Supplementary material

Synthesis, molecular docking studies and biological evaluation of *N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl) benzamides as potential antioxidant, and anticancer agents

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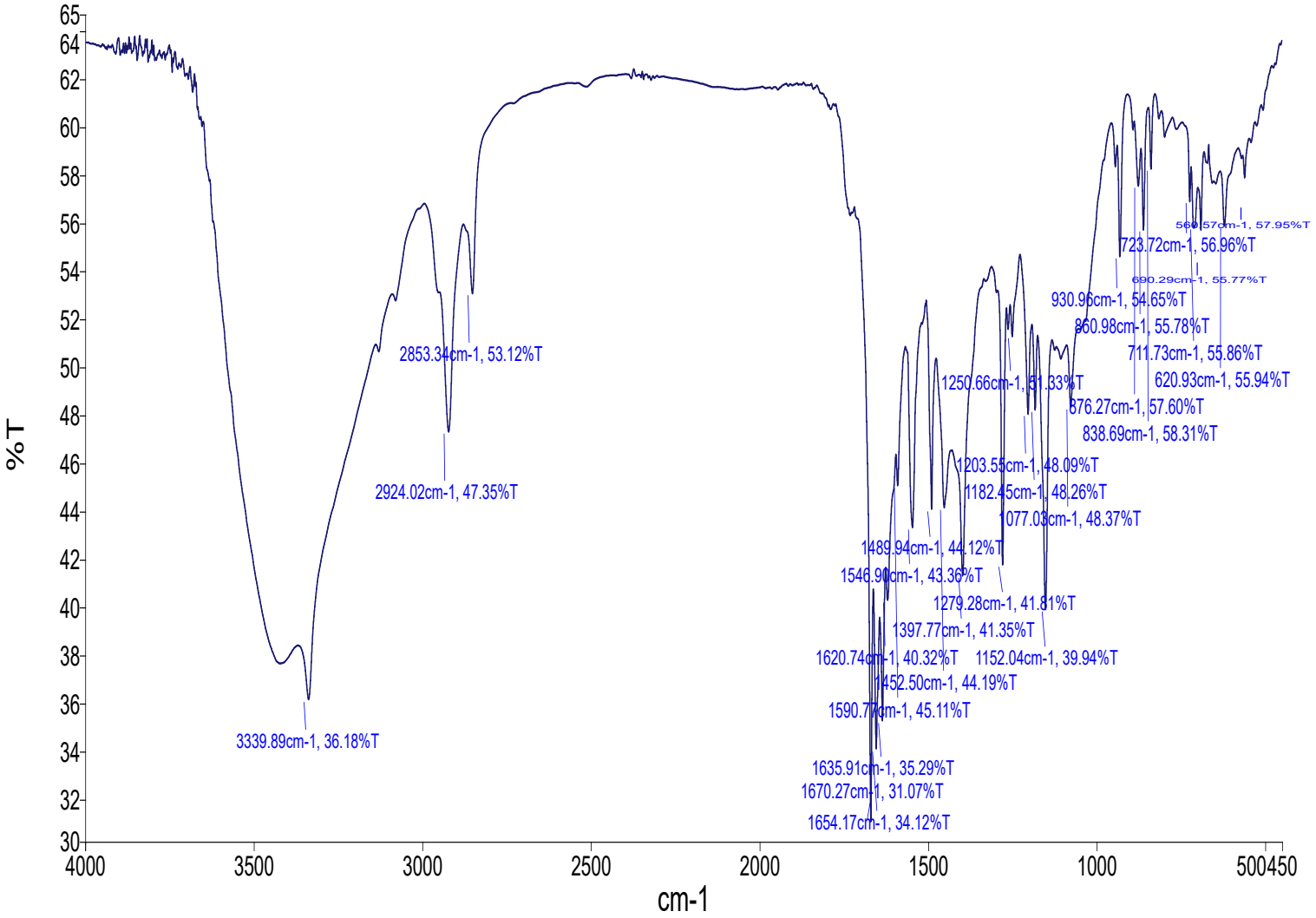

Figure 1. IR spectrum of *N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide* (4c).

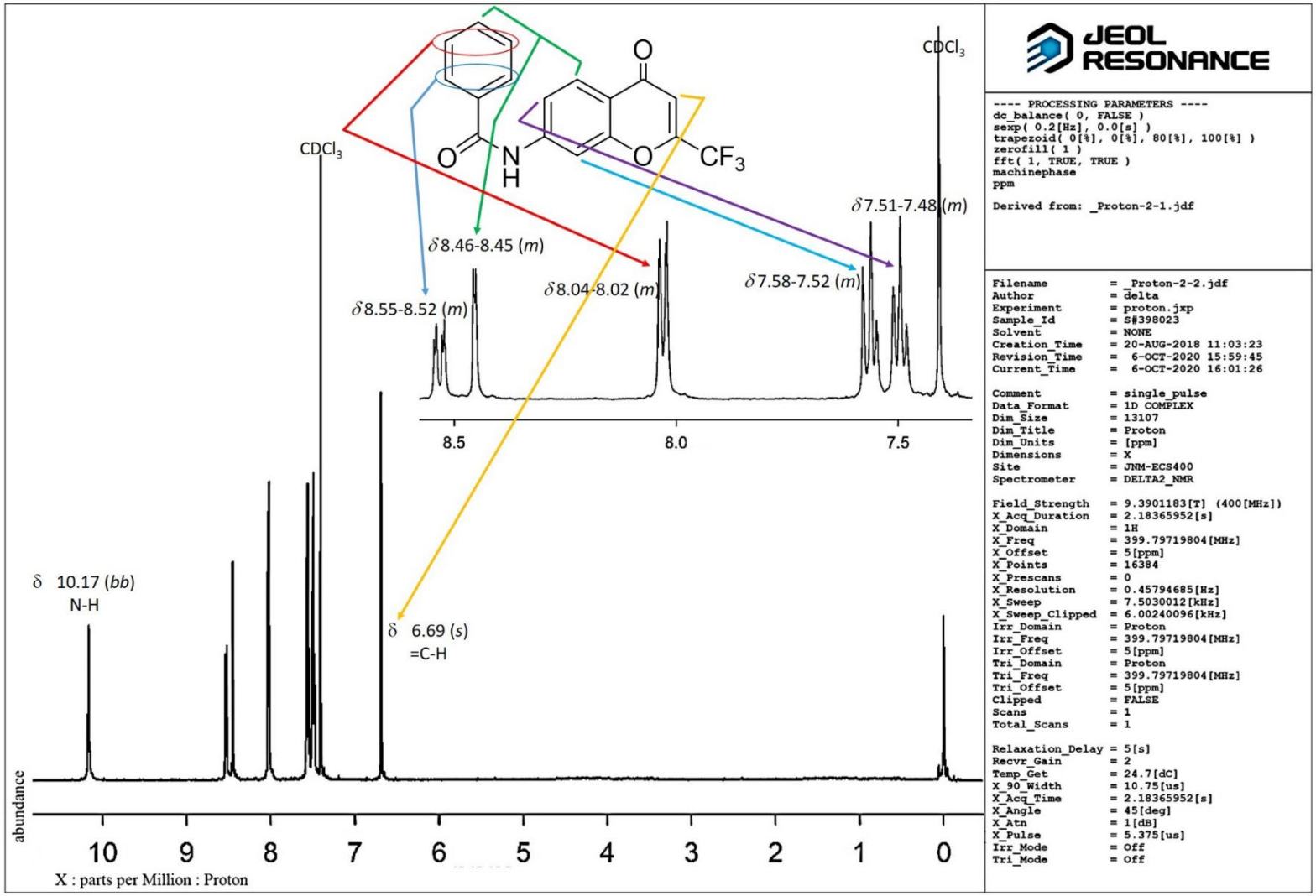

Figure 2. ^{1}H-NMR Spectrum of *N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide* (4c)

