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Antibacterial activity of new silatrane pyrrole-2-carboxamide hybrids

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Experimental details

The organic solvents used were dried and purified according to the standard procedure [S1].

1-(3-Aminopropyl)silatrane (**1**) was synthesized by the method [S2].

2-(Trichloroacetyl)pyrroles **2a-d** were purchased from Aldrich.

^{1}H (400.1 MHz), ^{13}C (100.6 MHz), ^{29}Si (79.5 MHz), and ^{15}N (40.6 MHz) NMR spectra were recorded on a Bruker AV400 instrument in DMSO-d_6 at rt. Chemical shifts δ are quoted in parts per million (ppm). The residual solvent peak δ_H 2.50 and δ_C 39.5 (DMSO-d_6) were used as references. The assignment of signals in the ^{1}H NMR spectra was made using COSY and NOESY 2D experiments. Resonance signals of carbon atoms were assigned based on 2D ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC experiments. The values of the δ ^{15}N were measured through the 2D ^{1}H-^{15}N HMBC experiment and were referenced to CH_3NO_2 (0.0 ppm).

IR spectra were recorded on a Bruker IFS25 spectrophotometer (KBr).

Mass spectra were recorded on an HR-TOF-ESI-MS Agilent 6,210 with the registration mode of positive ions with acetonitrile as a solvent and 0.1% perfluorobutyric acid as an ionizing agent.

Elemental analysis was performed on a Thermo Finnigan Flash series 1,112 Elemental analyzer.

Melting points were measured with a Mel Temp II device.

Minimal inhibitory concentration (MIC) measurement

The antimicrobial activity and MIC of compounds **1**, **3a-d** were determined using the broth microdilution method [S3]. Test cultures were *Enterococcus durans* B-603, *Bacillus subtilis* B-407 and *Escherichia coli* B-1238 (provided by All-Russian Collection of Micro-organisms, VKM). The *E. durans* was grown on a modified medium for lactic acid bacteria with Tween-80 (medium No. 75, VKM), *B. subtilis* – on potato agar, *E. coli* – on meatpeptone agar. Growth medium (100 μl) containing 1.25–1000 μg ml^{-1} of test compound **1**, **3a-d** (in 1% DMSO) was added to a 48-well microtiter plate.
As a control, the growth medium was used without the addition of test compounds. Agar culture suspensions were diluted to 0.5 McFarland standard (1.5x108 CFU ml^{-1}). The optical density was measured using a P-5400UF spectrophotometer. The microbial suspension was diluted to 1:10 (up to 1×10^5 CFU ml^{-1}) and 100 μl was added to each well. The plates were incubated at 37 °C for 24 h. Each test was performed in two replications. The MIC of compounds **1**, **3a-d** was measured as the maximum dilution of compounds showing no visible growth of bacteria.

Prediction of physicochemical and pharmacokinetic properties

The properties of the obtained compounds were evaluated using SwissADME software (http://www.swissadme.ch). Selected data on physical–chemical and pharmacokinetic properties, drug-likeness, and bioavailability of silatranes **3a-d** are presented in Tables S1 and S2.

Prediction of pharmacological activity

The profiles of potential pharmacological activity of obtained compounds were studied *in silico* using the PASS software [S4,S5]. Selected data on antitumor activity of compounds **3a-d** are presented in Tables S3.

General procedure for the synthesis of silatranylpropyl-1*H*-pyrrole-2-carboxamides (3a-d).

A mixture of silatrane **1** (1 mmol) and the corresponding 2-(trichloroacetyl)pyrroles **2a-d** (1 mmol) in 15 ml of solvent: CH_2Cl_2, CH_3CN, benzene (best of all in THF) was stirred at 65 °C for 1-2 hr. The solvent was distilled off and the residue was washed with diethyl ether and dried *in vacuo* to obtain pure powder **3a-d**.

N-[3-(2,8,9-Trioxa-5-aza-1-silabicyclo[3.3.3]undec-1-yl)propyl]-1H-pyrrole-2-carboxamide (3a)

Yield 95%, yellow solid, m.p. 207 °C.

IR (ν, cm^{-1}): 588 (Si←N), 771, 1051 (Si-O), 1271 (O-CH_2), 1362 (CH_2-N), 1528 (C=C), 1625 (C=O), 3221 (NH), 3342 (NH).

^{1}H NMR (DMSO-d_6) δ: 0.16 (m, 2 H, CH_2Si), 1.47 (m, 2 H, C*H*$_2$$CH_2Si$), 2.76 (t, 6 H, NCH_2, *J* 5.7 Hz), 3.05 (m, 2 H, NCH_2), 3.59 (t, 6 H, OCH_2, *J* 5.7 Hz), 6.04 (m, 1 H, H-4), 6.71 (m, 1 H, H-3), 6.80 (m, 1H, H-5), 7.79 (br. t, 1H, CONH, *J* 5.4 Hz), 11.30 (br. s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 14.62 (CH_2Si), 25.87 (*C*$H_2$$CH_2Si$), 42.24 ($CH_2N$), 49.95 ($NCH_2$), 56.67 ($OCH_2$), 108.30 (C-4), 109.33 (C-3), 120.73 (C-5), 126.68 (C-2), 160.26 (C=O).

^{15}N NMR (DMSO-d_6) δ: –356.8 (CH_2N), –271.9 (CONH), –221.5 (NH).

^{29}Si NMR (DMSO-d_6) δ: –70.3.

ESI-HRMS (m/z): calcd. for ($C_{14}H_{23}N_3O_4Si$) $[M+H]^+$ 326,15305; found 326,15346.

Found (%): C, 51.92; H, 6.88; N, 12.82. Calc. for $C_{14}H_{23}N_3O_4Si$ (%): C, 51.66; H, 7.12; N, 12.91.

3,4,5-Trimethyl-N-[3-(2,8,9-trioxa-5-aza-1-silabicyclo[3.3.3]undec-1-yl)propyl]-1H-pyrrole-2-carboxamide (3b)

Yield 96%, yellow solid, m.p. 198 °C.

IR (ν, cm^{-1}): 590 (Si←N), 762, 1054 (Si-O), 1266 (O-CH_2), 1375 (CH_2-N), 1520 (C=C), 1609 (C=O), 3271 (NH), 3404 (NH).

^{1}H NMR (DMSO-d_6) δ: 0.15 (m, 2 H, CH_2Si), 1.46 (m, 2 H, C*H*$_2CH_2Si$), 1.81 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.77 (t, 6 H, NCH_2, *J* 5.7 Hz), 3.05 (m, 2 H, NCH_2), 3.59 (t, 6 H, OCH_2, *J* 5.7 Hz), 6.94 (br. t, 1H, CONH, *J* 5.4 Hz), 10.52 (br. s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 8.57 (CH_3), 10.51 (CH_3), 10.79 (CH_3), 14.59 (CH_2Si), 25.72 (*C*H_2CH_2Si), 42.12 (CH_2N), 49.96 (NCH_2), 56.68 (OCH_2), 114.41 (C-4), 119.90 (C-3), 121.38 (C-5), 125.80 (C-2), 161.10 (C=O).

^{15}N NMR (DMSO-d_6) δ: –357.1 (CH_2N), –271.7 (CONH), –228.7 (NH).

^{29}Si NMR (DMSO-d_6) δ: –70.5.

ESI-HRMS (m/z): calcd. for ($C_{18}H_{29}N_3O_4Si$) $[M+H]^+$ 368,19999; found 368,20044.

Found (%): C, 57.22; H, 7.35; N, 10.99. Calc. for $C_{18}H_{29}N_3O_4Si$ (%): C, 56.96; H, 7.70; N, 11.07.

5-Phenyl-N-[3-(2,8,9-trioxa-5-aza-1-silabicyclo[3.3.3]undec-1-yl)propyl]-1H-pyrrole-2-carboxamide (3c)

Yield 94%, yellow solid, m.p. 219 °C.

IR (ν, cm^{-1}): 588 (Si←N), 761, 1053 (Si-O), 1270 (O-CH_2), 1367 (CH_2-N), 1535 (C=C), 1629 (C=O), 3237 (NH), 3343 (NH).

^{1}H NMR (DMSO-d_6) δ: 0.17 (m, 2 H, CH_2Si), 1.52 (m, 2 H, C*H*$_2CH_2Si$), 2.76 (t, 6 H, NCH_2, *J* 5.7 Hz), 3.10 (m, 2 H, NCH_2), 3.59 (t, 6 H, OCH_2, *J* 5.7 Hz), 6.53 (m, 1 H, H-4), 6.78 (m, 1 H, H-3), 7.20 (m, 1 H, H_p), 7.35 (m, 2 H, H_m),7.76 (m, 2 H, H_o), 7.89 (br. t, 1 H, CONH, *J* 5.4 Hz), 11.53 (br. s, 1 H, NH).

^{13}C NMR (DMSO-d_6) δ: 15.00 (CH_2Si), 26.21 (*C*H_2CH_2Si), 42.90 (CH_2N), 50.82 (NCH_2), 57.44 (OCH_2), 107.20 (C-4), 112.35 (C-3), 125.05 (Co), 126.94 (Cp), 128.70 (C-2), 129.07 (Cm), 132.63 (Ci), 134.62 (C-5), 160.57 (C=O).

