Supplementary Data

Tacrine-allyl/propargylcysteine-benzothiazole trihybrids as potential anti-Alzheimer´s drug candidates

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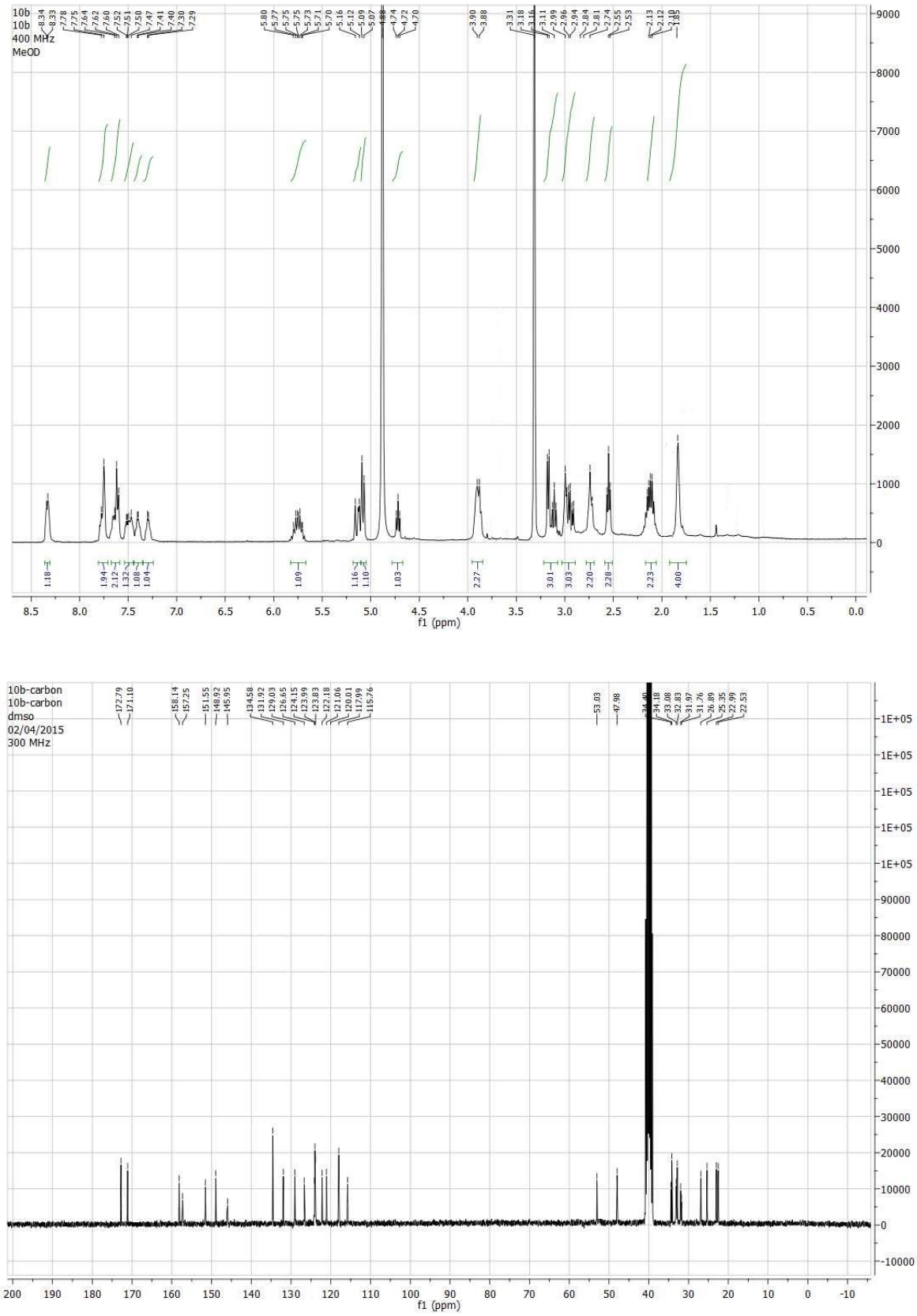


Fig. S1 - ^{1}H & ^{13}C NMR *N*-(3-(Allylthio)-1-(benzo[d]thiazol-2-ylamino)-1-oxopropan-2-yl)-4-(1,2,3,4-tetrahydroacridin-9-ylamino)butanamide (**10a)**

