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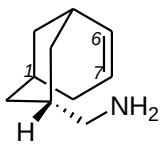
General information

All starting materials and reagents were purchased as high-grade commercial products and used without further purification; the solvents were technical grade and distilled from standard drying agents. Liquid column chromatography was performed using silica gel Acros (40–60 μm). Thin-layer chromatography (TLC) was performed on Silufol-UV254 silica gel sheets.

^{1}H and ^{13}C NMR spectra were recorded on Agilent 400-MR spectrometer (400.0 MHz for ^{1}H; 100.6 MHz for ^{13}C) at 28^{o}C. Chemical shifts (δ) are reported in ppm referenced to solvent signals ($CDCl_3$, δ_H=7.24 ppm, δ_C=77.0 ppm; D_2O, δ_H=4.80 ppm); spin-spin coupling constants (*J*) are reported in Hz.

Liquid chromatography (LC) and ElectroSpray ionization mass spectrometry (ESI-MS) data were obtained on an Agilent 1100 LC/MSD with an Agilent 1100 SL quadrupole mass spectrometer, eluting with 0.05% TFA in H_2O and 0.05% TFA in MeCN (positive-ion monitoring mode). ElectroSpray ionization high-resolution mass spectroscopy (ESI-HRMS) was carried out on a Micromass LCT ESI mass spectrometer (positive-ion monitoring mode). CHN elemental analysis was performed using a Carlo-Erba ER-20 analyzer. IR-spectra were registered on FT-IR Termo Nicolet IR200 Spectrometer with 4 cm^{-1} resolution, absorption bands are given in cm^{-1}. Melting points were determined using a capillary melting point apparatus and were uncorrected.

(*endo*-3-Bicyclo[3.3.1]non-6-enyl)methylamine (4) was obtained using modified procedures described in [T. Sasaki, S. Eguchi, T. Toru. *J. Org. Chem*. 1970. **35**. 4109; A. Hassner, T. K. Morgan (Jr.), A. R. McLaughlin. *J. Org. Chem*. 1979. **44**. 1999].



A solution of *endo*-bicyclo[3.3.1]non-6-ene-3-carbonitrile (1 g, 6.8 mmol) in diethyl ether (25 ml) was added dropwise to the ice-cooled mixture of $LiAlH_4$ (0.51 g,13.6 mmol) and $AlCl_3$ (1.8 g, 13.6 mmol) in diethyl ether (55 ml). In 2 h, the reaction mixture was gently quenched with 50% aqueous solution of NaOH (25 ml) and filtered. The precipitate was washed with hot $CHCl_3$(3×30 ml), the combined organic filtrates were died over

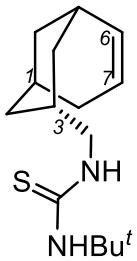
Na_2SO_4, filtered and evaporated under reduced pressure. Amine **4** was obtained (0.9 g, yield 88 %) as a light yellow oil and used without further purification.

Updated spectral characteristics:

^{1}H NMR (δ, $CDCl_3$): 1.15–1.26 (m, 4H), 1.43 (m, *J*=12.1 Hz, 1H), 1.58 – 1.65 (m, 2H), 1.76 – 1.83 (m, 2H), 1.92 (m, *J*=13.8, 7.9, 7.0 Hz, 1H), 2.13 (m, 1H), 2.23 – 2.28 (m, 2H), 2.54 – 2.64 (m, 2H, CH_2N), 5.50 (m, *J*=9.6 Hz, 1H, H^7), 5.83 (m, *J*=9.6, 7.5 Hz, 1H, H^6).

^{13}C NMR (δ, $CDCl_3$): 25.08, 27.47, 28.27, 31.19, 32.29, 34.01, 34.12, 48.36 (CH_2NH_2), 125.49 (C^7), 134.86 (C^6).

1-[(*endo*-Bicyclo[3.3.1]non-6-en-3-yl)methyl]-3-*tert*-butylthiourea (5). *endo*-3-Bicyclo-[3.3.1]non-6-enylmethylamine (**4**) (610 mg, 4.04 mmol) dissolved in CH_2Cl_2 (10 ml) was treated with DIPEA (1.05 ml, 6.06 mmol) and *tert*-butyl isothiocyanate (767 μl, 6.06 mmol). The reaction mass was stirred overnight at room temperature, concentrated and purified by column chromatography (eluent: 2% MeOH in $CHCl_3$) to give **5** as a white solid (904 mg, yield 84%). M.p. 119–121^{0}C.



