

Supplementary

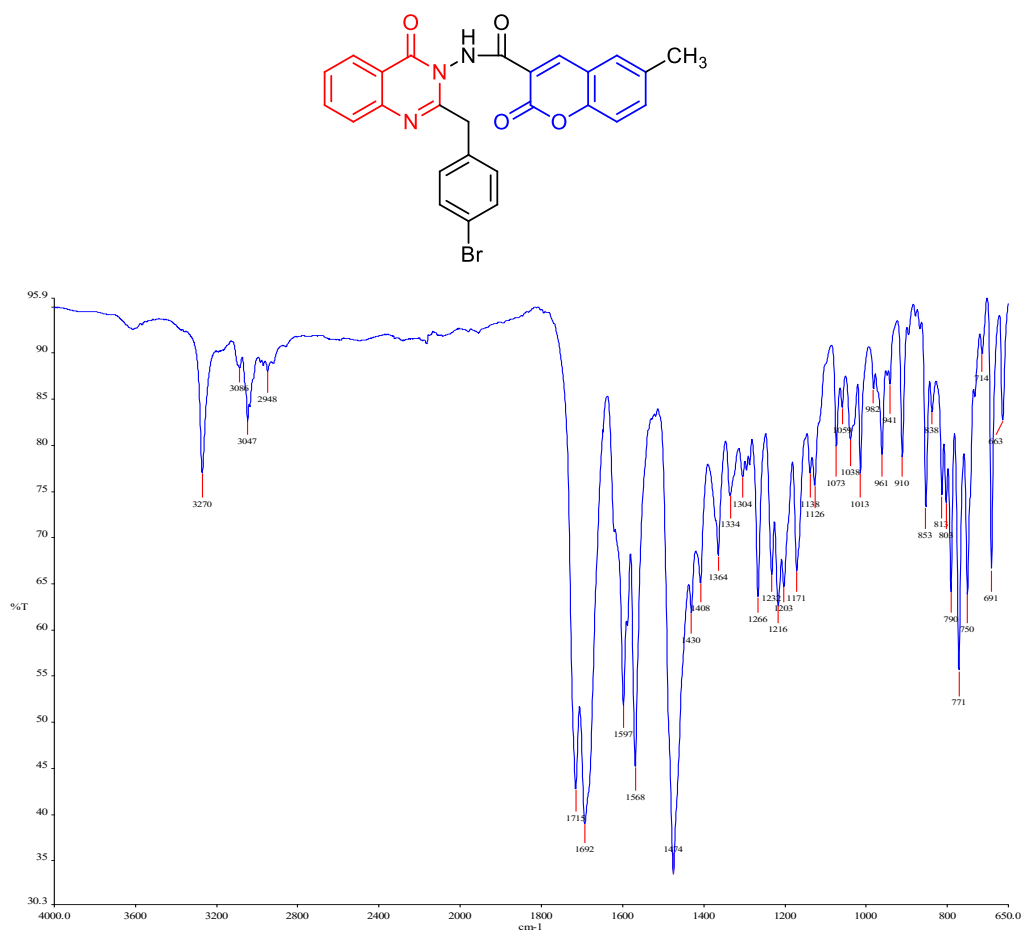
Synthesis, Molecular Docking, and ADMET Evaluation of Novel Quinazolinone-Coumarin Hybrid Derivatives as Dual Inhibitors of Urease and Acetylcholinesterase

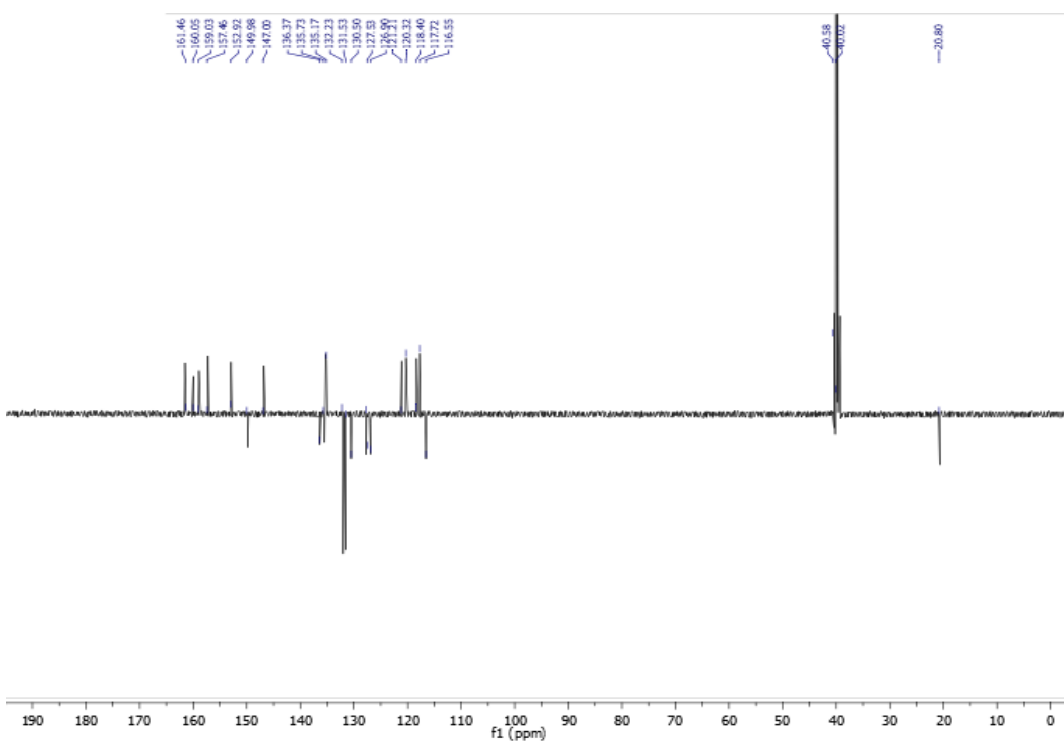
Nedime Çalışkan, Gülay Akyüz, Fatih İslamoğlu, *Emre Menteşe

1- Copies of NMR and IR spectra of synthesized compounds **4a-n** 1-22

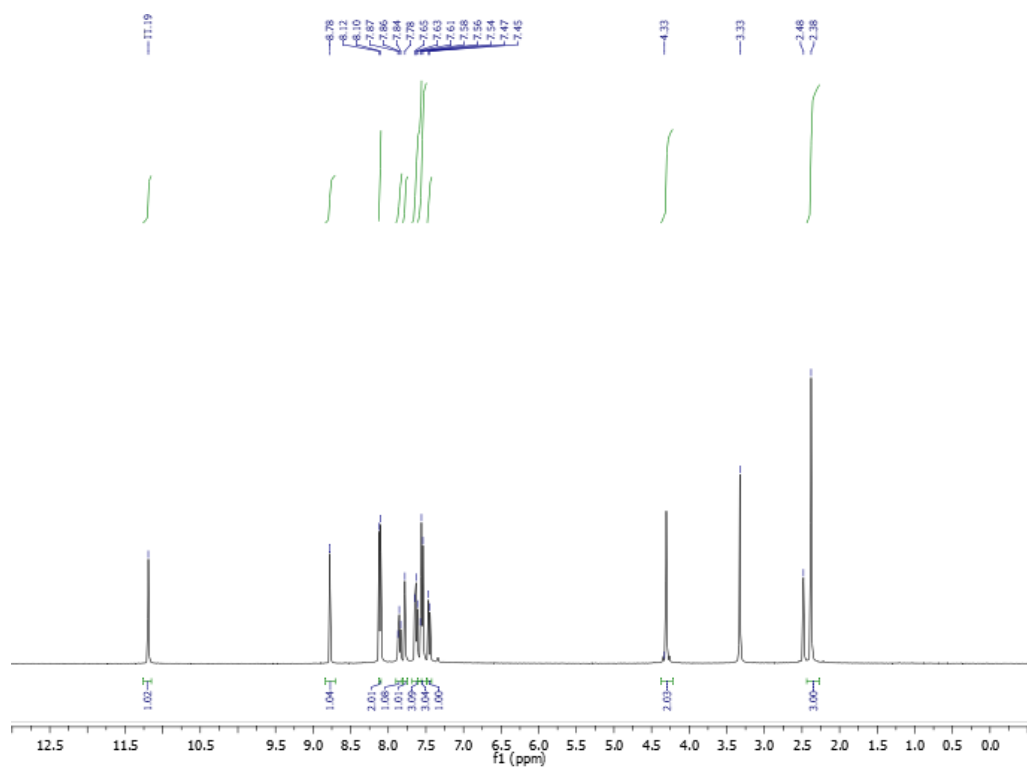
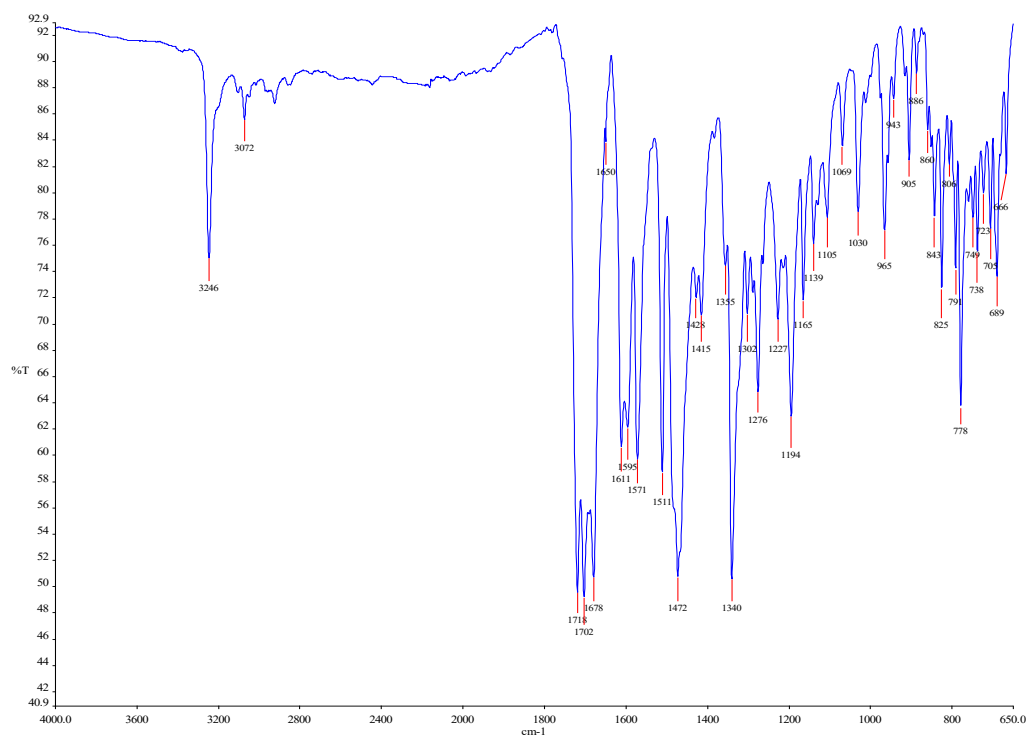
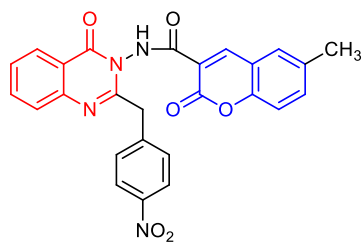
2- Table 2. ADMET Properties for molecules **4a-4n** 23-25

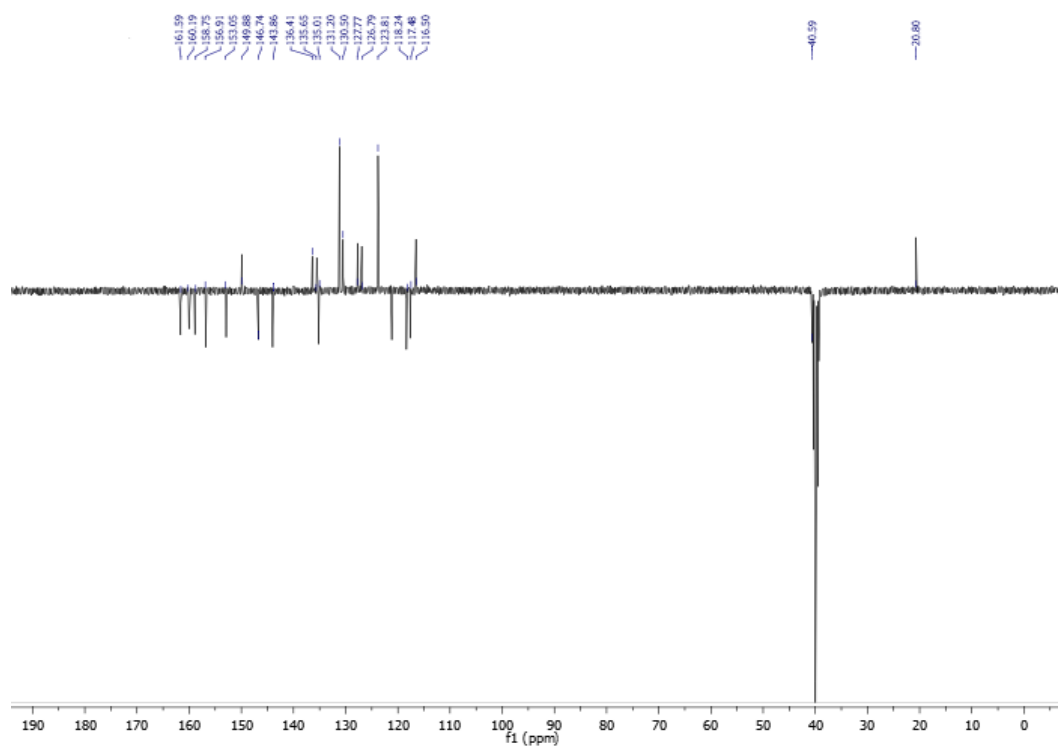
***N*-(2-(4-bromobenzyl)-4-oxoquinazolin-3(4*H*)-yl)-6-methyl-2-oxo-2*H*-chromene-3-carboxamide (**4a**)**



