Synthesis, molecular modeling and QSAR study of new *N*-phenyl acetamide-2-oxoindole benzensulfonamide conjugates as carbonic anhydrase inhibitors with antiproliferative activity

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Index:

Cytotoxicity:

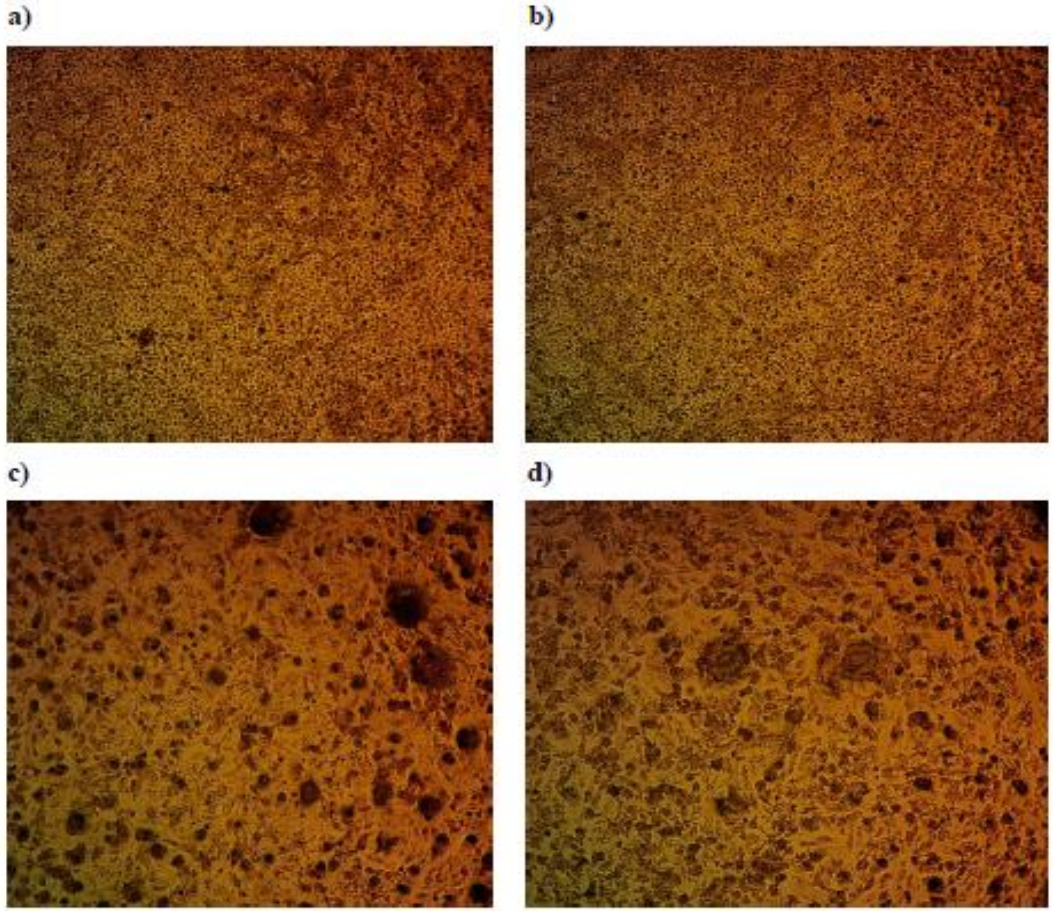

Figure S1. Cytotoxic effect of tested compounds **2h**, **3c**, **3d** at concentration 100 μM on human skin fibroblast cell line (HSF). a) Control. b) Cytotoxic effect of compound **2h**. c) Cytotoxic effect of compound **3c**. d) Cytotoxic effect of compound **3d.**

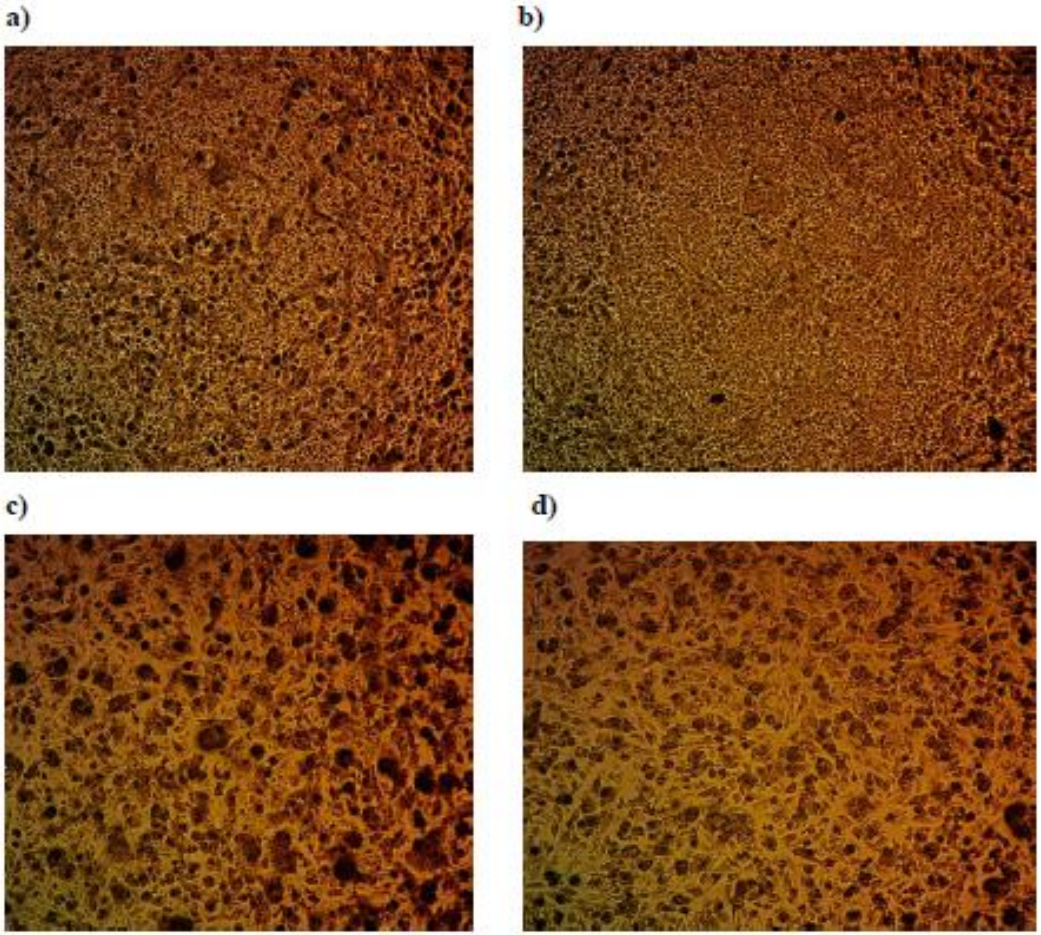

Figure S2. Cytotoxic effect of tested compounds **2h**, **3c**, **3d** at concentration 100 μM on human breast cancer cell line (MCF-7). a) Control. b) Cytotoxic effect of compound **2h**. c) Cytotoxic effect of compound **3c**. d) Cytotoxic effect of compound **3d.**

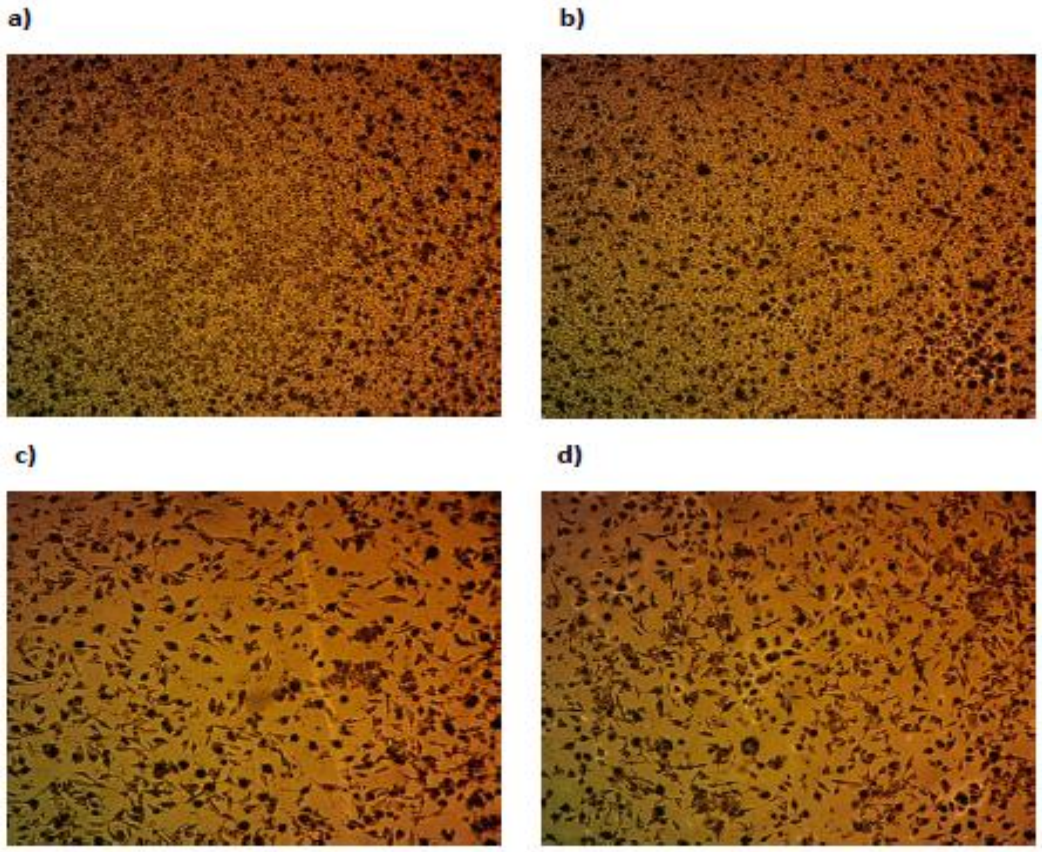

Figure S3. Cytotoxic effect of tested compounds **2h**, **3c**, **3d** at concentration 100 μM on human lung adenocarcinoma (A549). a) Control. b) Cytotoxic effect of compound **2h**. c) Cytotoxic effect of compound **3c**. d) Cytotoxic effect of compound **3d.**

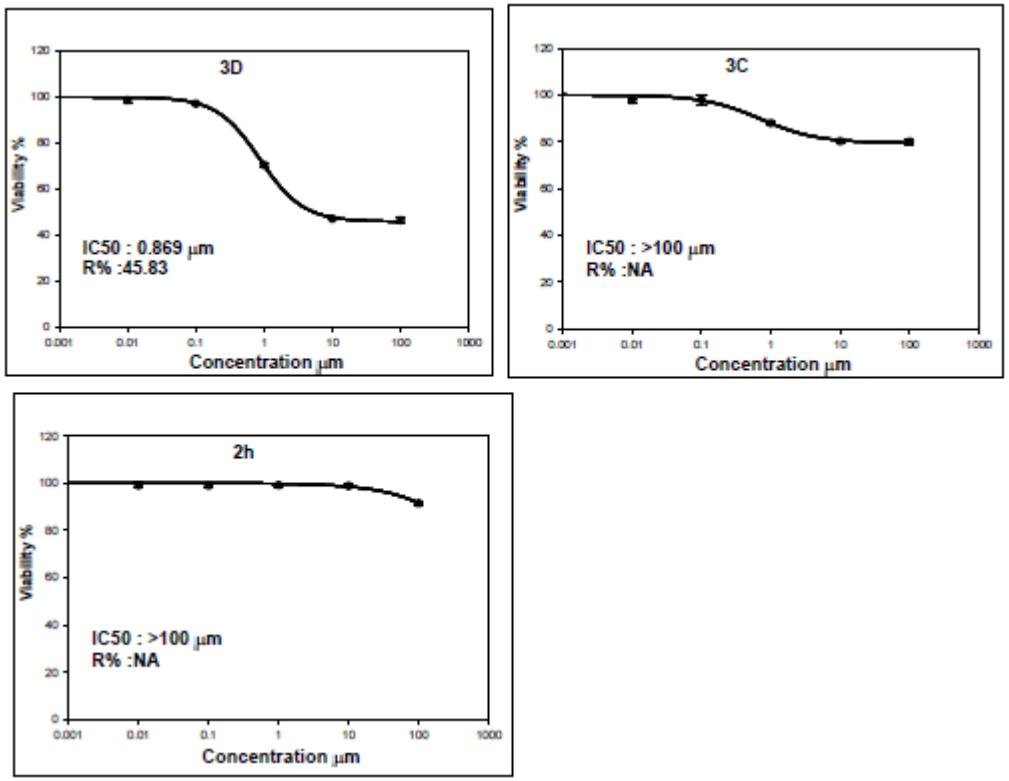

Figure S4. IC_{50} curves for compounds **2h**, **3c** and **3d** against MCF-7 breast cancer cell line.

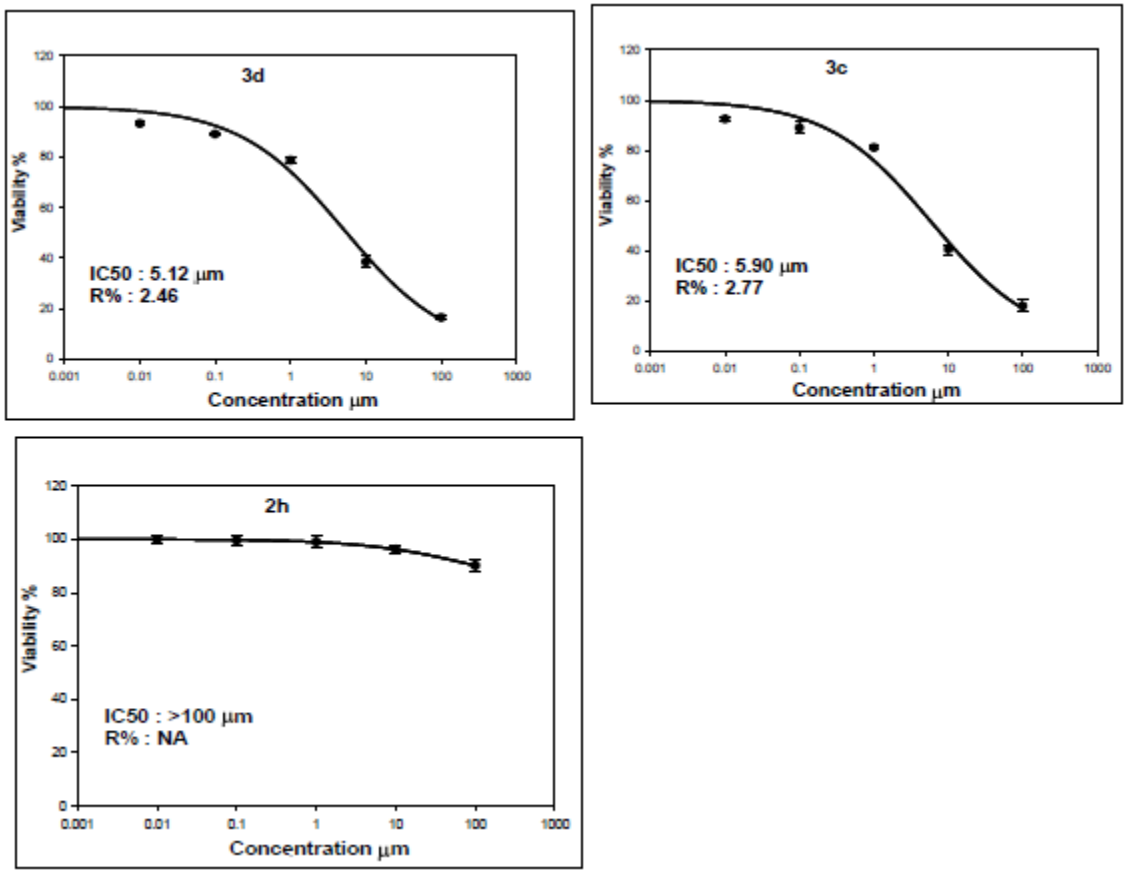

Figure S5. IC_{50} curves for compounds **2h**, **3c** and **3d** against A549 lung cancer cell line.

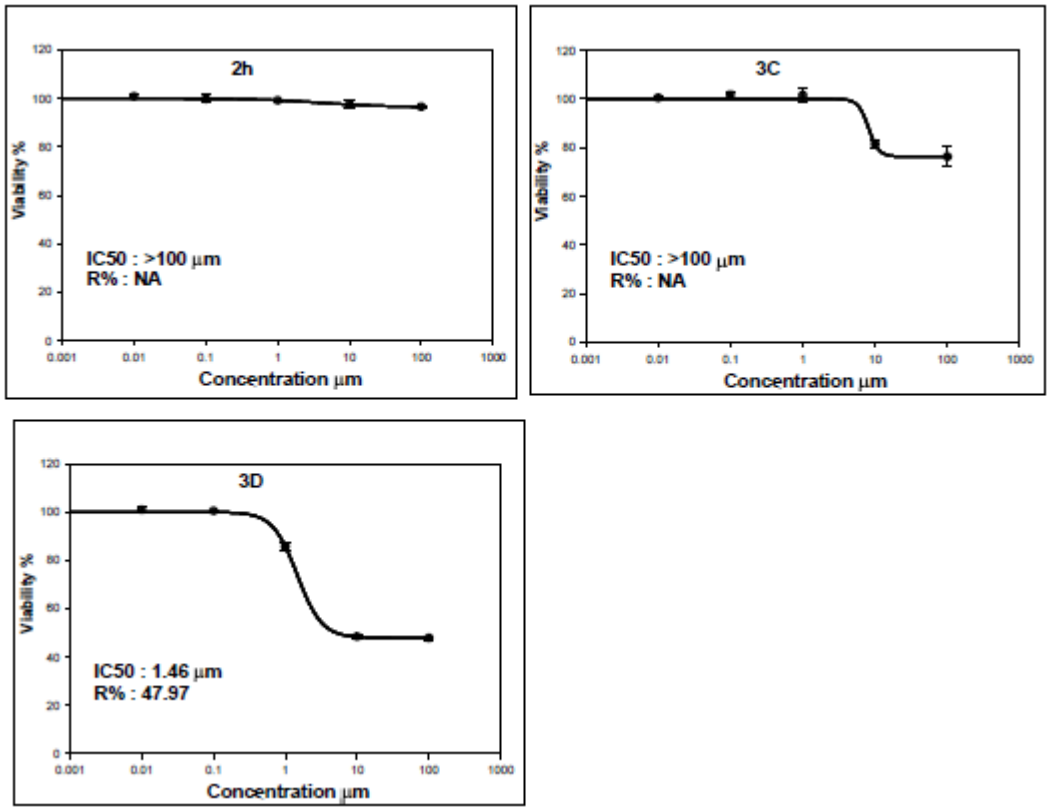

Figure S6. IC_{50} curves for compounds **2h**, **3c** and **3d** against HSF human skin fibroblasts.

Compound 2h

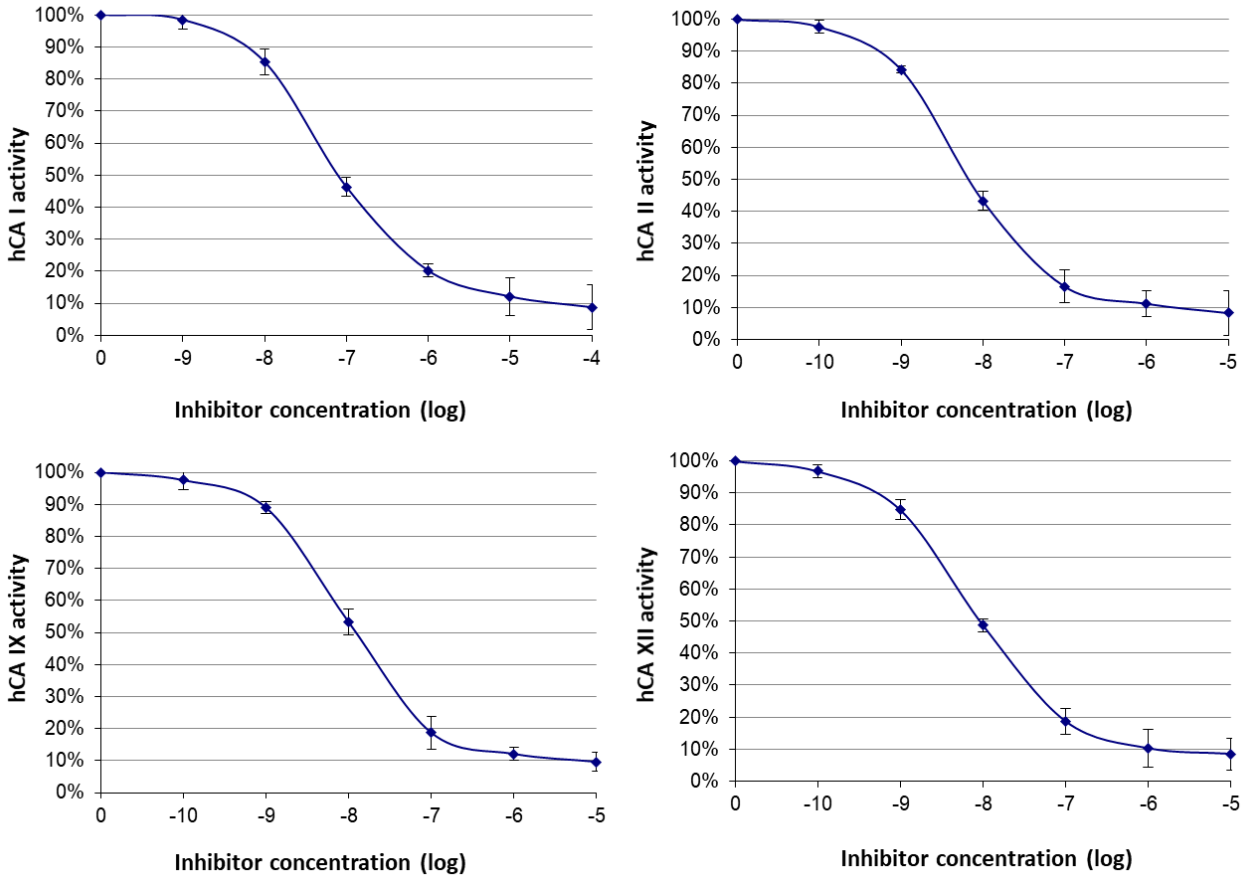

Figure S7. Effect of compound **2h** on the activity of CA I, CA II, CA IX and CA XII isoforms.

