Supplementary Material

The development of Tyrosyl-DNA phosphodiesterase 1 inhibitors. Combination of monoterpene and adamantine moieties via amide or thioamides bridges

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Figure S1. Intrinsic fluorescence spectroscopy of Tdp1 in the presence of compounds **44b**, **45a**, **46a**, **47a** and **51**. Samples contained 10 μM Tdp1 and 1 mM compound (if applicable) dissolved in a buffer containing 20 mM Tris (pH 8.0) and 250 mM NaCl. Control experiments were conducted with DMSO, which is the solvent that the compounds were dissolved in. Excitation wavelength was 280 nm and intrinsic fluorescence was measured between 300 and 450 nm. Maximum fluorescence intensity was reported. Other compounds

Table S1. Results of the scoring function for the ligands with and without two water molecules present.

Ligand	ASP		ChemPLP		ChemScore		GoldScore	
	H_2O		H_2O		H_2O		H_2O	
50a	24.5	18.5	57.4	53.0	30.5	24.8	56.9	48.3
50b	26.8	19.4	60.3	50.6	30.3	25.0	57.7	50.6
44a	25.7	19.4	58.5	53.8	31.6	26.5	55.7	48.9
45a	27.0	21.2	59.8	54.0	32.5	26.6	55.3	51.0
44b	28.6	20.0	57.6	51.1	31.5	27.1	59.0	51.2
45b	28.2	19.8	62.8	54.4	32.4	26.9	59.6	48.8
46a	27.0	17.4	59.1	55.4	32.5	26.3	59.2	50.2
51	28.2	19.8	58.4	49.7	33.1	26.3	62.8	50.6
47a	28.6	19.2	58.9	54.5	32.6	28.8	63.8	46.1
46b	28.6	19.2	57.6	53.3	32.5	27.3	61.0	50.1
47b	29.4	19.5	60.5	52.9	32.9	28.9	61.4	49.5

Table S2. The calculated molecular descriptors for the ligands.

Ligand	MW	HB Donor	HB Acceptor	Log P	PSA	Rot. Bonds	KDI_{2a}	KDI_{2b}
50a	303.5	1	2.5	4.5	28.7	6	5.20	0.41
50b	303.5	1	2.5	4.4	30.4	6	5.22	0.42
44a	319.5	1	2.5	5.1	33.2	8	4.99	0.32
45a	319.5	1	2.5	5.0	32.1	8	5.00	0.33
44b	315.5	1	2.5	4.7	33.9	6	5.23	0.43
45b	315.5	1	2.5	4.7	32.1	6	5.22	0.42
46a	335.6	1	2.0	6.3	16.8	8	4.60	0.18
51	319.5	1	2.0	5.8	13.3	6	4.81	0.24
47a	335.6	1	2.0	6.3	15.2	8	4.58	0.18
46b	331.6	1	2.0	6.0	16.3	6	4.82	0.24
47b	331.6	1	2.0	6.0	15.4	6	4.81	0.24

Table S3. Definition of lead-like, drug-like and Known Drug Space (KDS) in terms of molecular descriptors. The values given are the maxima for each descriptor for the volumes of chemical space used.

	Lead-like Space	Drug-like Space	Known Drug Space
Molecular weight (g mol^{-1})	300	500	800
Lipophilicity (Log P)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area ($Å^2$) (PSA)	60	140	180
Rotatable bonds (RB)	3	10	17

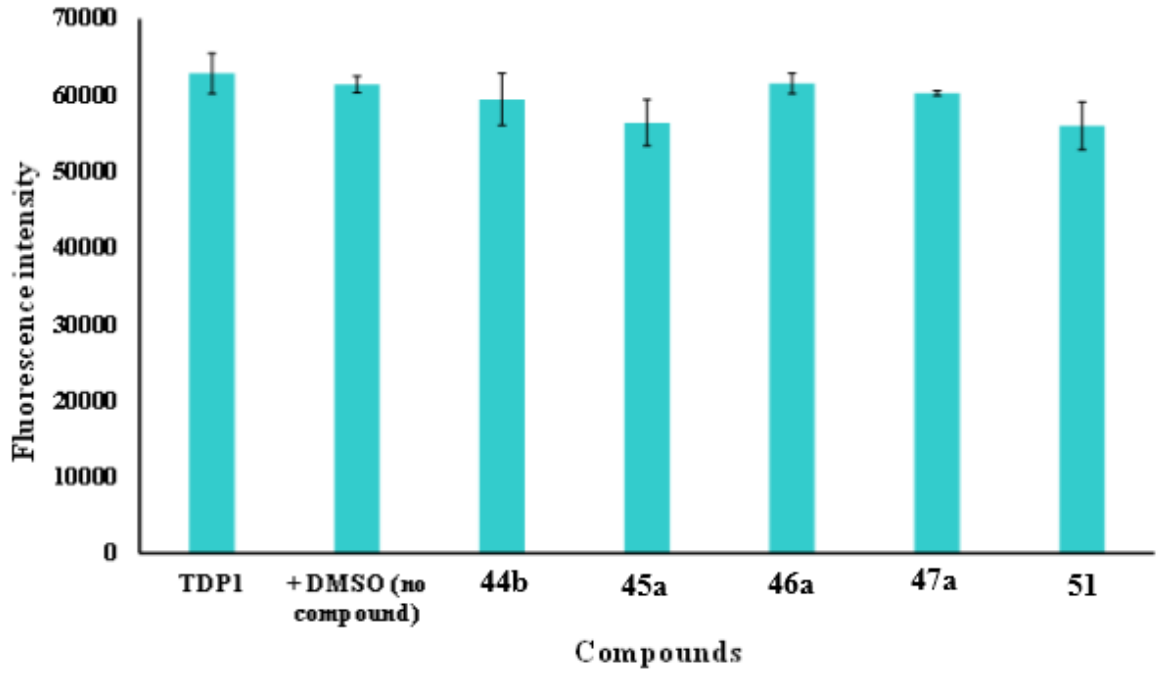

Figure S1. Intrinsic fluorescence spectroscopy of Tdp1 in the presence of compounds **44b**, **45a**, **46a**, **47a** and **51**. Samples contained 10 μM Tdp1 and 1 mM compound (if applicable) dissolved in a buffer containing 20 mM Tris (pH 8.0) and 250 mM NaCl. Control experiments were conducted with DMSO, which is the solvent that the compounds were dissolved in. Excitation wavelength was 280 nm and intrinsic fluorescence was measured between 300 and 450 nm. Maximum fluorescence intensity was reported. Other compounds were not tested because they are not soluble at the required concentration in aqueous buffer.