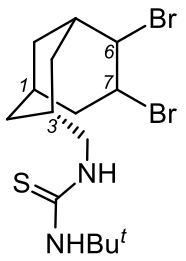
^{1}H NMR (δ, $CDCl_3$): 1.31–1.38 (m, 2H), 1.43 (s, 9H, *t*-Bu), 1.53 (m, *J* =12.5 Hz, 1H), 1.62 (m, *J*=12.5 Hz, 1H), 1.81 – 2.07 (m, 4H), 2.18 (m, 1H), 2.30 – 2.36 (m, 2H), 3.47 (m, 1H, CH_2NH), 3.63 (m, 1H, CH_2NH), 5.62 (m, 1H, *J*=8.5 Hz, H^7), 5.65 – 6.1 (br s, 2H, 2NH), 5.88 (m, 1H, *J*=6.8, 8.5 Hz, H^6).

^{13}C NMR (δ, $CDCl_3$): 24.96 (C^5), 27.33 (C^4), 28.51 (C^6), 29.57 ($C(CH_3)_3$), 30.18, 31.18, 32.52, 33.84, 51.32 (CH_2NH), 52.61 ($C(CH_3)_3$), 126.37 (C^7), 134.40 (C^6), 180.77 (C=S).

MS (ESI): 267 $[M+H]^+$, 211 $[M-C_4H_8+H]^+$, 135 $[M-NHC(S)NHBu^t]^+$.

Anal. Calcd for $C_{15}H_{26}N_2S$: C, 67.62, H, 9.84, N, 10.51. Found: C, 67.60, H, 9.78, N, 10.56.

1-[(3-*endo*-6,7-Dibromobicyclo[3.3.1]non-3-yl)methyl]-3-*tert*-butyl-thiourea (6). A solution of thiourea **5** (0.098 g, 0.37 mmol) in CH_2Cl_2 (5 ml) was treated with Br_2 (25 μl, 0.48 mmol) and stirred in darkness at room temperature for 24 h. The mixture was then shaken with $NaHCO_3$ (aq., 5 ml). The organic layer was separated, the aqueous one was extracted with CH_2Cl_2 (2×10 ml), the organic extracts were dried over Na_2SO_4, filtered, concentrated and the residue was purified by column chromatography (eluent: CH_2Cl_2, then 0.5–5% MeOH in $CHCl_3$) to yield **6** as white crystalline solid (0.101 g, yield 67%). M.p. 170–172 °C.



^{1}H NMR (δ, $CDCl_3$): 1.29 (s, 9H, *t*-Bu), 1.65 (m, *J* =13.6 Hz, 1H), 1.76 – 2.08 (m, 7H), 2.26 (m, 1H, H^3), 2.46-2.55 (m, 2H), 3.00 (br s, 2H, CH_2NH), 4.60 (br s, 1H, NH), 4.68 (m, 1H, H^6), 4.77 (m, 1H, H^7), 4.80 (br s, 1H, NH).

^{13}C NMR (δ, $CDCl_3$): 21.43, 24.42, 29.58 (C($\underline{C}H_3)_3$), 29.95, 30.69, 31.09, 34.92, 36.38, 45.79 ($\underline{C}H_2NH$), 48.64, 50.14 ($\underline{C}(CH_3)_3$), 60.50, 157.83 (C=O).