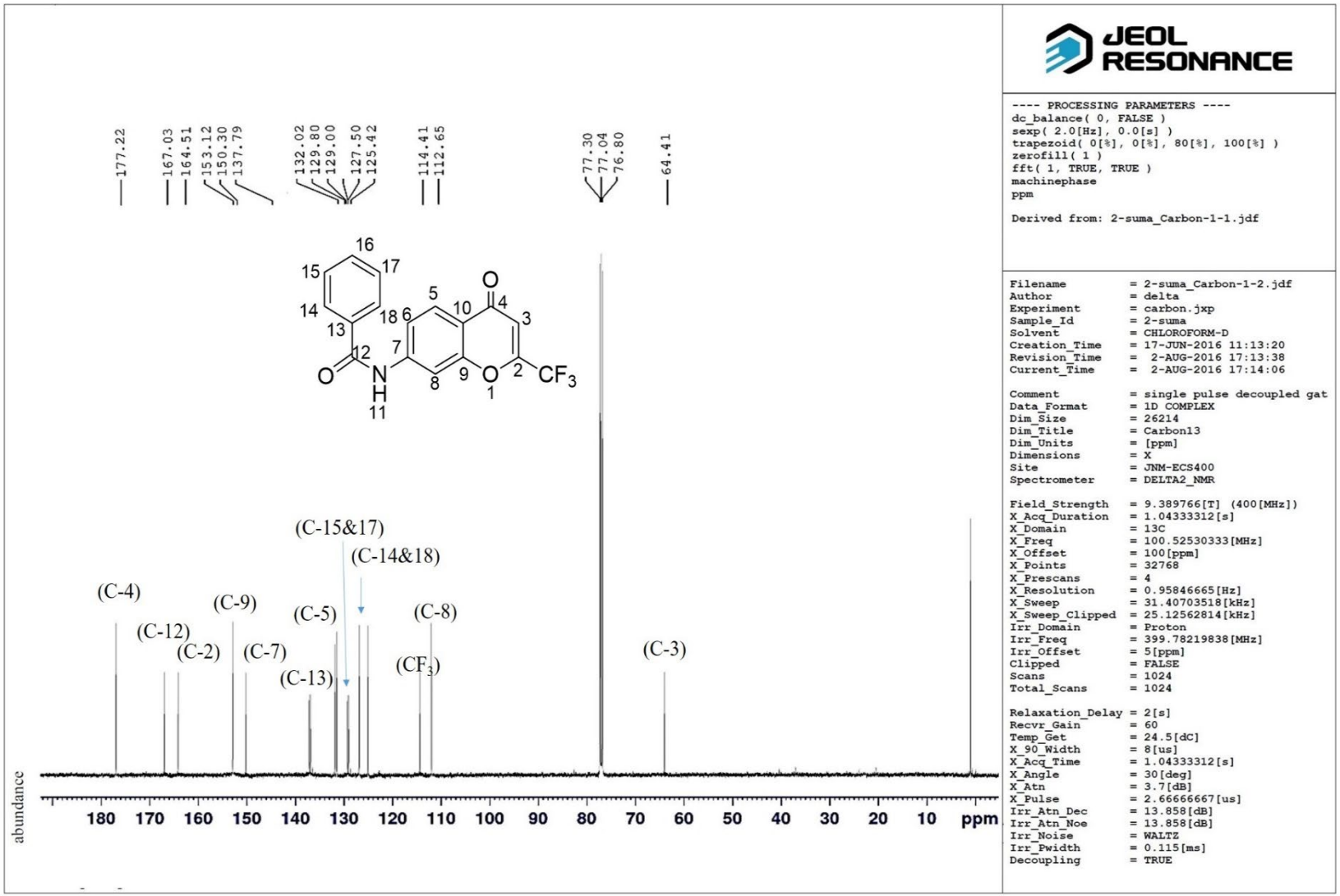

Figure 3. ^{13}C-NMR Spectrum of *N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide* (4c)

LCMS-2010A DATA REPORT
SHIMADZU

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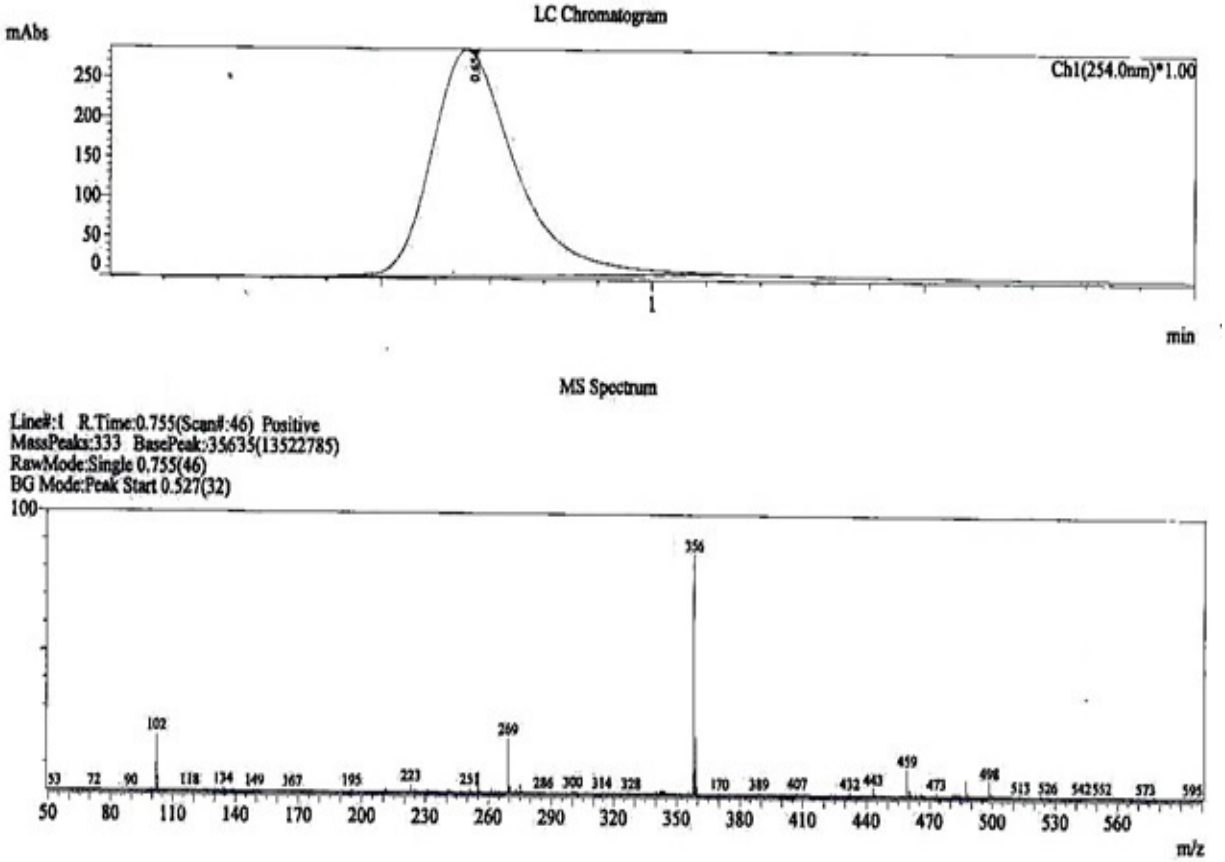