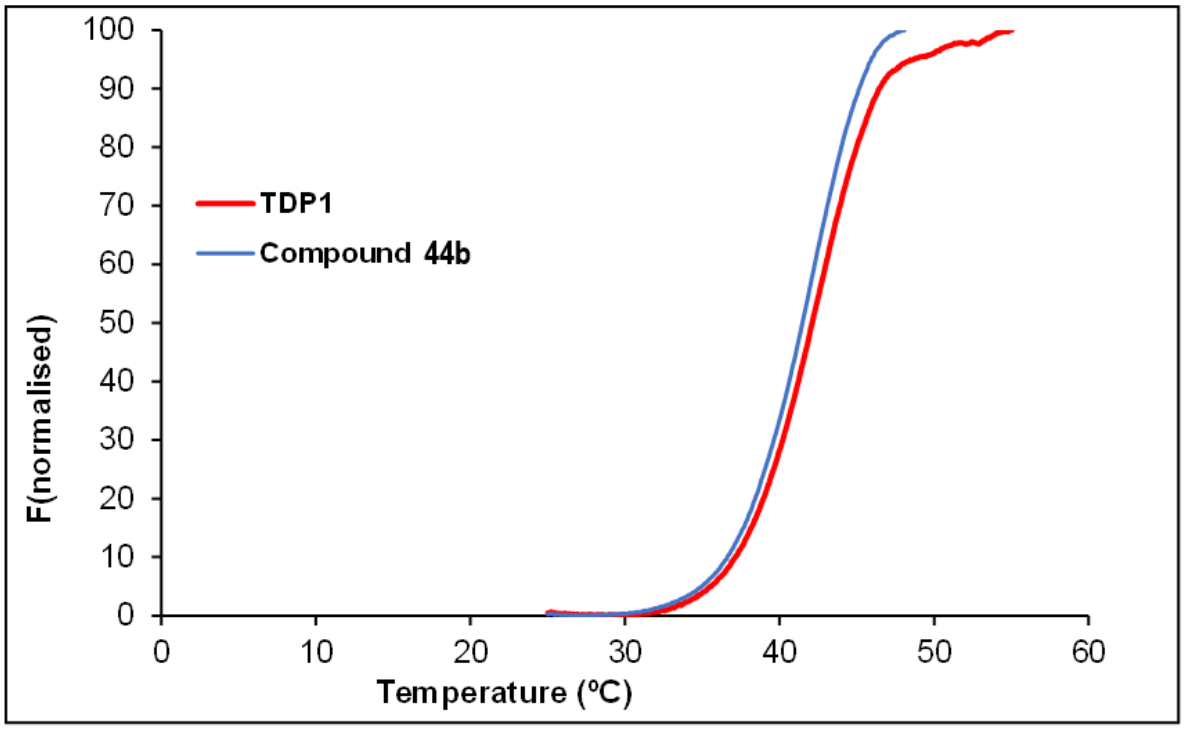

Figure S2. Protein melt curves showing the denaturing temperature of Tdp1 (10 μM, red) and Tdp1 (10 μM) in the presence of compound **44b** (100 μM, blue) as monitored by thermal shift assay. Buffer was 20 mM Tris (pH 8.0) and 250 mM NaCl. Changes in denaturing temperature was found to be -0.27 °C.

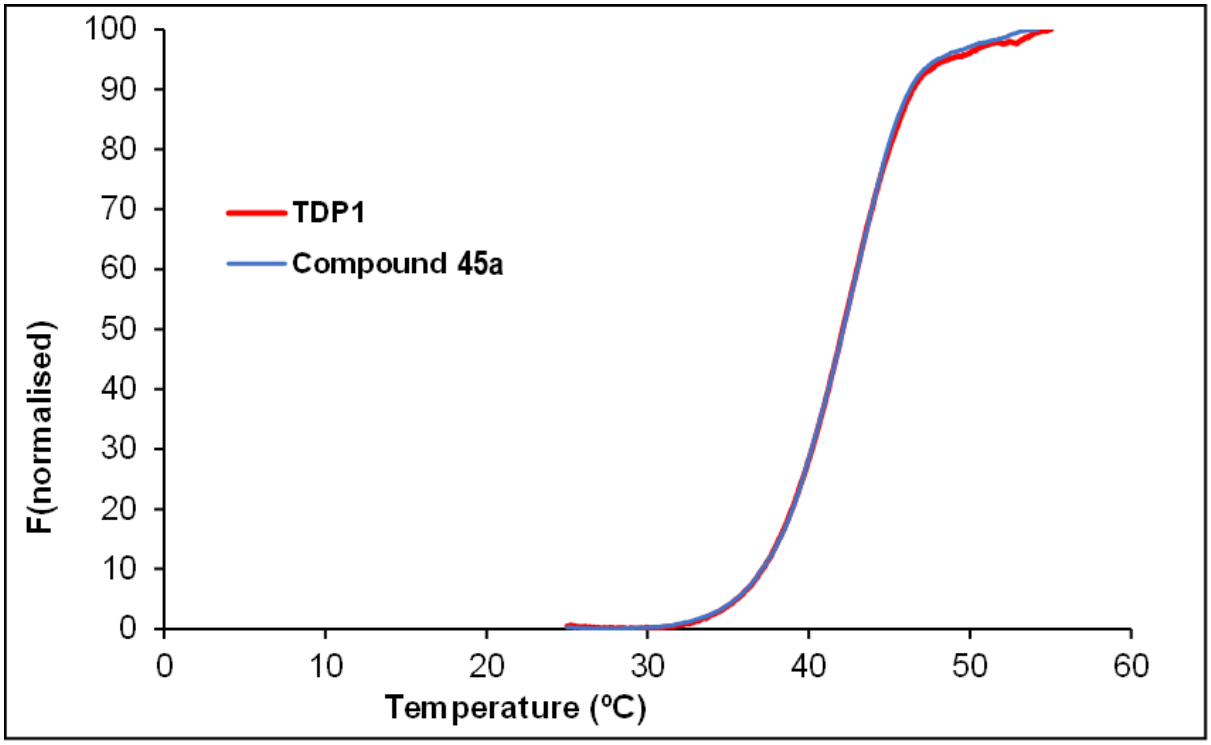

Figure S3. Protein melt curves showing the denaturing temperature of Tdp1 (10 μM, red) and Tdp1 (10 μM) in the presence of compound **45a** (100 μM, blue) as monitored by thermal shift assay. Buffer was 20 mM Tris (pH 8.0) and 250 mM NaCl. Changes in denaturing temperature was found to be 0.04 °C.