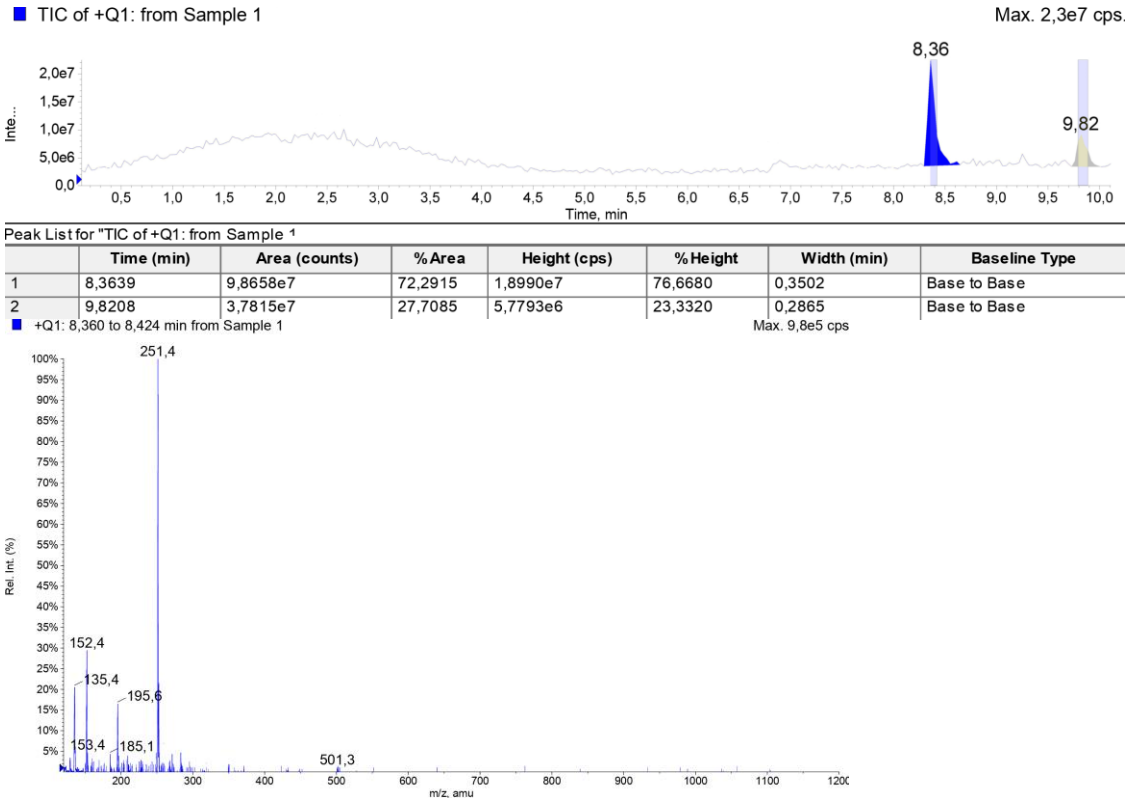
MS (EI, m/z, I%): 412 (19) $[M+4]^{+\cdot}$, 410 (35) $[M+2]^{+\cdot}$, 408 (19) $[M]^+$, 396 (26), 394 (50), 392 (26), 331 (100) $[M\text{-}Br+2]^{+\cdot}$, 329 (100) $[M\text{-}Br]^{+\cdot}$. MS (ESI): 413 $[M+H+4]^+$, 411 $[M+H+2]^+$, 409 $[M+H]^+$, 331 $[M+2+H\text{-}HBr]^+$, 329 $[M+H\text{-}HBr]^+$.

Anal. Calcd for $C_{15}H_{26}Br_2N_2O$: C, 43.92, H, 6.39, N, 6.83. Found: C, 43.90, H, 6.41, N, 6.55.

Reaction of compound 5 with iodine.

A solution of thiourea **5** (0.120 g, 0.45 mmol) in CH_2Cl_2 (5 ml) was treated with I_2 (0.170 g, 0.67 mmol) and stirred at room temperature for 24 h. The reaction mass was shaken with $Na_2S_2O_3$ (aq., 5 ml), then with $NaHCO_3$ (aq., 5 ml) and finally washed with water. The organic layer was separated, dried over Na_2SO_4, filtered, concentrated and the residue was analyzed without purification. In ^{1}H NMR spectra the following selected signals were observed, (δ, $CDCl_3$): 1.23–1.27 (m, 1H), 1.48 (m, *J* =13.3 Hz, 1H), 1.56 (s, 9H, *t*-Bu), 1.79 – 2.03 (m, 4H), 2.12 (m, 1H), 2.20 – 2.42 (m, 3H), 3.52 – 3.62 (m, 2H, $C\underline{H}_2NH$), 5.62 (m, 1H, *J* = 9.6 Hz, H^7), 5.91 (m, 1H, *J* = 9.6 Hz, H^6).

LC-MS spectrum of reaction mass: t_R = 8.3 min, peak area 72%, m/z 251.

