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Supplementary material

Syntheses and Characterization of Liposome-incorporated Adamantyl Aminoguanidines

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Fig. S1. ^{1}H NMR (300 MHz, DMSO-d_6) of 1-(3-aminoguanidino)adamantane hydroiodide (**1**).

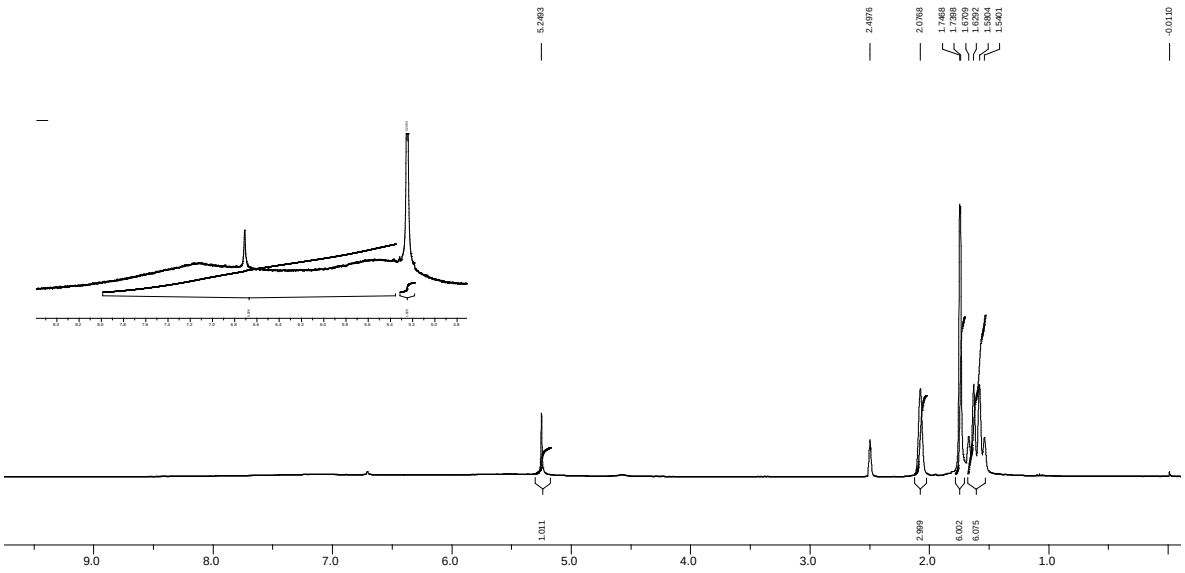


Fig. S2. ^{13}C NMR (75 MHz, DMSO-d_6) of 1-(3-aminoguanidino)adamantane hydroiodide (**1**).

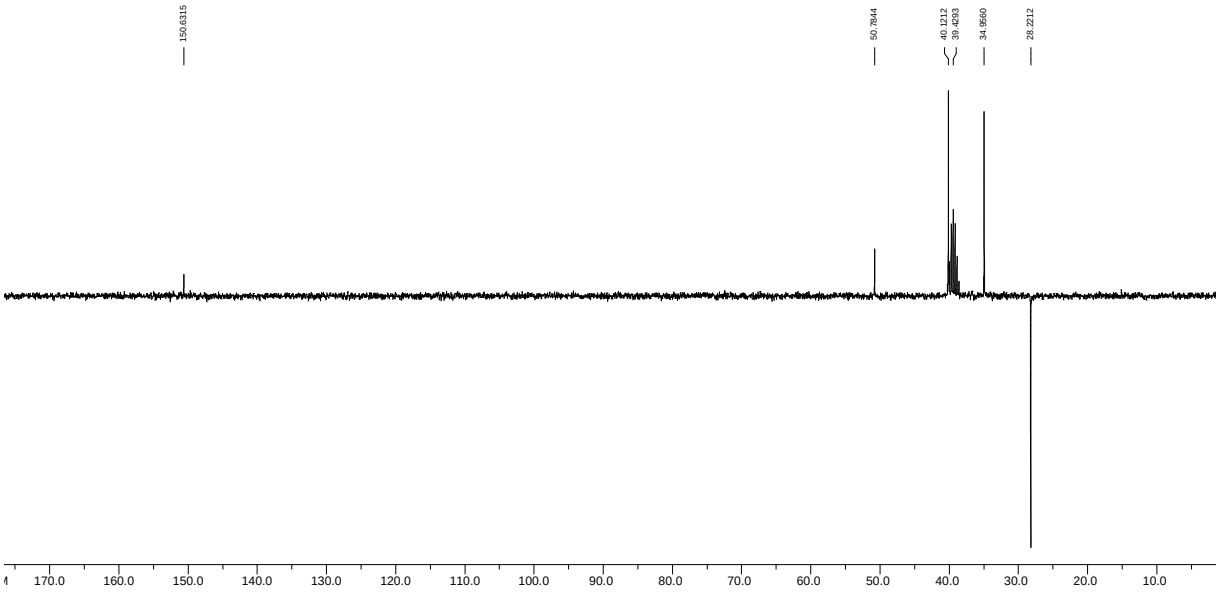


Fig. S3. ^{1}H NMR (300 MHz, DMSO-d_6) of 2-(3-aminoguanidino)adamantane hydroiodide (**2**).

