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Supplementary Material

Two dibenzodiazepinone molecules with dissimilar associations and apparent different tautomeric forms

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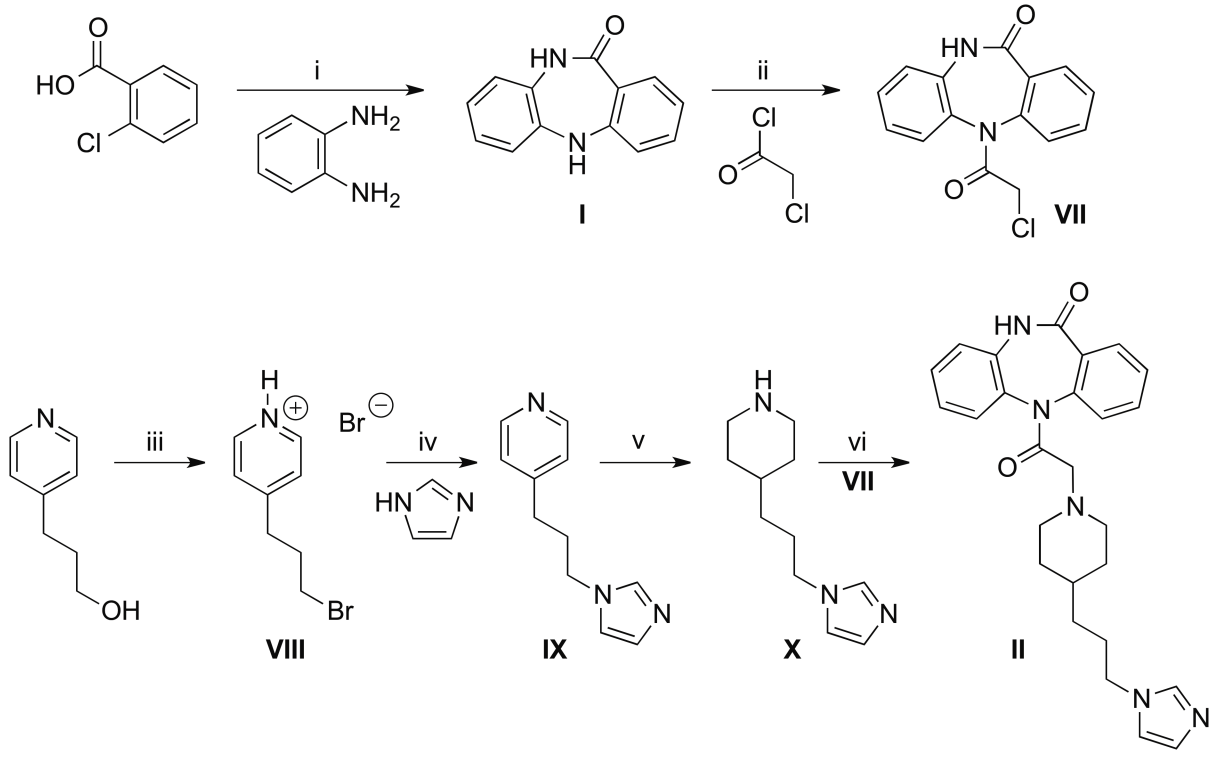
1. Synthesis of 5-((4-(3-(1H-Imidazol-1-yl)propyl)piperidin-1-yl)acetyl)-5H-dibenzo[b,e][1,4]diazepin-11(10H)-one (II)

The synthetic route for the preparation of dibenzodiazepinone derivative (**II**) is depicted in Scheme 1. 2-Chlorobenzoic acid and o-phenylenediamine were cyclocondensed following a reported protocol[1] to yield dibenzodiazepinone (**I**). As described previously, compound **I** was *N*-acylated with 2-chloroacetyl chloride to give dibenzodiazepinone derivative **VII**, a building block for the preparation of various dibenzodiazepinone-derived muscarinic receptor ligands.[2, 3]

Bromination of commercially available 3-pyridin-4-ylpropanol using 48% aqueous hydrobromic acid yielded the desired compound, which was isolated as the hydrobromide salt **VIII**.[4, 5] *N*-Alkylation of 1*H*-imidazole with bromide **VIII** gave compound **IX**, which was subjected to hydrogenation in acidic medium (MeOH, 32% hydrochloric acid) using platinum(IV) oxide as catalyst. These conditions afforded a selective reduction of the pyridine moiety to give piperidine derivative **X**. A previously reported alternative synthesis of compound **X** began from 3-pyridin-4-ylpropanol and involved reduction of the pyridine entity, then introduction of the imidazole heterocycle.[6] The final alkylation of compound **VII** with piperidine **X**, using acetonitrile as solvent and potassium carbonate as base, yielded dibenzodiazepinone derivative **II** (Scheme 1).



Reagents and conditions: i) copper-bronze, chlorobenzene, reflux, 8 h, 27%; ii) *N*,*N*-dimethylaniline, tetrahydrofuran, reflux, 5 h, 79%; iii) hydrobromic acid (48%), sulphuric acid (98%), reflux, 3 h, 86%; iv) potassium carbonate, acetonitrile, 90 °C (microwave reactor), 2 h, 67%; v) platinum(IV) oxide, hydrogen, hydrochloric acid (32%), methanol, r.t., 24 h, 80%; vi) potassium carbonate, acetonitrile, 100 °C (microwave reactor), 100 min, 48%.

Scheme 1. Synthesis of 5-((4-(3-(1H-Imidazol-1-yl)propyl)piperidin-1-yl)acetyl)-5H-dibenzo[b,e][1,4]-diazepin-11(10H)-one (**II**).

2. Experimental protocols and analytical data

General experimental conditions. 2-Chlorobenzoic acid, *o*-phenylenediamine, 2-chloroacetyl chloride, 3-(pyridin-4-yl)propanol, chlorobenzene, imidazole, platinum(IV) oxide and copper-bronze were purchased from Sigma-Aldrich. Solvents were obtained from commercial suppliers and used without further purification. Thin layer chromatography was performed on Merck silica gel 60 F254 TLC aluminum plates. For column chromatography silica gel DAVISIL (0.040-0.063 mm; GRACE Davison, Worms, Germany) was used. NMR spectra were recorded on Bruker Avance 300 (7.05 T, ^{1}H: 300 MHz, ^{13}C: 75 MHz), Bruker Avance 600 (14.1 T, ^{1}H: 600 MHz, ^{13}C: 150 MHz) and Bruker Avance 700 (16.4 T, ^{1}H: 700 MHz) instruments (Bruker, Karlsruhe, Germany). Low-resolution mass spectrometry (MS) was performed on a Waters Micromass ZQ^{TM} Detector (Waters, Milford, MA, US). High-resolution mass spectrometry (HRMS) was performed on an Orbitrap LTQ XL ion trap mass spectrometer (Thermo Fisher Scientific, San Jose, CA, US) using an electrospray ionization (ESI) source. The instrument was calibrated with a standard calibration solution (as outlined in the instrument manual) on each day of analysis using direct infusion into the ESI source. The instrument conditions were optimized for sensitivity on both solvent (background) and analyte using LC tune software. The analysis was carried out in positive ion mode with an FTMS analyser at a resolution of 60000. Data were acquired in full scan mode over 60 seconds and analyzed using the Qual Browser feature in Xcalibur 2.1 (Thermo Fisher Scientific, San Jose, CA, USA). Elemental analysis was carried out by the Microanalytical Unit, Research School of Chemistry, The Australian National University, Canberra, on a Carlo Erba 1106 instrument. IR spectra were measured on a Nicolet^{TM} 380 spectrophotometer (Thermo Electron Corporation). Melting points were determined with a MEL-TEMP II apparatus (Laboratory Devices Inc., US) and are uncorrected.

Overview of NMR experiments							
Compd.	^{1}H	^{13}C	DEPT135	^{1}H-COSY	HSQC	HMBC	NOESY
I	√	√	√	√	√	√	-
II	√	√	√	√	√	√	√
VII	√	√	√	√	√	√	√
VIII	√	√	-	-	-	-	-
IX	√	√	-	-	-	-	-
X	√	√	-	-	-	-	-

5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (I).[1, 7] Compound **I** was prepared from 2-chlorobenzoic acid and *o*-phenylenediamine as previously described.[1] The resulting olive coloured plates, (11.54 g, 27%) were used in later reactions without recrystallization. A minor portion of diazepinone **I** was recrystallized from EtOH/EtOAc to yield yellow-green rhombic and hexagonal plates mp 259-261 °C (lit.[1] mp 256-257 °C). IR (Nujol) 3320, 3175, 1640, 1605 cm^{-1}. ^{1}H-NMR (300 MHz, [D_6]DMSO): δ (ppm) 6.87-6.91 (m, 2H), 6.93-6.97 (m, 2H), 6.98-7.01 (m, 2H), 7.33 (m, 1H), 7.68 (dd, 1H, *J* 7.8, 1.4 Hz), 7.83 (s, 1H), 9.83 (s, 1H). ^{13}C-NMR (75 MHz, [D_6]DMSO): δ (ppm) 119.0, 119.7, 120.7, 121.2, 122.8, 122.9, 124.5, 129.8, 132.1, 133.2, 139.9, 150.4, 167.9. MS (ESI, MeOH) *m/z* (%) 653 (18) [3*M*+Na]$^+$, 448 (28), 443 (82) [2*M*+Na]$^+$, 440 (43), 249 (45) [*M*+K]$^+$, 233 (77) [*M*+Na]$^+$, 211 (100) [*M*+H]$^+$. $C_{13}H_{10}N_2O$ (210.2).