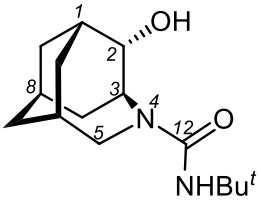


	Time (min)	Area (counts)	% Area	Height (cps)	% Height	Width (min)	Baseline Type
1	8,3639	9,8658e7	72,2915	1,8990e7	76,6680	0,3502	Base to Base
2	9,8208	3,7815e7	27,7085	5,7793e6	23,3320	0,2865	Base to Base

(1*RS*,2*RS*,3*RS*,6*SR*,8*RS*)-*N*-*tert*-butyl-2-hydroxy-4-azatricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (8) A solution of thiourea **5** (0.124 g, 0.47 mmol) in CH_2Cl_2 (5 ml) was treated with I_2 (0.118 g, 0.46 mmol) and *tert*-butyl hydroperoxide (45 μl, 0.47 mmol) and stirred at room

temperature for 24 h. The reaction mass was shaken with $Na_2S_2O_3$ (aq., 5 ml), then with $NaHCO_3$ (aq., 5 ml) and finally washed with water. The organic layer was separated, dried over Na_2SO_4, filtered, concentrated, and the residue purified by column chromatography (eluent: CH_2Cl_2, then 0.5–5% MeOH in $CHCl_3$) to yield **8** as white crystalline solid (0.051 g, yield 41%). M.p. 151–153 °C.

^{1}H NMR (δ, $CDCl_3$): 1.28 – 1.33 (m, 1H), 1.36 (s, 9H, *t*-Bu), 1.42 (m, *J*=14.7 Hz, 1H), 1.56 – 1.59 (m, *J*=12.6 Hz, 2H), 1. 09 – 2.00 (m, 4H), 2.06 (m, *J*=12.1 Hz, 1H), 2.21 (m, 1H), 2.30 (m, *J*=14.5, 6.4, 4.6, 1.9 Hz, 1H, C^9H), 2.58 (br s, H, OH), 3.27 (dd, *J*=10.6, 2.0 Hz, 1H, C^5H), 3.43 (dd, *J*=10.6, 4.2 Hz, 1H, C^5H), 3.66 (m, 1H, C^2H), 4.33 (br s, 1H, NH), 4.51 (m, *J*=4.6 Hz, 1H, C^3H).

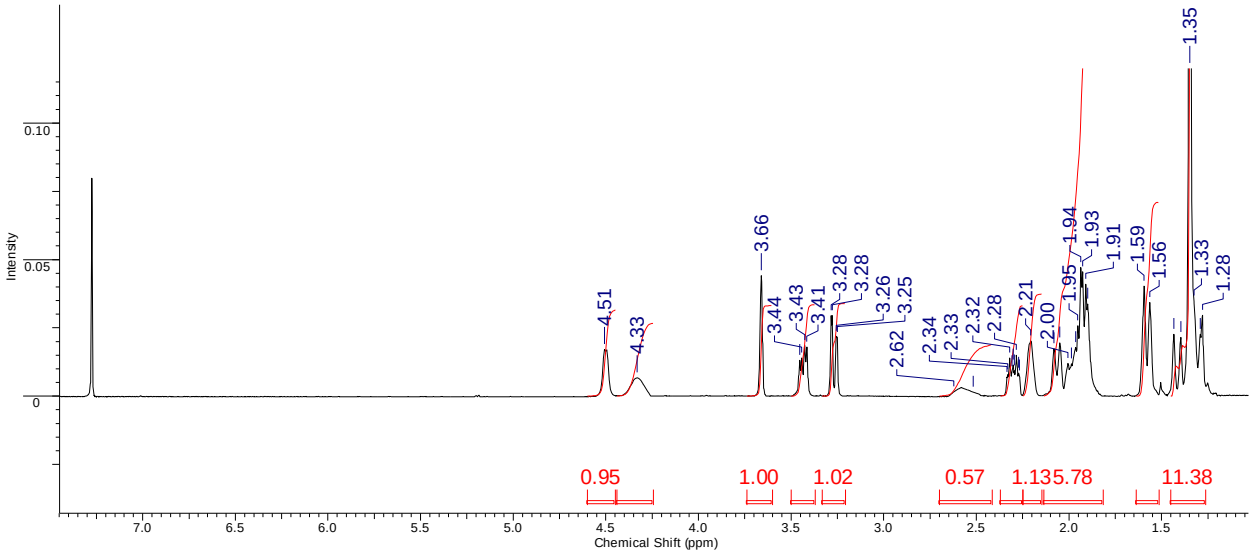


^{13}C NMR (δ, $CDCl_3$): 25.80, 27.70, 29.51, 29.54 ($C(\underline{C}H_3)_3$), 30.29, 30.91, 32.03, 38.40, 50.84 ($\underline{C}(CH_3)_3$), 52.93 (C^5H_2N), 53.70 (C^3HN), 74.52 (C^2HOH), 157.19 (C=O).