Figure 4. Mass spectrum of ***N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide*** (**4c**)

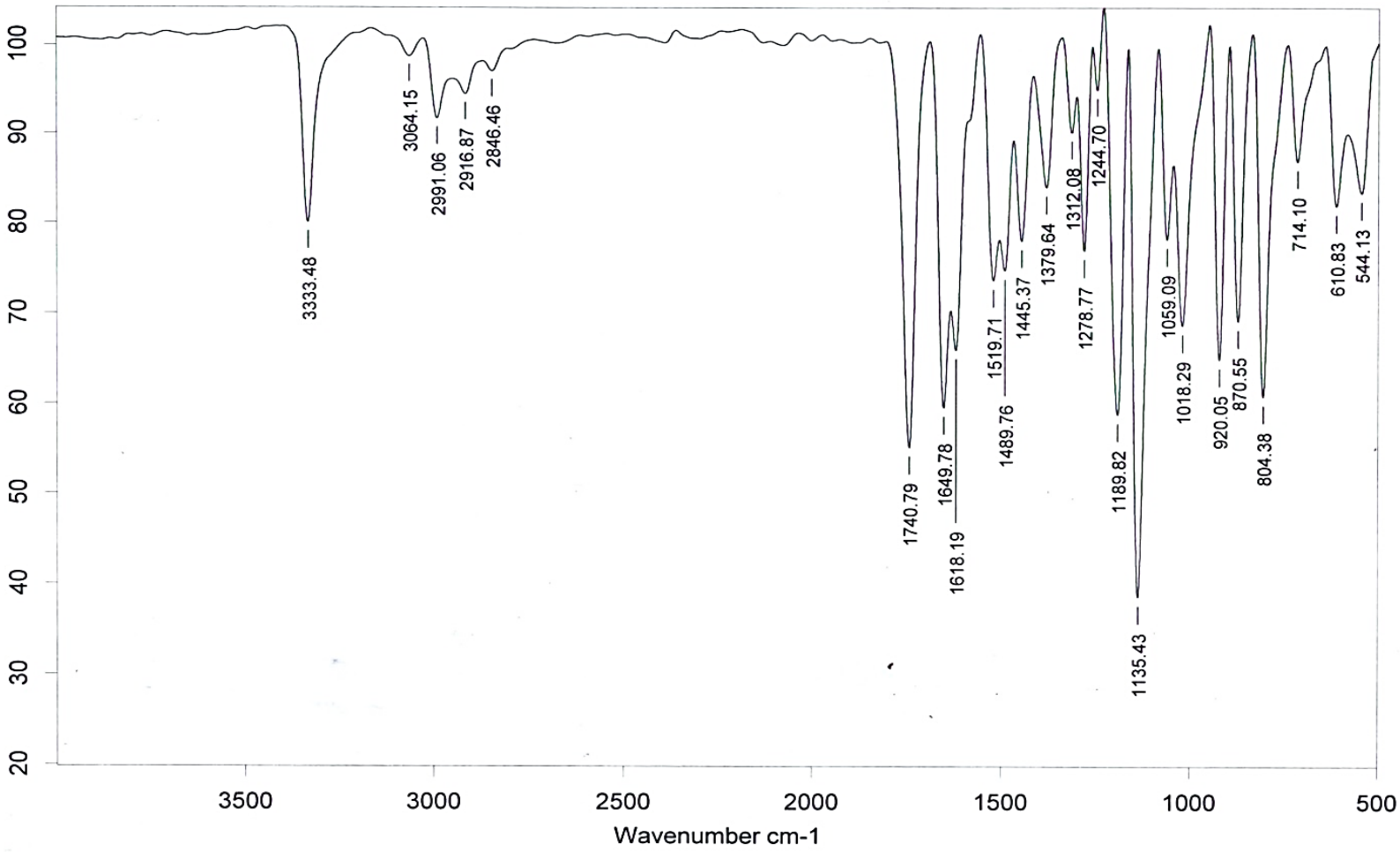


Figure 5. IR spectrum of ***N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)acetamide*** **(4d).**