^{15}N NMR (DMSO-d_6) δ: –356.3 (CH_2N), –270.9 (CONH), –230.2 (NH).

^{29}Si NMR (DMSO-d_6) δ: –70.4.

ESI-HRMS (m/z): calcd. for ($C_{20}H_{27}N_3O_4Si$) $[M+H]^+$ 402,18435; found 402,18505.

Found (%): C, 60.17; H, 6.45; N, 10.49. Calc. for $C_{20}H_{27}N_3O_4Si$ (%): C, 59.82; H, 6.77; N, 10.46.

N-[3-(2,8,9-Trioxa-5-aza-1-silabicyclo[3.3.3]undec-1-yl)propyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (3d)

Yield 92%, red solid, m.p. 238 °C.

IR (ν, cm^{-1}): 590 (Si←N), 775, (Si-O), 1271 (O-CH_2), 1359 (CH_2-N), 1542 (C=C), 1619 (C=O), 3238 (NH), 3321 (NH).

^{1}H NMR (DMSO-d_6) δ: 0.12 (m, 2 H, CH_2Si), 1.44 (m, 2 H, C*H*$_2CH_2Si$), 1.65 (m, 4 H, CH_2), 2.38 (m, 4 H, CH_2), 2.76 (t, 6 H, NCH_2, *J* 5.7 Hz), 3.01 (m, 2 H, NCH_2), 3.59 (t, 6 H, OCH_2, *J* 5.7 Hz), 6.40 (d, 1 H, H-3, *J* 2.0 Hz), 7.54 (br. t, 1 H, CONH, *J* 5.4 Hz), 10.78 (br. s, 1 H, NH).

^{13}C NMR (DMSO-d_6) δ: 15.06 (CH_2Si), 22.84, 22.97, 23.27, 23.90 (CH_2), 26.37 (*C*H_2CH_2Si), 42.66 (CH_2N), 50.40 (NCH_2), 57.13 (OCH_2), 108.76 (C-3), 117.08 (C-3a), 124.89 (C-2), 130.47 (C-7a), 161.01 (C=O).

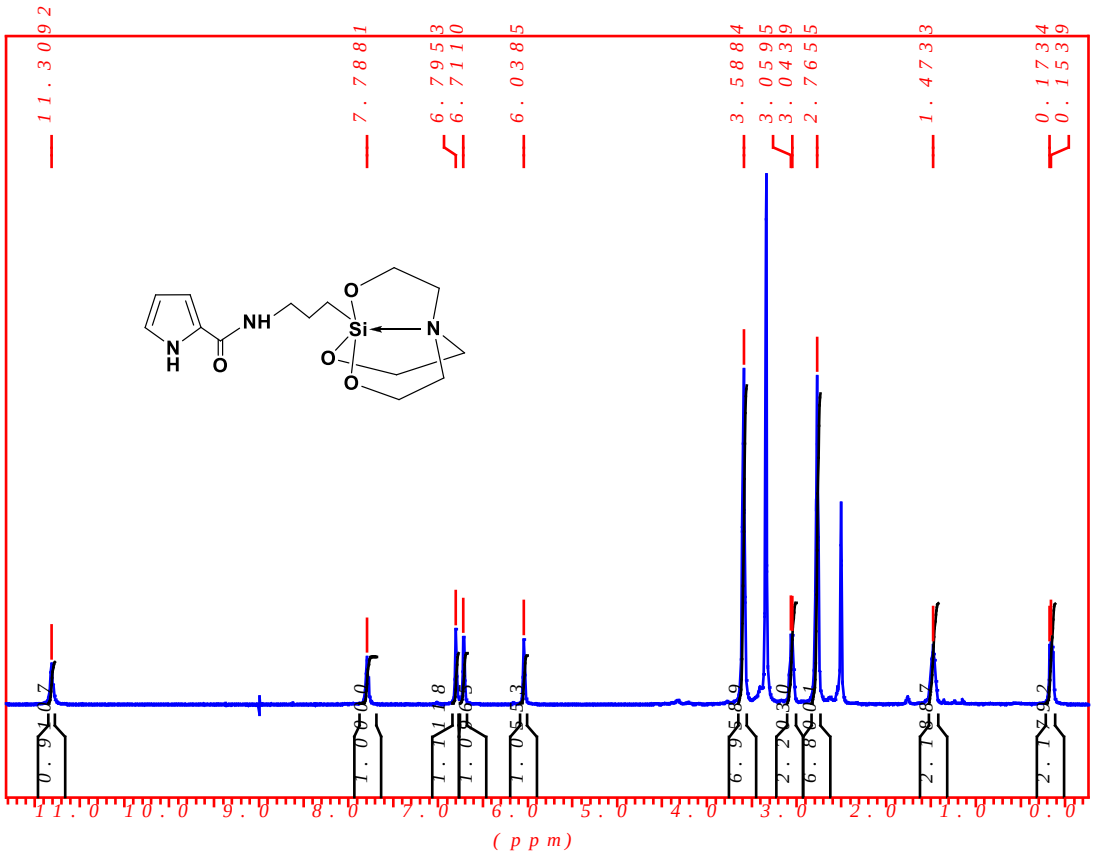
^{15}N NMR (DMSO-d_6) δ: –356.3 (CH_2N), –273.3 (CONH), –228.7 (NH).

^{29}Si NMR (DMSO-d_6) δ: –70.3.

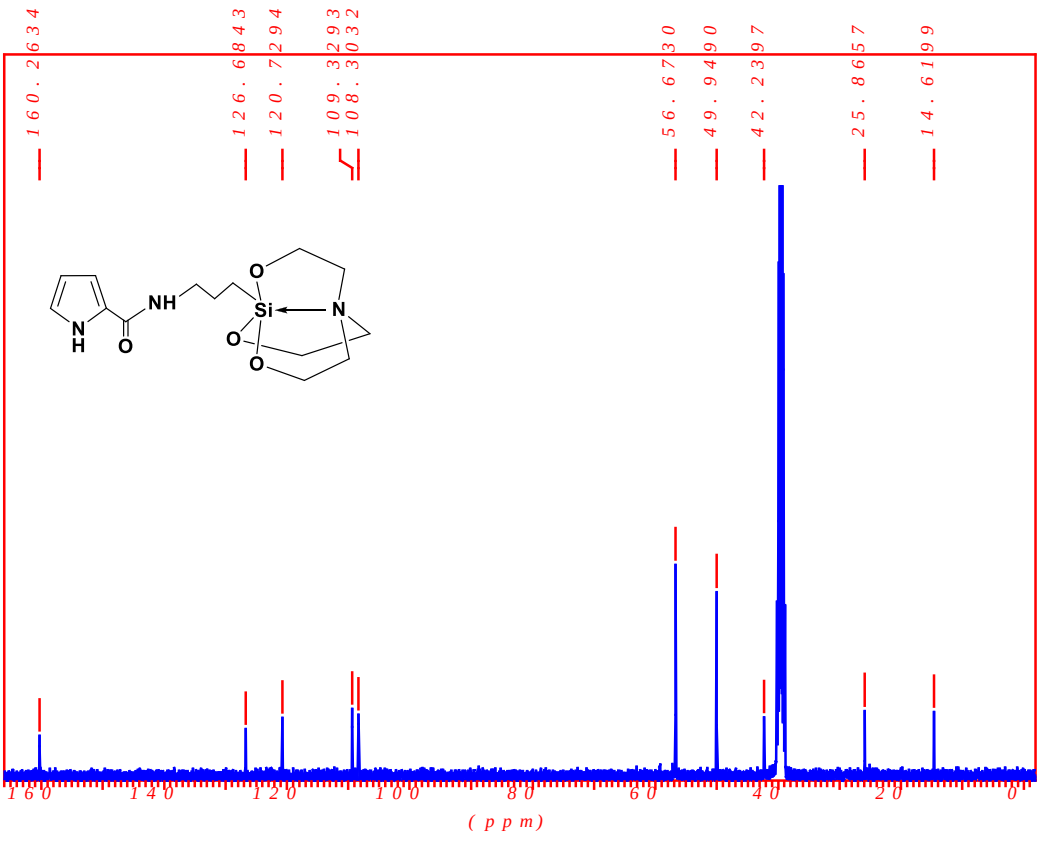
ESI-HRMS (m/z): calcd. for ($C_{17}H_{29}N_3O_4Si$) $[M+H]^+$ 380,19999; found 380,20063.

Found (%): C, 55.89; H, 7.58; N, 11.48. Calc. for $C_{17}H_{29}N_3O_4Si$ (%): C, 55.55; H, 7.95; N, 11.43.