MS (ESI): 267 $[M+H]^+$, 193 $[M-C_4H_{11}N]^+$, 150 $[M-C_5H_{10}NO_2]^+$.

Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63, H, 9.84, N, 10.52. Found: C, 67.59, H, 9.68, N, 10.83.

*^{1}H NMR spectrum of compound **8***

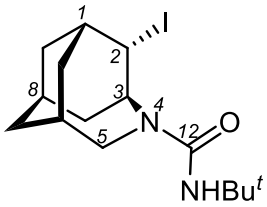


(1*RS*,2*RS*,3*RS*,6*SR*,8*RS*)-*N*-*tert*-Butyl-2-iodo-4-azatricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (9) and (1*RS*,2*RS*,3*RS*,6*SR*,8*RS*)-2-iodo-4-azatricyclo[4.3.1.1^{3,8}]undecane-4-carbonitrile (10). A solution of thiourea **5** (0.120 g, 0.45 mmol) in CH_2Cl_2 (5 ml) was treated with I_2 (0.228 g, 0.90 mmol) in the presence of anhydrous K_2CO_3 (0.124 g, 0.90 mmol) and stirred at room temperature for 24 h. The reaction mass was shaken with $Na_2S_2O_3$ (aq., 5 ml), then with $NaHCO_3$ (aq., 5 ml) and finally washed with water. The organic layer was separated, dried over Na_2SO_4, filtered, concentrated, and the residue purified by column chromatography

(eluent: CH_2Cl_2, then 0.5–5% MeOH in $CHCl_3$) to yield compounds **9** (0.024 g, yield 14%) and **10** (0.060 g, yield 44%) as yellowish crystalline solids.

Data for compound **9**:

^{1}H NMR (δ, $CDCl_3$): 1.36 (s, 9H, *t*-Bu), 1.44 (m, *J*=14.9 Hz, 1H), 1.50 (m, *J*=13.7 Hz, 1H), 1.58 (m, *J* =14.9 Hz, 1H), 1.73 (m, *J*=13.7 Hz, 1H), 1.96 – 2.02 (m, 3H), 2.17 (m, 1H), 2.22 – 2.26 (m, 1H), 2.30 (m, *J*=12.9, 5.1, 2.7 Hz, 1H), 2.59 (m, *J* =14.9, 6.7, 4.3, 2.3 Hz, 1H, C^9H), 3.16 (dd, *J*=11.2, 2.0 Hz, 1H, C^5H), 3.52 (dd, *J*=11.2, 5.1 Hz, 1H, C^5H), 4.25 (br s, 1H, NH), 4.39 (m, 1H, C^3H), 4.82 (m, *J*= 5.5 Hz, 1H, C^2H).

