Supplementary Material

Novel asymmetric biscarbothioamides as Alzheimer's disease associated cholinesterase inhibitors: Synthesis, biological activity, and molecular docking studies

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Table S1. FT-IR values of the novel asymmetric bis(carbothioamides) (**3a-l**) (cm^{-1}).

Compounds ID	N^1H	N^2H	N^3H	Ar H	Aliph. H	C=S	NO_2 [a]	C-N	Specific Peak
3a	3265	3194	3119	3028	2949	1375	-	1189 1153 1097	-
3b	3243	3195	3110	2999	2937	1338	-	1186 1169 1039	-
3c	3206	3106		3004	2935	1337	-	1181 1102 1026	-
3d	3181		3108	3010	2936	1336	-	1183 1160 1086	C-Cl: 958
3e	3212	3108		3007	2935	1334	-	1100 1070 1024	C-F: 1183
3f	3193	3105		3013	2936	1337	-	1184 1105 1069	-
3g	3393	3252	3155	3048	2914	1389	1505 1323	1186 1108 1046	-
3h	3329	3205	3161	3082	2891	1352	1468 1321	1204 1109 1050	-
3i	3218	3105		3006	2934	1295	1504 1344	1189 1103 1028	-
3j	3323	3214	3160	3043	2897	1323	1496 1297	1186 1002 961	C-F: 1107
3k	3329	3272	3102	2991	2878	1372	1502 1330	1166 1104 1068	-
3l	3327	3183	3072	3033	2812	1370	1476 1332	1241 1198 1110	C-Cl: 999

[a] The asymmetric and symmetric stretching vibrations.

Table S2. ADME/T related parameters [a] of the novel asymmetric bis(carbothioamides) (**3a-l**) and clinically used reference inhibitor tacrine.

Compound ID	#stars	#rtvFG	CNS	MW	Dipole	SASA	Volume	donorHB	accptHB	QPlogPC16	QPlogPoct	QPlogPw	QPlogS	QPPCaco	QPlogBB	QPPMDCK	QPlogKp	#metab	QPlogKhsa	HOA	PSA	Rule of Five	Rule of Three
3a	0	1	–1	254.37	2.0	535.2	859.9	4.0	5.0	9.7	4.0	5.0	4.0	1862	–0.9	4284	–1.9	1	–0.28	100	66.4	0	0
3b	0	1	–1	332.44	1.5	646.5	1065.0	4.0	5.8	12.9	4.0	5.8	4.0	1778	–0.2	4356	–1.3	3	0.34	100	73.3	0	0
3c	0	1	–1	332.44	1.5	647.6	1066.0	4.0	5.8	12.9	4.0	5.8	4.0	1830	–0.2	4784	–1.3	2	0.36	100	73.4	0	0
3d	1	1	0	336.86	2.3	637.7	1035.8	4.0	5.0	13.2	4.0	5.0	4.0	1780	0.0	10000	–1.4	1	0.10	100	65.1	0	1
3e	0	1	0	320.40	3.0	602.4	995.0	4.0	5.0	12.0	4.0	5.0	4.0	2228	0.5	8409	–1.2	2	0.22	100	64.8	0	0
3f	2	1	–1	316.44	2.4	646.3	1052.2	4.0	5.0	12.8	4.0	5.0	4.0	1778	–0.2	4573	–1.4	3	0.14	100	65.1	0	1
3g	1	1	–2	311.38	8.3	597.3	976.4	4.0	6.0	11.5	4.0	6.0	4.0	217	–1.3	418	–3.6	2	–0.23	80	111.2	0	0
3h	1	1	–2	377.44	6.8	686.4	1139.3	4.0	6.8	14.0	4.0	6.8	4.0	211	–1.4	435	–3.2	3	0.21	84	118.3	0	1
3i	1	1	–2	377.44	8.6	686.7	1139.6	4.0	6.8	14.0	4.0	6.8	4.0	217	–1.4	477	–3.2	2	0.22	85	118.4	0	1
3j	1	1	–2	365.40	6.6	661.1	1081.0	4.0	6.0	13.2	4.0	6.0	4.0	210	–1.2	821	–3.3	2	0.29	85	110.1	0	1
3k	1	1	–2	361.44	8.3	661.7	1108.7	4.0	6.0	13.8	4.0	6.0	4.0	246	–1.3	449	–3.0	2	0.67	86	110.8	0	0
3l	2	1	–2	381.85	6.7	676.2	1109.1	4.0	6.0	14.2	4.0	6.0	4.0	210	–1.2	1122	–3.3	2	0.93	87	110.1	0	1
THA [b]	0	0	1	198.27	4.2	430.7	709.9	1.5	2.0	6.9	10.7	6.4	–3.1	2931	0.0	1582	–1.8	3	0.71	100	34.2	0	0

[a] Various computational pharmacodynamic and pharmacokinetic parameters of synthesized compounds in this research were predicted such as number of property or descriptor values that fall outside the 95% range of similar values for known drugs. (#stars; 0 - 5), number of reactive functional groups (#rtvFG; 0 - 2), central nervous system activity (CNS; –2 inactive, +2 active), molecular weight of the compound (MW; 130.0 - 725.0), computed dipole moment of the compound (Dipole; 1.0 - 12.5), total solvent accessible surface area (SASA; 300.0 - 1000.0), total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å Radius (Volume; 500.0 - 2000.0), number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (donorHB; 0.0 - 6.0), number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (accptHB; 2.0 - 20.0), hexadecane/gas partition coefficient (QPlogPC16; 4.0 - 18.0), octanol/gas partition coefficient (QPlogPoct; 8.0 - 35.0), water/gas partition coefficient (QPlogPw; 4.0 - 45.0), aqueous solubility (QPlogS; –6.5 - 0.5), apparent Caco-2 cell permeability in nm/sec (QPPCaco; <25 poor, great>500), brain/blood partition coefficient (QPlogBB; –3.0 - 1.2), apparent MDCK cell permeability in nm/sec (QPPMDCK; <25 poor, great>500), skin permeability (QPlogKp; –8.0 - –1.0), number of likely metabolic reactions (#metab; 1 - 8),prediction of binding to human serum albumin (QPlogKhsa; –1.5 - 1.5), human oral absorption (HOA; <25% poor, high>80%), van der Waals surface area of polar nitrogen and oxygen atoms (PSA; 7.0 - 200.0), number of violations of Lipinski's rule of five (max. 4), and number of violations of Jorgensen's rule of three (max. 3).

[b] Tacrine.

Table S3. Pharmacokinetic properties [a] of the novel asymmetric bis(carbothioamides) (**3a-l**) and clinically used reference inhibitor tacrine.

Compounds ID	GI absorption	BBB permeant	P-gp substrate	CYP inhibitor				
				CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
3a	High	No	No	No	Yes	No	No	No
3b	High	No	No	No	Yes	Yes	Yes	No
3c	High	No	No	No	Yes	Yes	Yes	No
3d	High	No	No	No	Yes	Yes	No	Yes
3e	High	No	No	No	Yes	Yes	No	Yes
3f	High	No	No	No	Yes	Yes	No	Yes
3g	Low	No	No	No	No	No	No	No
3h	Low	No	No	No	No	Yes	Yes	No
3i	Low	No	No	No	No	Yes	Yes	No
3j	Low	No	No	No	No	Yes	No	No
3k	Low	No	No	No	No	Yes	No	No
3l	Low	No	No	No	No	Yes	No	No
THA [b]	High	Yes	Yes	Yes	No	No	No	Yes

[a] Various pharmacokinetic parameters, such as the GI absorption, human gastrointestinal absorption; BBB permeant, blood-brain barrier permeation; P-gp substrate, prediction of being substrate or non-substrate of P-glycoprotein; CYP inhibitor, prediction of being inhibitor or non-inhibitor of cytochromes P450 (CYP) five major isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4); and log K_p, prediction of the skin permeability coefficient of targeted compounds in this research, were predicted using SwissADME platform.

[b] Tacrine.

Table S4. Drug-likeness descriptors [a] of the novel asymmetric bis(carbothioamides) (**3a-l**) and clinically used reference inhibitor tacrine.

Compounds ID	Ghose	Veber	Egan	Muegge	Bioavailability Score
3a	Yes	Yes	Yes	Yes	0.55
3b	Yes	Yes	Yes	Yes	0.55
3c	Yes	Yes	Yes	Yes	0.55
3d	Yes	Yes	Yes	Yes	0.55
3e	Yes	Yes	Yes	Yes	0.55
3f	Yes	Yes	Yes	Yes	0.55
3g	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
3h	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
3i	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
3j	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
3k	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
3l	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
THA [b]	Yes	Yes	Yes	No; 1 violation: MW<200	0.55

[a] Drug-likeness parameters, such as the Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) methods and bioavailability score (Abbot) of targeted compounds in this research, were predicted using SwissADME platform.

[b] Tacrine.

Table S5. Medicinal Chemistry pattern recognition methods [a] of the novel asymmetric bis(carbothioamides) (**3a-l**) and clinically used reference inhibitor tacrine.

Compounds ID	PAINS	Brenk	Lead-likeness	SA score
3a	0 alert	1 alert: thiocarbonyl group	Yes	2.52
3b	0 alert	1 alert: thiocarbonyl group	No; 1 violation: Rotors>7	2.78
3c	0 alert	1 alert: thiocarbonyl group	No; 1 violation: Rotors>7	2.61
3d	0 alert	1 alert: thiocarbonyl group	No; 1 violation: XLOGP3>3.5	2.67
3e	0 alert	1 alert: thiocarbonyl group	Yes	2.88
3f	0 alert	1 alert: thiocarbonyl group	Yes	2.54
3g	0 alert	4 alerts: isolated alkene, nitro group, oxygen-nitrogen single bond, thiocarbonyl group	No; 1 violation: Rotors>7	2.82
3h	0 alert	3 alerts: nitro group, oxygen-nitrogen single bond, thiocarbonyl group	No; 2 violations: MW>350, Rotors>7	2.99
3i	0 alert	3 alerts: nitro group, oxygen-nitrogen single bond, thiocarbonyl group	No; 2 violations: MW>350, Rotors>7	2.86
3j	0 alert	3 alerts: nitro group, oxygen-nitrogen single bond, thiocarbonyl group	No; 2 violations: MW>350, Rotors>7	2.91
3k	0 alert	3 alerts: nitro group, oxygen-nitrogen single bond, thiocarbonyl group	No; 2 violations: MW>350, Rotors>7	2.79
3l	0 alert	3 alerts: nitro group, oxygen-nitrogen single bond, thiocarbonyl group	No; 2 violations: MW>350, Rotors>7	2.90
THA [b]	0 alert	0 alert	No; 1 violation: MW>350	2.08

[a] Medicinal Chemistry pattern recognition method, such as the PAINS, pan assay interference structure alert filter; Brenk, structural alert filter; Lead-likeness, lead-likeness criteria; and SA score, synthetic accessibility score (ranges from 1, very easy, to 10, very difficult) of targeted compounds in this research, were predicted using SwissADME platform.

[b] Tacrine.

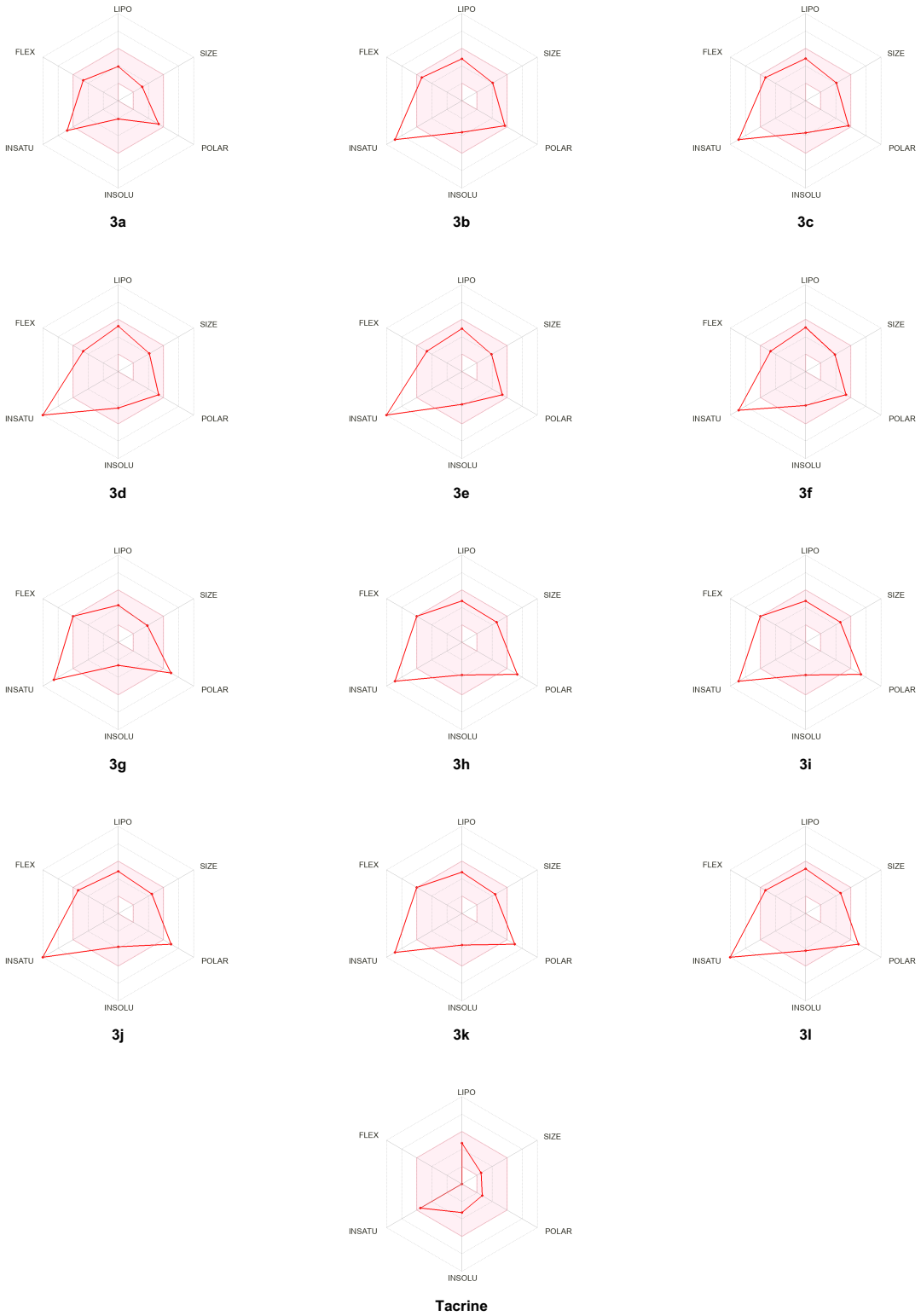

Fig. S1. Diagrams showing 'drug-likeness' descriptors for the novel asymmetric bis(carbothioamides) (**3a-l**) and clinically used reference inhibitor tacrine. The red-colored zone has been identified as a feasible physicochemical domain to enhance oral bioavailability. LIPO, lipophilicity; SIZE, molecular weight; POLAR, polarity; INSOLU, insolubility; INSATU, saturation; and FLEX, flexibility.