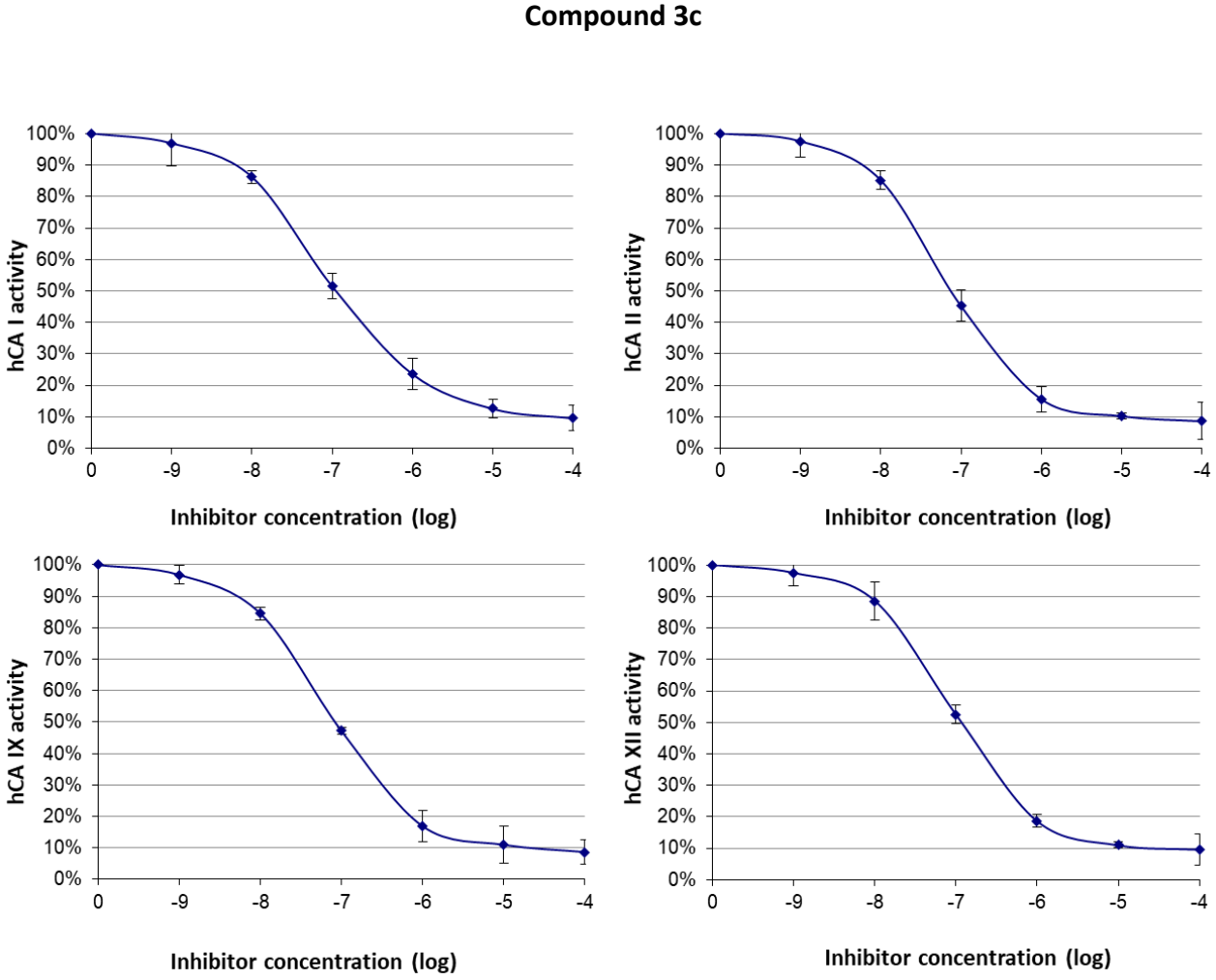

Figure S8. Effect of compound **3c** on the activity of CA I, CA II, CA IX and CA XII isoforms.

Compound 3d

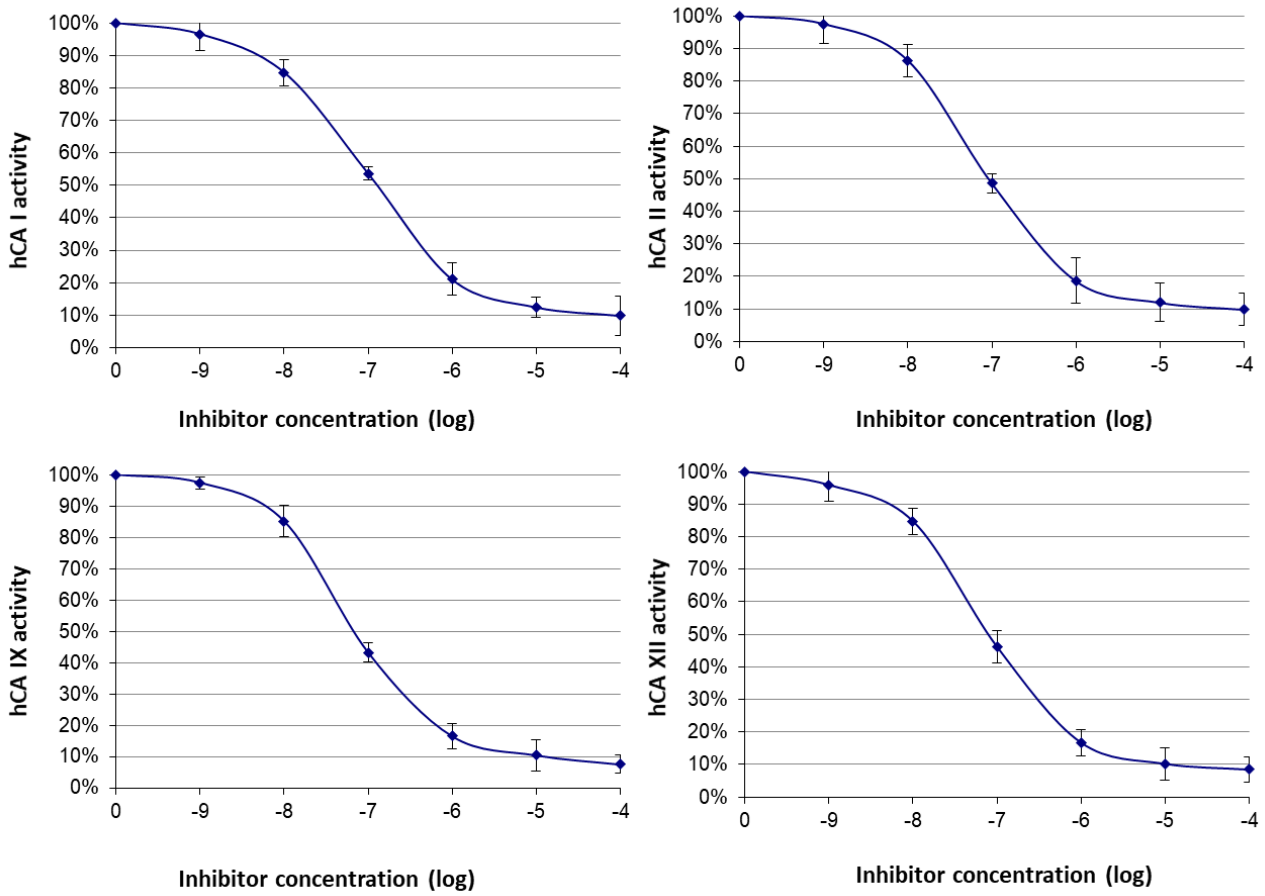

Figure S9. Effect of compound **3d** on the activity of CA I, CA II, CA IX and CA XII isoforms.

Molecular docking study

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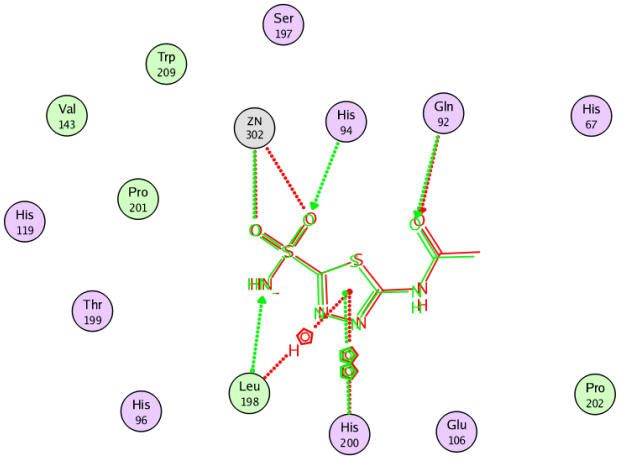
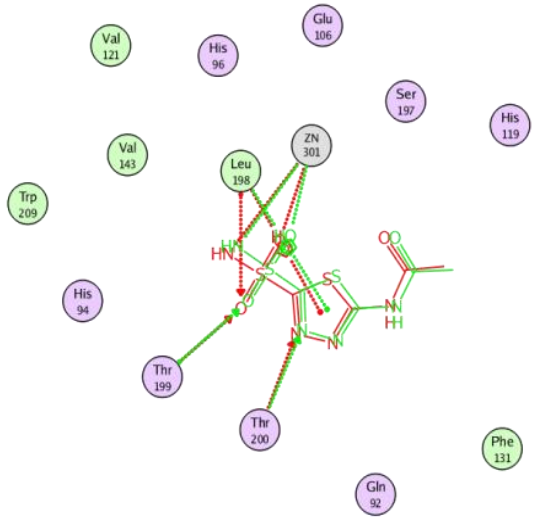


b)



c) **d)**

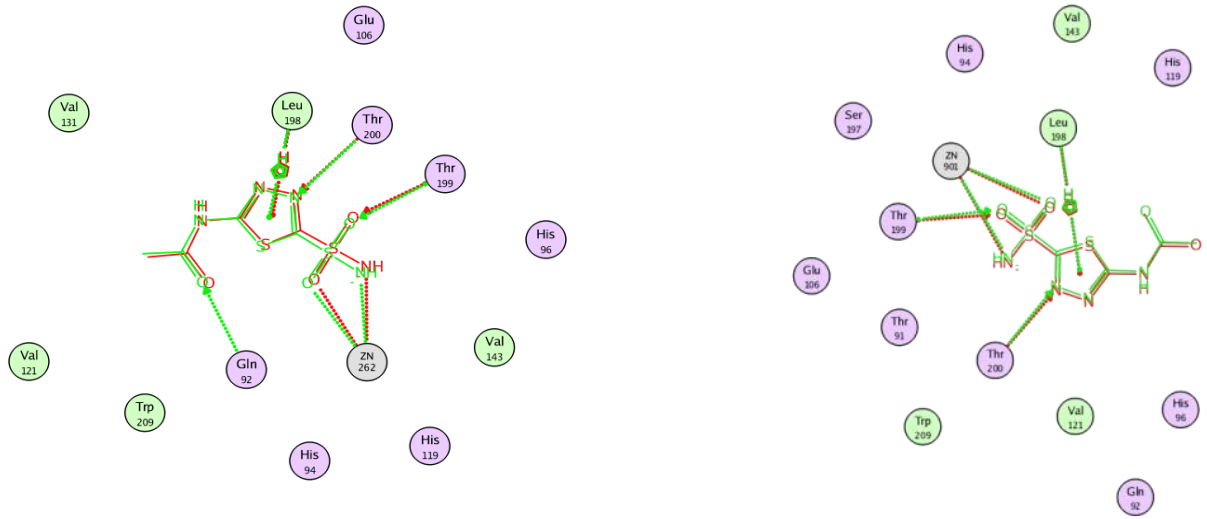
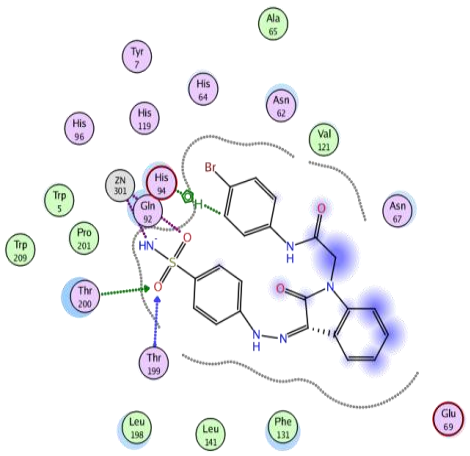
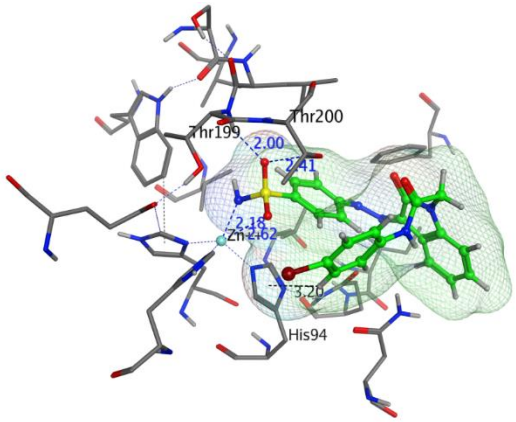


Figure S10. The 2D presentations of molecular docking method validation using PDB ID: 3W6H (a), 3HS4 (b), 3IAI (c) and 1JD0 (d) for CA I, II, IX and XII, respectively.

a)

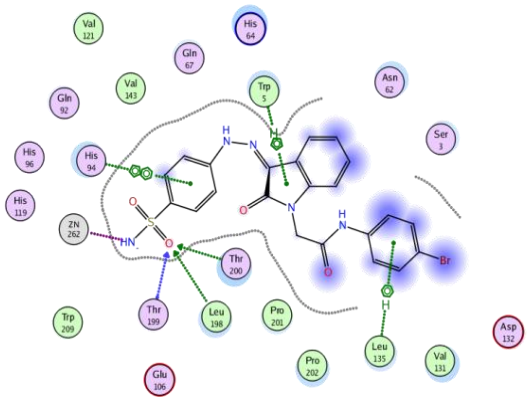

Ala 65
Tyr 7
His 64
Asn 62
His 96
His 119
Val 121
ZN 301
His 94
Br
Trp 5
Gln 92
Asn 67
Pro 201
Trp 209
HN
O
N
H
Thr 200
Thr 199
Leu 198
Leu 141
Phe 131
Glu 69

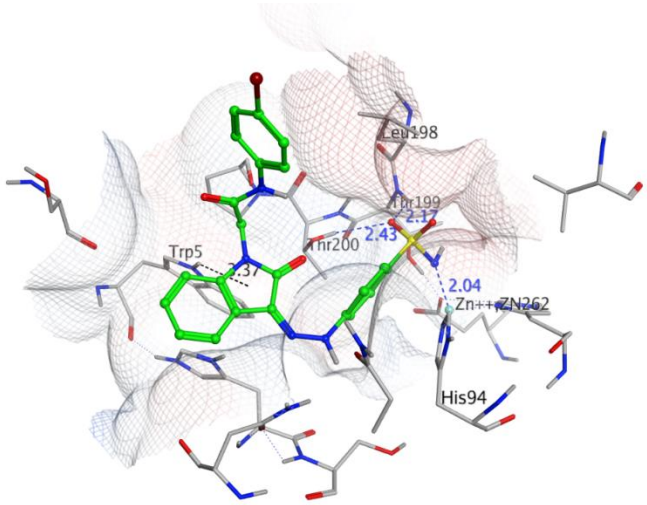
b)


Thr200
Thr199
2.00
2.41
2.18
Zn
2.62
3.20
His94

c)

d)


Val 121
His 64
Gln 67
Val 143
Trp 5
Asn 62
Gln 92
Ser 1
His 96
His 94
His 119
ZN 262
Thr 200
Thr 199
Leu 198
Pro 201
Trp 209
Leu 135
Val 131
Asp 132
Pro 202
Glu 106
Br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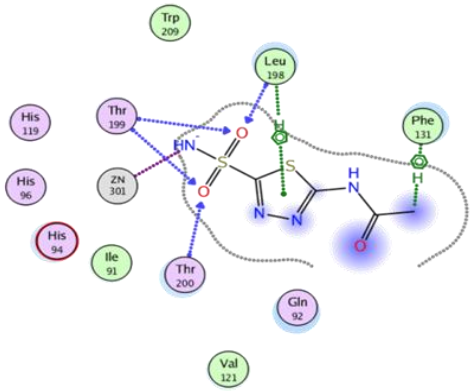
Thr200
Trp5
2.37
2.04
Zn++
ZN262
His94

e)


Trp 209
Leu 198
His 119
Thr 199
Phe 131
ZN 301
His 96
His 94
Ile 91
Thr 200
Gln 92
Val 121

f)

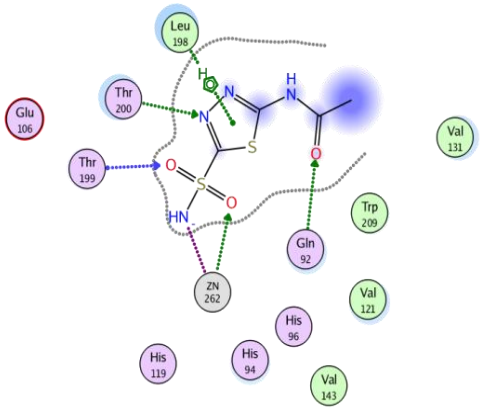

Leu 198
Glu 106
Thr 200
Val 131
Thr 199
Trp 209
Gln 92
ZN 262
Val 121
His 96
His 119
His 94
Val 143

Figure S11. The 2D and 3D interactions of **3c** molecular docking study using PDB ID 3HS4 (a, b) and 3IAI (c,d) for *h*CA isoforms II and IX, respectively showing **3c** in green ball and stick model with the formed H-bonds and arene-H were shown in blue and black dotted lines, respectively with their distance in Å highlighting the interaction site.. The 2D interactions of **AAZ** using *h*CA II 3HS4 (e) and *h*CA IX PDB ID 3IAI (f).

a) **b)**

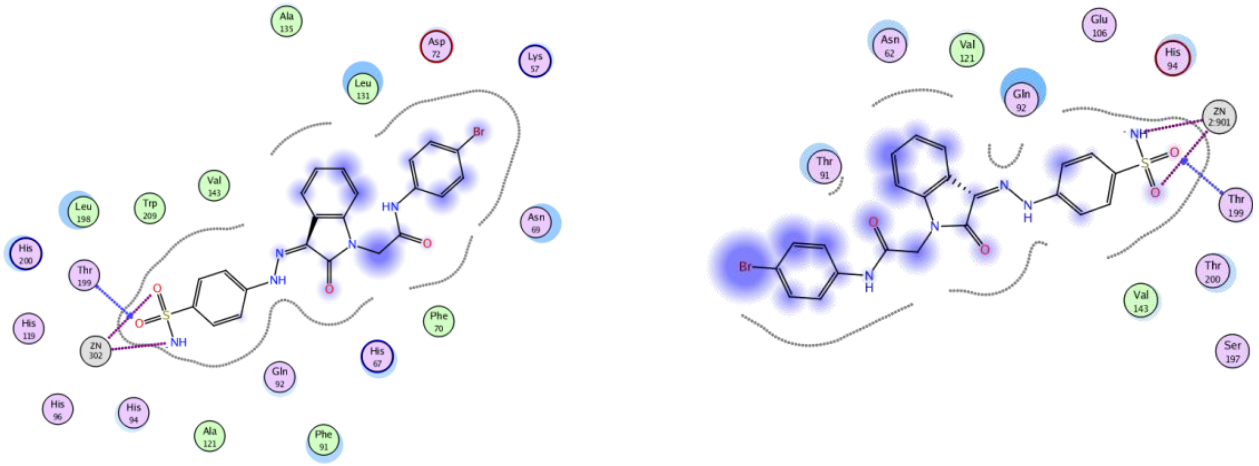


Figure S12. The 2D interactions of **3c** molecular docking data using PDB ID3W6H (a) and PDB ID 1JD0 (b) for CA I and CA XII, respectively.