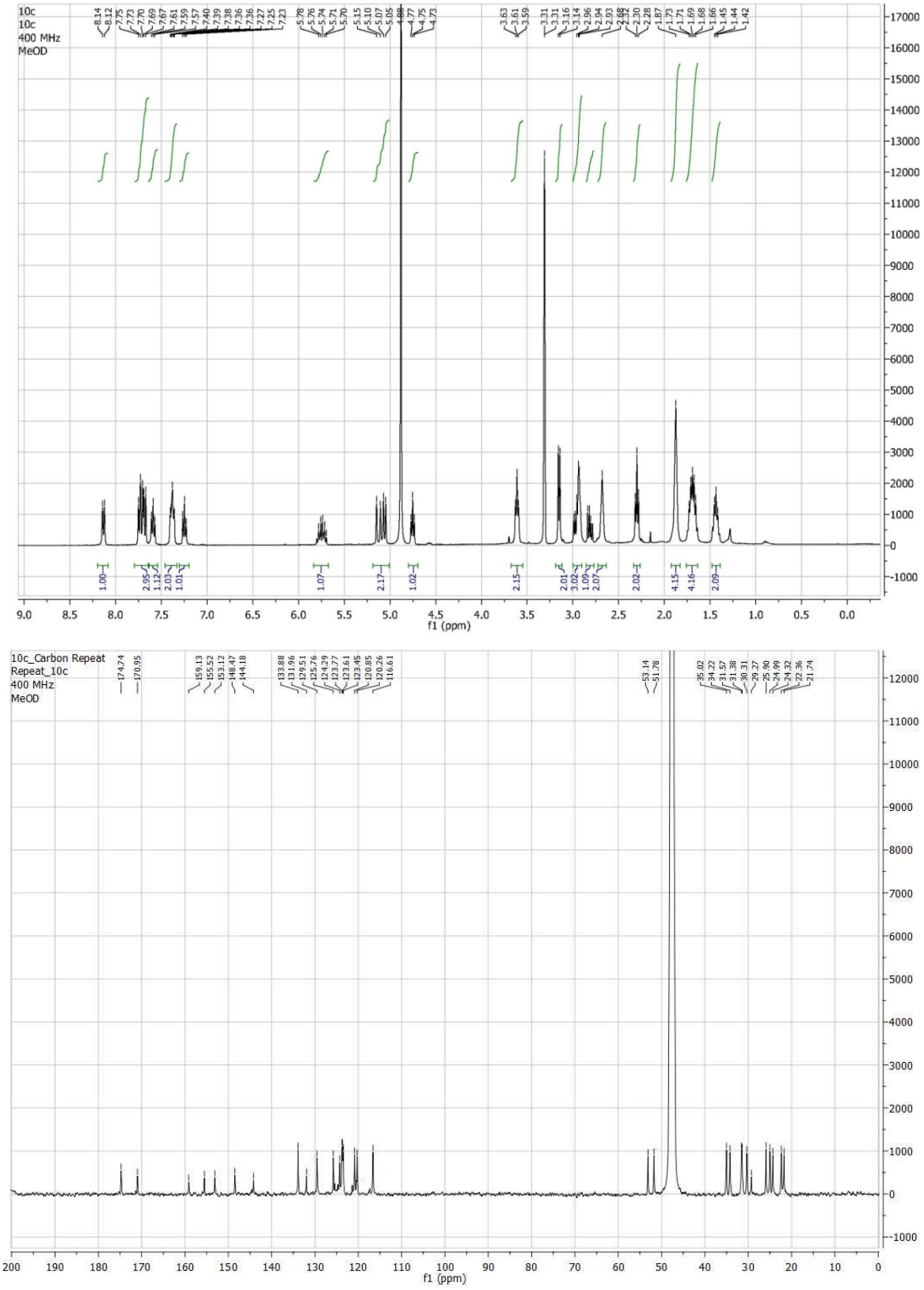


Fig. S2 - ^{1}H & ^{13}C NMR of *N-(3-(Allylthio)-1-(benzo[d]thiazol-2-ylamino)-1-oxopropan-2-yl)-6-(1,2,3,4-tetrahydroacridin-9-ylamino)hexanamide* (**10b**)