Copies of NMR Spectra



^{1}H NMR spectrum of **3a** (DMSO)



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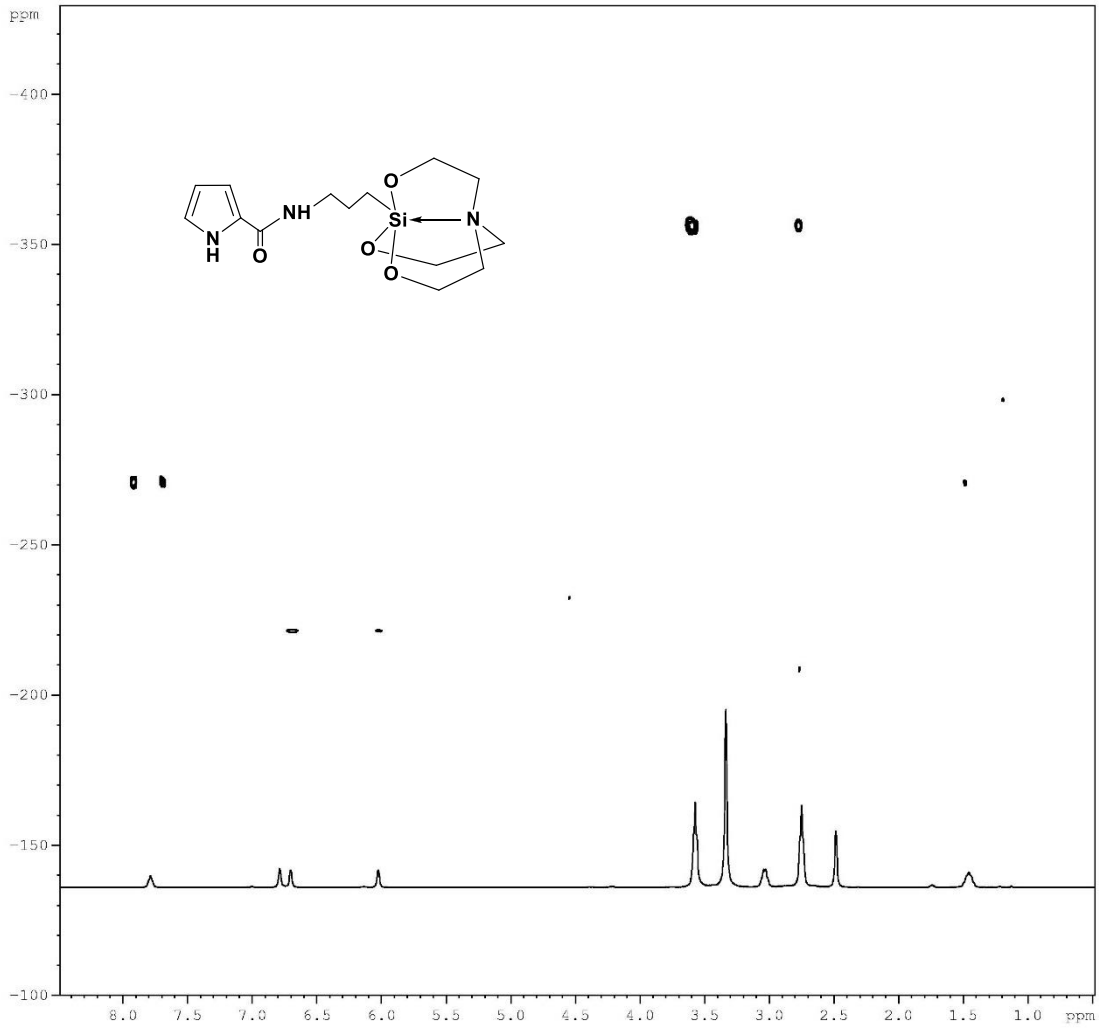
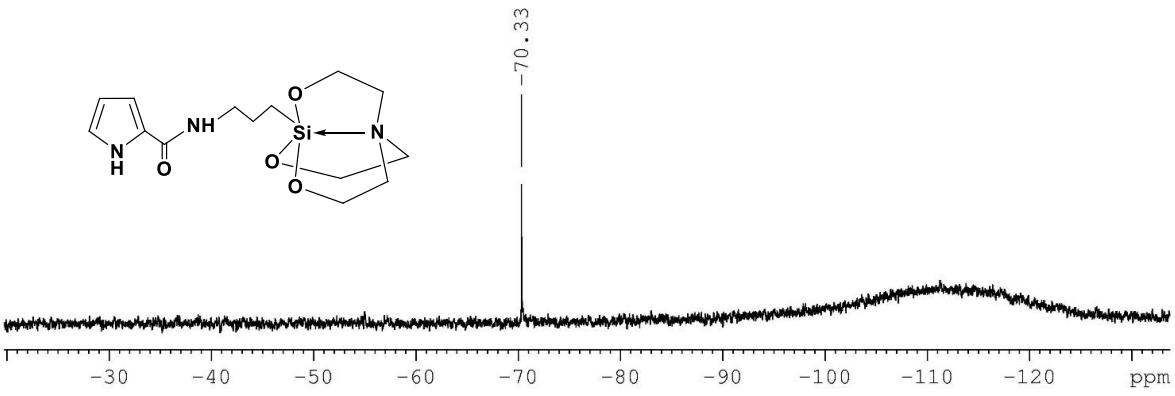
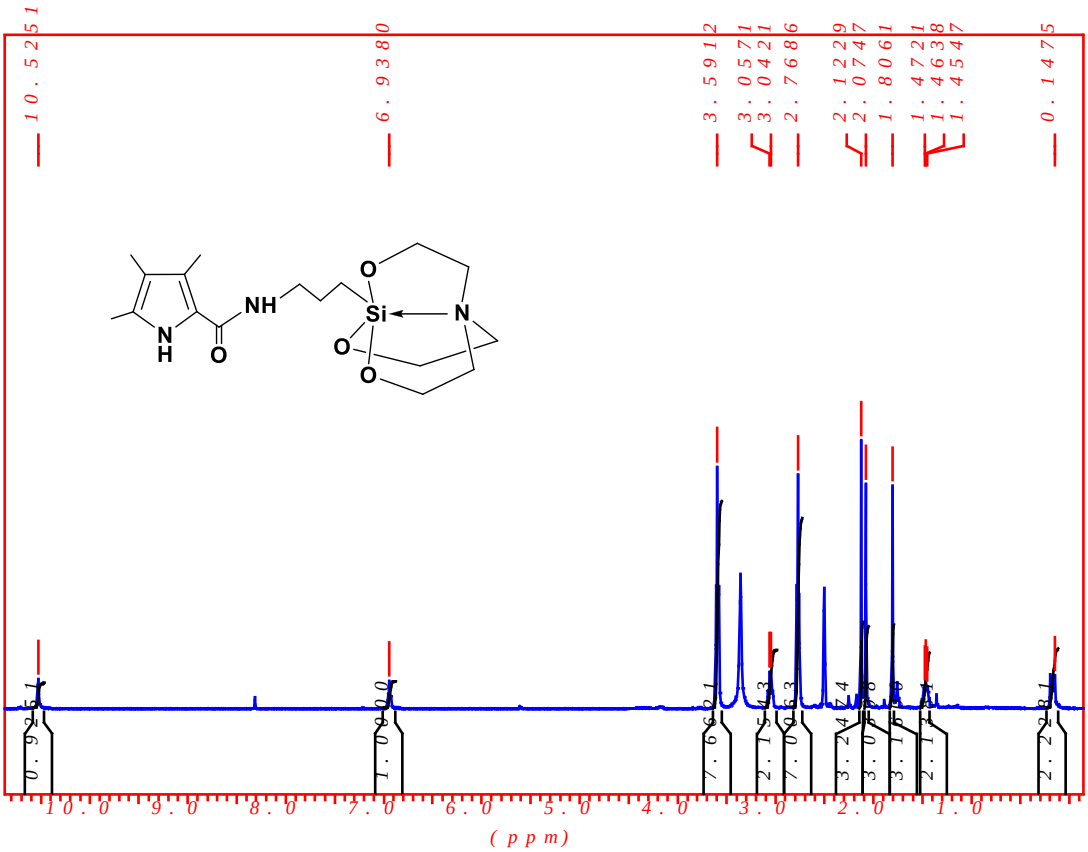


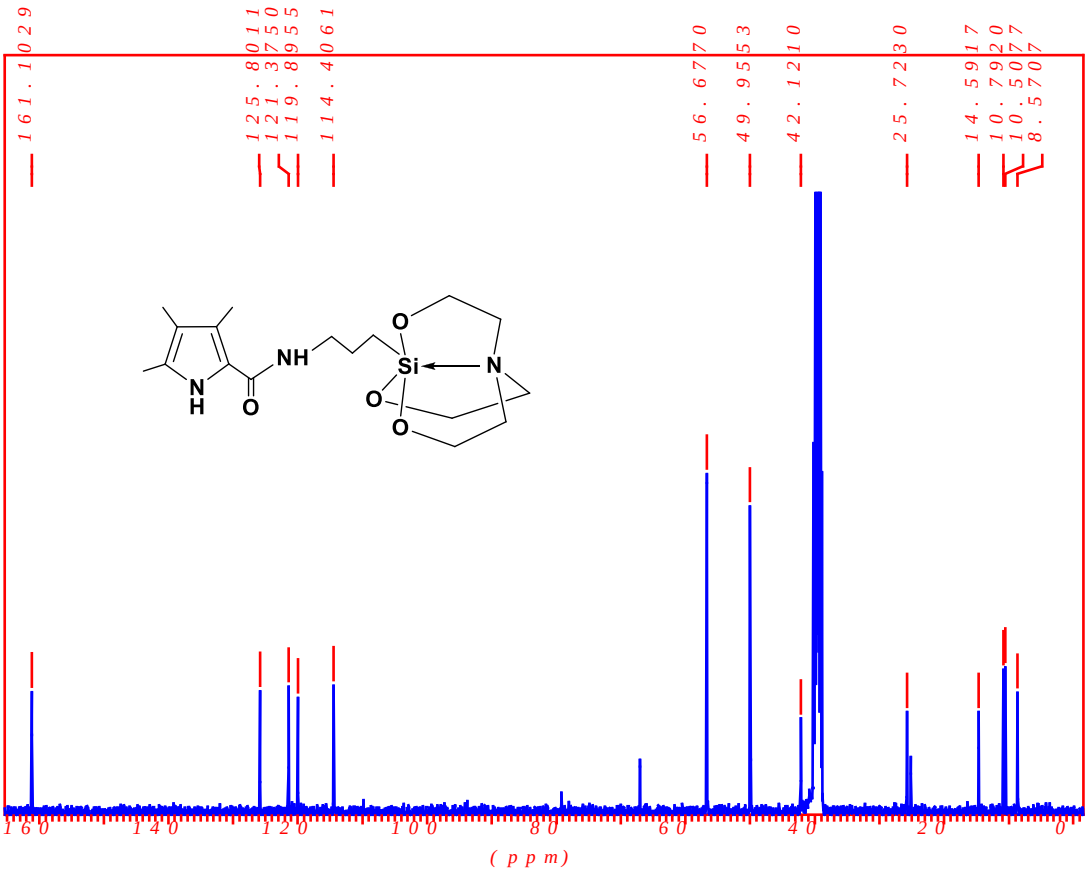
2D ^{1}H-^{15}N NMR spectrum of **3a** (DMSO)