QSAR study

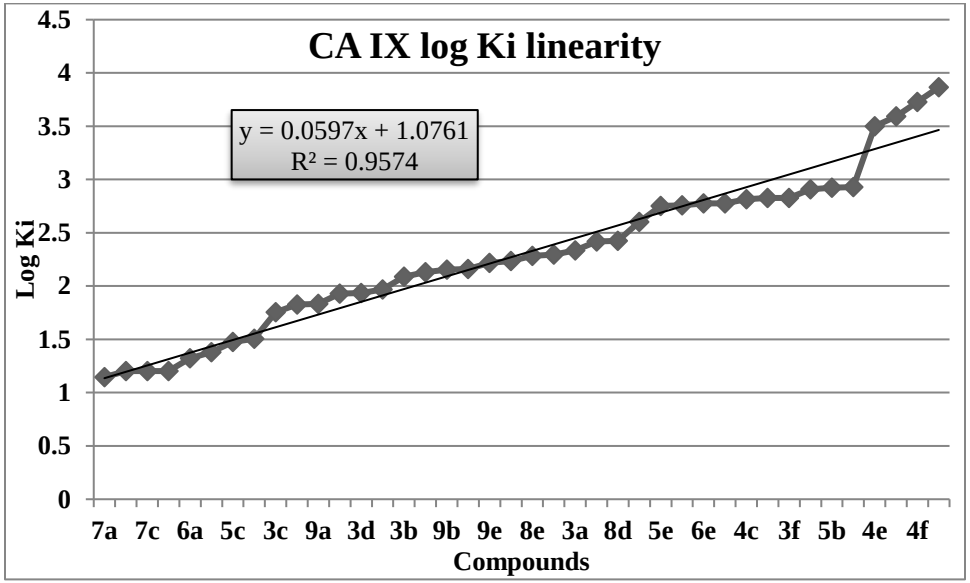


Figure S13. Chart presentation of the linearity of the achieved CA IX Ki value in its Logarithmic form.

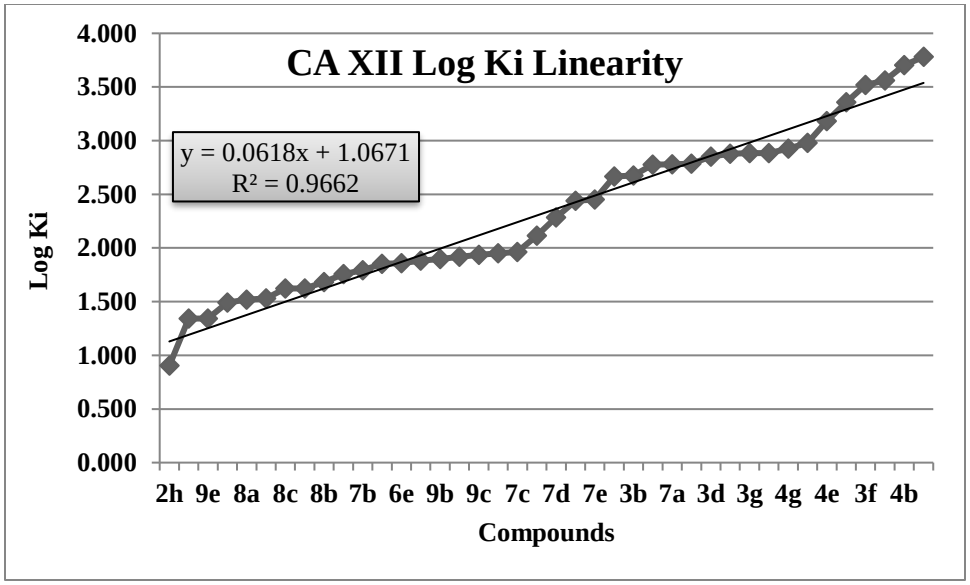


Figure S14. Chart presentation of the linearity of the achieved CA XII Ki value in its Logarithmic form.

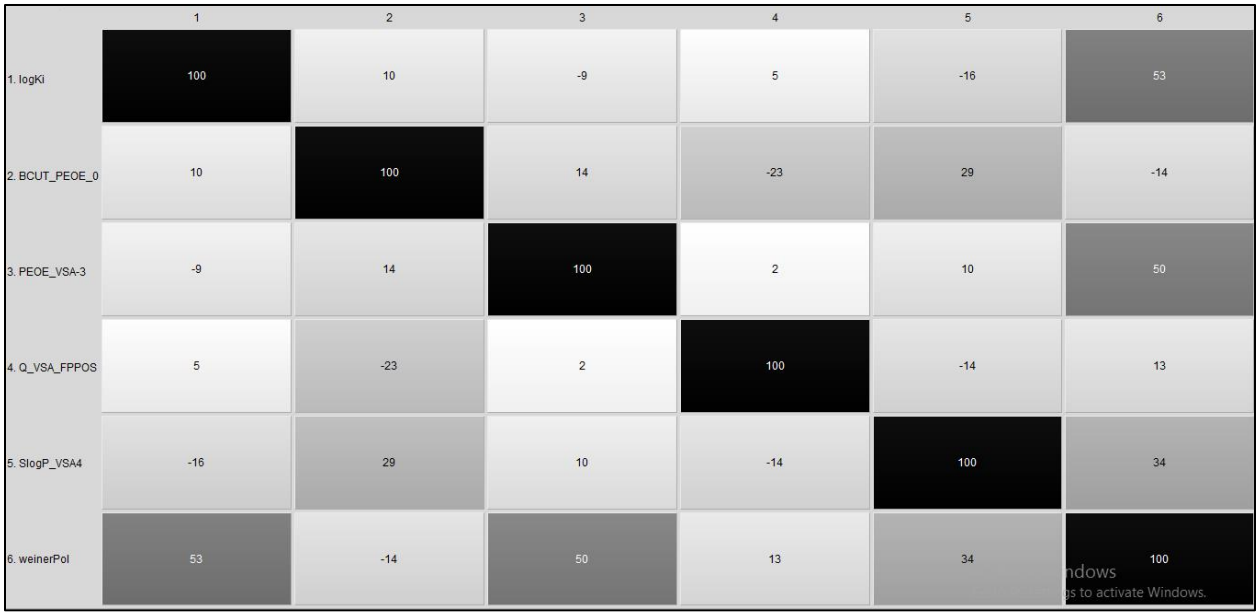


Figure S15. The correlation matrix of the selected descriptors for the 2D QSAR model of CA IX inhibitors.

Figure S16. The correlation matrix of the selected descriptors for the 2D QSAR model of CA XII inhibitors.

Table S1. The calculated 2D descriptors of the training set analogs against *h*CA IX that governed the activity according to equation 1.

Training Set						
Compound	**logK_i**	**BCUT_PEOE_0**	**PEOE_VSA-3**	**Q_VSA_FPPOS**	**SlogP_VSA4**	**weinerPol**
7a	1.146	-2.386	18.465	0.29	3.186	38
6d	1.204	-2.385	22.34	0.2	3.186	40
7c	1.204	-2.461	18.465	0.268	3.186	44
6a	1.322	-2.327	22.34	0.226	3.186	33
5c	1.477	-2.461	9.044	0.193	3.186	38
7b	1.505	-2.386	18.465	0.308	3.186	42
3c	1.756	-2.388	22.34	0.2	3.186	52
2h	1.826	-2.389	9.044	0.256	27.048	40
9a	1.833	-2.386	18.465	0.233	30.233	55
3d	1.935	-2.393	22.34	0.206	6.371	52
9c	1.968	-2.386	18.465	0.224	30.233	57
3b	2.09	-2.388	22.34	0.206	3.186	52
5a	2.13	-2.319	9.044	0.207	3.186	32
9b	2.155	-2.386	18.465	0.231	30.233	57
9e	2.217	-2.386	18.465	0.27	30.233	59
8b	2.236	-2.327	22.34	0.175	30.233	52
8e	2.283	-2.327	22.34	0.223	30.233	54
9d	2.294	-2.386	18.465	0.218	30.233	57
3a	2.334	-2.388	22.34	0.214	3.186	50
8d	2.423	-2.327	22.34	0.165	30.233	52
3g	2.603	-2.386	22.34	0.2	3.186	53
5e	2.752	-2.403	9.044	0.165	6.371	45
4d	2.759	-2.394	18.465	0.252	6.371	57
4c	2.816	-2.39	18.465	0.246	3.1860	57

5d	2.828	-2.385	9.044	0.183	3.1860	39
3f	2.828	-2.386	22.34	0.206	3.1860	53
4a	2.907	-2.39	18.465	0.261	3.1860	55
5b	2.923	-2.332	9.044	0.238	3.1860	36
4e	3.498	-2.391	18.465	0.294	3.1860	59
4b	3.594	-2.39	18.465	0.252	3.1860	57
4f	3.729	-2.389	18.465	0.252	3.1860	58
4g	3.865	-2.389	18.465	0.246	3.1860	58

*Compounds **6c** and **7e** were excluded as statistical outliers with *Z*-score exceeded 2.4.

Table S2. The calculated 2D descriptors of the training set analogs against *h*CA XII that governed the activity according to equation 2.

Training set					
Compd.	**Log K_i**	**PEOE_VSA_FHYD**	**PEOE_VSA_FPPOS**	**Q_PC+**	**SlogP_VSA1**
2h	0.903	0.658	0.118	6.221	82.388
9a	1.342	0.73	0.097	7.933	84.716
9e	1.342	0.743	0.09	8.145	84.716
8e	1.491	0.781	0.072	6.776	79.334
8a	1.519	0.769	0.078	6.564	79.334
8c	1.623	0.779	0.074	6.591	79.334
5e	1.623	0.813	0.047	6.057	56.187
8b	1.681	0.741	0.077	6.604	79.334
6b	1.756	0.799	0.055	5.484	74.075
7b	1.792	0.747	0.082	6.853	79.457

5c	1.881	0.781	0.055	5.163	56.187
9b	1.898	0.706	0.096	7.973	84.716
5a	1.919	0.744	0.064	5.233	74.198
9c	1.934	0.74	0.093	7.96	84.716
7c	1.964	0.758	0.078	6.853	79.457
9d	2.114	0.747	0.091	7.894	84.716
7d	2.283	0.768	0.075	7.441	79.457
6a	2.439	0.779	0.06	5.554	92.086
7e	2.452	0.788	0.069	7.747	79.457
3b	2.676	0.797	0.068	7.378	97.345
3e	2.777	0.798	0.066	7.563	97.345
7a	2.78	0.726	0.088	6.923	97.468
3c	2.787	0.802	0.067	7.312	97.345
3d	2.851	0.796	0.069	7.345	97.345
3g	2.884	0.802	0.067	7.312	97.345
4a	2.884	0.75	0.09	8.72	102.726
4g	2.926	0.764	0.085	8.681	102.726
6d	2.98	0.818	0.05	6.072	74.075
4e	3.182	0.76	0.084	8.932	102.726
3f	3.518	0.797	0.068	7.378	97.345
3a	3.562	0.788	0.071	7.351	97.345
4b	3.703	0.758	0.087	8.747	102.726
4d	3.78	0.758	0.087	8.714	102.726

*Compound **6e** was excluded as statistical outlier with *Z*-score exceeded 2.4.