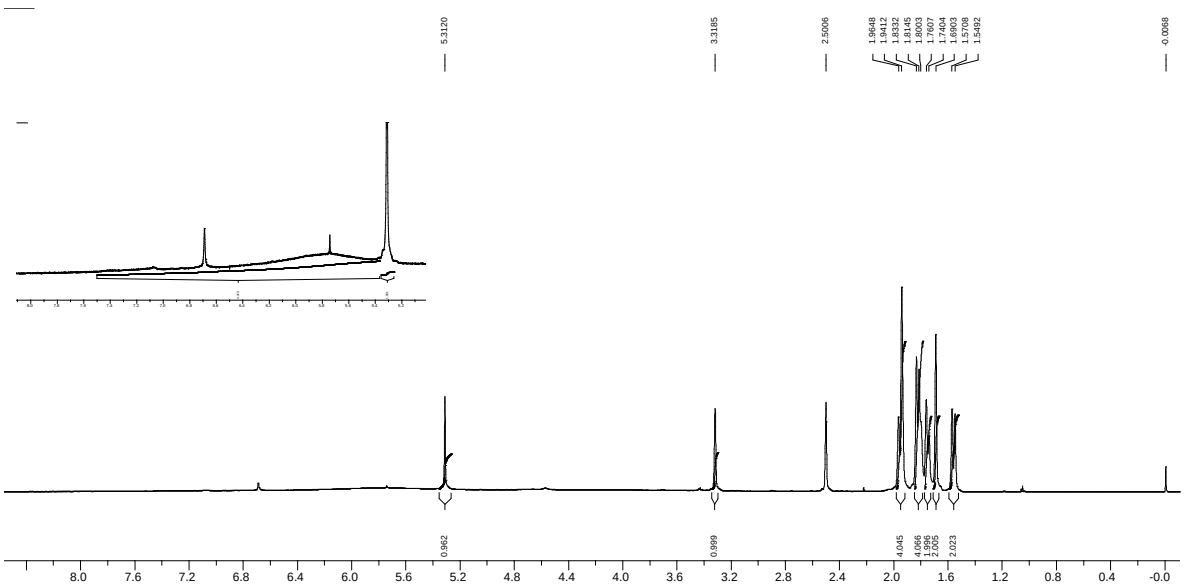


Fig. S4. ^{13}C NMR (75 MHz, DMSO-d_6) of 2-(3-aminoguanidino)adamantane hydroiodide (**2**).

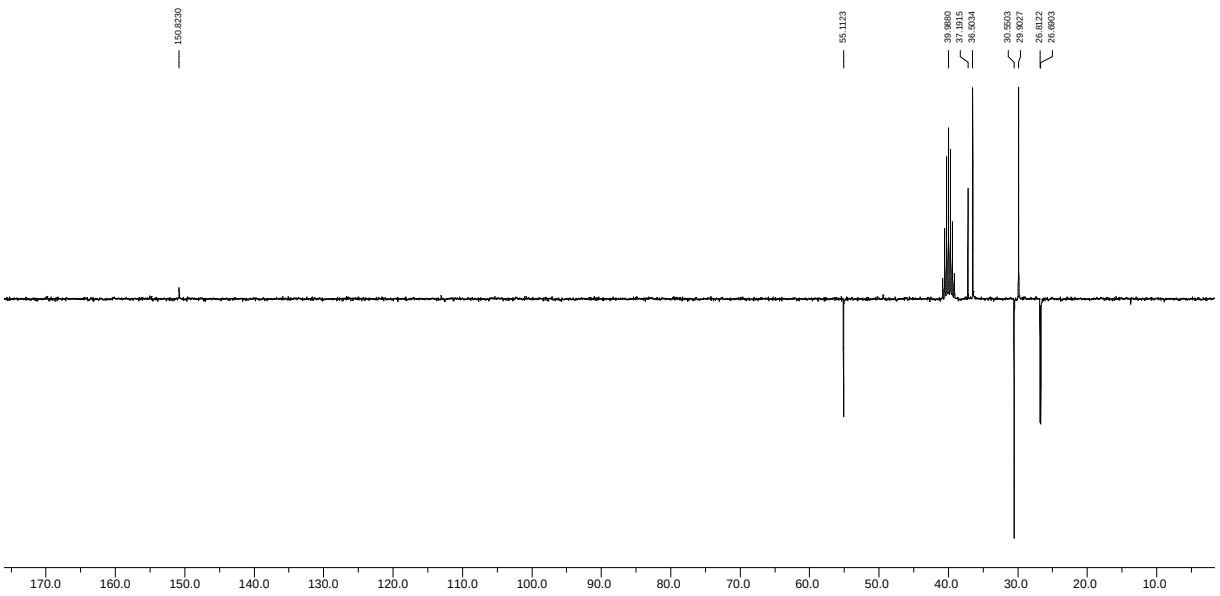


Fig. S5. ^{1}H NMR (300 MHz, DMSO-d_6) of 2,6-bis-(3-aminoguanidino)adamantane dihydroiodide (**3**).

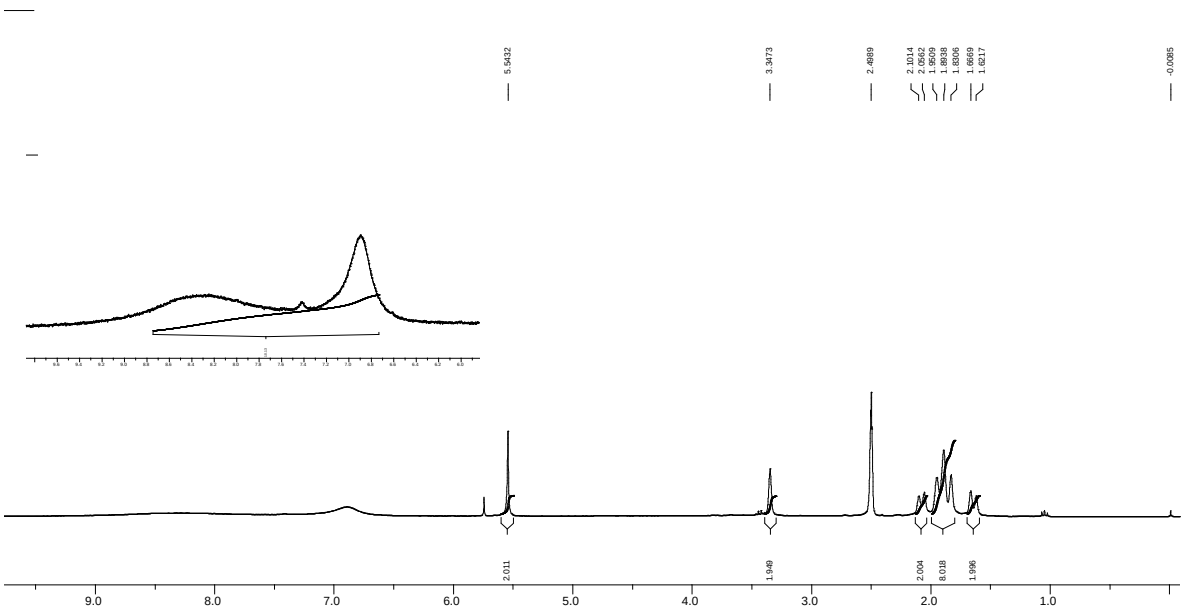


Fig. S6. ^{13}C NMR (75 MHz, DMSO-d_6) of 2,6-bis-(3-aminoguanidino)adamantane dihydroiodide (**3**).