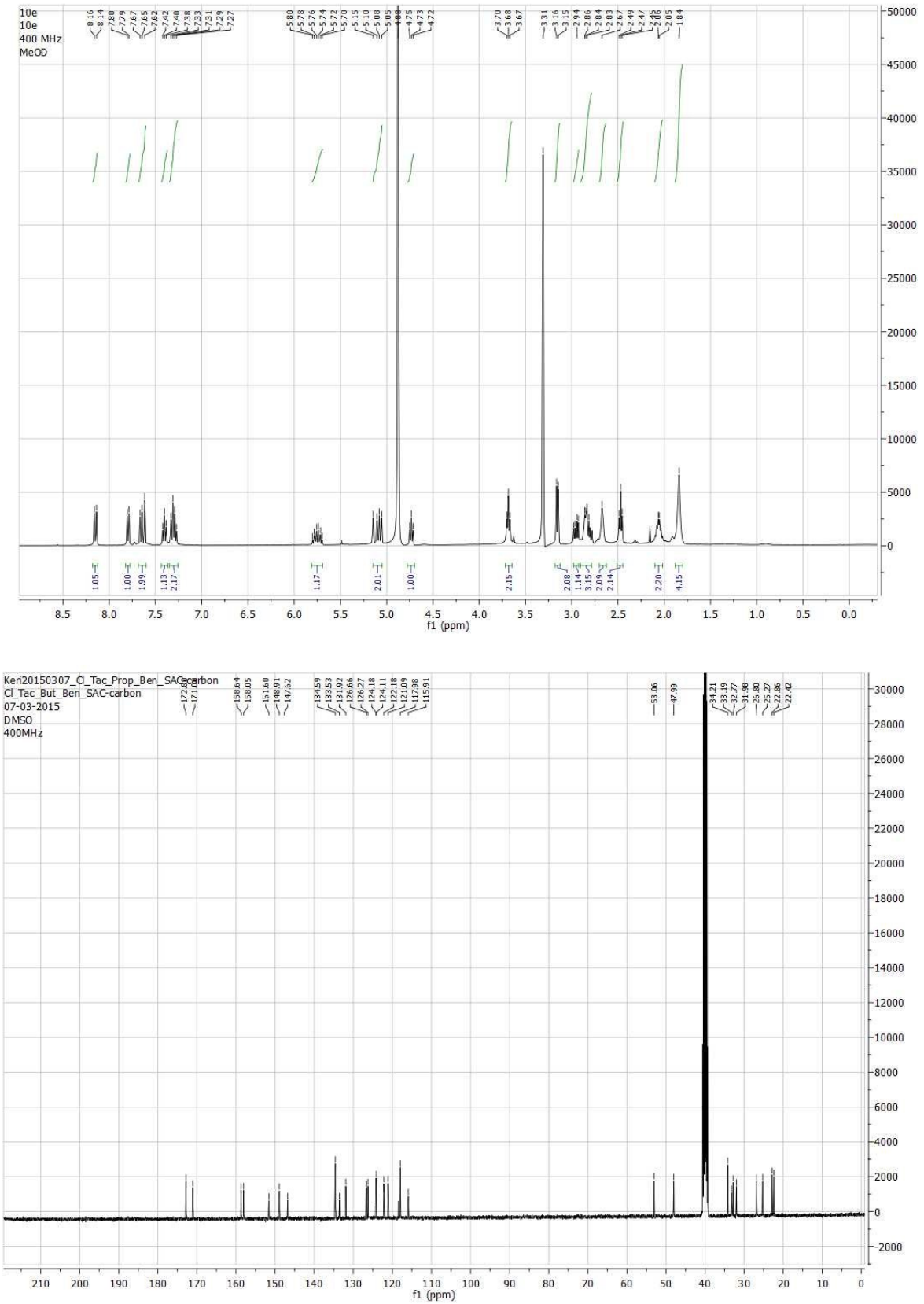


Fig. S3 - ^{1}H & ^{13}C NMR of *N*-(3-(Allylthio)-1-(benzo[d]thiazol-2-ylamino)-1-oxopropan-2-yl)-4-(6-chloro-1,2,3,4-tetrahydroacridin-9-ylamino)butanamide (**10c**)

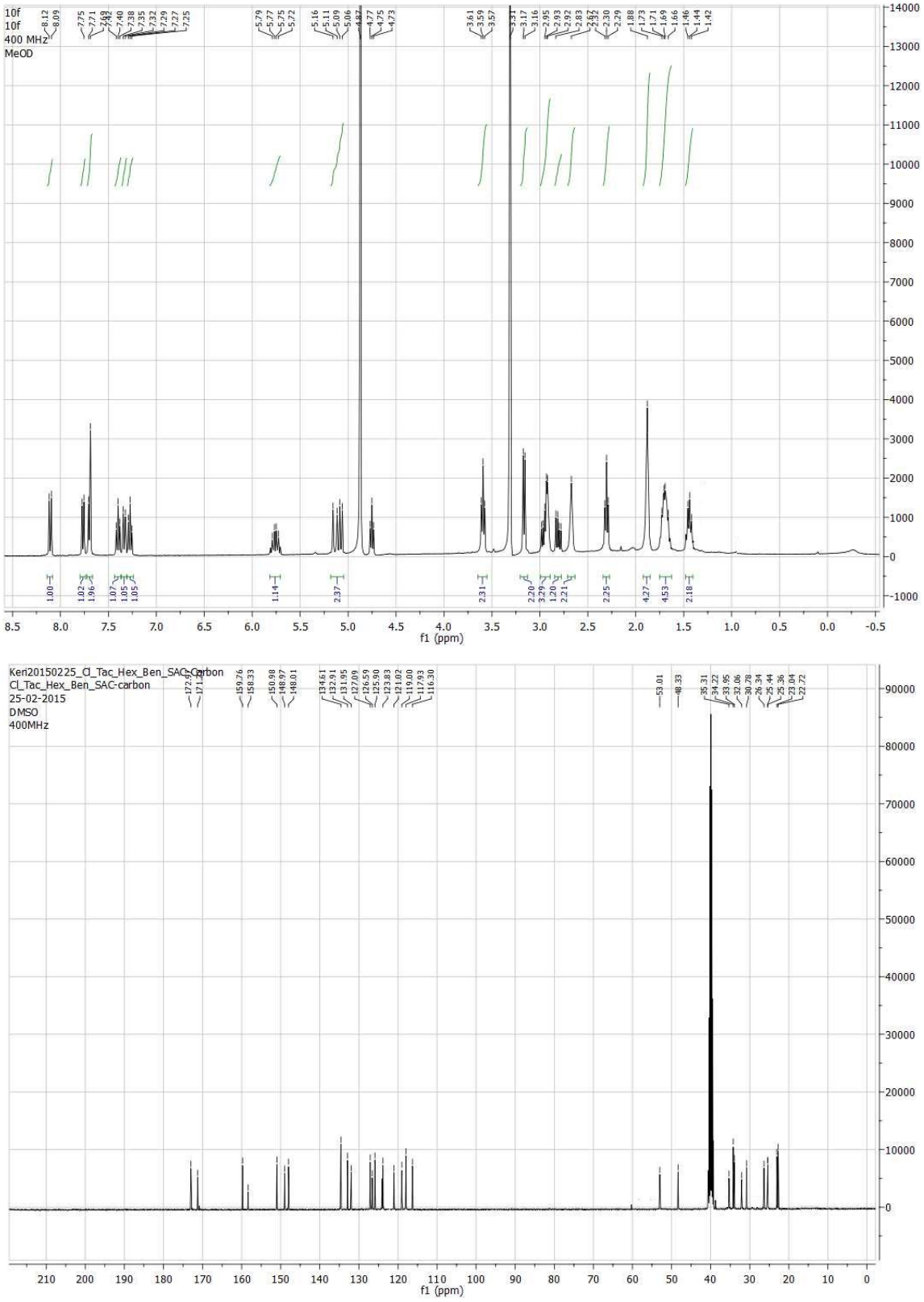


Fig. S4 - ^{1}H & ^{13}C NMR of *N*-(3-(Allylthio)-1-(benzo[d]thiazol-2-ylamino)-1-oxopropan-2-yl)-6-(6-chloro-1,2,3,4-tetrahydroacridin-9-ylamino)hexanamide **(10d)**