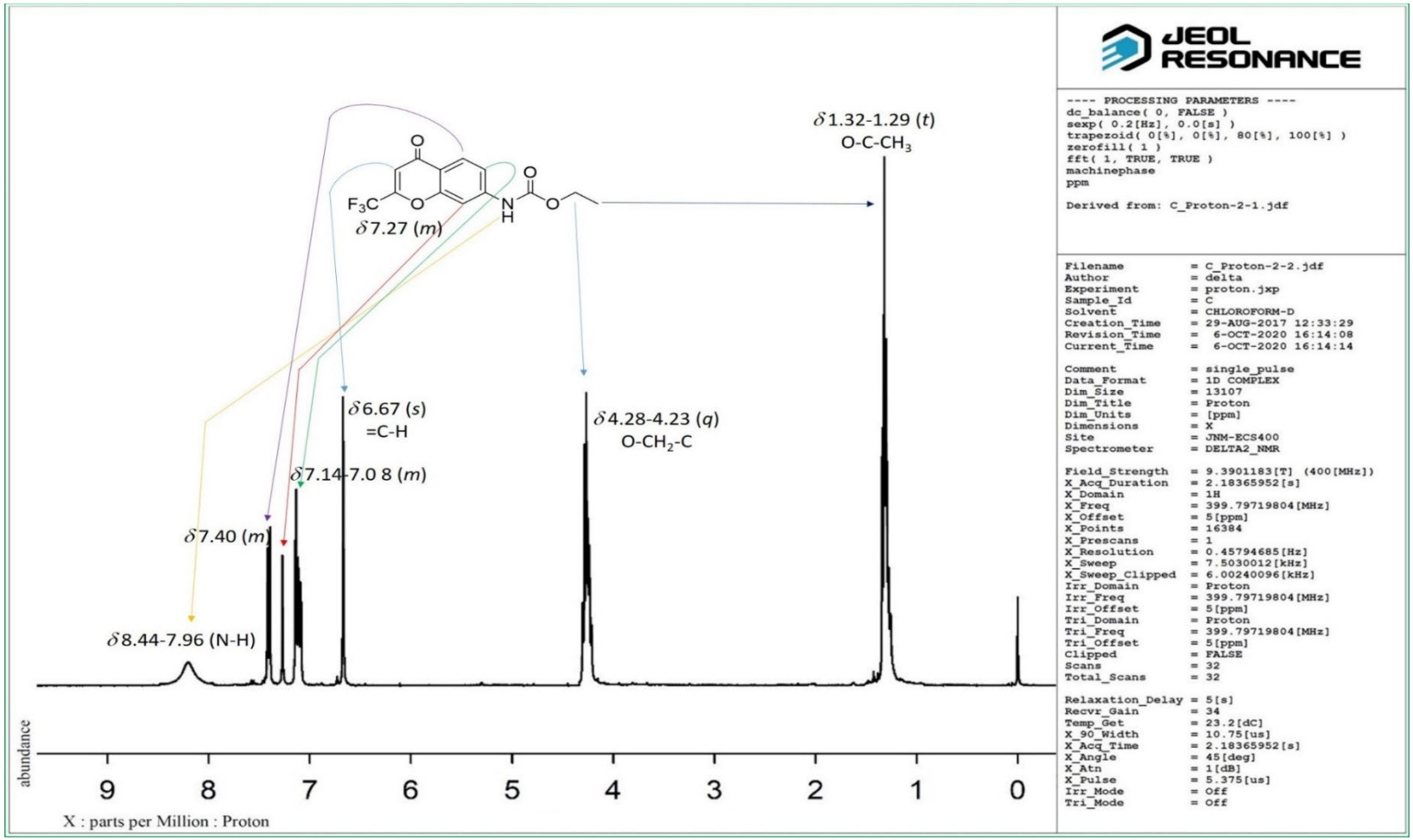


Figure 6. ^{1}H-NMR Spectrum of ***N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)acetamide*** **(4d).**

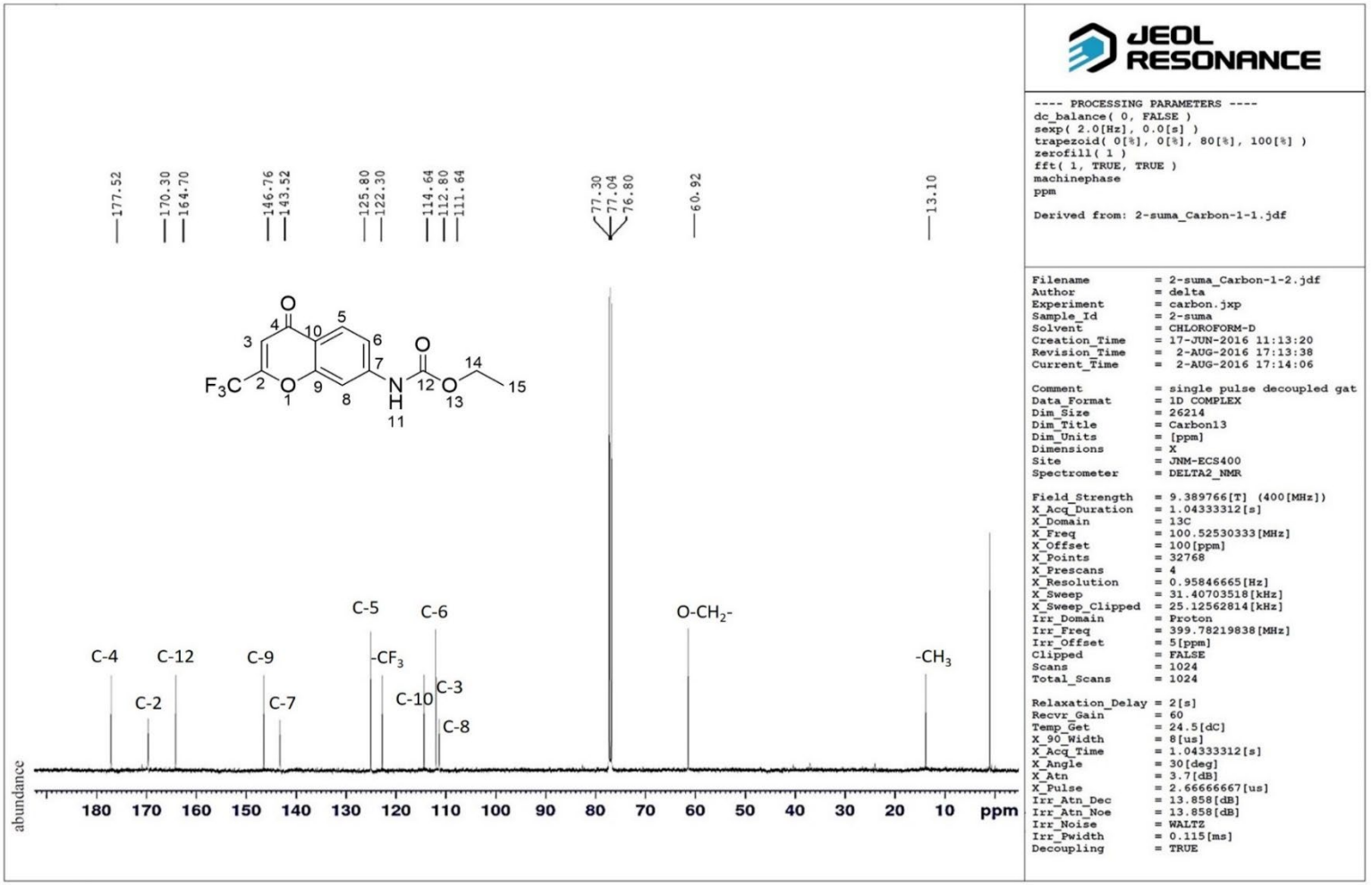


Figure 7. ^{13}C-NMR Spectrum of ***N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)acetamide*** **(4d).**