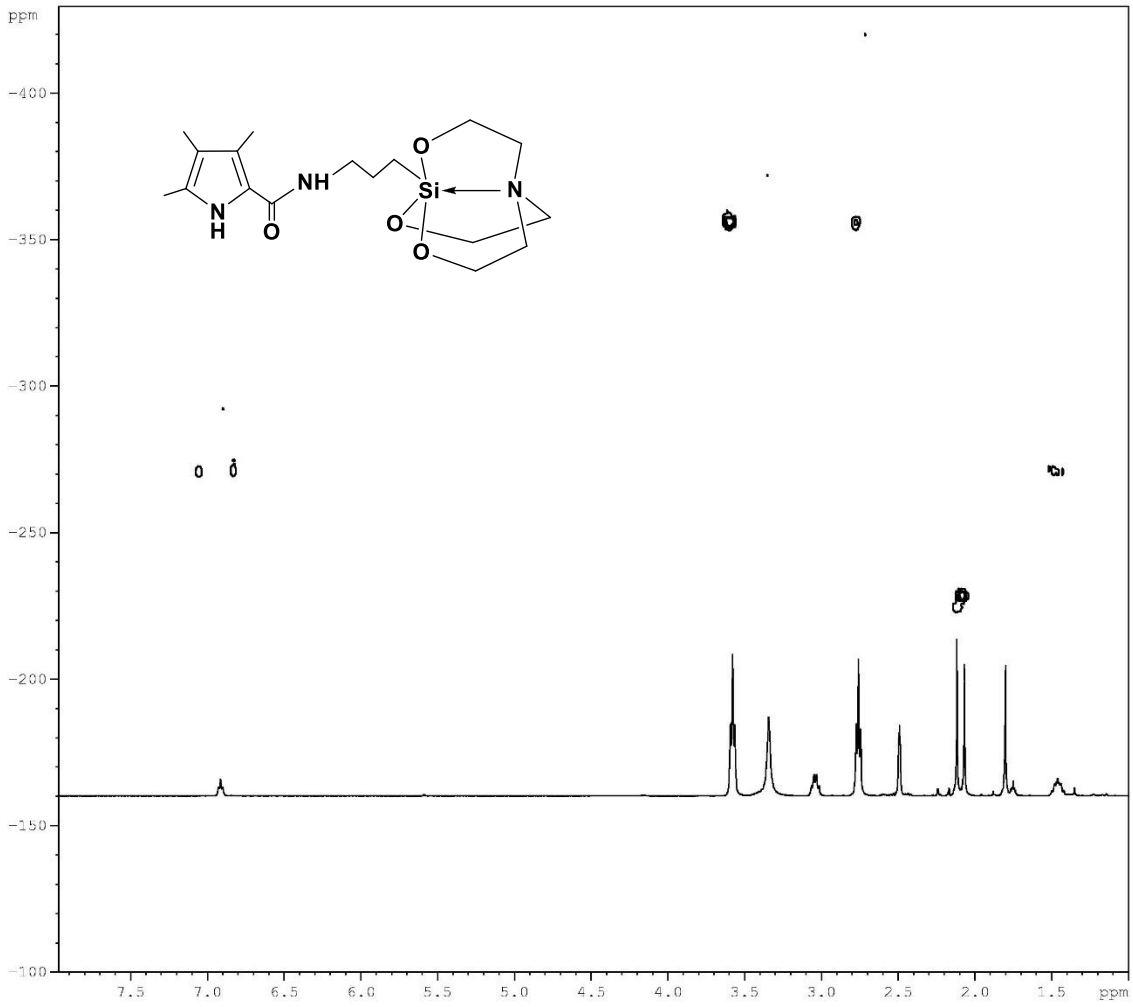
^{29}Si NMR spectrum of **3a** (DMSO)



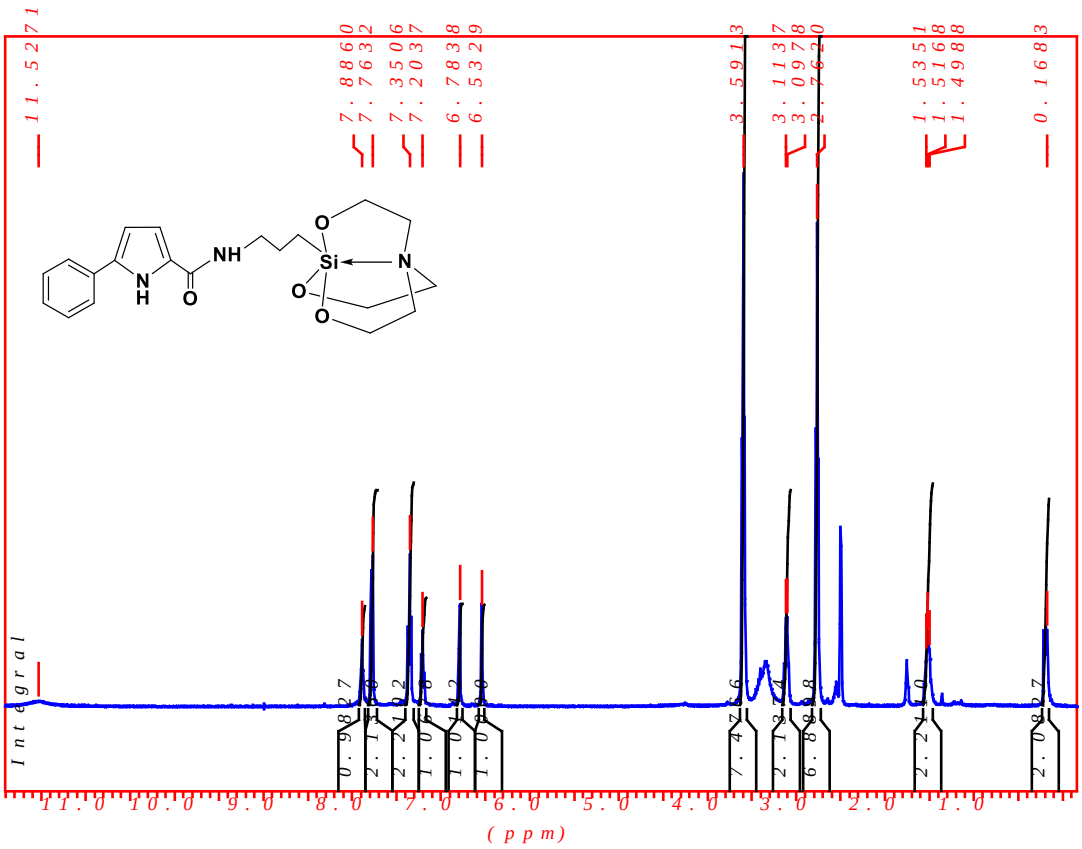
^{1}H NMR spectrum of **3b** (DMSO)