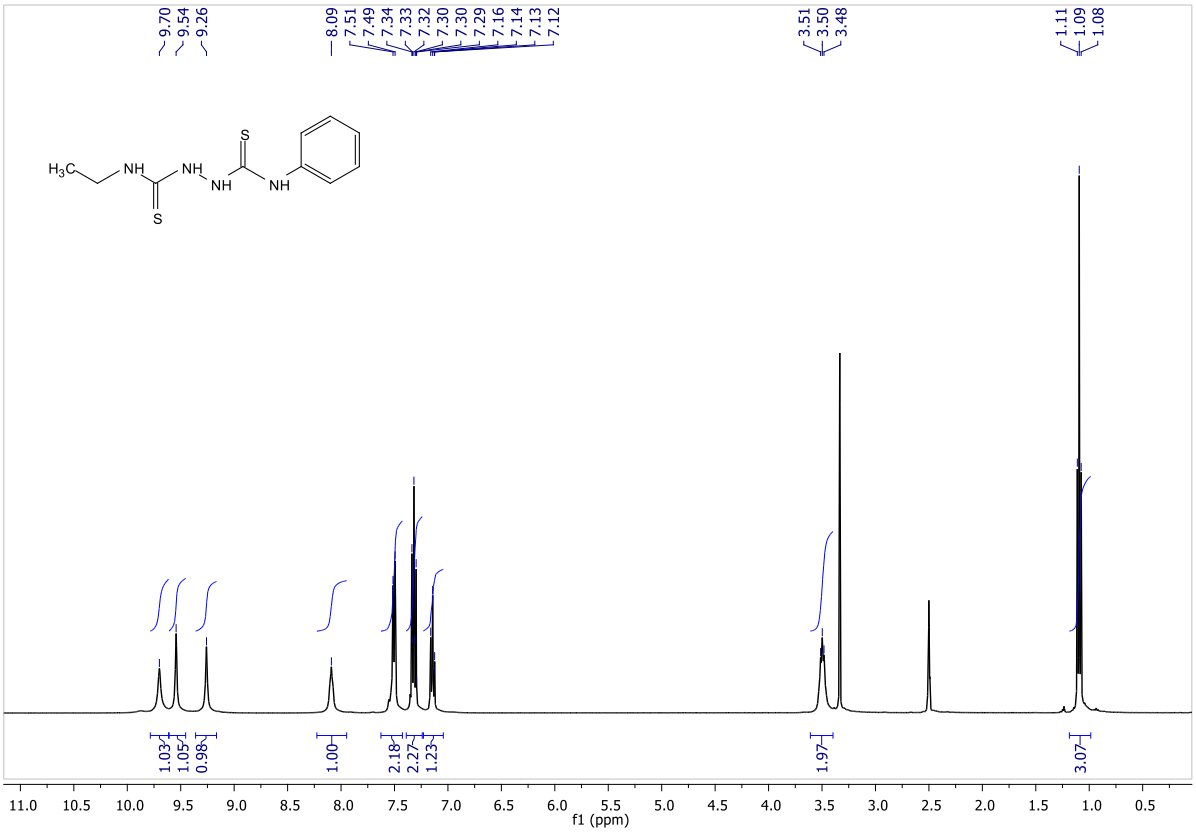

Fig. S2. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3a** (N^1-ethyl-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

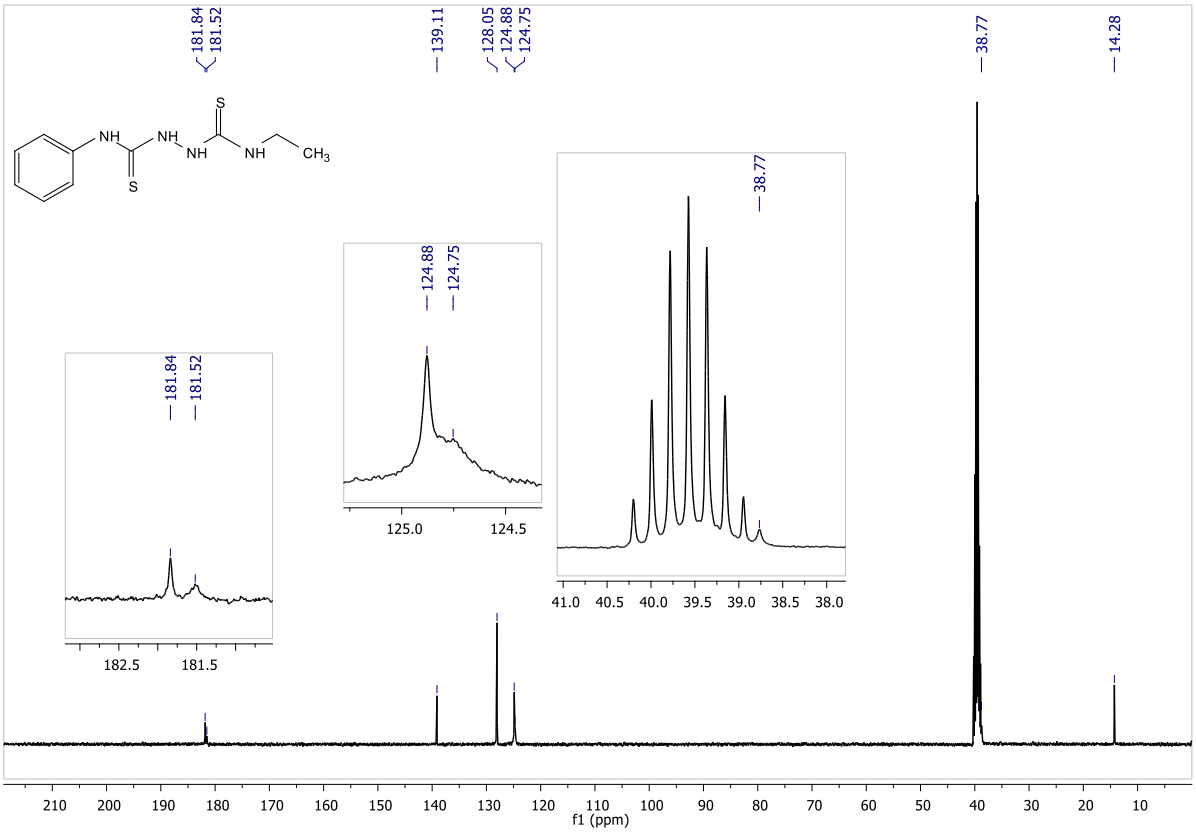

Fig. S3. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3a** (N^1-ethyl-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

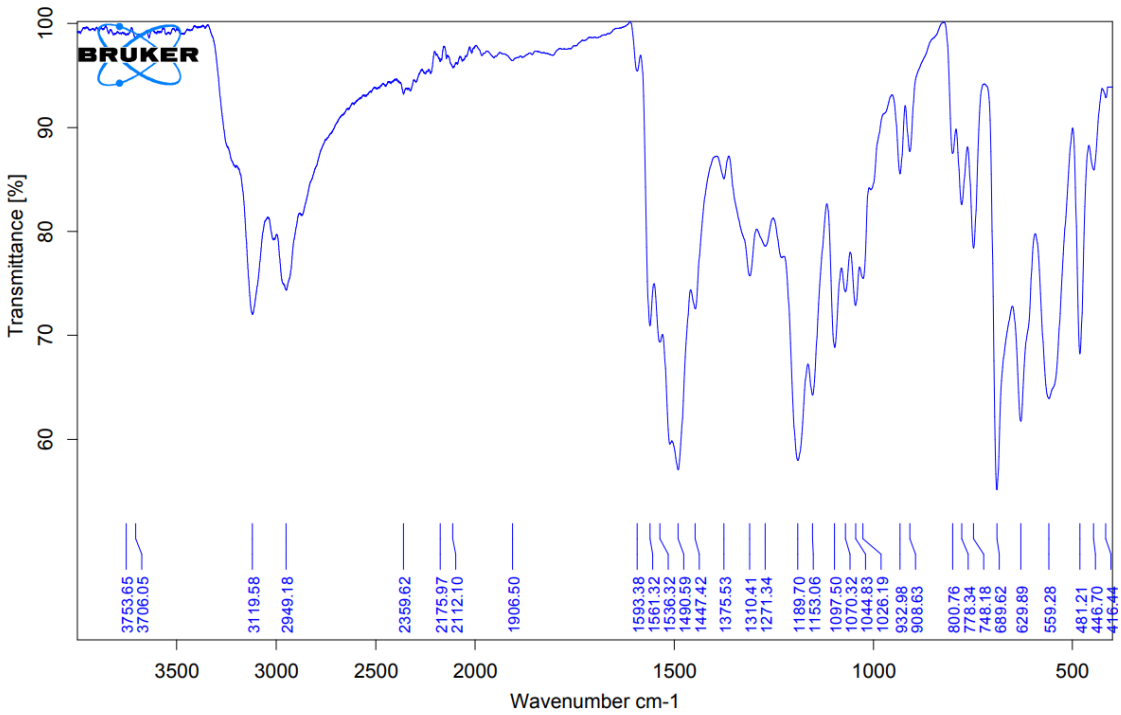

Fig. S4. FT-IR spectra of compound **3a** (N^1-ethyl-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

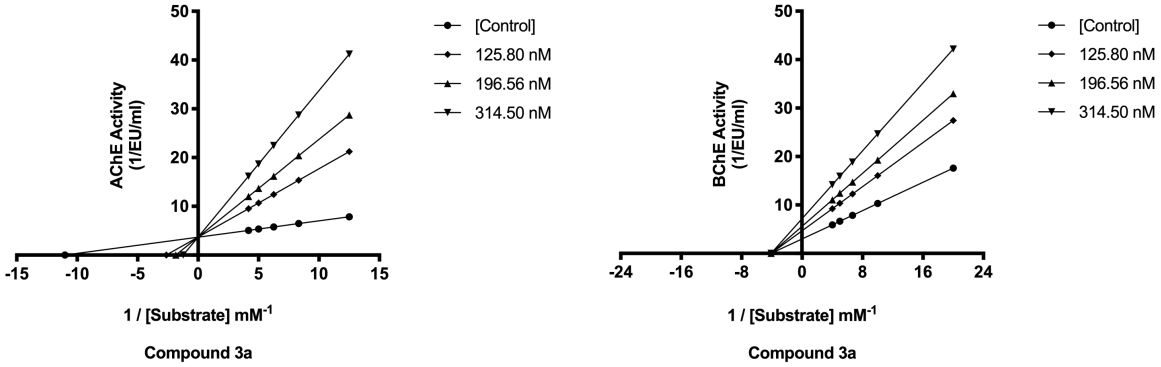

Fig. S5. Lineweaver-Burk plots of compound **3a** (N^1-ethyl-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

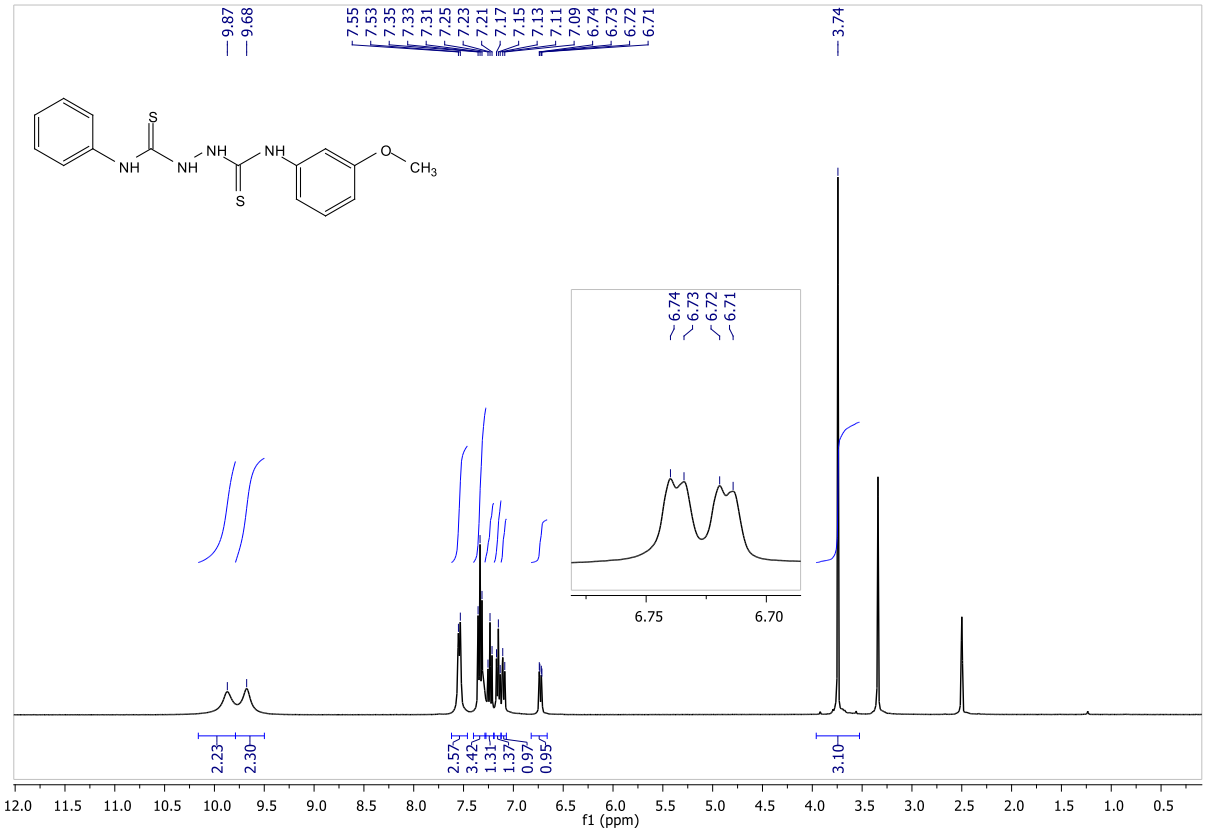

Fig. S6. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3b** (N^1-(3-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

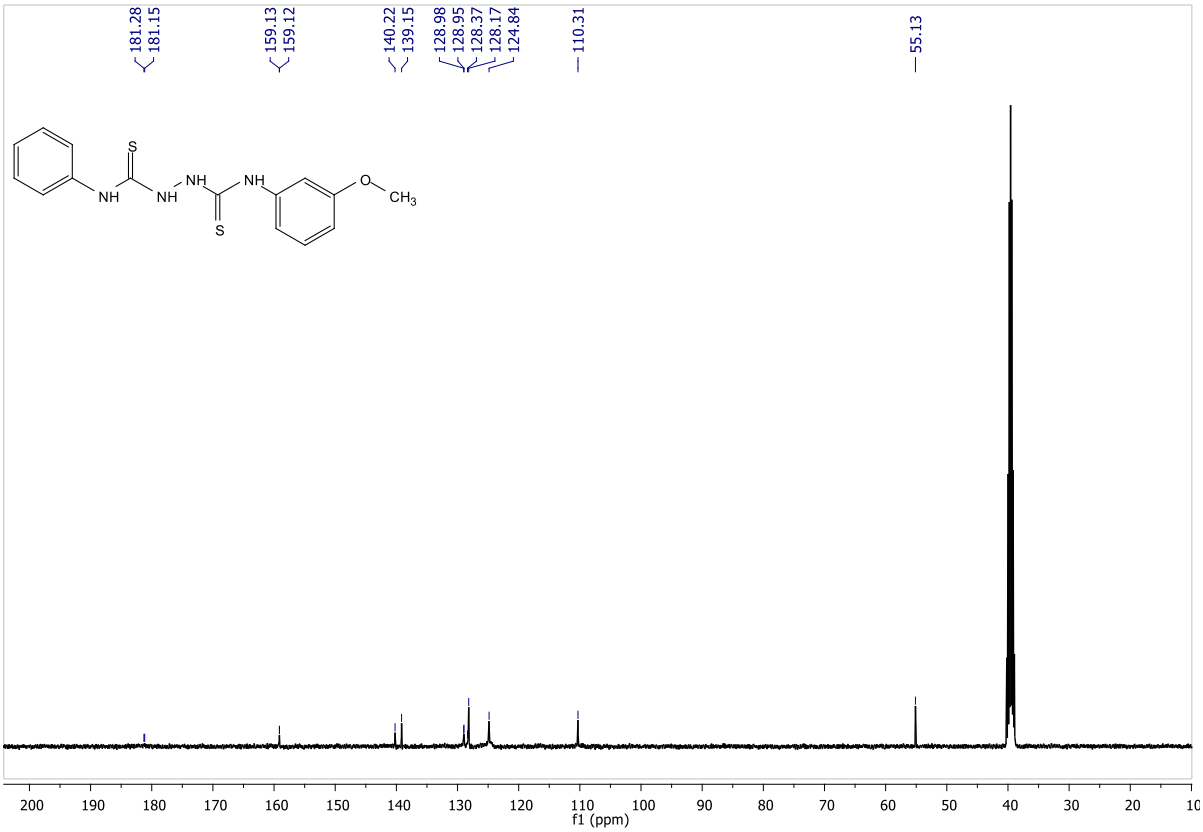

Fig. S7. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3b** (N^1-(3-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

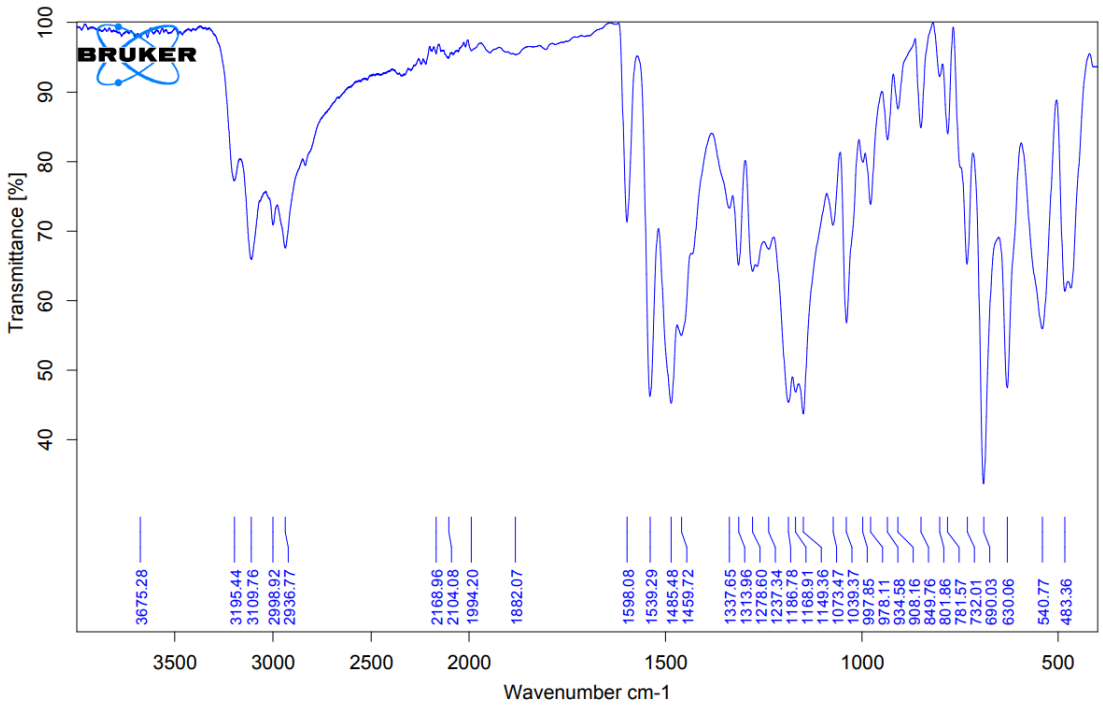

Fig. S8. FT-IR spectra of compound **3b** (N^1-(3-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