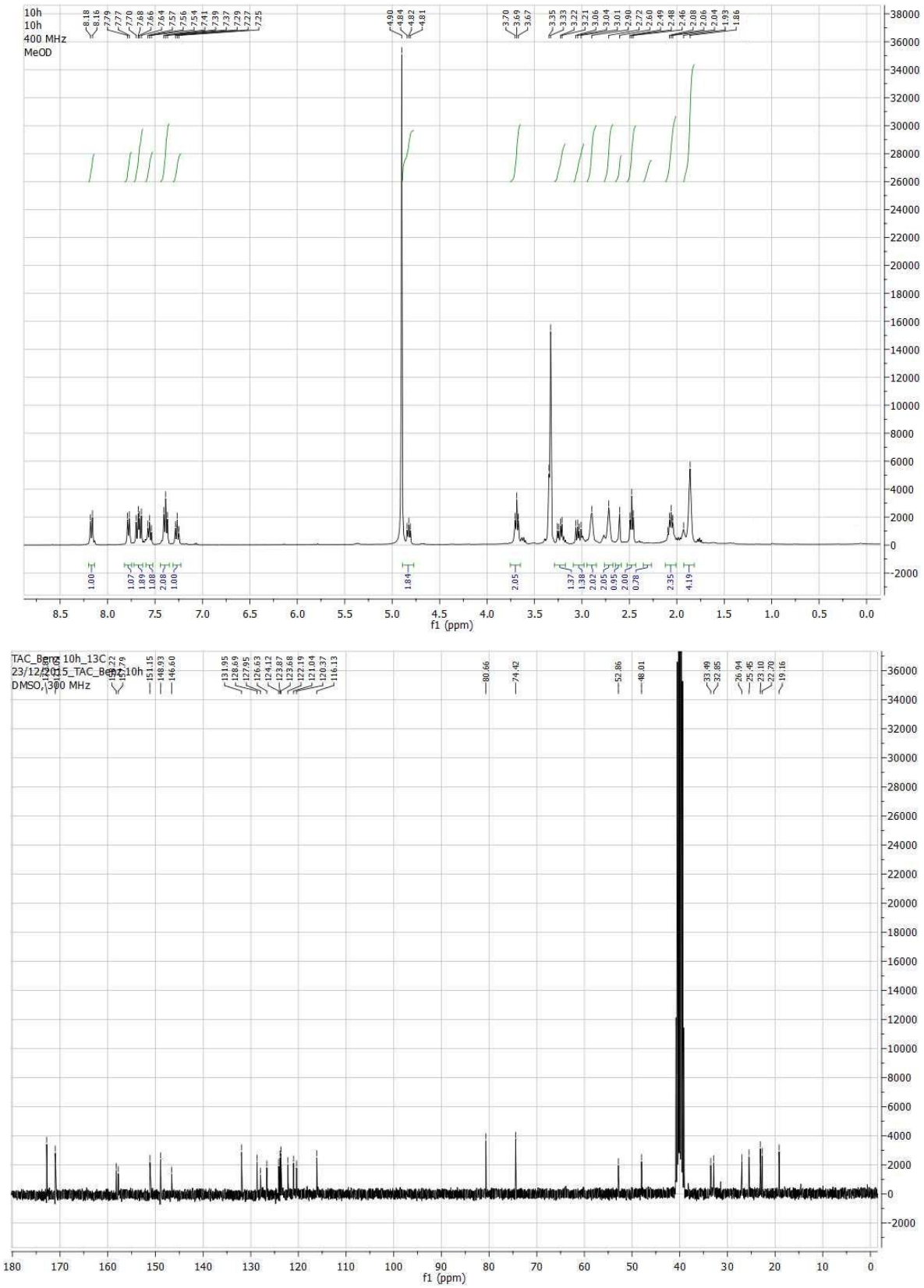


Fig. S5 - ^{1}H & ^{13}C NMR of *N*-(1-(Benzo[d]thiazol-2-ylamino)-1-oxo-3-(prop-2-ynylthio)propan-2-yl)-4-(1,2,3,4-tetrahydroacridin-9-ylamino)butanamide (**10e**)