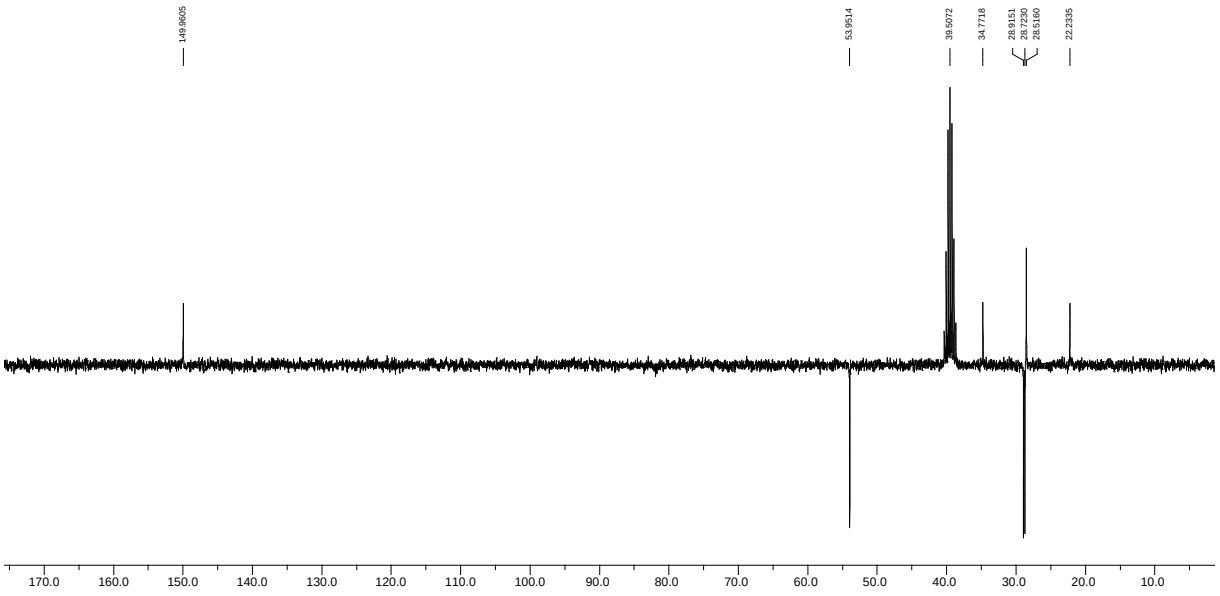


Fig. S7. ^{1}H NMR (300 MHz, DMSO-d_6) of 1,3-bis-(3-aminoguanidino)adamantane dihydroiodide (**4**).

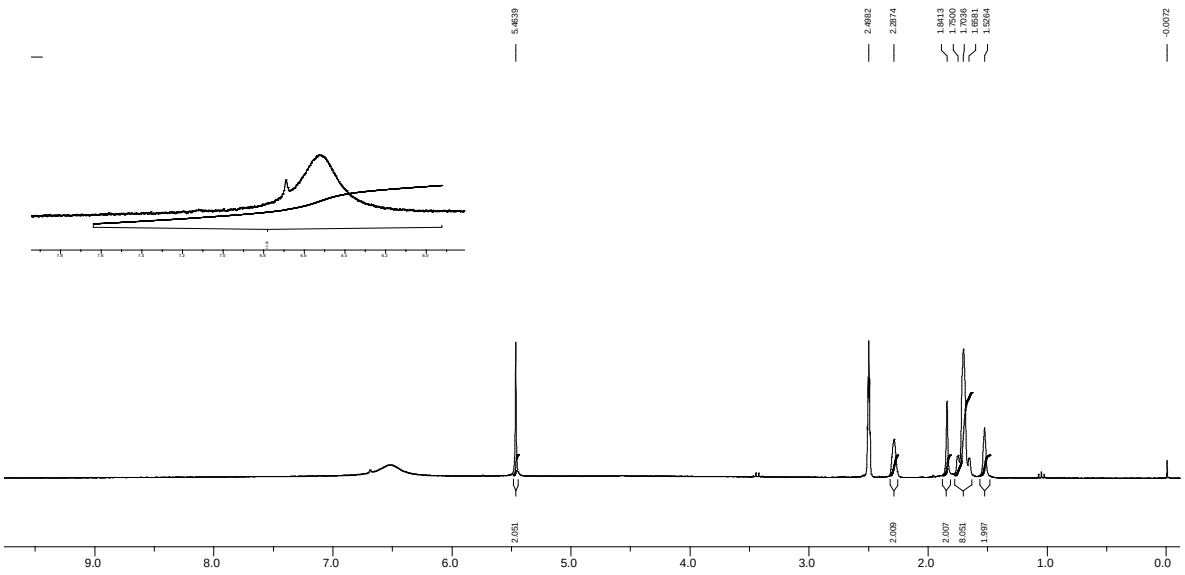


Fig. S8. ^{13}C NMR (75 MHz, DMSO-d_6) of 1,3-bis-(3-aminoguanidino)adamantane dihydroiodide (**4**).