^{1}H NMR and ^{13}C spectra for the new synthesized compounds

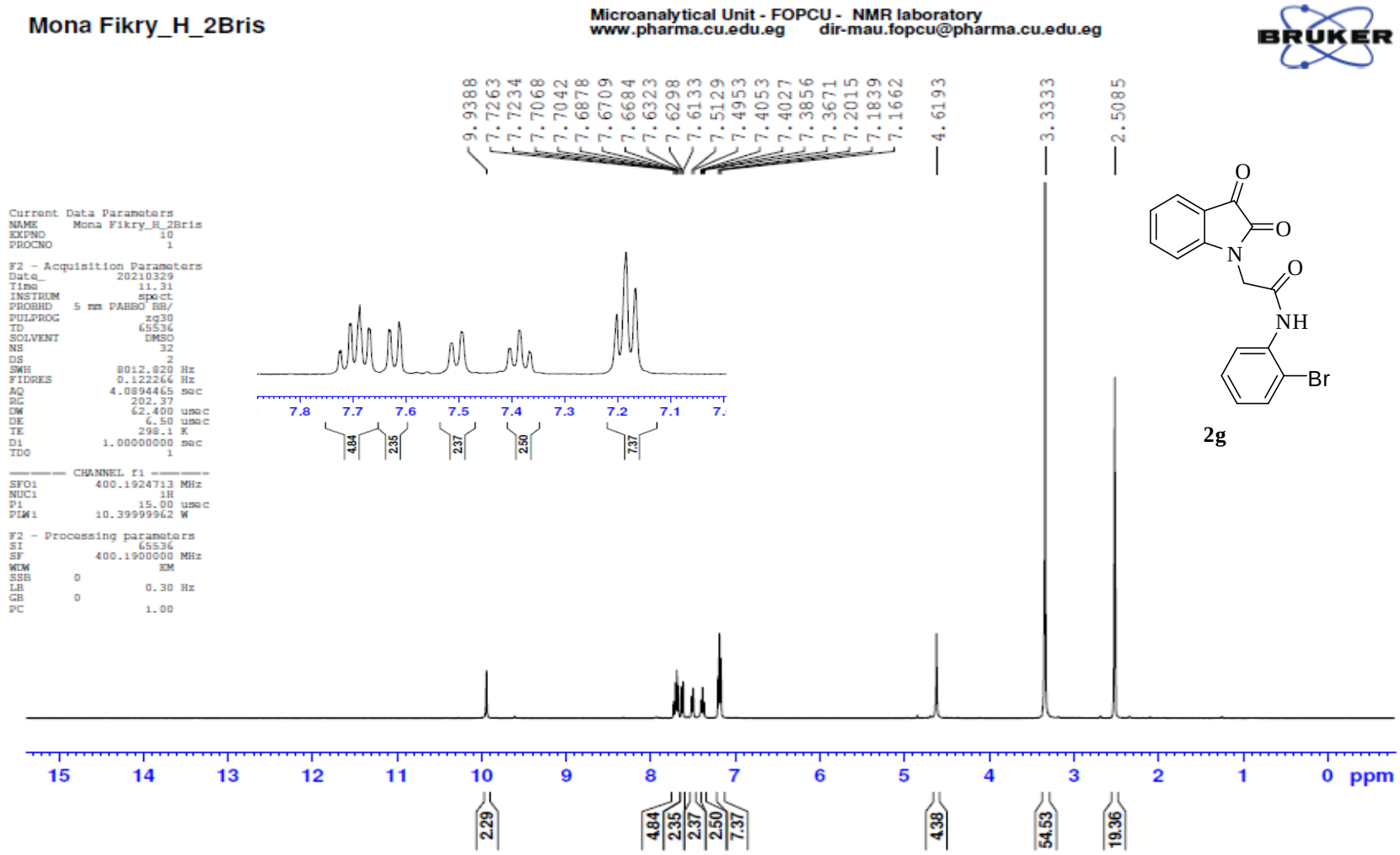


Figure S17. ^{1}H NMR of compound **2g.**

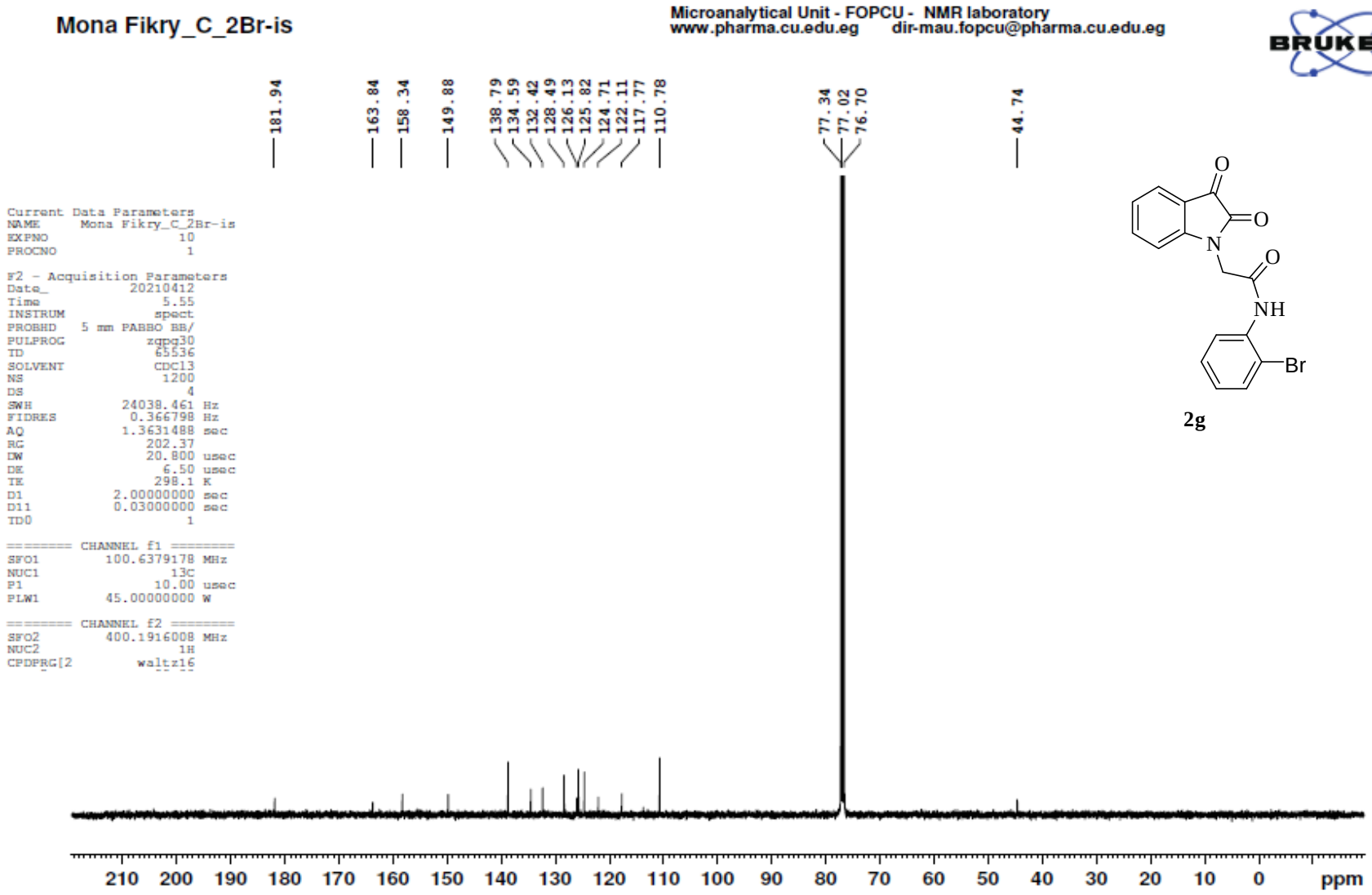


Figure S18. ^{13}C NMR of compound **2g.**

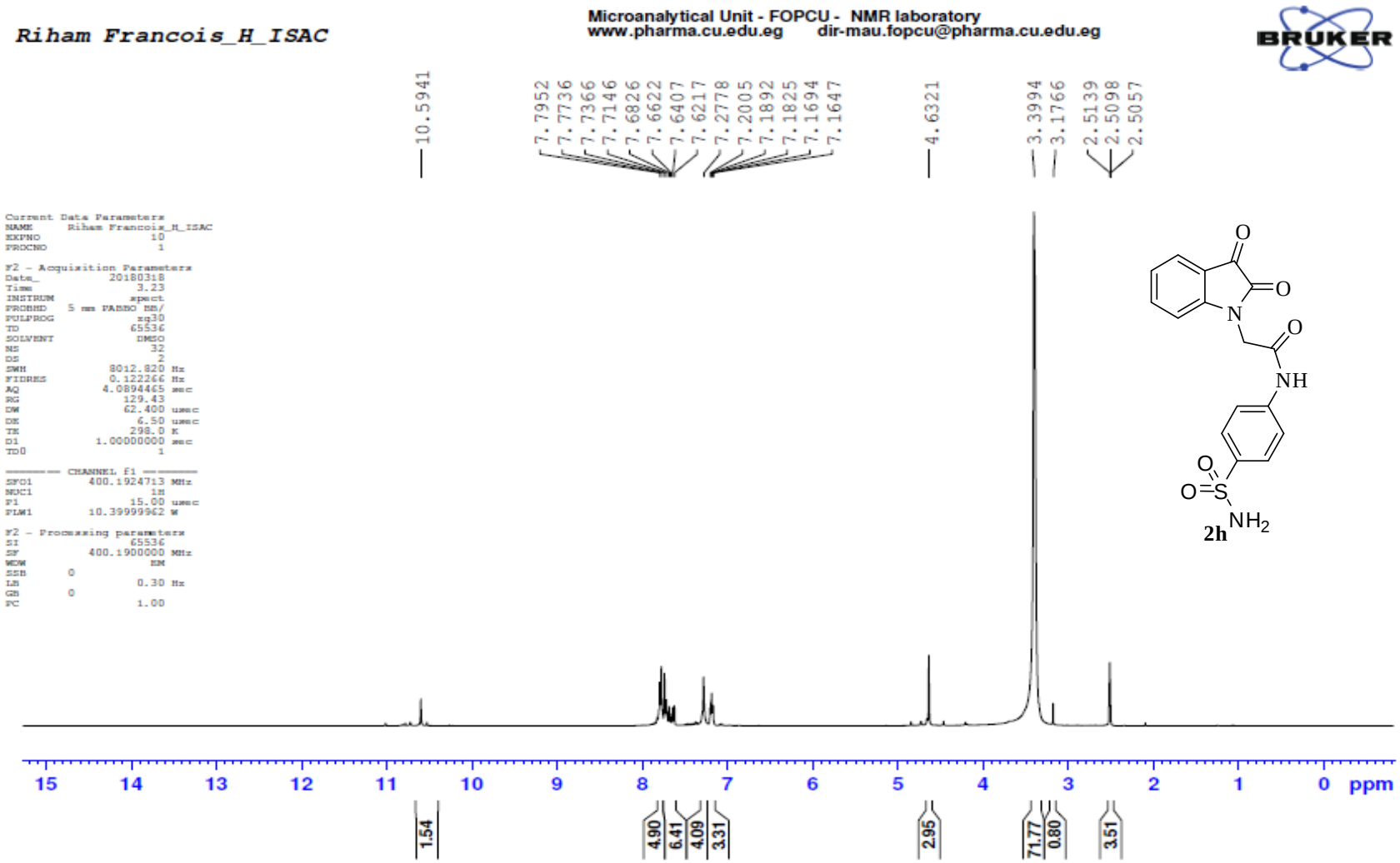


Figure S19. ^{1}H NMR of compound **2h.**

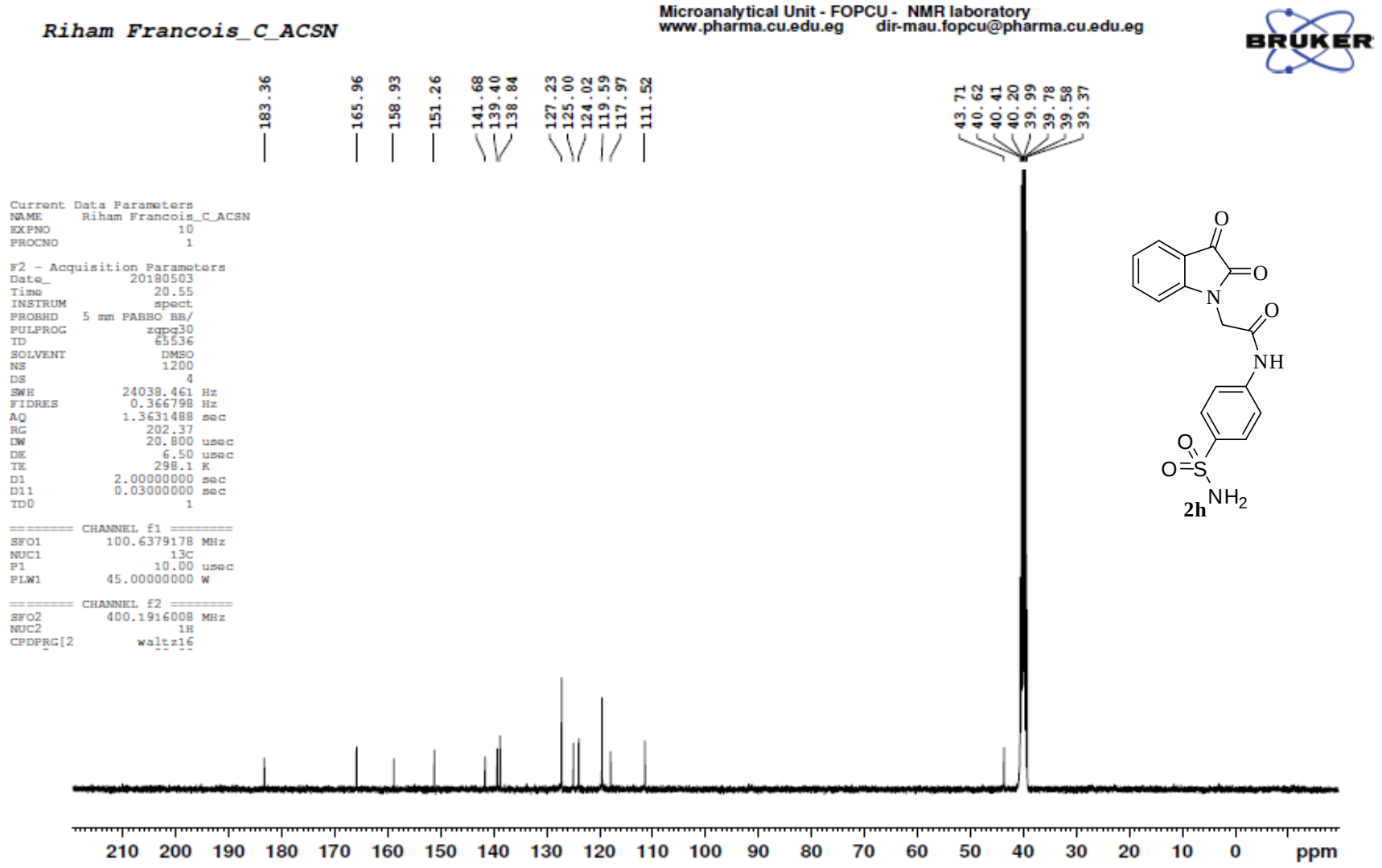


Figure S20. ^{13}C NMR of compound **2h.**

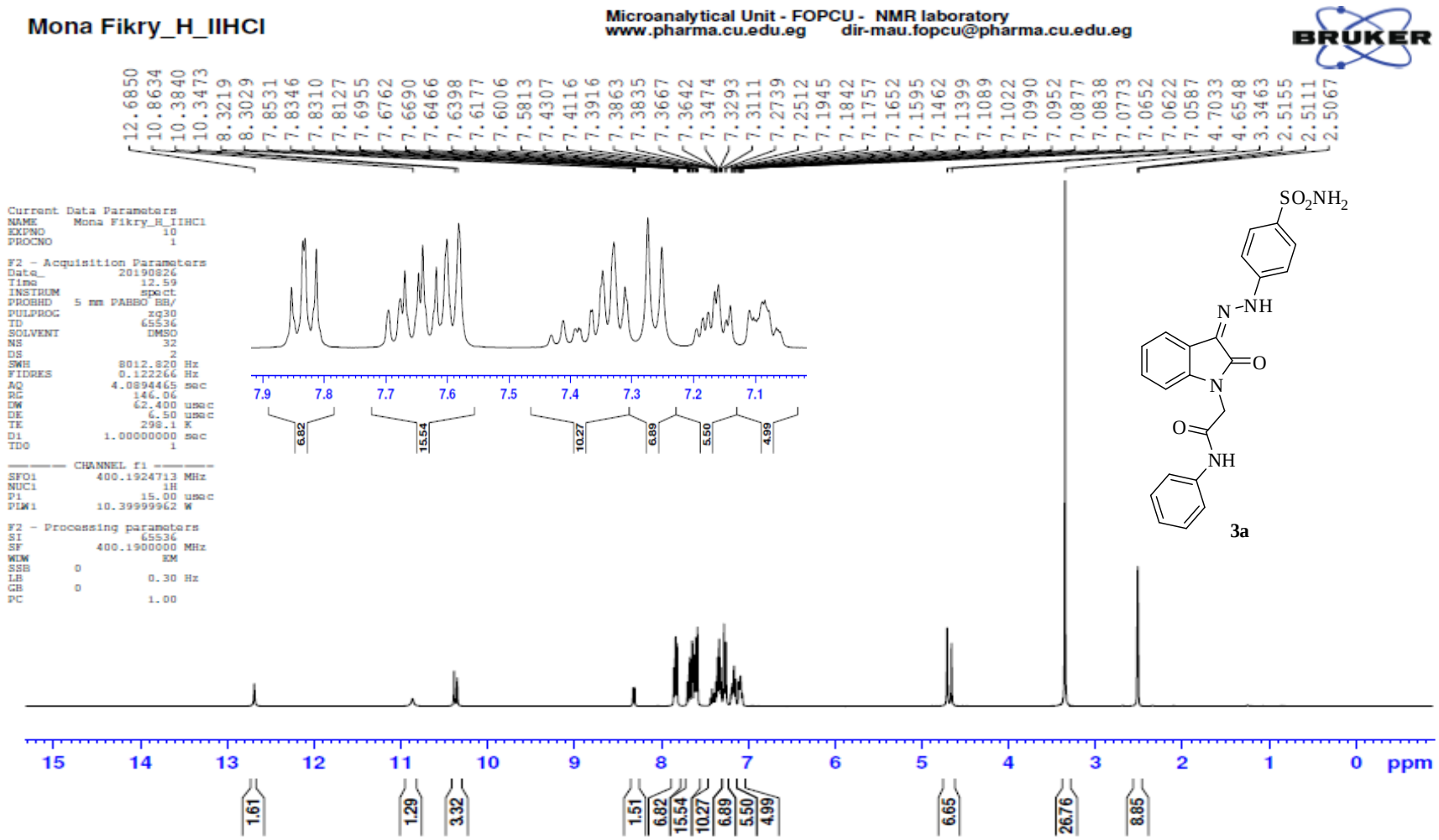


Figure S21. ^{1}H NMR of compound **3a.**

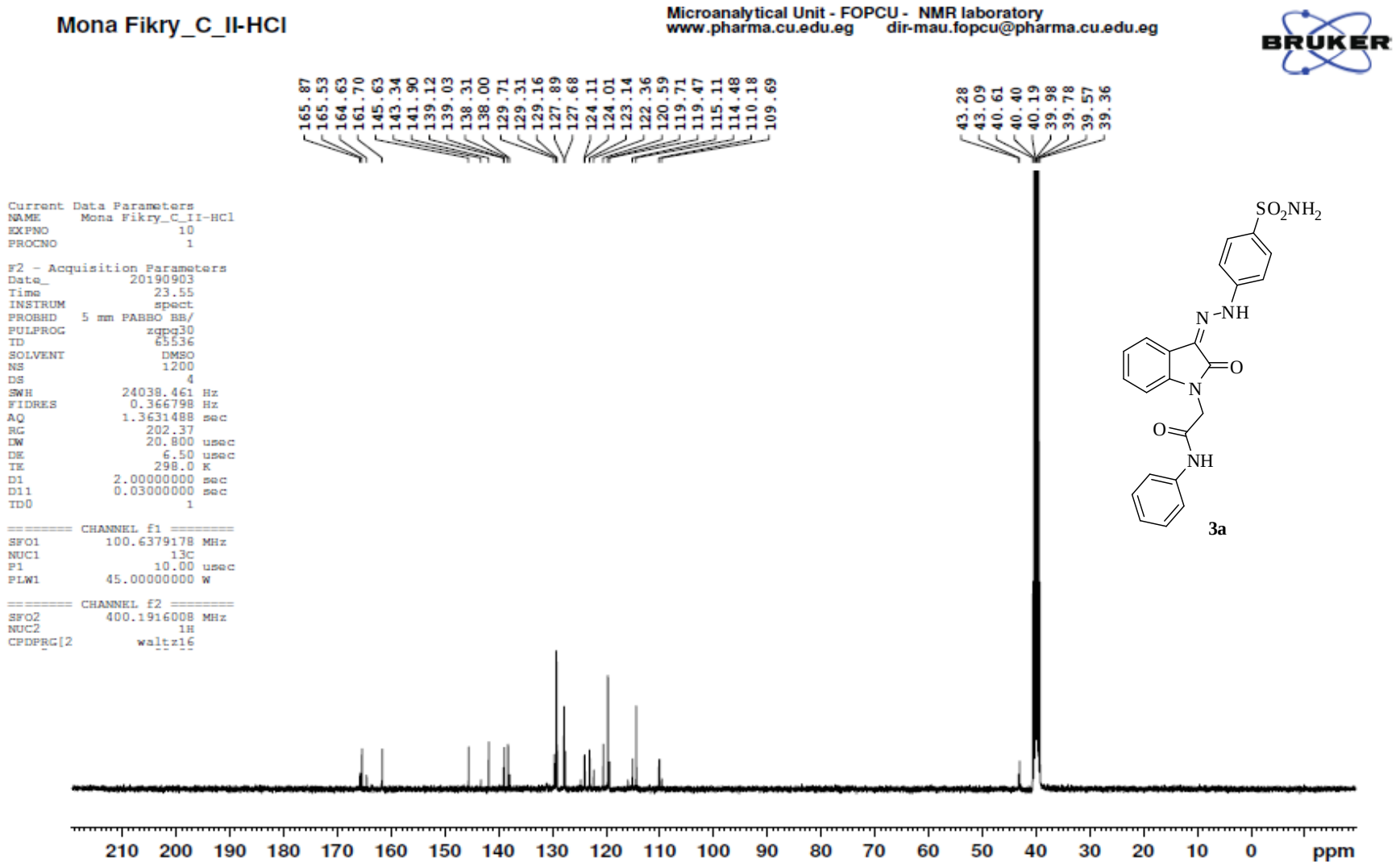


Figure S22. ^{13}C NMR of compound **3a.**

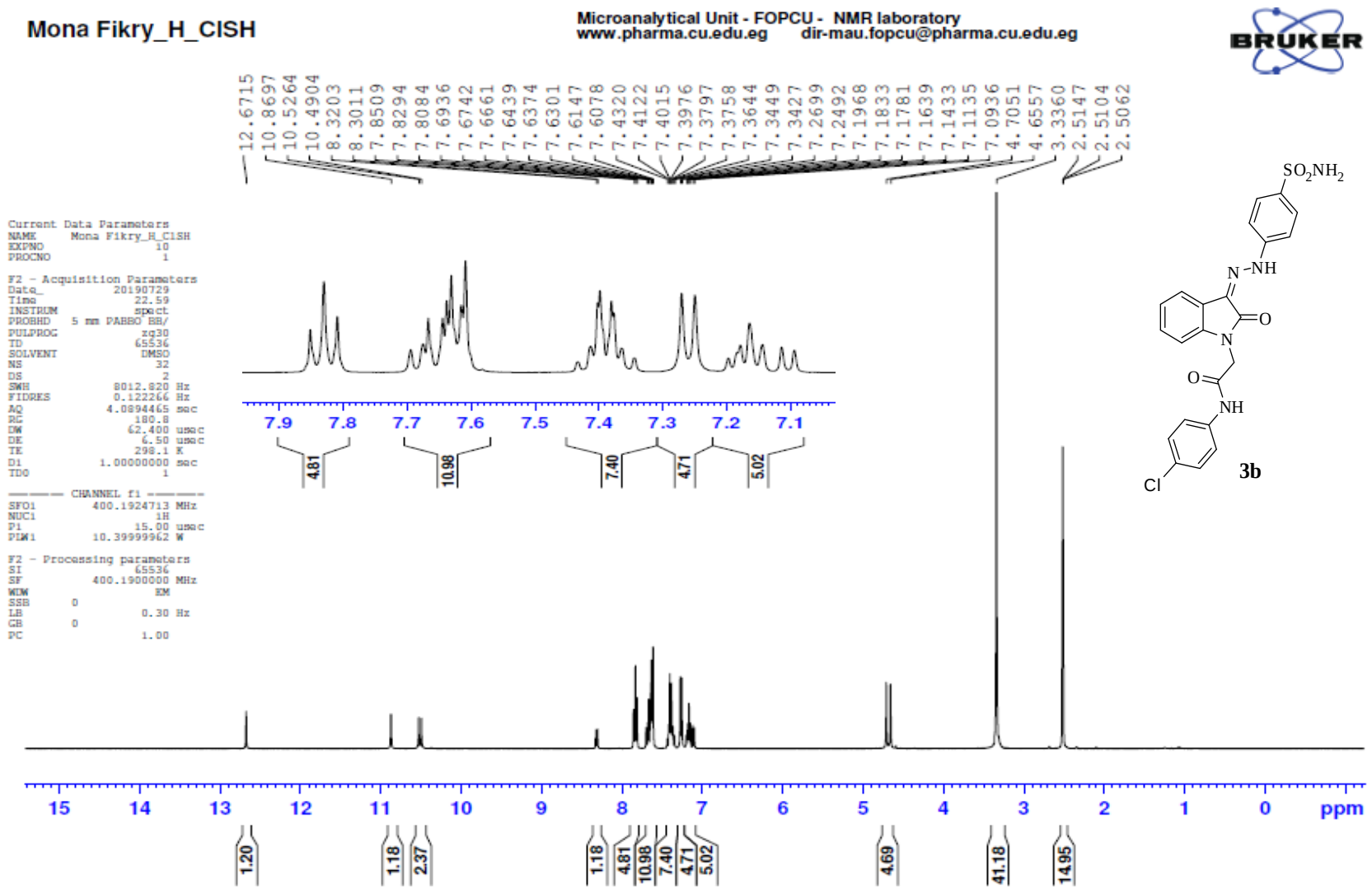