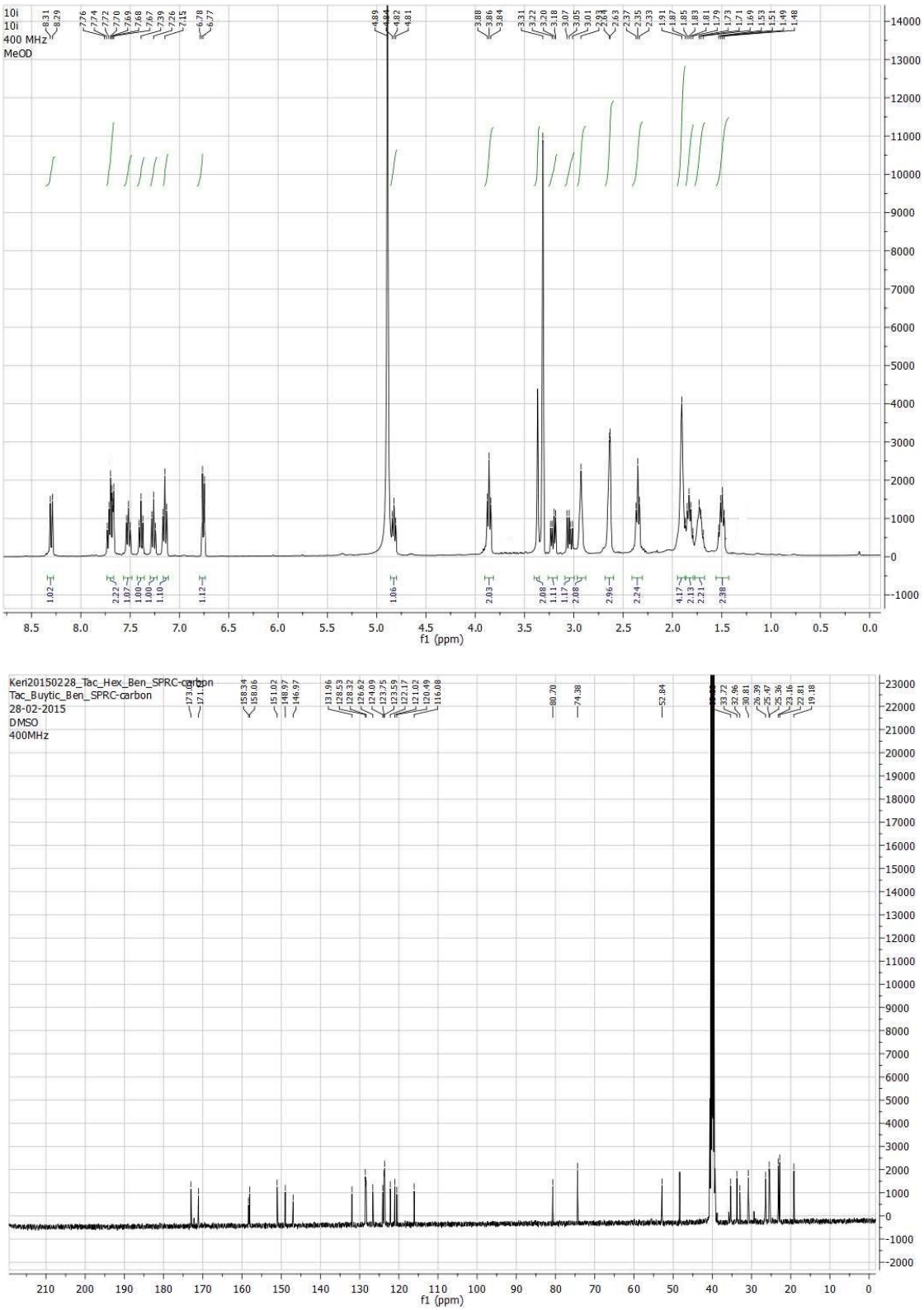


Fig. S6 - ^{1}H & ^{13}C NMR of *N*-(1-(Benzo[d]thiazol-2-ylamino)-1-oxo-3-(prop-2-ynylthio)propan-2-yl)-6-(1,2,3,4-tetrahydroacridin-9-ylamino)hexanamide (**10f**)

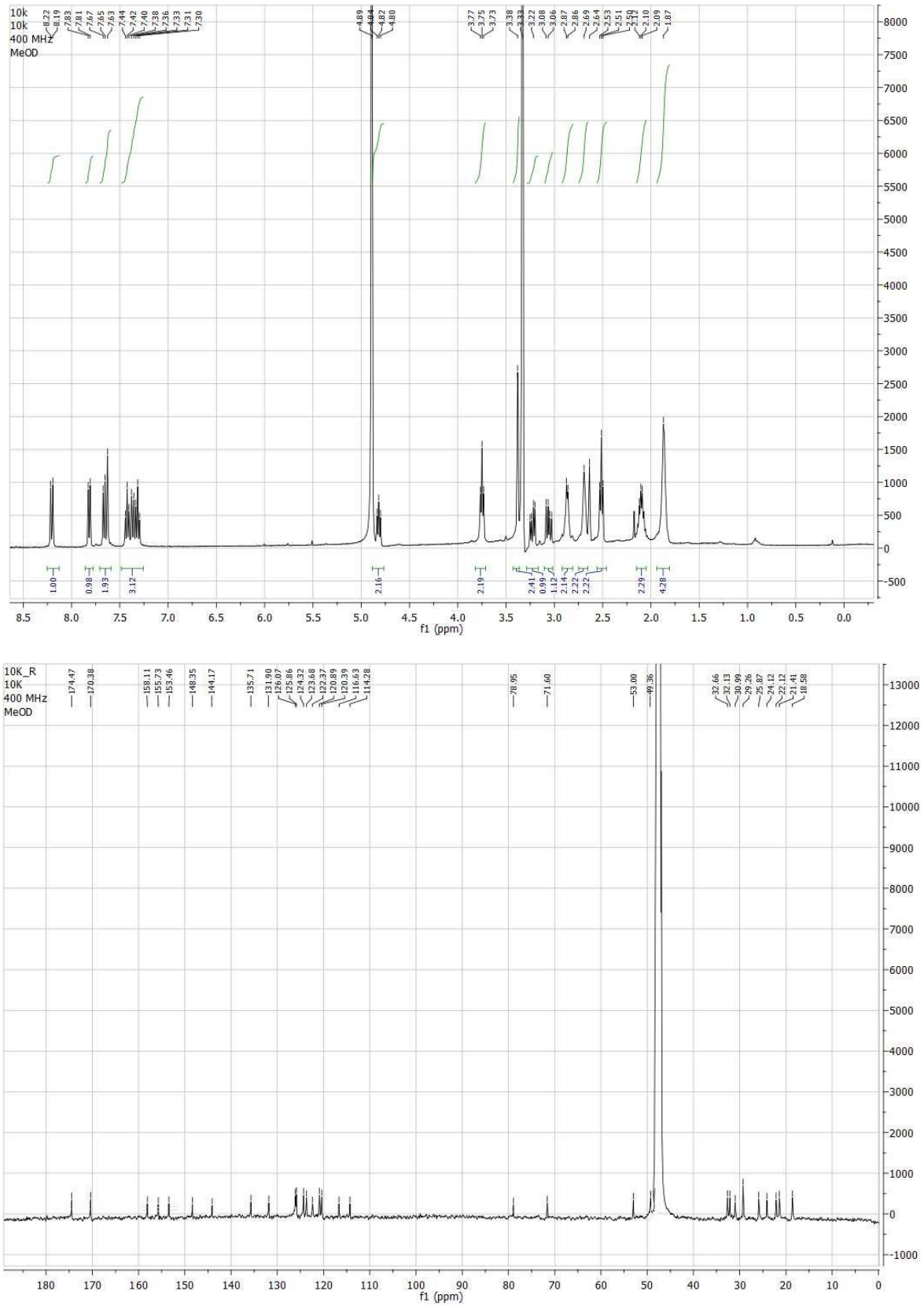


Fig. S7 - ^{1}H & ^{13}C NMR of *N*-(1-(Benzo[d]thiazol-2-ylamino)-1-oxo-3-(prop-2-ynylthio)propan-2-yl)-4-(6-chloro-1,2,3,4-tetrahydroacridin-9-ylamino)butanamide **(10g)**