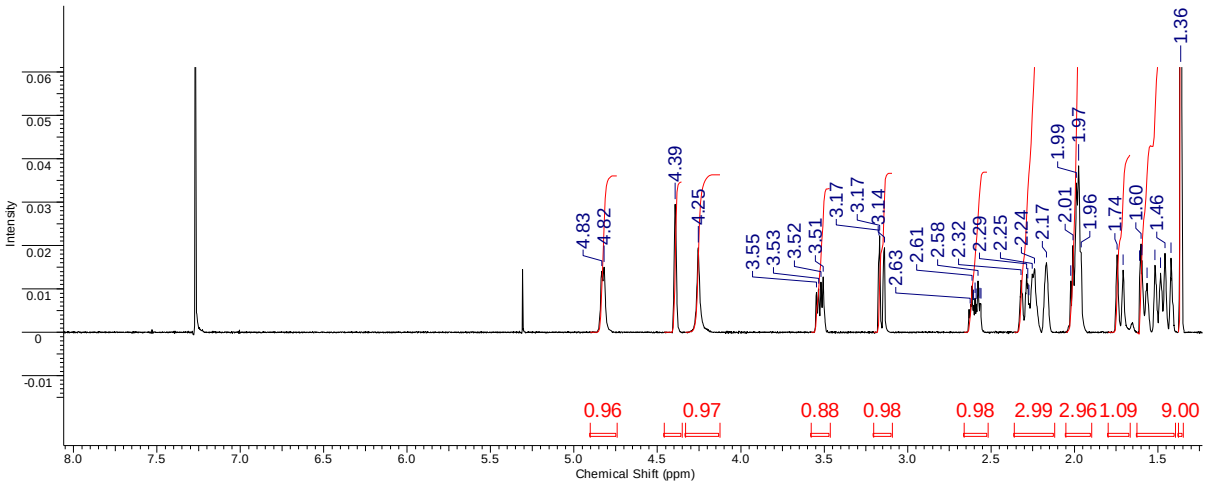


^{13}C NMR (δ, $CDCl_3$): 25.89, 29.04, 29.51 ($C(\underline{C}H_3)_3$), 30.62, 30.81, 34.36, 35.29, 39.10, 40.17, 50.93 ($\underline{C}(CH_3)_3$), 53.71 (C^3HN), 54.89 (C^2HOH), 156.48 (C=O).

MS (ESI): 377 $[M+H]^+$.

ESI-HRMS: calcd for, $C_{15}H_{25}IN_2O$, 337.1090 $[M+H]^+$. Found: 337.1087.

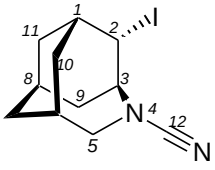
*^{1}H NMR spectrum of compound **9***



Data for compound **10:**

M.p. 82–84 °C (dec).

^{1}H NMR (δ, $CDCl_3$): 1.48 (m, *J* =13.2 Hz, 1H, $C^{11}H^{cis}$), 1.56 (m, *J*=12.8 Hz, 1H, C^7H), 1.62 (m, *J*=14.9, 1.8 Hz, 1H, C^9H^{cis}), 1.77 (m, *J*=14.9 Hz, 1H, $C^{10}H^{cis}$), 1.97 – 2.07 (m, 3H, $C^7H+C^8H+C^{10}H^{trans}$), 2.20 – 2.30 (m, 3H, $C^1H+C^6H+C^{11}H^{trans}$), 2.59 (m, *J* =14.9, 6.8, 4.5, 2.3 Hz, 1H, C^9H^{trans}), 3.41 (dd, *J* =11.7, 2.0 Hz, 1H, C^5H), 3.49 (dd, *J*=11.7, 4.7 Hz, 1H, C^5H), 3.98 (m, *J*=5.5, 1.1 Hz, 1H, C^3H), 4.54 (m, *J*=3.8, 1.9 Hz, 1H, C^2H).



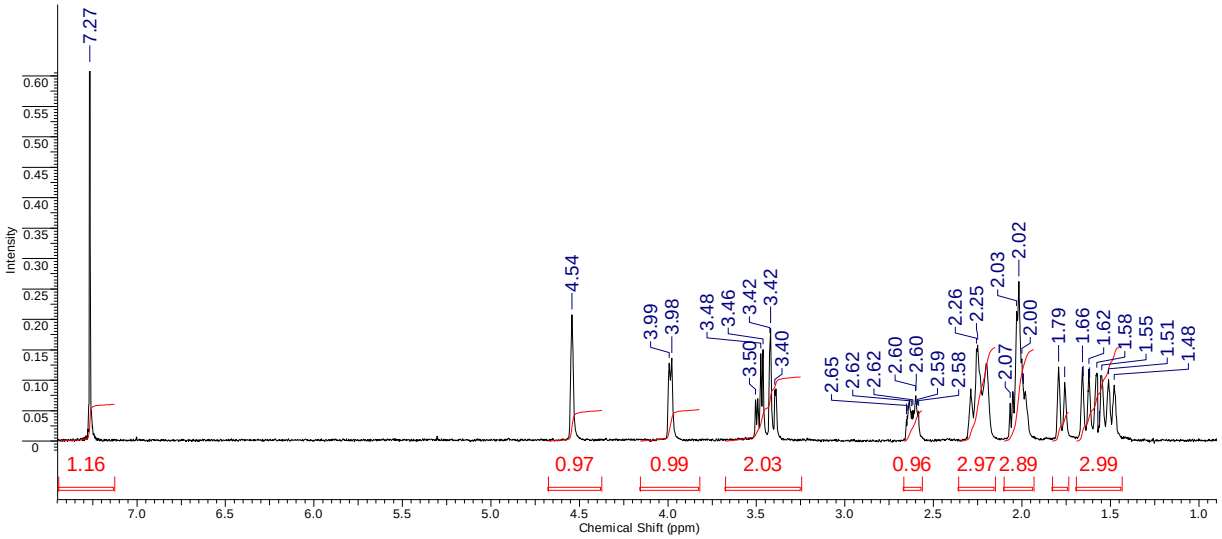
^{13}C NMR (δ, $CDCl_3$): 25.77 (C^8), 29.58 (C^9), 30.32 (C^{11}), 30.81(C^6), 34.32 (C^{10}), 34.99 (C^1), 36.21 (C^2), 38.31 (C^7), 58.49 (C^5), 63.82 (C^3), 118.44 (C≡N).

