Supplementary information for

New Flavonoid – *N*,*N*-Dibenzyl(*N*-methyl)amine Hybrids: Multi-Target-Directed Agents for Alzheimer´s Disease Endowed with Neurogenic Properties

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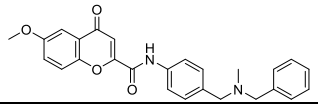
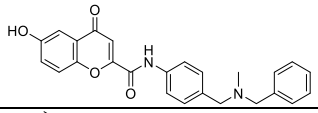
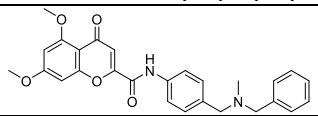
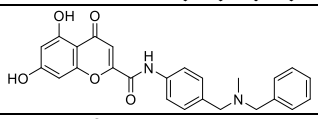
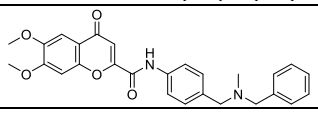
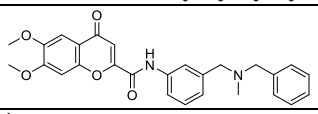
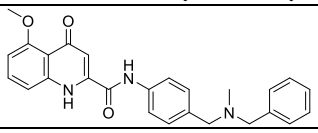
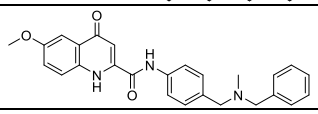
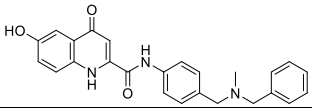
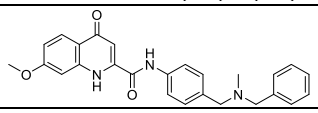
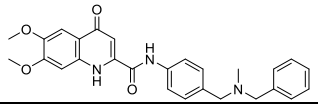
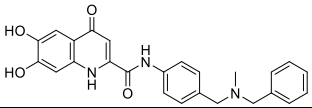
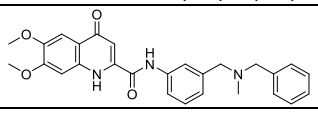
Medicinal chemistry alerts of hybrids 1-13

Table S1. Medicinal chemistry alerts of hybrids **1-13** according to ZINC15 (http://zinc15.docking.org/) [1] and SwissADME (http://www.swissadme.ch/) [2] web sites.

	Structure	SMILES	Aggregator[a]	PAINS Alerts[a,b]	Brenk Alerts[b]
1		O=C(C1=CC(C2=C(O1)C=CC(OC)=C2)=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
2		O=C(C1=CC(C2=C(O1)C=CC(O)=C2)=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
3		O=C(C1=CC(C2=C(O1)C=C(OC)C=C2OC)=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
4		O=C(C1=CC(C2=C(O1)C=C(O)C=C2O)=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
5		O=C(C1=CC(C2=C(O1)C=C(OC)C(OC)=C2)=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
6		O=C(C1=CC(C2=C(O1)C=C(OC)C(OC)=C2)=O)NC3=CC=CC(CN(CC4=CC=CC=C4)C)=C3	No	0	0
7		O=C(C(NC1=C2C(OC)=CC=C1)=CC2=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
8		O=C(C(NC1=C2C=C(OC)C=C1)=CC2=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
9		O=C(C(NC1=C2C=C(O)C=C1)=CC2=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
10		O=C(C(NC1=C2C=CC(OC)=C1)=CC2=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
11		O=C(C(NC1=C2C=C(OC)C(OC)=C1)=CC2=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	0
12		O=C(C(NC1=C2C=C(O)C(O)=C1)=CC2=O)NC3=CC=C(CN(CC4=CC=CC=C4)C)C=C3	No	0	1 (catechol)
13		O=C(C(NC1=C2C=C(OC)C(OC)=C1)=CC2=O)NC3=CC=CC(CN(CC4=CC=CC=C4)C)=C3	No	0	0

[a] ZINC15 (http://zinc15.docking.org/). [b] SwissADME (http://www.swissadme.ch/).

***In silico* study of toxicity of hybrid 6**

Chart S1. Toxicity endpoints predicted at the level of "impossible" for hybrid **6** after *in silico* prediction with Derek Nexus v6.0.1 [3].

5-αReductase inhibition	Mitochondrial dysfunction
Adrenal gland toxicity	Mutagenicity *in vitro*
Alpha-2-mu-Globulin nephropathy	Mutagenicity *in vivo*
Anaphylaxis	Nephrotoxicity
Androgen receptor modulation	Neurotoxicity
Bladder disorders	Non-specific genotoxicity *in vitro*
Bladder urothelial hyperplasia	Non-specific genotoxicity *in vivo*
Blood in urine	Occupational asthma
Bone marrow toxicity	Ocular toxicity
Bradycardia	Oestrogen receptor modulation
Carcinogenicity	Oestrogenicity
Cardiotoxicity	Peroxisome proliferation
Cerebral oedema	Phospholipidosis
Chloracne	Photo-induced chromosome damage *in vitro*
Chromosome damage *in vitro*	Photo-induced non-specific genotoxicity *in vitro*
Chromosome damage *in vivo*	Photo-induced non-specific genotoxicity *in vivo*
Cumulative effect on white cell count and immunology	Photoallergenicity
Cyanide-type effects	Photocarcinogenicity
Developmental toxicity	Photomutagenicity *in vitro*
Glucocorticoid receptor agonism	Phototoxicity
Hepatotoxicity	Pulmonary toxicity
High acute toxicity	Respiratory sensitisation
Irreversible cholinesterase inhibition	Splenotoxicity
Irritation (of the gastrointestinal tract)	Teratogenicity
Kidney disorders	Testicular toxicity
Kidney function-related toxicity	Thyroid toxicity
Lachrymation	Uncoupler of oxidative phosphorylation
Methaemoglobinaemia	Urolithiasis