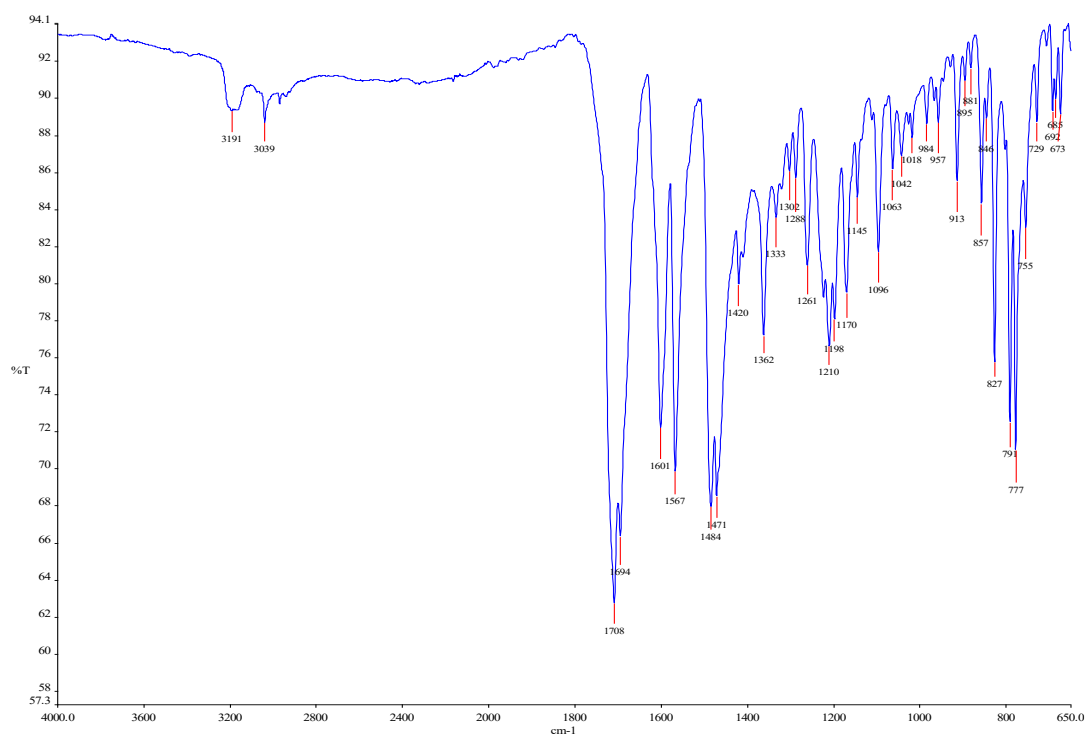
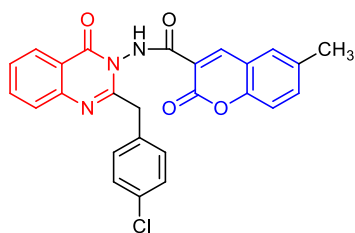


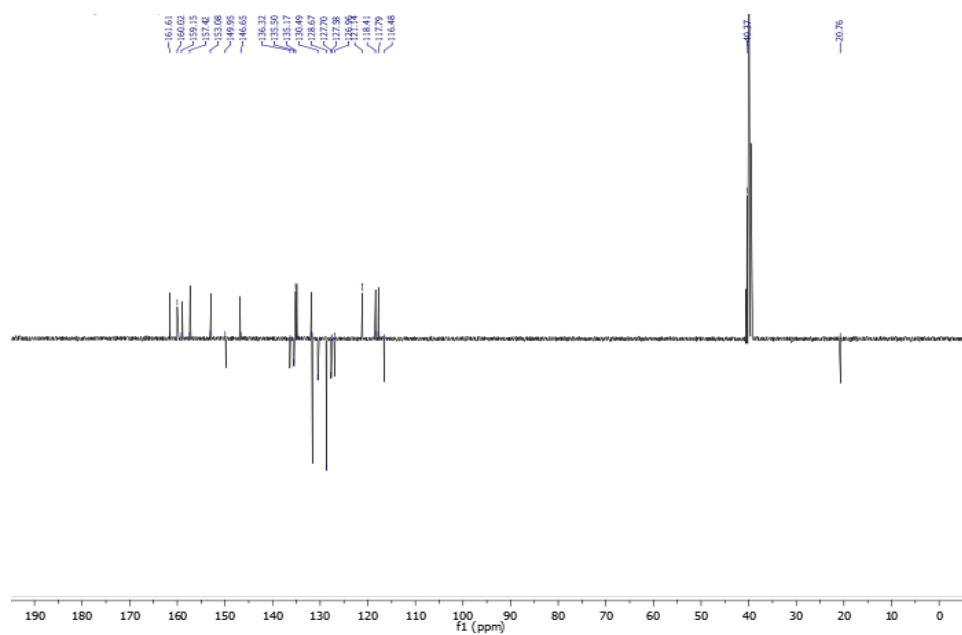
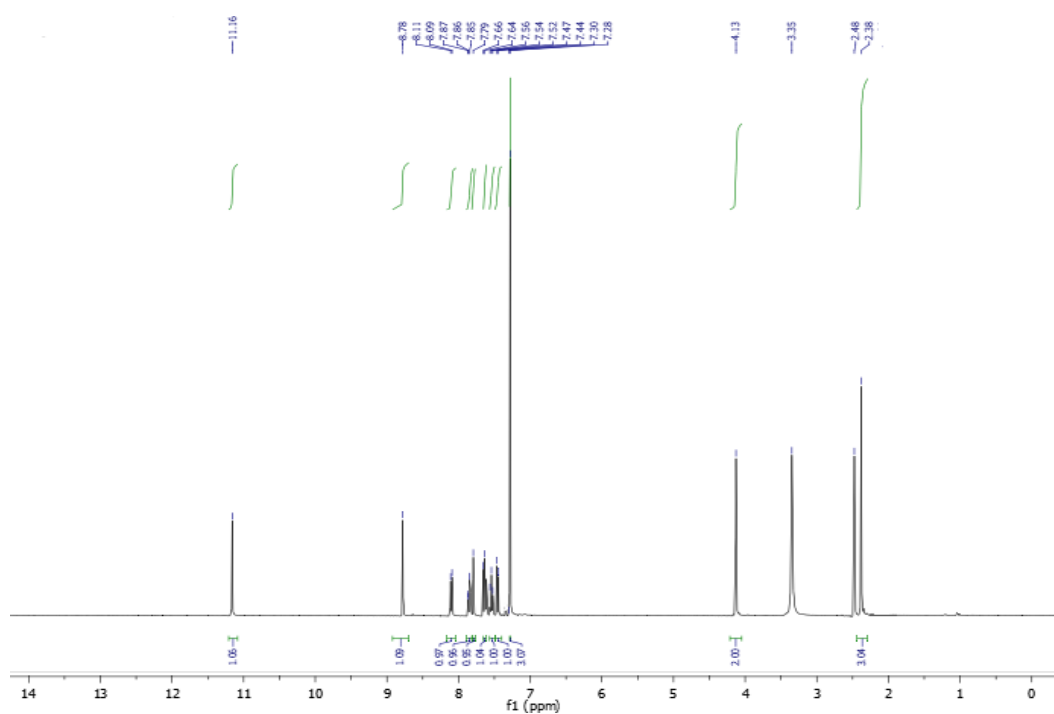
6-methyl-*N*-(2-(4-nitrobenzyl)-4-oxoquinazolin-3(4*H*)-yl)-2-oxo-2*H*-chromene-3-carboxamide (4b)



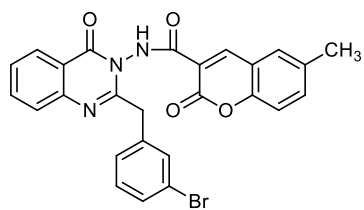


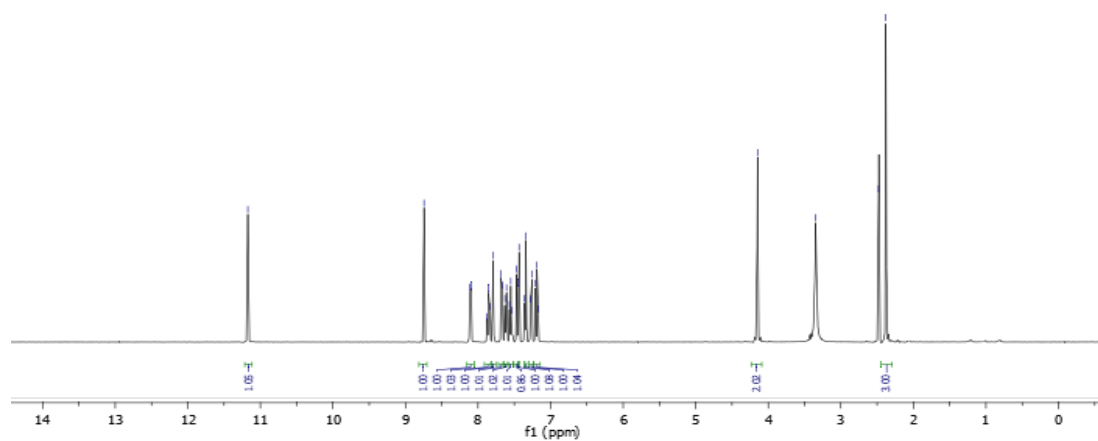
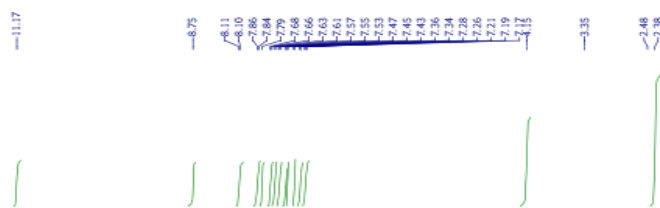
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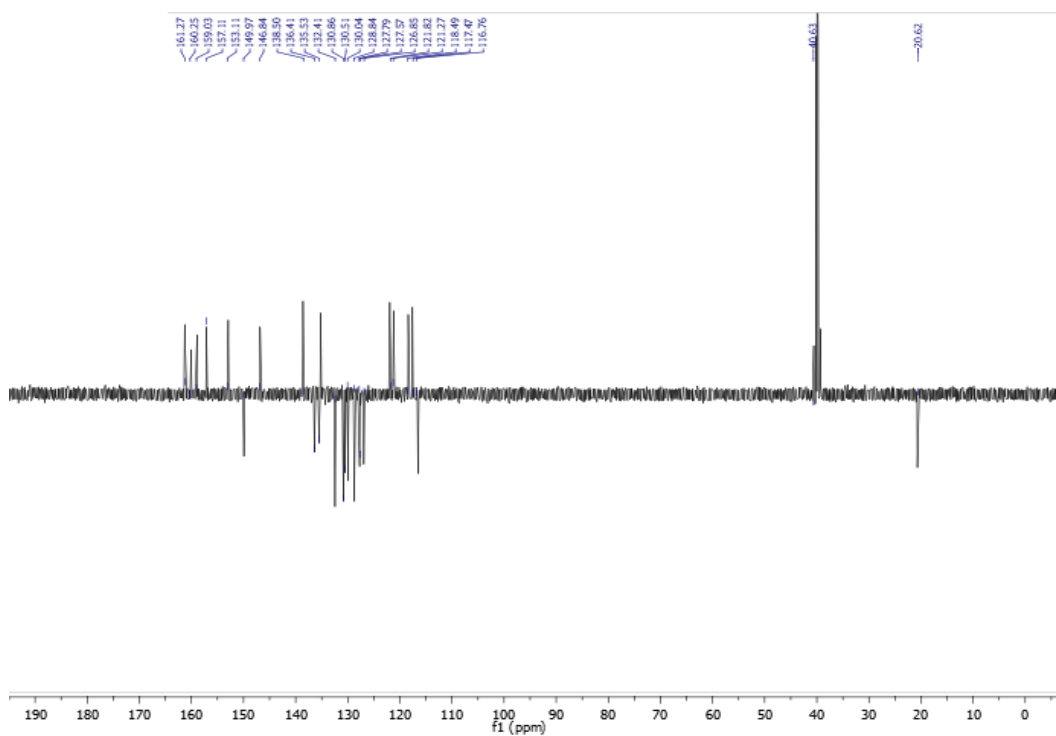