5-((4-(3-(1*H*-Imidazol-1-yl)propyl)piperidin-1-yl)acetyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (II). Chloroacetamide **VII** (254 mg, 0.886 mmol) and piperidine **X** (180 mg, 0.93 mmol) were dissolved together in anhyd. MeCN (2 mL). Finely ground potassium carbonate (122 mg, 0.886 mmol) was added and the mixture kept under stirring in a microwave reactor (Biotage Initiator 8) at 100 °C (pressure: ca. 2 bar) for 100 min. Solid material was removed by filtration, the filtrate evaporated to dryness, and the residue subjected to column chromatography using mixtures of CH_2Cl_2, Et_2O and MeOH as solvent (R_f = 0.4 for CH_2Cl_2/MeOH 5:1 (v/v)). The major fraction (CH_2Cl_2/Et_2O/MeOH 20:4:1 to 10:2:1) was evaporated to dryness under reduced pressure, then taken up in CH_2Cl_2 (0.5 mL) and pentane (0.8 mL). Removal of the solvent *in vacuo* afforded the product **II** as a pale tan coloured glass (187 mg, 48%) mp 95-97 °C. IR (Nujol) 1660, 1600 cm^{-1}. A portion (150 mg) of this material was dissolved in EtOH (0.8 mL), Et_2O (1 mL) was added, and the solution was kept at −20 °C to afford white rosettes (ca. 100 mg), which were kept *in vacuo* at 80 °C for 7 h. Separation of the mother liquor and storage at −20 °C afforded a solvate of the same substance (**II** • EtOH) as translucent needles (10 mg) mp 98-100 °C that were suitable for x-ray crystallographic analysis (contained 1 equivalent of co-crystallized EtOH as evident from NMR spectroscopic and X-ray crystallographic analyses). Anal. calcd for $C_{26}H_{29}N_5O_2$ • C_2H_6O: C 68.83, H 7.01, N 14.33; found: C 68.78, H 7.13, N 14.18. Due to a slow rotation about the exocyclic amide group on the NMR time scale, two isomers (ratio 1:1) were evident in the NMR spectra. ^{1}H-NMR (700 MHz, [D_4]MeOH): δ (ppm) 1.00-1.11 (m, 1H), 1.12-1.30 (m, 6.5H), 1.49 (d, 0.5H, *J* 11.8 Hz), 1.56 (m, 1H), 1.64 (d, 0.5H, *J* 12.2 Hz), 1.79 (m, 2H), 1.90-2.04 (m, 2H), 2.50 (d, 0.5H, *J* 9.5 Hz), 2.65 (d, 0.5H, *J* 10.1 Hz), 2.82 (d, 1H, *J* 10.2 Hz), 2.85 (d, 1H, *J* 10.2 Hz), 3.06 (m, 0.5H), 3.16 (m, 0.5H), 3.20-3.25 (m, 1H), 3.64 (q, 1.3H, *J* 7.1 Hz), 4.01 (t, 2H, *J* 7.0 Hz), 6.97 (t, 1H, *J ca.* 0.9 Hz), 7.13 (t, 1H, *J ca.* 1.1 Hz), 7.23-7.31 (m, 2H), 7.36 (t, 0.5H, *J* 7.2 Hz), 7.42 (t, 0.5H, *J* 7.4 Hz), 7.46-7.52 (m, 1.5H), 7.54 (t, 0.5H, *J* 7.4 Hz), 7.58 (t, 1H, *J* 7.7 Hz), 7.65 (s, 1H), 7.68 (m, 1H), 7.89 (d, 0.5H, *J* 7.5 Hz), 7.92 (d, 0.5H, *J* 7.4 Hz). ^{1}H-NMR (600 MHz, [D_6]DMSO/D_2O 15:1

(v/v), rosettes): δ (ppm) 0.64-0.79 (m, 1H), 0.92-1.10 (m, 4H), 1.24-1.48 (m, 2H), 1.62 (m, 2H), 1.73-1.86 (m, 2H), 2.11 (d, 0.5H, *J* 10.0 Hz), 2.66 (d, 0.5H, *J* 10.1 Hz), 2.57 (m, 1H), 2.86 (d, 0.5H, *J* 14.3 Hz), 2.93 (d, 0.5H, *J* 14.5 Hz), 3.11 (d, 0.5H, *J* 14.5 Hz), 3.29 (d, 0.5H, *J* 14.3 Hz), 3.88 (bs, 2H), 6.86 (s, 1H), 7.13 (s, 1H), 7.14-7.23 (m, 2H), 7.25-7.32 (m, 1H), 7.37-7.46 (m, 2H), 7.54-7.63 (m, 3H), 7.73-7.79 (m, 1H). ^{13}C-NMR (150 MHz, [D$_6$]DMSO/D$_2$O 15:1 (v/v), rosettes):[a] δ (ppm) 28.1, 33.3/33.67/33.74/31.9, 32.9, 34.4/34.5, 46.5, 52.8/53.0/53.36/53.41, 60.3/60.8, 119.6, 121.7/121.8, 124.9/125.2, 126.4, 127.5, 128.17, 128.24, 128.30, 128.37, 128.5/128.9, 129.2, 130.2, 130.7, 130.8, 132.9/133.2, 134.6, 134.9, 135.0, 135.8, 137.4, 142.6/142.9, 166.8, 169.0/169.4. MS (ESI, MeOH): *m/z* (%) 887 (8) [2*M*+H]$^+$, 444 (100) [*M*+H]$^+$. HRMS (ESI, MeOH) *m/z* calcd. for [$C_{26}H_{30}N_5O_2$]$^+$ 444.2394; found: 444.2390. $C_{26}H_{29}N_5O_2$ (443.5).

[a]Provided that adjacent signals in the ^{13}C-NMR spectra could be unambiguously clarified (using ^{1}H-COSY and HSQC spectra) to arise from one carbon nucleus, these signals were depicted as a set of signals (e.g. 123.7/123.9 ppm).

5-(2-chloroacetyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (VII).[2] Amine **I** and chloroacetyl chloride were combined as previously described[2] to yield amide **VII** as a grey powder (19.7 g, 79%) mp 240-242 °C (lit.[2] mp 241-242 °C). IR (Nujol) 3180, 1685, 1655 cm^{-1}. Due to a slow rotation about the exocyclic amide group on the NMR time scale, two isomers were evident in the NMR spectra (ratio major : minor 1.5 : 1). ^{1}H-NMR (300 MHz, [D$_6$]DMSO): δ (ppm) 4.09 (d, 0.6H, *J* 13.8 Hz), 4.18 (d, 0.4H, *J* 13.6 Hz), 4.39 (d, 1H, *J* 13.7 Hz), 7.17-7.31 (m, 2H), 7.31-7.58 (m, 3H), 7.61-7.87 (m, 3H), 10.69 (s, 0.4H), 10.75 (s, 0.6H). ^{13}C-NMR (75 MHz, [D$_6$]DMSO): δ (ppm) 42.1, major: 122.1, 125.4, 127.5, 127.7, 128.4, 129.6, 129.8, 130.8, 132.9, 133.2, 135.8, 141.8, 165.4, 166.2, minor: 121.8, 124.8, 126.7, 128.5, 128.6, 129.2, 130.6, 131.1, 133.6, 133.9, 134.8, 140.9, 165.0, 166.1. MS (ESI, MeOH): *m/z* (%) 595/597 (26/16) [2*M*+Na]$^+$, 325/327 (19/7) [2*M*+K]$^+$, 309/311 (100/34) [*M*+Na]$^+$. $C_{15}H_{11}ClN_2O_2$ (286.7).