^{1}H-NMR, ^{13}C-NMR and HRMS data of selected flavonoid – DBMA hybrids

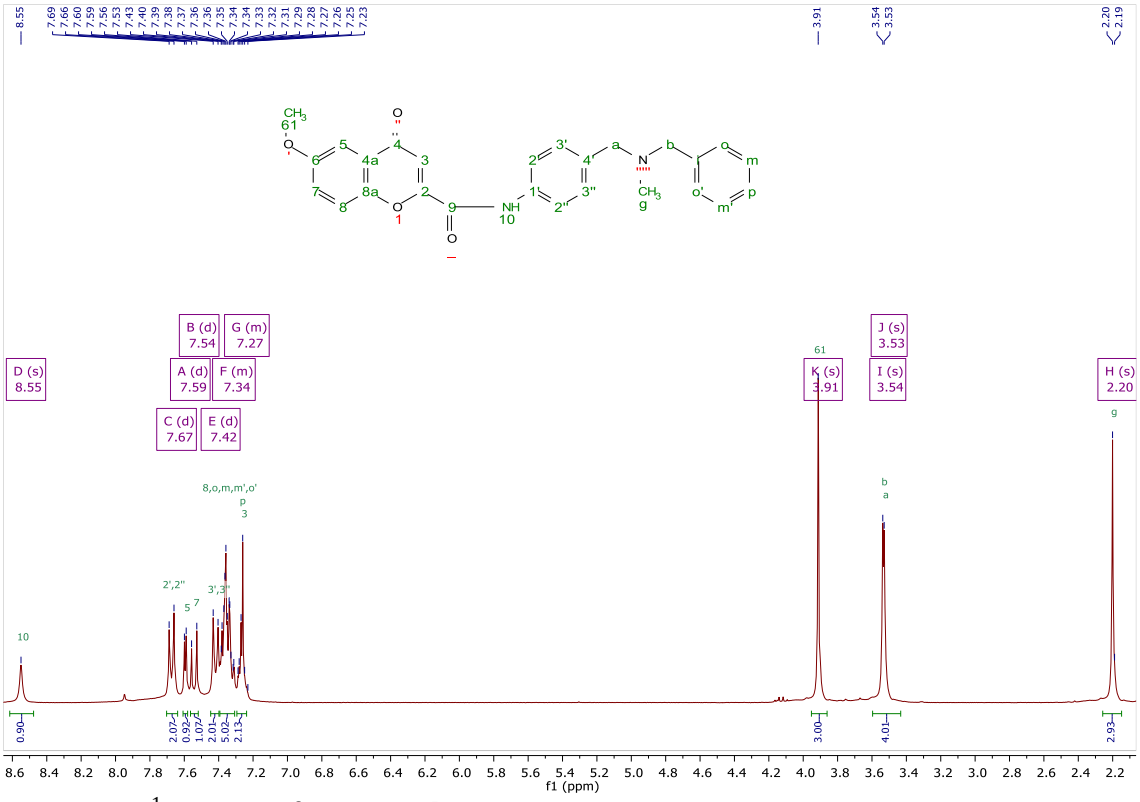


Figure S1. ^{1}H NMR of **1** in $CDCl_3$

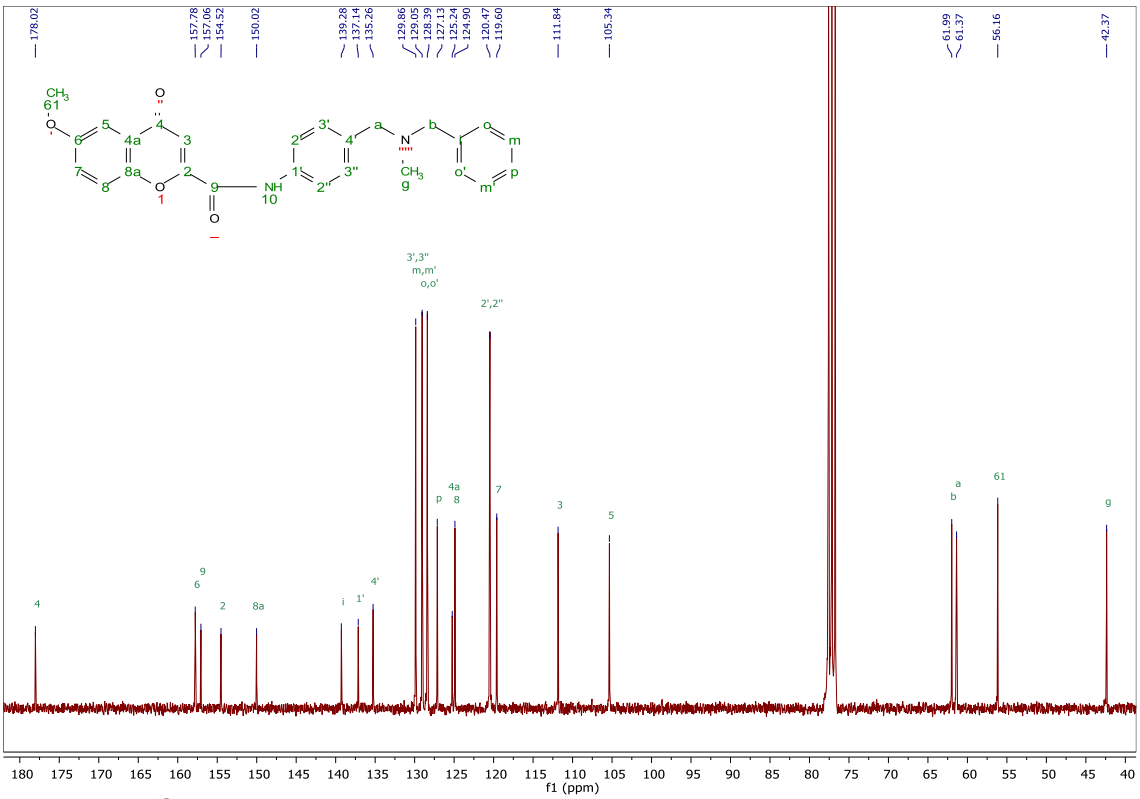


Figure S2. ^{13}C NMR of **1** in $CDCl_3$

Data File	5521_mev_303_01.d	**Sample Name**	mev_303
Sample Type	Sample	**Position**	Vial 22
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Success
DA Method	Default.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C26 H24 N2 O4	1.166	428.1754	29865	C26 H24 N2 O4	428.1736	4.17

Compound Label	RT	Algorithm	Mass
Cpd 1: C26 H24 N2 O4	1.166	Find By Formula	428.1754