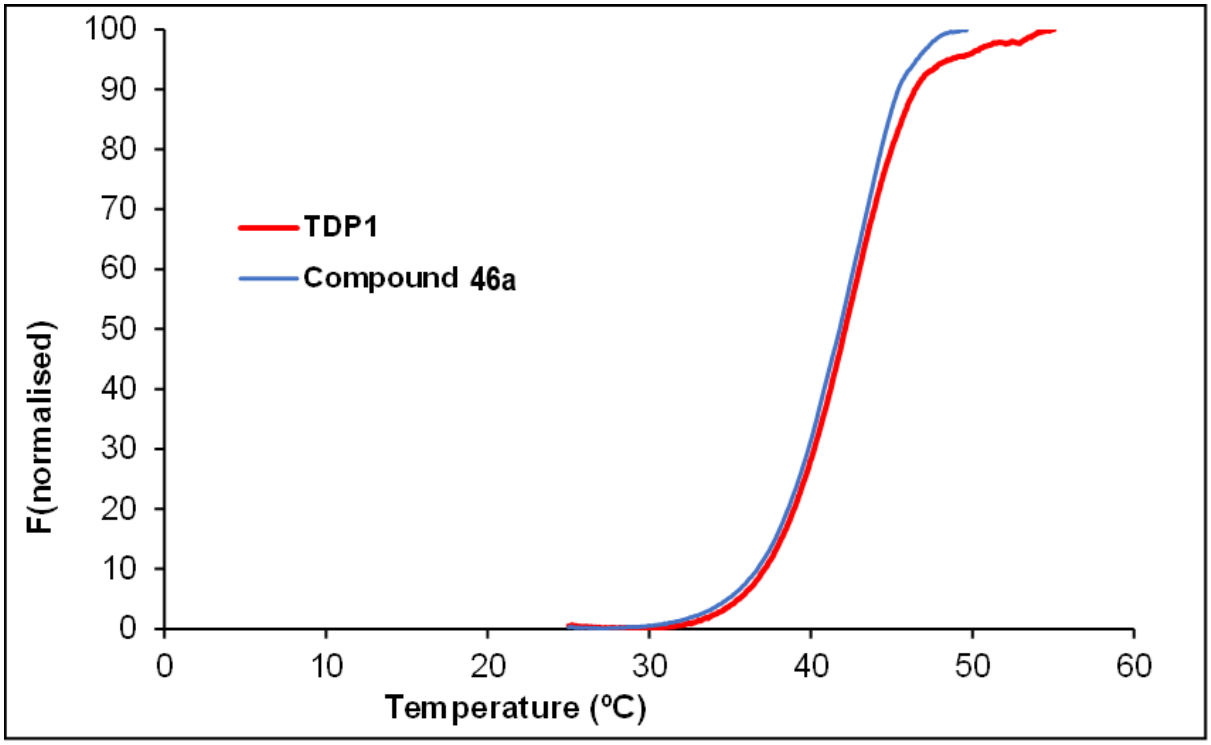

Figure S4. Protein melt curves showing the denaturing temperature of Tdp1 (10 μM, red) and Tdp1 (10 μM) in the presence of compound **46a** (100 μM, blue) as monitored by thermal shift assay. Buffer was 20 mM Tris (pH 8.0) and 250 mM NaCl. Changes in denaturing temperature was found to be -0.1 °C.

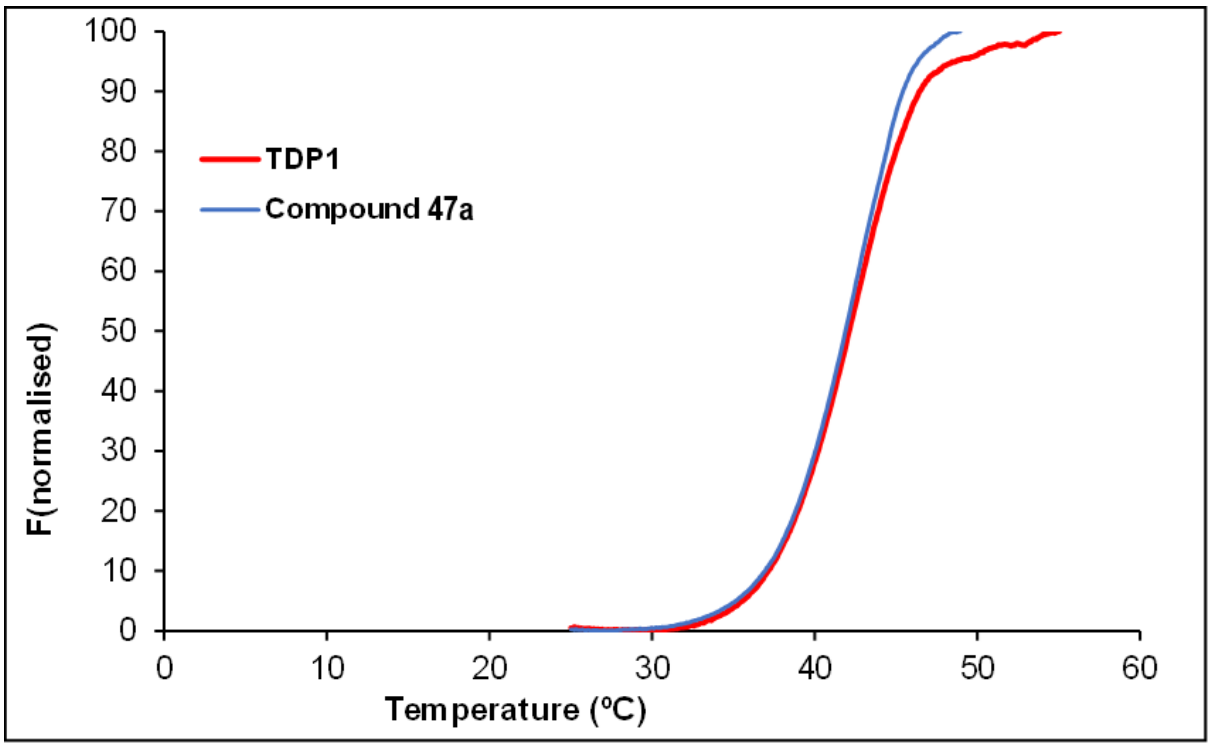

Figure S5. Protein melt curves showing the denaturing temperature of Tdp1 (10 μM, red) and Tdp1 (10 μM) in the presence of compound **47a** (100 μM, blue) as monitored by thermal shift assay. Buffer was 20 mM Tris (pH 8.0) and 250 mM NaCl. Changes in denaturing temperature was found to be 0.08 °C.