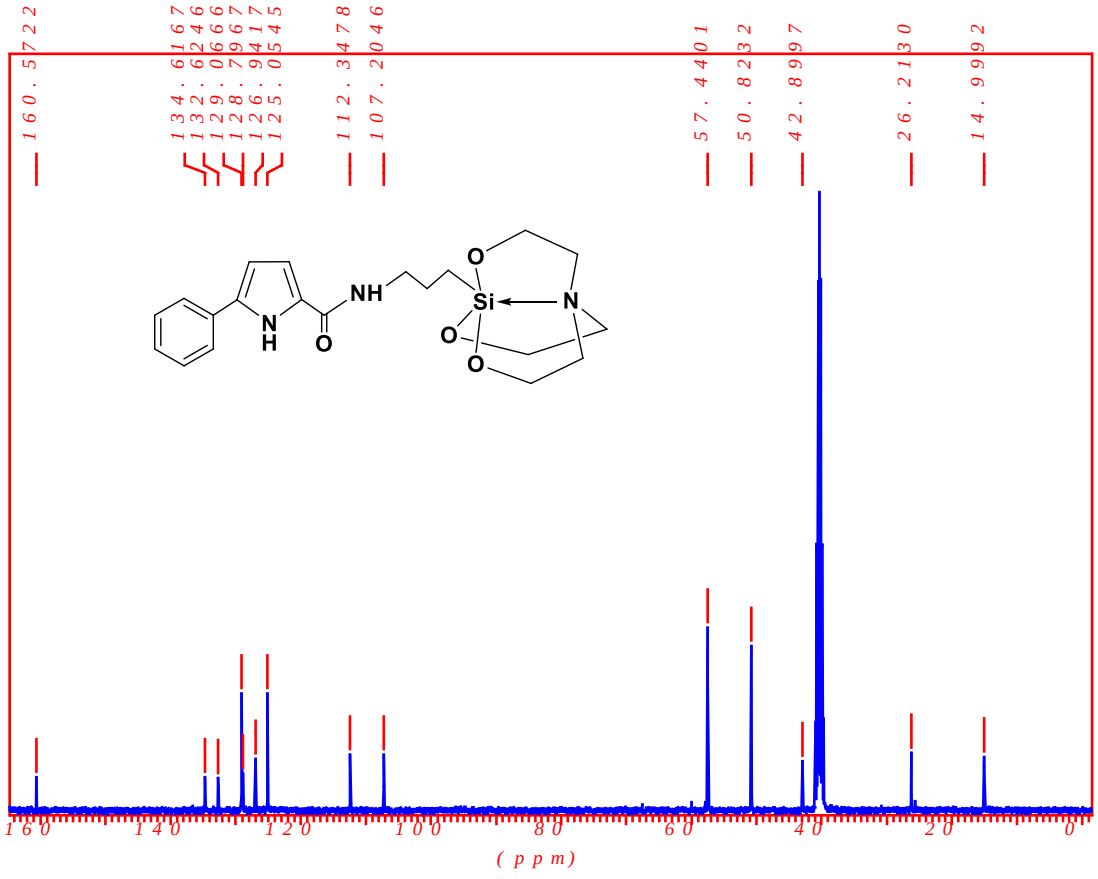
^{13}C NMR spectrum of **3b** (DMSO)



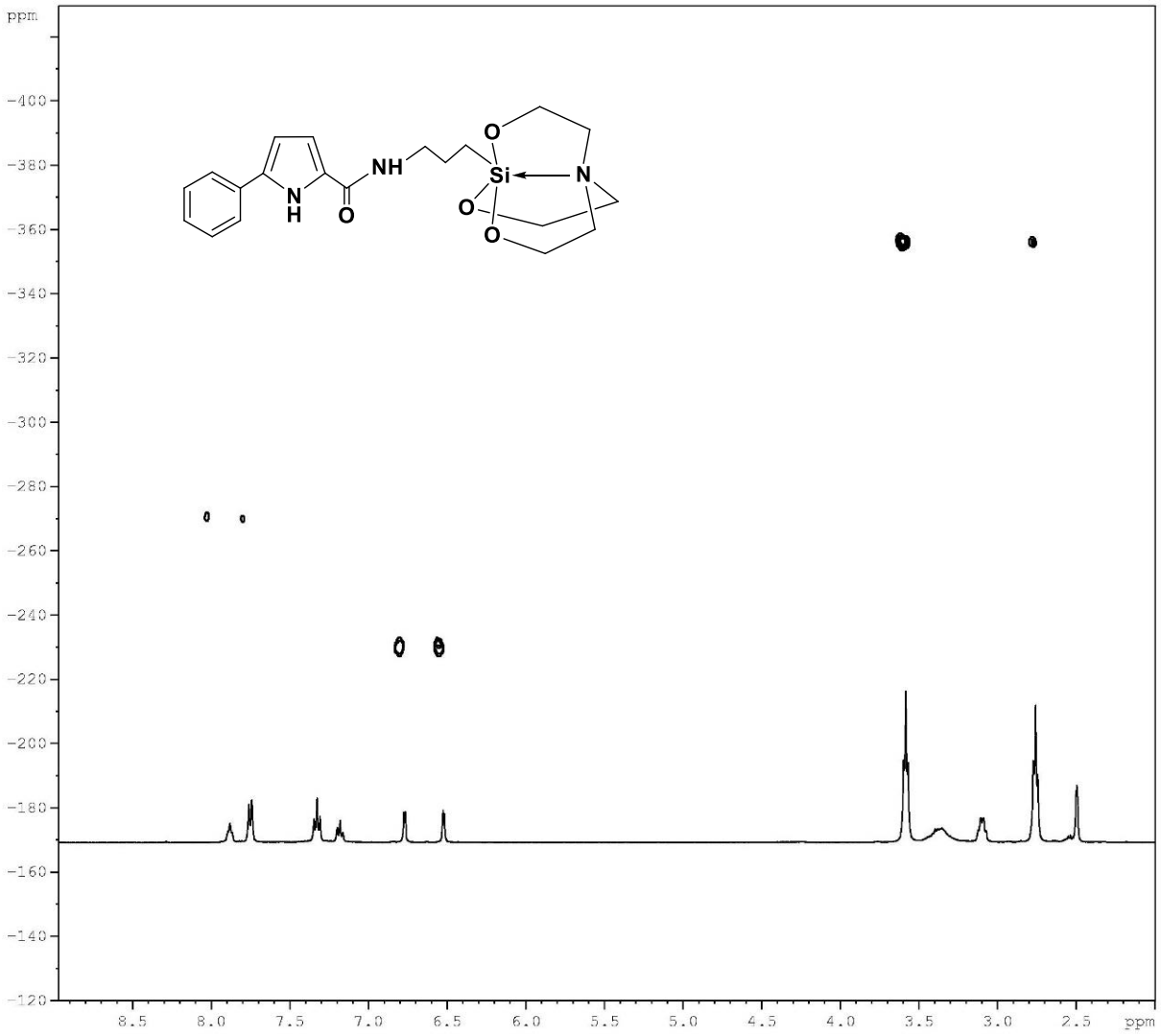
2D ^{1}H-^{15}N NMR spectrum of **3b** (DMSO)



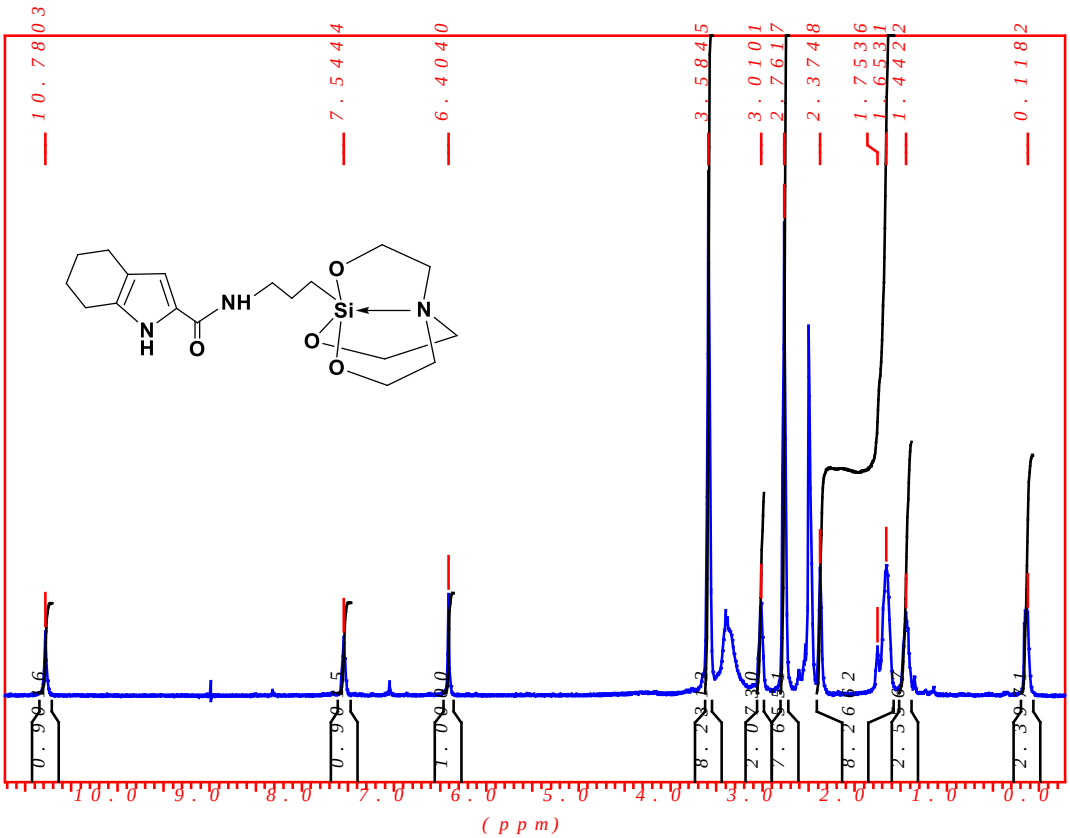
^{1}H NMR spectrum of **3c** (DMSO)