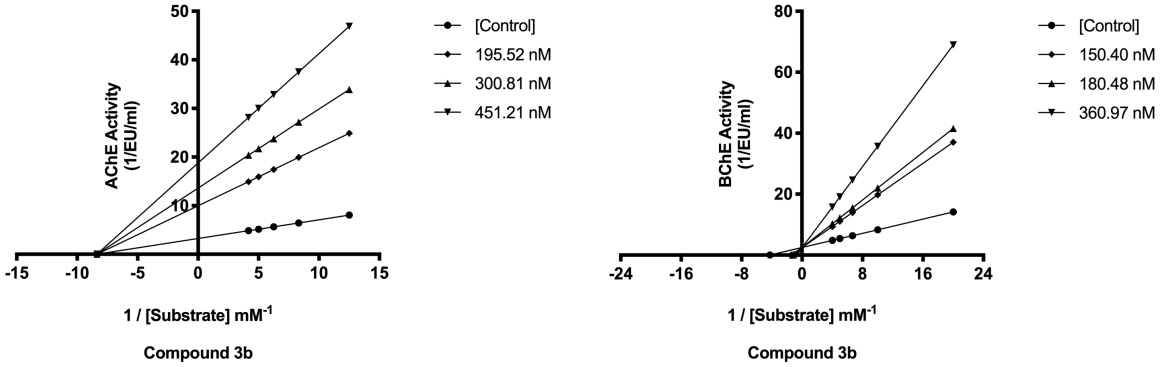

Fig. S9. Lineweaver-Burk plots of compound **3b** (N^1-(3-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

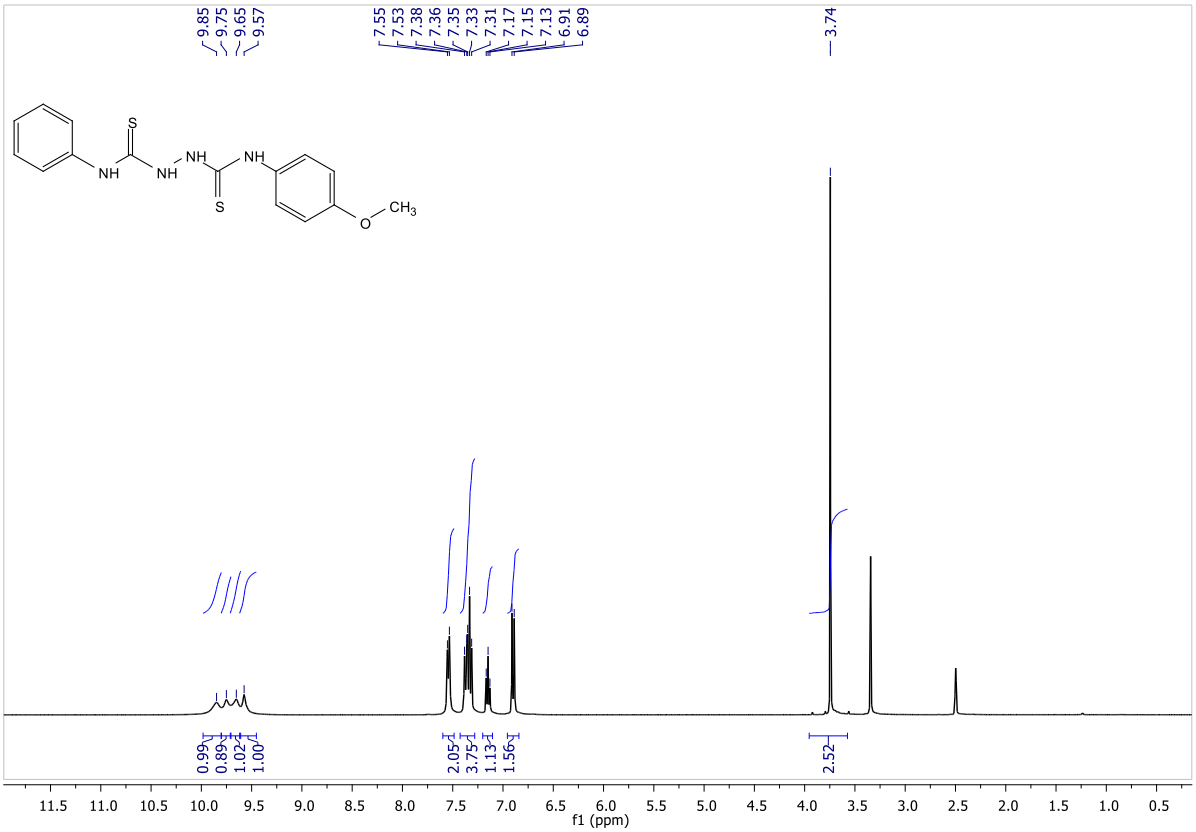

Fig. S10. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3c** (N^1-(4-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

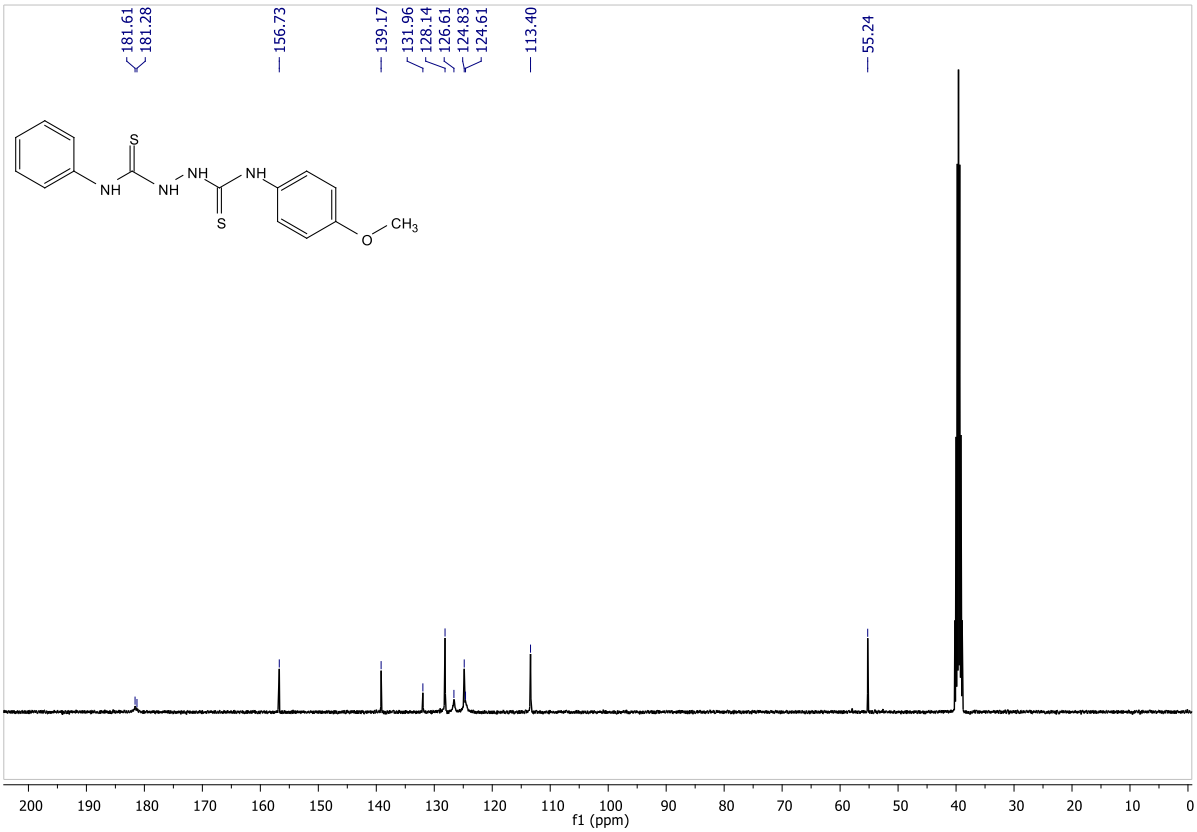

Fig. S11. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3c** (N^1-(4-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

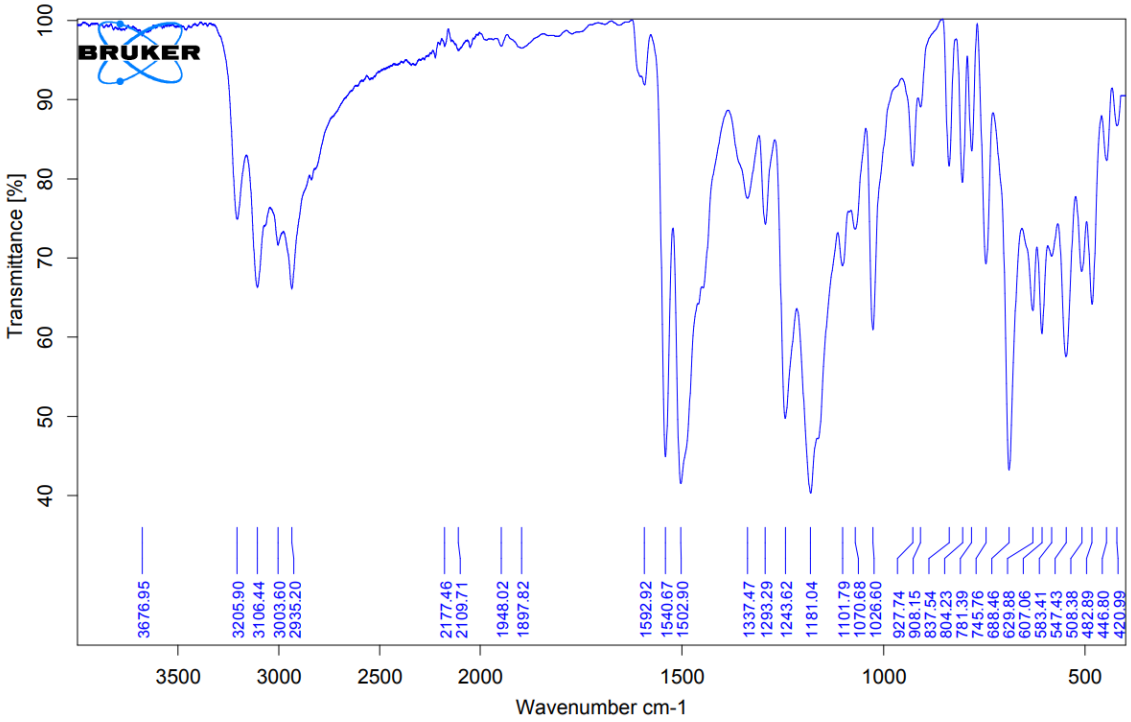

Fig. S12. FT-IR spectra of compound **3c** (N^1-(4-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

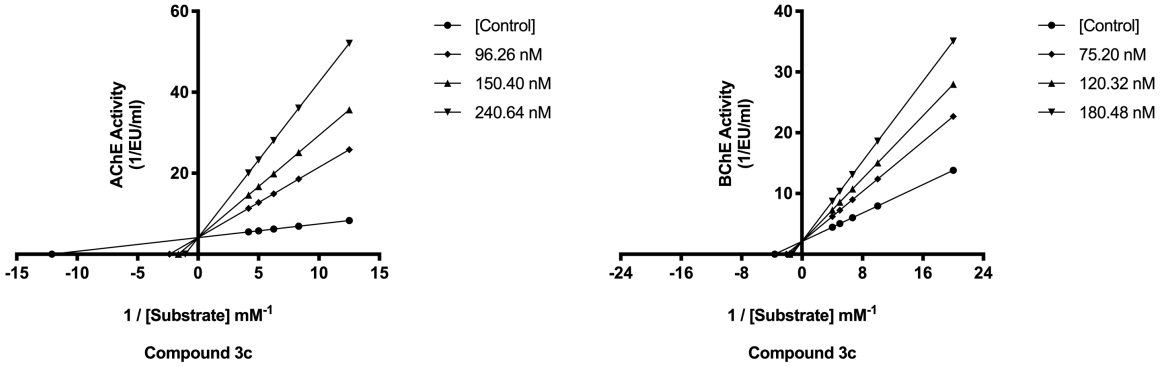

Fig. S13. Lineweaver-Burk plots of compound **3c** (N^1-(4-methoxyphenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

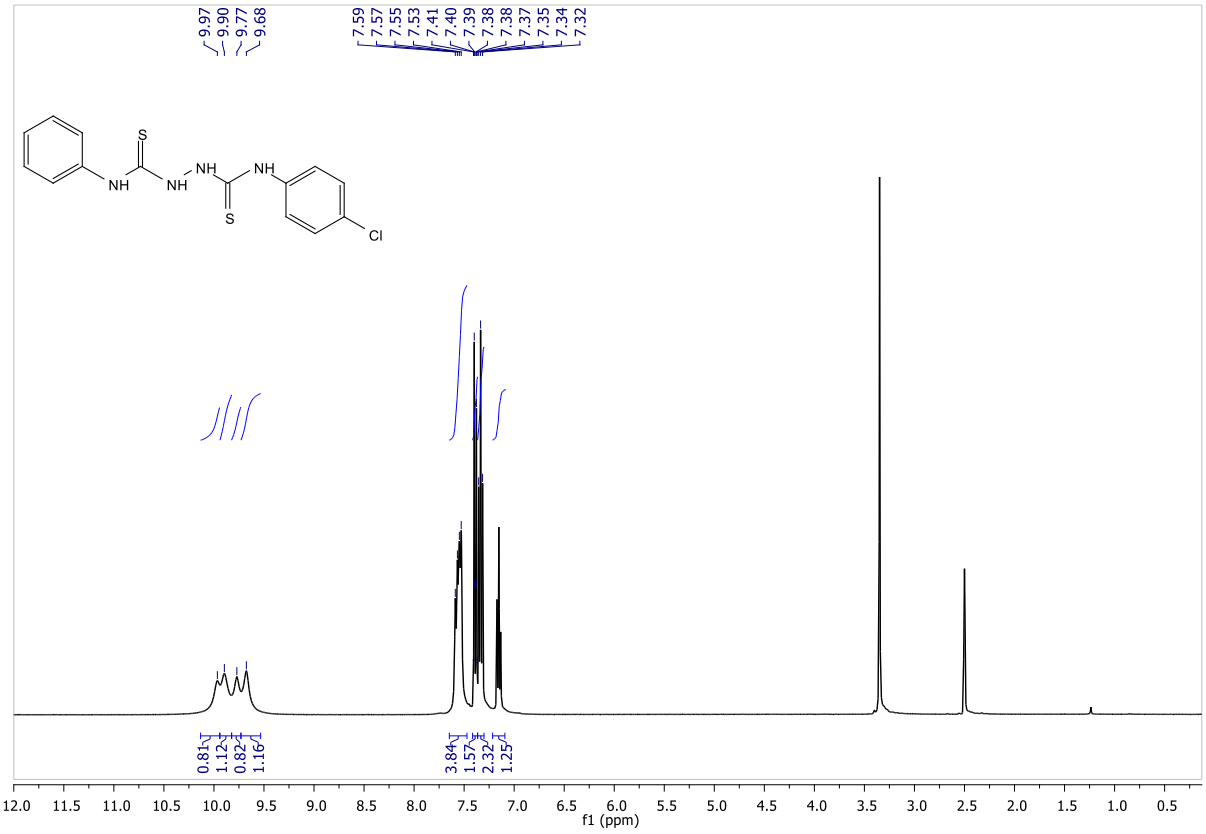

Fig. S14. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3d** (N^1-(4-chlorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

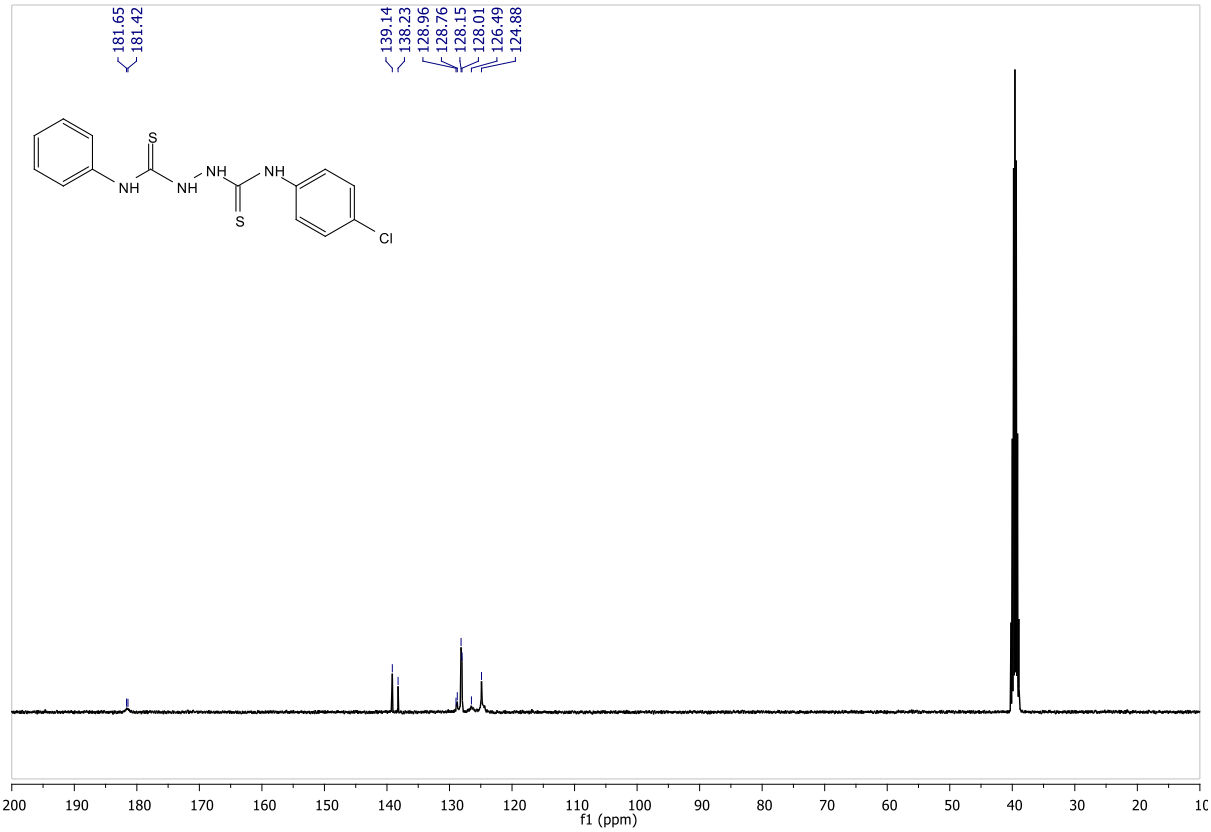

Fig. S15. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3d** (N^1-(4-chlorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