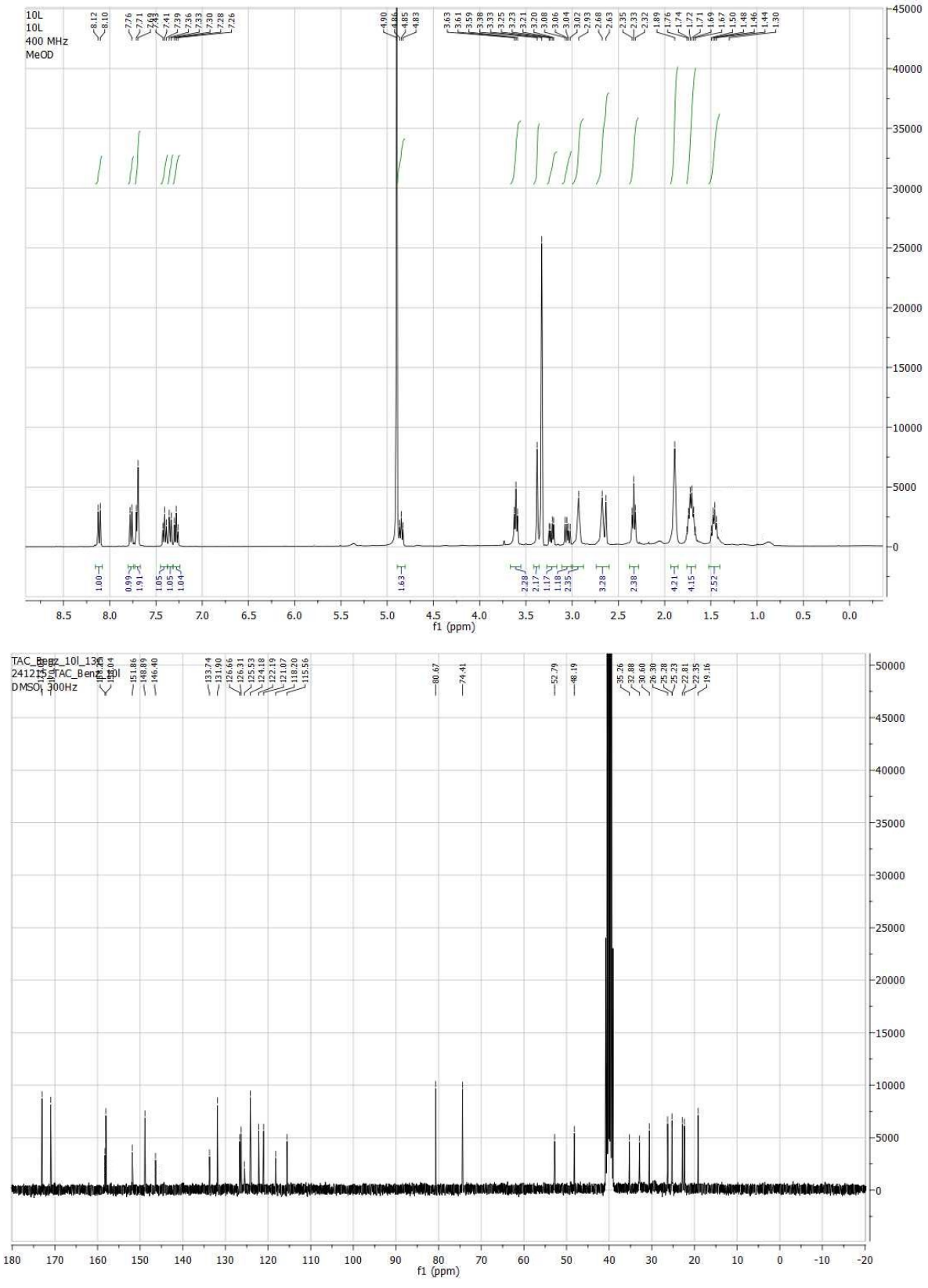
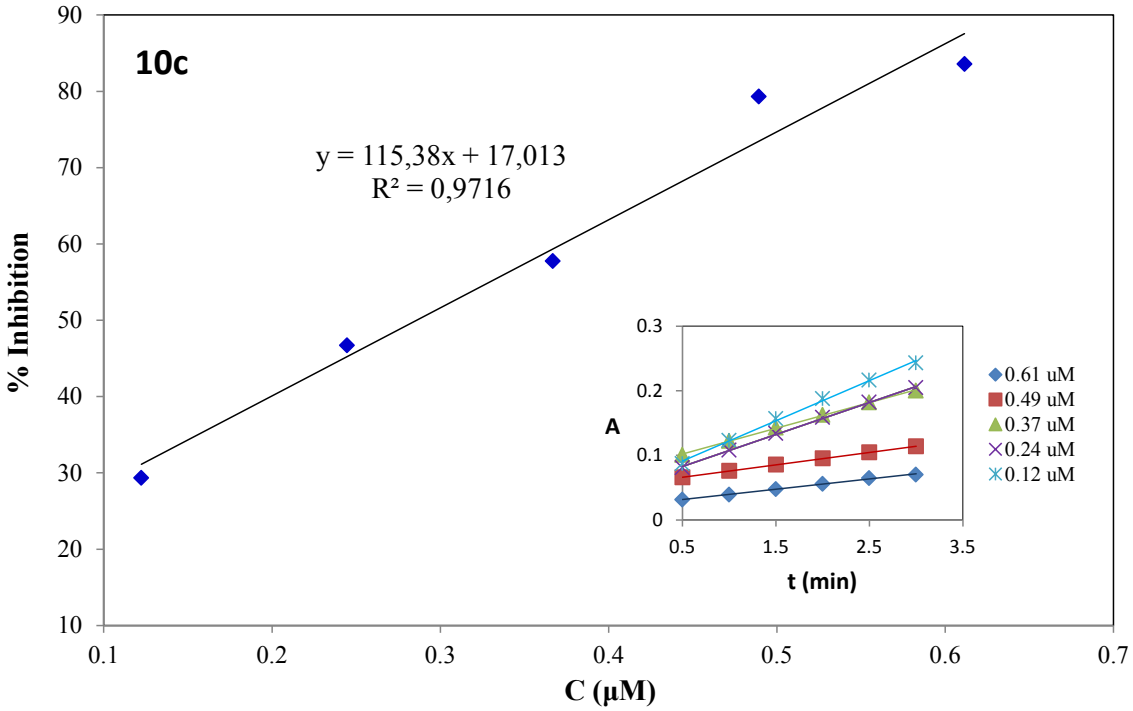