MS Zoomed Spectrum

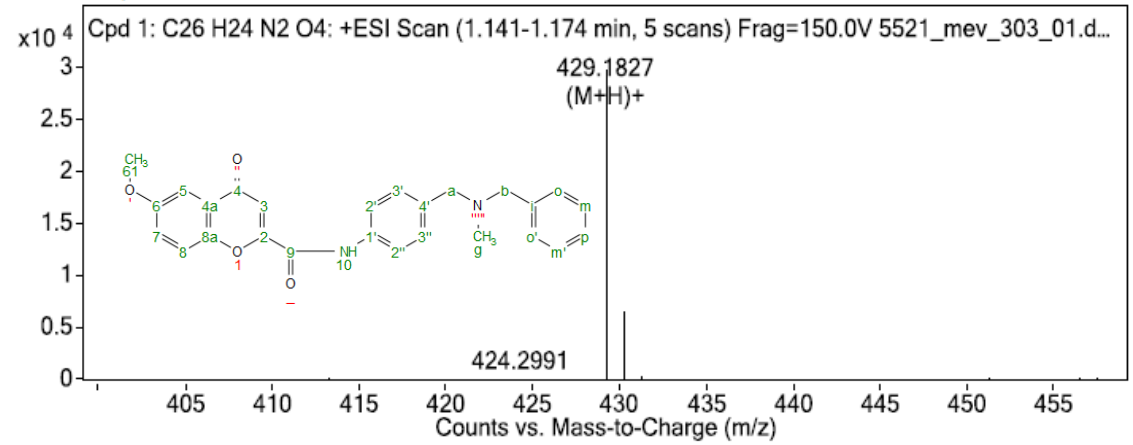


Figure S3. HRMS for hybrid **1**

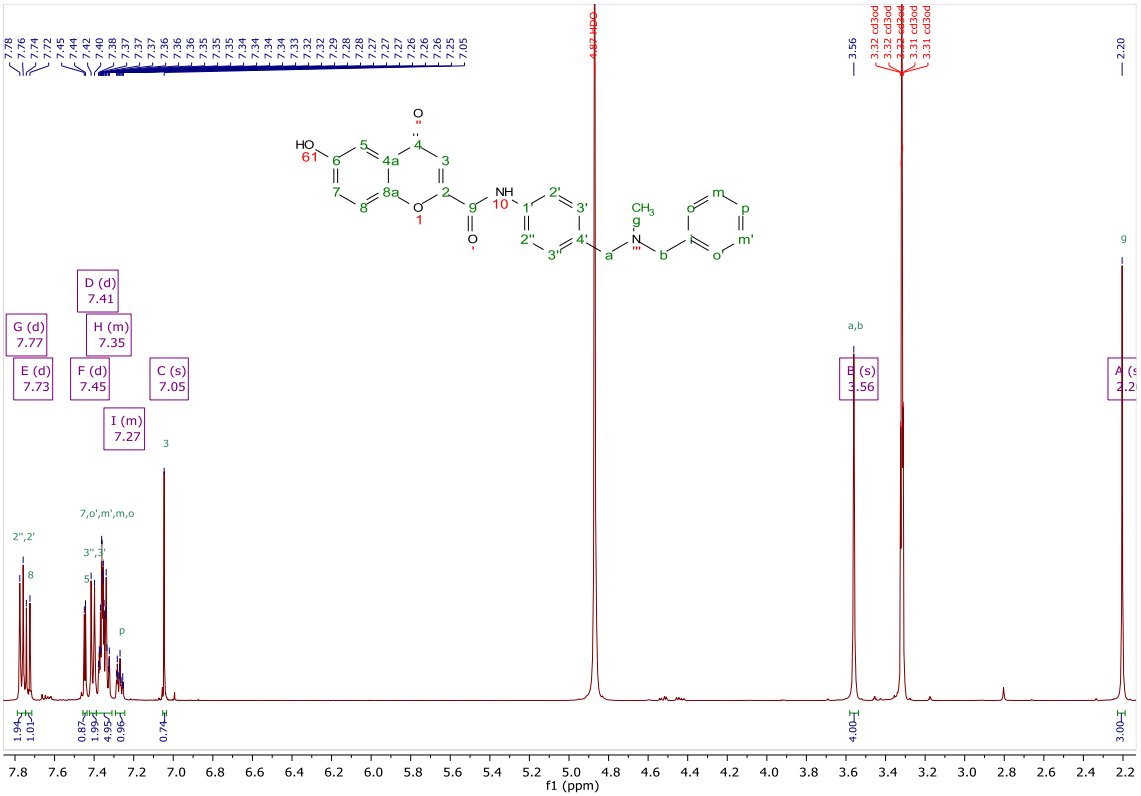


Figure S4. ^{1}H NMR of **2** in MeOD

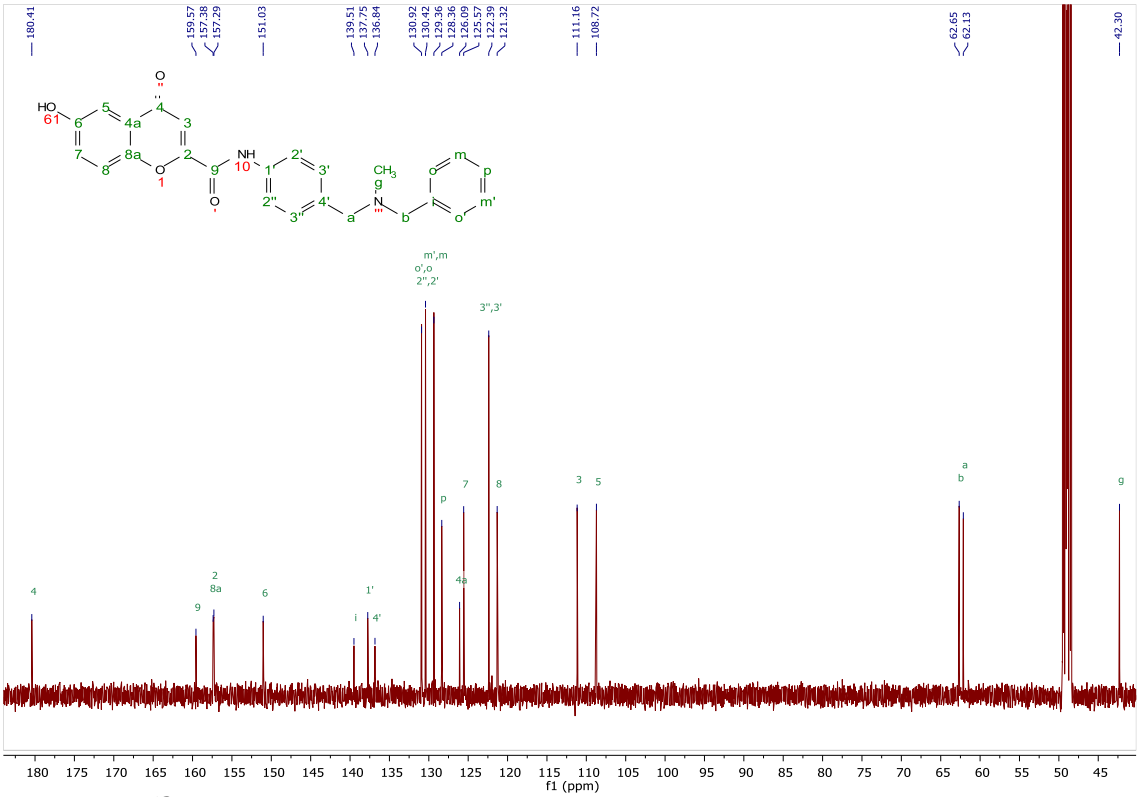


Figure S5. ^{13}C NMR of **2** in MeOD

Data File	6347_mev_419_01.d	**Sample Name**	mev_419
Sample Type	Sample	**Position**	Vial 7
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Success
DA Method	01_busqueda.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C25 H22 O4 N2	1.242	414.1583	492443	C25 H22 O4 N2	414.158	0.91

Compound Label	RT	Algorithm	Mass
Cpd 1: C25 H22 O4 N2	1.242	Find By Formula	414.1583