4-(3-bromopropyl)pyridine hydrobromide (VIII).[4, 5] 98% Sulphuric acid (3 mL) was added dropwise to a stirred solution of 3-(pyridin-4-yl)propanol (5.00 g, 36.5 mmol) in 48% aq. hydrobromic acid (16.5 mL) and the mixture was stirred in a bath at 130 °C. After 3 h the mixture was cooled to rt and water (25 mL) was added prior to basification with 28% NH_3 (13 mL). The product was extracted with Et_2O (70 mL, 50 mL). The extracts were combined, washed with water (15 mL) and then brine (30 mL), and dried over sodium sulphate. The solution was filtered, 48% aq. hydrobromic acid (3.7 mL) was added, and diethyl ether was removed under reduced pressure. Acetonitrile (30 mL) was added to the residue, the solvent was evaporated, and the process repeated. The residue (pale yellow oil) was treated with CH_2Cl_2 (15 mL), the volatiles were evaporated, and the residue again taken up in CH_2Cl_2 (15 mL). A precipitate was deposited and collected as a white granular, hygroscopic solid (8.75 g,

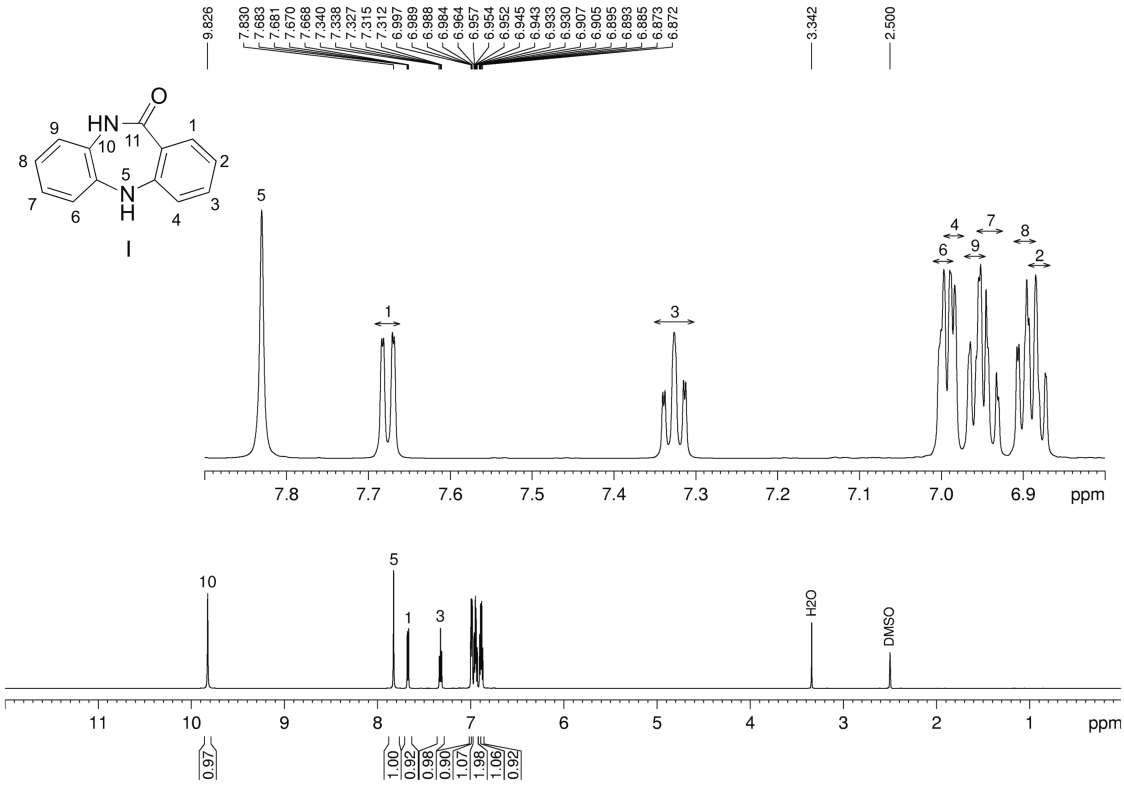
85%) mp 122-124 °C. Anal. calcd for $C_8H_{10}BrN$ • HBr: C 34.20, H 3.95, N 4.98; found: C 34.39, H 4.13, N 4.76. IR (Nujol) 2600 br, 1630, 1605 cm^{-1}. ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 2.34 (m, 2H), 3.18 (t, 2H, *J* 7.7 Hz), 3.56 (t, 2H, *J* 6.5 Hz), 8.05 (d, 2H, *J* 7.0 Hz), 8.80 (d, 2H, *J* 6.8 Hz). ^{13}C-NMR (75 MHz, [D_4]MeOH): δ (ppm) 33.7, 34.3, 36.2, 129.6, 143.1, 165.9. MS (ESI, MeOH): *m/z* (%) 200/202 (100) $[M+H]^+$. $C_8H_{10}BrN$ + HBr (200.1 + 80.9).

4-(3-(1*H*-imidazol-1-yl)propyl)pyridine (IX). Imidazole (0.72 g, 10.5 mmol) and bromide **10** (1.97 g, 7.0 mmol) were dissolved in anhydrous MeCN (15 mL). Finely ground potassium carbonate (5.8 g, 42 mmol) was added and the mixture was kept under stirring in a microwave reactor (Biotage Initiator 8) at 90 °C (pressure: 1-2 bar) for 2 h. Insoluble material was filtered off and the filtrate diluted with MeCN to a volume of 200 mL. Water (20 mL) and brine (10 mL) were added and the phases separated. The aqueous phase was extracted with acetonitrile (2 x 50 mL). The organic extracts were pooled and dried over sodium sulphate. Evaporation of the volatiles and column chromatography of the residual orange oil using mixtures of dichloromethane, MeOH and 28% aq. NH_3 as eluent (R_f = 0.6 for CH_2Cl_2/MeOH/28% aq. NH_3 90:9:1) afforded the product **IX** as a yellow oil (1.10 g, 67%). Anal. calcd for $C_{11}H_{13}N_3$: C 70.56, H 7.00, N 22.44; found: C 70.20, H 7.37, N 22.06. IR (neat) 3380 br, 3105, 3025, 2935, 1600 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.12 (p, 2H, *J* 7.3 Hz), 2.58 (t, 2H, *J* 7.7 Hz), 3.97 (t, 2H, *J* 6.9 Hz), 6.91 (s, 1H), 7.06 (m, 3H), 7.60 (d, 1H, *J* 5.4 Hz), 8.49 (d, 2H, *J* 6.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 31.3, 31.9, 46.3, 118.8, 123.8, 129.2, 137.1, 149.3, 150.1. MS (ESI, MeOH): *m/z* (%) 210 (33) $[M+Na]^+$, 188 (100) $[M+H]^+$. $C_{11}H_{13}N_3$ (187.2).