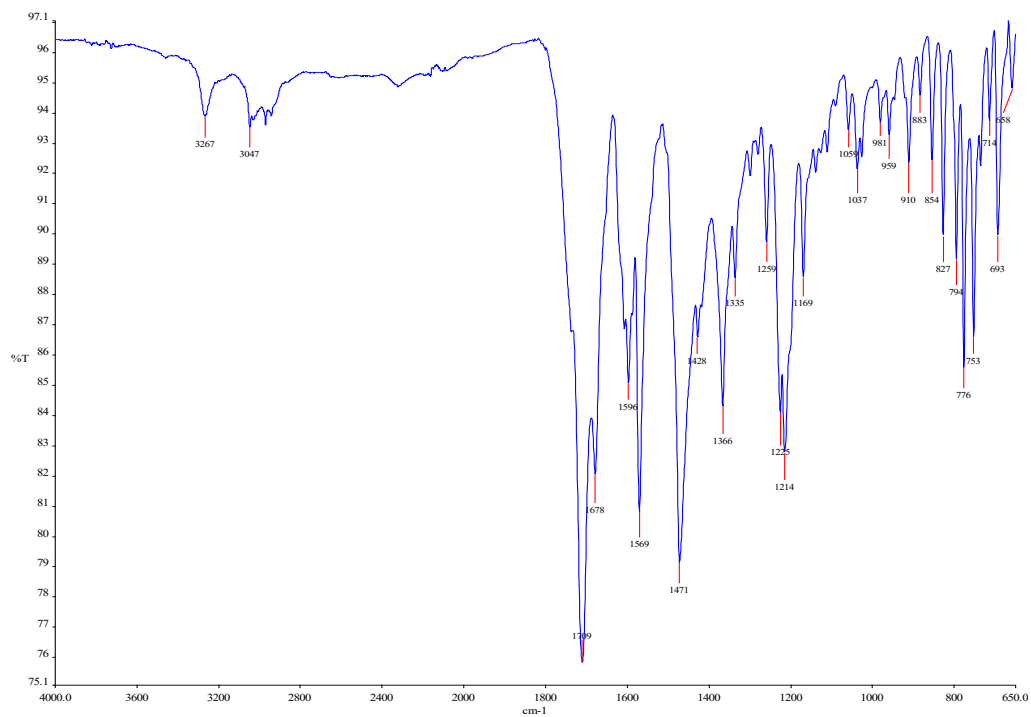
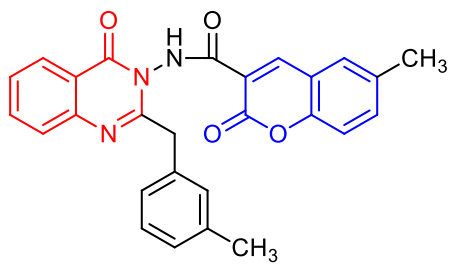
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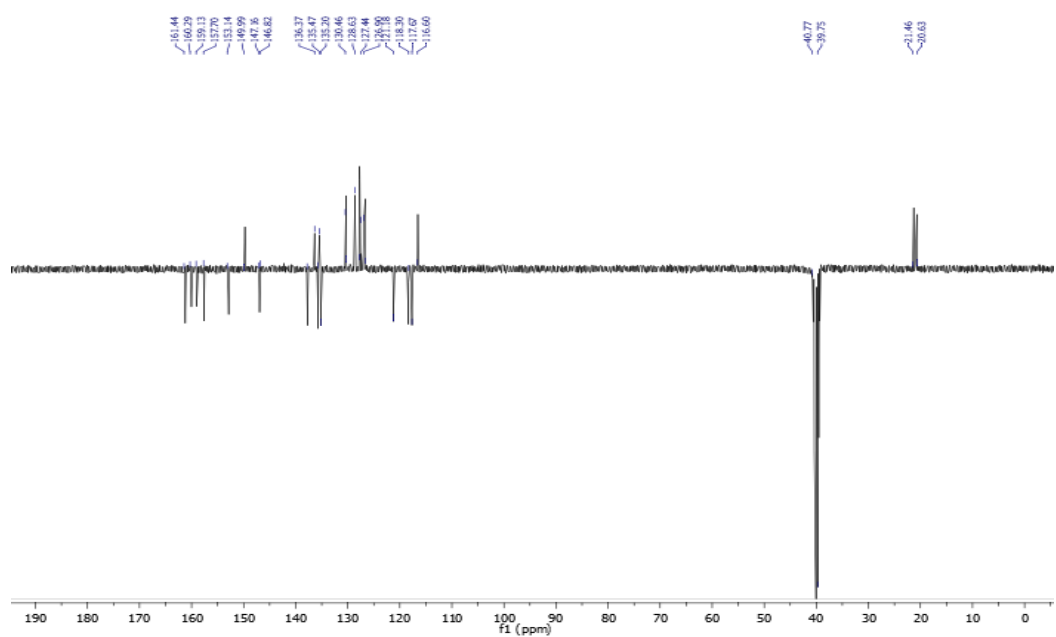
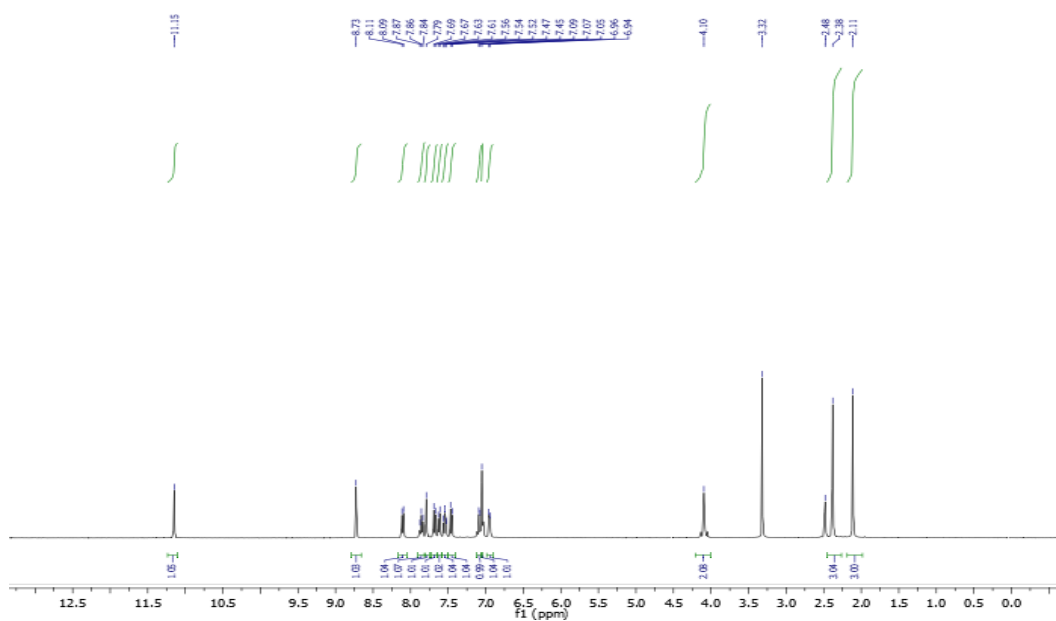




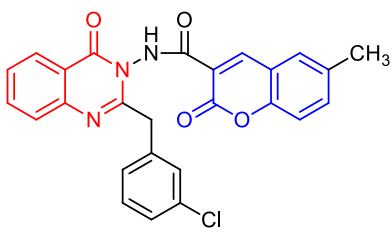


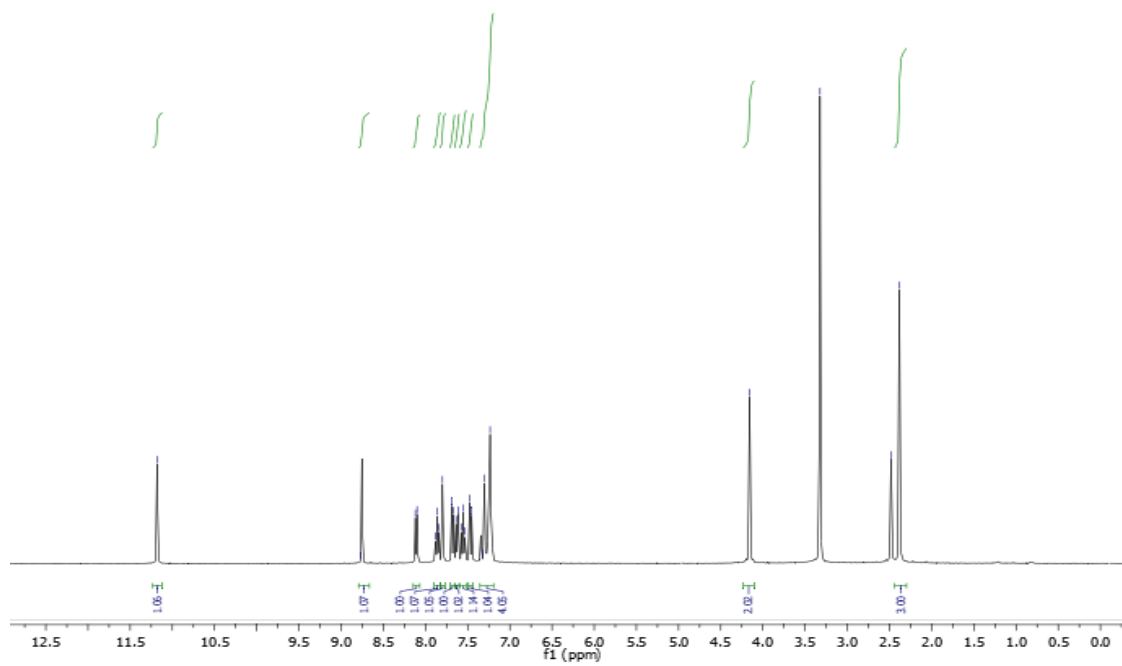
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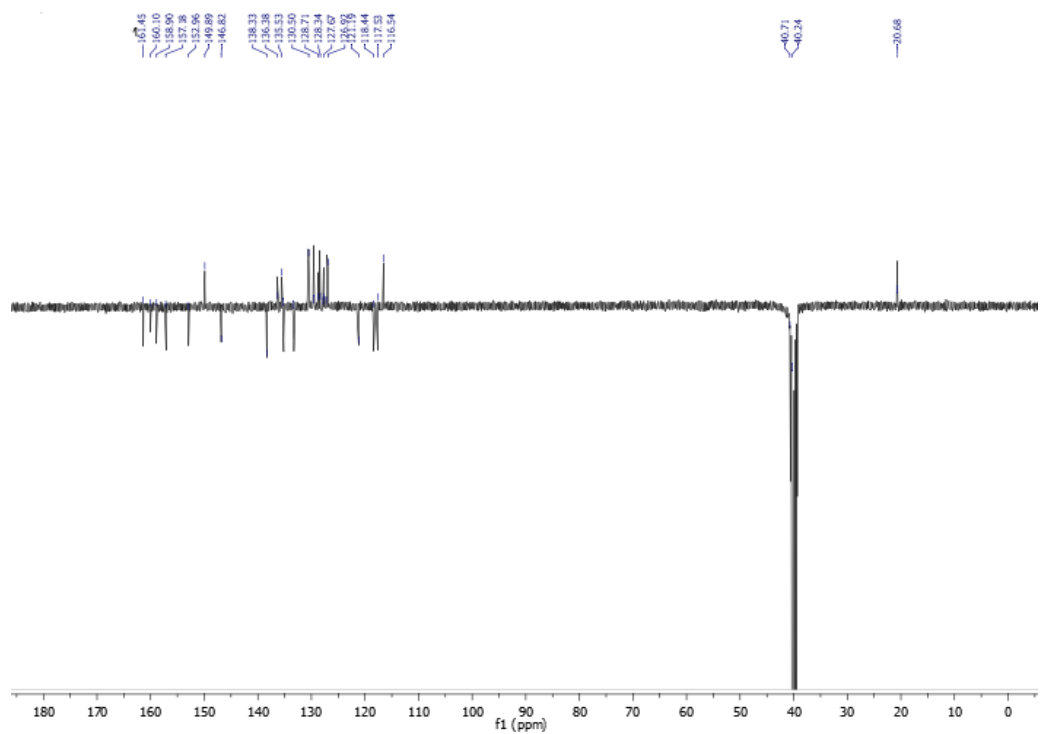