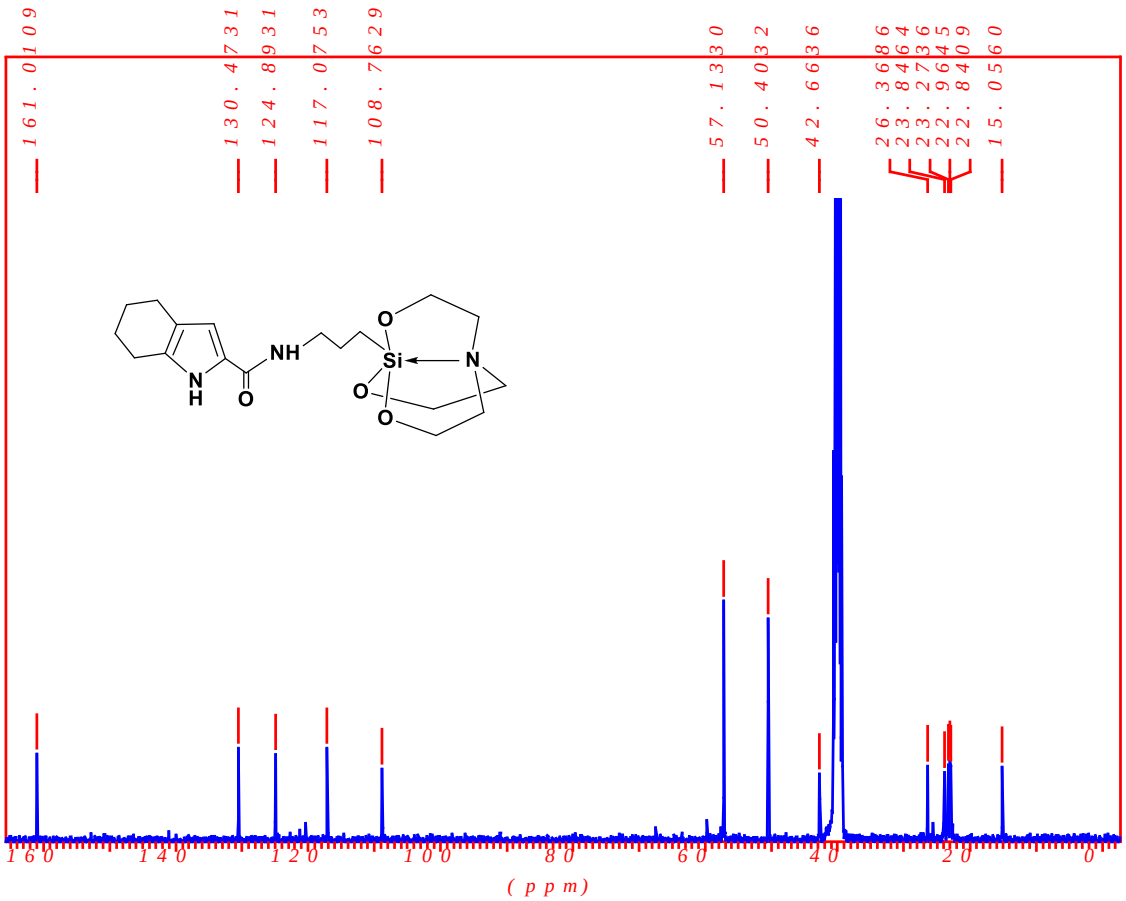
^{13}C NMR spectrum of **3c** (DMSO)



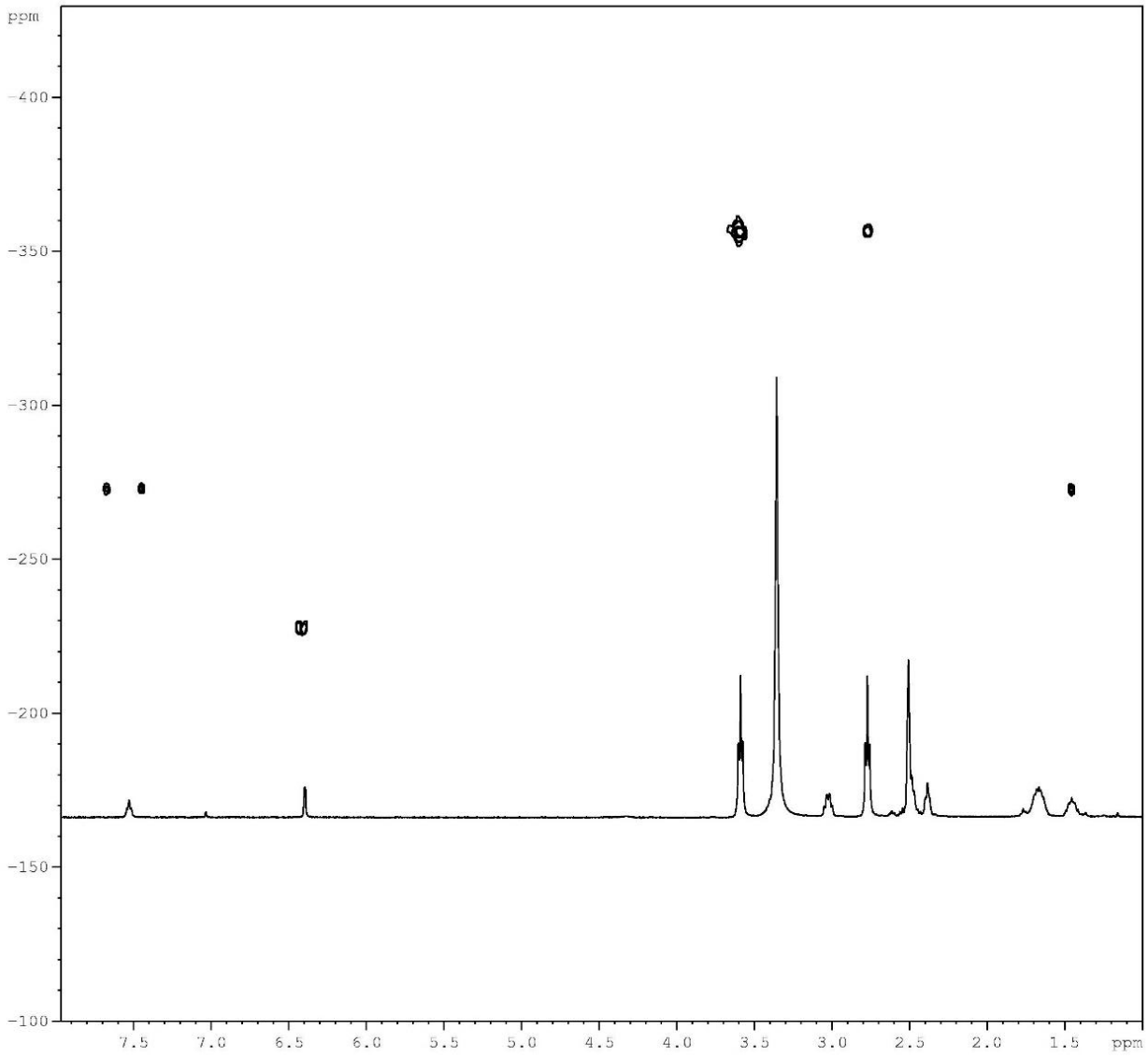
2D ^{1}H-^{15}N NMR spectrum of **3c** (DMSO)



^{1}H NMR spectrum of **3d** (DMSO)

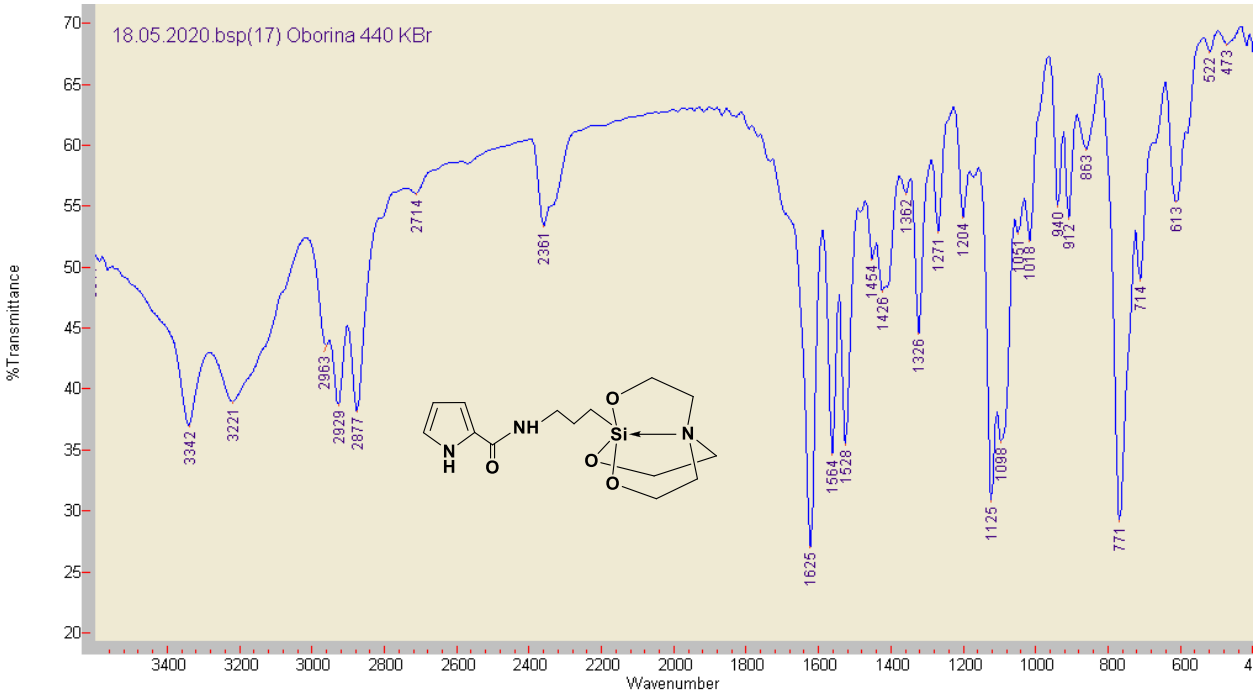


^{13}C NMR spectrum of **3d** (DMSO)