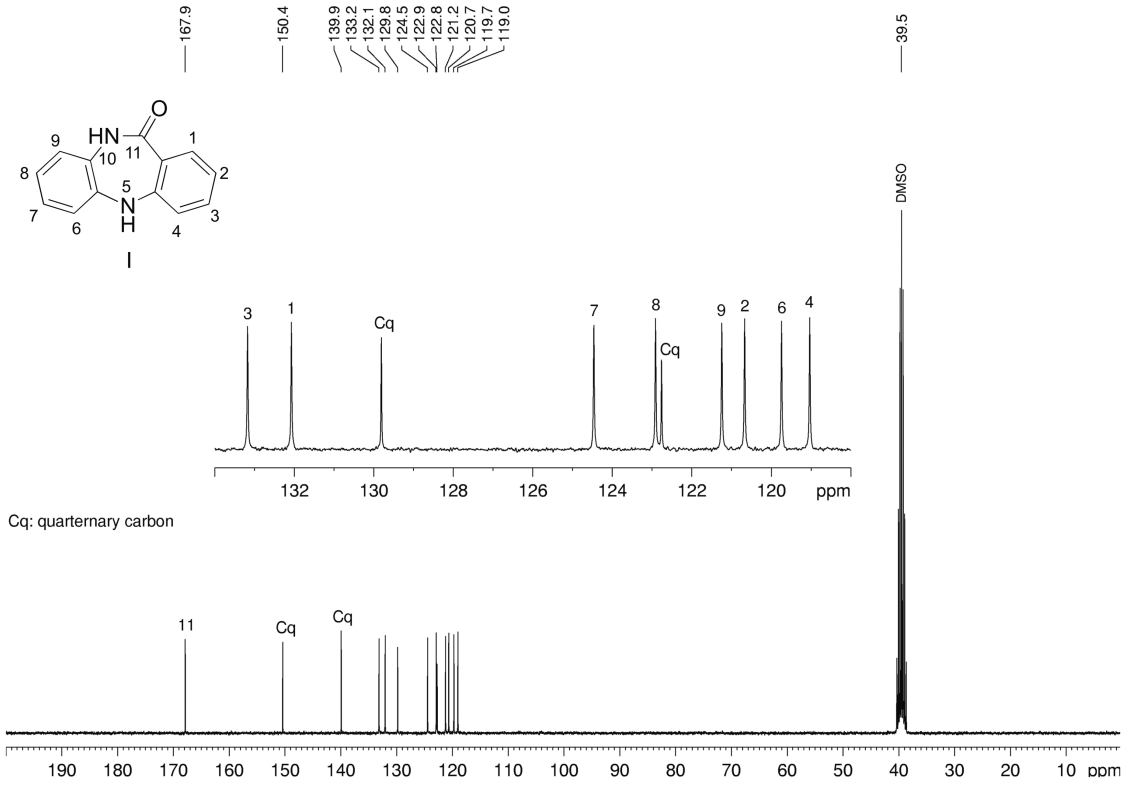
4-(3-(1*H*-imidazol-1-yl)propyl)piperidine (X).[6] Under an atmosphere of argon platinum(IV) oxide (0.215 g, 0.95 mmol) was added to a solution of compound **11** (0.4 g, 2.14 mmol) in MeOH (5 mL) and 32% hydrochloric acid (525 µL). A slow stream of hydrogen was passed through a glass tube into the vigorously stirred suspension for 24 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The oily residue was taken up in $CHCl_3$ (30 mL), water (5 mL) and 10% aq. NaOH (5 mL). The mixture was shaken, the phases were separated and the aqueous phase treated with $CHCl_3$ (2 x 20 mL). The pooled extracts were washed with water (5 mL) and dried over sodium sulphate. Evaporation of the volatiles yielded a pale yellow oil, which was subjected to column chromatography. The fraction eluted with CH_2Cl_2, MeOH and 28% aq. NH_3 (150:75:1 to 75:75:1) (R_f = 0.2 for CH_2Cl_2/MeOH/28% aq. NH_3 150:75:1) gave piperidine **X** as a pale yellow wax-like solid (0.33 g, 80%) mp 34-36 °C. Anal. calcd for $C_{11}H_{19}N_3$: C 68.35, H 9.91, N 21.74; found: C 68.47, H 9.56, N 21.36. IR (Nujol) 3350 br, 1640 cm^{-1}. ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 1.12 (dq, 2H, *J* 12.4, 4.0 Hz), 1,25 (m, 2H), 1.42 (m, 1H), 1.71 (d, 2H, *J* 13.0 Hz), 1.84 (m, 2H), 2.58 (dt, 2H, *J* 12.4, 2.6 Hz), 3.03 (td, 2H, *J* 12.2, 2.8 Hz), 4.04 (t, 2H, *J* 7.1 Hz), 6.99 (s, 1H), 7.15 (s, 1H), 7.67 (s, 1H). ^{13}C-NMR (75

MHz, [D_4]MeOH): δ (ppm) 30.0, 34.6, 35.8, 37.6, 47.8, 48.9, 121.4, 129.8, 139.3. MS (ESI, MeOH): *m/z* (%) 216 (12) $[M+Na]^+$, 194 (100) $[M+H]^+$, 126 (65). $C_{11}H_{19}N_3$ (193.3).