MS Zoomed Spectrum

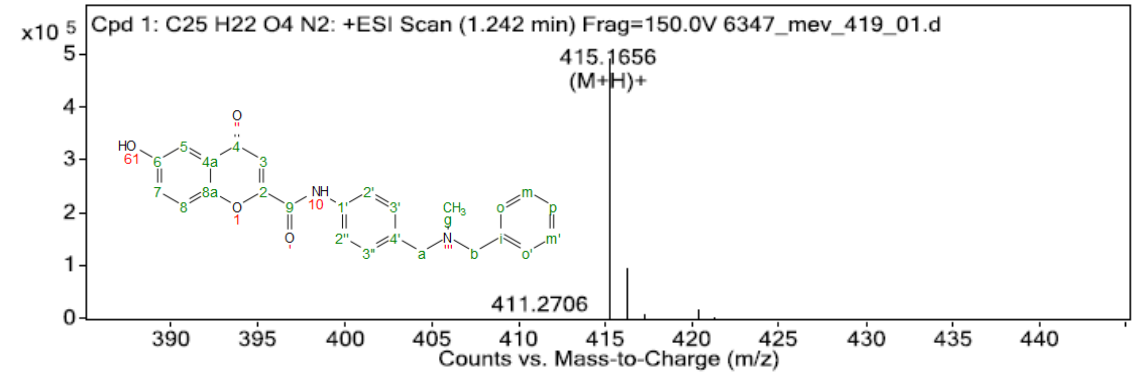


Figure S6. HRMS for compound **2**

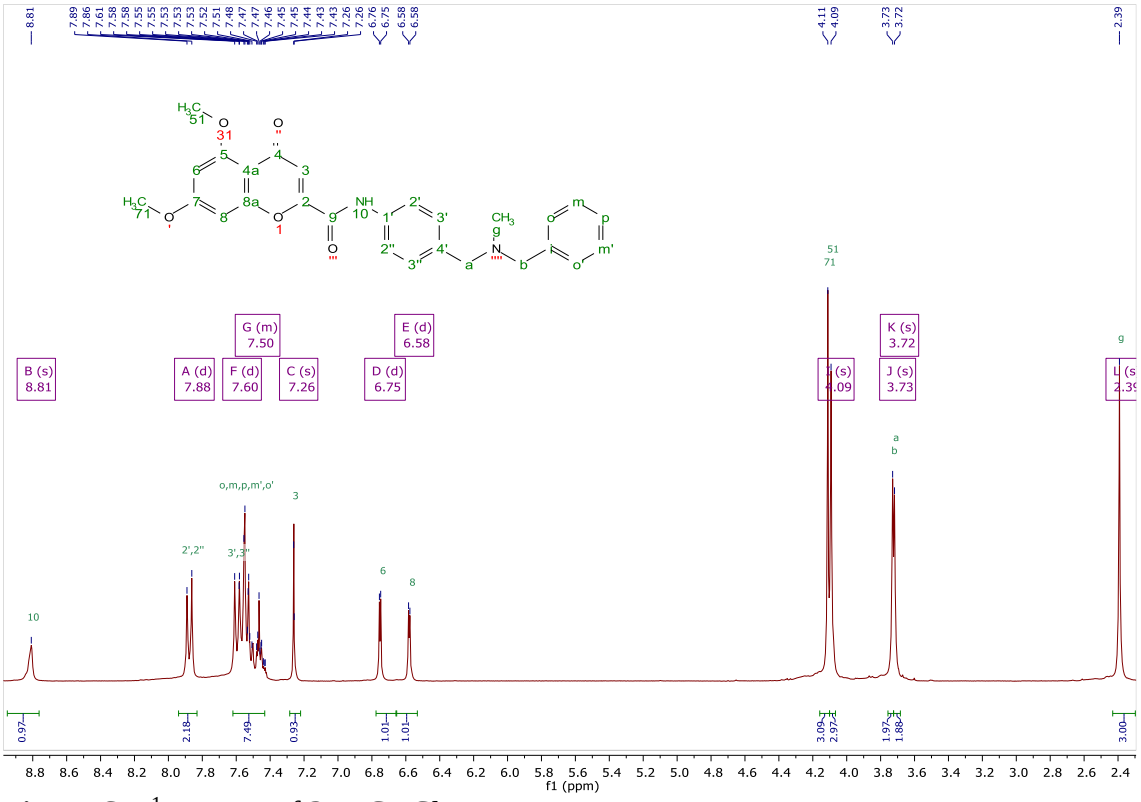


Figure S7. ^{1}H NMR of **3** in $CDCl_3$

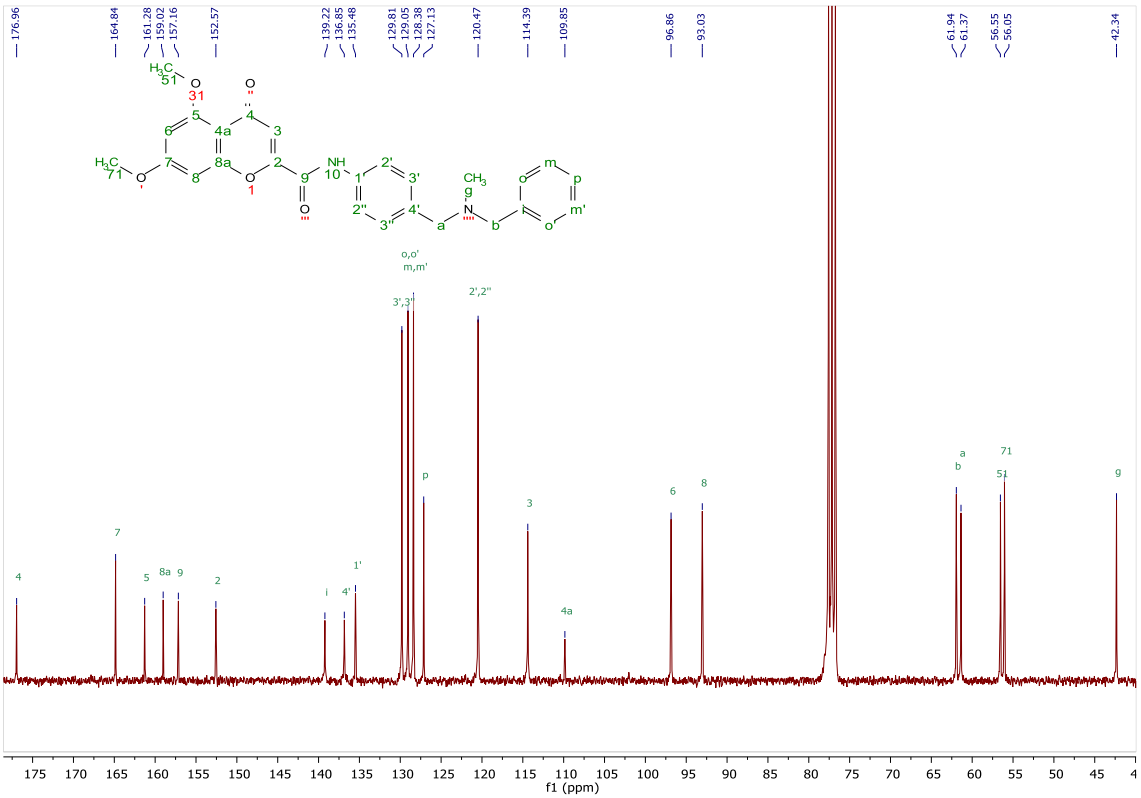


Figure S8. ^{13}C NMR of **3** in $CDCl_3$

Data File	5522_mev_304_01.d	**Sample Name**	mev_304
Sample Type	Sample	**Position**	Vial 23
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	All Ions Missed
DA Method	Default.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C27 H26 N2 O5	1.15	458.1863	77121	C27 H26 N2 O5	458.1842	4.64

Compound Label	RT	Algorithm	Mass
Cpd 1: C27 H26 N2 O5	1.15	Find By Formula	458.1863

MS Zoomed Spectrum

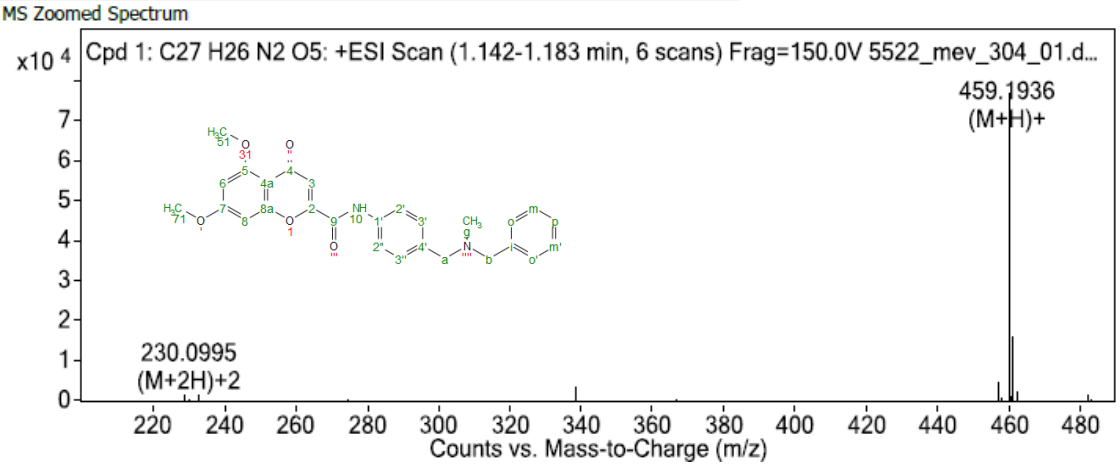


Fig S9. HRMS for compound **3**

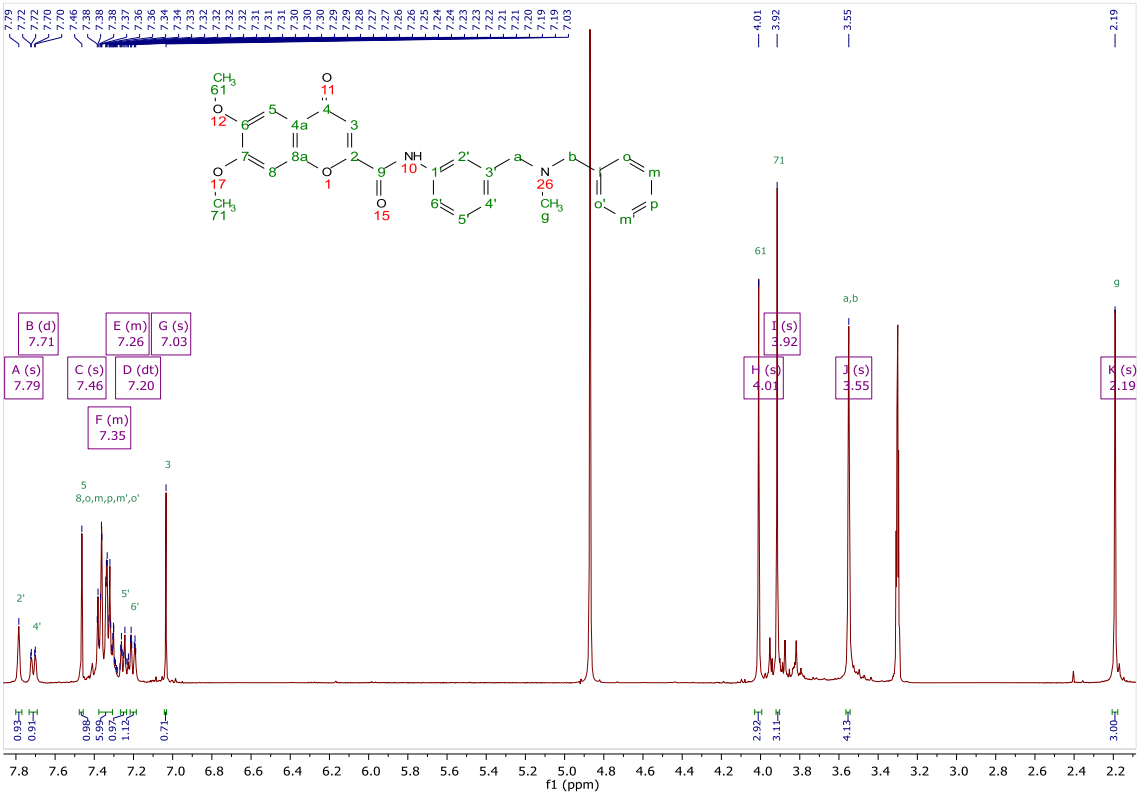


Figure S10. ^{1}H NMR of **6** in MeOD

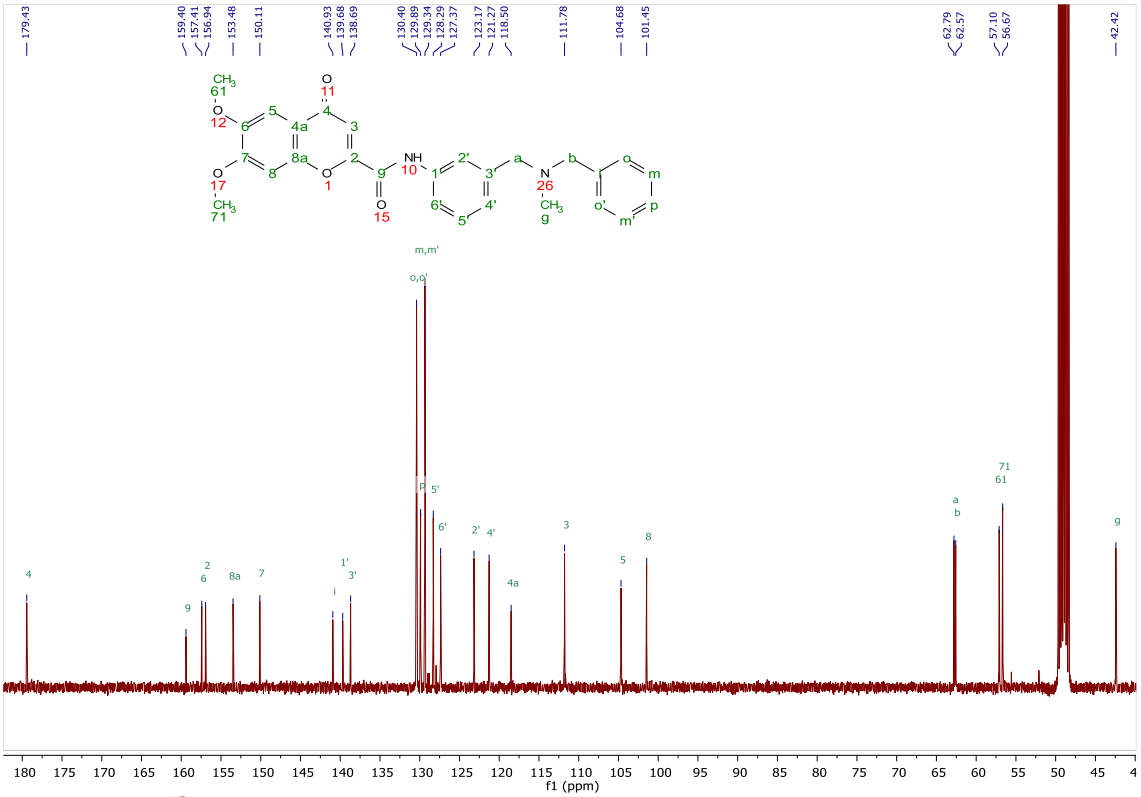


Figure S11. ^{13}C NMR of **6** in MeOD

Data File	7789_mev_658_01.d	**Sample Name**	mev_658
Sample Type	Sample	**Position**	Vial 3
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Some Ions Missed
DA Method	defecto.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C27 H26 N2 O5	0.689	458.18405	182379	C27 H26 N2 O5	458.18417	-0.27