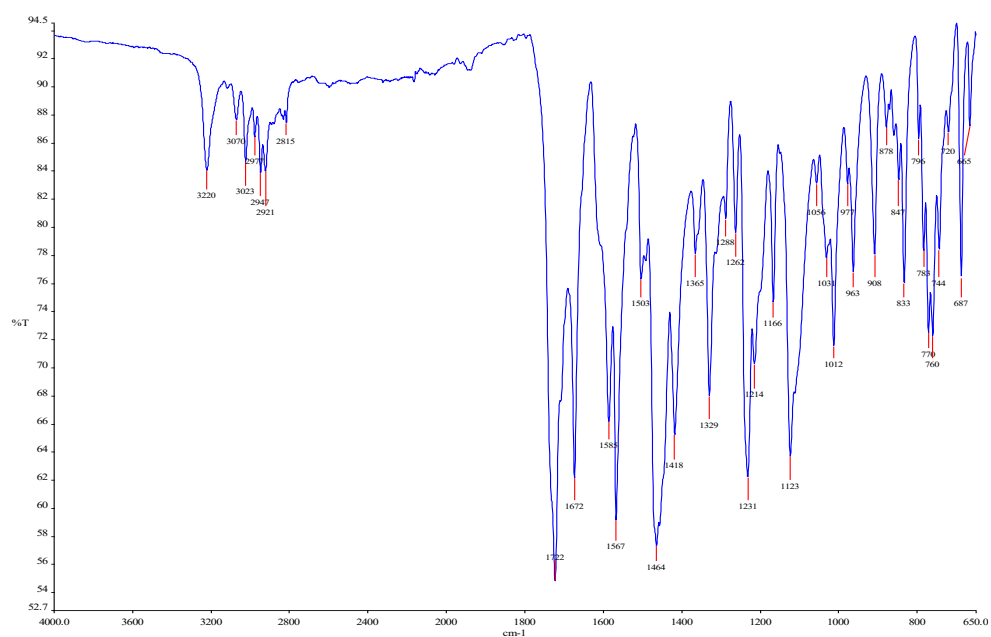
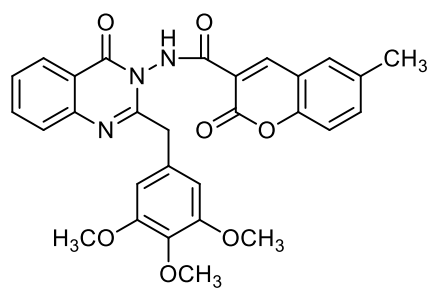
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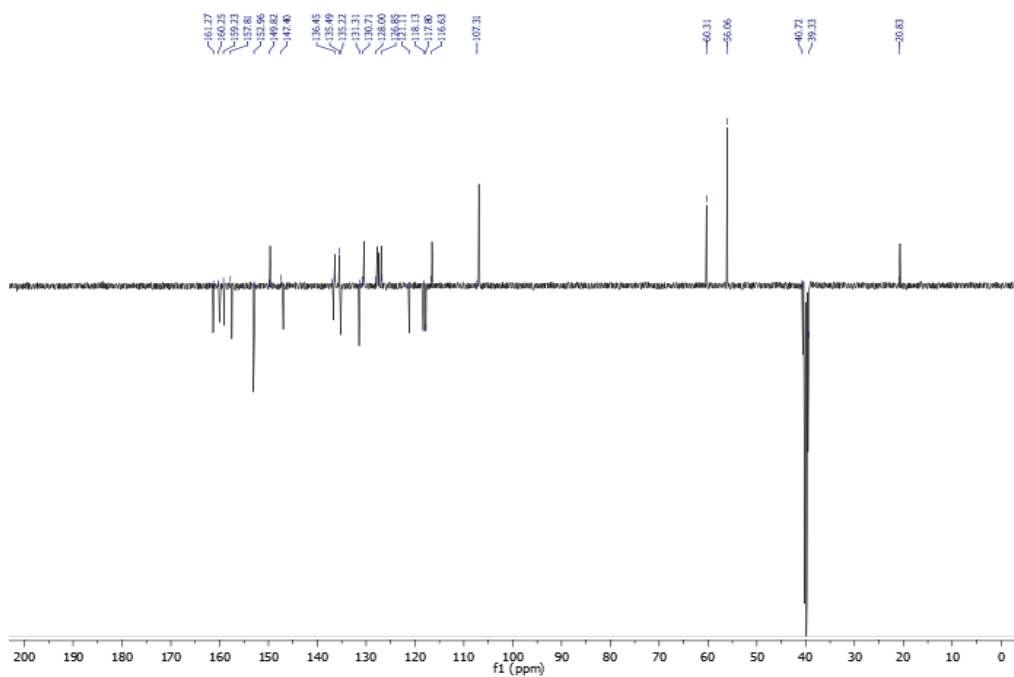
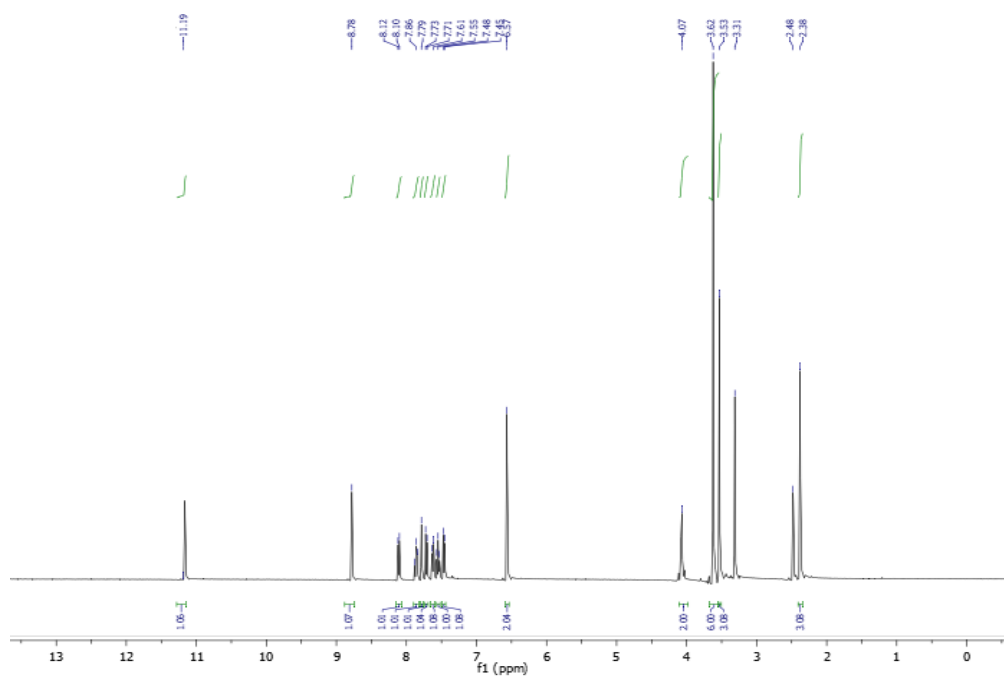




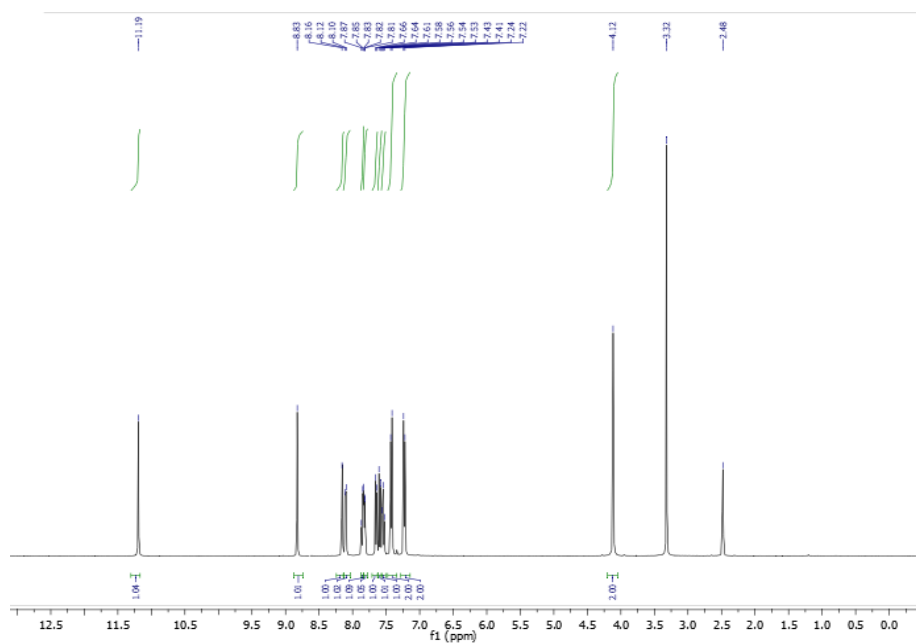
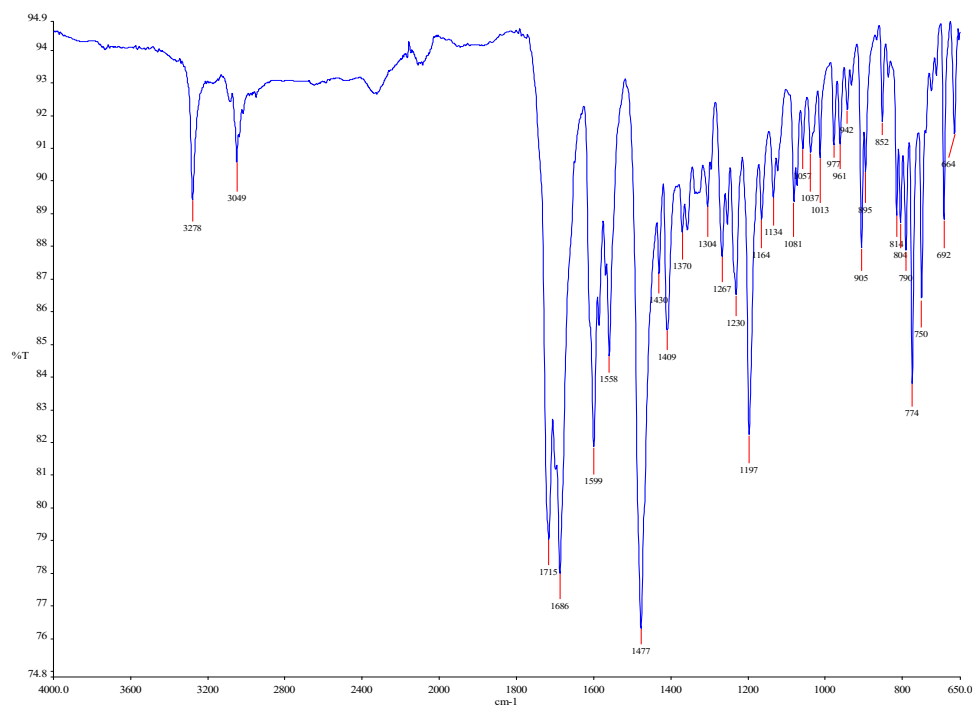
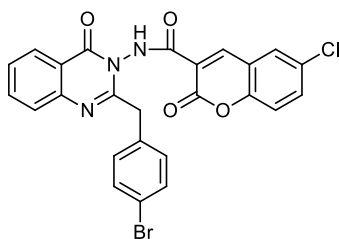


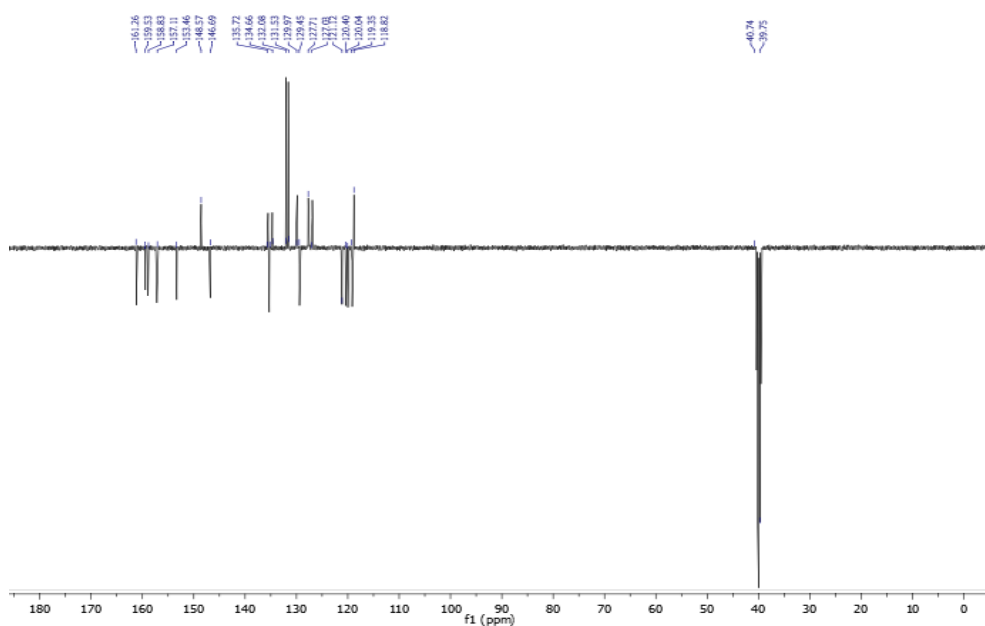
6-methyl-2-oxo-*N*-(4-oxo-2-(3,4,5-trimethoxybenzyl)quinazolin-3(4*H*)-yl)-2*H*-chromene-3-carboxamide (4g)