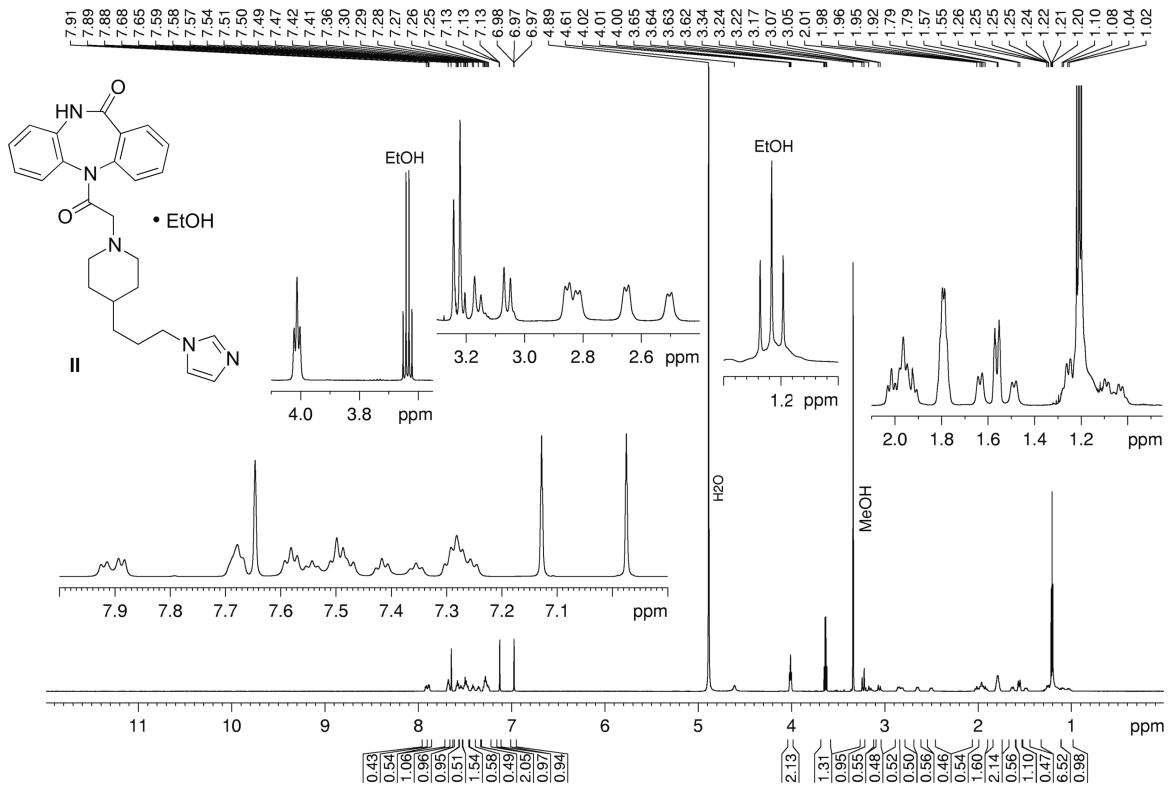
3. ^{1}H-NMR and ^{13}C-NMR spectra



^{1}H-NMR spectrum (600 MHz, [D_6]DMSO) of compound **I**

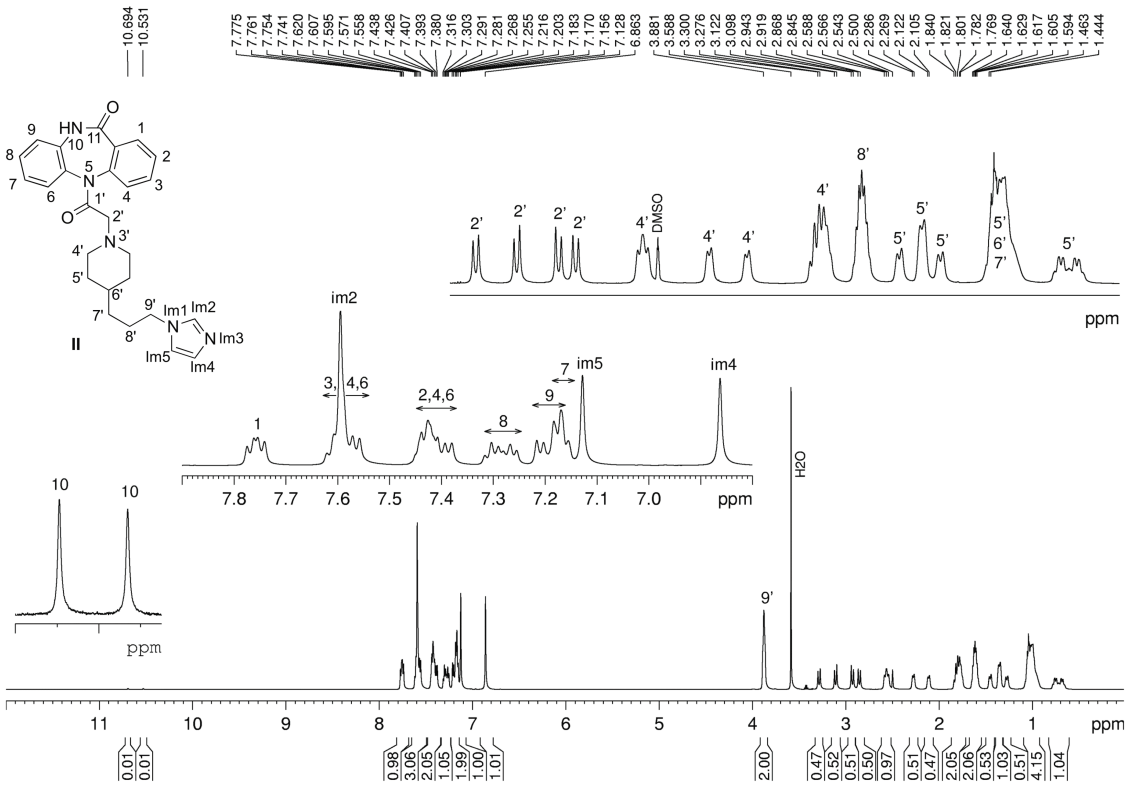


^{13}C-NMR spectrum (75 MHz, [D_6]DMSO) of compound **I**



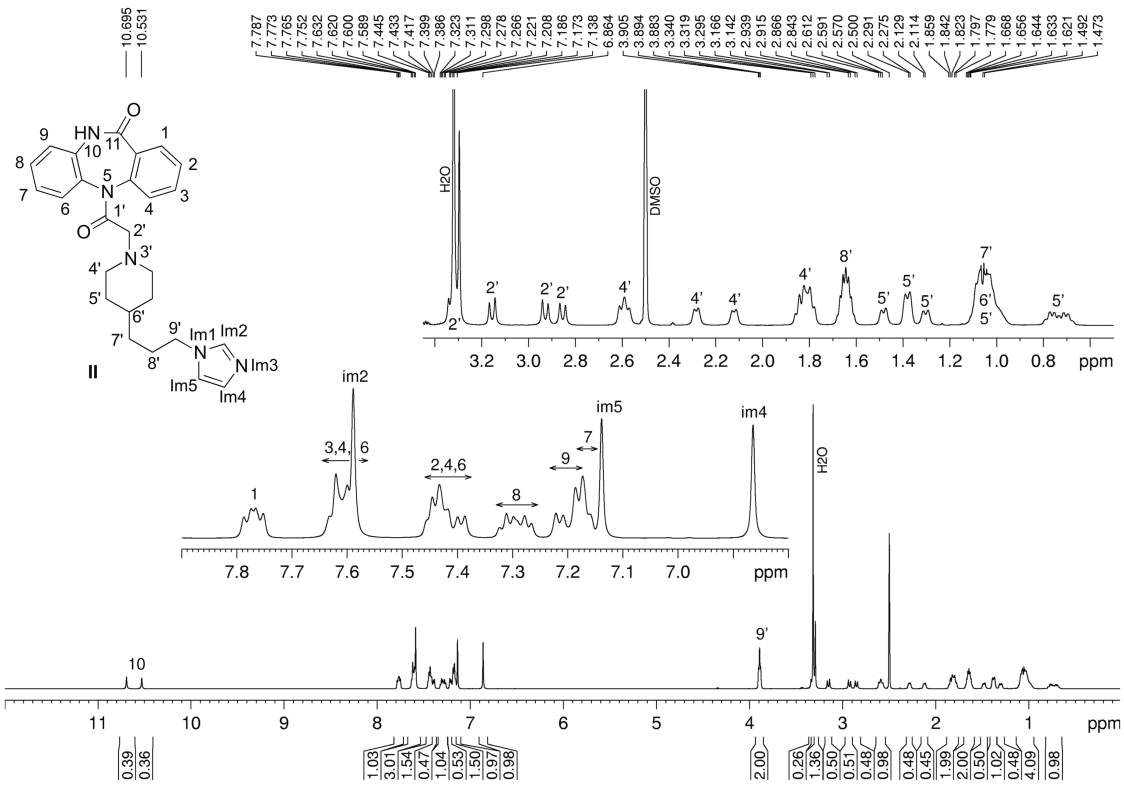
II • EtOH

^{1}H-NMR spectrum (700 MHz, [D_4]MeOH) of compound **II** • EtOH

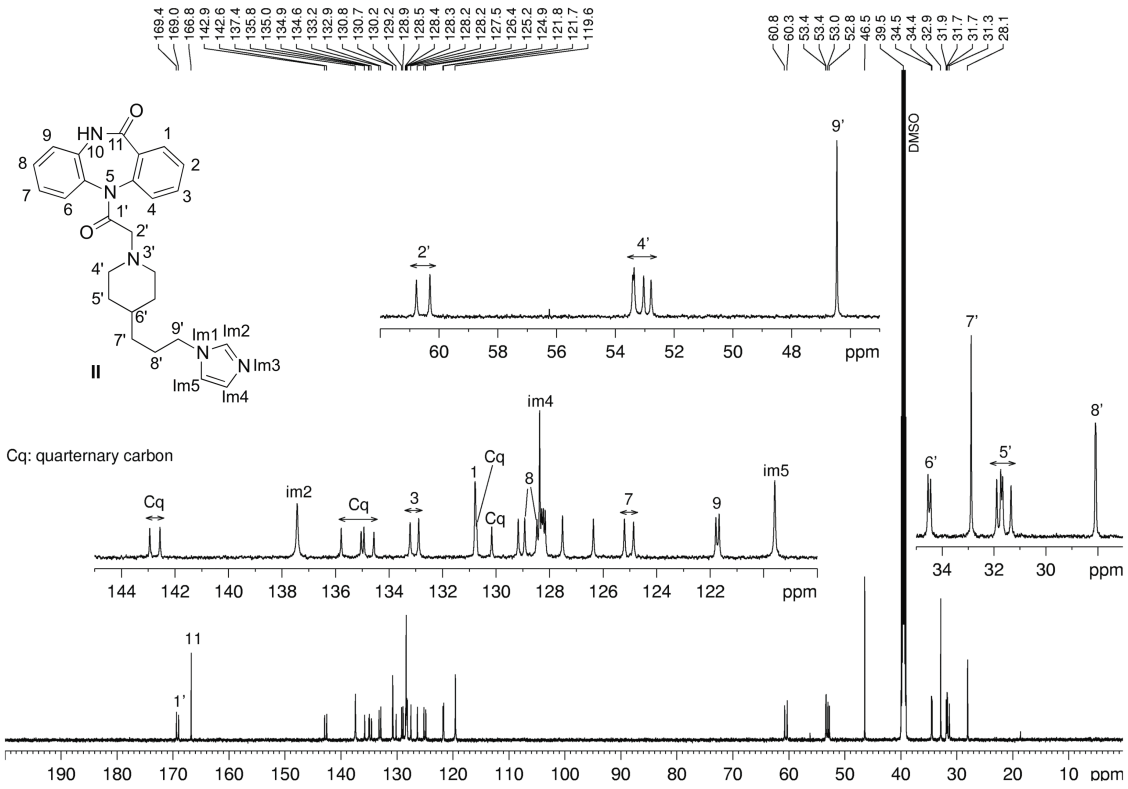


II

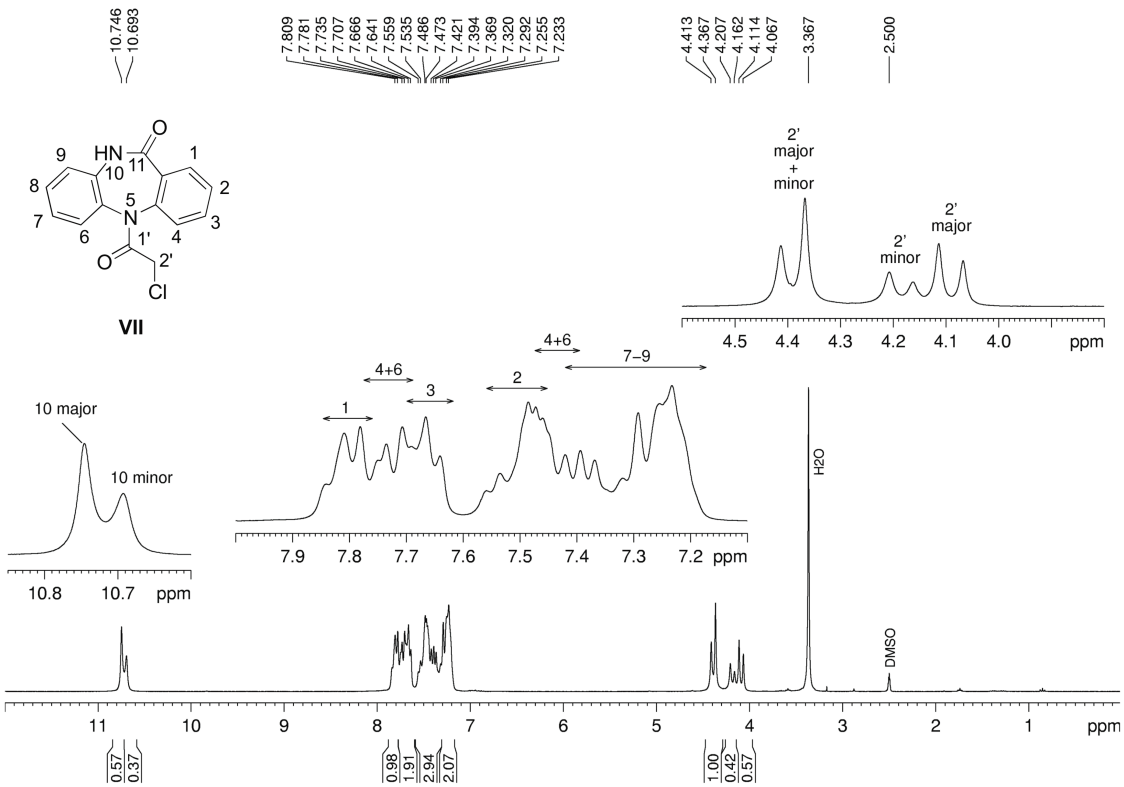
^{1}H-NMR spectrum (600 MHz, [D_6]DMSO/D_2O 15:1) of compound **II** (rosettes)