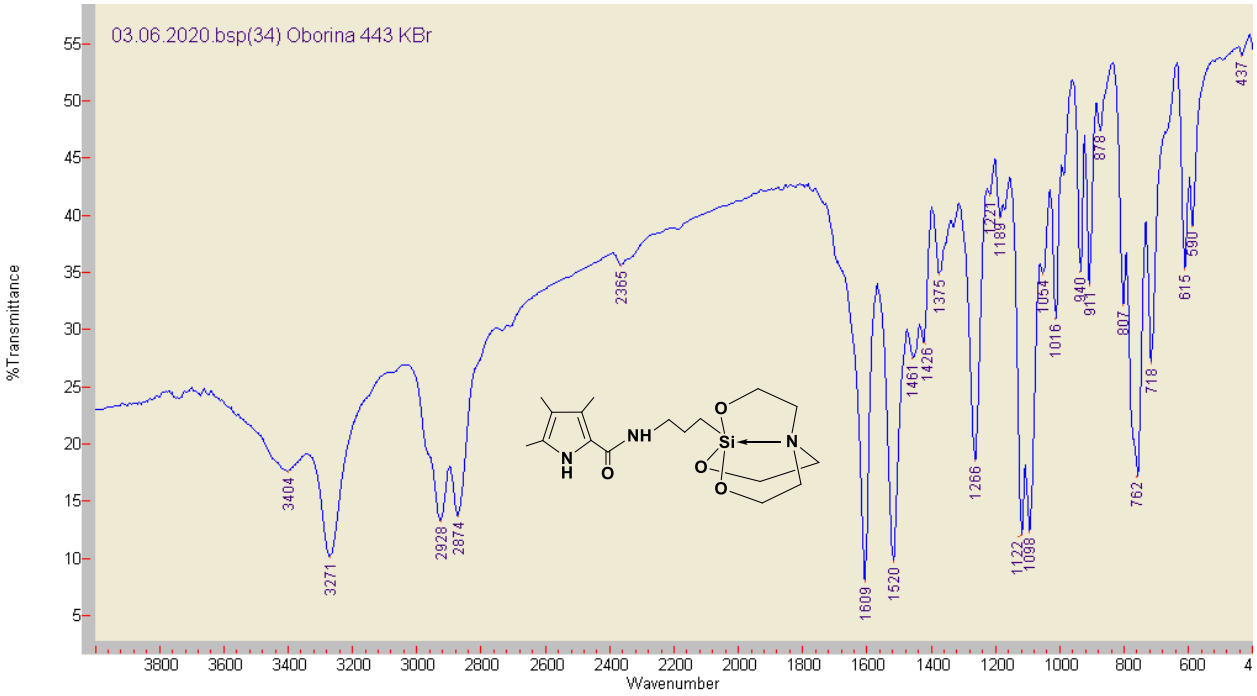


2D ^{1}H-^{15}N NMR spectrum of **3d** (DMSO)