Compound Label	RT	Algorithm	Mass
Cpd 1: C27 H26 N2 O5	0.689	Find By Formula	458.18405

MS Zoomed Spectrum

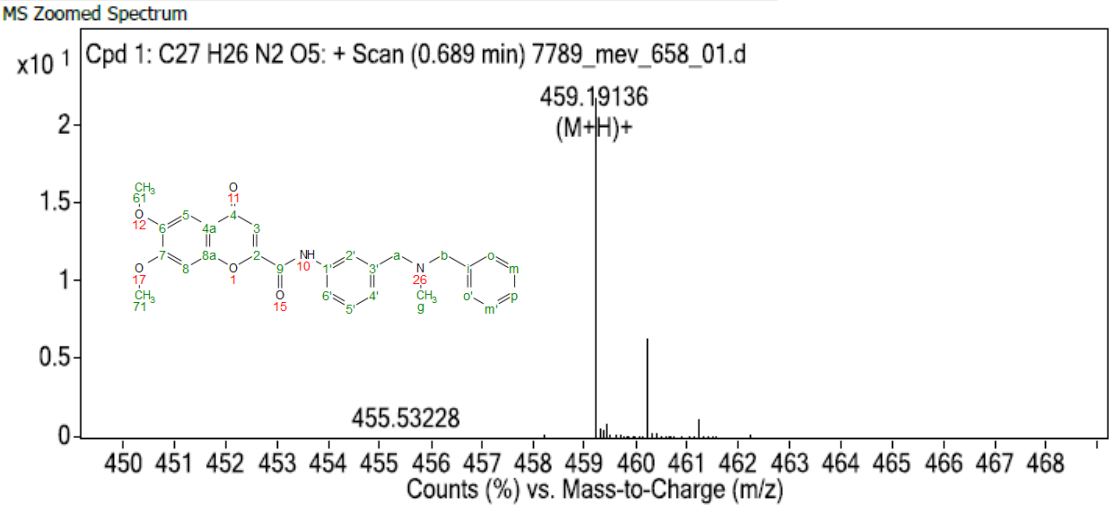


Figure S12. HRMS for compound **6**

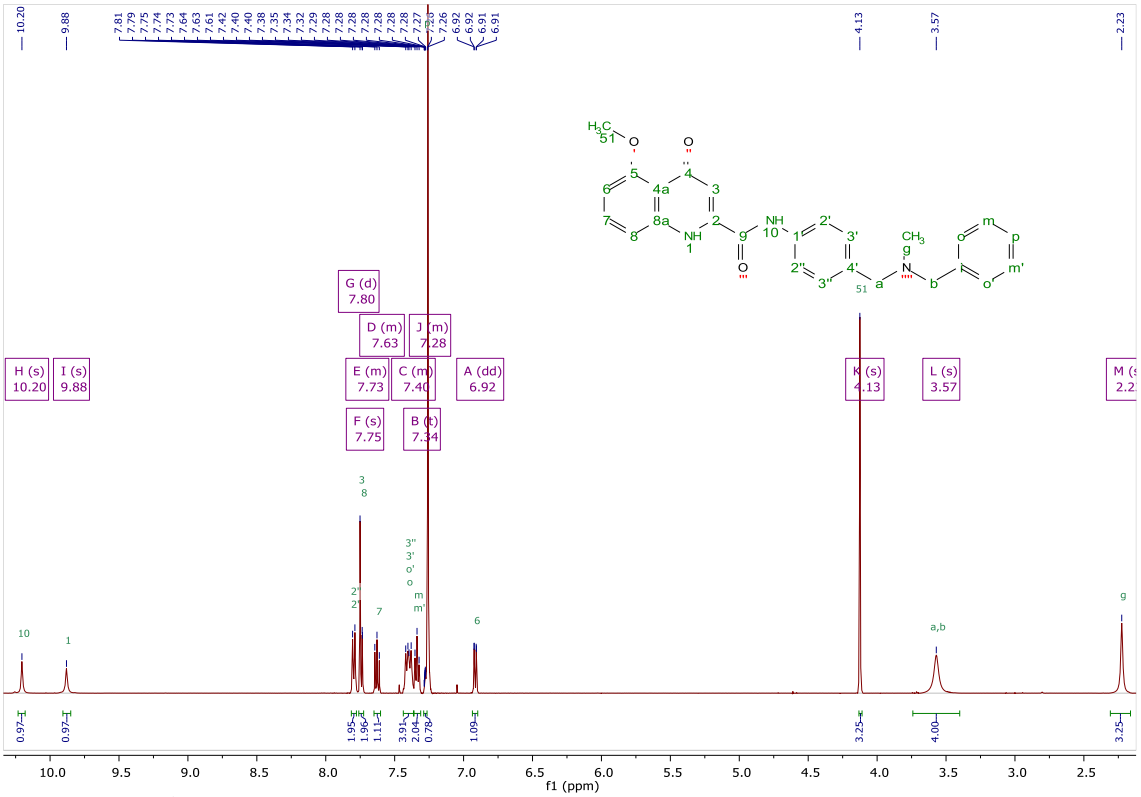


Figure S13. ^{1}H NMR of **7** in $CDCl_3$

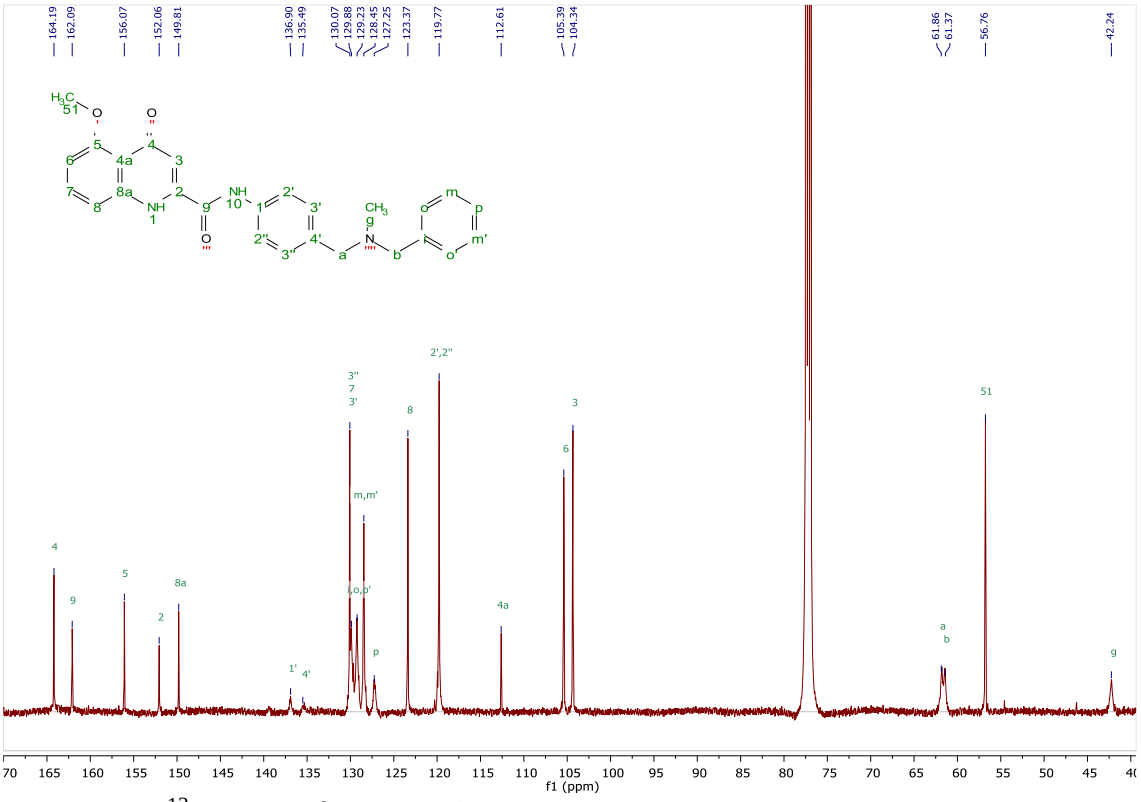


Figure S14. ^{13}C NMR of **7** in $CDCl_3$

Data File	7618_mev_454_f1_01.d	**Sample Name**	mev_454_f1
Sample Type	Sample	**Position**	Vial 2
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Some Ions Missed
DA Method	defecto.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C26 H25 N3 O3	0.607	427.19001	618453	C26 H25 N3 O3	427.18959	0.98