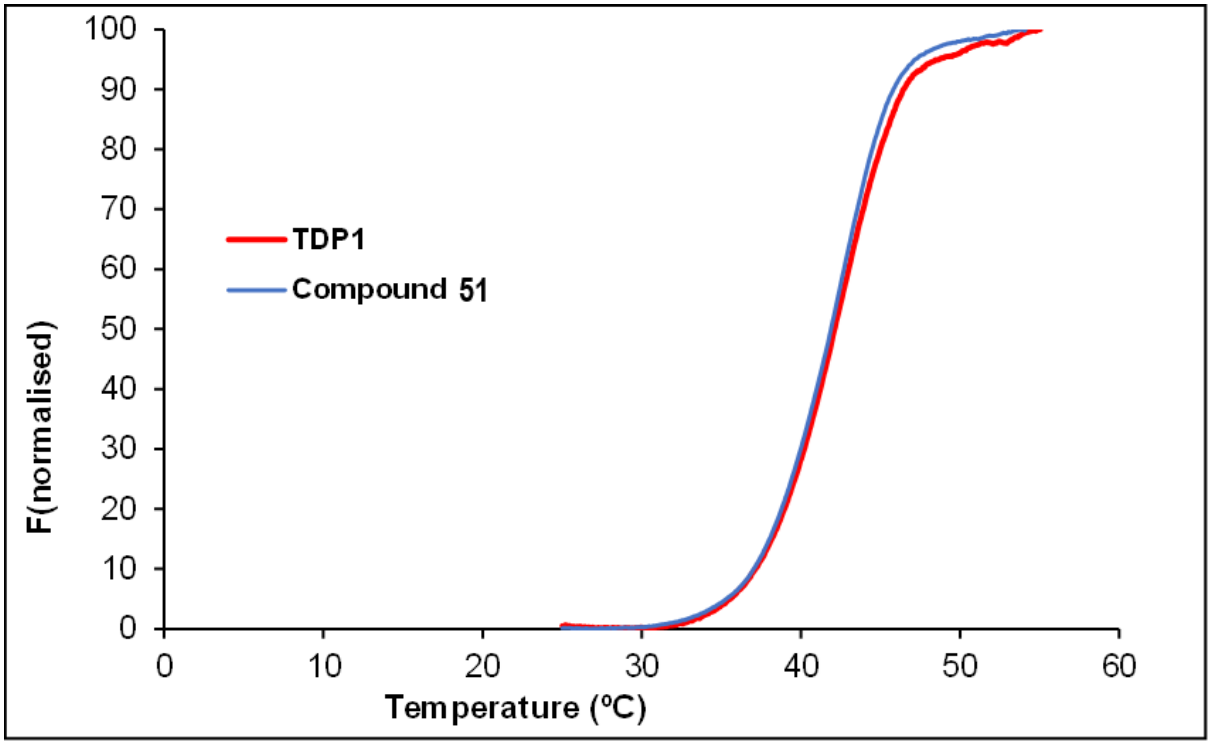

Figure S6. Protein melt curves showing the denaturing temperature of Tdp1 (10 μM, red) and Tdp1 (10 μM) in the presence of compound **51** (100 μM, blue) as monitored by thermal shift assay. Buffer was 20 mM Tris (pH 8.0) and 250 mM NaCl. Changes in denaturing temperature was found to be -0.22 °C.

Figure S7. ^{1}H-NMR spectrum of *N*-(3,7-Dimethyloctyl)adamantane-1-carboxamide **44a**.

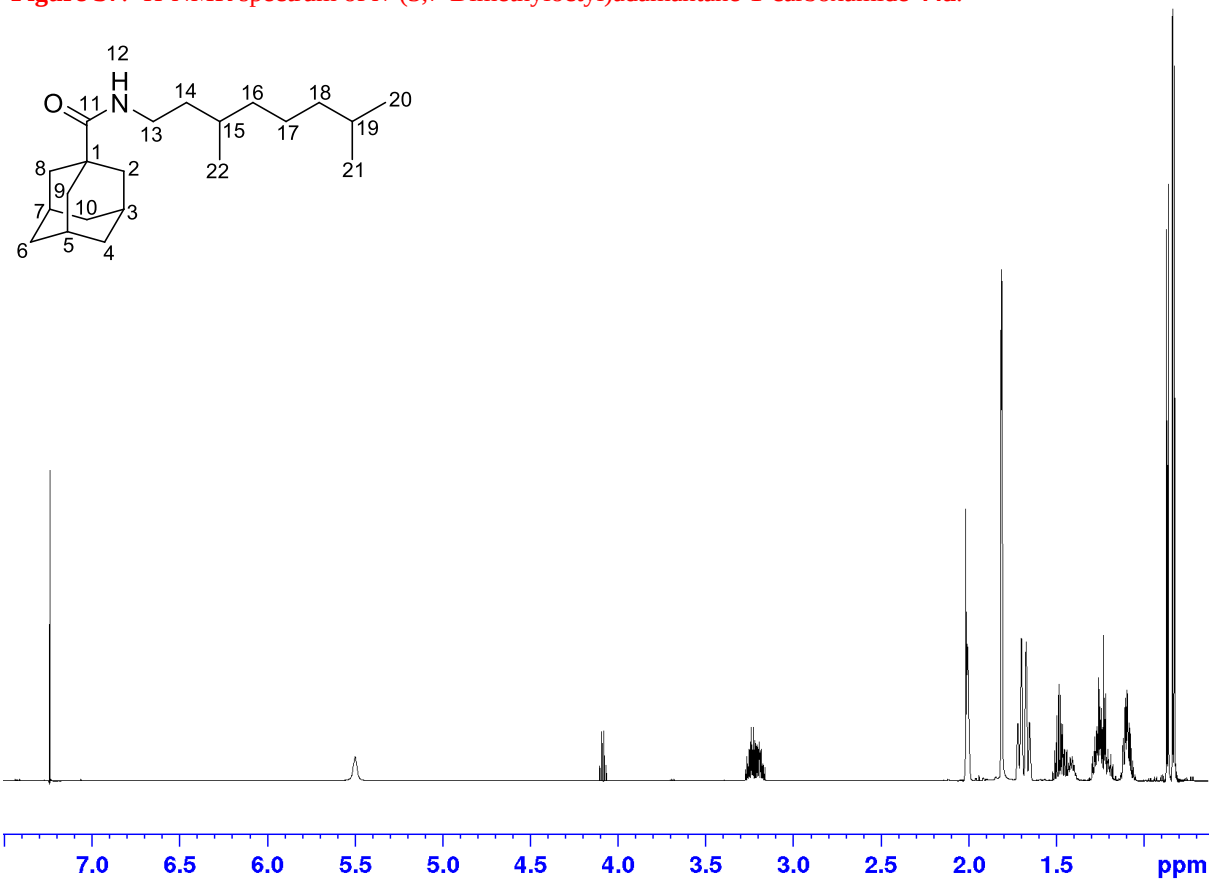

Figure S8. ^{1}H-NMR spectrum of *N*-((*Z*)-3,7-Dimethylocta-2,6-dien-1-yl)adamantane-1-carboxamide **44b.**