IR (KBr): 2203 (C≡N), 2852 – 2918 (C-H).

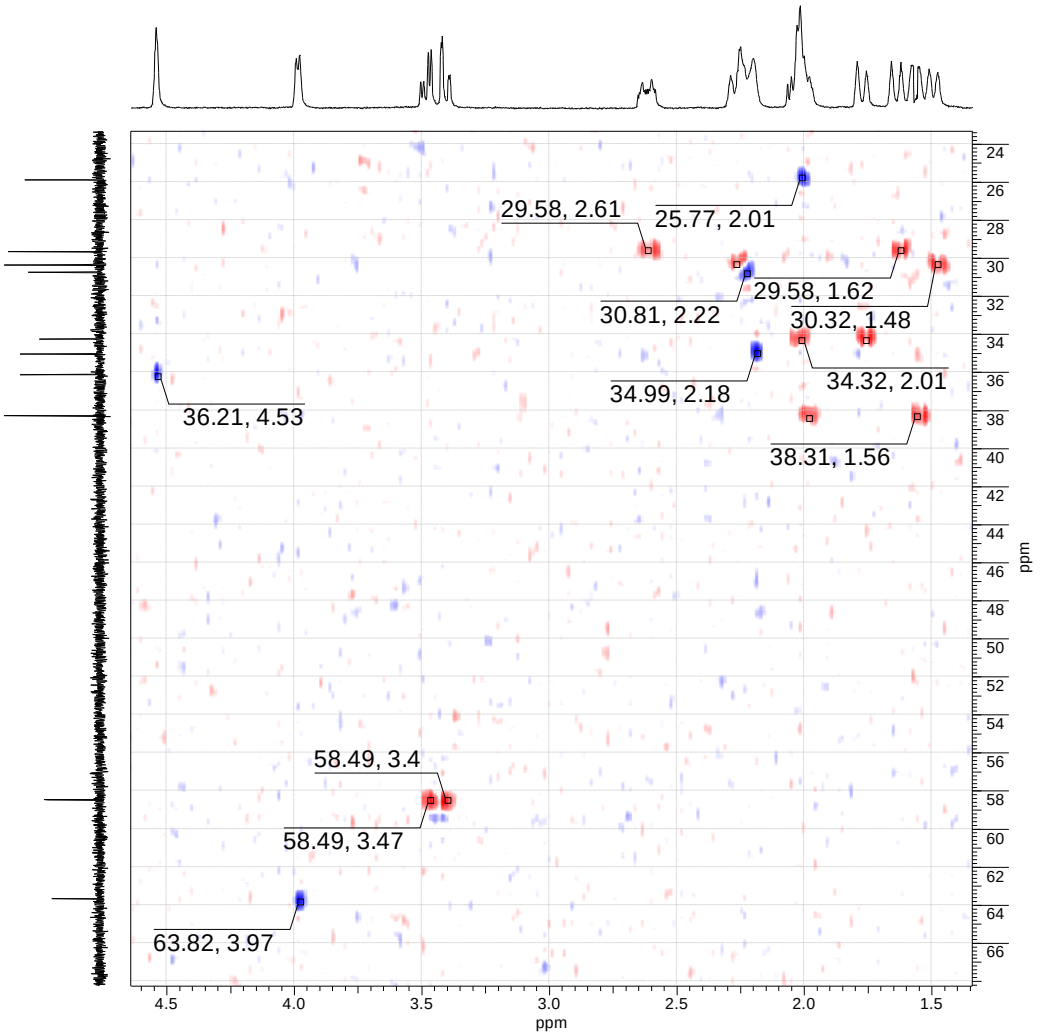
MS (ESI): 303 $[M+H]^+$.

ESI-HRMS: calcd for, $C_{11}H_{15}IN_2$, 303.0358 $[M+H]^+$. Found: 303.0355.