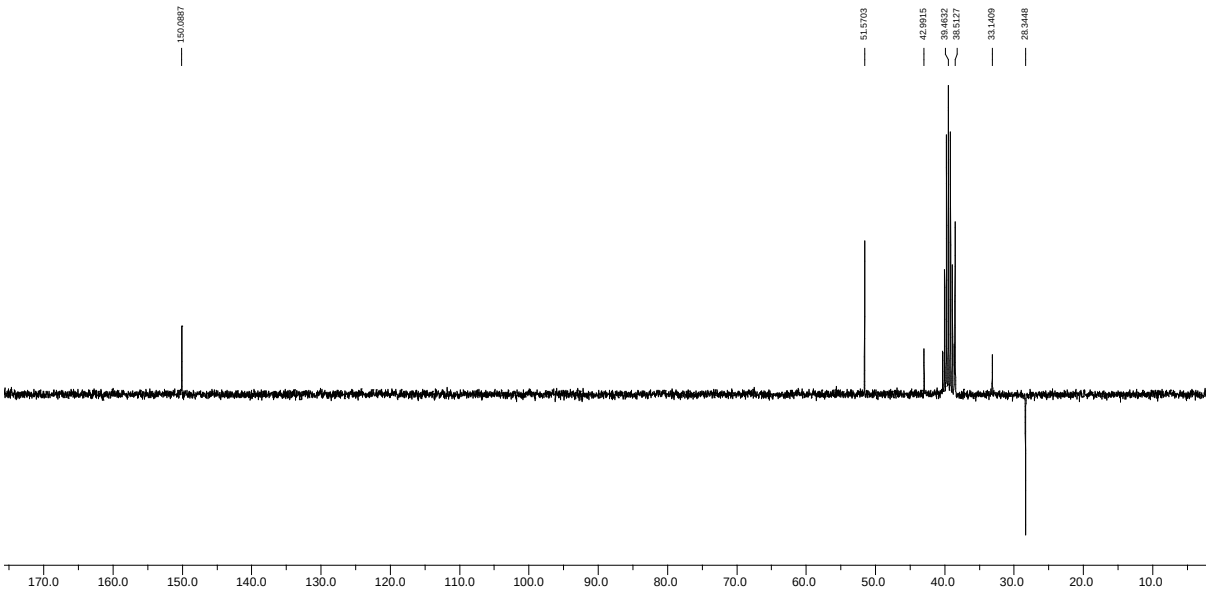


Fig. S9. ^{1}H NMR (300 MHz, DMSO-d_6) of *E*-2-(3-aminoguanidino)-5-hydroxyadamantane hydroiodide (**5**).

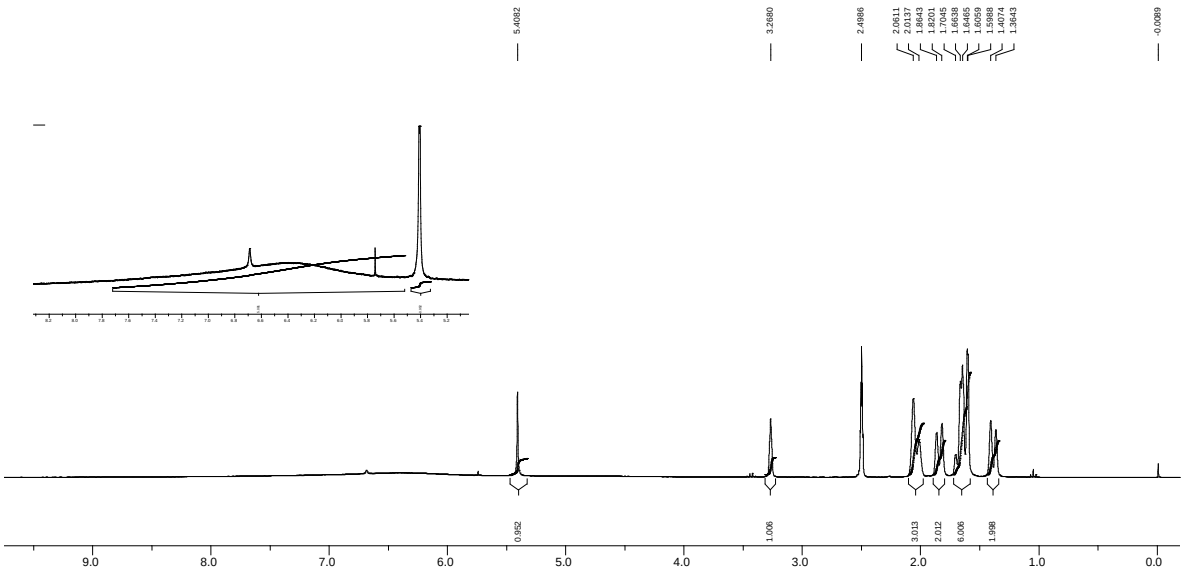


Fig. S10. ^{13}C NMR (75 MHz, DMSO-d_6) of *E*-2-(3-aminoguanidino)-5-hydroxyadamantane hydroiodide (**5**).

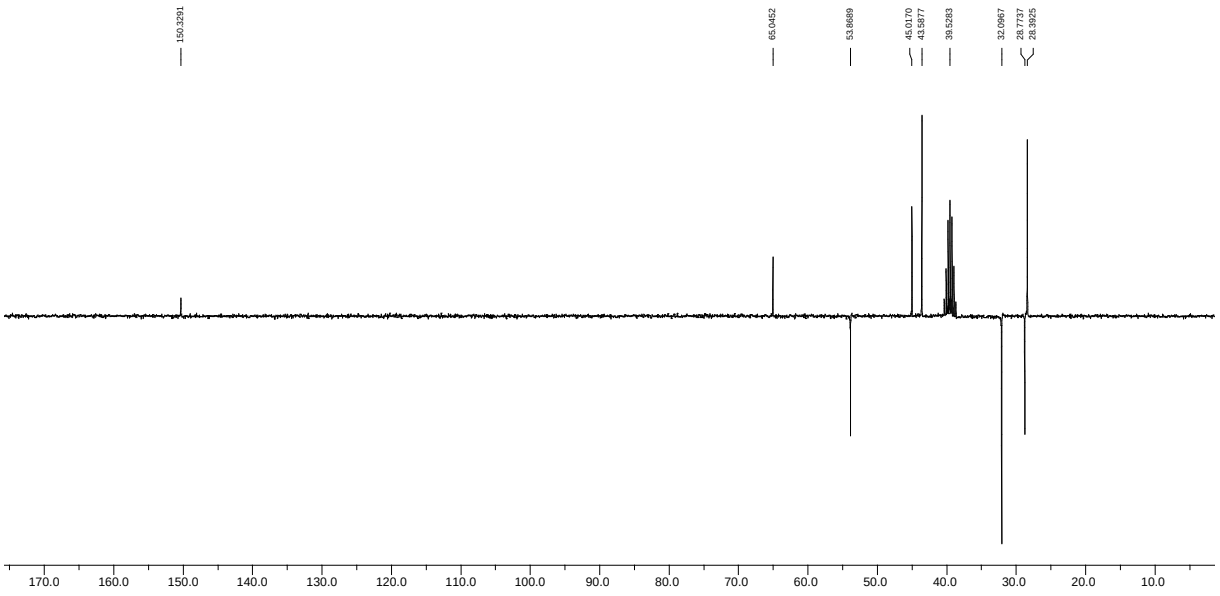


Fig. S11. ^{1}H NMR (300 MHz, DMSO-d_6) of *Z*-2-(3-aminoguanidino)-5-hydroxyadamantane hydroiodide (**6**).