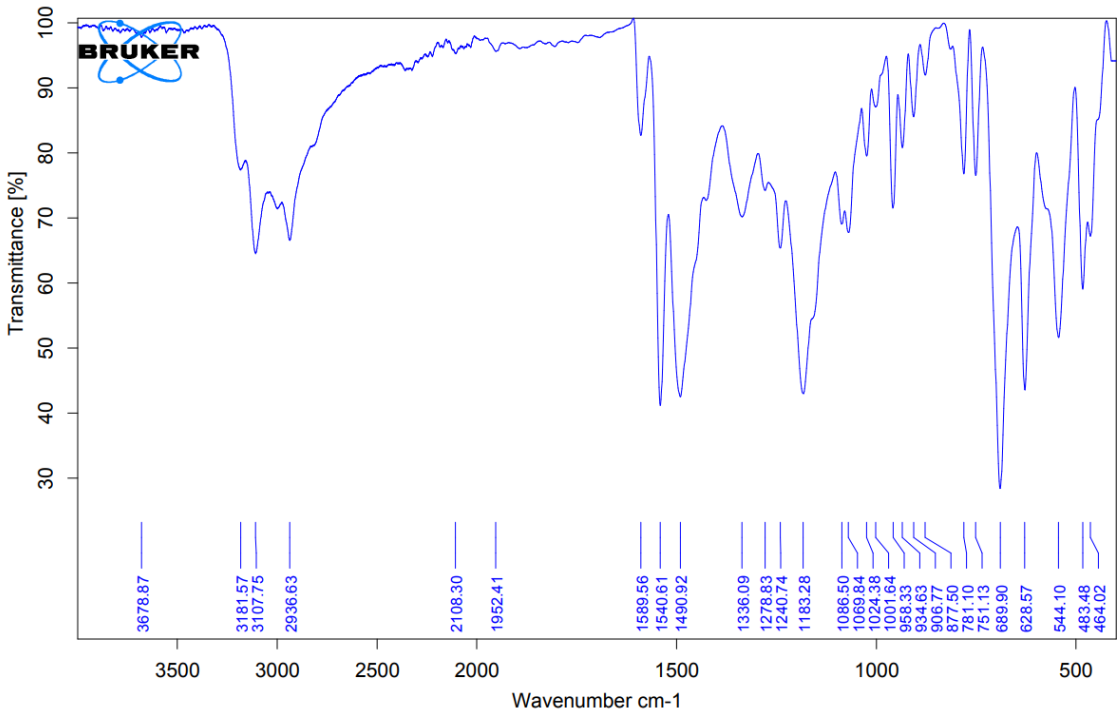

Fig. S16. FT-IR spectra of compound **3d** (N^1-(4-chlorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

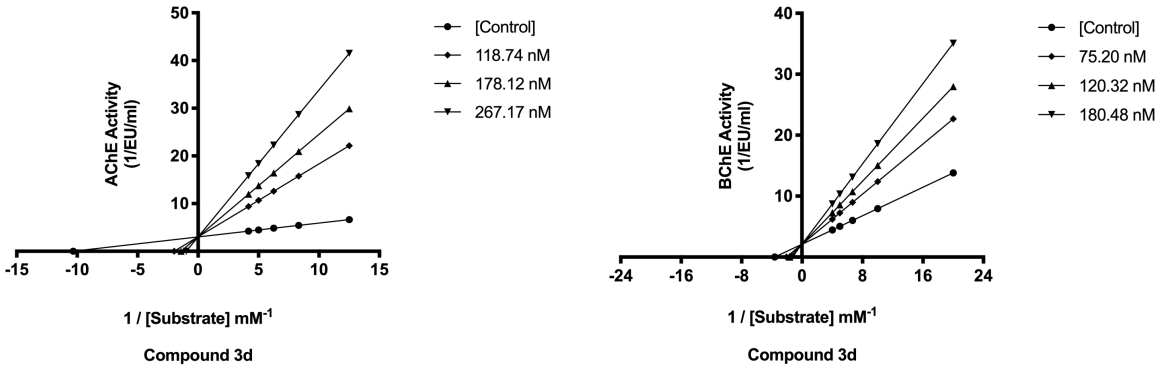

Fig. S17. Lineweaver-Burk plots of compound **3d** (N^1-(4-chlorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

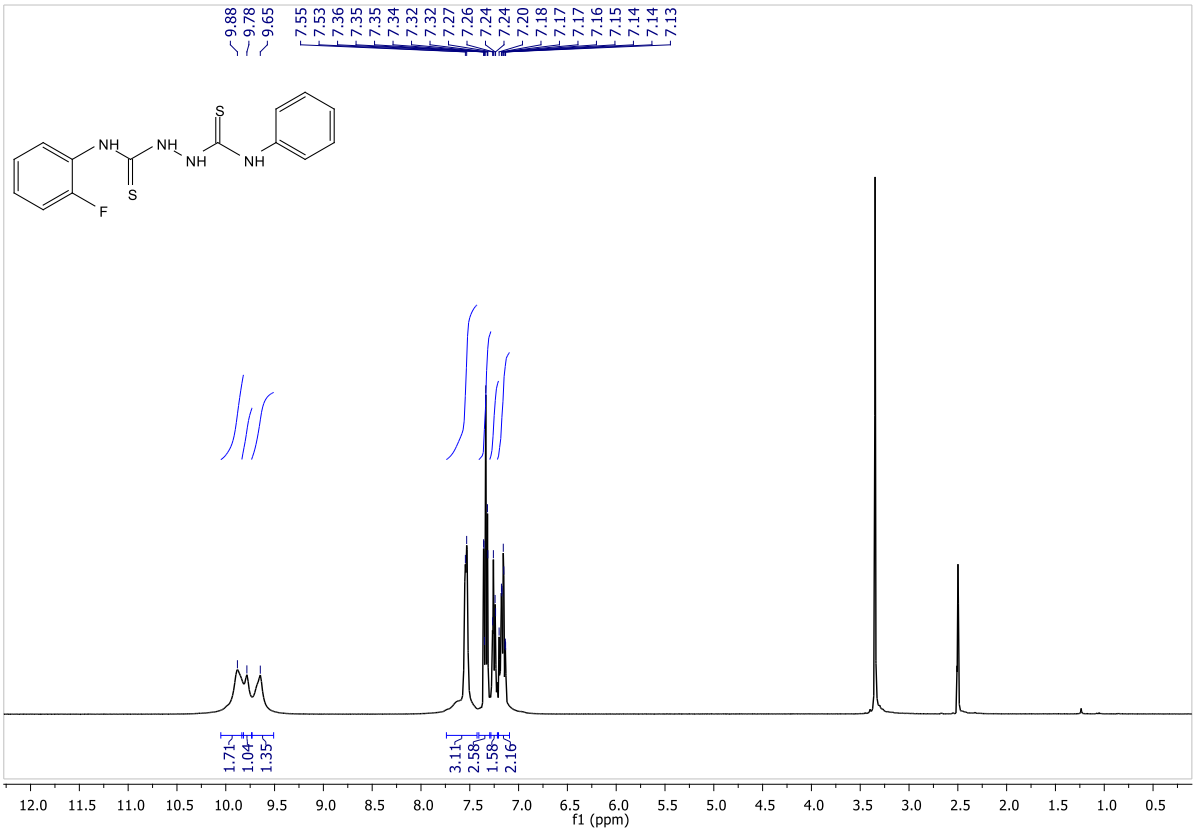

Fig. S18. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3e** (N^1-(2-fluorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

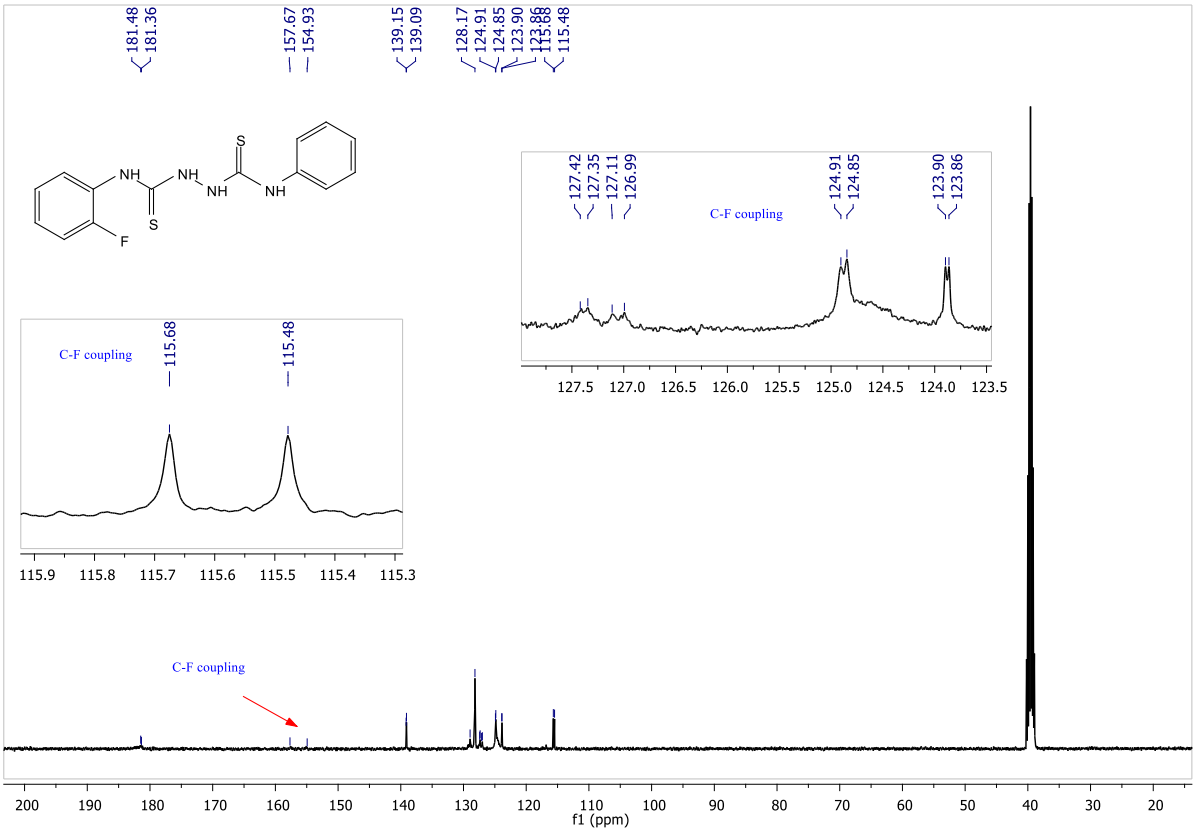

Fig. S19. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3e** (N^1-(2-fluorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

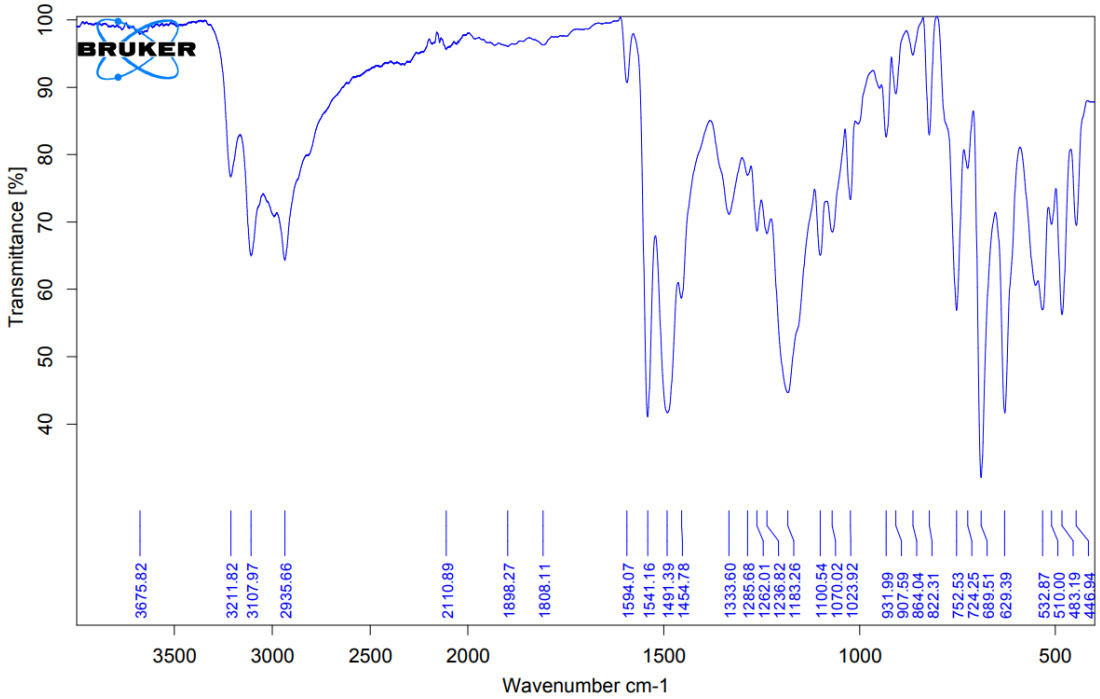

Fig. S20. FT-IR spectra of compound **3e** (N^1-(2-fluorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

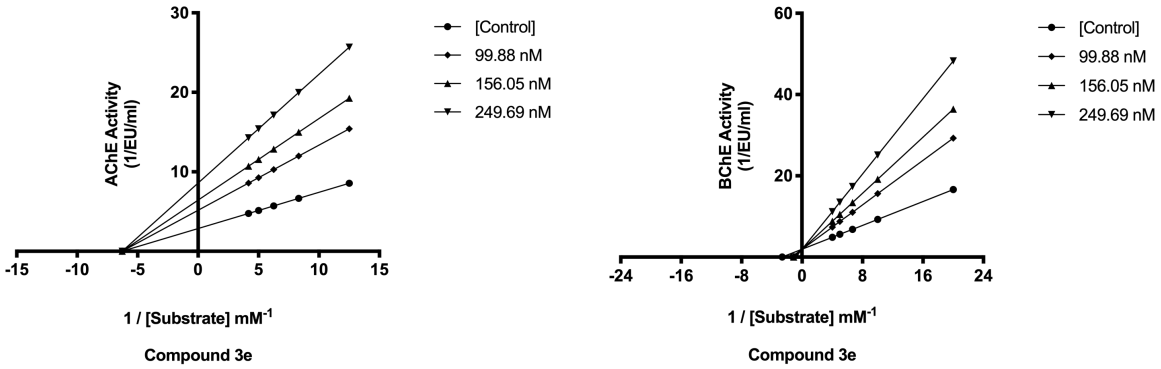

Fig. S21. Lineweaver-Burk plots of compound **3e** (N^1-(2-fluorophenyl)-N^2-phenylhydrazine-1,2-bis(carbothioamide)).

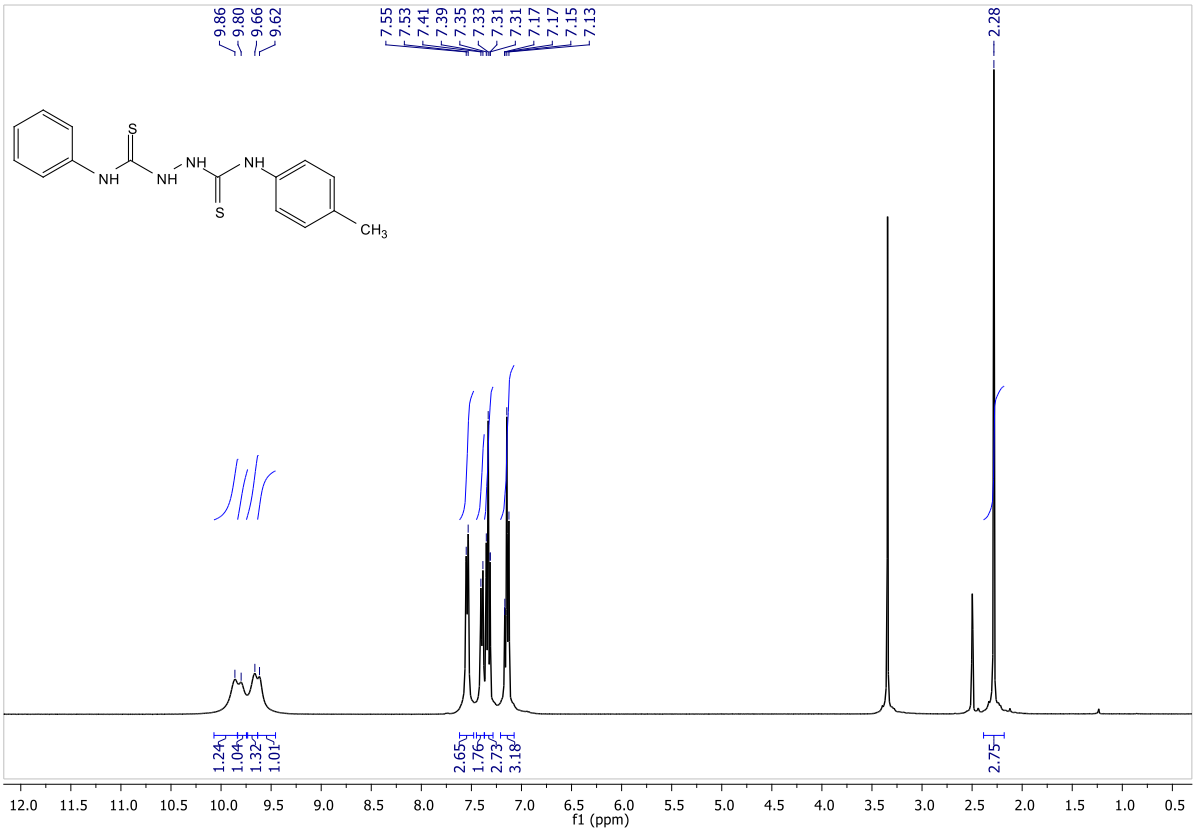

Fig. S22. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3f** (N^1-phenyl-N^2-(p-tolyl)hydrazine-1,2-bis(carbothioamide)).