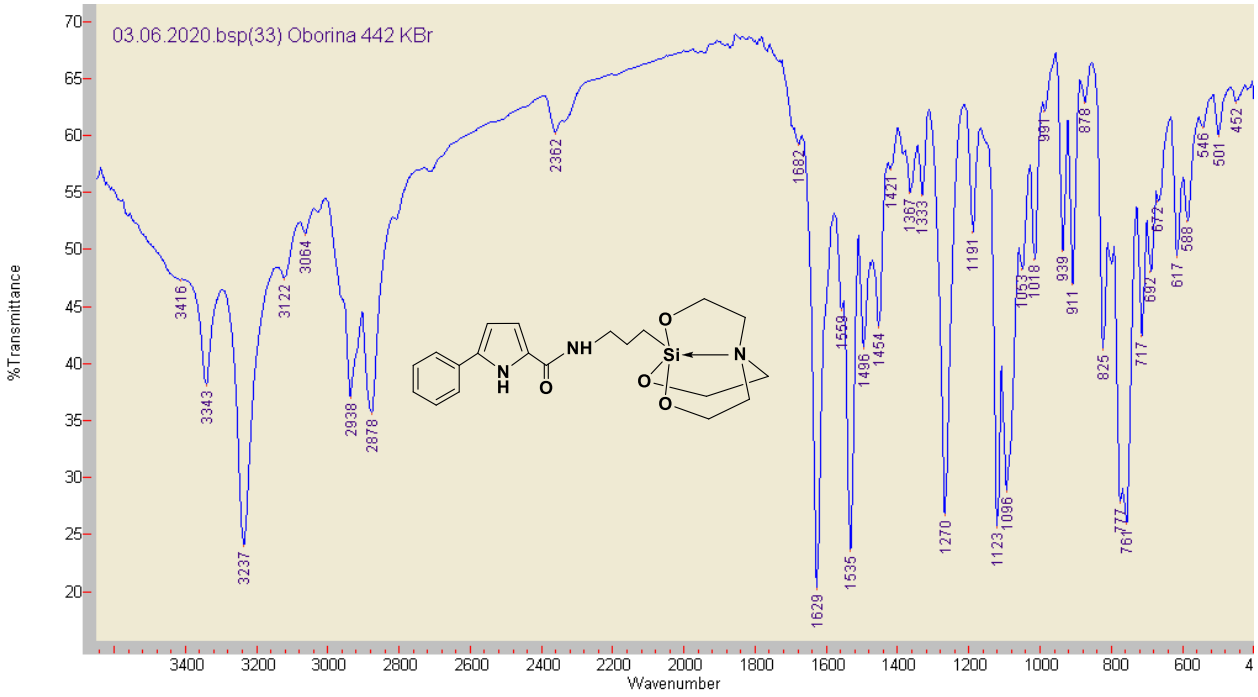
Copies of IR Spectra



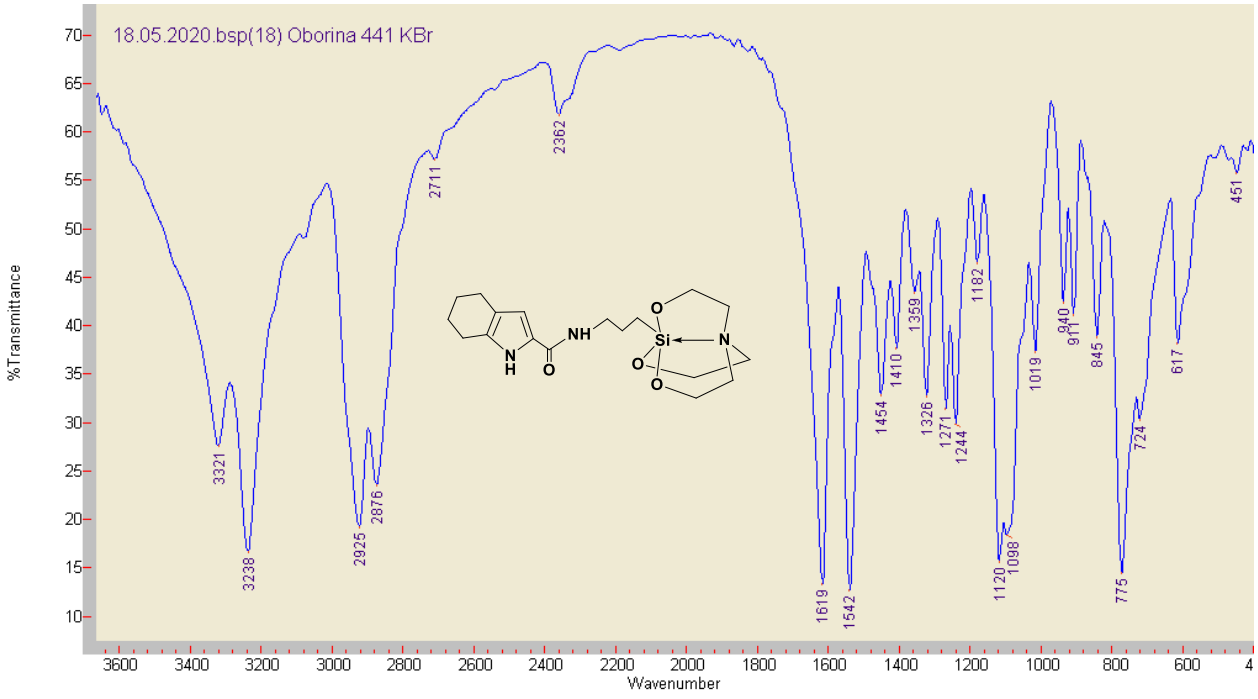
IR spectrum of **3a**



IR spectrum of **3b**

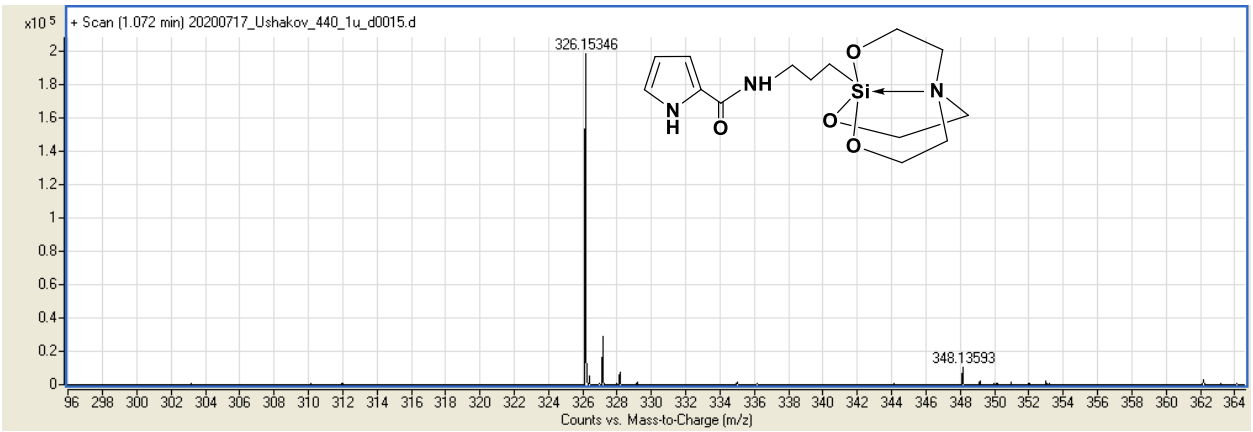


IR spectrum of **3c**

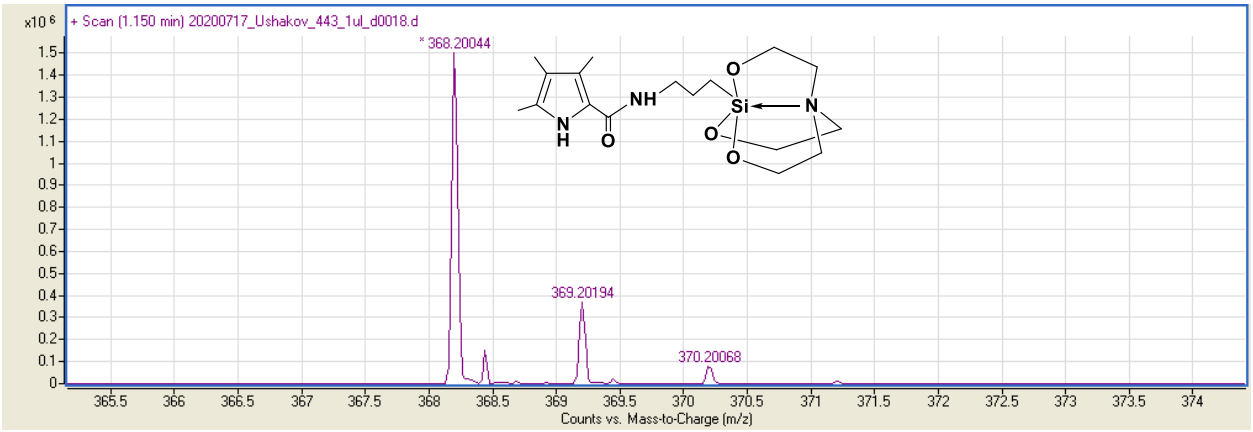


IR spectrum of **3d**

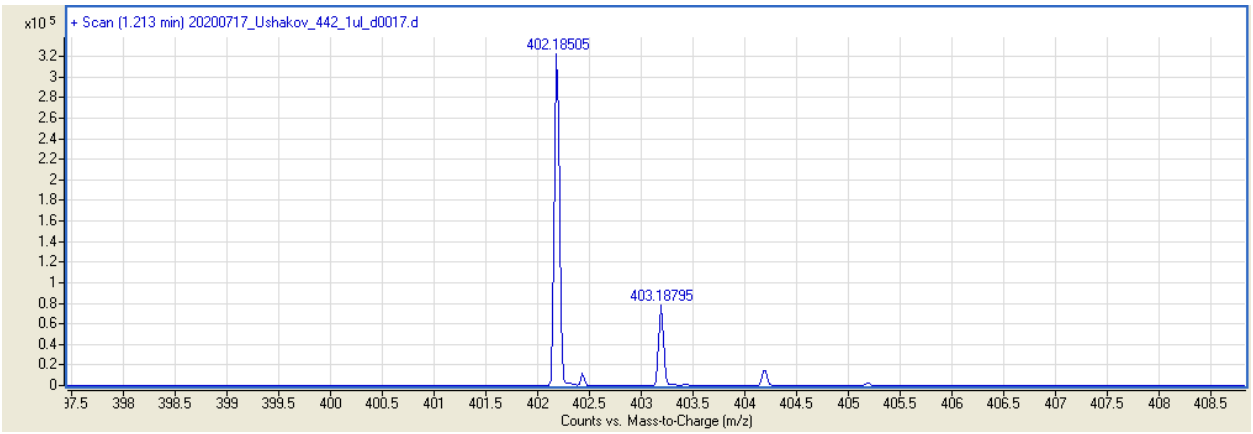
Copies of HR-MS spectra



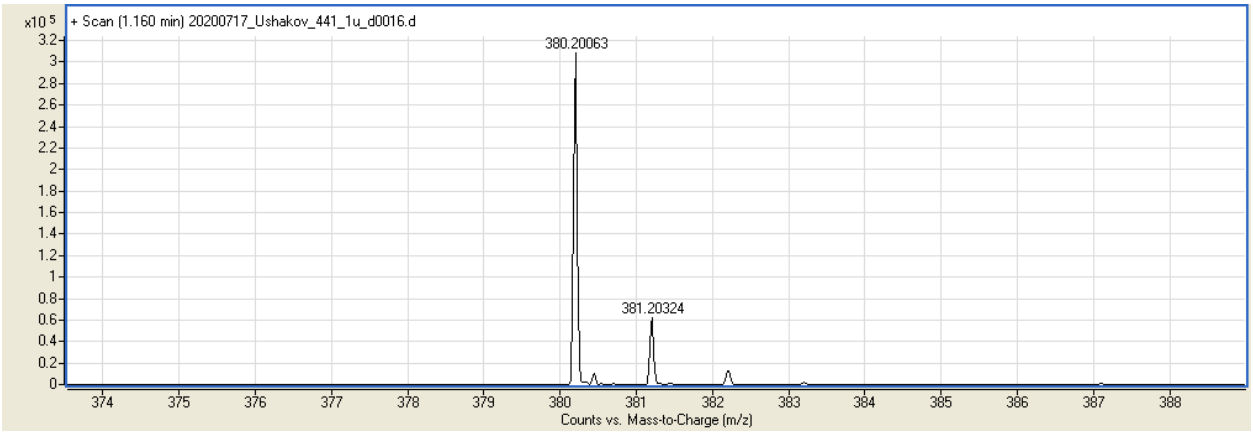
HR-MS spectrum of **3a**



HR-MS spectrum of **3b**



HRMS spectrum of **3c**



HRMS spectrum of **3d**

Table S1. Physicochemical properties of silatranes **3a-d**

Comp. ID	M.W.	Log *P*	PSA	HBA	HBD	RB	DrugL
3a	325.44	2.96	75.82	5	2	6	**Yes**
3b	367.52	3.07	75.82	5	2	6	**Yes**
3c	401.53	3.88	75.82	5	2	7	**Yes**
3d	379.53	3.63	75.82	5	2	6	**Yes**

M.W. - Molecular weight
Log P - Octanol–water partition coefficient
PSA - Polar surface area
HBA - Hydrogen bond acceptors
HBD - Hydrogen bond donors
RB - Rotatable bonds
DrugL - Druglikeness (Lipinski rule)

Table S2. Pharmacokinetic properties of silatranes **3a-d**

Comp. ID	GI	BBB	Log K_p	Log *S*	BA
3a	High	No	-7.79	-2.07	0.55
3b	High	No	-7.24	-3.02	0.55
3c	High	No	-7.07	-3.65	0.55
3d	High	No	-7.25	-3.15	0.55

GI - Gastrointestinal absorption
BBB - Blood brain barrier permeant
Log Kp - Skin permeation
Log *S* - Water solubility
BA – Bioavailability

Table S3. Predicted pharmacological activity of silatranes **3a-d** evaluated by PASS

Prediction activity	Probability, Pa/Pi			
	Compound			
	3a	3b	3c	3d
Antineoplastic	**0.962**/0.004	**0.0956**/0.004	**0.953**/0.004	**0.948**/0.004

References

[S1] A. I. Vogel, *A Text Book of Practical Organic Chemistry*, 4th edn., Longman, London, 1978.
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