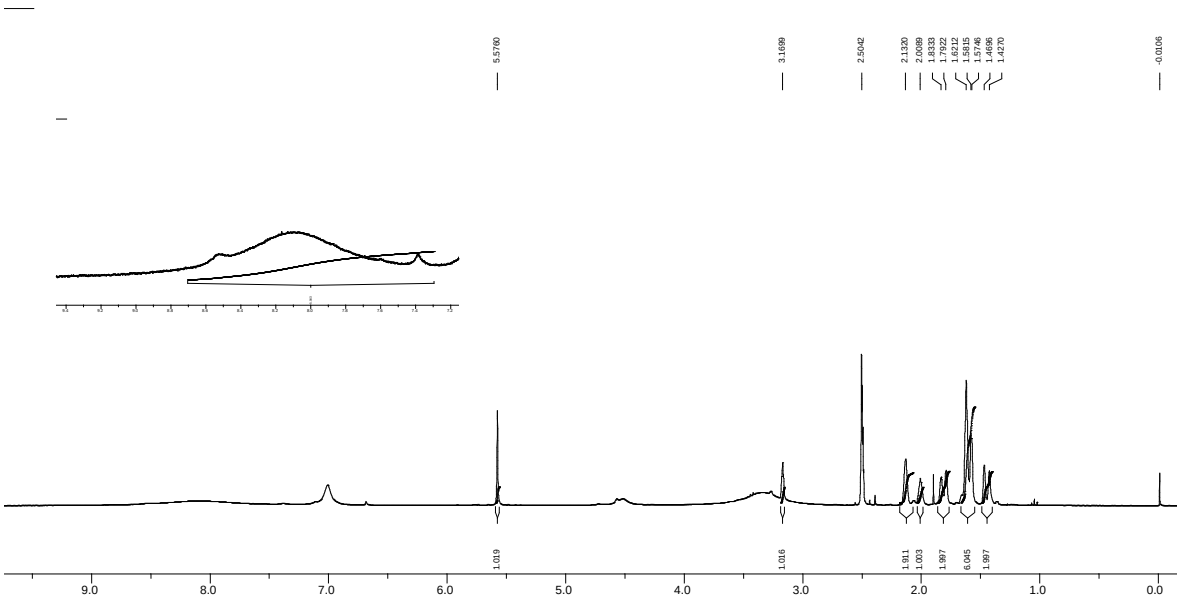


Fig. S12. ^{13}C NMR (75 MHz, DMSO-d_6) of *Z*-2-(3-aminoguanidino)-5-hydroxyadamantane hydroiodide (**6**).

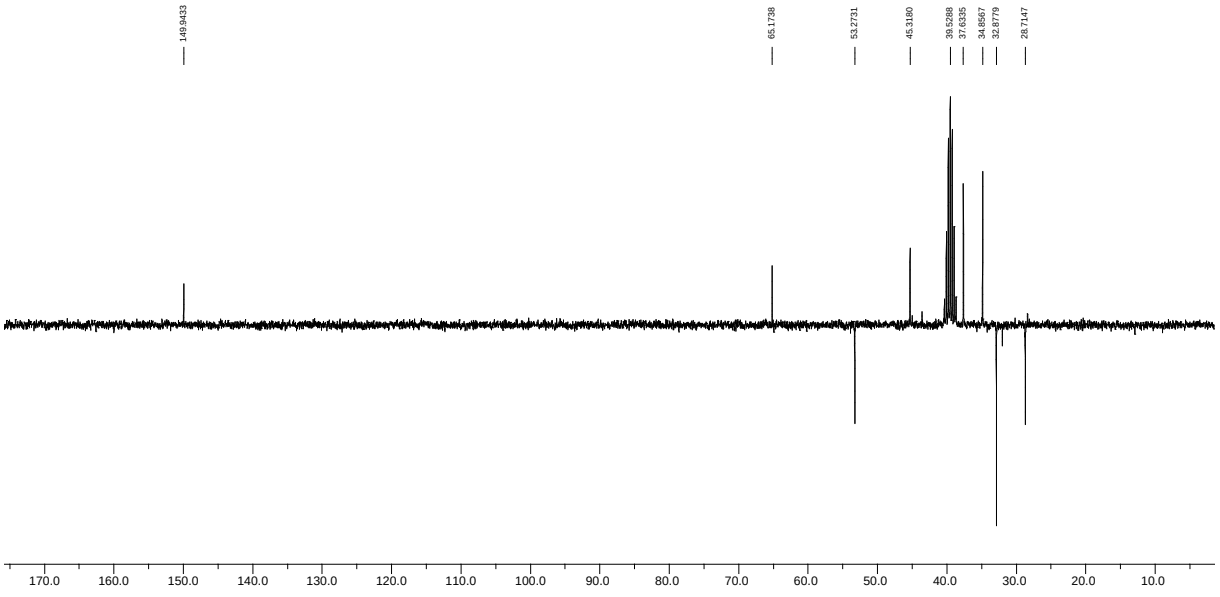
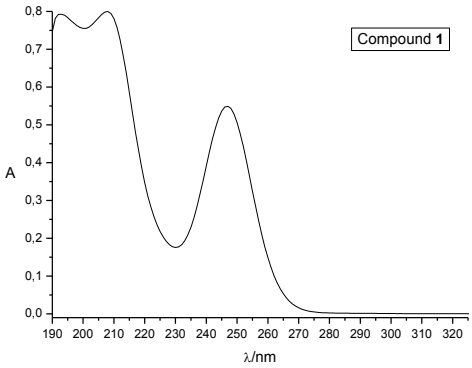
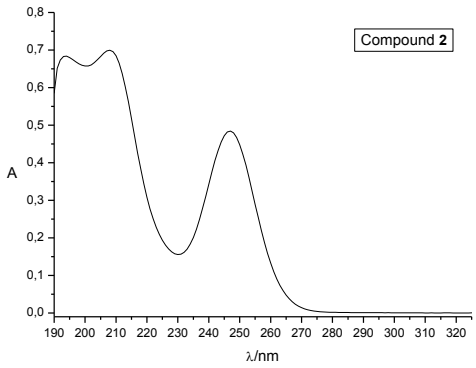


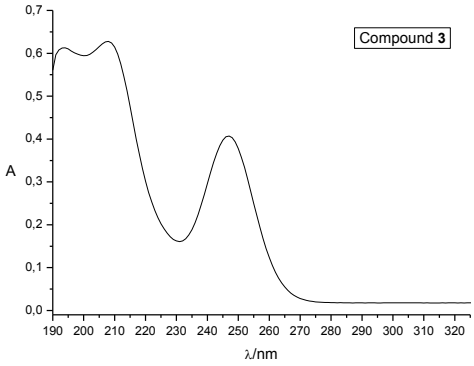
Fig. S13. UV spectra of adamantyl aminoguanidines **1-6** in CH_3CN at 25 °C.