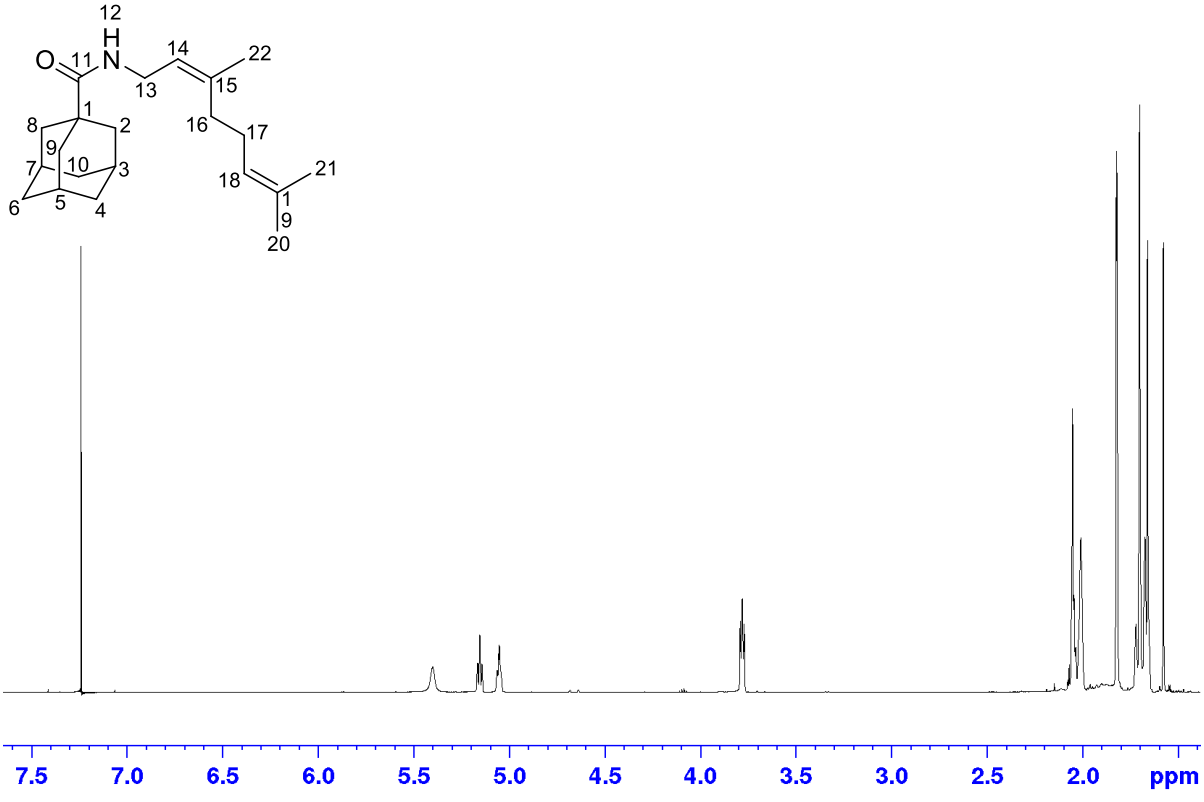

Figure S9. ^{1}H-NMR spectrum of *N*-(3,7-Dimethyloctyl)adamantane-2-carboxamide **45a**.

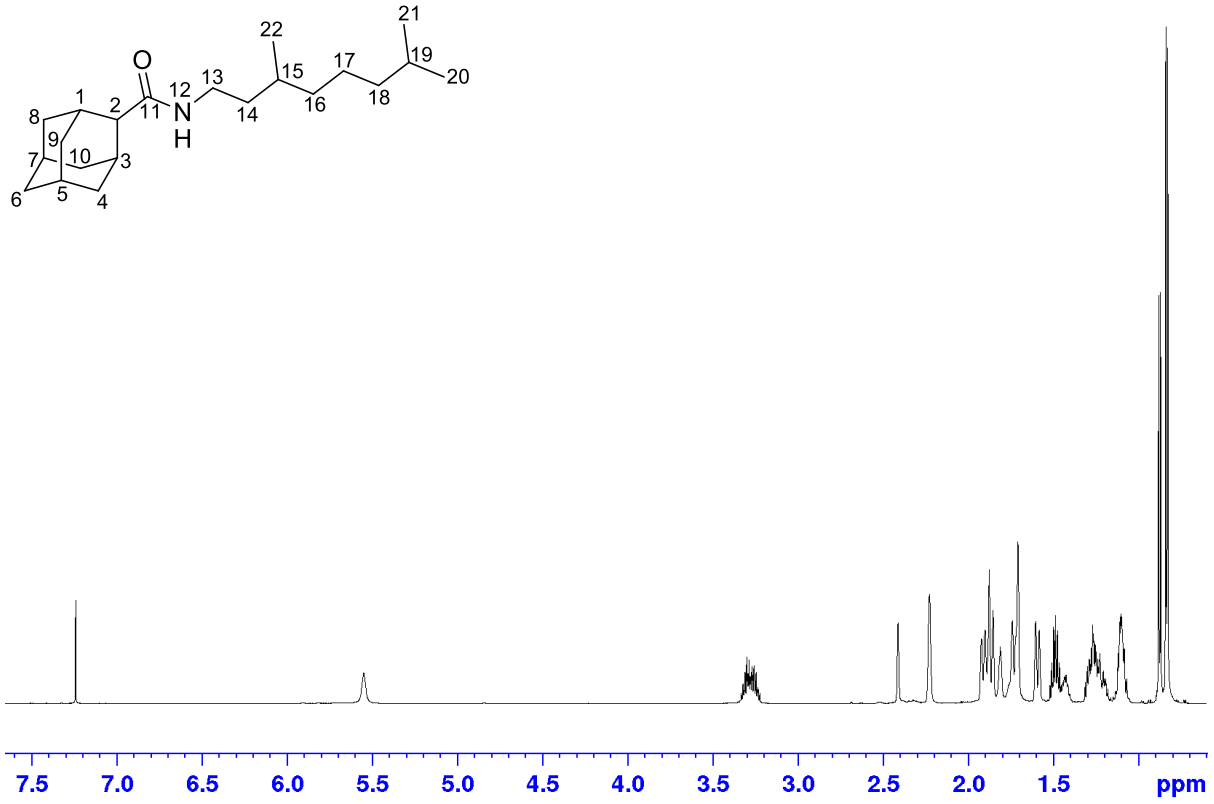

Figure S10. ^{1}H-NMR spectrum of *N*-((*Z*)-3,7-Dimethylocta-2,6-dien-1-yl)adamantane-2-carboxamide **45b**.