Fig. S8 - ^{1}H & ^{13}C NMR of *N*-(1-(Benzo[d]thiazol-2-ylamino)-1-oxo-3-(prop-2-ynylthio)propan-2-yl)-6-(6-chloro-1,2,3,4-tetrahydroacridin-9-ylamino)hexanamide (**10h**).



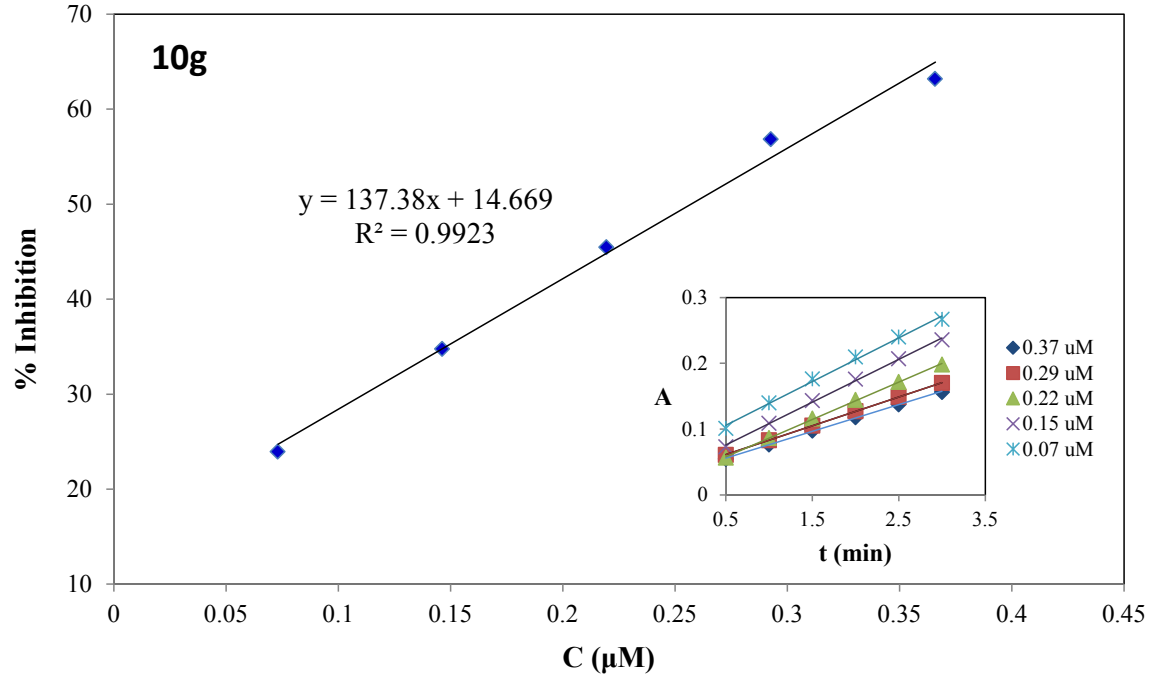
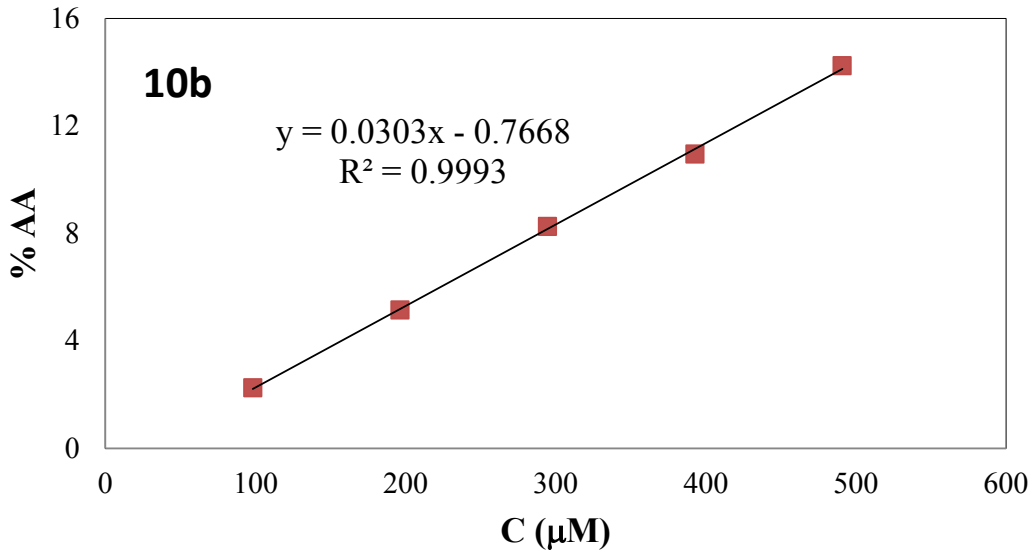


Fig. S9 - Representative examples of IC_{50} plots for AChE inhibition assays of compounds **10c** and **10g**: insets contain representative plots of absorbance versus time for the same compounds at different concentrations of inhibitor.