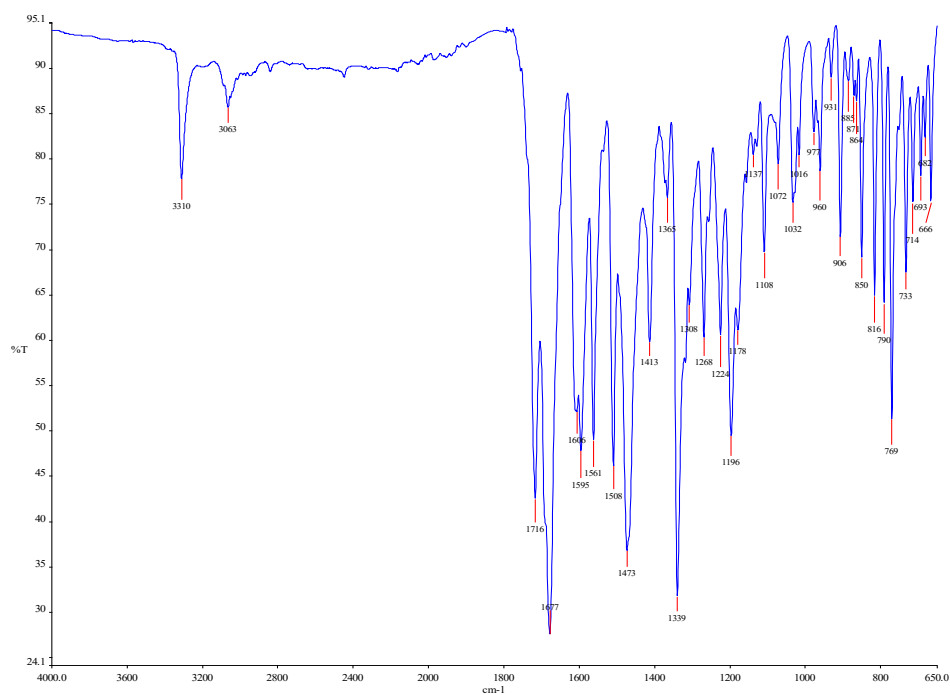
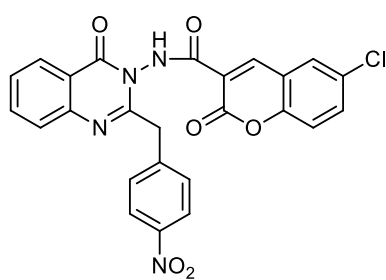


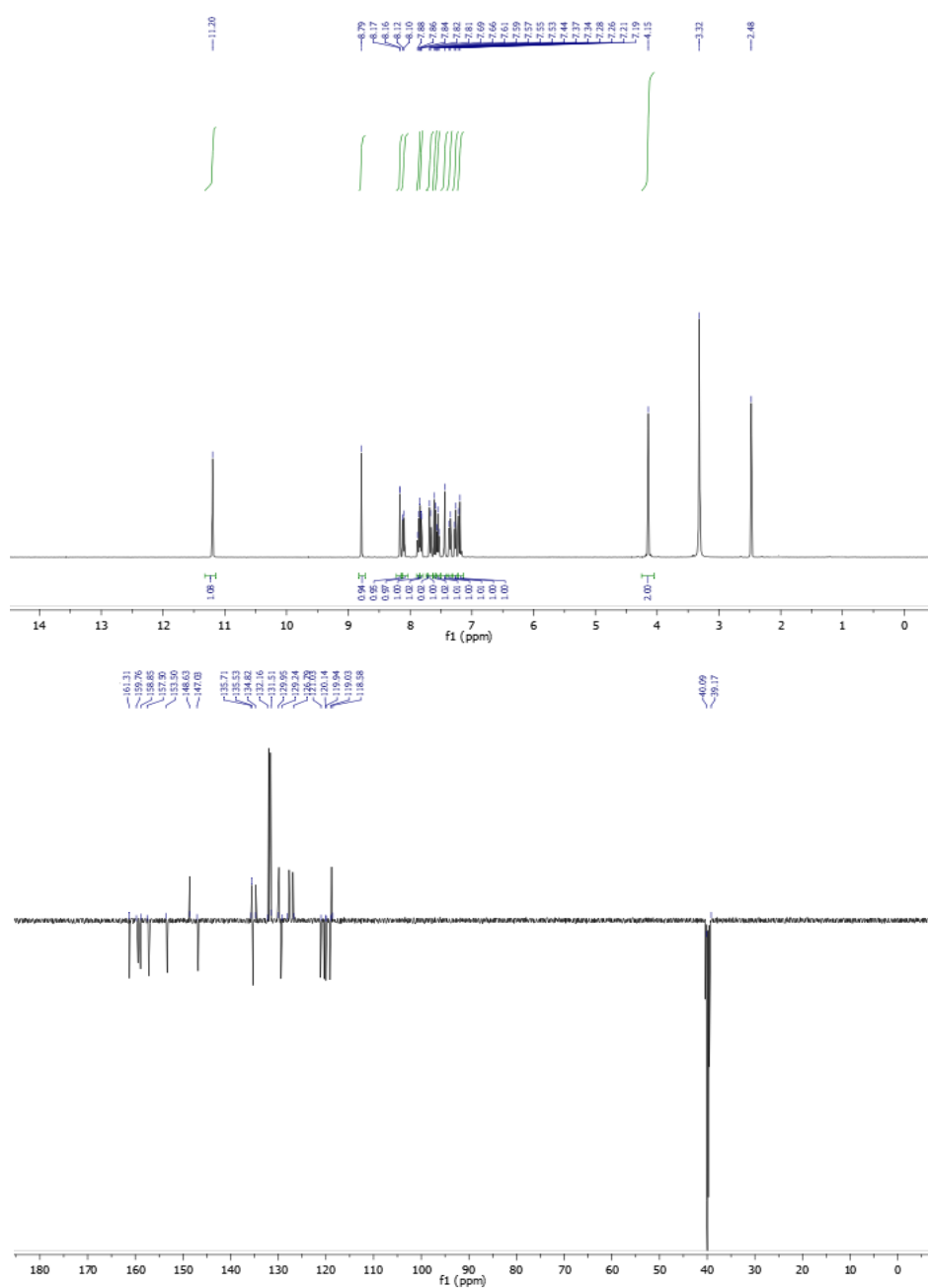
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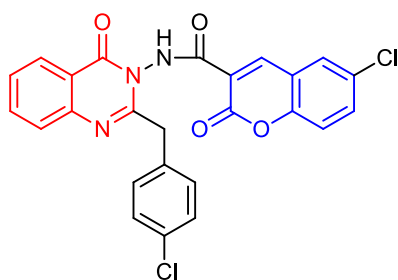


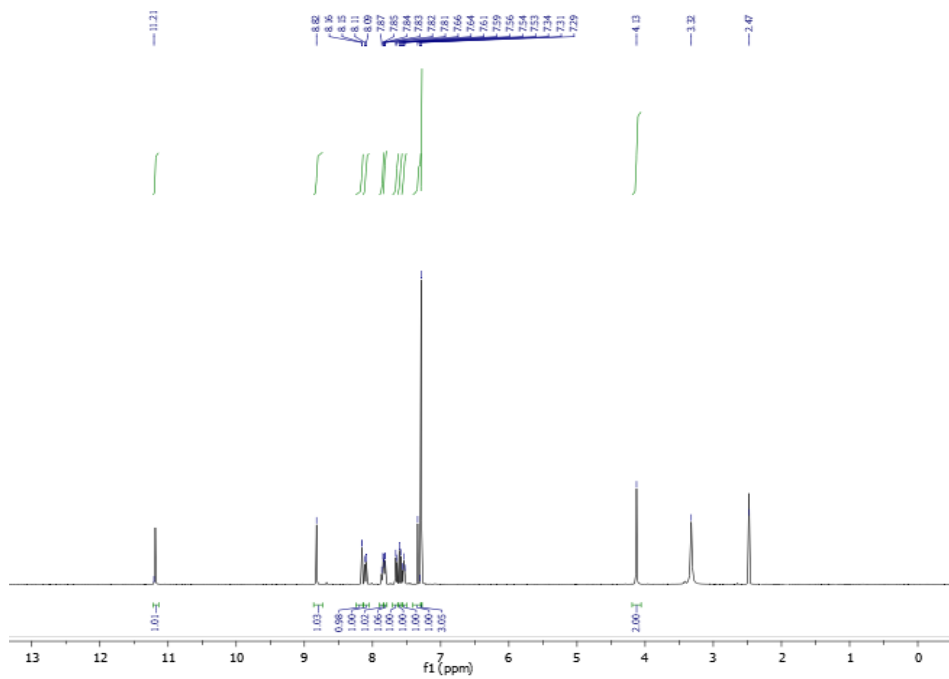
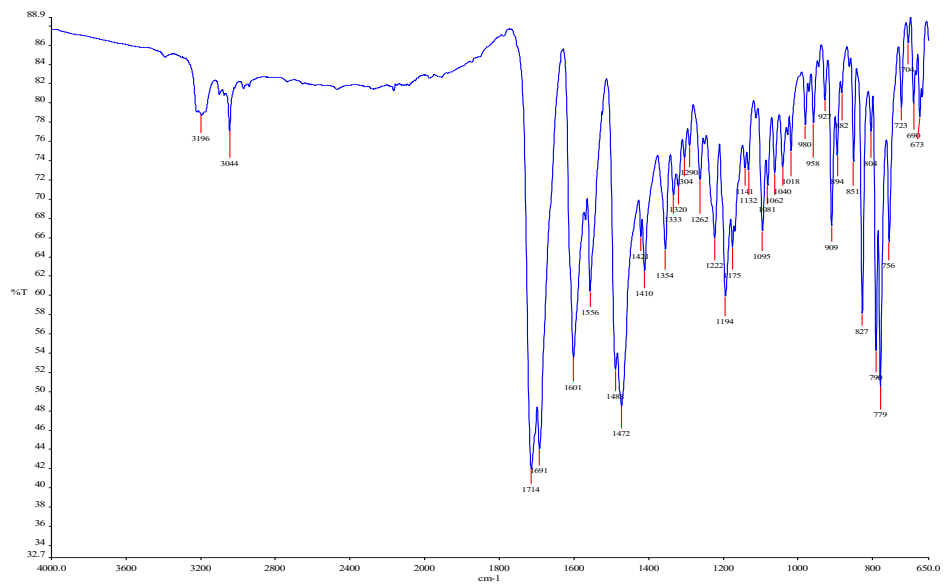
6-chloro-*N*-(2-(4-nitrobenzyl)-4-oxoquinazolin-3(4*H*)-yl)-2-oxo-2*H*-chromene-3-carboxamide hydrochloride (4i)

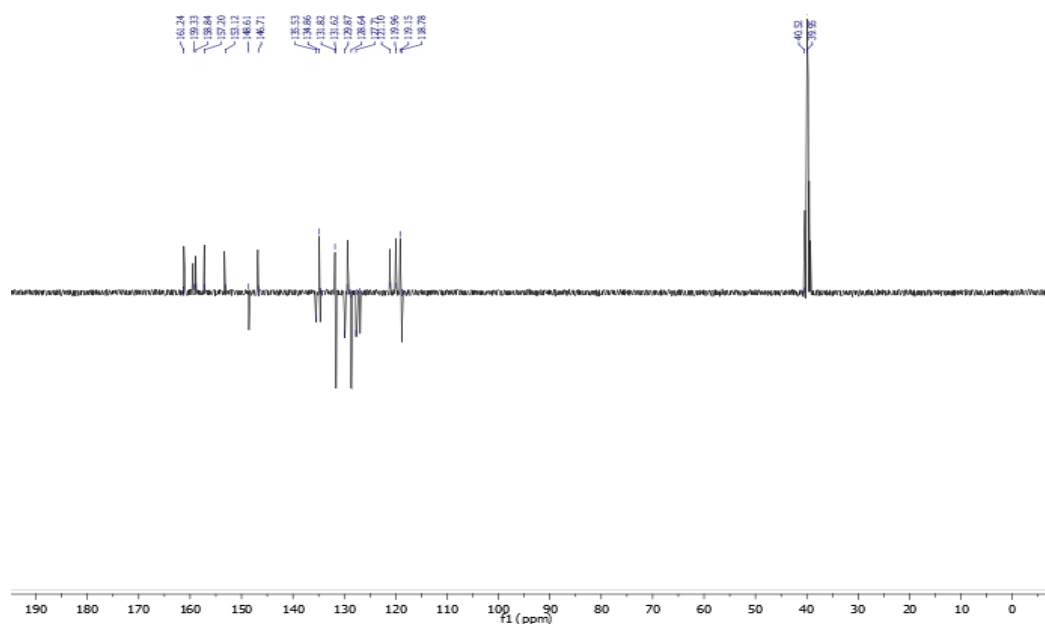




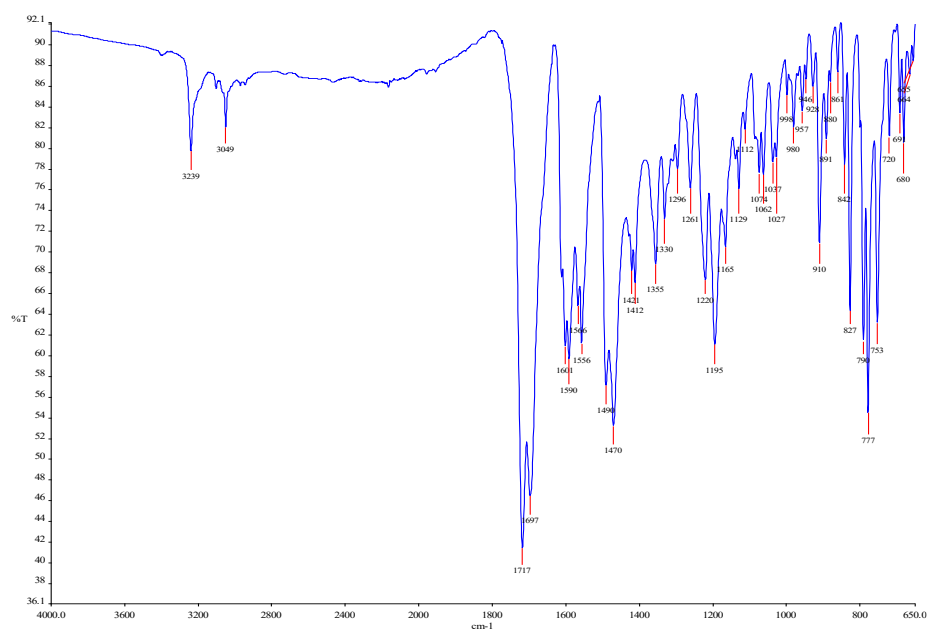
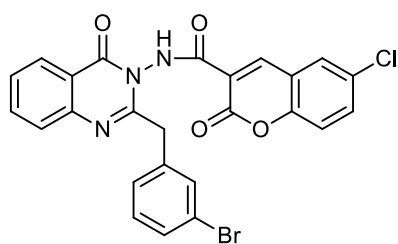
6-chloro-N-(2-(4-chlorobenzyl)-4-oxoquinazolin-3(4H)-yl)-2-oxo-2H-chromene-3-carboxamide (4j)