Compound Label	RT	Algorithm	Mass
Cpd 1: C26 H25 N3 O3	0.607	Find By Formula	427.19001

MS Zoomed Spectrum

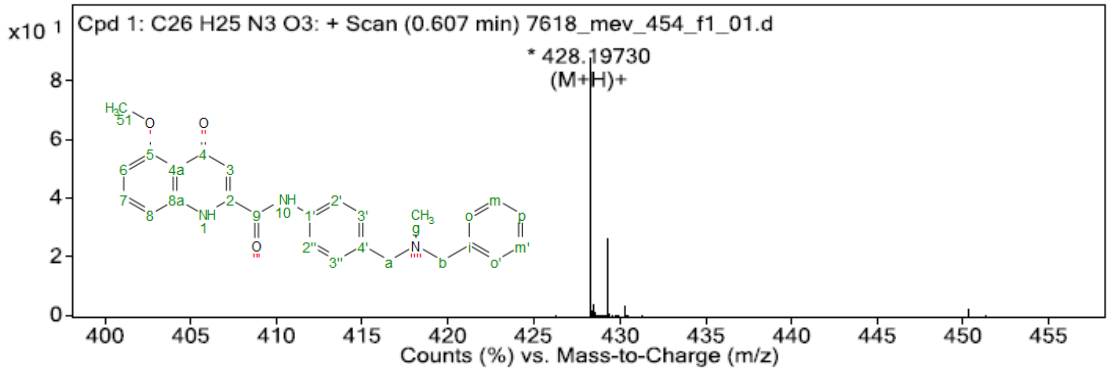


Figure S15. HRMS for Compound **7**

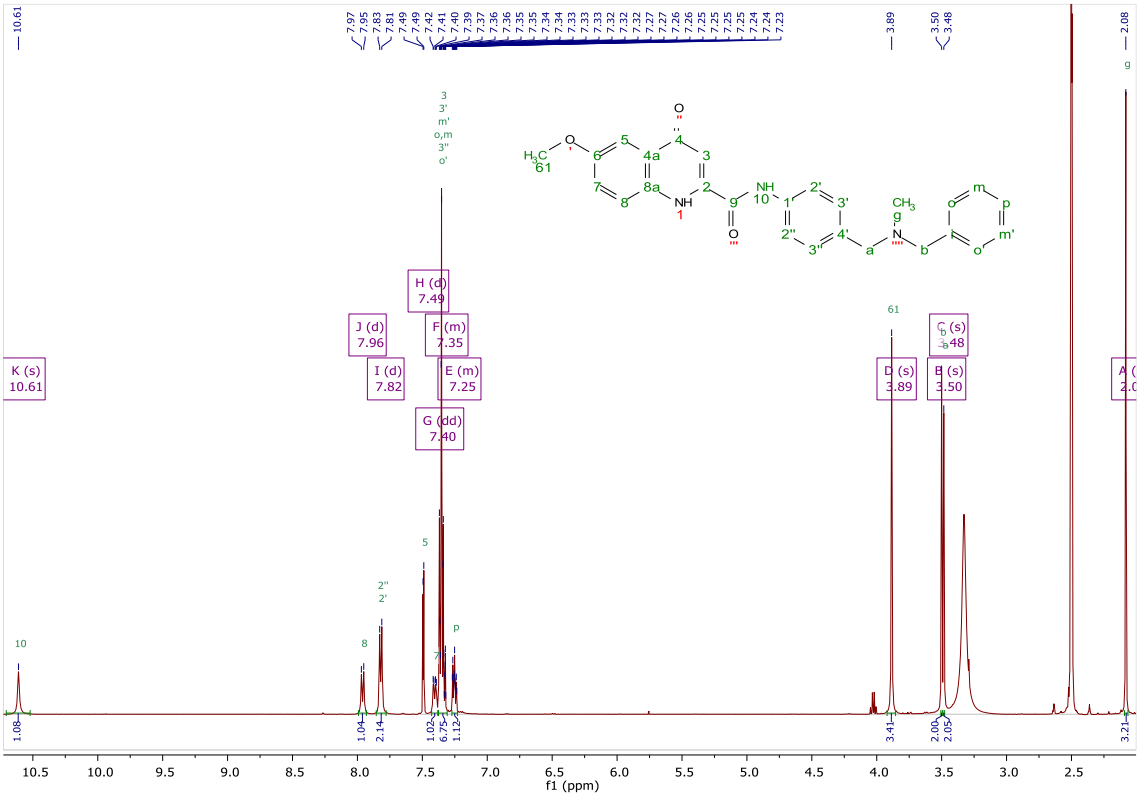


Figure S16. ^{1}H NMR of **8** in DMSO-d6

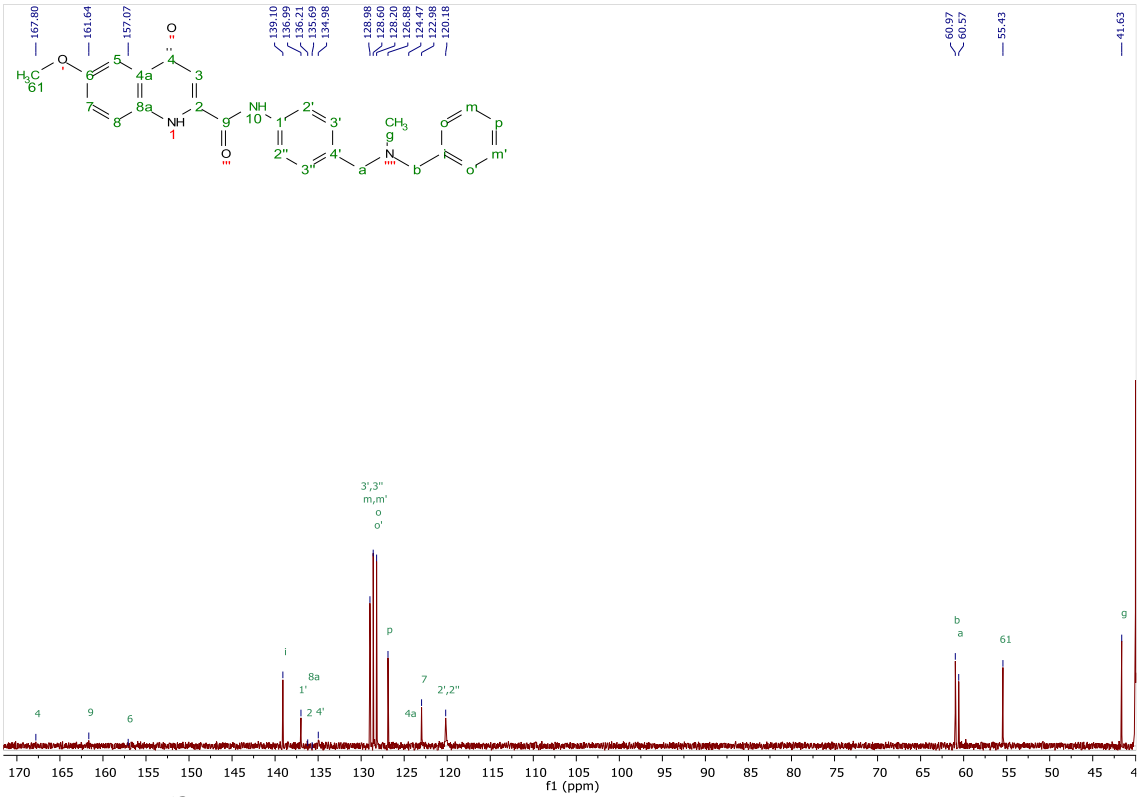


Figure S17. ^{13}C NMR of **8** in DMSO-d$_6$

Data File	6355_mev_456_01.d	**Sample Name**	mev_456
Sample Type	Sample	**Position**	Vial 15
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Success
DA Method	01_busqueda.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C26 H25 O3 N3	0.56	427.1905	344225	C26 H25 O3 N3	427.1896	2.13

Compound Label	RT	Algorithm	Mass
Cpd 1: C26 H25 O3 N3	0.56	Find By Formula	427.1905