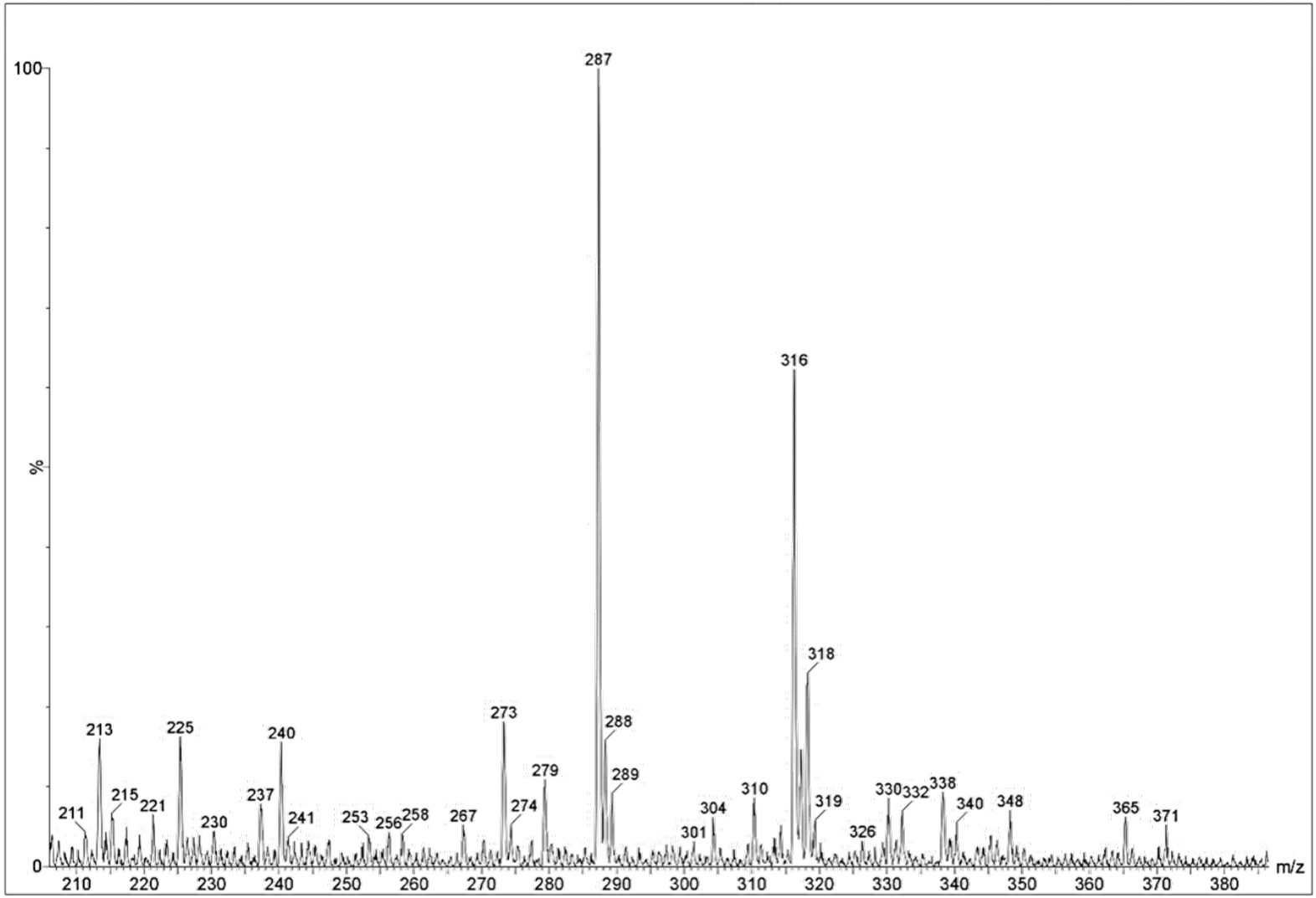


Figure 8. Mass spectrum of the compound *N*-***(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)acetamide*** **(4d)**.

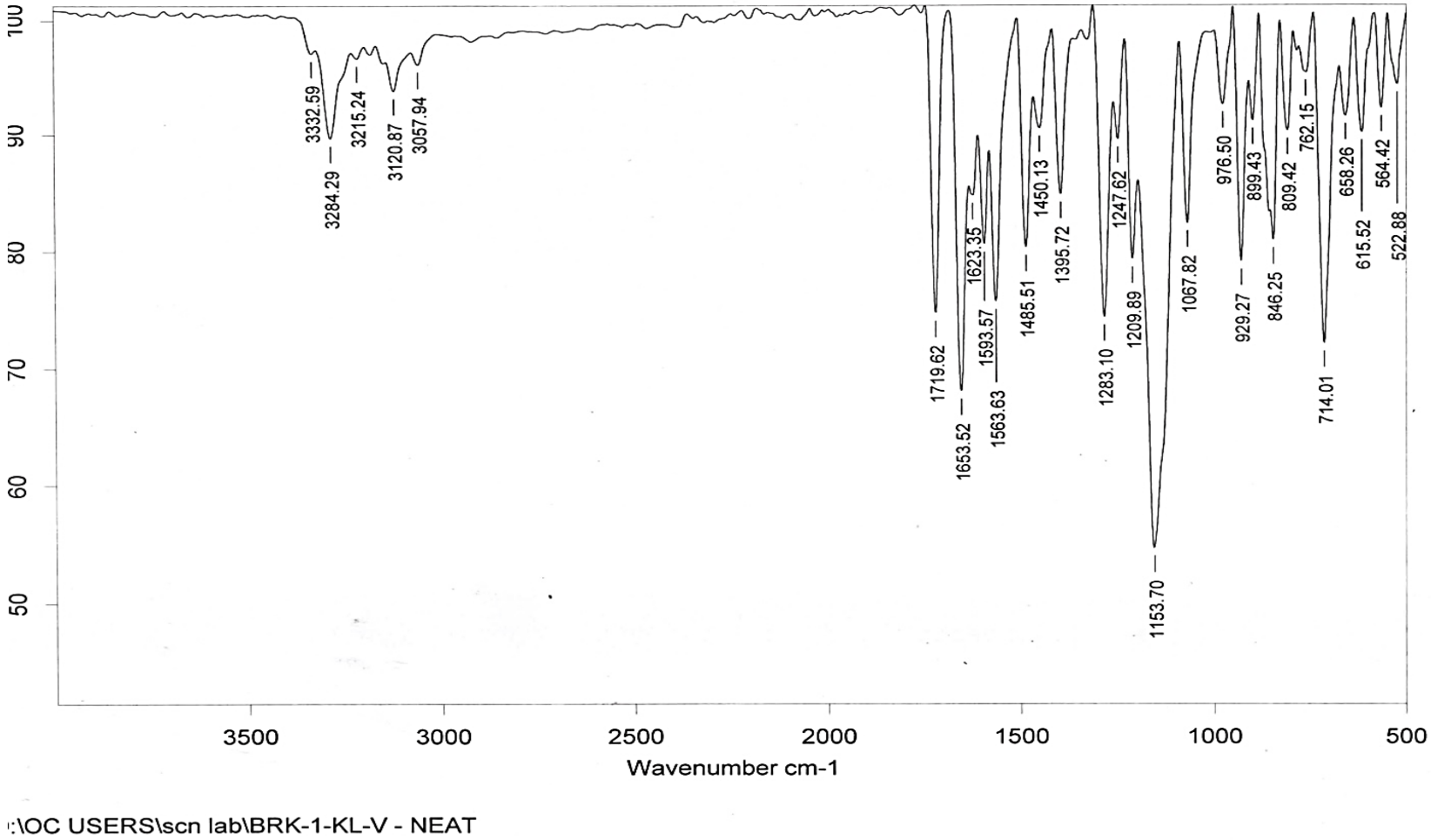


Figure 9. IR spectrum of ***2,2,2-trifluoro-N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)acetamide*(4e).**