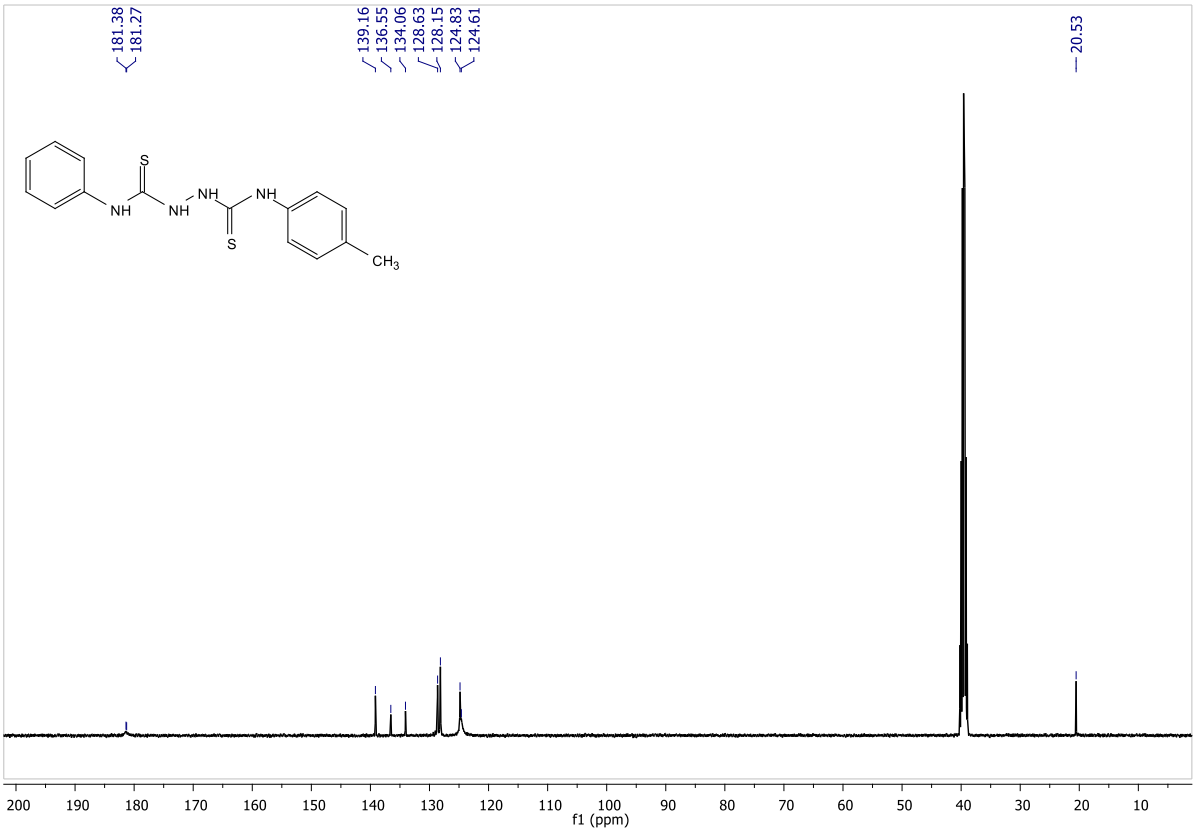

Fig. S23. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3f** (N^1-phenyl-N^2-(p-tolyl)hydrazine-1,2-bis(carbothioamide)).

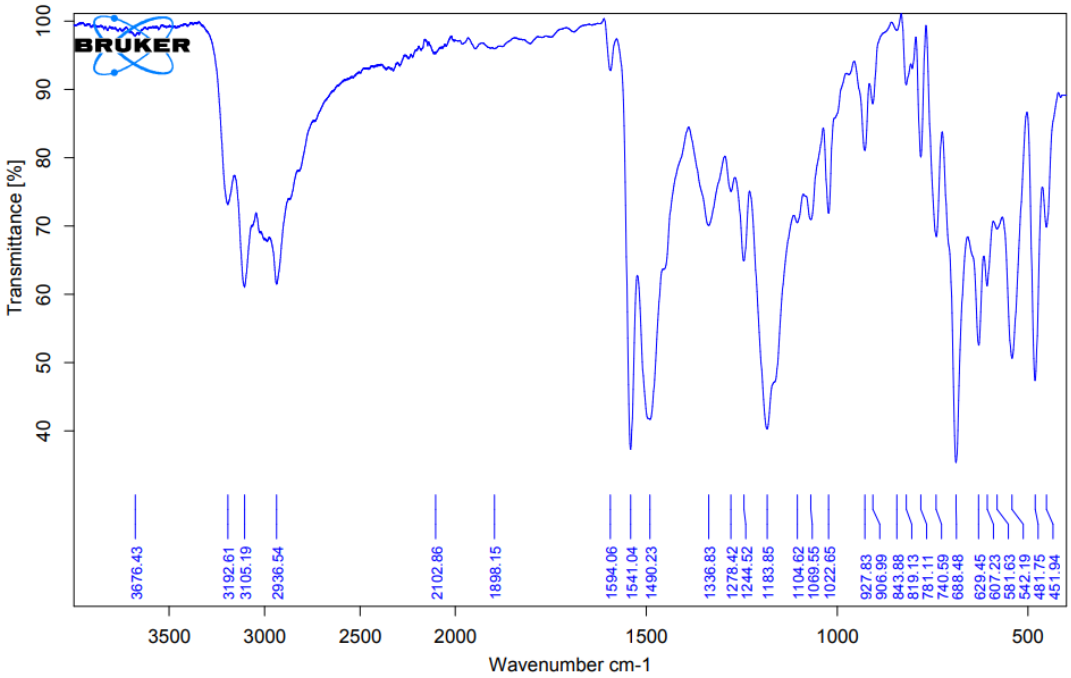

Fig. S24. FT-IR spectra of compound **3f** (N^1-phenyl-N^2-(p-tolyl)hydrazine-1,2-bis(carbothioamide)).

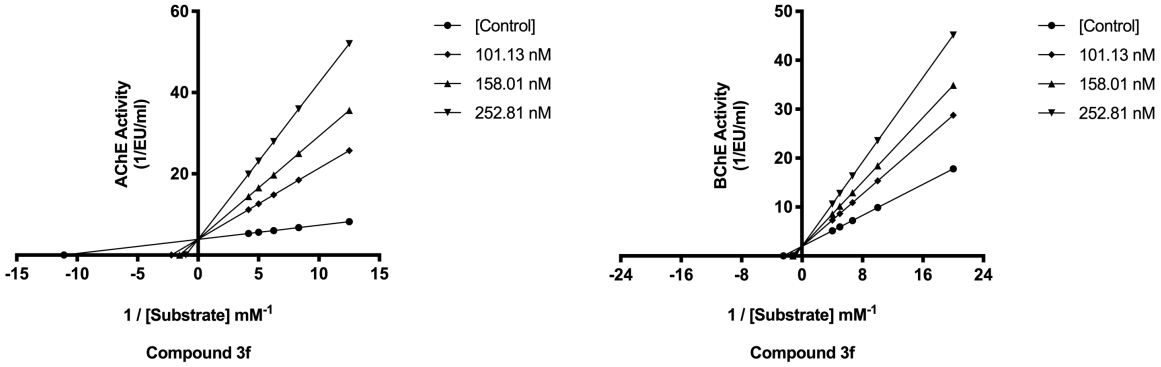

Fig. S25. Lineweaver-Burk plots of compound **3f** (N^1-phenyl-N^2-(p-tolyl)hydrazine-1,2-bis(carbothioamide)).

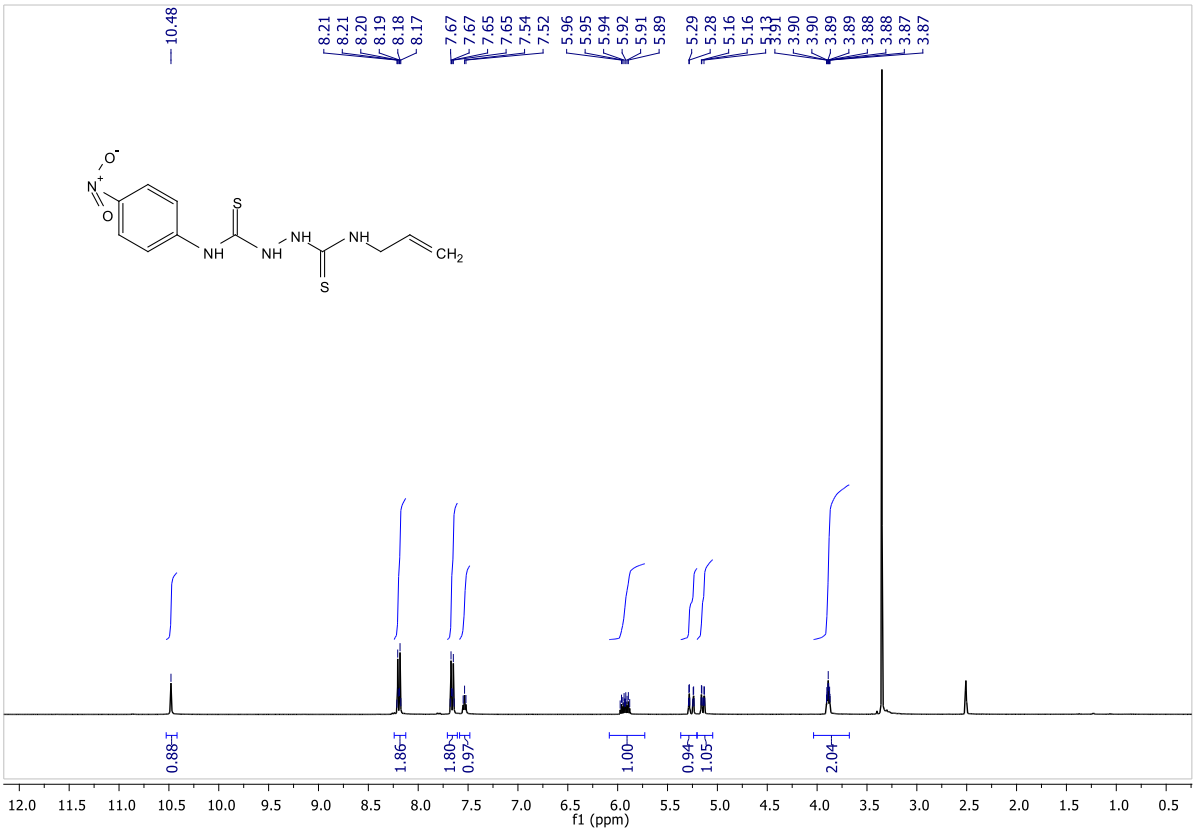

Fig. S26. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3g** (N^1-allyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

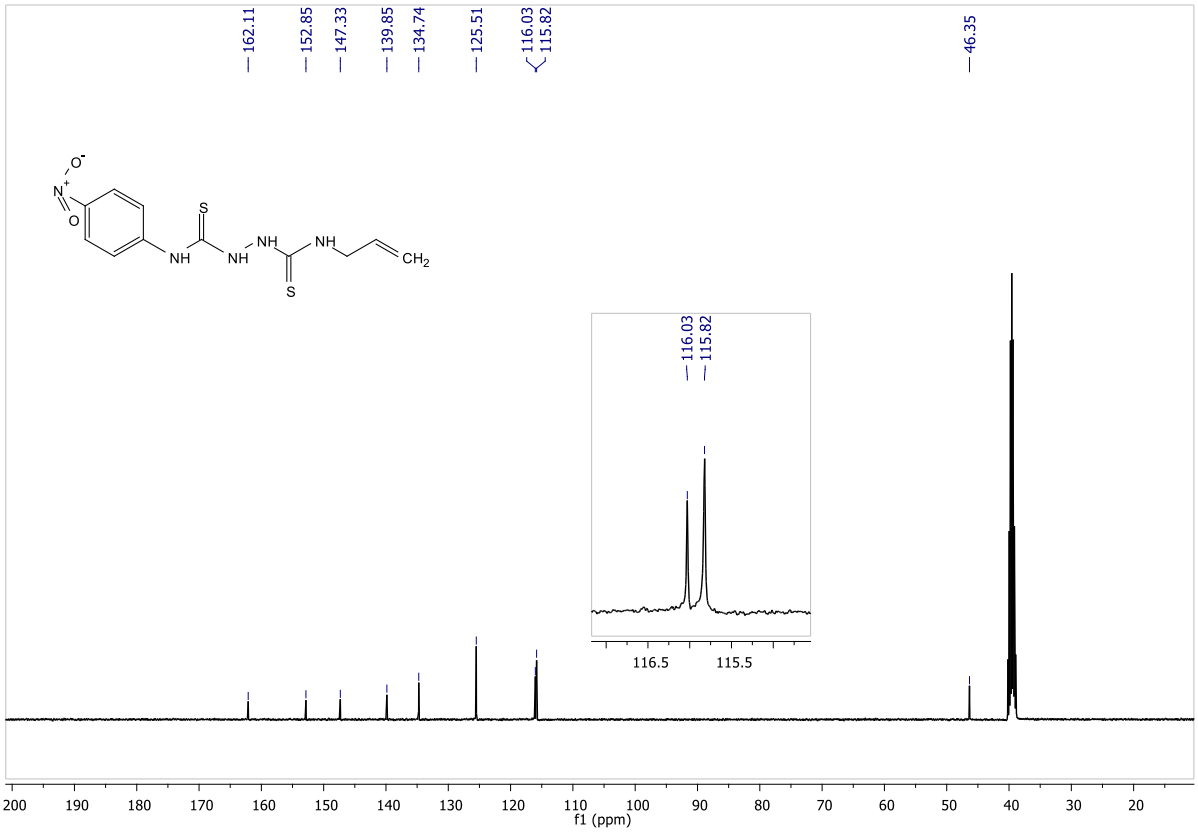

Fig. S27. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3g** (N^1-allyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

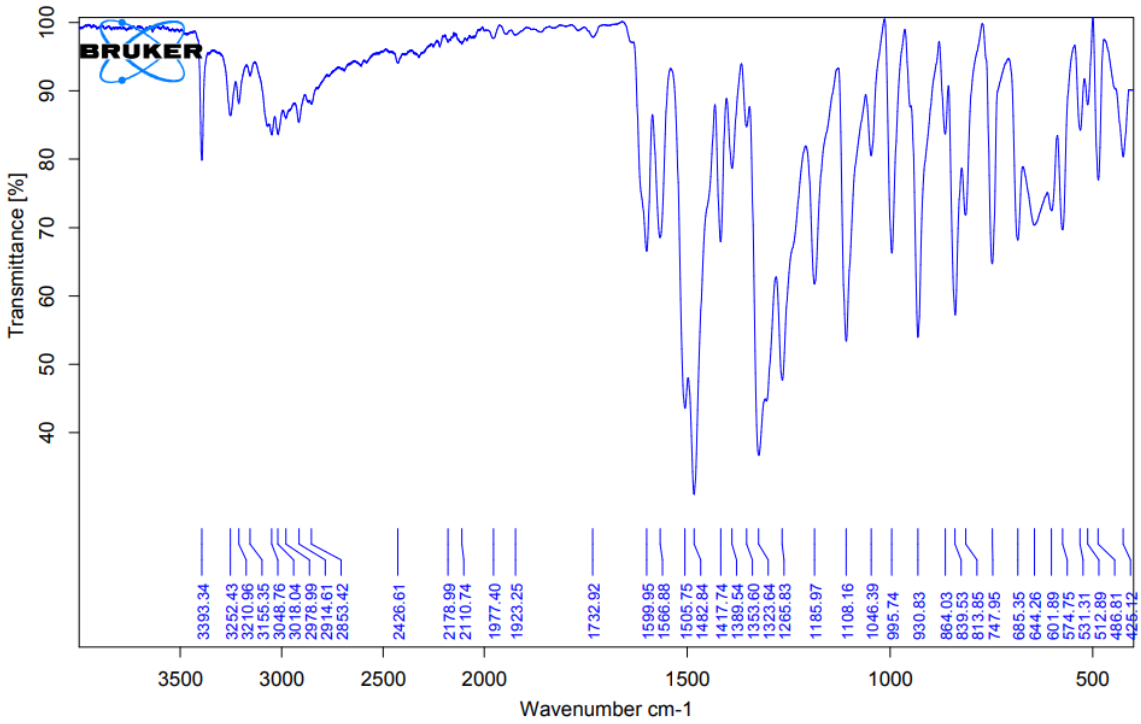

Fig. S28. FT-IR spectra of compound **3g** (N^1-allyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