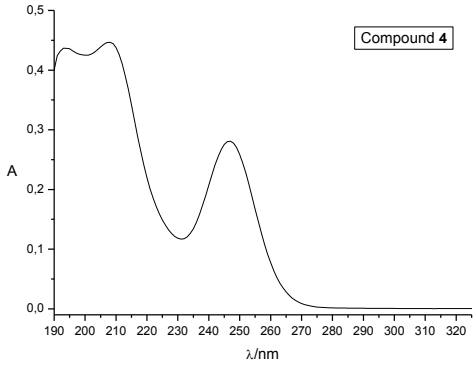
$c = 4.0 \times 10^{-5}$ mol/dm^3



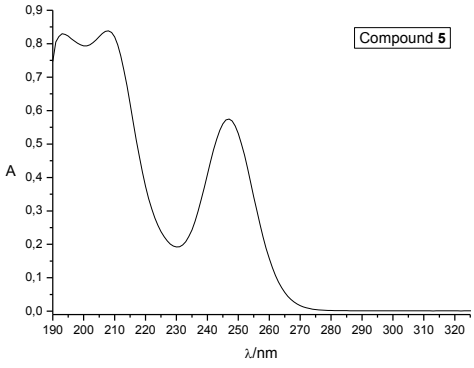
$c = 3.9 \times 10^{-5}$ mol/dm^3



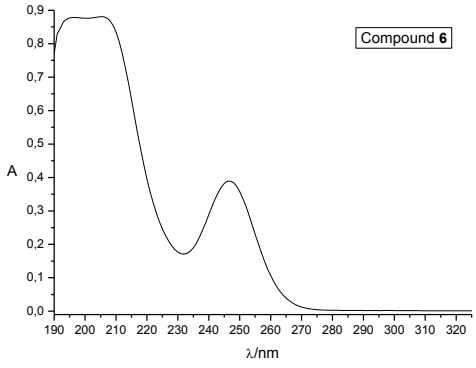
$c = 4.0 \times 10^{-5}$ mol/dm^3



$c = 3.5 \times 10^{-5}$ mol/dm^3



$c = 5.7 \times 10^{-5}$ mol/dm^3



$c = 4.8 \times 10^{-5}$ mol/dm^3

Table S1. Spectroscopic characteristics of adamantyl aminoguanidines **1-6** in CH_3CN at 25 °C.

Compound	log (ε_{194} / dm^3 mol^{-1} cm^{-1})	log (ε_{208} / dm^3 mol^{-1} cm^{-1})	log (ε_{247} / dm^3 mol^{-1} cm^{-1})
1	4.28 ± 0.01	4.303 ± 0.004	4.143 ± 0.002
2	4.373 ± 0.004	4.373 ± 0.006	4.210 ± 0.005
3	4.44 ± 0.01	4.45 ± 0.01	4.23 ± 0.02
4	4.350 ± 0.009	4.394 ± 0.007	4.20 ± 0.02
5	4.299 ± 0.009	4.334 ± 0.004	4.179 ± 0.003
6	4.365 ± 0.009	4.396 ± 0.003	4.140 ± 0.002

Table S2. Calculated geometries at the stationary points for adamantyl aminoguanidines **1-6**.

1

	X	Y	Z
C	1.9536510	0.8134630	1.2610320
C	2.7599470	-0.4989870	1.2593400
C	2.4099360	-1.3111550	-0.0017010
C	0.9004980	-1.6242920	-0.0016440
C	0.0846760	-0.3112930	0.0000680
C	0.4421550	0.4898960	1.2713940
C	2.2927300	1.6355230	0.0016330
C	0.4414370	0.4927720	-1.2696440
C	2.7592540	-0.4961430	-1.2611180
C	1.9529420	0.8162970	-1.2594060
N	-1.3549500	-0.7442970	0.0000080
C	-2.4748290	-0.0249340	0.0000760

N	-3.6677530	-0.6753310	0.0000060
N	-4.8509490	0.0669360	-0.0000860
N	-2.5056930	1.3036860	0.0001530
H	2.1898630	1.3928210	2.1578350
H	3.8316120	-0.2793570	1.2771880
H	2.5419180	-1.0809550	2.1614630
H	2.9616470	-2.2550480	-0.0029080
H	0.6407440	-2.2148720	-0.8886090
H	0.6412570	-2.2168680	0.8840840
H	-0.1233020	1.4261930	1.3304230
H	0.1793460	-0.0953250	2.1584170
H	1.7379970	2.5813340	0.0028180
H	3.3551440	1.8961820	0.0016130
H	0.1781110	-0.0904810	-2.1578640
H	-0.1239980	1.4292140	-1.3262810
H	2.5407150	-1.0760850	-2.1644430
H	3.8309190	-0.2765010	-1.2790770
H	2.1886240	1.3976290	-2.1550650
H	-1.4828760	-1.7473510	0.0000620
H	-3.6892640	-1.6867890	-0.0001490
H	-5.3983270	-0.1234410	0.8337020
H	-5.3981170	-0.1233280	-0.8340490
H	-3.4160230	1.7457820	0.0000370
H	-1.6649670	1.8534060	0.0000630