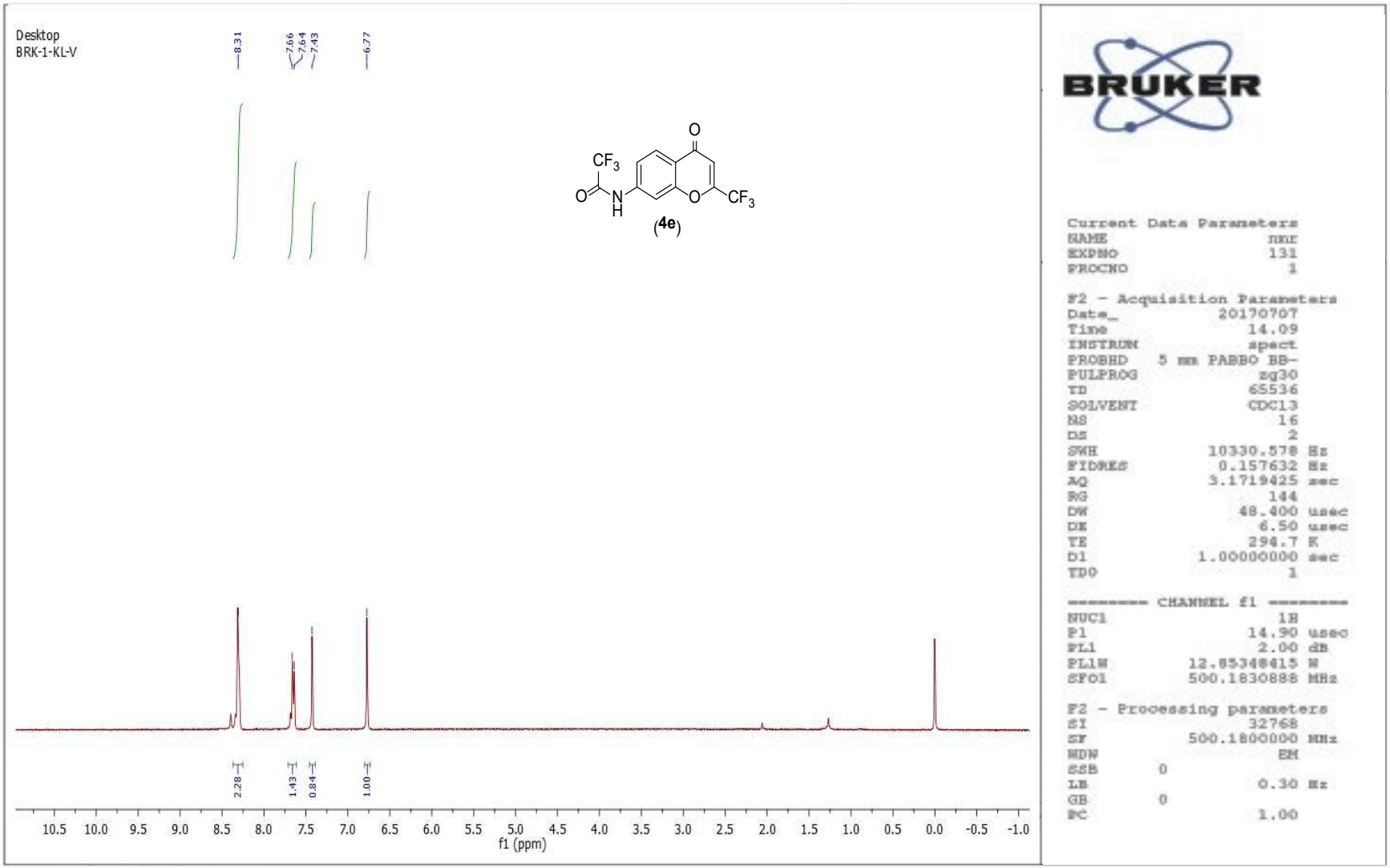
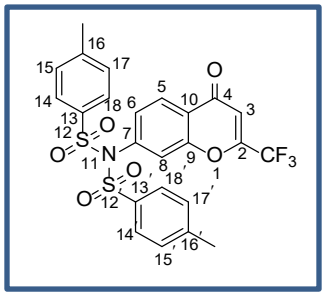


Figure 10. [1]H-NMR Spectrum of ***2,2,2-trifluoro-N-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)acetamide*** **(4e).**

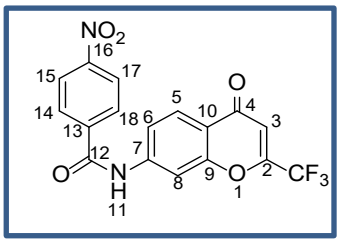
Physical and Spectral Characterization of Synthesized Compounds (4a-k).

1) 4-methyl-*N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)-*N*-tosylbenzenesulfonamide (4a).



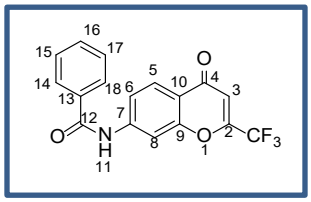
IR (KBr) ν_{max}: 3078.8, 3030.3 (C=$C_{Stretch}$), 2926.2 & 2855.7 (C-$H_{Stretch}$), 1675.9 (C=O), 1602.4 (C-), 1476.1 & 1449.0 (C-H_{Bend}), 1380.1 (S=$O_{Stretch}$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.87 (4H, *d*, $^{3}J_{H\text{-}H}$ = 8.0 Hz, Ar-$H_{(14,14',18\&18')}$), 7.78 (4H, *d*, $^{3}J_{H\text{-}H}$ = 8.0 Hz, Ar-$H_{(15,15',17\&17')}$), 7.58-7.56 (1H, *d*, $^{3}J_{H\text{-}H}$ = 10.0 Hz, Ar-$H_{(5)}$), 7.54 (1H, *s*, =$CH_{(3)}$), 6.85-6.76 (2H, *m*, Ar-$H_{(6\&8)}$); ^{13}C NMR ($CDCl_3$) δ: 177.1 (C-4), 160.4 (C-2), 149.2 (C-9), 145.3 (C-7), 124.8 (C-16&16′), 122.5 (C-13&13′), 119.4 (C-5), 109.4 (C-15,15′,17&17′), 103.6 (C-14,14′,18&18′), 98.9 (-CF_3), 95.1 (C-8), 61.6 (C-3), 14.1 (-CH_3); Mass $[M+Na]^{+\bullet}$ = 560.