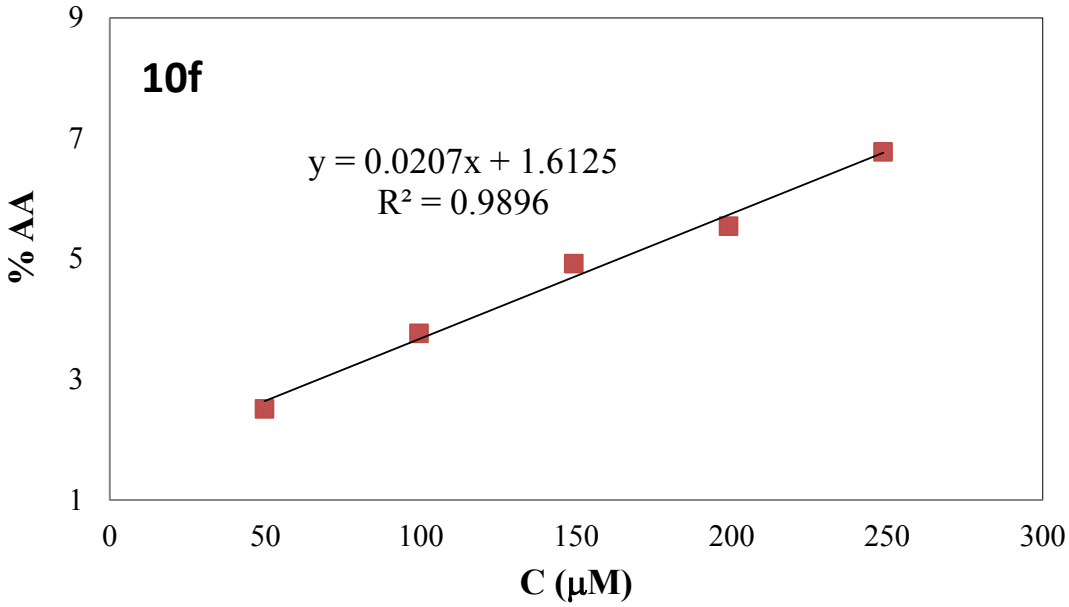
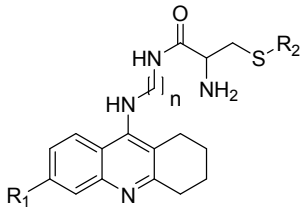


Fig. S10 - Antioxidant activity (AA) plots for compounds **10b** and **10f**

Table S1 – In vitro activities of TAC-SAC, **9(a-f)**, and TAC-SPRC, **9(g-l)**, hybrids, towards AChE inhibition, antioxidant activity (DPPH) and anti-Aβ aggregation (from ref. 19 and 20)

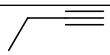
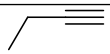
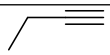
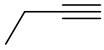


9(a-l)

Comp. code	**R_1**	**R_2**	**n**	**AChE inhibit.** IC_{50} (μM)[a]	**Antioxid.** EC_{50} (10×μM)[b]	**Aβ aggreg. Inhib.[c] (%)**	**Cu-induc Aβ aggreg. Inhib.[c] (%)**
9a	H	$CH_2CH=CH_2$	2	1.59	65.7	8.5	30.9
9b	H	»	3	0.88	86.5	-	-
9c	H	»	4	1.20	73.5	-	-
9d	Cl	»	2	0.30	55.8	10.9	50.3
9e	Cl	»	3	0.68	50.5	14.7	35.1
9f	Cl	»	4	0.51	99.2	10.3	32.1
9g	H	$-CH_2C\equiv CH$	2	1.21	2.0	13.0	44.4
9h	H	»	3	1.72	41.7	-	-
9i	H	»	4	1.21	52.5	-	-
9j	Cl	»	2	0.56	56.3	11.4	49.3
9k	Cl	»	3	0.59	55.1	12.1	34.3
9l	Cl	»	4	0.97	75.6	-	-
Tac	-	-	-	0.19	>100	-	-

[a] Standard deviation within 10 %; [b] EC_{50} values for DPPH assay; [c] Inhibition of Aβ (1-42) aggregation (40 μM) with or without copper (40 μM); thioflavin-T fluorescence method with 80 μM of inhibitor.

Table 1S (supplementary): Summary of some calculated pharmacokinetic descriptors[a]

S.No.	Comp. Code	R_1	R_2	MW	clog *P* [b]	log BB[c]	Caco-2 permeability (nm/sec)	Violations of Lipinski's rule of 5	CNS activity
1	**10b**	H		559.75	5.859	-1.355	590	2	--
2	**10c**	H		587.80	6.684	-1.550	613	2	--
3	**10e**	Cl		594.19	6.187	-0.740	1263	2	-
4	**10f**	Cl		622.24	7.366	-1.281	890	2	--
5	**10h**	H		557.73	5.786	-1.508	445	2	--
6	**10i**	H		585.78	6.671	-1.308	999	2	--
7	**10k**	Cl		592.17	6.231	-1.280	477	2	--
8	**10l**	Cl		620.23	6.918	-1.020	1350	2	--

a Predicted values using program QikProp v. 2.5[34]. [b] Calculated octanol/water partition coefficient. [c] Brain/blood partition coefficient.