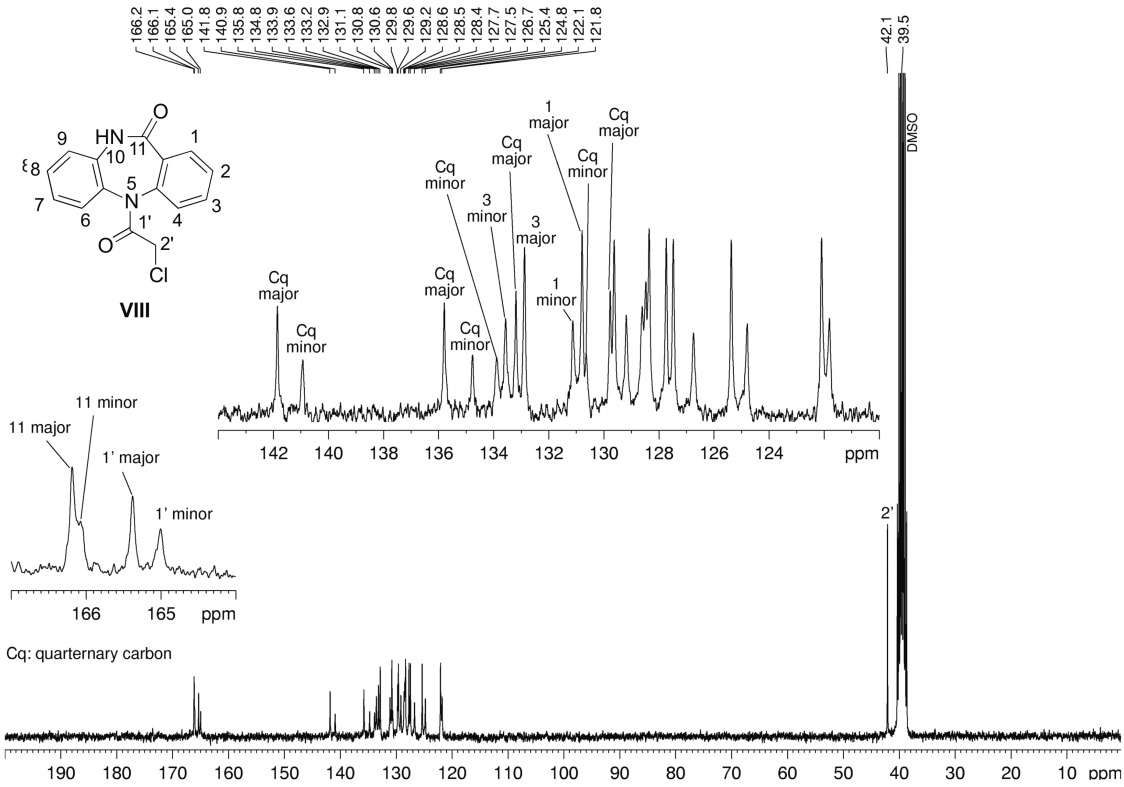
^{1}H-NMR spectrum (600 MHz, [D_6]DMSO) of compound **II** (rosettes)



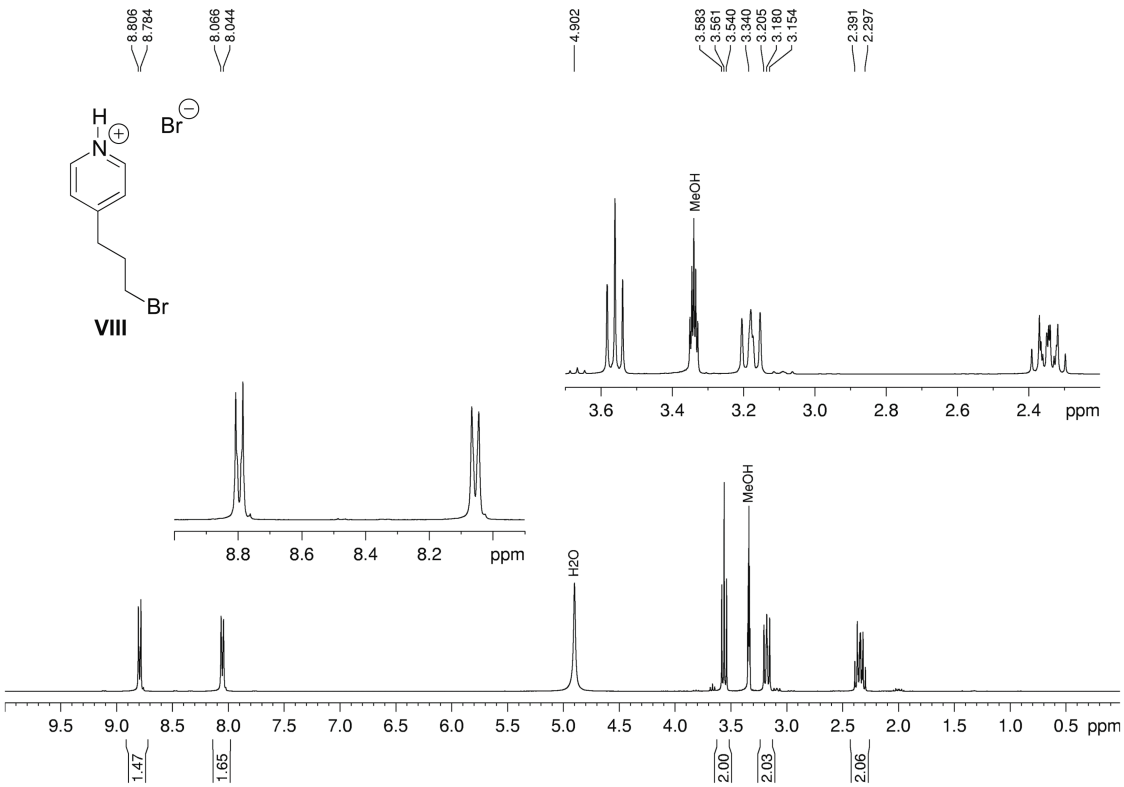
^{13}C-NMR spectrum (150 MHz, [D_6]DMSO /D_2O 15:1) of compound **II** (rosettes)



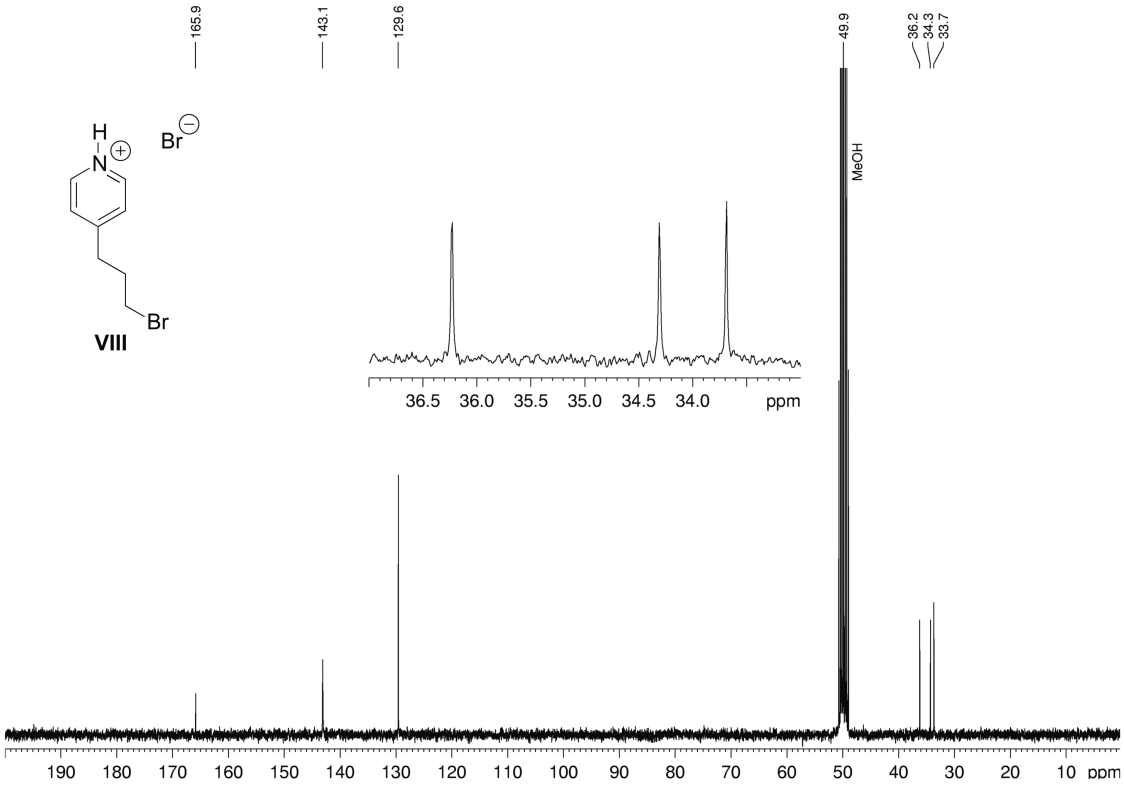
^{1}H-NMR spectrum (300 MHz, [D_6]DMSO) of compound **VII**