Figure S23. ^{1}H NMR of compound **3b.**

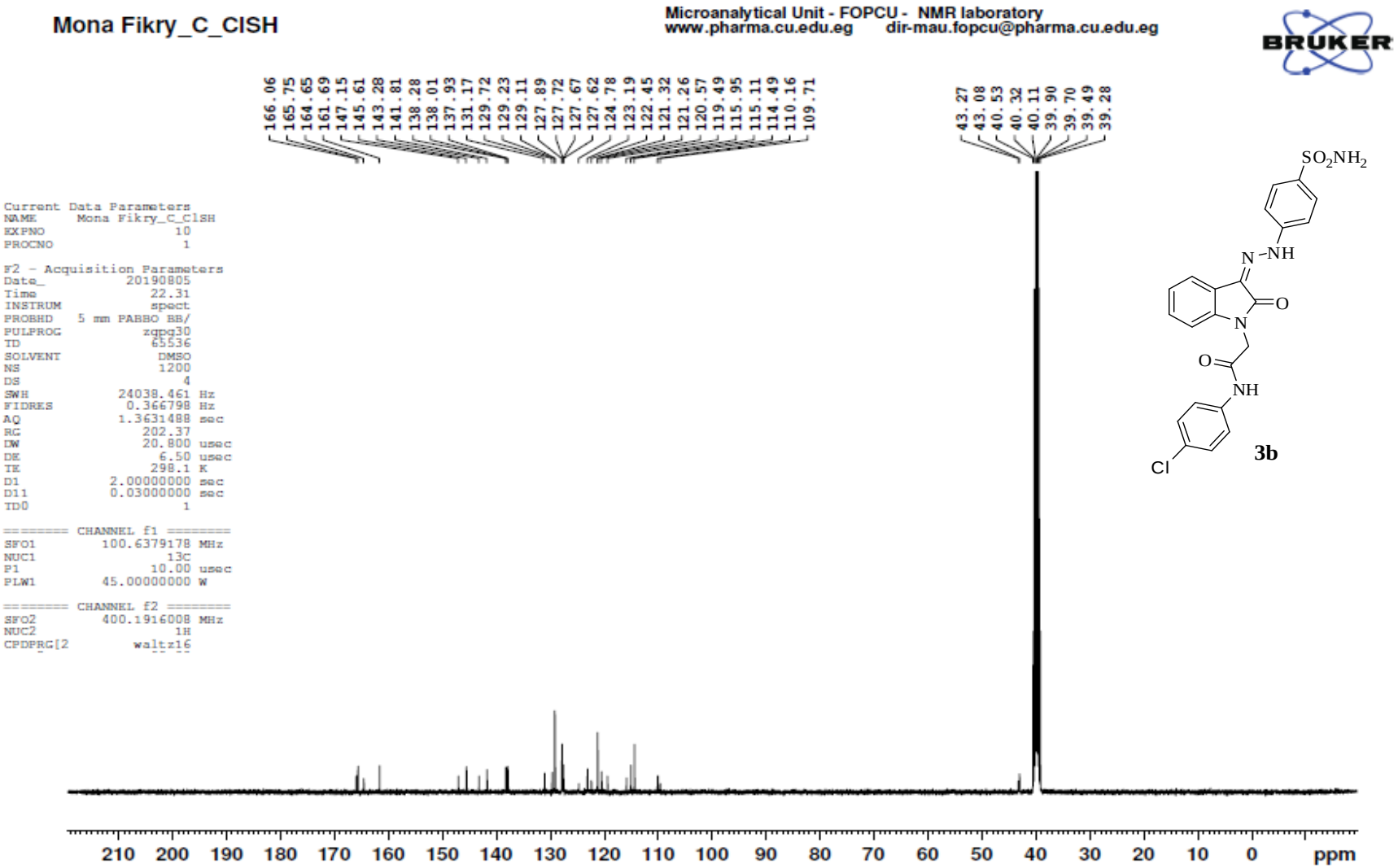


Figure S24. ^{13}C NMR of compound **3b.**

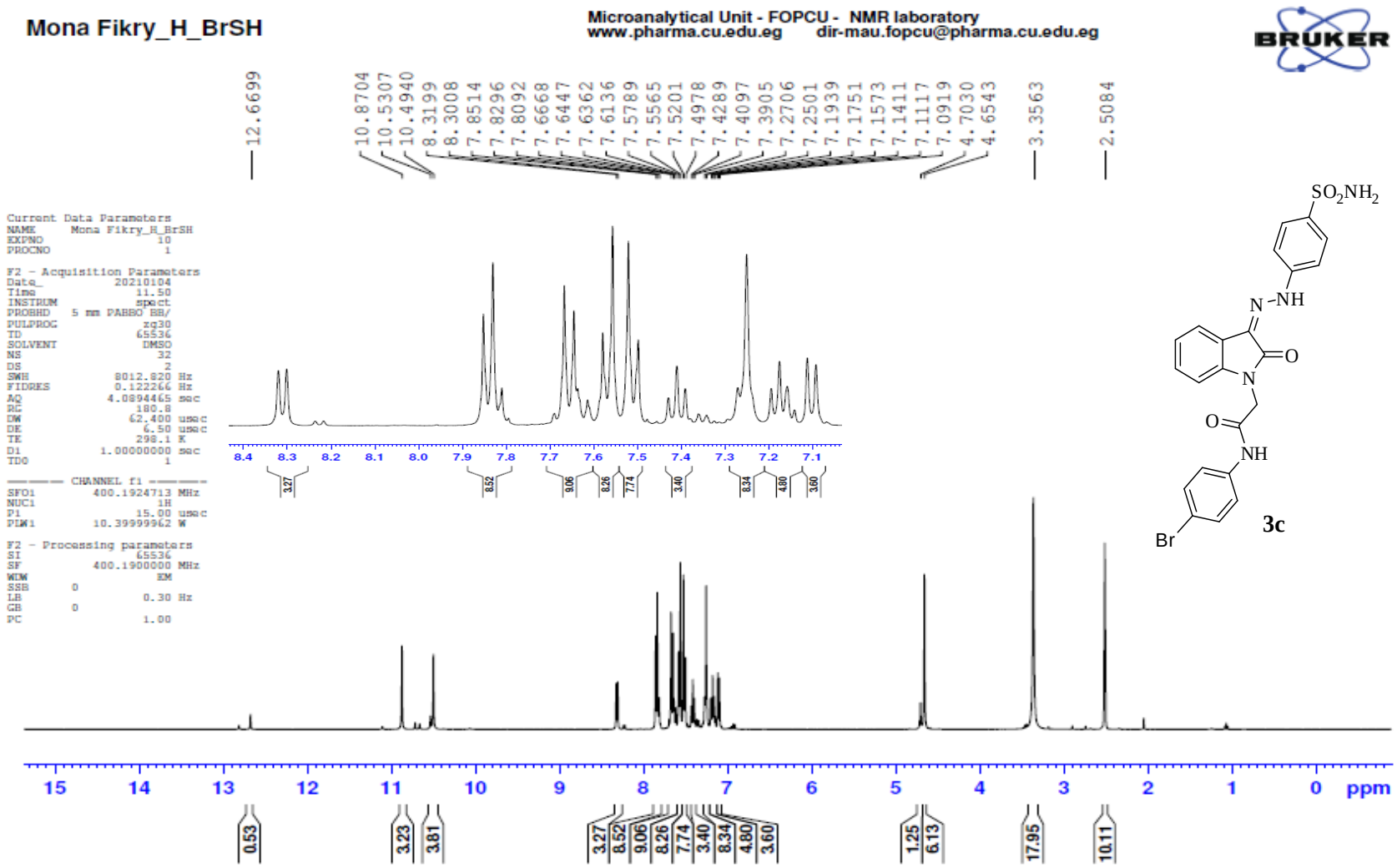


Figure S25. ^{1}H NMR of compound **3c.**

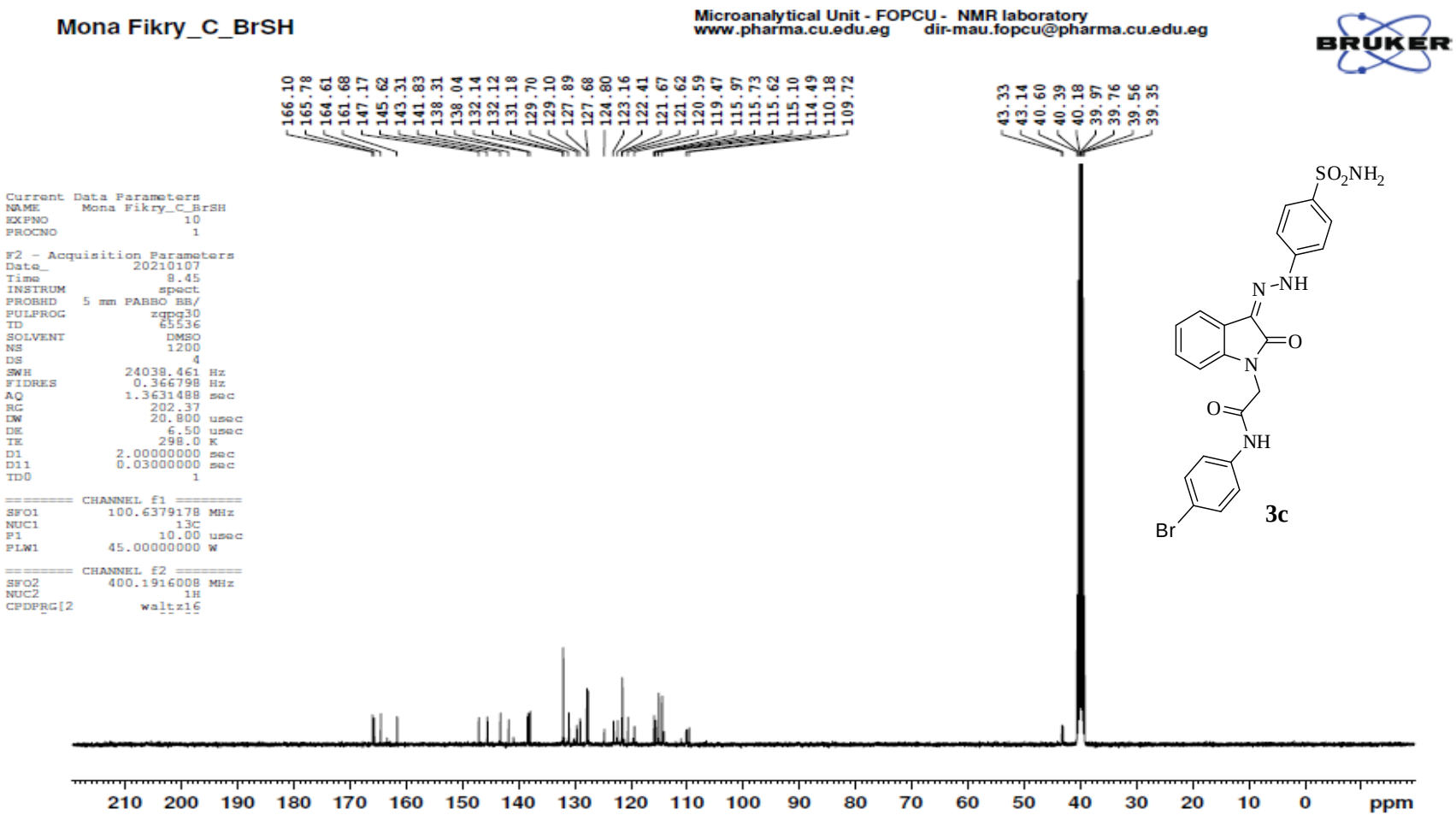


Figure S26. ^{13}C NMR of compound **3c.**

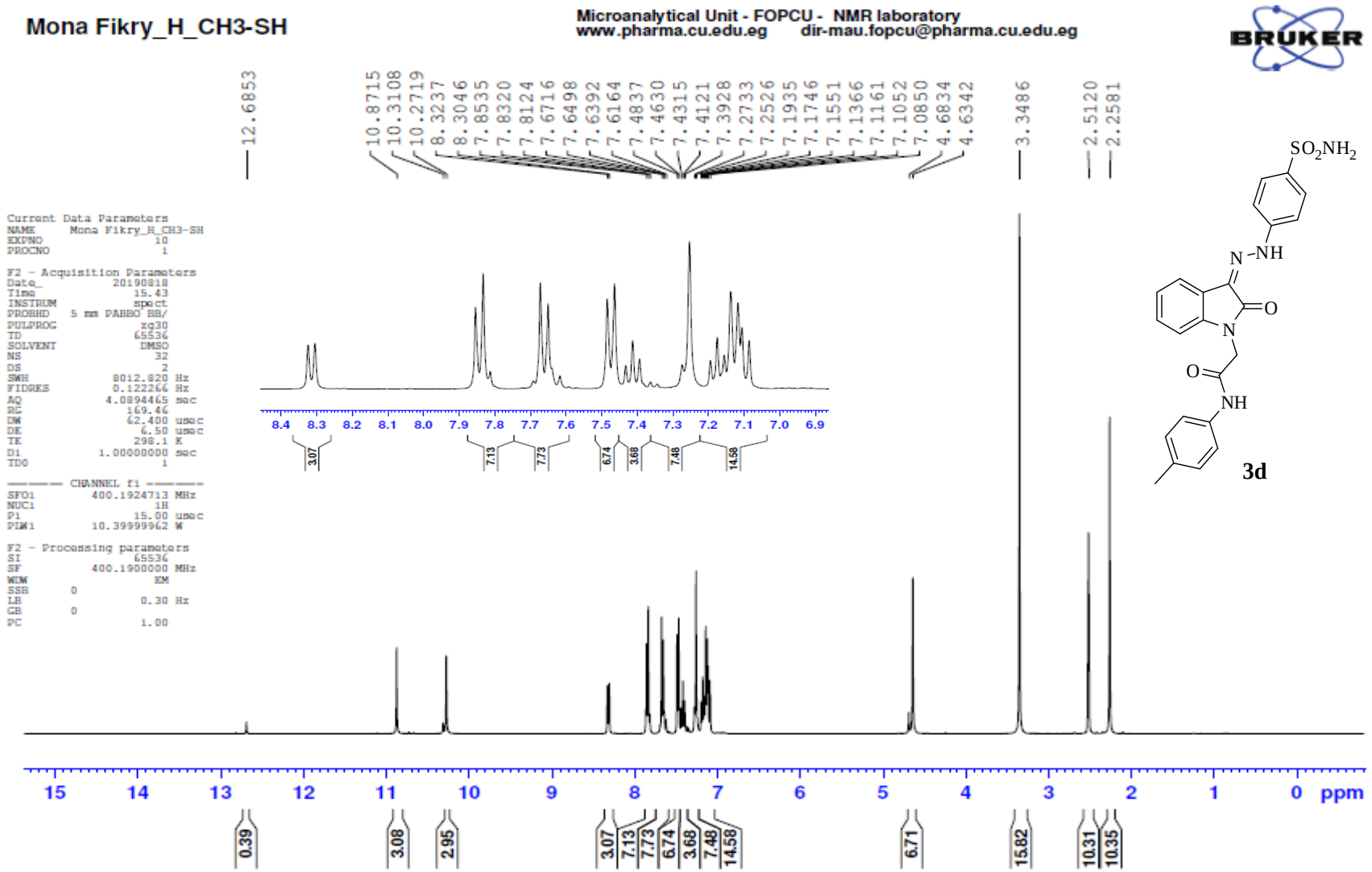


Figure S27. ^{1}H NMR of compound **3d.**

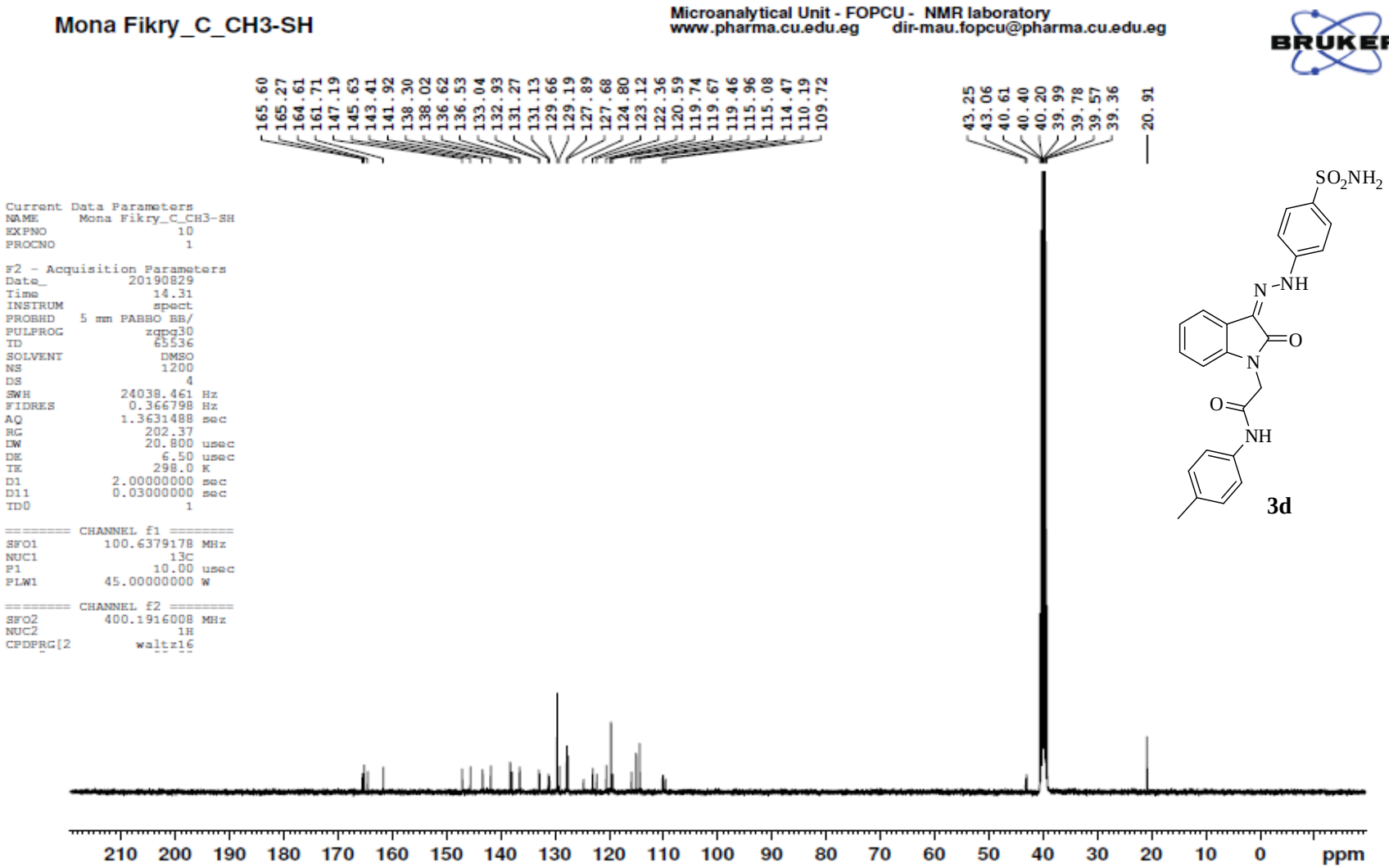


Figure S28. ^{13}C NMR of compound **3d.**

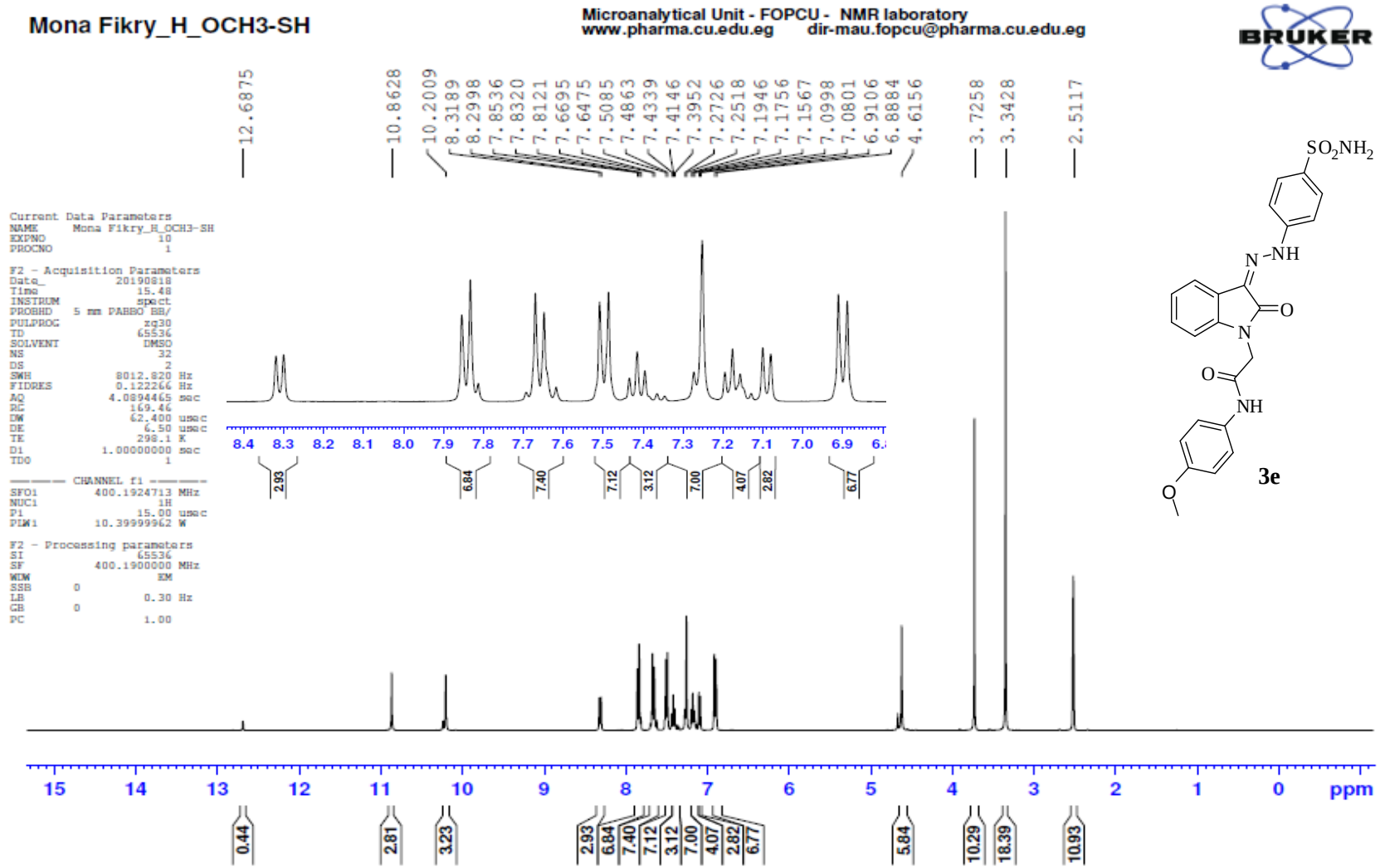


Figure S29. ^{1}H NMR of compound **3e.**

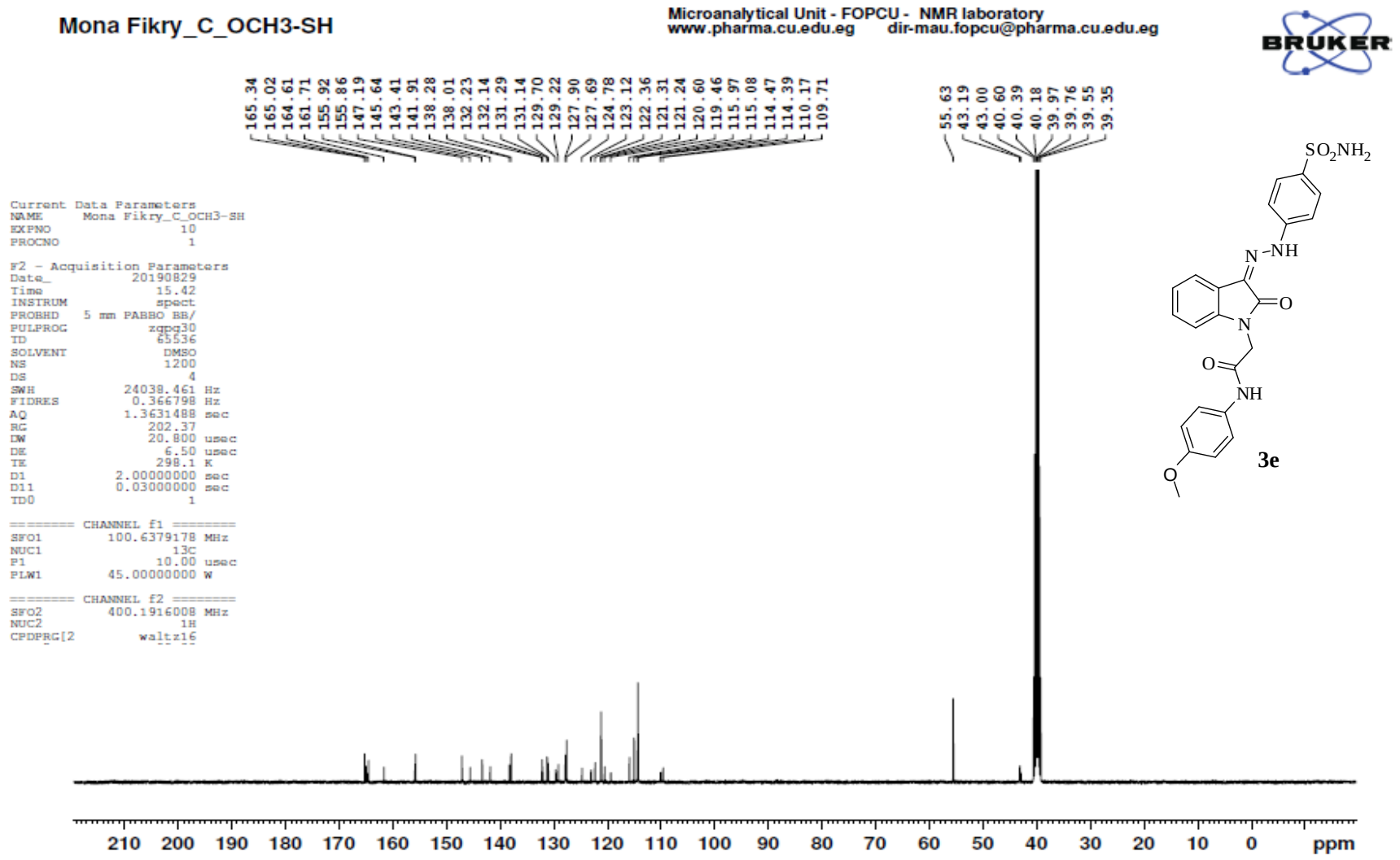
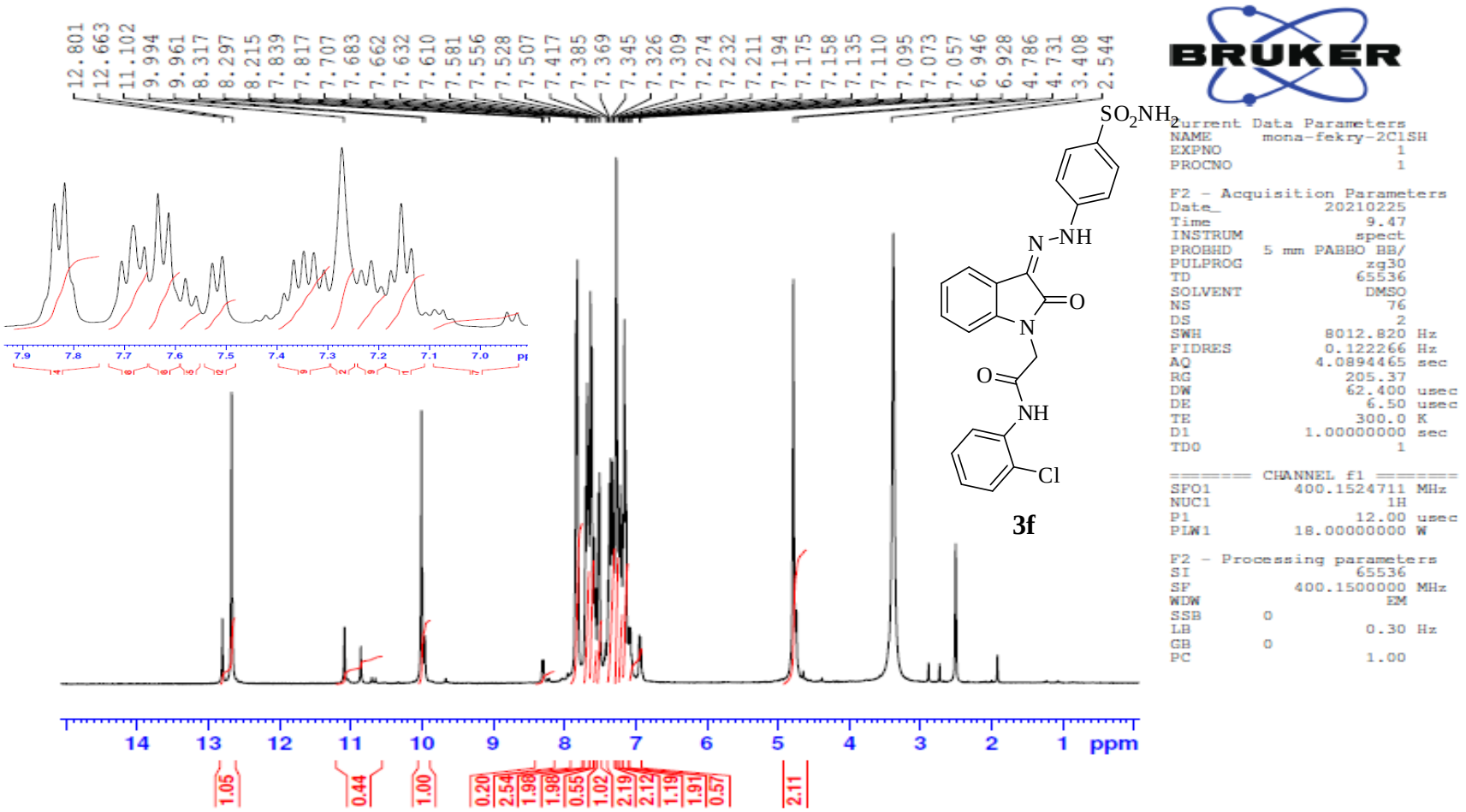