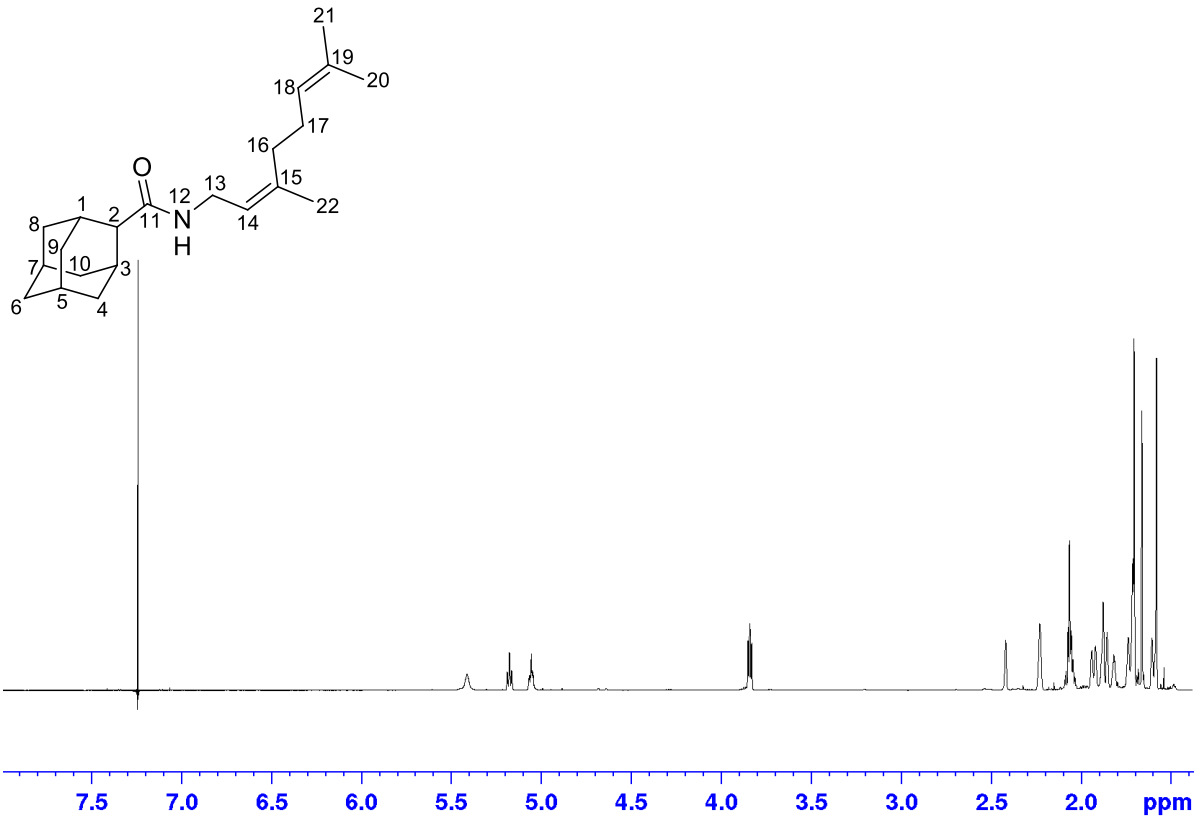

Figure S11. ^{1}H-NMR spectrum of *N*-(3,7-Dimethyloctyl)adamantane-1-carbothioamide **46a**.

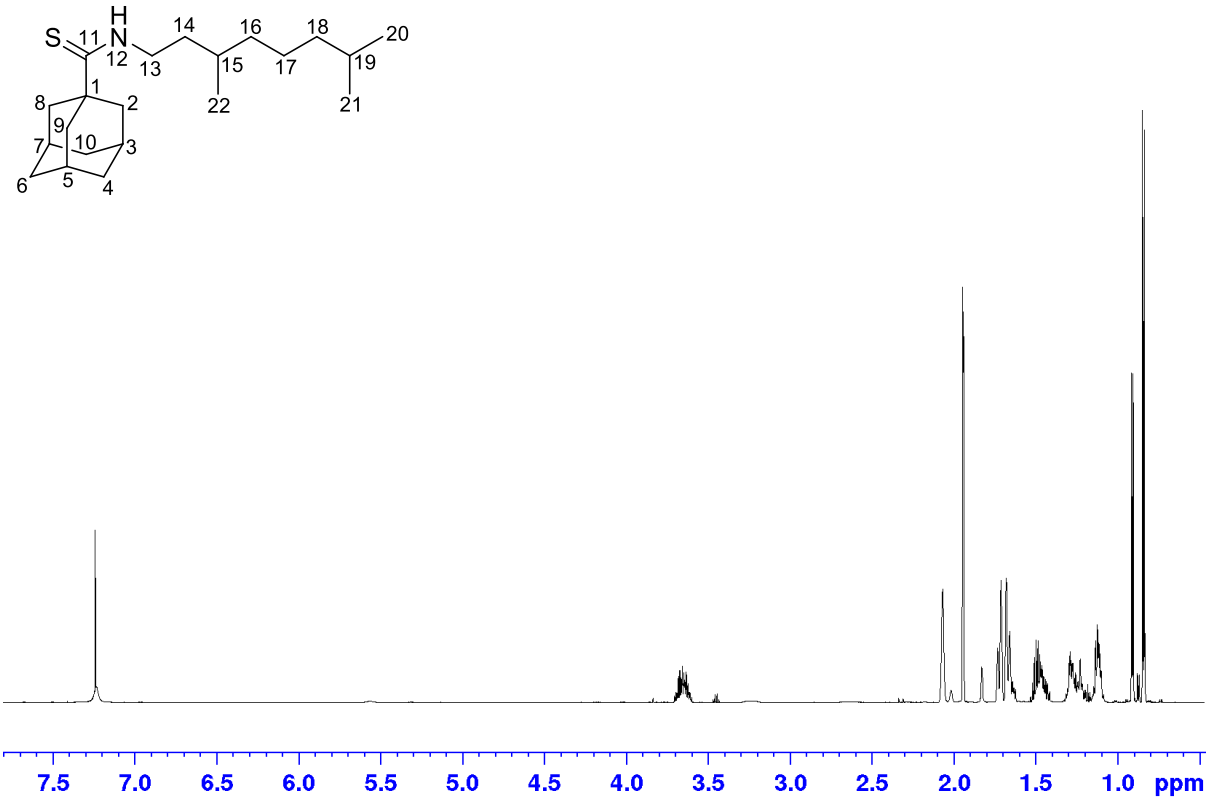

Figure S12. ^{1}H-NMR spectrum of *N*-(3,7-Dimethyloctyl)adamantane-2-carbothioamide **47a**.