MS Zoomed Spectrum

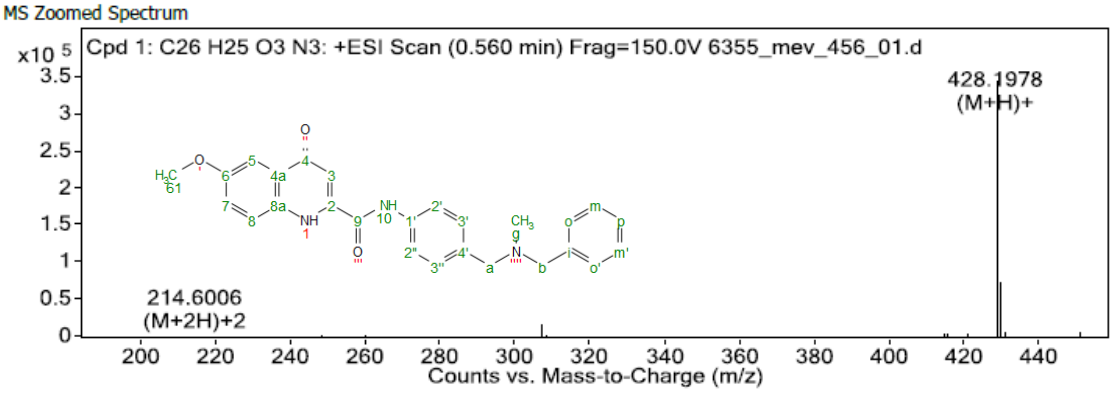


Figure S18. HRMS for compound **8**

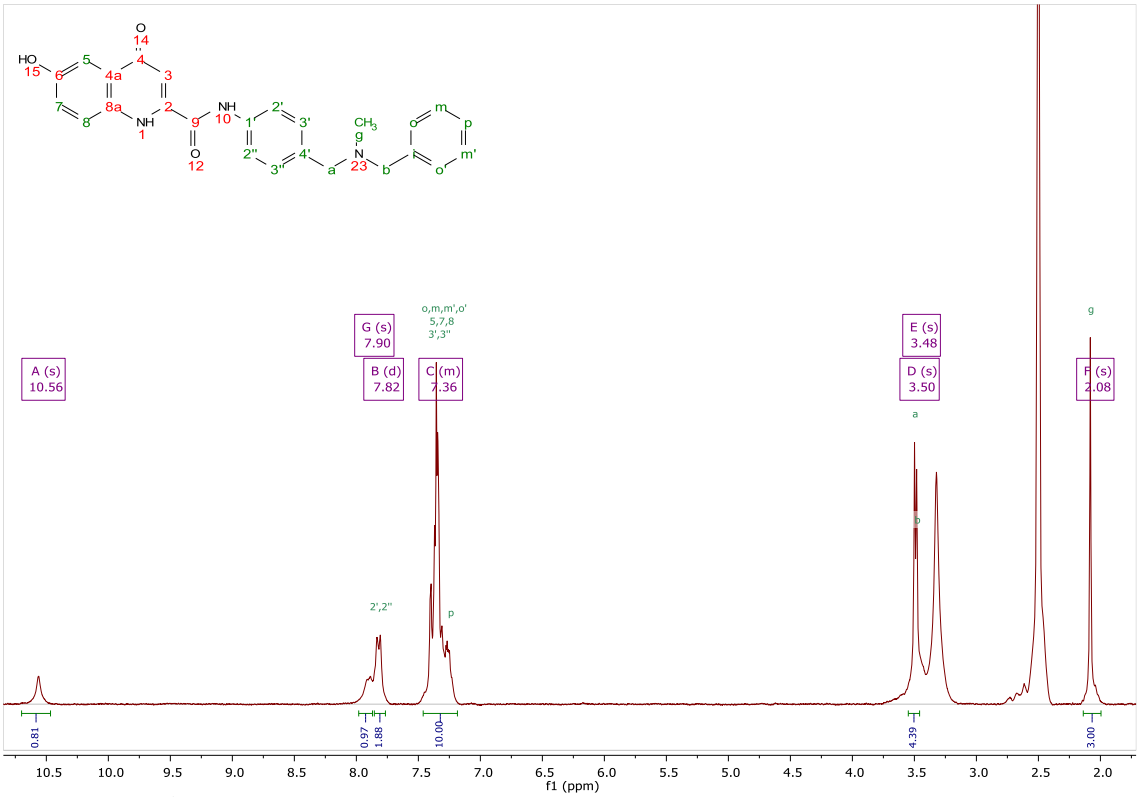


Figure S19. ^{1}H NMR of **9** in DMSO-d$_6$

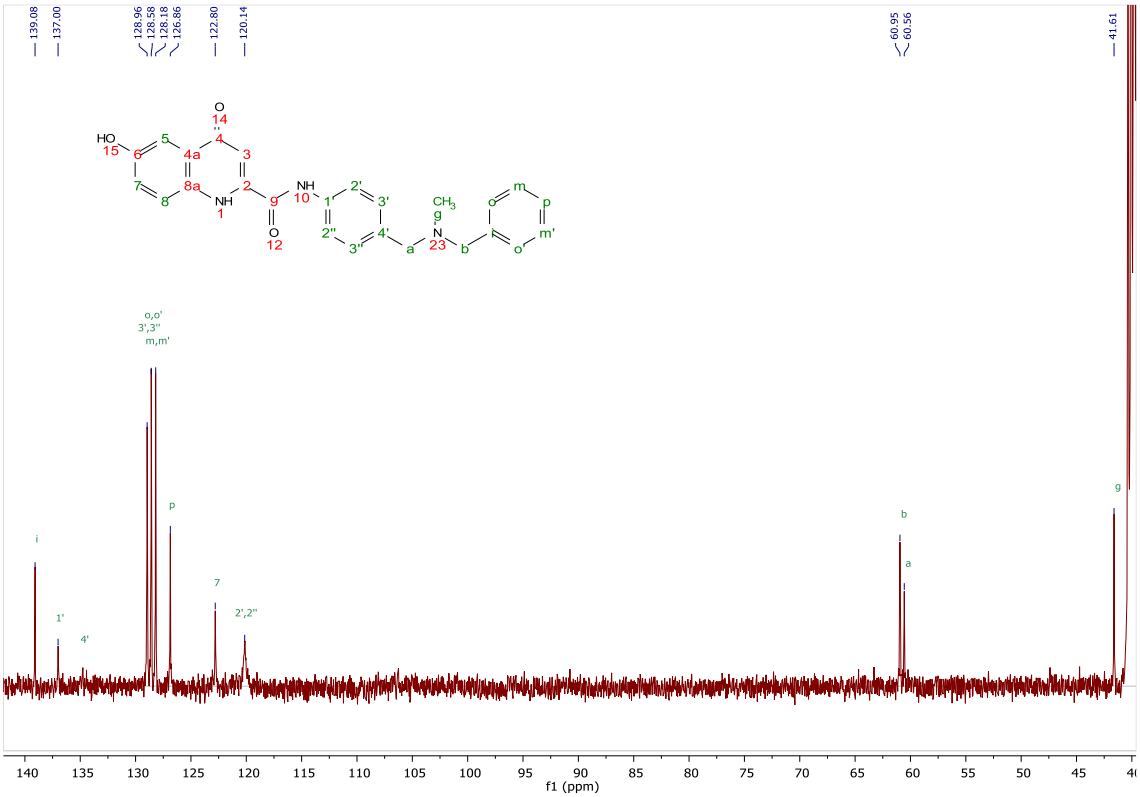


Figure S20. ^{13}C NMR of **9** in DMSO-d6

Data File	6354_mev_458_01.d	**Sample Name**	mev_458
Sample Type	Sample	**Position**	Vial 14
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Success
DA Method	01_busqueda.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C25 H23 O3 N3	0.883	413.1751	349781	C25 H23 O3 N3	413.1739	2.84

Compound Label	RT	Algorithm	Mass
Cpd 1: C25 H23 O3 N3	0.883	Find By Formula	413.1751