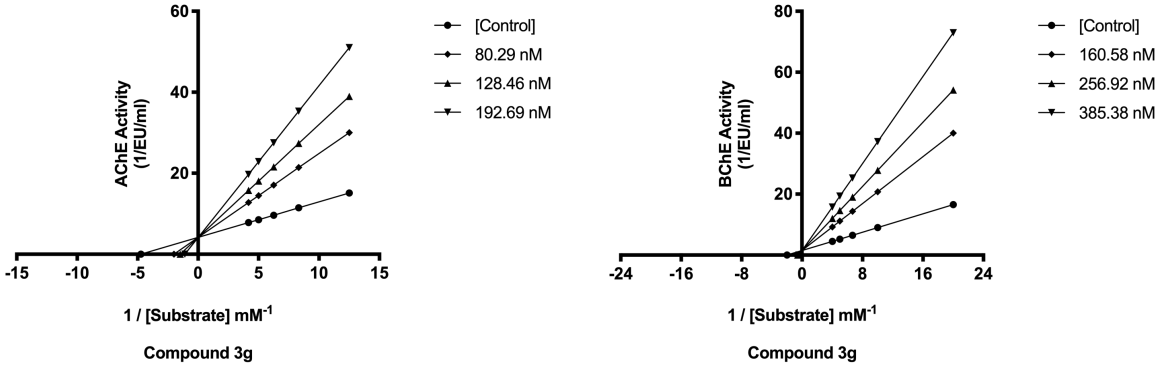

Fig. S29. Lineweaver-Burk plots of compound **3g** (N^1-allyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

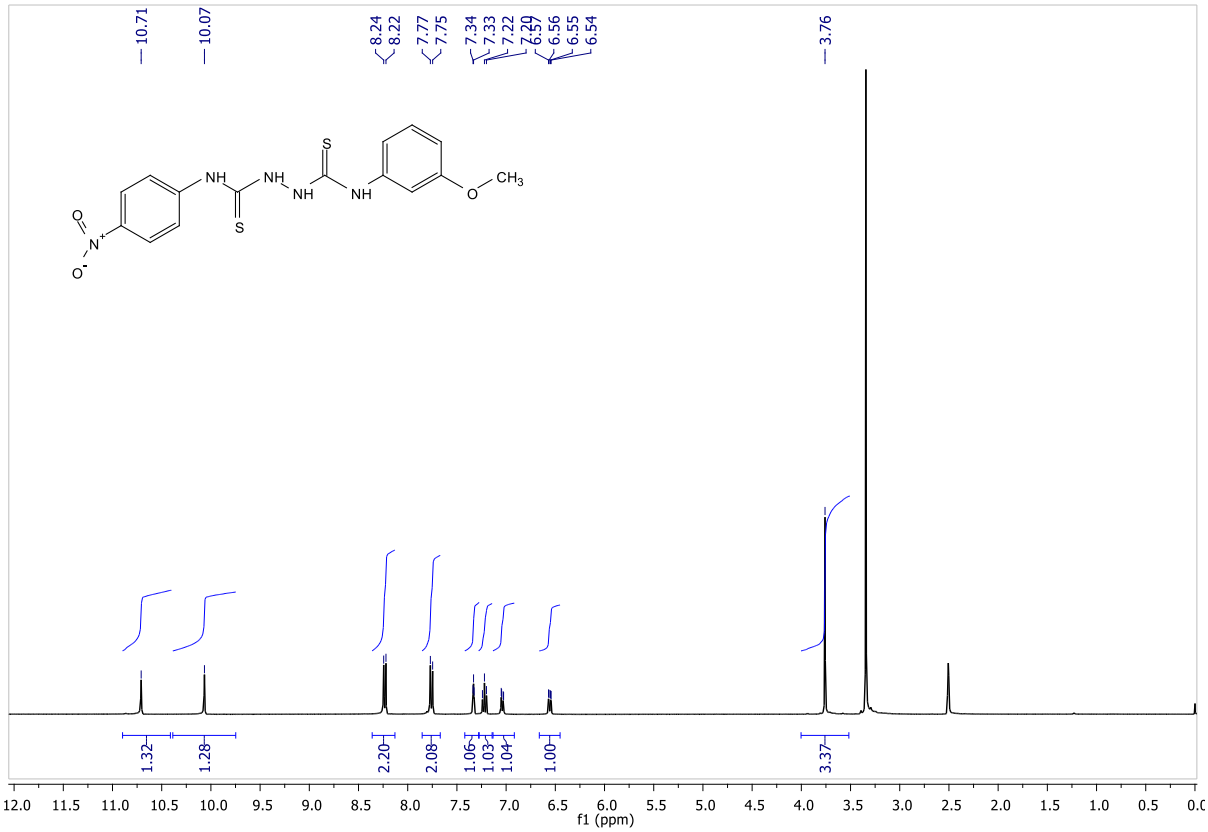

Fig. S30. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3h** (N^1-(3-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

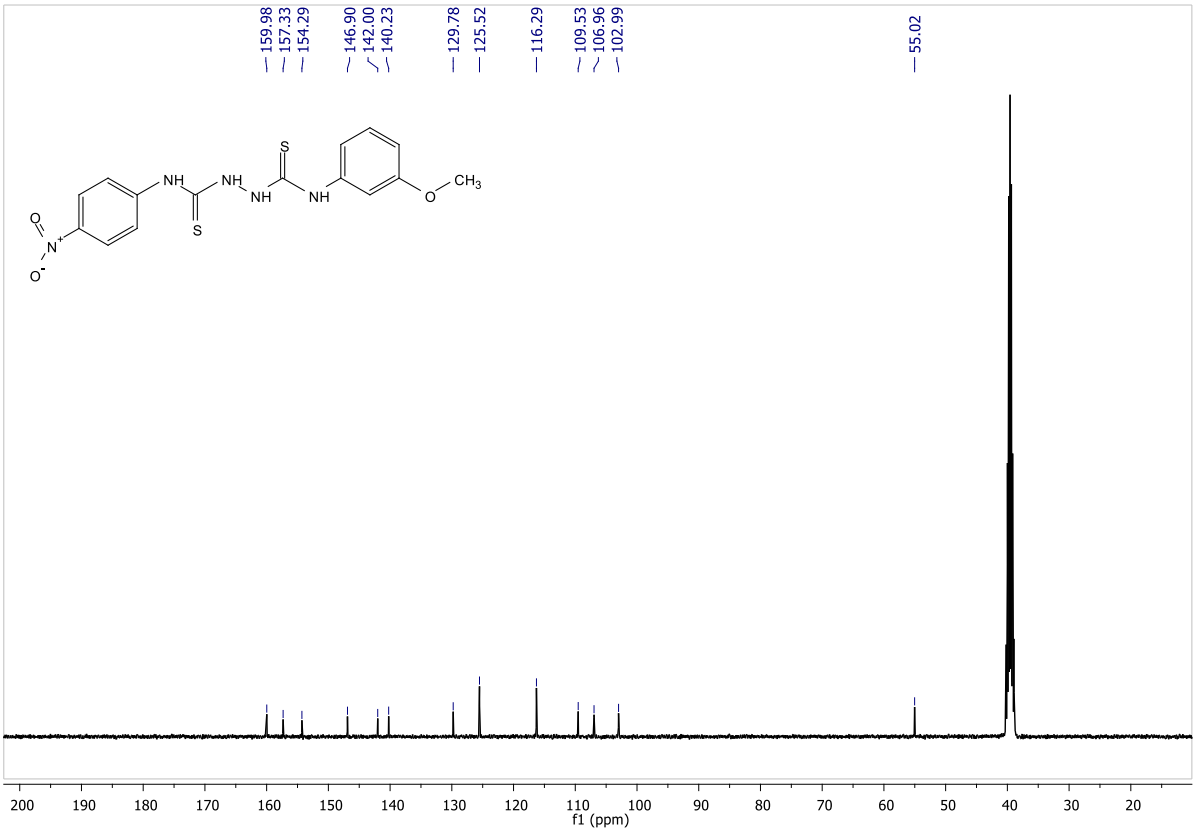

Fig. S31. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3h** (N^1-(3-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

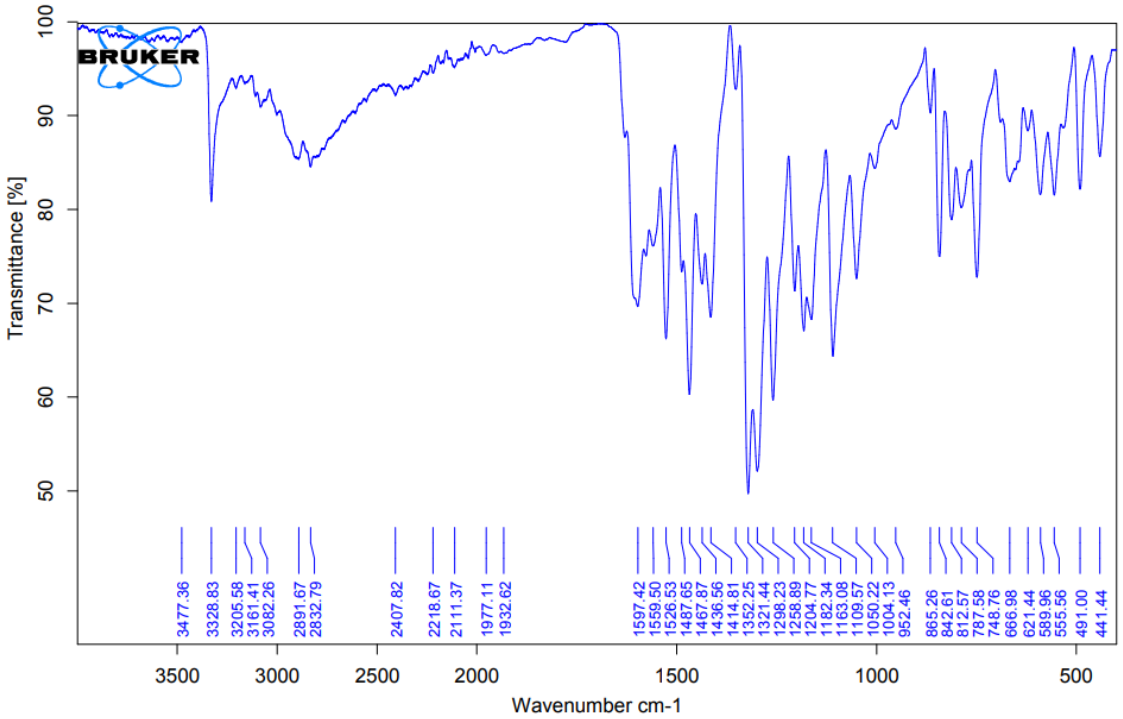

Fig. S32. FT-IR spectra of compound **3h** (N^1-(3-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

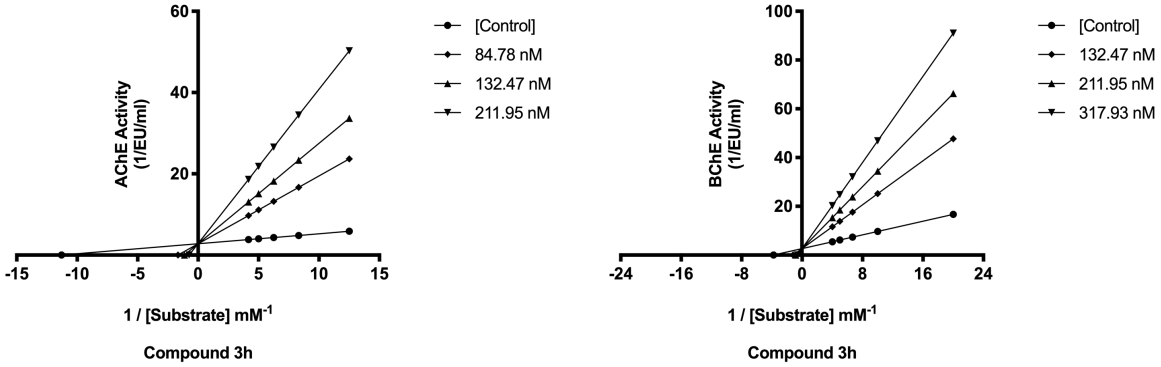

Fig. S33. Lineweaver-Burk plots of compound **3h** (N^1-(3-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

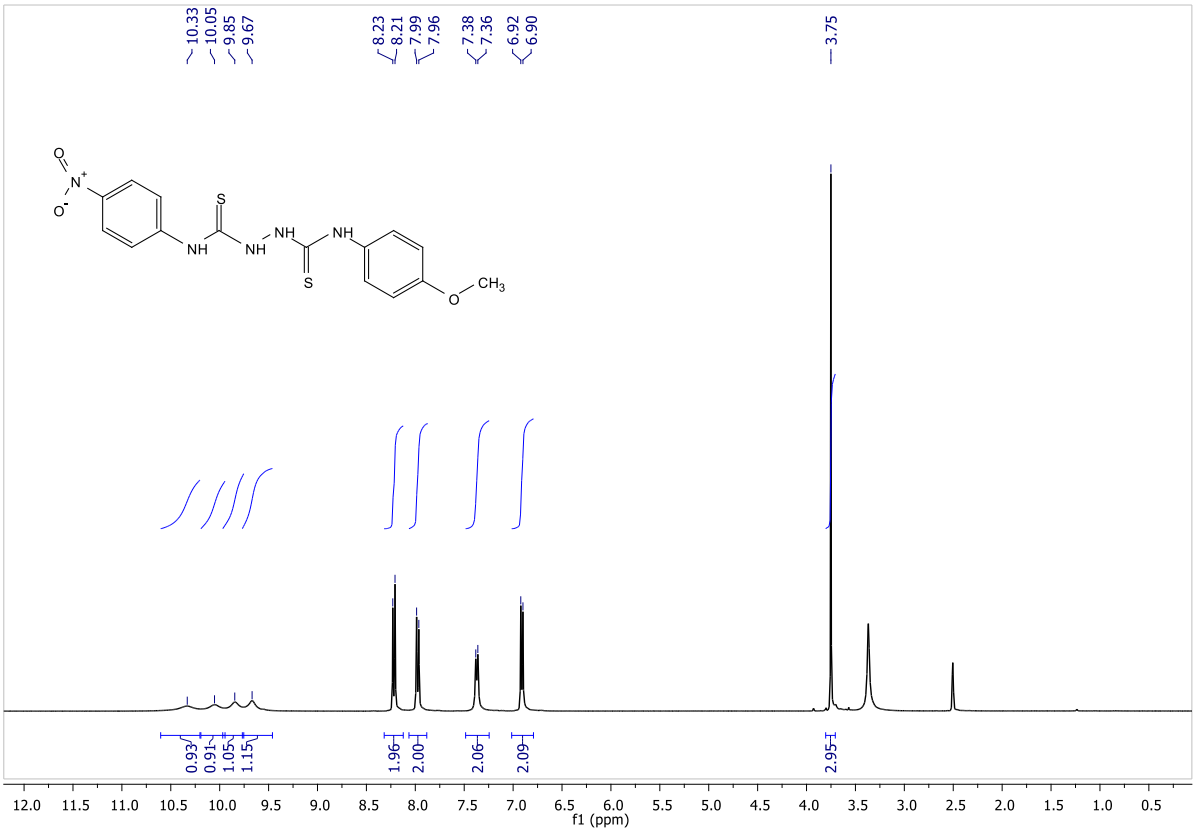

Fig. S34. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3i** (N^1-(4-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

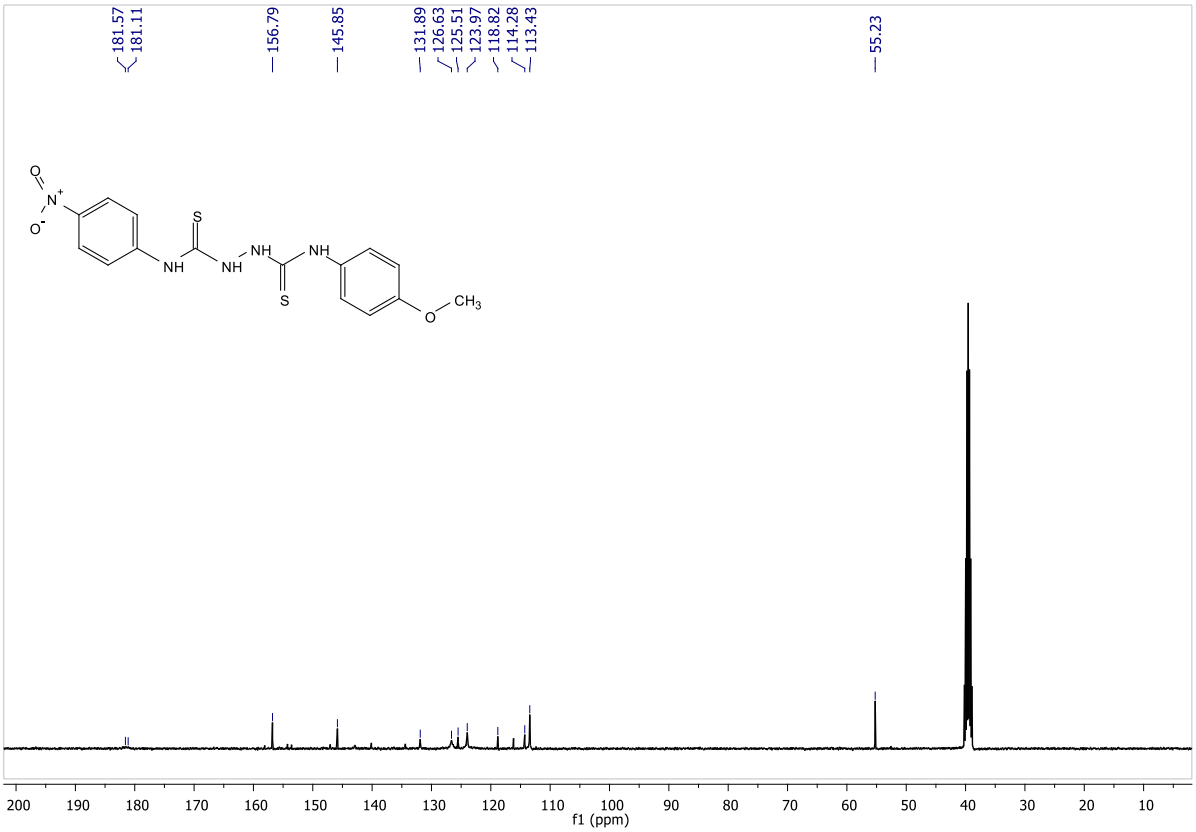

Fig. S35. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3i** (N^1-(4-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