2) 4-Nitro-*N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)benzamide (4b)



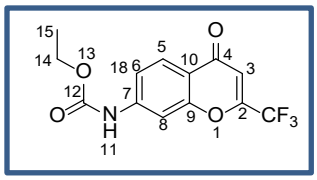
IR (KBr) ν_{max}: 3308.3 (N-$H_{Stretch}$), 3097 (C=$C_{Stretch}$), 2920.2 & 2850.8 (C-$H_{Stretch}$), 1651.9 (C=O), 1524.6 & 1486.9 (C-H_{Bend}) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.56-8.52 (1H, *bb*, N-H), 8.29-8.27 (2H, *m*, Ar-$H_{(15\&17)}$), 8.11-8.03 (2H, *m*, Ar-$H_{(14\&18)}$), 7.58-7.56 (1H, *d*, $^{3}J_{H\text{-}H}$ = 10.1 Hz, Ar-$H_{(5)}$), 7.51 (1H, *s*, =$CH_{(3)}$), 6.95-6.83 (2H, *m*, Ar-$H_{(6\&8)}$); ^{13}C NMR ($CDCl_3$) δ: 177.3 (C-4), 160.1 (C-2), 149.5 (C-9), 146.1 (C-16), 145.0 (C-7), 124.9 (C-13), 122.9 (C-5), 119.4 (C-14&18), 115.4 (C-15&17), 103.6 (-CF_3), 95.6 (C-8), 61.5 (C-3); Mass $[M+1]^{+\bullet}$ = 379.

3) *N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)benzamide (4c).



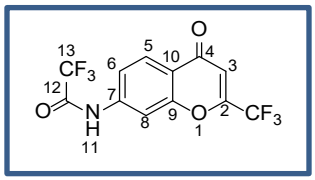
IR (KBr) ν_{max}: 3339.8 (N-H$_{Stretch}$), 2924.0 & 2853.3 (C=C$_{Stretch}$), 1670.2 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 10.17 (1H, *bb*, N-H), 8.55-8.52 (2H, *m*, Ar-H$_{(14\&18)}$), 8.46-8.45 (2H, *m*, Ar-H$_{(5\&16)}$), 8.04-8.02 (2H, *m*, Ar-H$_{(15\&17)}$), 7.58-7.52 (1H, *m*, Ar-H$_{(8)}$), 7.51-7.48 (1H, *m*, Ar-H$_{(7)}$), 6.69 (1H, *s*, =CH$_{(3)}$); ^{13}C NMR ($CDCl_3$) δ: 177.2 (C-4), 167.0 (C-12), 164.5 (C-2), 153.1 (C-9), 150.3 (C-7), 137.7 (C-13), 132.0 (C-5), 129.8 & 129.0 (C-15&17), 127.5 & 125.4 (C-14&18), 114.4 (-CF_3), 112.6 (C-8), 64.4 (C-3); Mass $[M+Na]^{+\bullet}$ = 356, $[M]^{+\bullet}$ = 333; Anal. Calcd. for $C_{17}H_{10}F_3NO_3$: C, 61.27; H, 3.02; N, 4.20; found: C, 61.25; H, 3.01; N, 4.21.

4) *N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)acetamide (4d).



IR (KBr) ν_{max}: 3333.4 (N-H), 1740.7 (C=O), 1649.7 (C=O), 1135 (C-F) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.44-7.96 (1H, *bb*, N-H), 7.40 (1H, *m*, Ar-H$_{(5)}$), 7.27 (1H, *m*, Ar-H$_{(8)}$), 7.14-7.08 (1H, *m*, Ar-H$_{(6)}$), 6.67 (1H, *s*, =CH$_{(3)}$), 4.28-4.23 (2H, *q*, $^{3}J_{H\text{-}H}$ = 8.0 Hz, (O-CH$_{2(14)}$), 1.33-1.29 (3H, *t*, $^{3}J_{H\text{-}H}$ = 8.0 Hz, (-CH$_{3(15)}$); ^{13}C NMR ($CDCl_3$) δ: 177.5 (C-4), 170.3 (C-2), 164.7 (C-12), 146.7 (C-9), 143.5 (C-7), 125.8 (C-5), 122.3 (-CF_3), 114.6 (C-10), 112.8 (C-6&C-3), 111.6 (C-8), 60.9 (O-CH_2-), 13.1 (-CH_3.

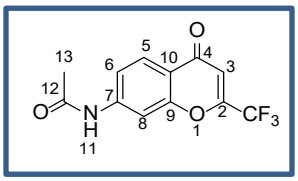
5) 2,2,2-trifluoro-*N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)acetamide (4e).



IR (KBr) ν_{max}: 3284.2 (N-H), 3215.2 (C=C), 1719.6 (C=O), 1653.5 (C=O), 1153 (C-F) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.31 (1H, *bb*, N-H),

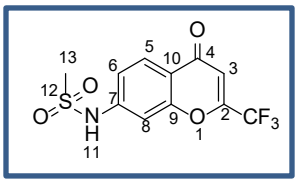
7.65 (1H, *m*, Ar-$H_{(5)}$), 7.43 (2H, *m*, Ar-$H_{(6\&8)}$), 6.77 (1H, *s*, $=CH_{(3)}$); ^{13}C NMR ($CDCl_3$) δ: 177.1, 171.4, 162.5, 152.5, 146.2, 126.8, 126.2, 122.4, 118.4, 112.4, 111.6, 61.6 (C-3.

6) *N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)acetamide (4f).



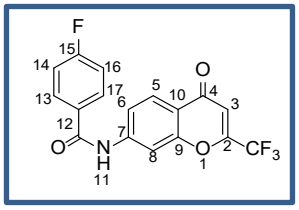
IR (KBr) ν_{max}: 3336, 1648.6 (C=O), 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.02 (1H, *bb*, N-H), 7.99 (1H, *m*, Ar-$H_{(5)}$), 7.56 (2H, *m*, Ar-$H_{(6\&8)}$), 6.78 (1H, *s*, $=CH_{(3)}$), 2.05 (3H, *s*, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ: 177.12, 170.43, 149.25, 145.30, 124.82, 122.48, 119.42, 109.45, 103.65, 61.5 (C-3), 45.67, 14.12.

7) *N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)methanesulfonamide (4g).



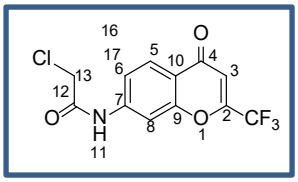
IR (KBr) ν_{max}: 3078, 2926, 1675.7 (C=O), 1351.3 ($S=O_{Stretch}$) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.22 (1H, *bb*, N-H), 7.76-7.68 (3H, *m*, Ar-$H_{(5,6\&8)}$), 6.80 (1H, *s*, $=CH_{(3)}$), 3.46 (3H, *s*, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ: 177.12, 170.43, 149.25, 145.30, 124.82, 122.48, 119.42, 109.45, 103.65, 61.5 (C-3), 45.67, 14.12.