2

	X	Y	Z
C	-2.8333910	0.8717450	0.3124070
C	-3.2956820	-0.3486790	-0.5085160
C	-2.0822660	-1.2388690	-0.8438330
C	-1.0572250	-0.4269110	-1.6612100
C	-0.5932720	0.8001670	-0.8493070
C	-1.8108090	1.6860050	-0.5052590
C	-2.1693030	0.3908290	1.6175170
C	0.0541870	0.3482350	0.4823200
C	-1.4215960	-1.7189350	0.4639530
C	-0.9524110	-0.5017820	1.2904320
N	1.3105270	-0.4181130	0.2856070
C	2.5237550	0.0958780	0.1145280
N	3.5915670	-0.7329670	0.0061920
N	4.8638380	-0.1860480	-0.1808770
N	2.7460270	1.4068370	0.0558290
H	-3.6926710	1.5036760	0.5529900
H	-4.0384070	-0.9224930	0.0553380
H	-3.7849100	-0.0194780	-1.4310220
H	-2.4091580	-2.1048430	-1.4262040
H	-0.2038030	-1.0565360	-1.9399100
H	-1.5044230	-0.0868580	-2.5999010
H	0.1291700	1.3788450	-1.4371220

H	-1.4940660	2.5713400	0.0587740
H	-2.2649680	2.0500180	-1.4316030
H	-1.8581310	1.2459810	2.2278020
H	-2.8811630	-0.1819330	2.2192210
H	0.3173780	1.2224020	1.0881080
H	-0.5944140	-2.4073170	0.2379960
H	-2.1288070	-2.3021840	1.0607960
H	-0.4757170	-0.8299590	2.2202530
H	1.2269670	-1.4251570	0.2722480
H	3.4643470	-1.7315040	0.1094620
H	5.4749990	-0.4153720	0.5970260
H	5.2690620	-0.5065920	-1.0549610
H	3.7016630	1.7123180	-0.0741460
H	1.9914080	2.0715750	0.0494080

3

	X	Y	Z
C	-1.1301580	0.8685610	0.9890170
C	-1.7508240	0.5327210	-0.3907640
C	-0.6271830	0.0972510	-1.3610900
C	0.3371070	1.2897780	-1.5379640
C	0.9633980	1.6731820	-0.1799210
C	-0.1645000	2.0580440	0.8004030
C	-0.3508620	-0.3414810	1.5429000

C	1.7386150	0.4815750	0.4308580
C	0.1682370	-1.0998590	-0.7961450
C	0.7819180	-0.7307480	0.5694400
N	2.9502060	0.1876090	-0.3661310
C	4.1039660	-0.2991860	0.1072750
N	5.1701700	-0.3971290	-0.7171210
N	6.3691790	-0.9106890	-0.2114700
N	4.2531780	-0.6968490	1.3659640
N	-2.8085470	-0.5002950	-0.3270540
C	-4.1065690	-0.2790020	-0.0852560
N	-4.9826830	-1.3039480	-0.1751180
N	-6.3348150	-1.0606010	0.0878720
N	-4.5811350	0.9180320	0.2407040
H	-1.9167630	1.1474030	1.6970360
H	-2.2170160	1.4297890	-0.8115270
H	-1.0675340	-0.1617280	-2.3282500
H	1.0943200	1.0280630	-2.2858640
H	-0.1885440	2.1563790	-1.9490420
H	1.6430950	2.5211440	-0.3031080
H	0.2507930	2.3517960	1.7687540
H	-0.6944460	2.9337520	0.4132820
H	0.0517660	-0.0903070	2.5289650
H	-1.0135400	-1.1984820	1.6956680
H	2.0837300	0.7892620	1.4233750

H	0.9416460	-1.3887150	-1.5140890
H	-0.4561300	-1.9929750	-0.6771660
H	1.3275420	-1.5921590	0.9669550
H	2.9401180	0.4629100	-1.3380040
H	5.1158540	-0.0393830	-1.6630280
H	6.6491360	-1.7416220	-0.7243850
H	7.1051090	-0.2108250	-0.2451690
H	5.1677750	-1.0422270	1.6346730
H	3.4962310	-0.7001900	2.0275990
H	-2.5442670	-1.4486930	-0.5521270
H	-4.6704520	-2.2131240	-0.4937100
H	-6.9008500	-1.2321390	-0.7383300
H	-6.6590090	-1.6312910	0.8631490
H	-5.5798770	0.9903040	0.3996570
H	-3.9864310	1.7151270	0.3886350

4

	X	Y	Z
C	0.1591700	1.7734820	1.5329080
C	-0.1846480	2.9542130	0.6083920
C	-0.2603490	2.4524610	-0.8440690
C	1.0928240	1.8427000	-1.2460570
C	1.4388990	0.6521450	-0.3215800
C	1.5219190	1.1696160	1.1310320

C	-0.9376180	0.6907040	1.4317320
C	0.3160900	-0.4093660	-0.4443600
C	-1.3648830	1.3845030	-0.9765090
C	-1.0498990	0.2042360	-0.0315120
N	2.7378980	0.1268260	-0.8416700
C	3.5537650	-0.8564660	-0.4301880
N	3.3400930	-1.5319200	0.7199160
N	4.2798430	-2.5015930	1.1013530
N	4.6068390	-1.2047710	-1.1655870
N	-2.0434700	-0.9052230	-0.1827730
C	-3.3775380	-0.8926660	-0.0354100
N	-4.0772760	-1.9936050	-0.3959310
N	-5.4623970	-2.0057650	-0.2054790
N	-4.0638310	0.1353020	0.4465240
H	0.2216500	2.1148750	2.5684760
H	-1.1359740	3.4051670	0.9069730
H	0.5722480	3.7380200	0.6998750
H	-0.4870150	3.2816370	-1.5176430
H	1.0568400	1.5004100	-2.2869020
H	1.8801320	2.5997620	-1.1735880
H	1.7638100	0.3716480	1.8419800
H	2.3138580	1.9187550	1.2115300
H	-0.7143890	-0.1583110	2.0860440
H	-1.8788770	1.1168400	1.7898210

H	0.2673590	-0.7613550	-1.4802200
H	0.5304690	-1.2741750	0.1935230
H	-1.4313360	1.0208400	-2.0066490
H	-2.3314170	1.8363620	-0.7399300
H	3.0416720	0.5845330	-1.6905100
H	2.6870550	-1.1605800	1.3946560
H	3.8238790	-3.3944990	1.2594900
H	4.7876110	-2.2117460	1.9326810
H	5.2144590	-1.9292140	-0.8015430
H	4.7938770	-0.8026190	-2.0703700
H	-1.6643700	-1.7738180	-0.5334280
H	-3.6089230	-2.7700800	-0.8466490
H	-5.7345030	-2.7555530	0.4236130
H	-5.9498560	-2.0931350	-1.0927310
H	-5.0679620	0.0137030	0.5283510
H	-3.6205720	0.9543980	0.8223980