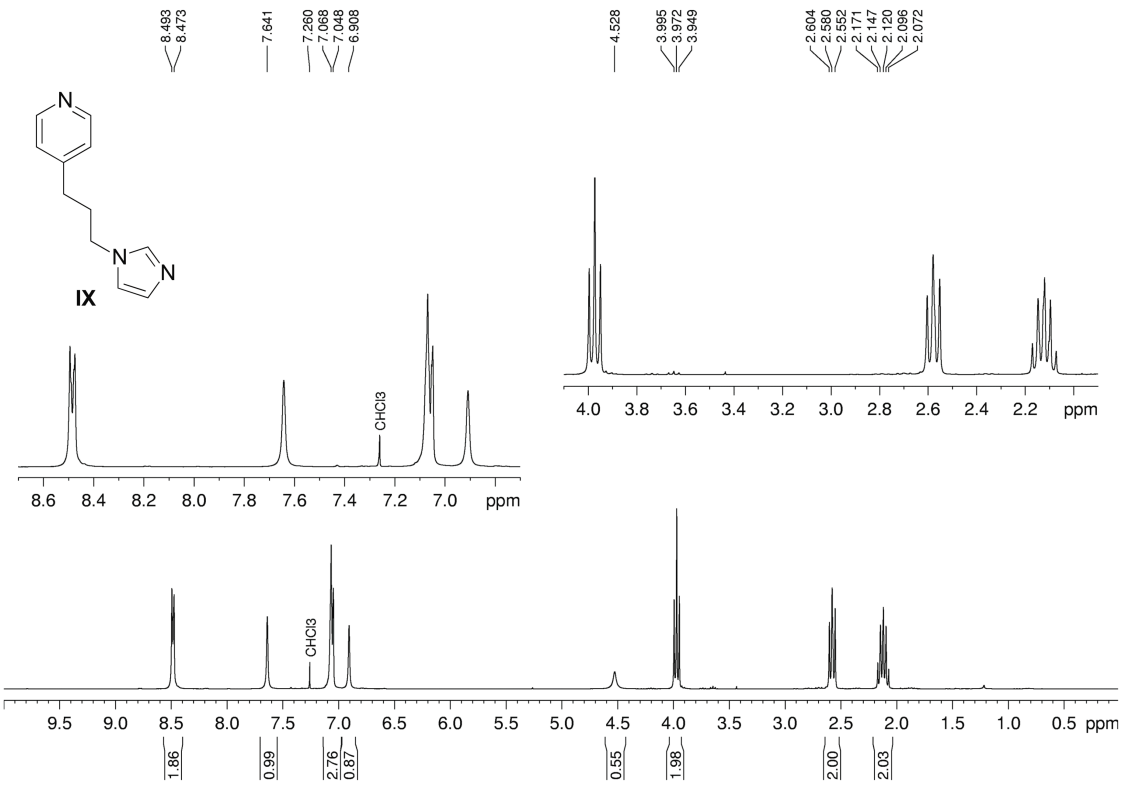
^{13}C-NMR spectrum (75 MHz, [D_6]DMSO) of compound **8**



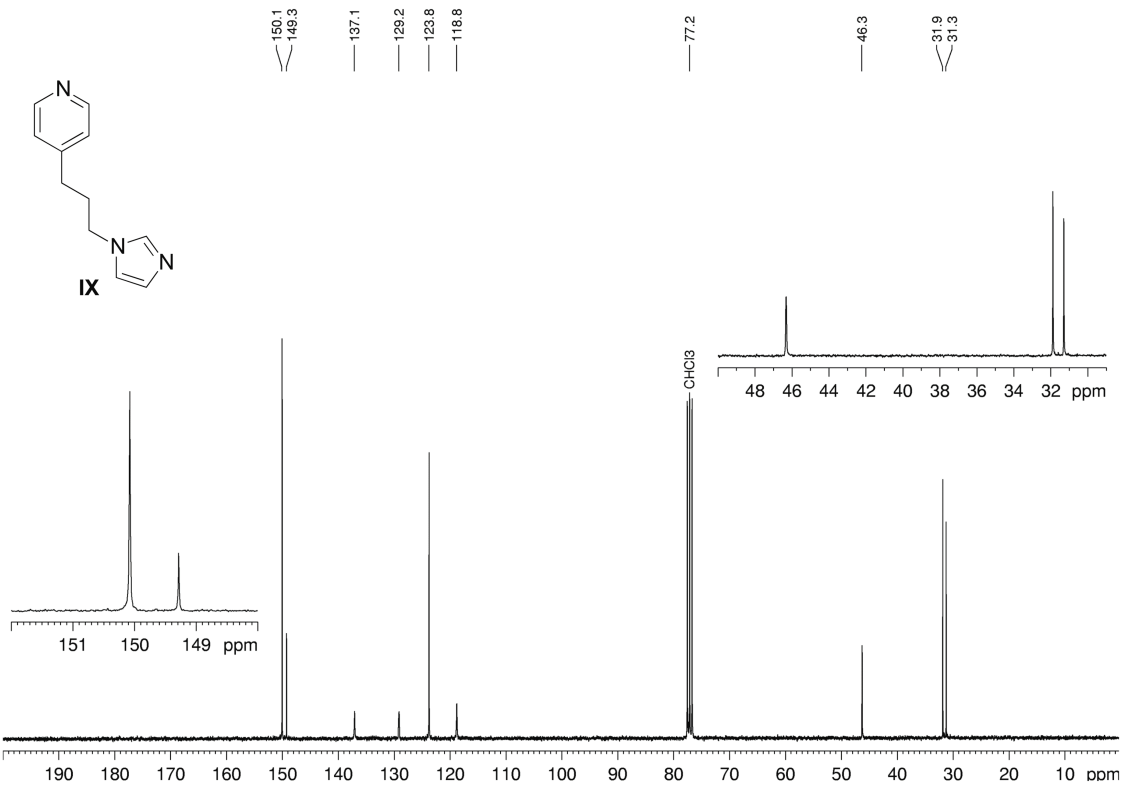
^{1}H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **VIII**