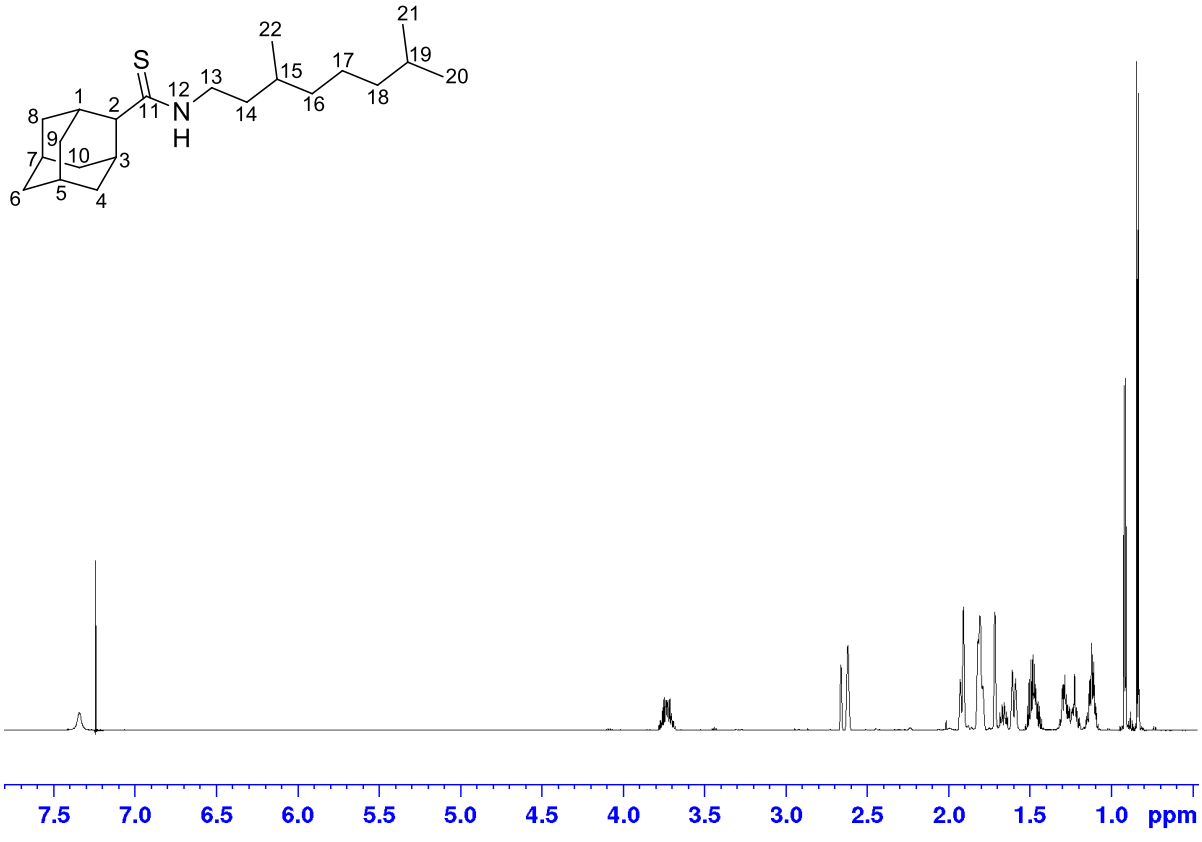

Figure S13. ^{1}H-NMR spectrum of *N*-(Adamantan-1-yl)-3,7-dimethyloct-6-enamide **50a**.

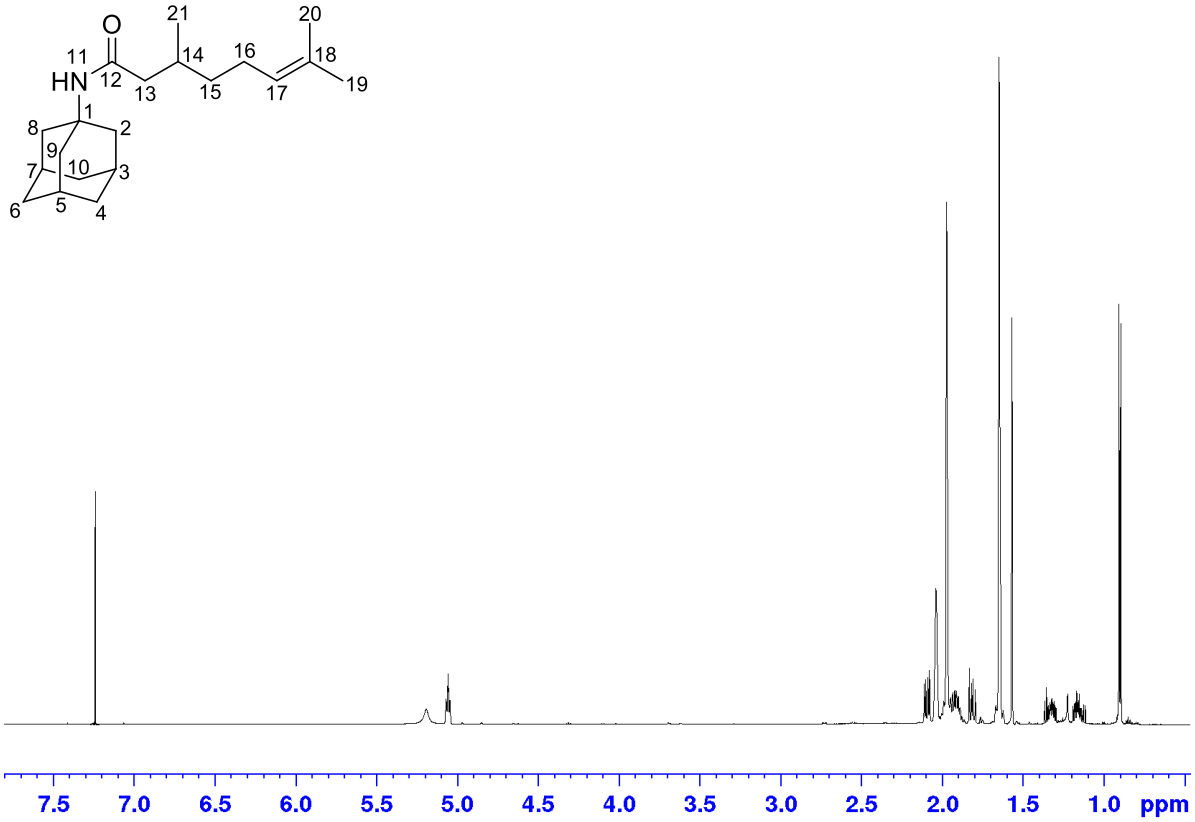

Figure S14. ^{1}H-NMR spectrum of *N*-(Adamantan-2-yl)-3,7-dimethyloct-6-enamide **50b**.