5

	X	Y	Z
C	-0.6857230	0.4693260	-1.3210260
C	0.2849860	-0.3282910	-0.4201930
C	-0.3491220	-0.5232400	0.9793050
C	-0.6879980	0.8434920	1.6085330
C	-1.6763160	1.6046160	0.7025870

C	-1.0290360	1.8303160	-0.6779020
C	-1.9770930	-0.3577670	-1.4799840
C	-2.9657580	0.7745220	0.5298700
C	-1.6415860	-1.3470850	0.7975120
C	-2.6319050	-0.5864240	-0.1091190
O	-3.7987530	-1.3610130	-0.3597470
H	0.4589500	-1.3006020	-0.8934410
N	1.5981950	0.3598690	-0.3675280
C	2.7743130	-0.2102580	-0.1249480
N	3.8982090	0.5480140	-0.1331210
N	5.1317160	-0.0587620	0.1189010
N	2.9043410	-1.5114190	0.1206860
H	-0.2232670	0.6150160	-2.3025010
H	0.3441810	-1.0674900	1.6306450
H	-1.1240140	0.6843460	2.5990600
H	0.2206610	1.4358610	1.7656650
H	-1.9202490	2.5694340	1.1552710
H	-1.7102070	2.3736820	-1.3387000
H	-0.1441620	2.4744150	-0.5766950
H	-2.6793970	0.1679570	-2.1317070
H	-1.7709500	-1.3257170	-1.9473970
H	-3.4452640	0.6187250	1.5037290
H	-3.6848860	1.3021830	-0.1036720
H	-2.0969490	-1.5311070	1.7764270

H	-1.4325170	-2.3262330	0.3534400
H	-4.3082810	-1.4537150	0.4534740
H	1.5871150	1.3609610	-0.5044510
H	3.8405250	1.5294280	-0.3728110
H	5.5708090	0.3460470	0.9401010
H	5.7460800	0.0206450	-0.6858350
H	3.8383780	-1.8639270	0.2850050
H	2.1076610	-2.1209490	0.1919770

6

	X	Y	Z
C	0.7448310	-0.3237920	1.4313600
C	-0.2851850	-0.6900570	0.3390700
C	0.3918230	-0.6265350	-1.0520030
C	0.9756280	0.7782210	-1.2964620
C	2.0172520	1.1143330	-0.2181040
C	1.3358410	1.0775370	1.1656860
C	1.8800060	-1.3687690	1.3877940
C	3.1449910	0.0678420	-0.2547400
C	1.5256340	-1.6738460	-1.0793020
C	2.5649110	-1.3383610	0.0078370
H	3.3705690	-2.0766610	-0.0170080
H	-0.6422950	-1.7057580	0.5395180
N	-1.4654640	0.2019260	0.4494170

C	-2.7048570	-0.0834130	0.0633490
N	-3.6953830	0.8152170	0.2840060
N	-4.9952920	0.5127000	-0.1311780
N	-3.0273620	-1.2334120	-0.5243670
H	0.2537250	-0.3514860	2.4095560
H	-0.3406210	-0.8552080	-1.8346520
H	1.4519120	0.8200690	-2.2791650
H	0.1961810	1.5473080	-1.2963300
O	2.4845490	2.4252410	-0.5200930
H	2.0618680	1.3153310	1.9499670
H	0.5829960	1.8756210	1.2070500
H	2.6018990	-1.1470910	2.1792010
H	1.4834450	-2.3685610	1.5946690
H	3.6399240	0.1069200	-1.2297710
H	3.9001850	0.3107090	0.5026080
H	1.9923310	-1.6738930	-2.0684750
H	1.1242520	-2.6812140	-0.9199020
H	-1.2987110	1.1242960	0.8273560
H	-3.4999050	1.6589570	0.8075280
H	-5.3292060	1.2025910	-0.7972060
H	-5.6253760	0.4550600	0.6632410
H	-3.9948060	-1.3626000	-0.7913710
H	-2.3269130	-1.8948070	-0.8133060
H	3.2614150	2.6245050	0.0151830

Table S3. Inhibition of butyrylcholinesterase by liposome-incorporated adamantyl aminoguanidines **2**, **3** and **6**.[a]

Liposome formulation of compound	Inhibition of enzymatic reaction (%)[b]
2	18.12
3	10.60
6	7.47

[a] **Butyrylcholinesterase activity assay**: Whole blood from healthy donors was collected into heparinized blood collection tubes. Samples were incubated at room temperature for 30-45 minutes and centrifuged for 20 minutes at 3 500 RCF. The supernatants were carefully aspirated and pooled. The serum was inspected for turbidity. The serum was diluted 10 times with phosphate buffer before using in butyrylcholinesterase activity assay. The enzyme activities were determined by the colorimetric method of Ellman *et al.* with acetylcholine iodide as substrate [*G.L. Ellman, K.D. Courtney, V. Andres Jr., R.M. Featherstone, Biochem. Pharmacol. 7 (1961) 88-95.*]. Briefly, in microtiter plates 25 μL of liposome suspension with encapsulated compound, 125 μL of 6.32 mM DTNB (5,5'-dithiobis-(2-nitrobenzoic acid), reagents and 25 μL of previously prepared human serum were added. The reaction mixture was incubated for 15 minute before the substrate acetyltiocholin-iodide, ATCh 25 μL of 21.66 mM solution was added. The increase in absorbance is measured at 412 nm for 10 minute. Enzyme activity was corrected for the spontaneous, nonenzymatic substrate hydrolysis. The blank contained the phosphate buffer instead of liposome suspension with encapsulated compounds and did not contain the substrate.

[b] The percentage of inhibition of the BChE activity was calculated from the linear regression curves obtained by plotting the absorption versus the reaction time for inhibited and uninhibited enzymatic reaction. The slope of linear regression curve represents the rate of enzymatic reaction. The percentage inhibition was calculated using the equation:

$$\text{Inhibition (\%)} = [(v_0 - v_i) / v_0] \times 100$$