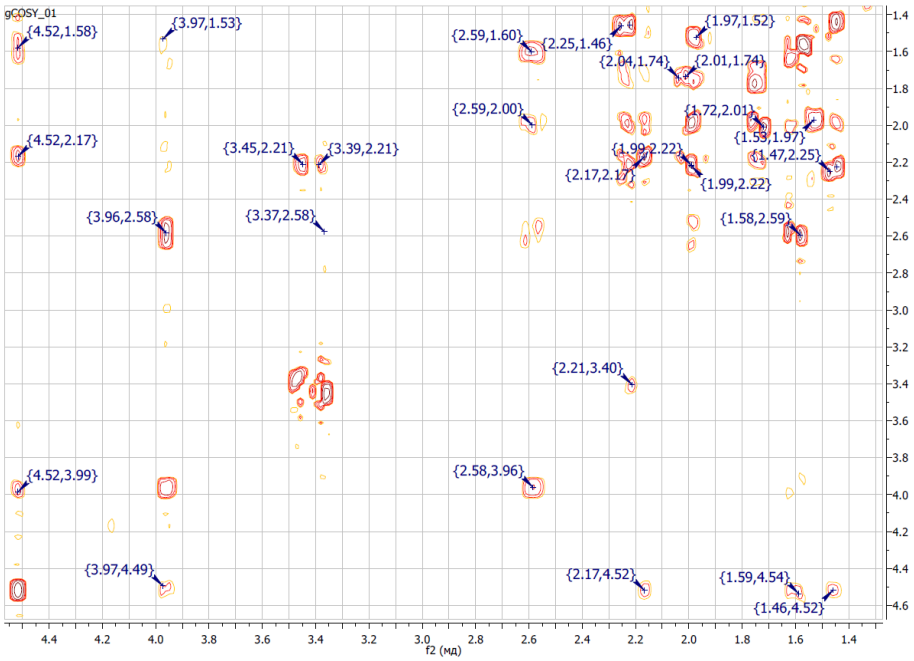
*^{1}H NMR spectrum of compound **10** in $CDCl_3$*

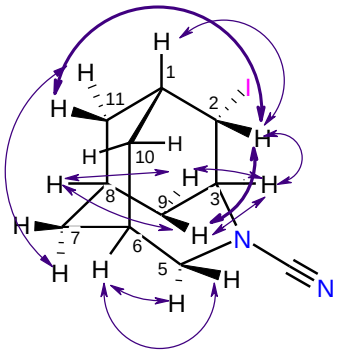


*^{1}H-^{13}C HSQC contour map of compound **10** in $CDCl_3$*



*^{1}H-^{1}H COSY contour map of compound **10** in $CDCl_3$*

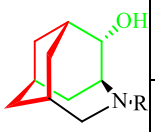
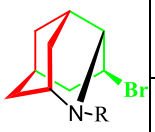




The most significative chemical structure correlations resolved by ^{1}H-^{1}H COSY of compound **10**. Bold arrows indicate "W-couplings".

Calculation of Zefirov–Palyulin (ZP) and Cremer–Pople (CP) puckering parameters for the cycles in the structures **8** and **3** was carried out by RICON program [A.Yu. Zotov, V.A. Palyulin, and N.S. Zefirov, *J. Chem. Inf. Comput. Sci.*, 1997, **37**, 766].

The results are summerized in the table:

Structure	Rings and conformation	ZP puckering parameters				CP puckering parameters		
		S	**θ**	**ψ$_2$**	**σ**	**Q**	**θ**	**φ$_2$**
 **8**	**C1-C2-C3-C9-C8-C11** intermediate between *chair* and *envelope*	1.121	7.6	3.1	0.5	0.569	14.7	4.2
	C1-C10-C6-C7-C8-C11 distorted *chair*	1.128	4.8	9.6	0.5	0.563	9.8	10.2
	C3-N4-C5-C6-C7-C8-C9	1.457	-	315.7	1.1	0.805	-	310.7
 **3**	**C7-C6-C5-C4-C3-C8*** intermediate between *boat* and *twist-boat*	0.993	87.6	23.0	0.4	0.829	88.3	24.8
	C9-C8-C7-C6-C10-C1 intermediate between *chair* and *half-chair*	1.234	9.5	25.6	1.7	0.658	18.6	24.3
	C9-C1-N2-C3-C8	0.670	-	14.4	0.5	0.479	-	12.7

* X-ray analysis of the structure **3** is described in [A.A. Alexeev, E.V. Nurieva, K.A. Lyssenko, Yu. K. Grishin and O. N. Zefirova, *Struct. Chem.*, 2019, **30**, 473].