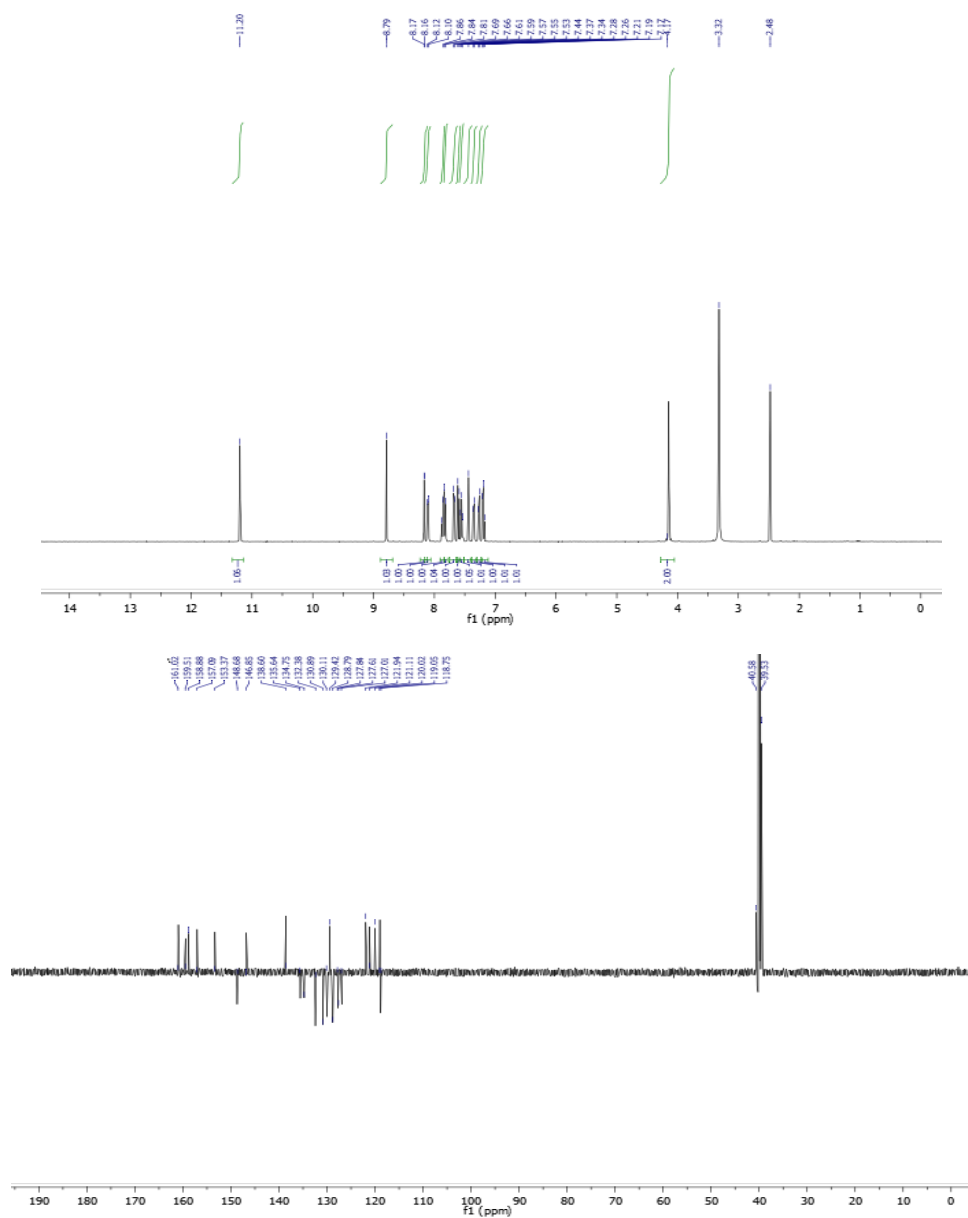




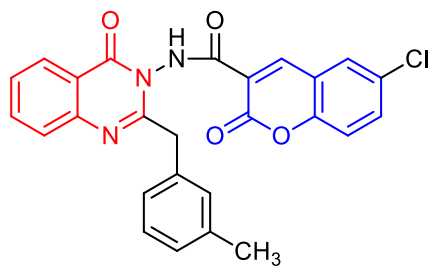


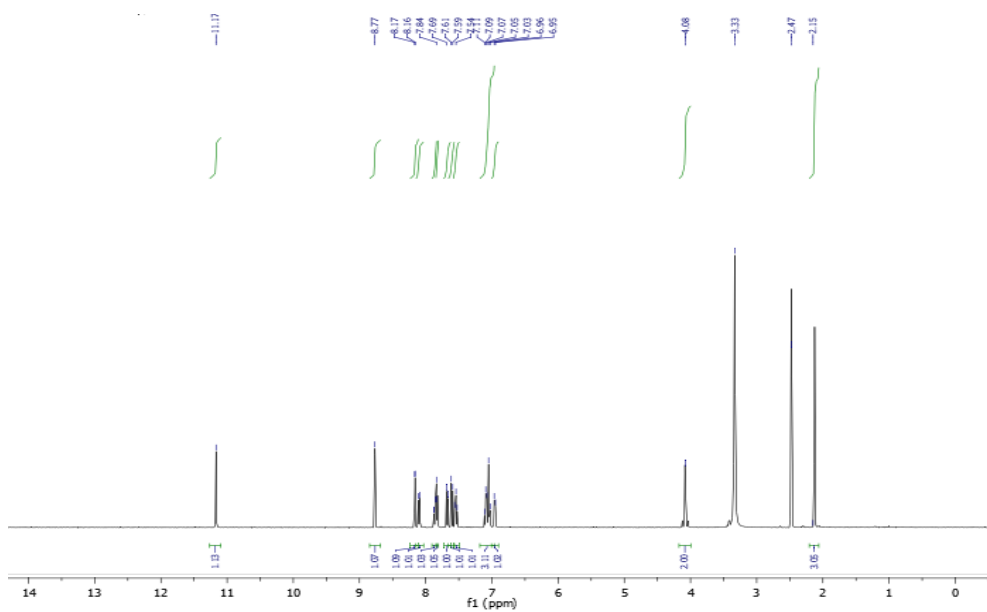
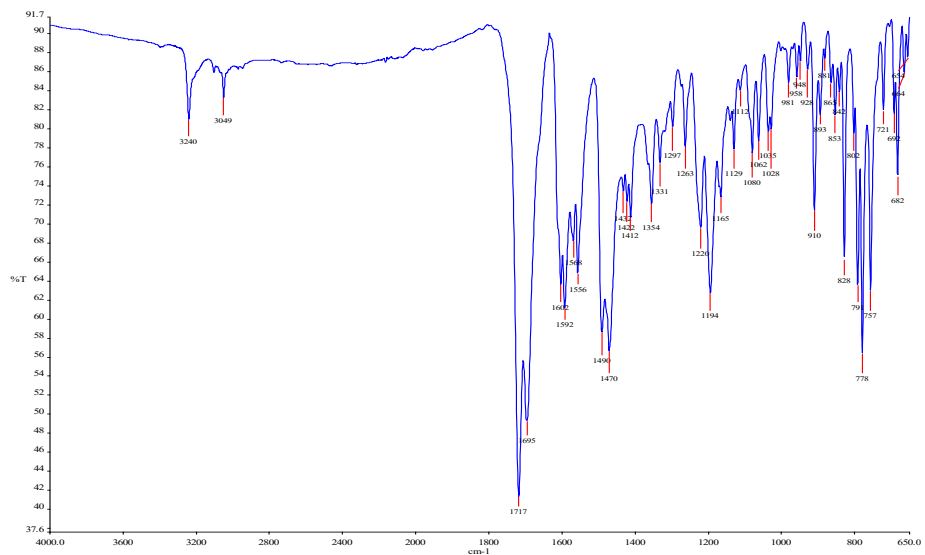
***N*-(2-(3-bromobenzyl)-4-oxoquinazolin-3(4*H*)-yl)-6-chloro-2-oxo-2*H*-chromene-3-carboxamide (4k)**