Figure S30. ^{13}C NMR of compound **3e.**

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Current Data Parameters
NAME      mona-fekry-2ClSH
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20210225
Time                9.47
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    76
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                205.37
DW                62.400 usec
DE                 6.50 usec
TE                300.0 K
D1             1.00000000 sec
TD0                    1

====== CHANNEL f1 ======
SFO1         400.1524711 MHz
NUC1               1H
P1                12.00 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.1500000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

Figure S31. ^{1}H NMR of compound **3f.**

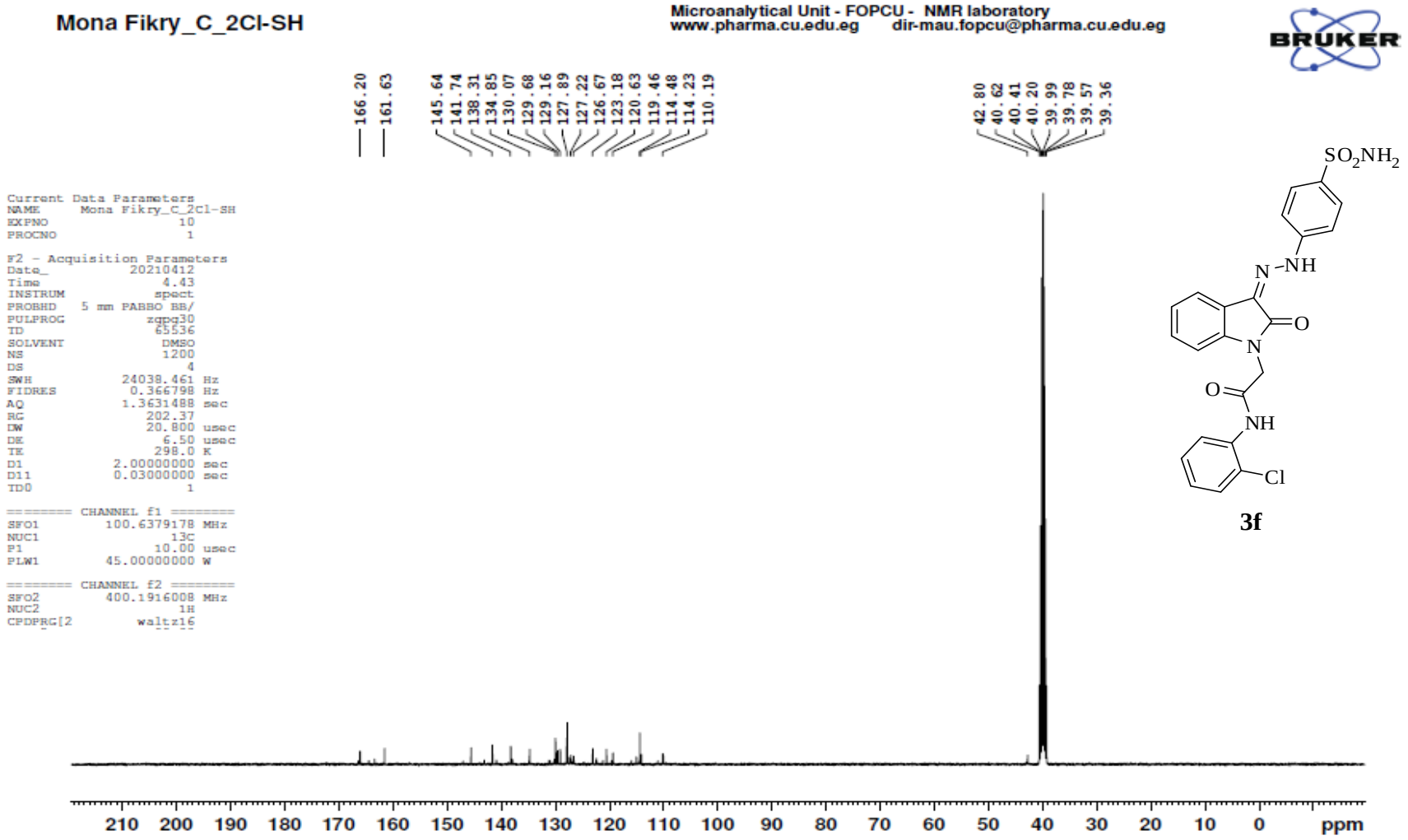

Figure S32. ^{13}C NMR of compound **3f.**

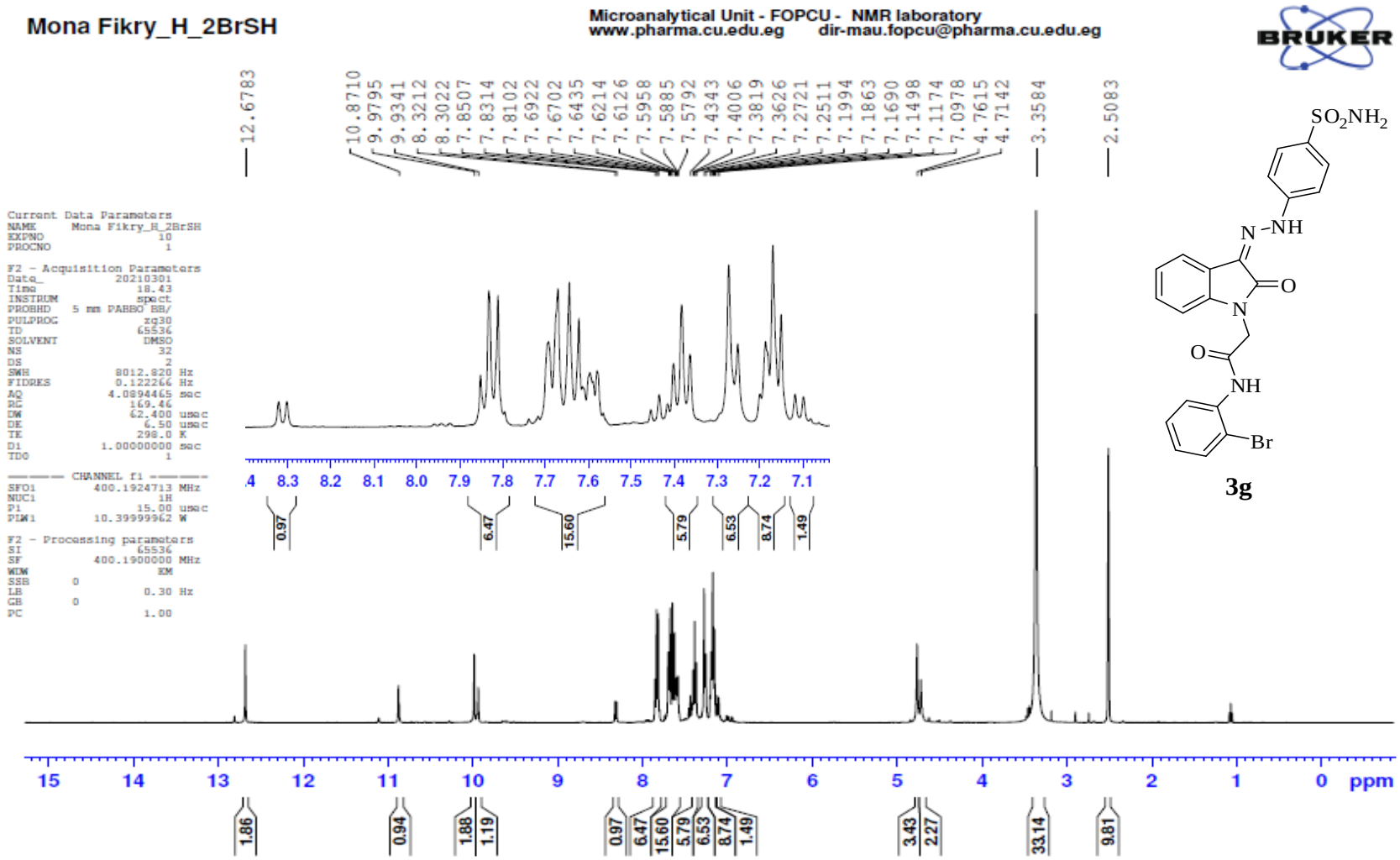

Figure S33. ^{1}H NMR of compound **3g.**

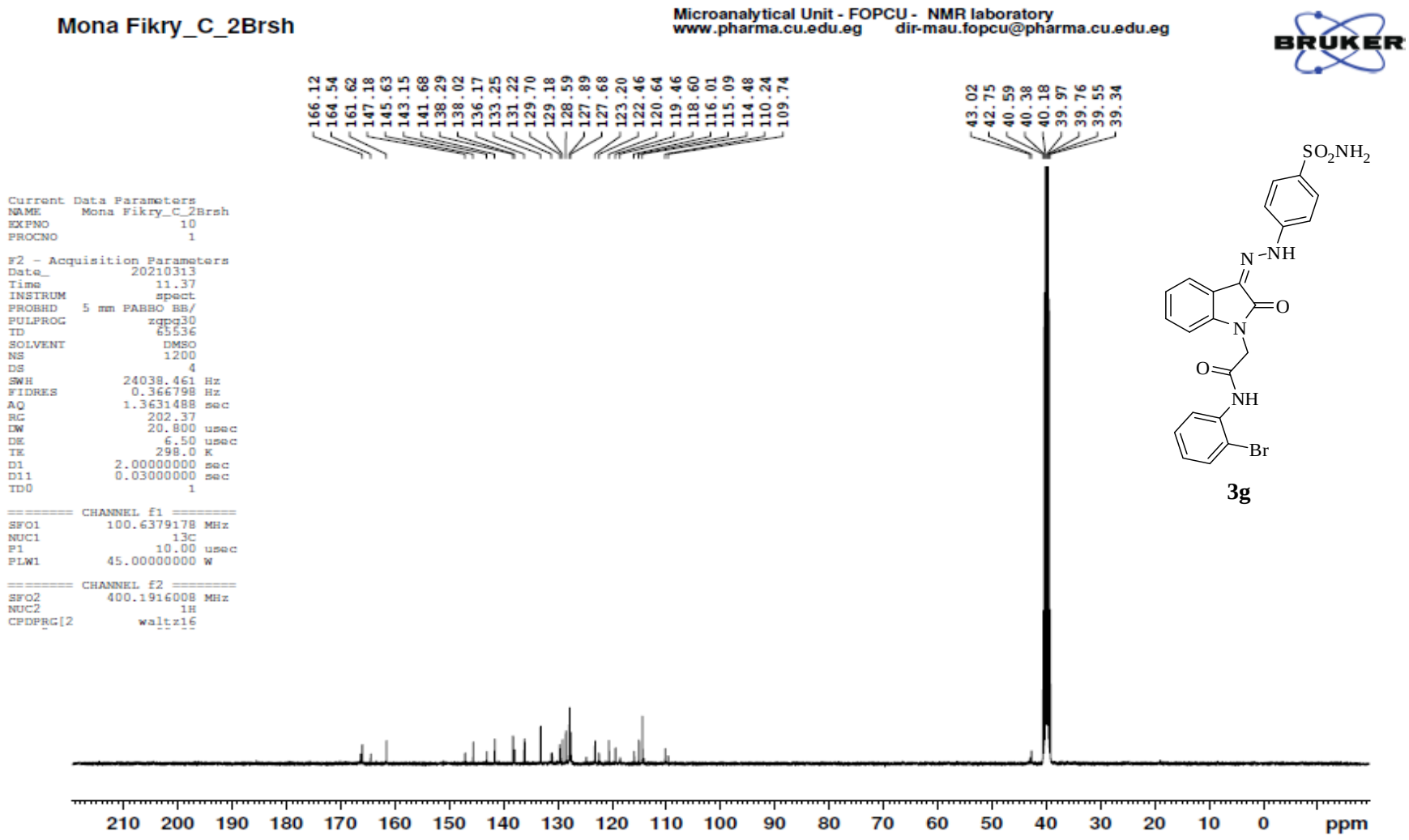

Figure S34. ^{13}C NMR of compound **3g.**

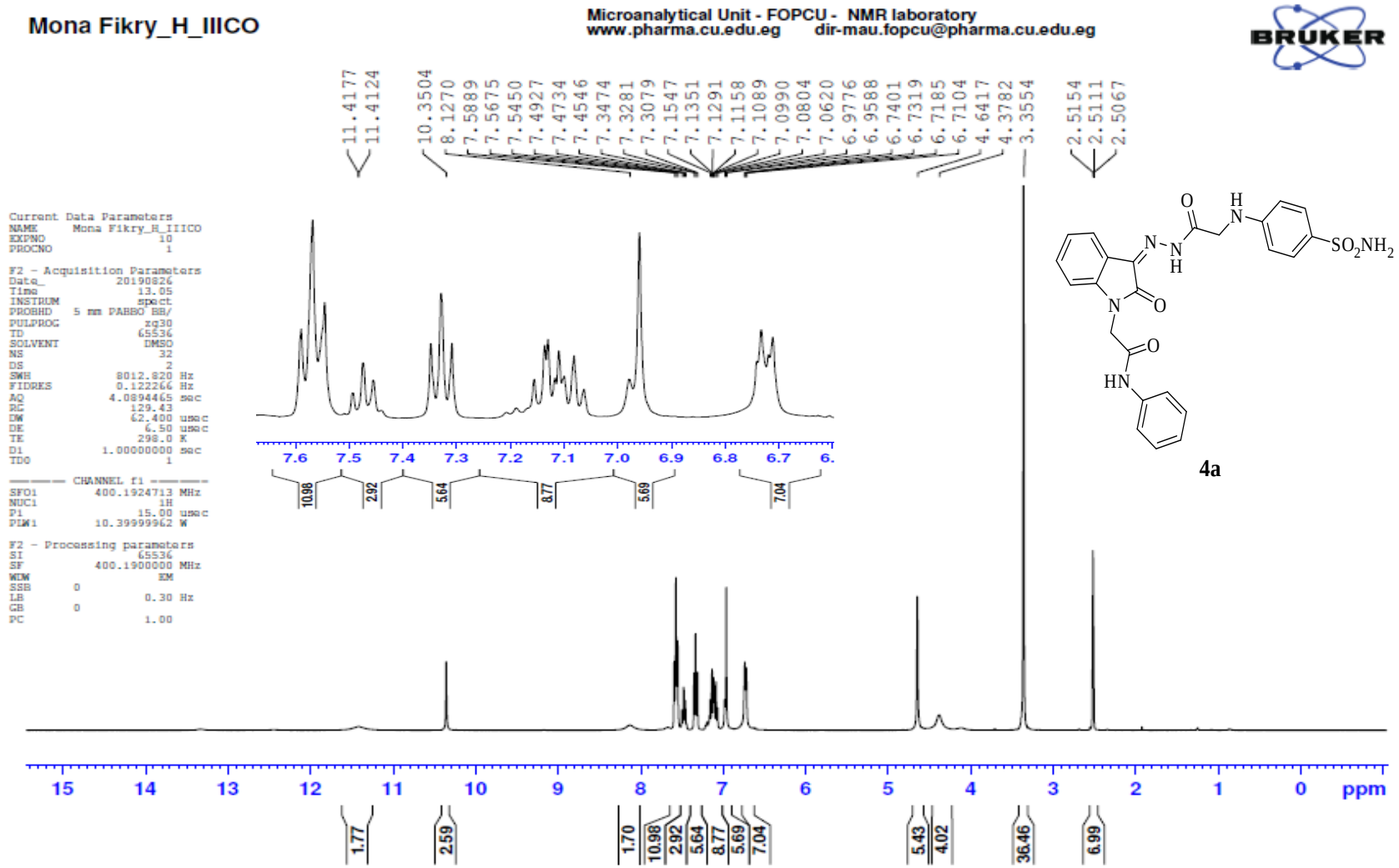

Figure S35. ^{1}H NMR of compound **4a.**

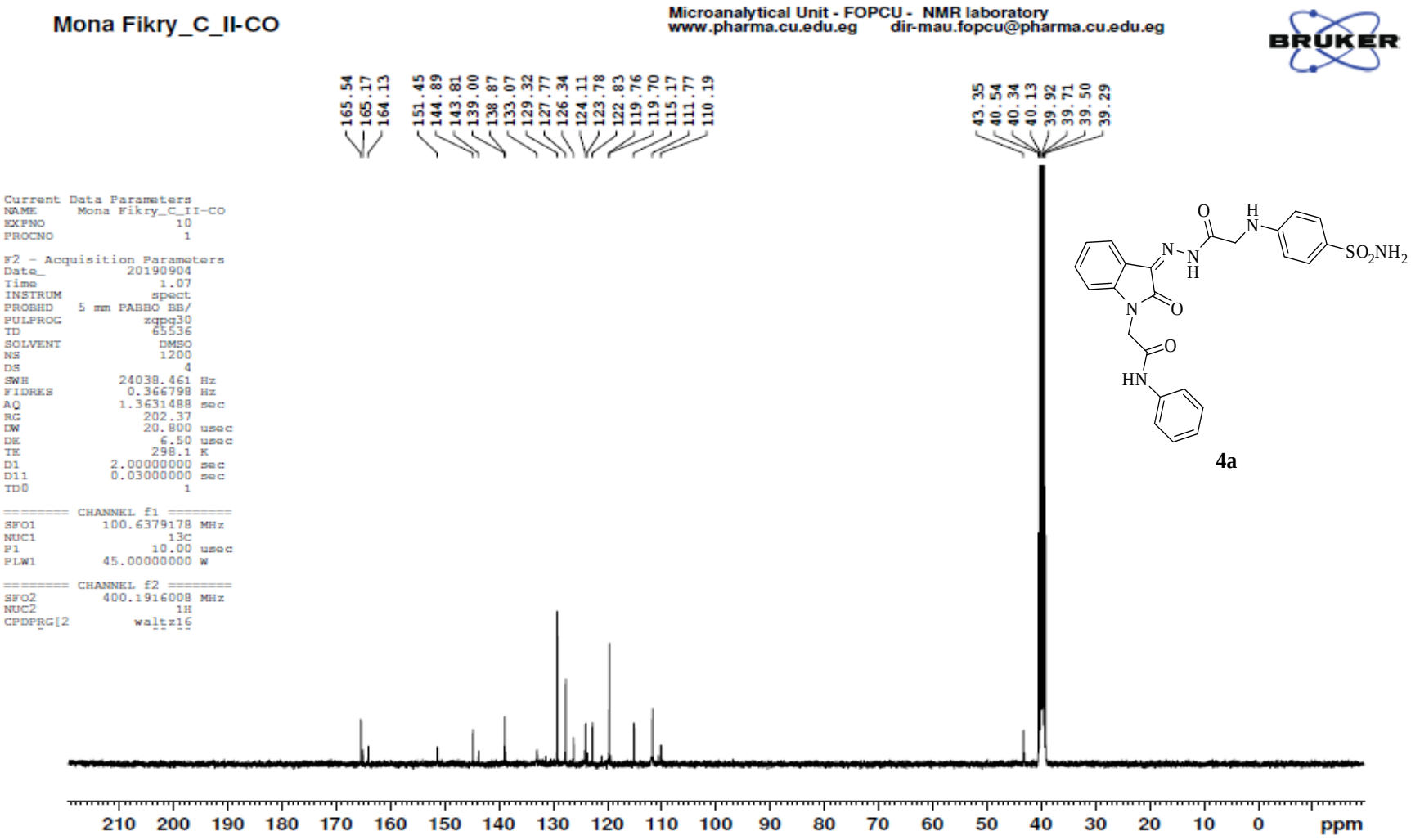

Figure S36. ^{13}C NMR of compound **4a.**

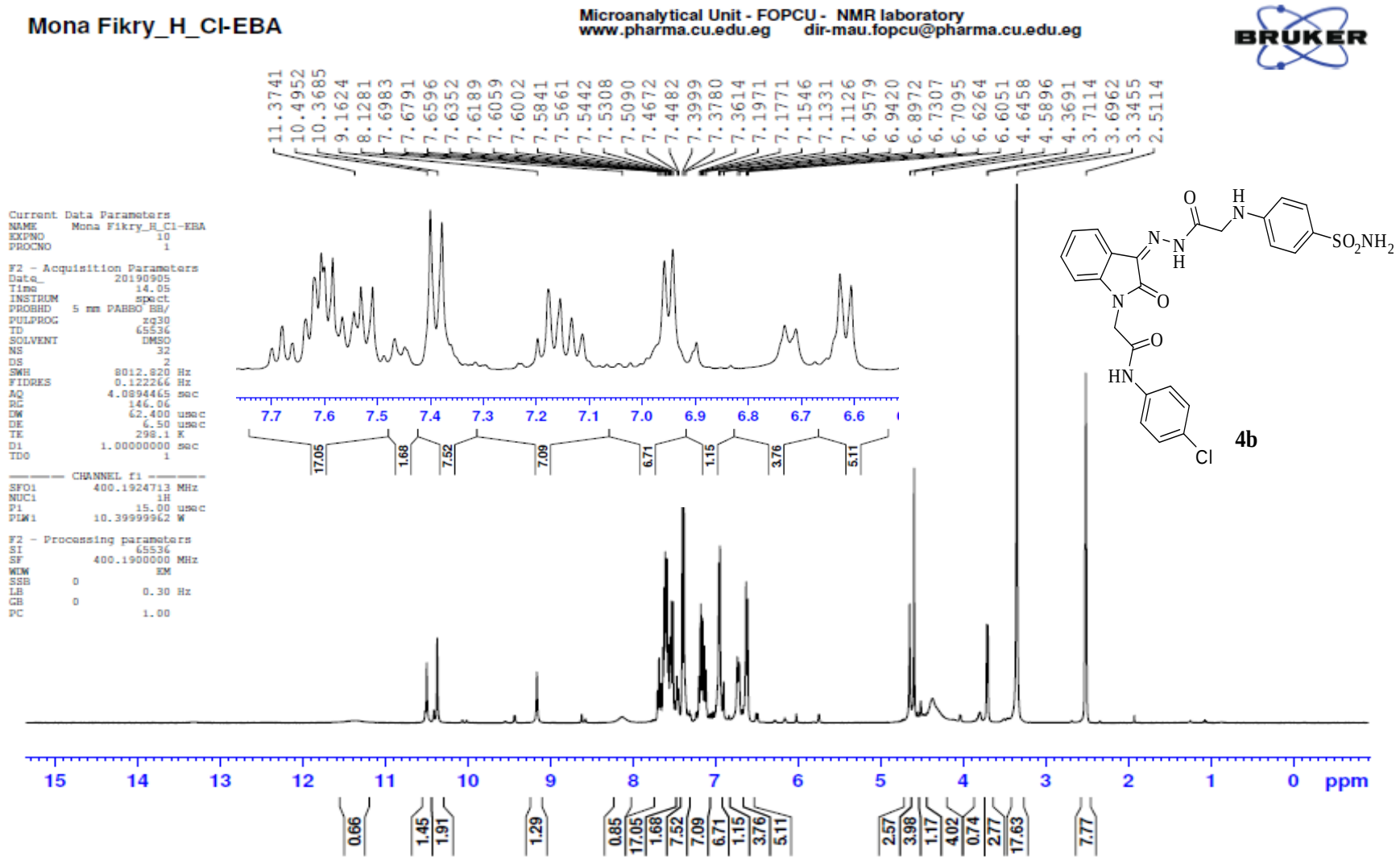

Figure S37. ^{1}H NMR of compound **4b.**

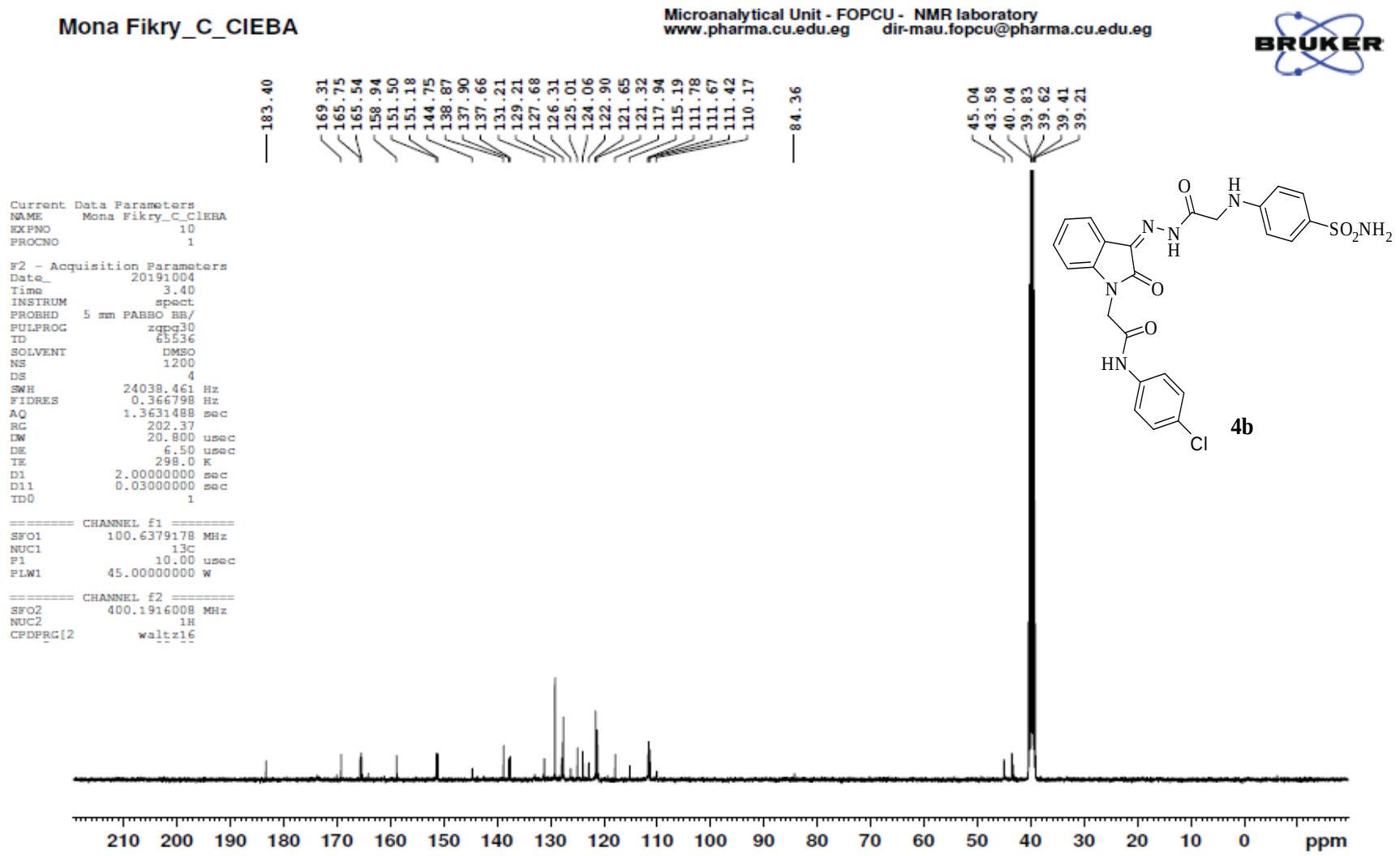

Figure S38. ^{13}C NMR of compound **4b.**

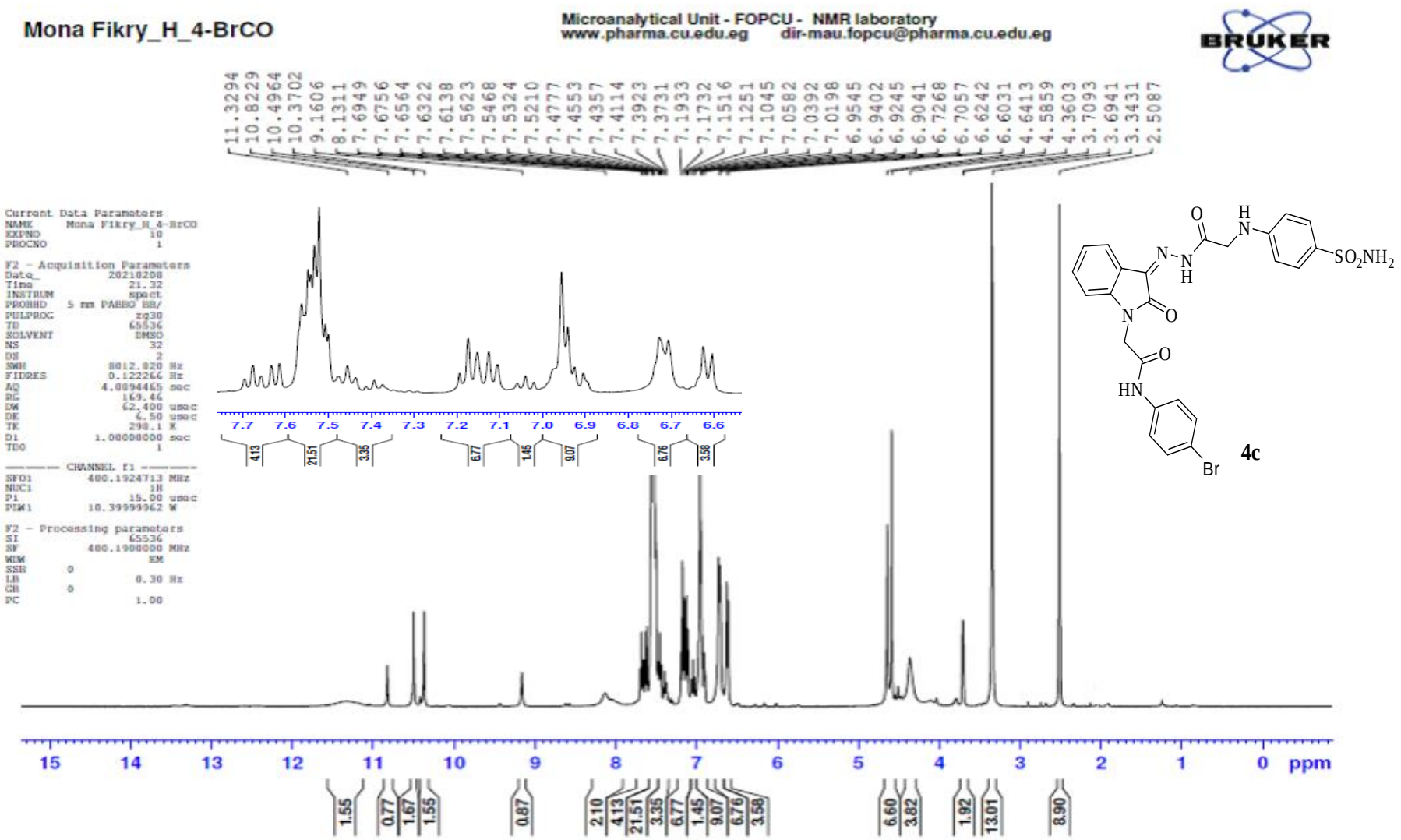