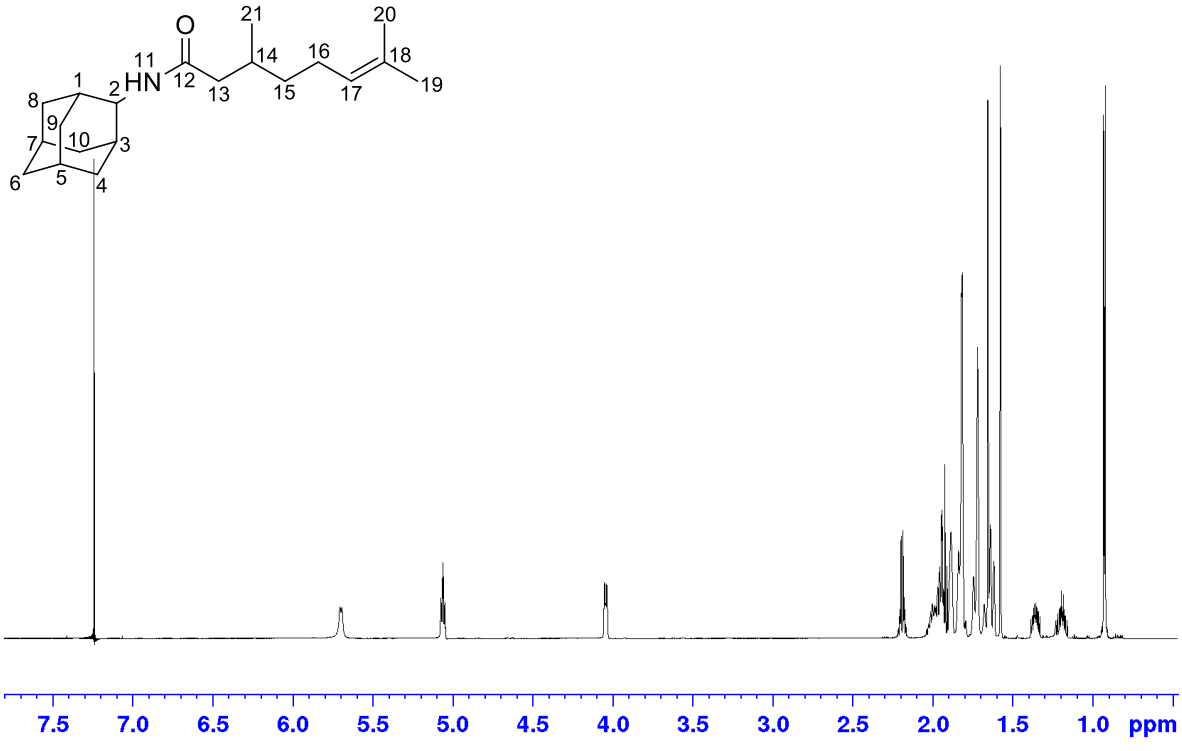

Figure S15. ^{1}H-NMR spectrum of *N*-(Adamantan-2-yl)-3,7-dimethyloct-6-enethioamide **51**.

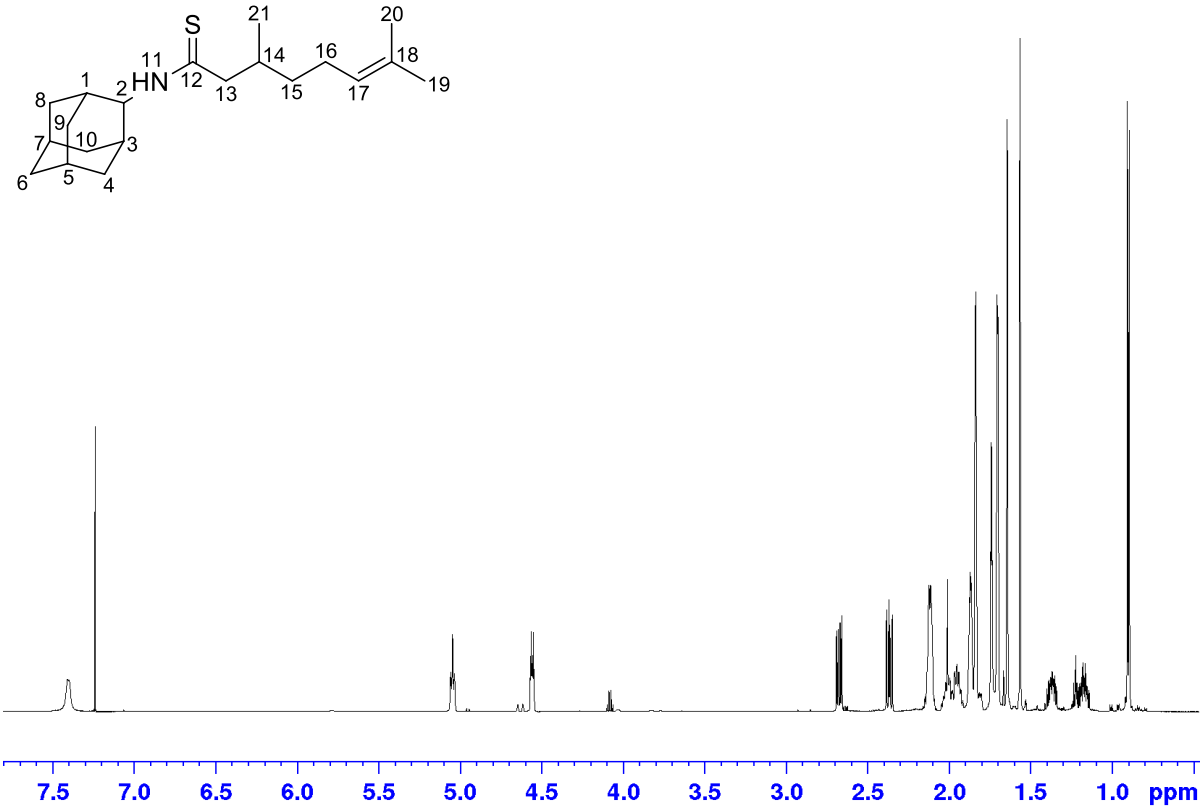

Figure S16. Dose-dependent influence of the adamantane derivatives on A-549 cell viability using the MTT assay.