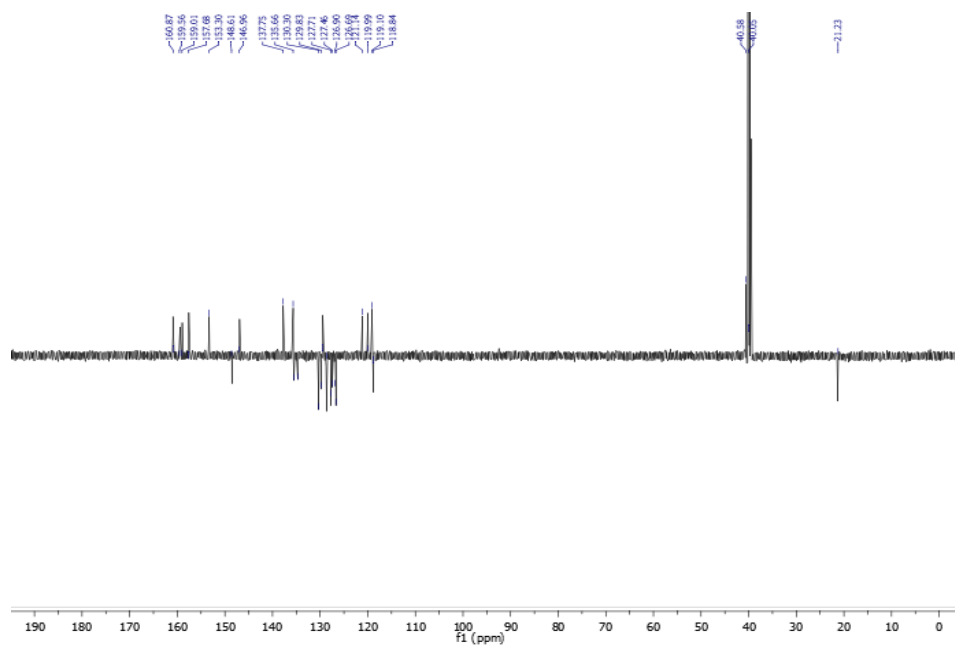




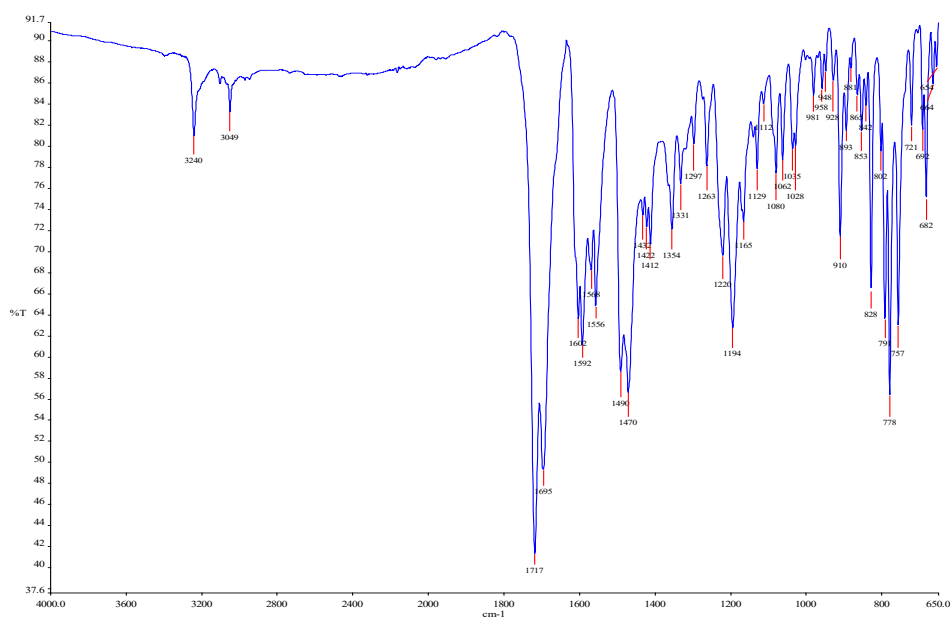
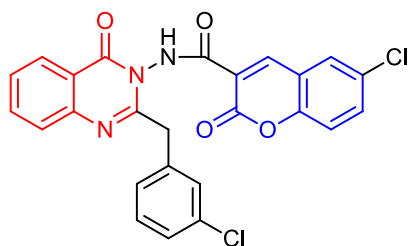
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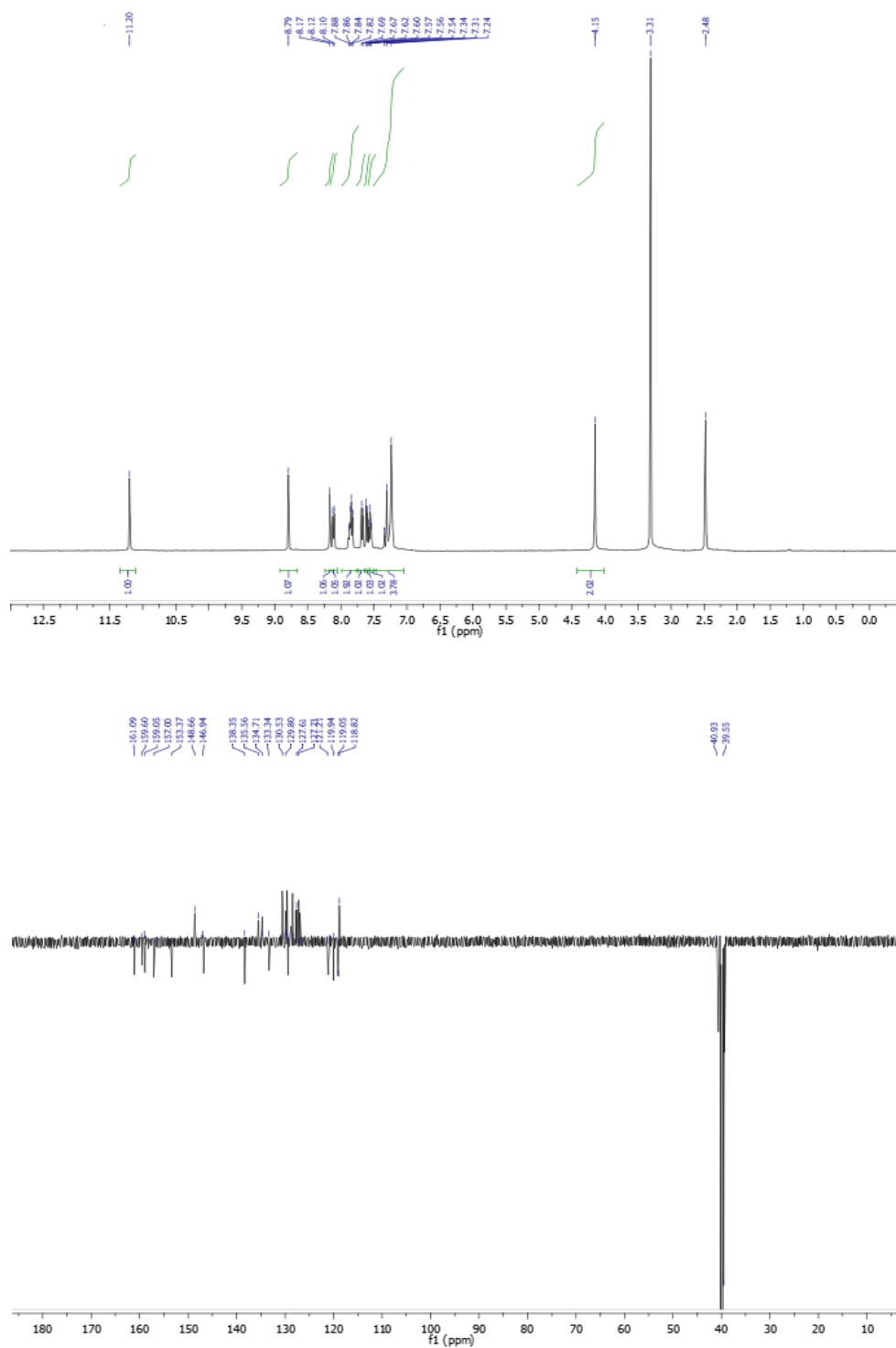




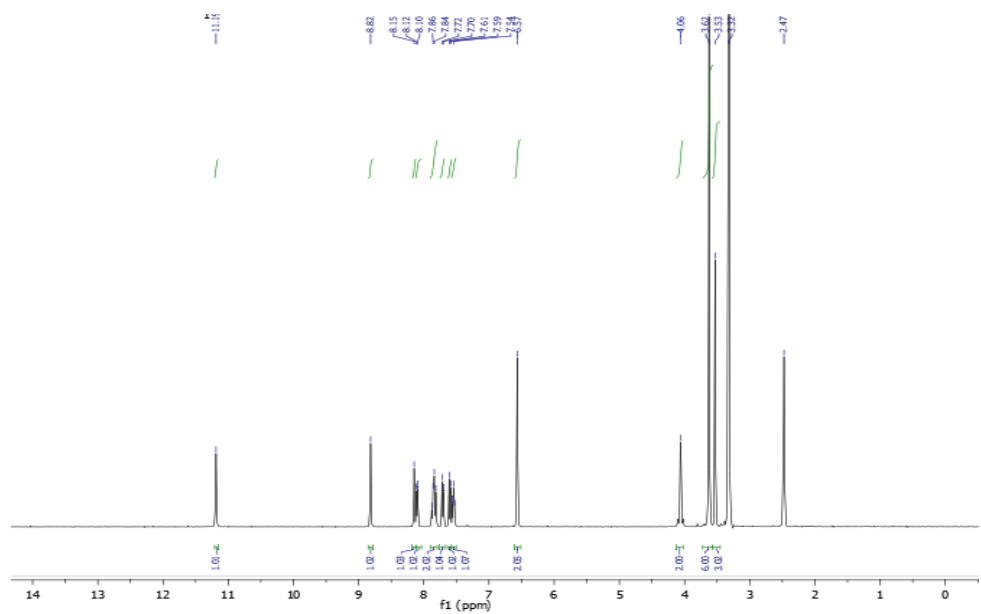
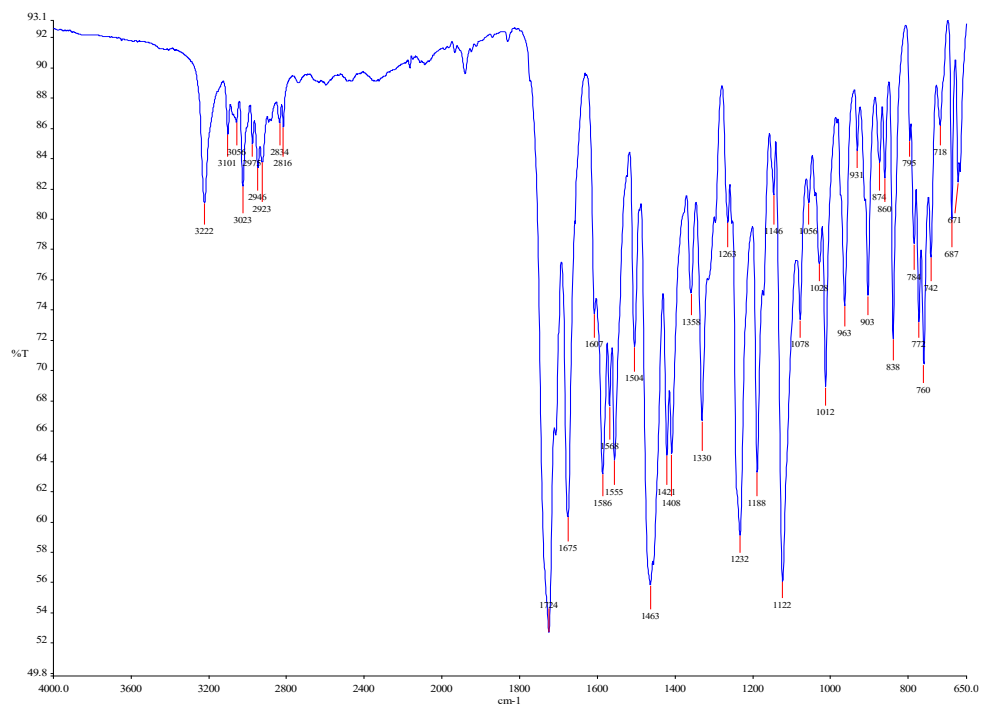
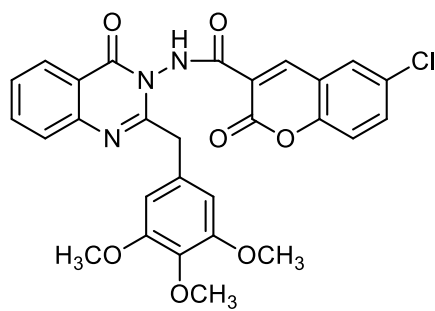


3-(((6-chloro-2-oxo-2H-chromen-3-yl)methyl)amino)-2-(3-chlorobenzyl)quinazolin-4(3H)-one (4m)





6-chloro-2-oxo-*N*-(4-oxo-2-(3,4,5-trimethoxybenzyl)quinazolin-3(4*H*)-yl)-2H-chromene-3-carboxamide (4n)