Figure S39. ^{1}H NMR of compound **4c.**

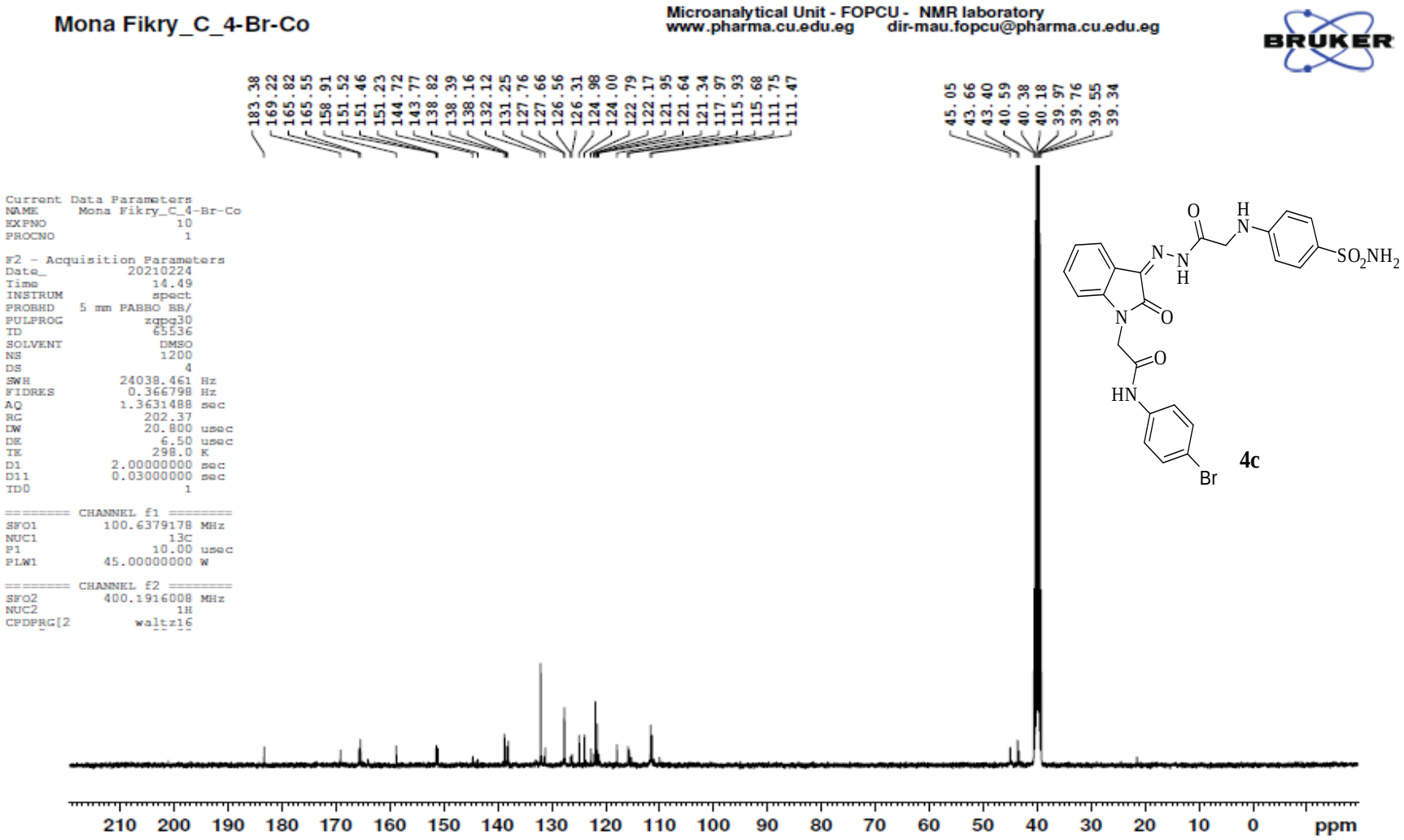

Figure S40. ^{13}C NMR of compound **4c**

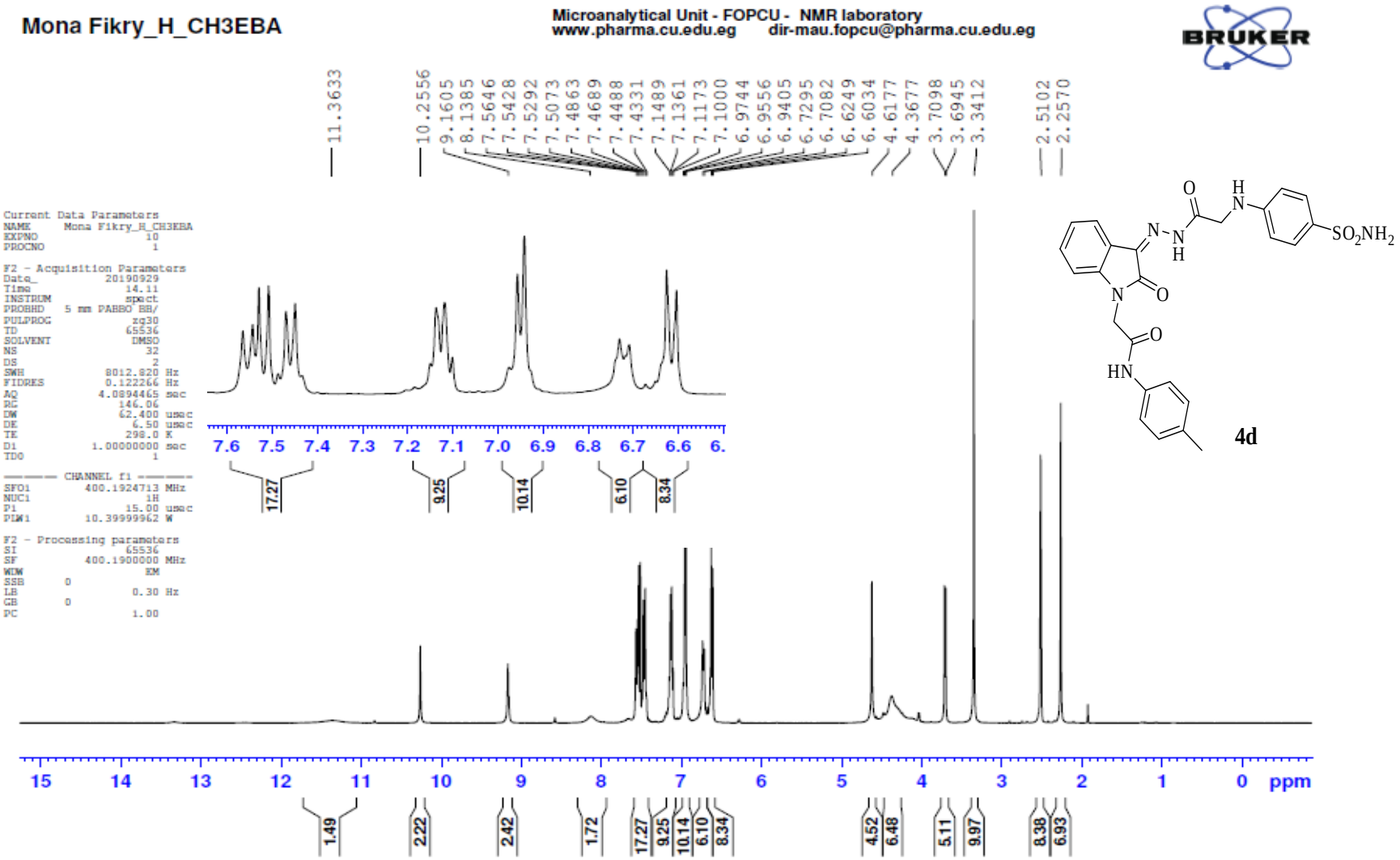

Figure S41. ^{1}H NMR of compound **4d**

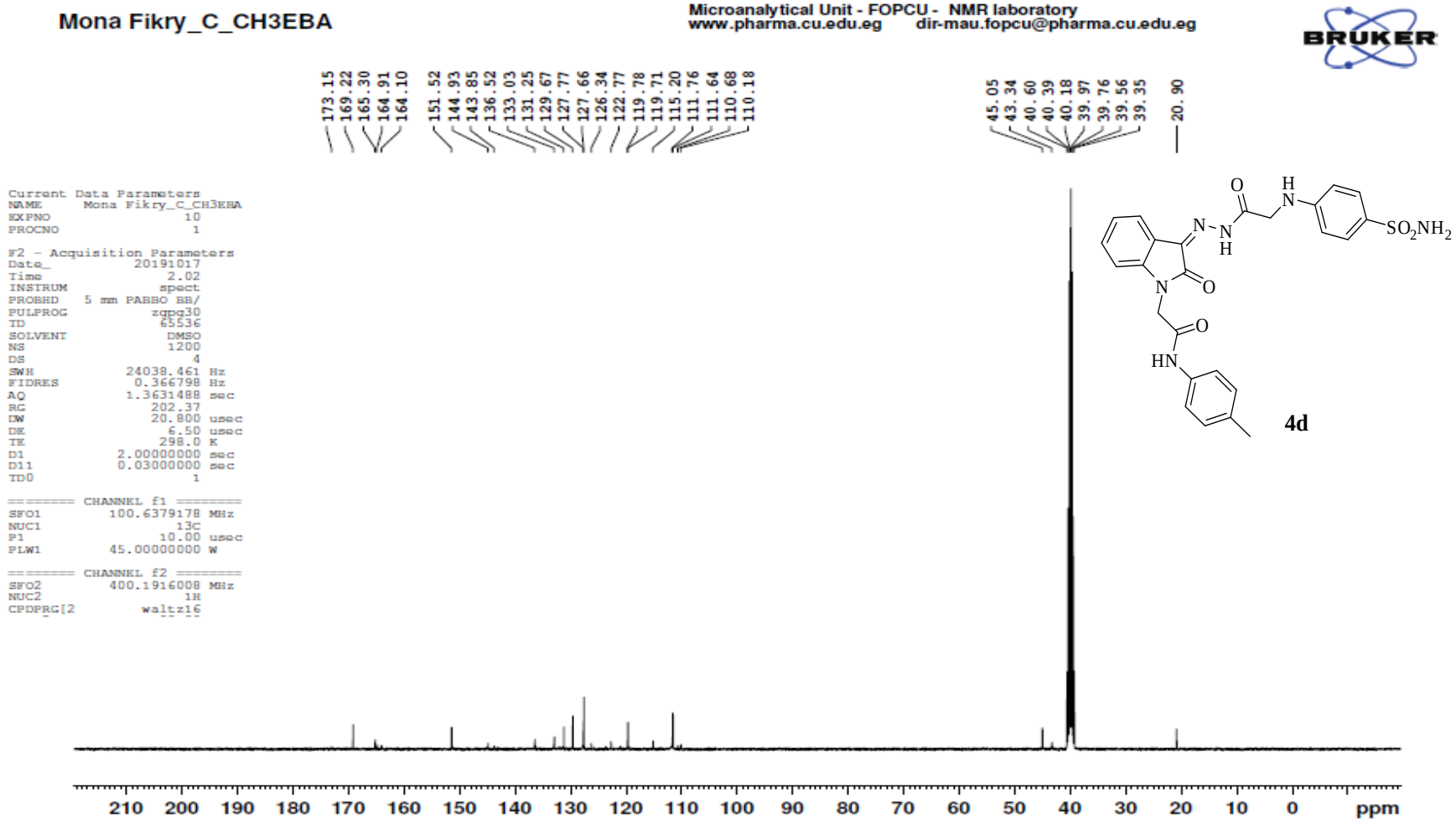

Figure S42. ^{13}C NMR of compound **4d**

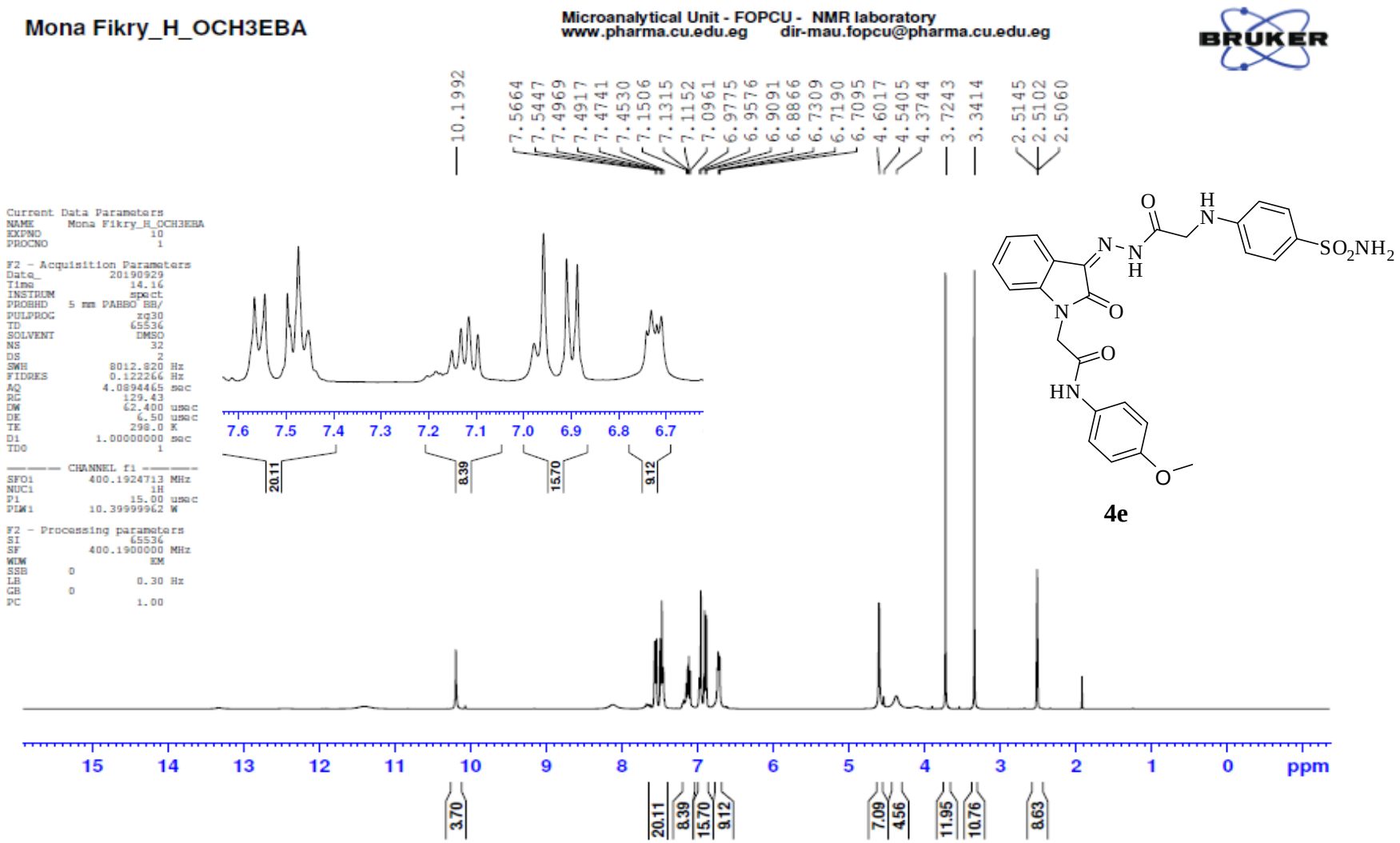

Figure S43. [1]H NMR of compound **4e.**

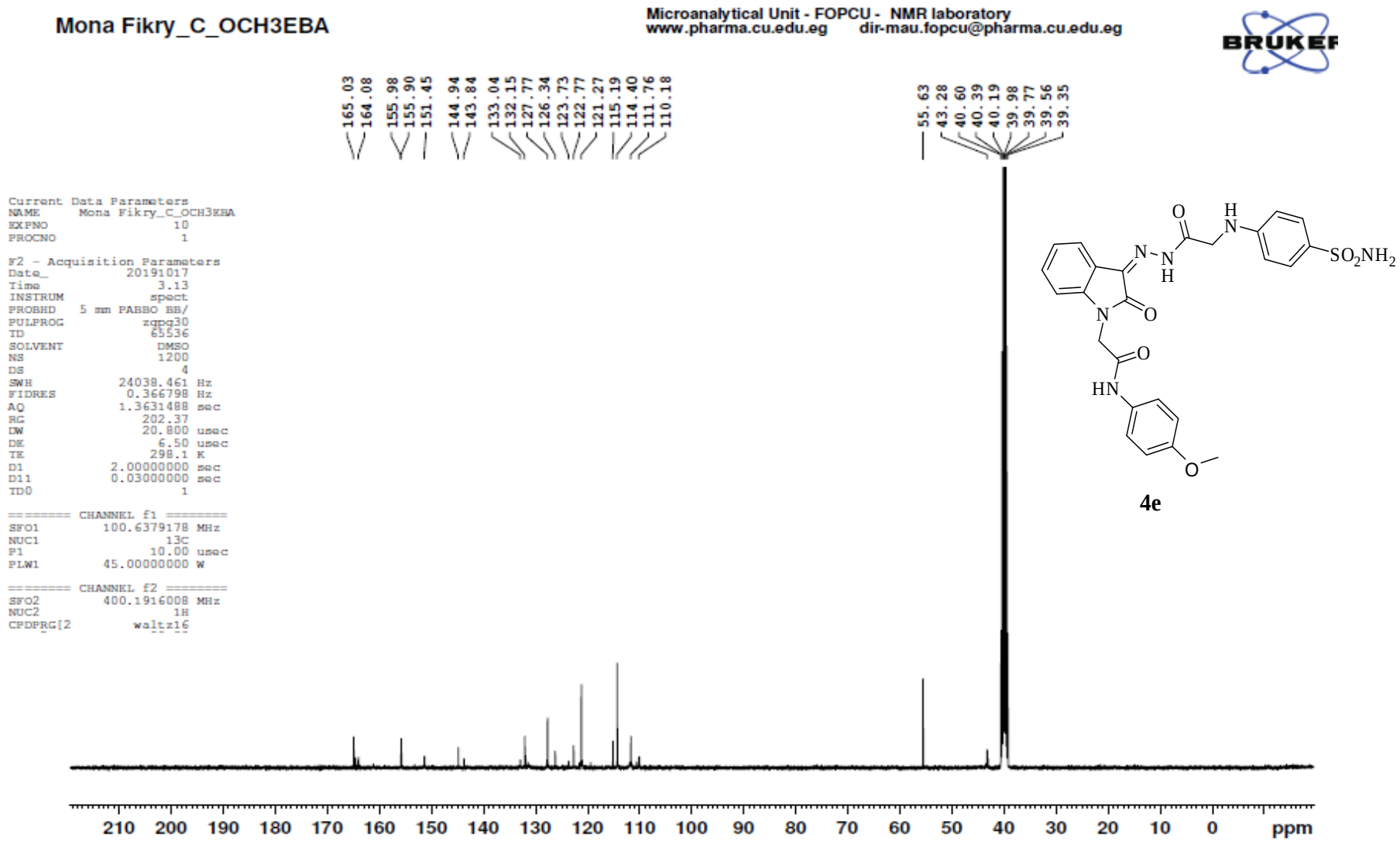

Figure S44. ^{13}C NMR of compound **4e.**

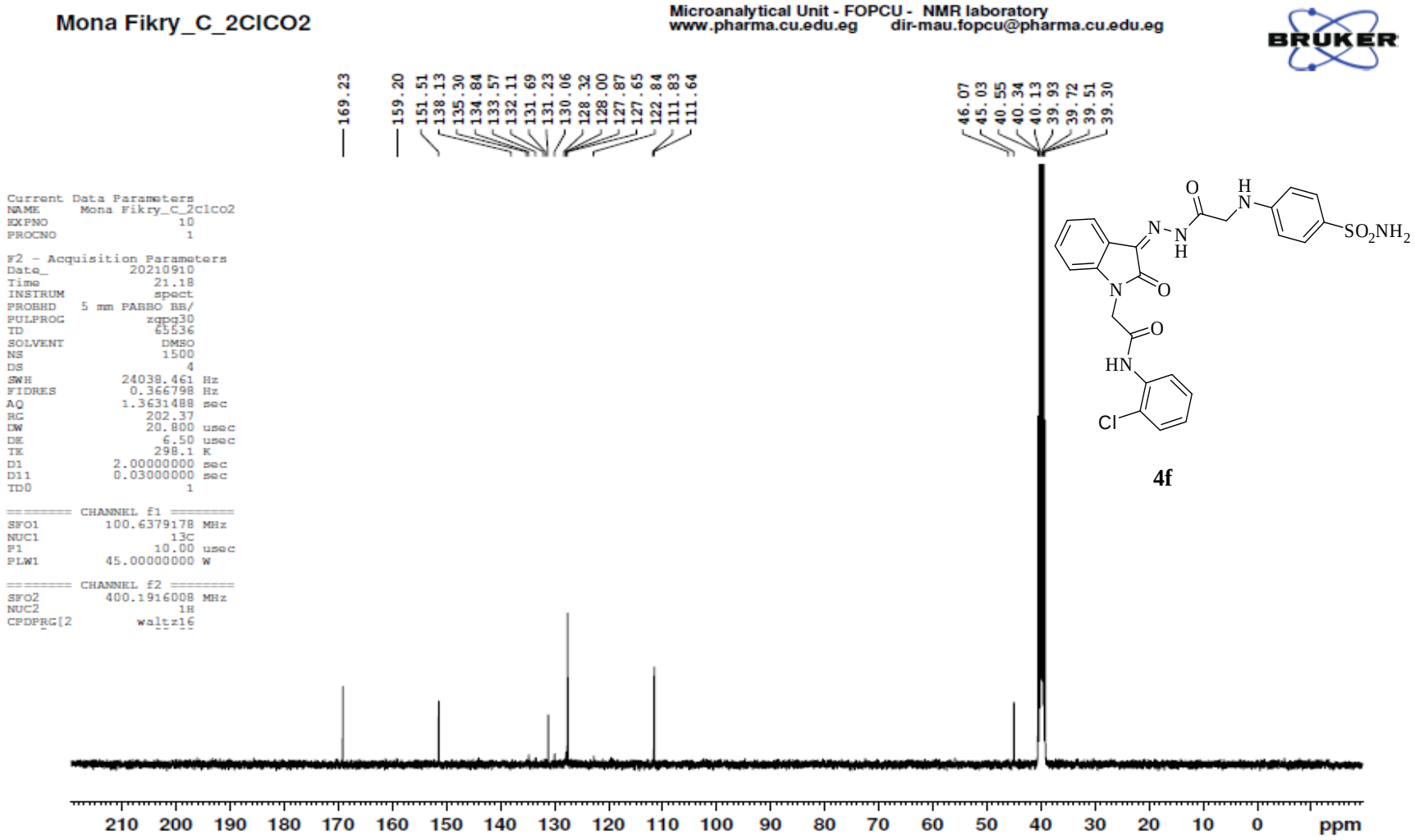

Figure S45. ^{13}C NMR of compound **4f.**

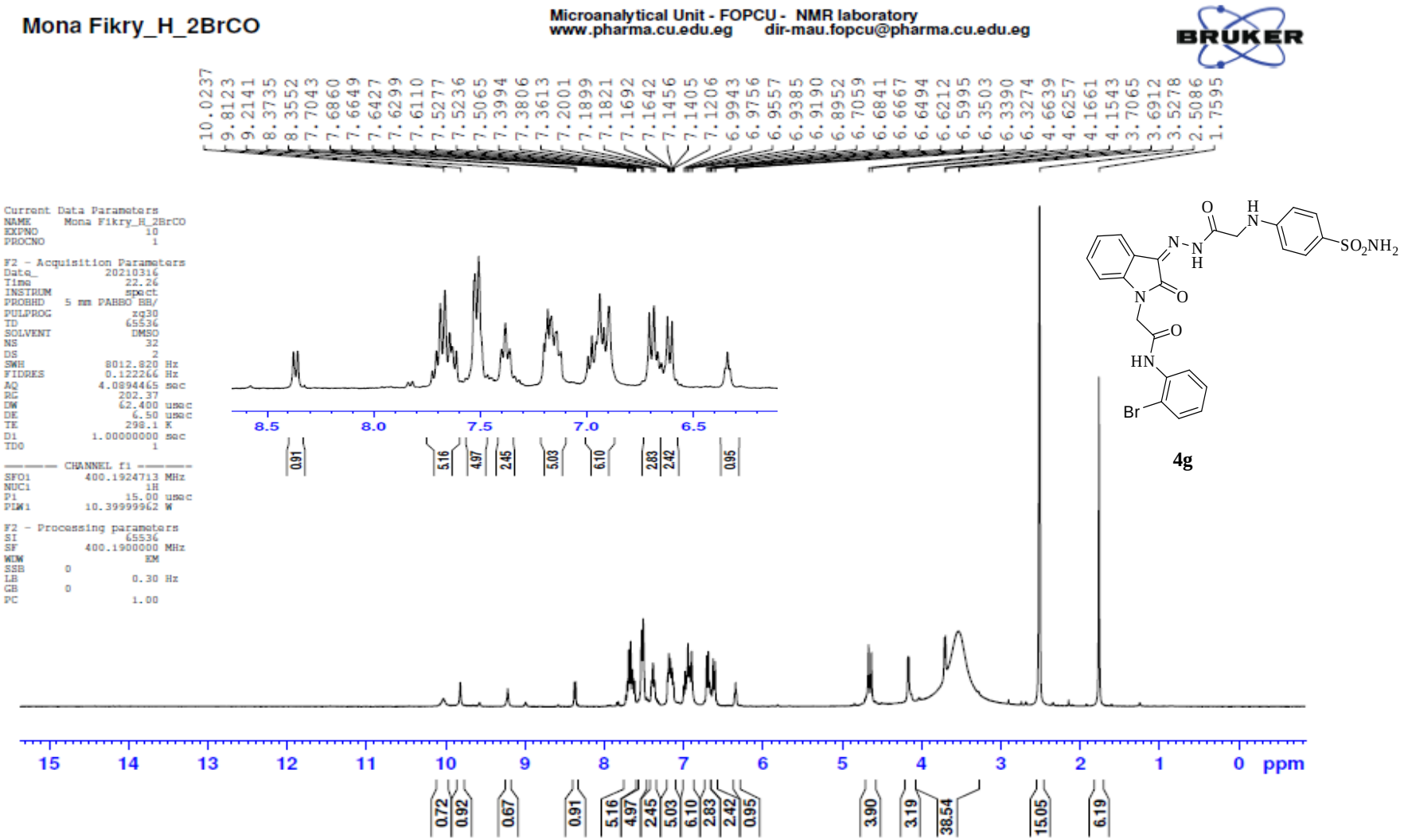

Figure S46. ^{1}H NMR of compound **4g.**

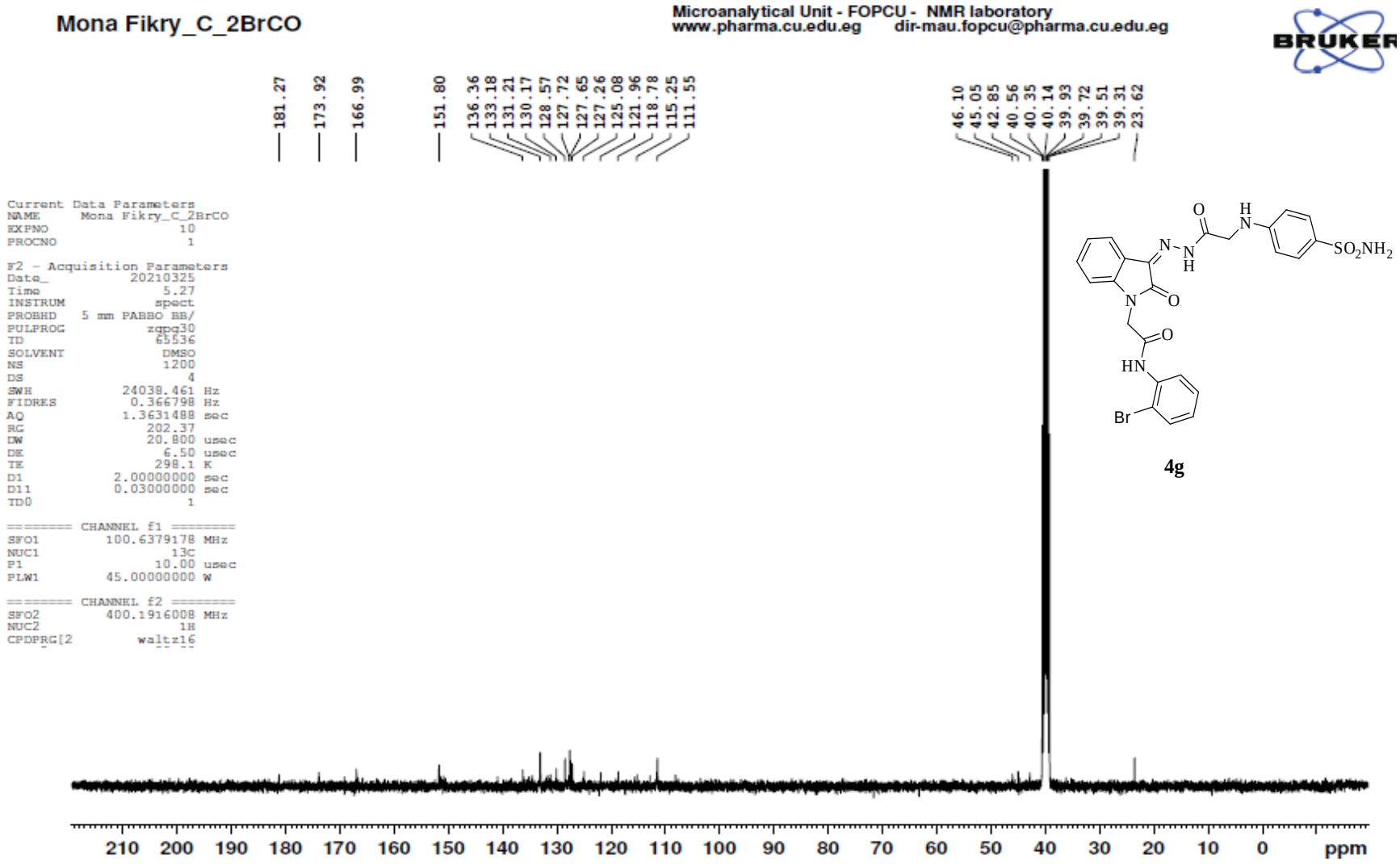

Figure S47. ^{13}C NMR of compound **4g.**