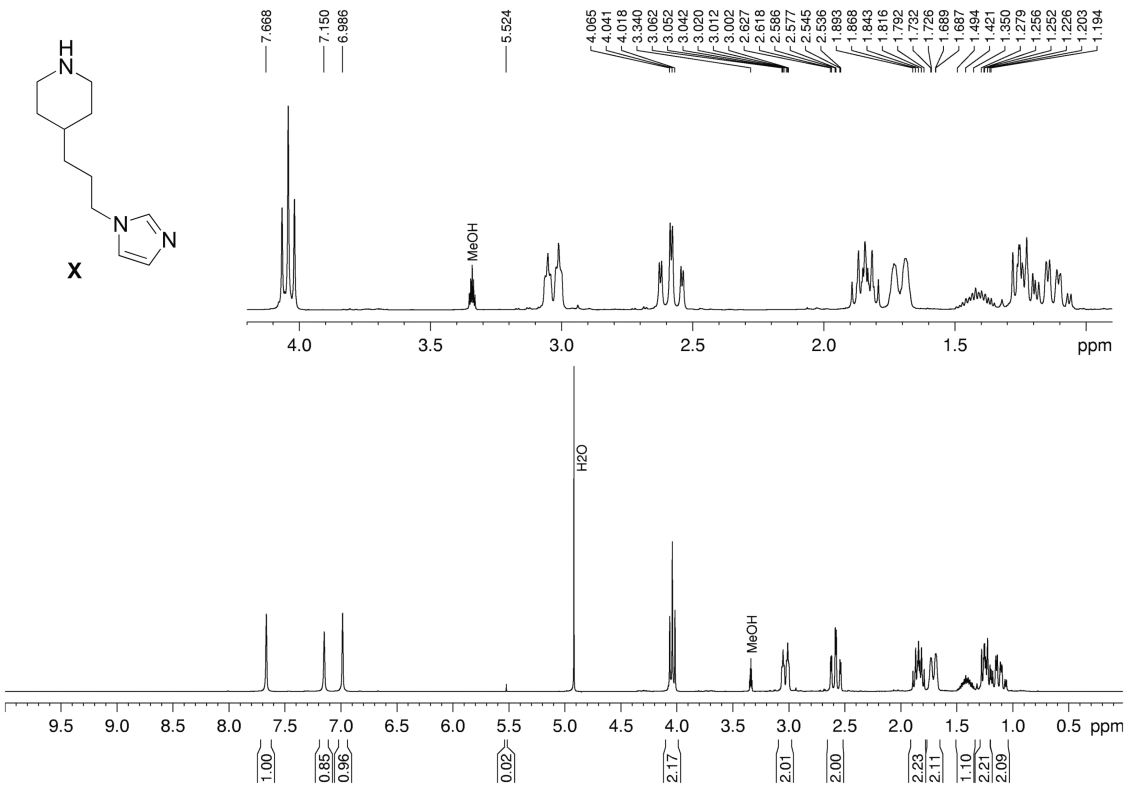
^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **VIII**



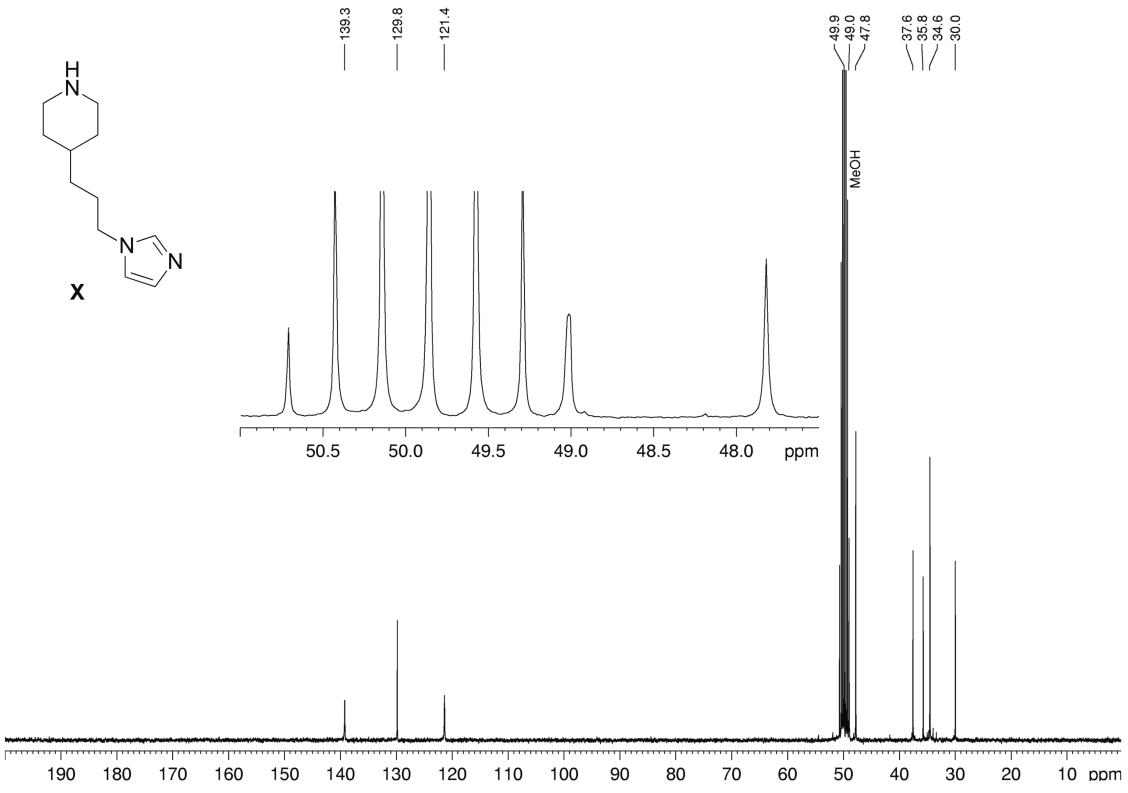
^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of compound **IX**



^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of compound **IX**

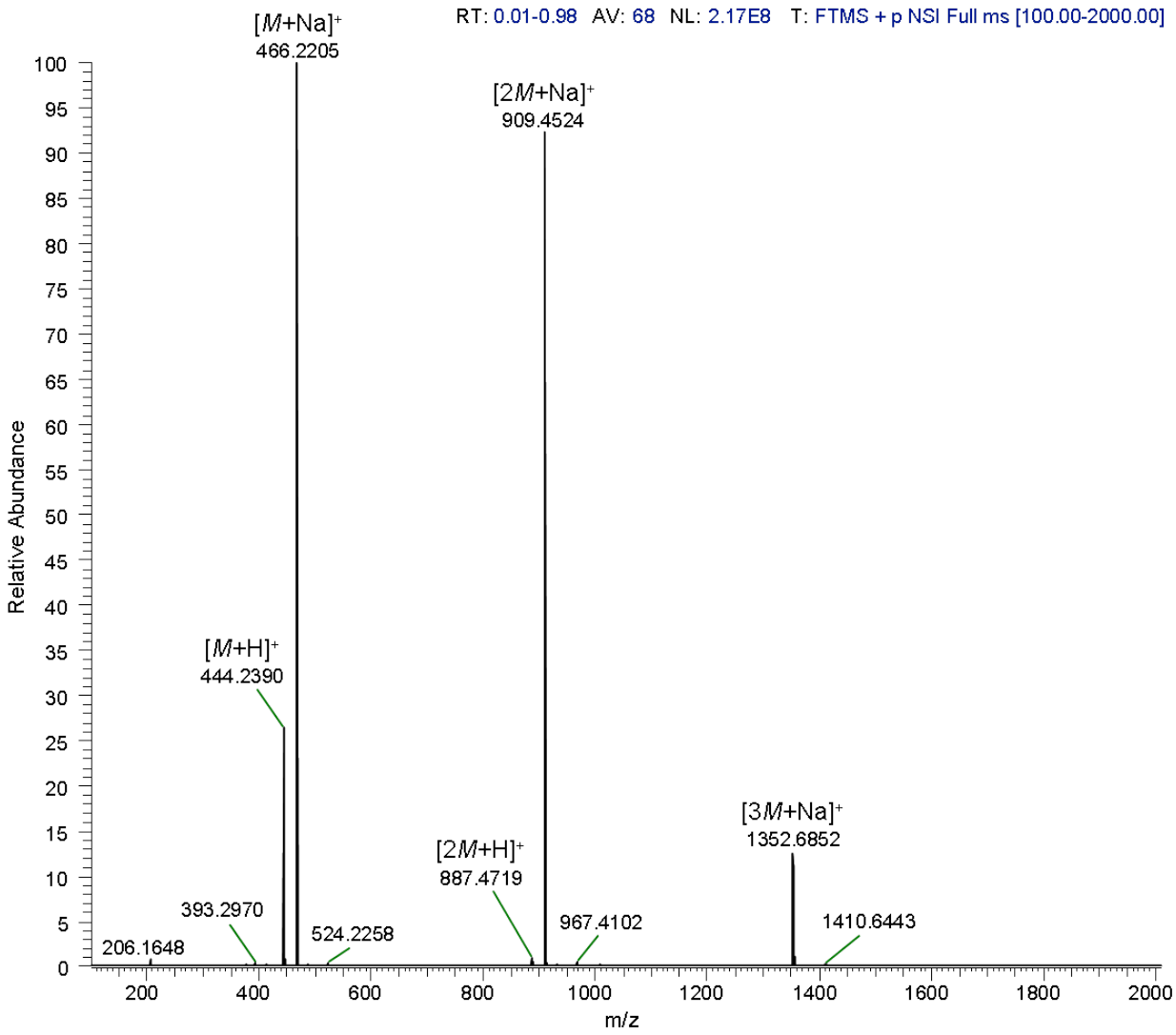


^{1}H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **X**



^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **X**

4. High resolution mass spectrometry analysis of compound II



HRMS spectrum of compound **II** (exact mass $[M+H]^+$ 444.2394)

5. References

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