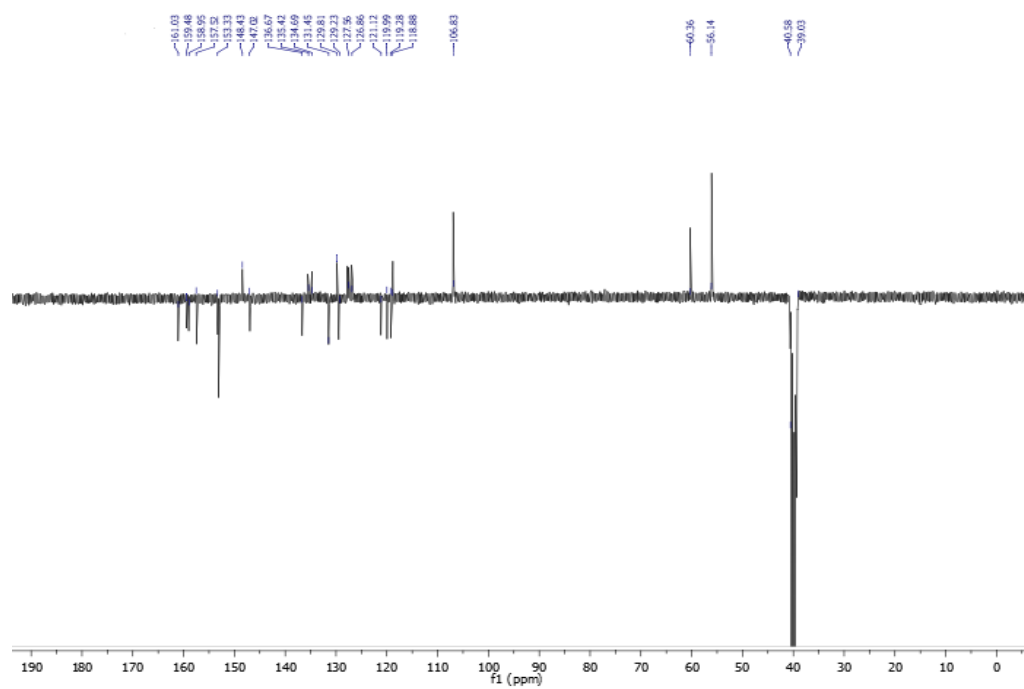


Table 2. ADMET Properties for **4a-4n** molecules

Properties	Molecules													
Absorption	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	4m	4n
Caco-2 Permeability	- 4.8 80	- 4.9 33	- 4.6 67	- 4.9 50	- 4.7 91	- 4.7 14	- 4.7 48	- 4.9 05	- 4.8 82	- 4.5 66	- 4.9 17	- 4.7 13	- 4.6 11	- 4.9 71
MDCK (Madin-Darby Canine Kidney) Permeability	- 4.5 42	- 4.5 16	- 4.6 08	- 4.5 31	- 4.6 35	- 4.6 04	- 4.4 98	- 4.4 77	- 4.4 73	- 4.5 94	- 4.4 87	- 4.6 03	- 4.5 89	- 4.5 02
PAMPA (ParallelArtificialMembranePermeabilityAssay)	0.3 12	0.6 24	0.3 21	0.3 11	0.3 33	0.3 14	0.1 21	0.2 95	0.6 05	0.3 03	0.2 94	0.3 15	0.2 97	0.1 12
P-glikoprotein-inhibitor	0.9 27	0.3 19	0.8 64	0.2 93	0.3 35	0.1 88	0.1 67	0.9 29	0.3 27	0.8 68	0.3 01	0.3 43	0.1 94	0.1 72
P-glikoprotein-substrate	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00
Human IntestinalAbsorption	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00
Oral Bioavailability (F% ₂₀)	0.0 58	0.1 03	0.0 62	0.2 47	0.3 00	0.2 31	0.3 60	0.0 09	0.0 17	0.0 10	0.0 46	0.0 59	0.0 42	0.0 05
Oral Bioavailability (F% ₃₀)	0.0 34	0.0 96	0.0 39	0.3 64	0.1 63	0.2 32	0.0 07	0.0 09	0.0 26	0.0 10	0.1 27	0.0 47	0.0 71	0.0 02
Oral Bioavailability (F% ₅₀)	0.0 10	0.0 22	0.0 19	0.0 49	0.0 56	0.0 61	0.0 13	0.0 06	0.0 13	0.0 11	0.0 29	0.0 33	0.0 36	0.0 07
TPSA (Topological Polar SurfaceArea)	94. 200	137 .34	94. 20	94. 20	94. 20	94. 20	121 .89	94. 20	137 .34	94. 20	94. 20	94. 20	94. 20	121 .89
Skin Permeation (cm/s)	- 5.9 80	- 6.3 80	- 5.7 50	- 5.9 80	- 5.8 20	- 5.8 20	- 6.6 00	- 5.9 20	- 6.3 20	- 5.6 90	- 5.9 20	- 5.7 50	- 5.6 90	- 6.5 30
GI Absorption	Hig h	Lo w	Hig h	Hig h	Hig h	Hig h	Hig h	Hig h	Lo w	Hig h	Hig h	Hig h	Hig h	Hig h
BBB Permeant	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Distribution														
PPB (Plasma Protein Binding)	98. 461	97. 832	98. 835	98. 397	98. 286	98. 714	98. 248	98. 903	98. 848	99. 186	98. 893	98. 914	99. 120	98. 858
VDss (Volume of Distribution at SteadyState)	- 0.1 25	- 0.2 33	- 0.3 16	- 0.1 29	- 0.3 64	- 0.3 40	- 0.3 16	- 0.0 39	- 0.3 50	- 0.3 28	- 0.0 83	- 0.3 71	- 0.3 98	- 0.3 67
(BBB) Blood-Brain BarrierPermeability	0.2 23	0.0 01	0.1 37	0.1 08	0.0 26	0.0 60	0.0 52	0.7 91	0.0 11	0.6 77	0.6 14	0.2 60	0.4 58	0.4 21
Fu (FractionUnbound in Plasma)	1.0 65	1.7 58	0.6 78	1.1 78	1.1 87	0.7 28	1.3 32	0.6 49	0.7 60	0.4 33	0.6 67	0.6 14	0.4 43	0.7 92
OATP1B1 inhibitor	0.9 94	0.9 30	0.9 93	0.9 77	0.9 96	0.9 76	0.9 95	0.9 88	0.8 68	0.9 85	0.9 55	0.9 92	0.9 53	0.9 90
OATP1B3 inhibitor	0.9 95	0.8 82	0.9 86	0.9 84	0.9 91	0.9 77	0.9 51	0.9 89	0.7 81	0.9 70	0.9 68	0.9 82	0.9 54	0.9 03
BCRP (BreastCancerResistance Protein) inhibitor	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00
MRP1 (MultidrugResistance-associated Protein) inhibitor	0.9 99	1.0 00	0.9 98	0.9 99	0.9 98	0.9 99	1.0 00	0.9 92	1.0 00	0.9 89	0.9 94	0.9 86	0.9 93	0.9 99
logS	- 5.5 13	- 5.0 57	- 5.4 92	- 5.2 72	- 4.8 12	- 5.2 75	- 5.1 16	- 5.7 46	- 5.2 28	- 5.6 58	- 5.5 01	- 5.3 11	- 5.4 53	- 5.5 48
logP	4.3 42	3.1 19	4.0 35	4.2 28	4.0 85	3.9 85	2.9 94	4.2 74	3.1 03	4.0 48	4.1 65	4.0 89	3.9 87	3.2 00
logD	3.8 66	3.3 03	3.6 62	3.7 08	3.6 49	3.5 83	3.0 19	3.7 44	3.2 46	3.6 22	3.6 01	3.6 49	3.5 38	3.1 19
Metabolism														
CYP1A2 inhibitor	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	00	01	04	03	00	01	00	02	02	16	13	01	05	00
CYP1A2 substrate	0.0 64	0.0 25	0.1 65	0.0 04	0.3 60	0.5 08	0.1 76	0.0 27	0.0 10	0.0 75	0.0 02	0.1 88	0.2 98	0.0 81
CYP2C19 inhibitor	0.4 60	0.2 08	0.2 54	0.2 66	0.2 79	0.1 10	0.0 59	0.5 05	0.2 40	0.2 90	0.3 02	0.3 17	0.1 29	0.0 70
CYP2C19 substrate	0.0 00	0.0 00	0.0 11	0.0 00	0.0 03	0.0 02	0.3 15	0.0 00	0.0 00	0.0 01	0.0 00	0.0 00	0.0 00	0.0 28
CYP2C9 inhibitor	0.6 50	0.0 48	0.1 44	0.7 63	0.2 59	0.6 88	0.3 59	0.4 84	0.0 25	0.0 78	0.6 18	0.1 50	0.5 27	0.2 20
CYP2C9 substrate	0.0 00	0.0 00	0.0 01	0.0 00	0.0 00	0.0 00	0.0 00	0.0 01	0.0 01	0.0 04	0.0 00	0.0 00	0.0 00	0.0 00
CYP2D6 inhibitor	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00
CYP2D6 substrate	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00	0.0 00
CYP3A4 inhibitor	0.9 57	0.9 68	0.9 80	0.9 68	0.9 98	0.9 57	0.9 98	0.9 49	0.9 62	0.9 76	0.9 62	0.9 97	0.9 49	0.9 98
CYP3A4 substrate	0.0 75	0.0 40	0.0 85	0.0 01	0.0 27	0.0 18	0.9 86	0.3 51	0.2 17	0.3 82	0.0 08	0.1 57	0.1 10	0.9 98
CYP2B6 inhibitor	0.0 02	0.0 01	0.1 22	0.0 43	0.0 31	0.2 90	0.0 01	0.0 05	0.0 02	0.2 83	0.1 12	0.0 83	0.5 38	0.0 04
CYP2B6 substrate	0.0 00	0.0 00	0.0 02	0.0 00	0.0 06	0.0 31	0.0 00	0.0 00	0.0 00	0.0 01	0.0 00	0.0 02	0.0 12	0.0 00
CYP2C8 inhibitor	1.0 00	1.0 00	0.9 94	1.0 00	1.0 00	0.9 92	1.0 00	1.0 00	1.0 00	0.9 99	1.0 00	1.0 00	0.9 99	1.0 00
HLM (Human LiverMicrosome) Stability	0.6 20	0.8 77	0.5 39	0.6 22	0.9 45	0.7 49	0.4 82	0.8 09	0.9 49	0.7 53	0.8 11	0.9 78	0.8 86	0.7 08
Excretion														
CL _{plasma} (PlasmaClearance)	1.3 48	1.8 38	1.4 84	2.2 52	2.6 18	2.1 84	2.5 46	0.9 98	1.1 91	1.3 13	1.6 59	2.1 08	1.6 06	2.0 29
T _{1/2} (Half-life)	0.8 77	0.8 69	0.8 91	0.7 22	0.7 76	0.8 71	0.9 74	1.0 02	0.9 83	1.1 02	0.8 22	0.8 68	1.0 75	1.1 01
Toxicity														
hERGBlockers	0.2 31	0.1 88	0.3 17	0.2 14	0.2 07	0.3 00	0.2 04	0.3 30	0.2 74	0.4 31	0.3 08	0.2 99	0.4 12	0.2 96
hERGBlockers (10µm)	0.5 15	0.4 40	0.5 87	0.5 04	0.4 64	0.5 69	0.4 18	0.6 14	0.5 41	0.6 80	0.6 04	0.5 65	0.6 64	0.5 18
DILI (Drug-InducedLiverInjury)	0.9 68	0.9 97	0.9 61	0.9 64	0.9 15	0.9 58	0.9 47	0.9 88	0.9 99	0.9 85	0.9 86	0.9 66	0.9 84	0.9 79
AMES Mutagenicity	0.3 09	0.8 44	0.3 52	0.3 42	0.4 78	0.3 78	0.2 98	0.2 19	0.7 73	0.2 54	0.2 46	0.3 65	0.2 76	0.2 11
Rat Oral AcuteToxicity	0.4 26	0.4 69	0.3 60	0.4 30	0.2 92	0.3 55	0.3 16	0.4 99	0.5 42	0.4 30	0.5 03	0.3 57	0.4 25	0.3 83
FDAMDD (FDA Maximum Daily Dose)	0.8 26	0.6 34	0.6 66	0.7 90	0.6 17	0.6 51	0.5 33	0.8 38	0.6 53	0.6 84	0.8 04	0.6 36	0.6 70	0.5 53
Skin Sensitization	0.6 88	0.8 73	0.6 12	0.7 28	0.5 87	0.6 29	0.3 03	0.6 92	0.8 75	0.6 16	0.7 31	0.5 91	0.6 33	0.3 06
Carcinogenicity	0.3 05	0.4 58	0.2 76	0.3 05	0.3 07	0.2 90	0.4 53	0.2 76	0.4 24	0.2 50	0.2 76	0.2 78	0.2 62	0.4 19
EyeCorrosion	0.0 01	0.0 01	0.0 01	0.0 03	0.0 01	0.0 01	0.0 00	0.0 01	0.0 01	0.0 00	0.0 02	0.0 01	0.0 00	0.0 00
EyeIrritation	0.8 39	0.9 14	0.5 70	0.8 90	0.8 12	0.6 23	0.5 37	0.6 58	0.7 97	0.3 28	0.7 49	0.6 13	0.3 78	0.2 99
Respiratory	0.5 58	0.7 27	0.5 66	0.6 10	0.6 40	0.5 82	0.5 77	0.5 13	0.6 90	0.5 21	0.5 66	0.5 97	0.5 37	0.5 32
Human Hepatotoxicity	0.4 45	0.6 10	0.5 26	0.4 00	0.5 29	0.5 14	0.5 35	0.4 29	0.5 94	0.5 10	0.3 85	0.5 12	0.4 97	0.5 19
Drug-inducedNephrotoxicity	0.2 90	0.2 84	0.5 37	0.2 59	0.3 27	0.5 05	0.3 78	0.4 65	0.4 58	0.7 12	0.4 27	0.5 09	0.6 85	0.5 65
Ototoxicity	0.2 24	0.2 51	0.3 22	0.2 03	0.2 72	0.3 09	0.4 51	0.2 56	0.2 84	0.3 61	0.2 33	0.3 13	0.3 47	0.4 74
Hematotoxicity	0.2 07	0.4 88	0.3 34	0.1 71	0.3 03	0.3 27	0.4 35	0.2 15	0.5 00	0.3 45	0.1 78	0.3 14	0.3 37	0.4 46
Genotoxicity	0.9 97	1.0 00	0.9 91	0.9 97	0.9 87	0.9 92	0.9 63	0.9 98	1.0 00	0.9 94	0.9 98	0.9 91	0.9 94	0.9 75

RPMI-8226 Immunitoxicity	0.0 27	0.0 25	0.0 27	0.0 28	0.0 31	0.0 30	0.0 52	0.0 25	0.0 23	0.0 25	0.0 26	0.0 29	0.0 27	0.0 48
A549 Cytotoxicity	0.0 71	0.0 84	0.1 33	0.0 62	0.0 57	0.1 16	0.0 76	0.1 53	0.1 78	0.2 65	0.1 34	0.1 24	0.2 36	0.1 62
Hek293 Cytotoxicity	0.3 13	0.3 60	0.4 84	0.3 07	0.2 48	0.4 37	0.2 36	0.5 35	0.5 87	0.7 03	0.5 28	0.4 54	0.6 62	0.4 38
Drug- inducedNeurotoxicity	0.6 92	0.0 80	0.7 37	0.6 96	0.6 75	0.7 23	0.7 28	0.6 99	0.0 83	0.7 43	0.7 03	0.6 82	0.7 29	0.7 35
EnvironmentalToxicity														
BioconcentrationFactors	1.1 15	0.9 23	1.0 58	0.9 69	0.7 89	0.9 21	0.8 41	1.4 00	1.1 70	1.2 75	1.2 85	0.8 57	1.1 94	0.9 70
IGC ₅₀ (50% GrowthInhibitoryConcentr ation in Tetrahymenapyriformis)	4.6 75	4.5 15	4.7 26	4.6 55	4.5 36	4.6 62	4.4 02	4.9 73	4.8 50	5.0 18	4.9 64	4.7 46	4.9 52	4.5 91
LC ₅₀ FM (FatheadMinnow 50% LethalConcentration)	5.6 28	5.3 19	5.6 38	5.4 40	5.1 00	5.3 48	4.9 91	6.3 58	5.9 79	6.3 01	6.2 03	5.5 58	6.0 76	5.3 06
LC ₅₀ DM (Daphniamagna 48-h LethalConcentration 50%)	5.6 10	5.1 88	5.5 65	5.3 08	4.8 21	5.1 80	4.7 75	6.4 94	5.9 37	6.4 00	6.2 28	5.3 46	6.1 19	5.2 50