MS Zoomed Spectrum

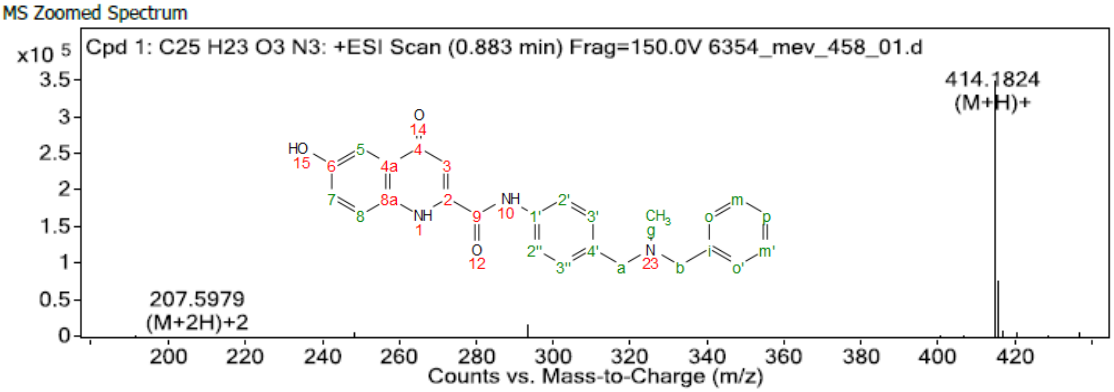


Figure S21. HRMS for compound **9**

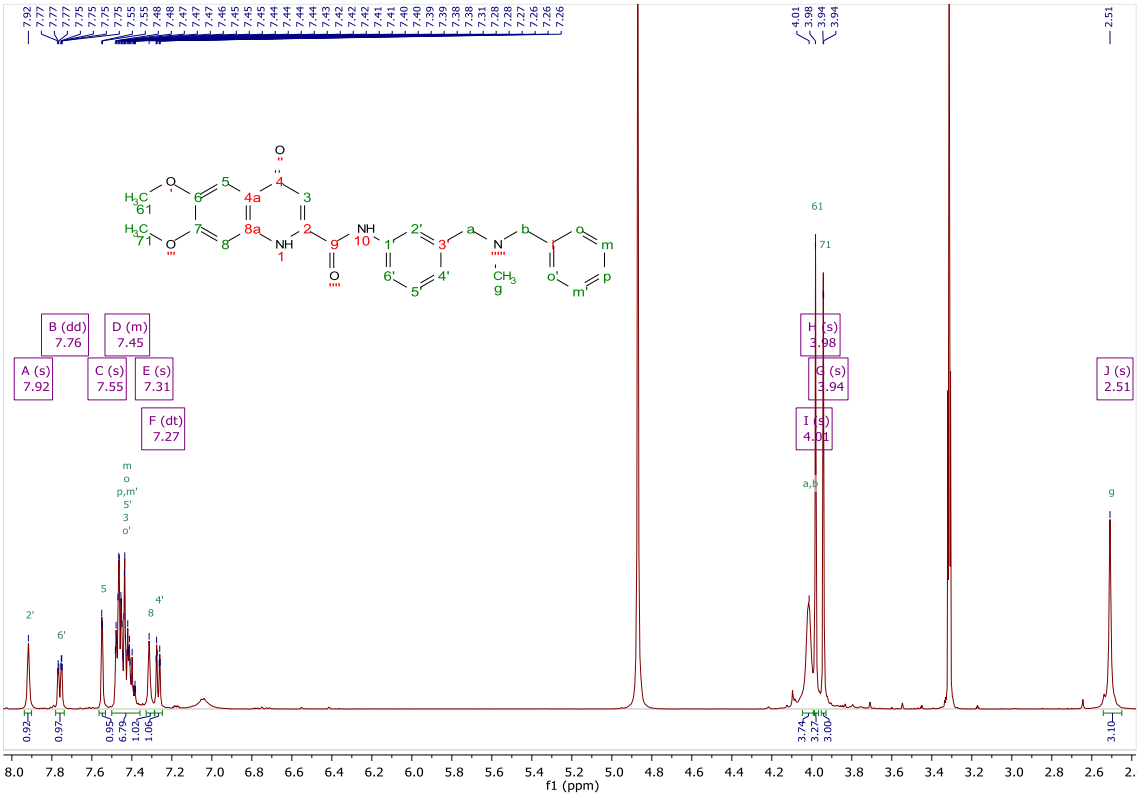


Figure S22. ^{1}H NMR of **13** in MeOD

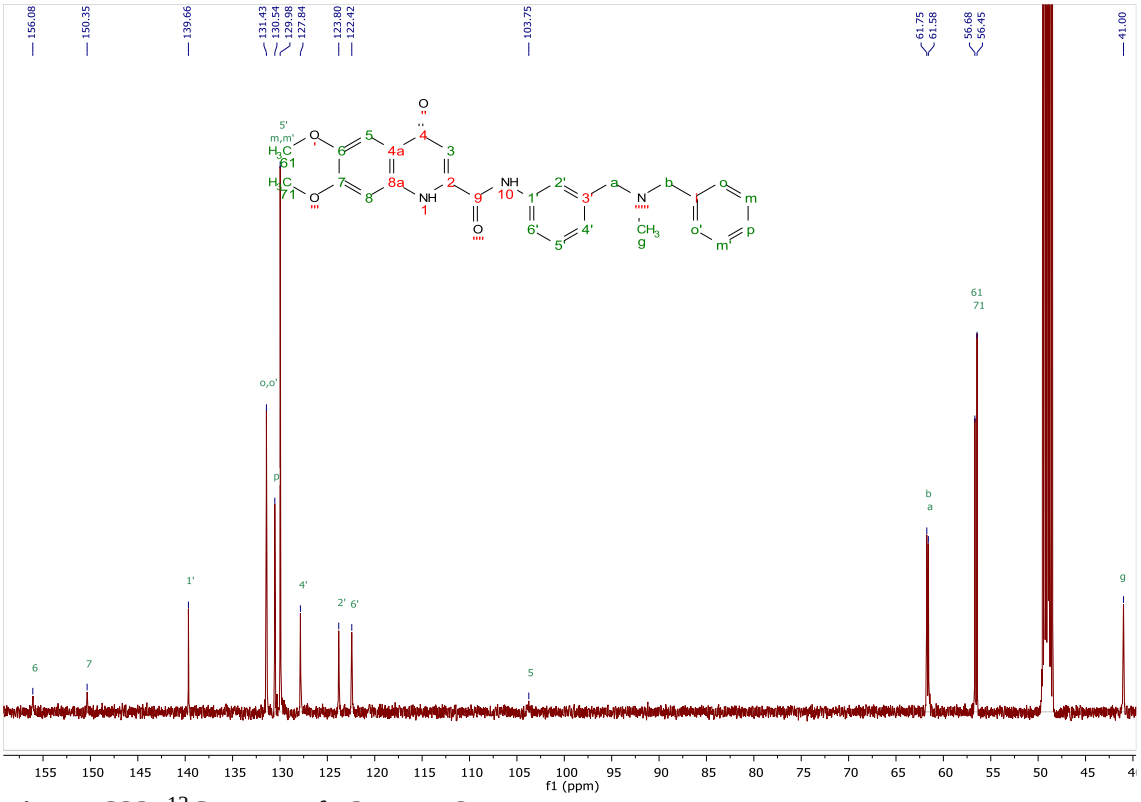


Figure S23. ^{13}C NMR of **13** in MeOD

Data File	7788_mev_657_01.d	**Sample Name**	mev_657
Sample Type	Sample	**Position**	Vial 2
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos.m	**IRM Calibration Status**	Success
DA Method	defecto.m	**Comment**	

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C27 H27 N3 O4	0.707	457.20024	180025	C27 H27 N3 O4	457.20016	0.17

Compound Label	RT	Algorithm	Mass
Cpd 1: C27 H27 N3 O4	0.707	Find By Formula	457.20024

MS Zoomed Spectrum

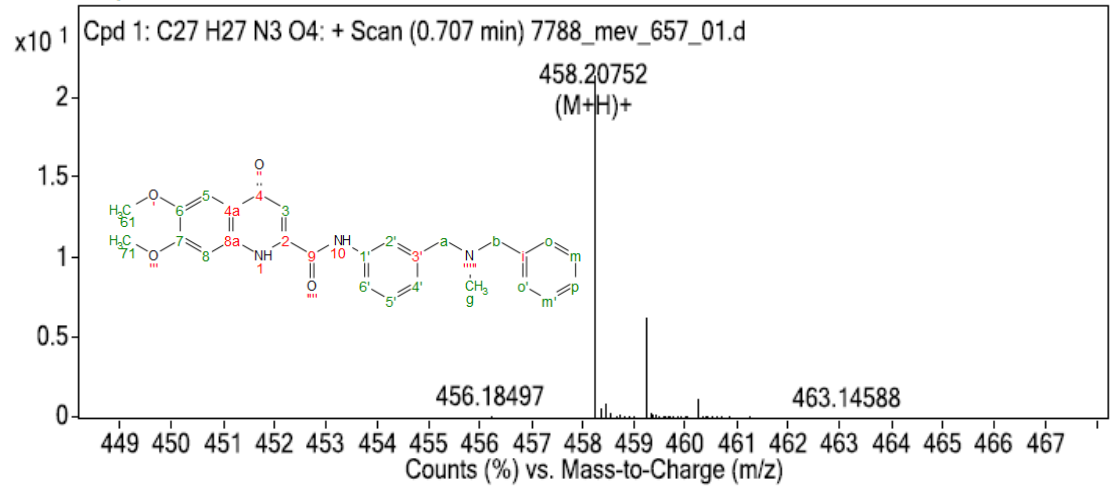


Figure S24. HRMS for compound **13**

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