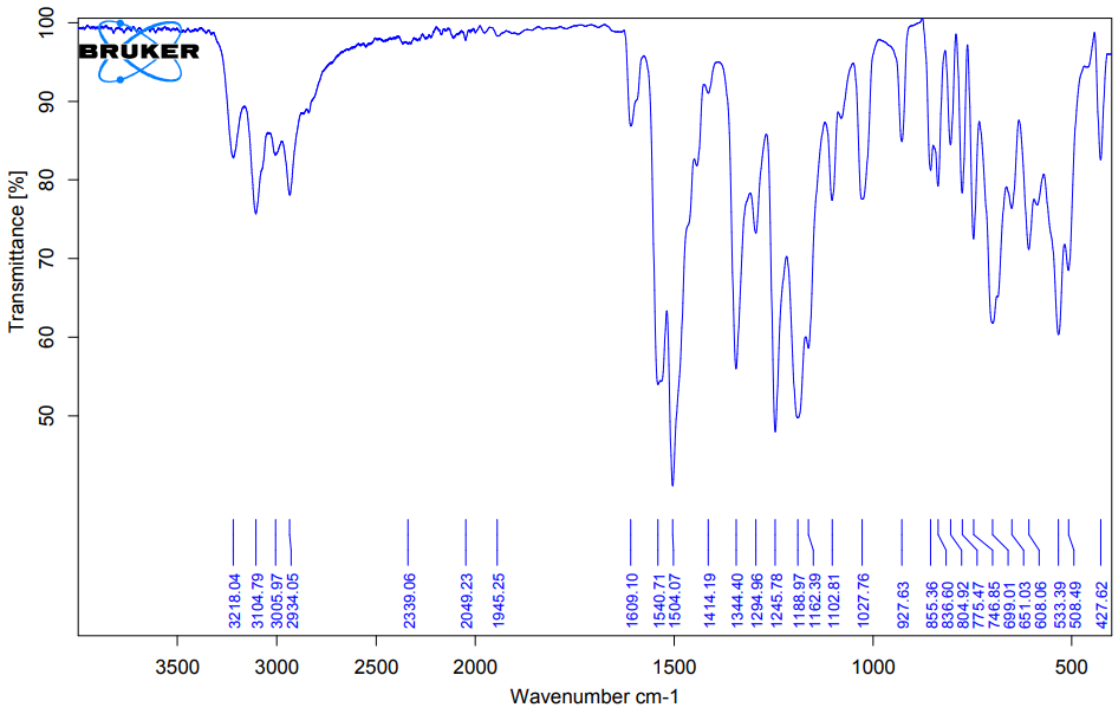

Fig. S36. FT-IR spectra of compound **3i** (N^1-(4-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

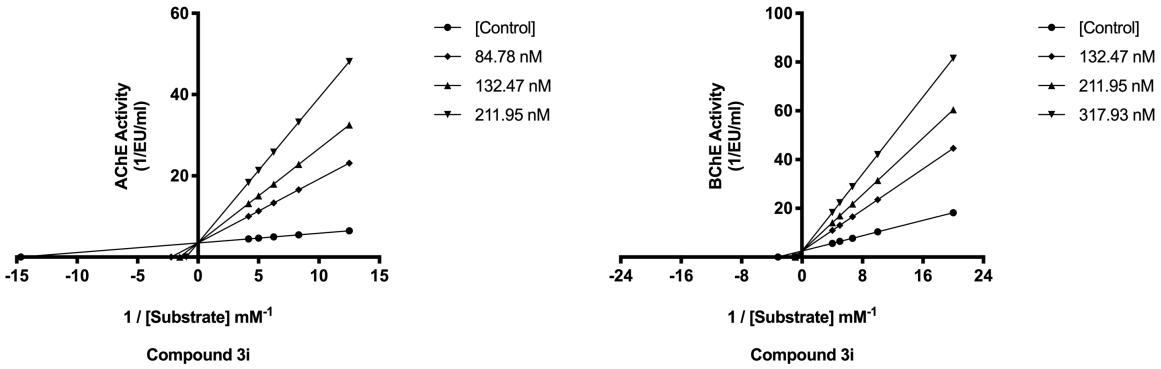

Fig. S37. Lineweaver-Burk plots of compound **3i** (N^1-(4-methoxyphenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

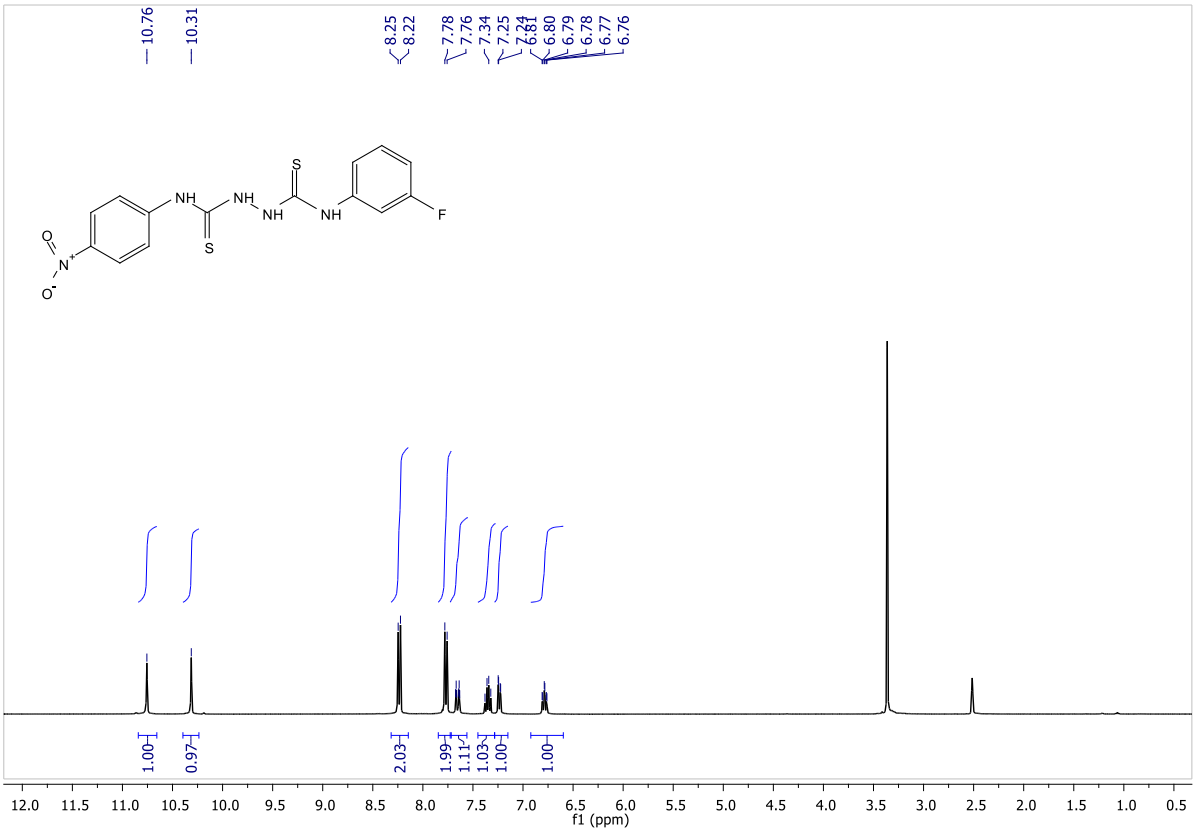

Fig. S38. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3j** (N^1-(3-fluorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

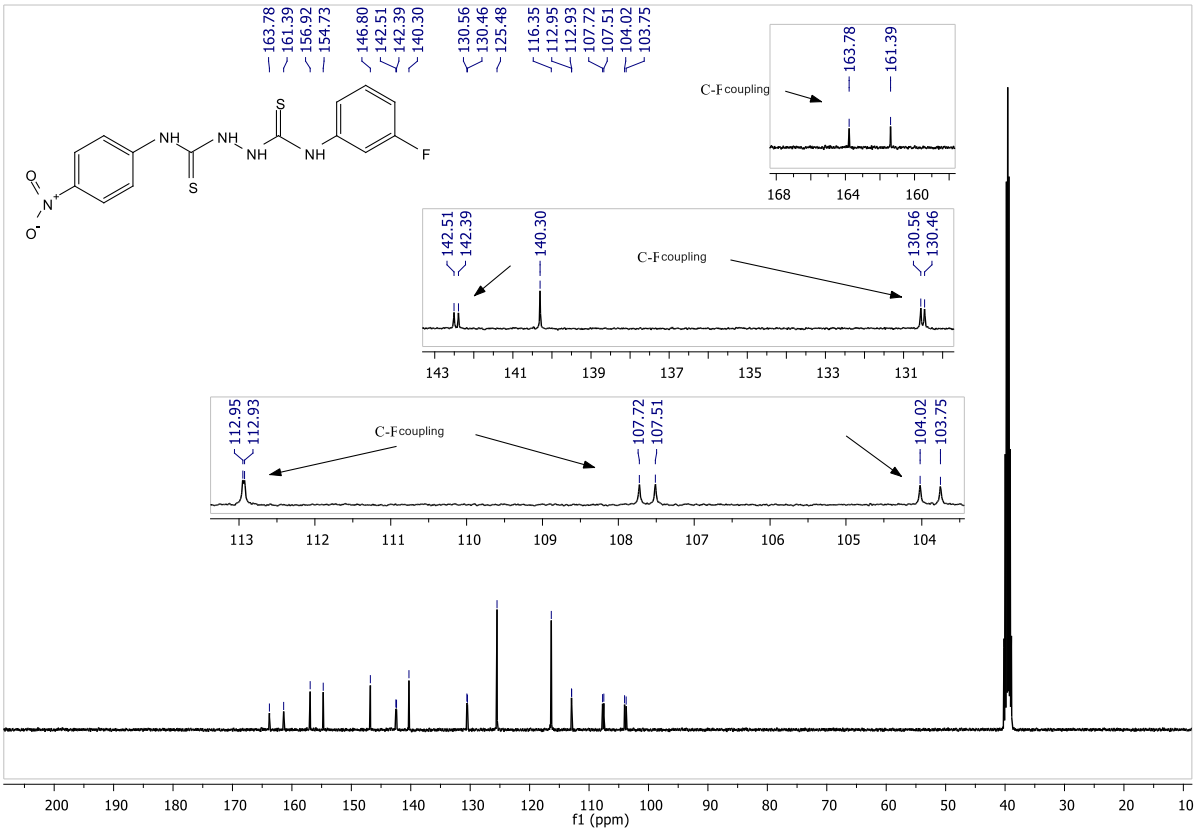

Fig. S39. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3j** (N^1-(3-fluorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

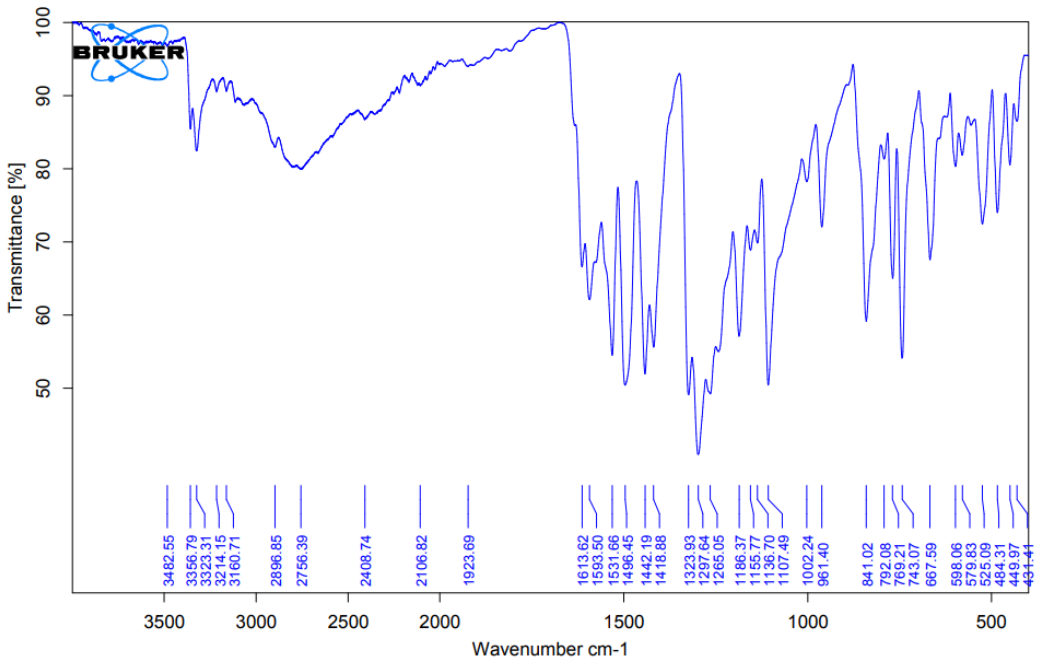

Fig. S40. FT-IR spectra of compound **3j** (N^1-(3-fluorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

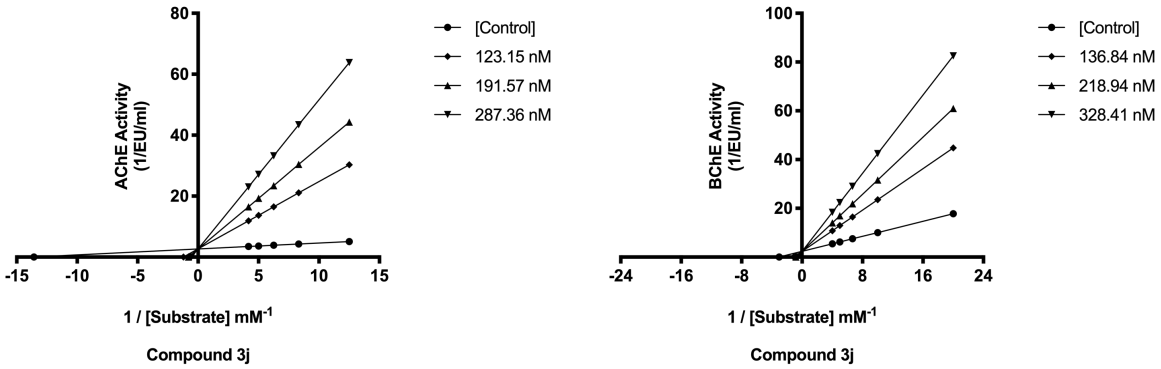

Fig. S41. Lineweaver-Burk plots of compound **3j** (N^1-(3-fluorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

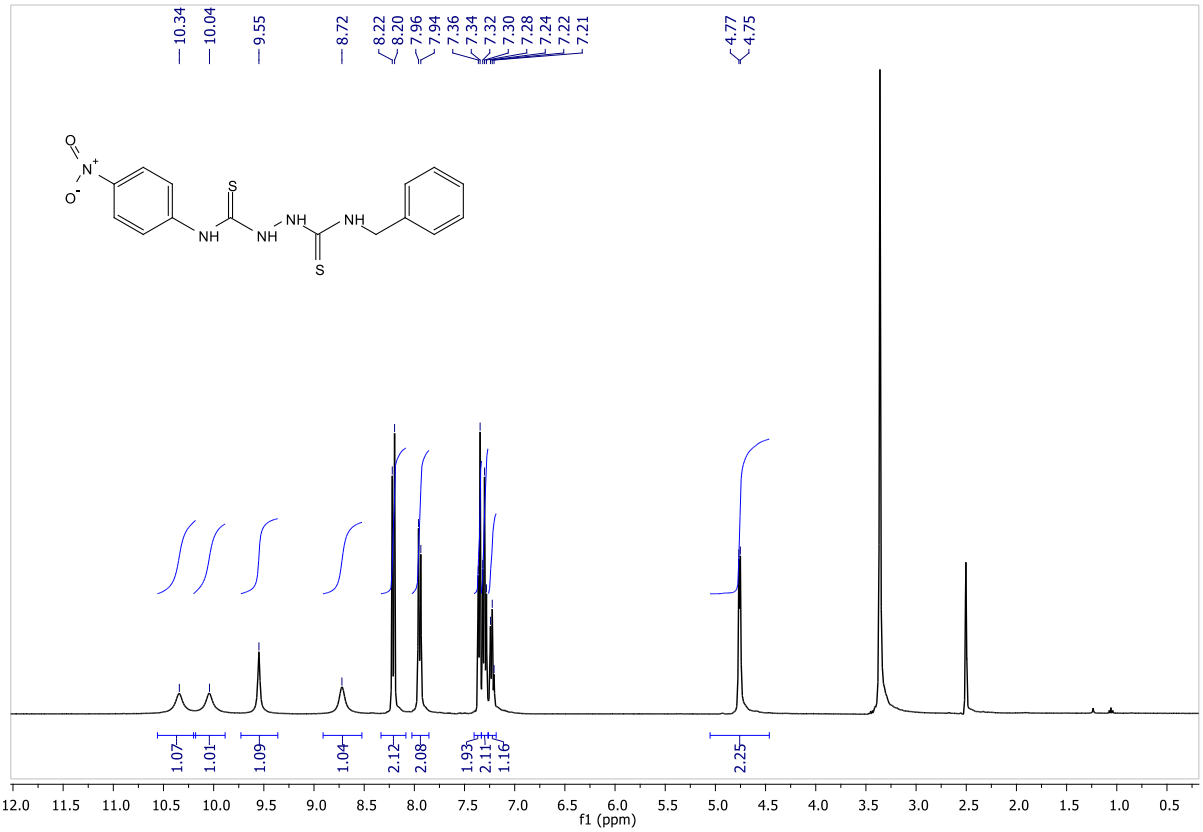

Fig. S42. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3k** (N^1-benzyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

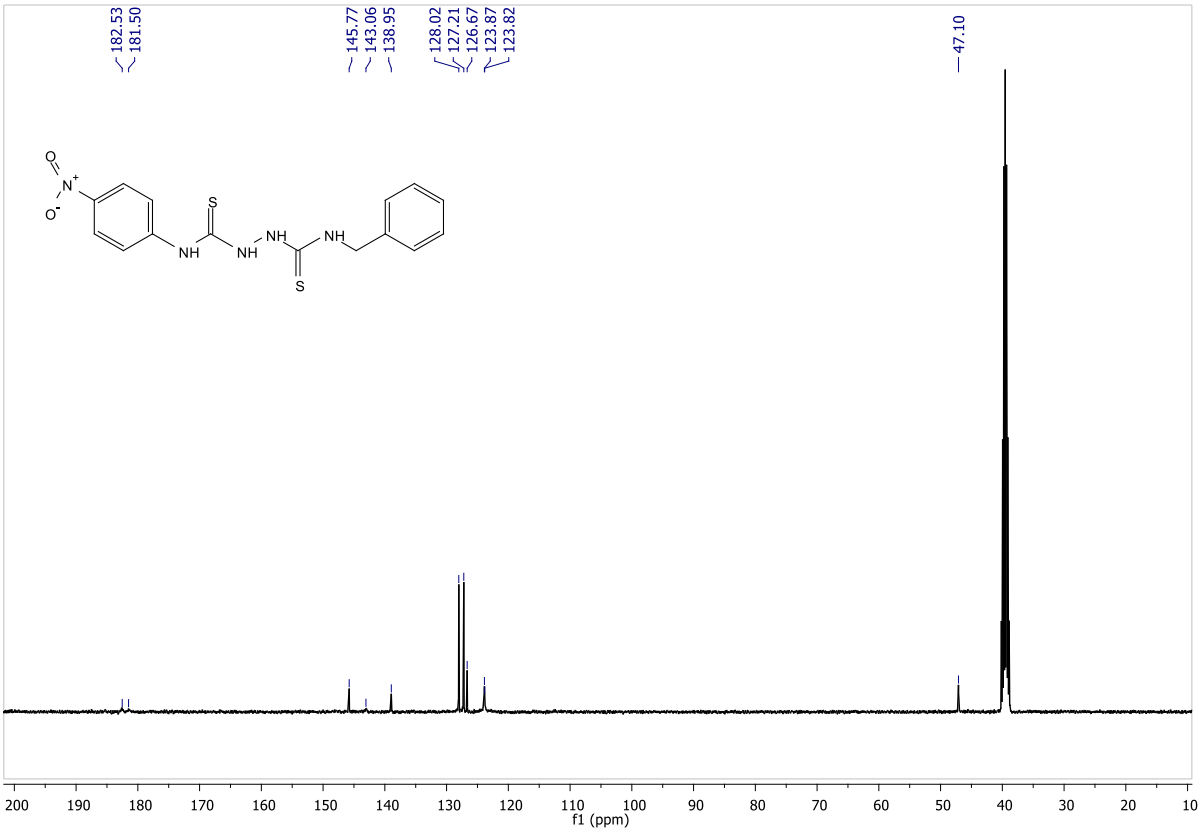

Fig. S43. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3k** (N^1-benzyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

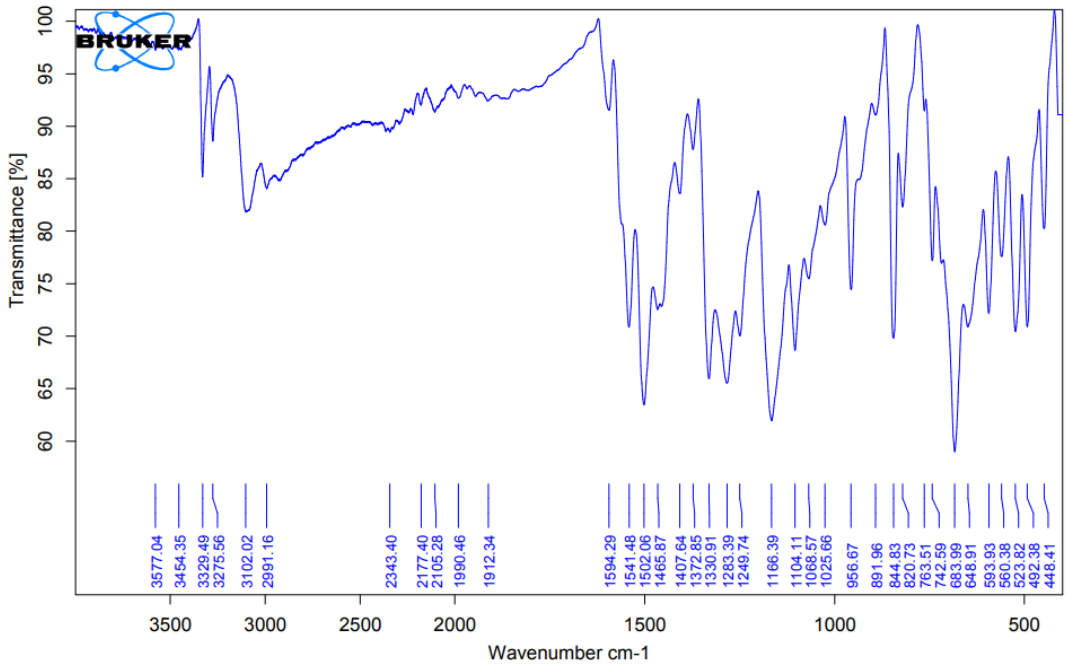

Fig. S44. FT-IR spectra of compound **3k** (N^1-benzyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

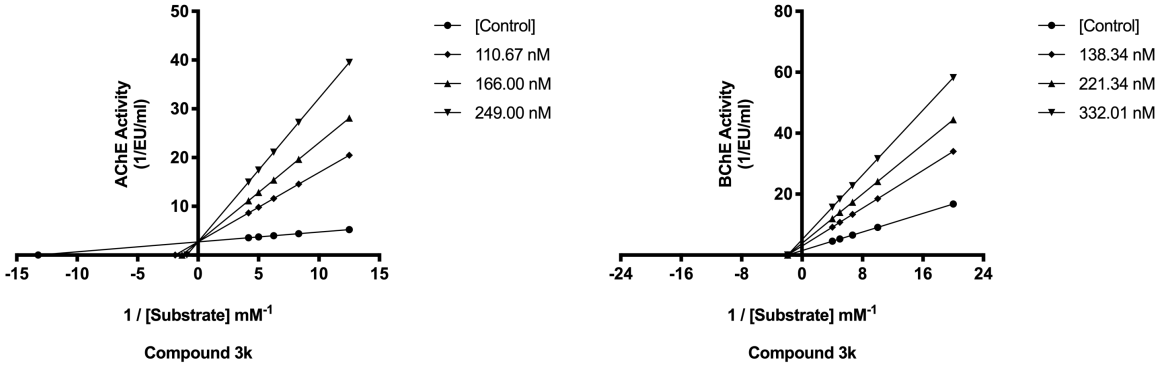

Fig. S45. Lineweaver-Burk plots of compound **3k** (N^1-benzyl-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

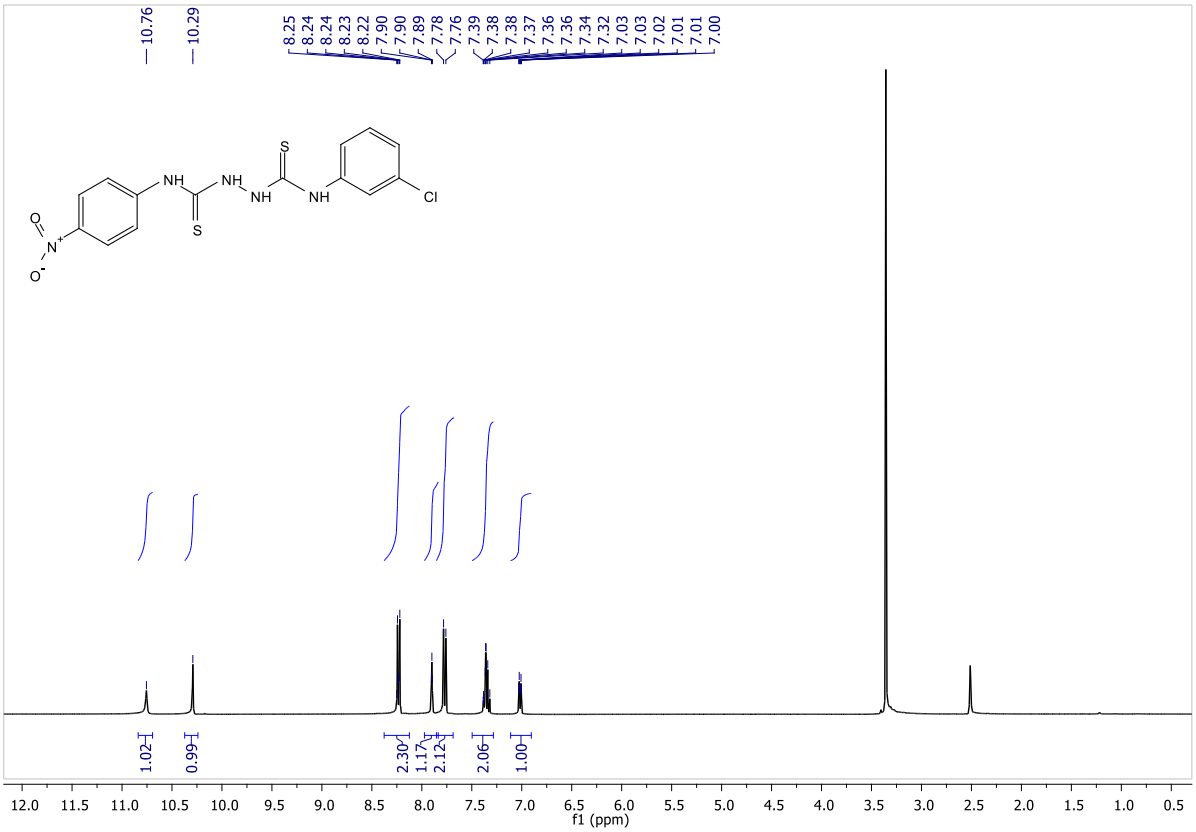

Fig. S46. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of compound **3l** (N^1-(3-chlorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

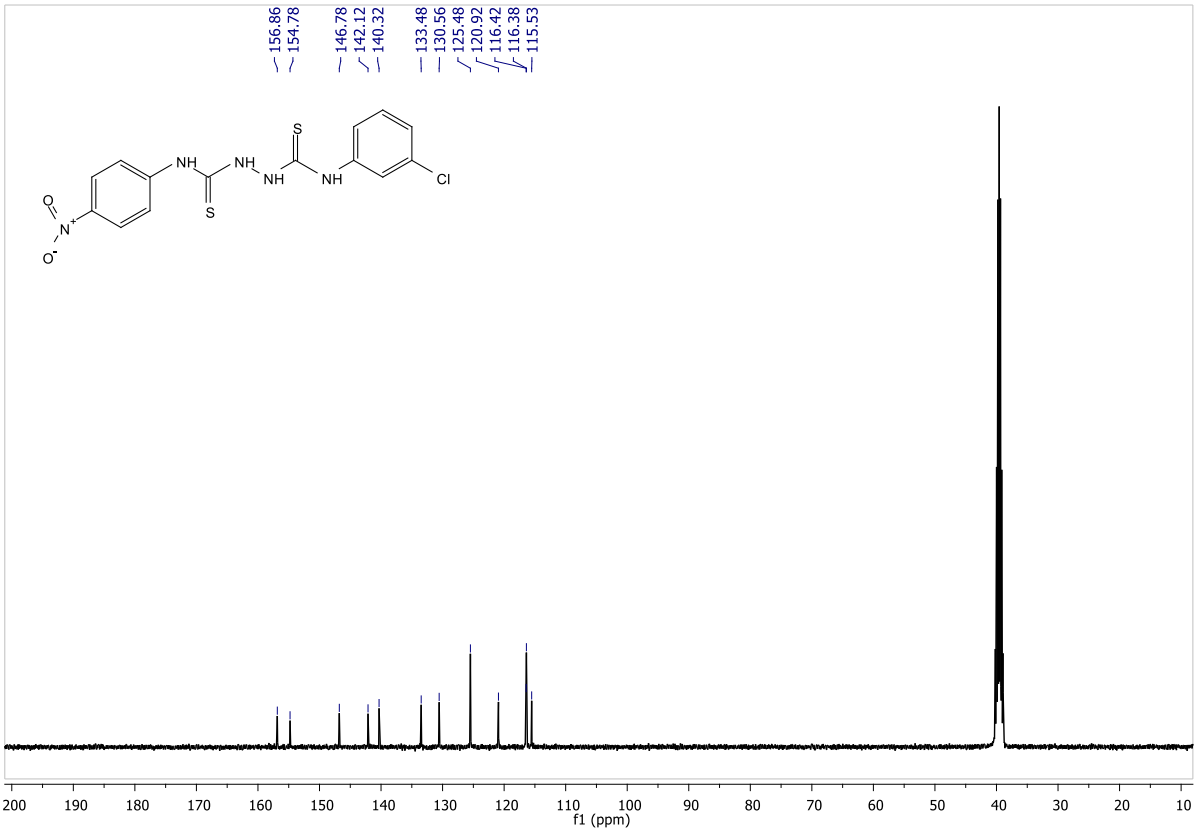

Fig. S47. ^{13}C-NMR (100 MHz, DMSO-d_6) spectra of compound **3l** (N^1-(3-chlorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

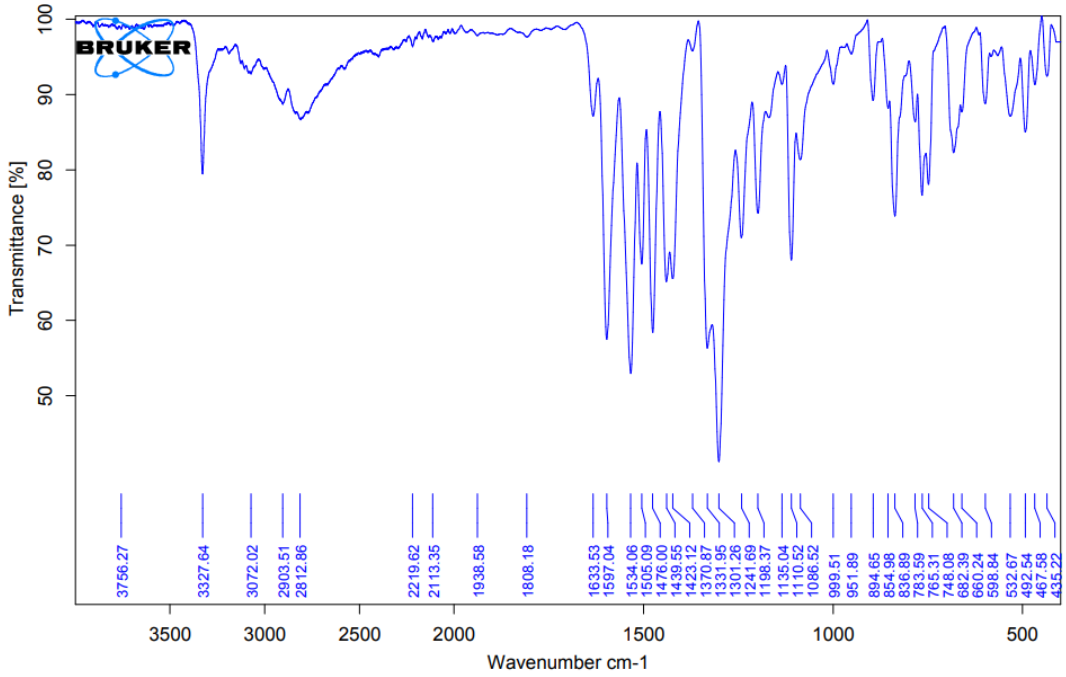

Fig. S48. FT-IR spectra of compound **3l** (N^1-(3-chlorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).

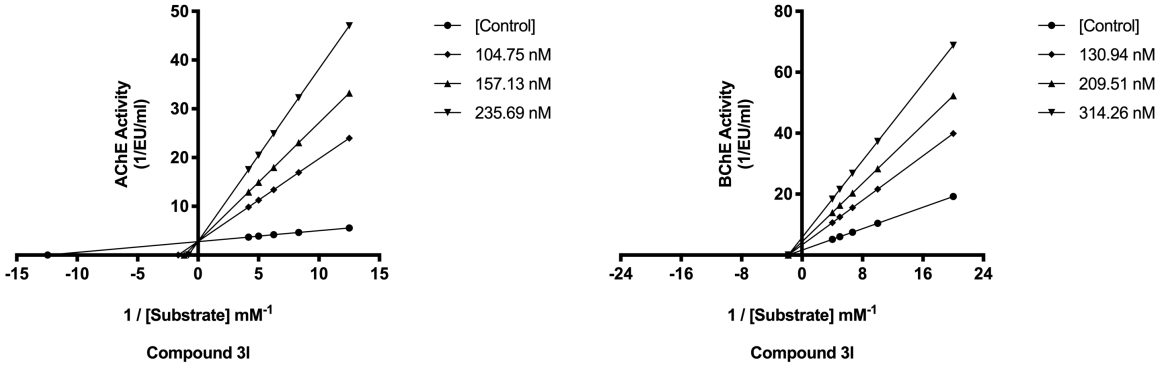

Fig. S49. Lineweaver-Burk plots of compound **3l** (N^1-(3-chlorophenyl)-N^2-(4-nitrophenyl)hydrazine-1,2-bis(carbothioamide)).