8) 4-fluoro-*N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)benzamide (4h).



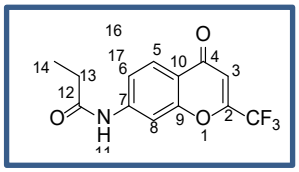
IR (KBr) ν_{max}: 3078, 2360, 1652.5 (C=O), 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.21 (1H, *bb*, N-H), 8.10 (2H, *m*, Ar-$H_{(13\&17)}$), 7.75 (1H, *m*, Ar-$H_{(5)}$), 7.38 (2H, *m*, Ar-$H_{(14\&16)}$); 7.27 (2H, *m*, Ar-$H_{(6\&8)}$), 6.50 (1H, *s*, $=CH_{(3)}$); ^{13}C NMR ($CDCl_3$) δ: 177.12, 170.43, 149.25, 145.30, 124.82, 122.48, 119.42, 109.45, 103.65, 61.56, 45.67, 14.12.

9) 2-chloro-*N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)acetamide (4i).



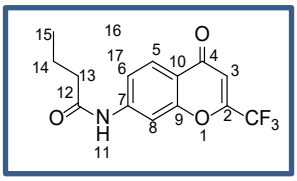
IR (KBr) ν_{max}: 3078, 2926, 1675.7 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.58 (1H, *bb*, N-H), 8.36-8.33 (1H, *m*, Ar-$H_{(5)}$), 8.13 (1H, *m*, Ar-$H_{(6)}$), 7.62 (1H, *m*, Ar-$H_{(8)}$), 6.75 (1H, *s*, =$CH_{(3)}$), 4.26 (2H, *s*, -$CH_{2(13)}$-); ^{13}C NMR ($CDCl_3$) δ: 177.12, 170.43, 149.25, 145.30, 124.82, 122.48, 119.42, 109.45, 103.65, 61.56, 45.67, 14.12.

10) *N*-(4-Oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)propionamide (4j).



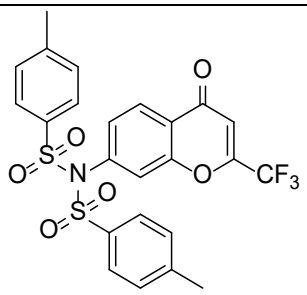
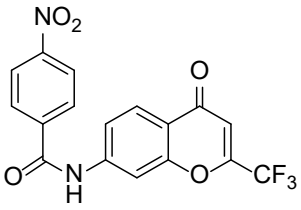
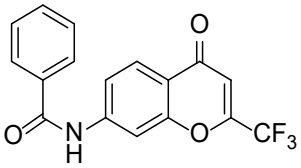
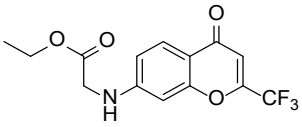
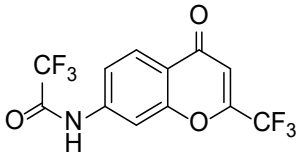
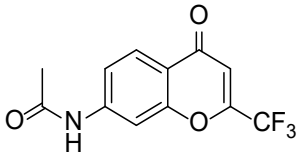
IR (KBr) νmax: 3385 (N-H), 3098 & 2920, 1651.8 (C=O) cm-1; 1H NMR (CDCl3) δ: 8.02 (1H, bb, N-H), 7.99 (1H, m, Ar-H(5)), 7.56 (2H, m, Ar-H(6&8)), 6.78 (1H, s, =CH(3)), 2.05-2.02 (2H, q, 3JH-H = 7.8 Hz, -CH2(13)-), 1.14-1.11 (3H, t, 3JH-H = 7.8 Hz, -CH3(14)); 13C NMR (CDCl3) δ: 177.12, 170.43, 149.25, 145.30, 124.82, 122.48, 119.42, 109.45, 103.65, 61.56, 45.67, 14.12.

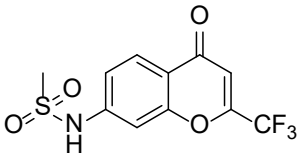
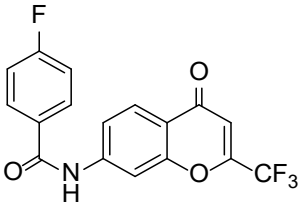
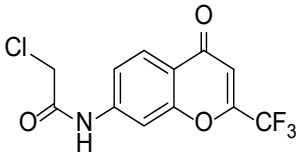
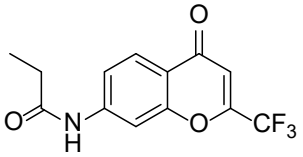
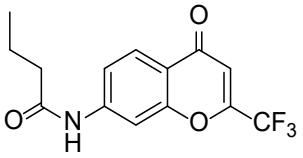
11) *N*-(4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)butyramide (4k)



IR (KBr) ν_{max}: 3078, 2926, 1675.3 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.51-8.48 (1H, *bb*, N-H), 8.01 (1H, *m*, Ar-$H_{(5)}$), 7.82 (2H, *m*, Ar-$H_{(6\&8)}$), 7.58 (1H, *s*, =$CH_{(3)}$), 2.47-2.44 (2H, *m*, $^{3}J_{H\text{-}H}$ = 7.4 Hz, -$CH_{2(13)}$-), 1.77-1.74 (2H, *m*, -$CH_{2(14)}$-), 1.44-1.00 (3H, *t*, $^{3}J_{H\text{-}H}$ = 7.8 Hz, -$CH_{3(15)}$); ^{13}C NMR ($CDCl_3$) δ: 177.12, 170.43, 149.25, 145.30, 124.82, 122.48, 119.42, 109.45, 103.65, 61.56, 45.67, 14.12.

Table S1. Synthesis of 4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl)benzamide derivatives (**4a-k**).

Compound	Product	Yield (%)	mp (°C)
4a		95	192-194
4b		96	213-215
4c		91	186-188
4d		88	163-165
4e		89	169-171
4f		93	155-157

4g		90	201-203
4h		91	197-199
4i		90	165-167
4j		87	168-170
4k		93	158-160

2.3. Computational studies

2.3.1 Molecular Properties Prediction

Table S2 contains a tabulation of the title compound's computed molecular characteristics. The majority of synthesized derivatives have zero or one violation rate. The obtained results proved that every synthetic derivative exhibited good drug-like properties and complied with Lipinski's criteria. The compounds have good oral bioavailability, as shown by the TPSA of less than 140.

BBB (blood-brain barrier penetration) and the amount of intestinal absorption in humans (HIA%) were projected for each derivative, in addition to the other molecular predictions. All the compounds were found to be well absorbed and to have high HIA% values between 94.54% and 98.58%. Furthermore, it was discovered that they had a moderate BBB-to-CNS penetration rate (0.02-3.63). Therefore, theoretically, all of these parameters showed that the compounds had adequate oral absorption, bioavailability, and reasonable permeability through the blood-brain barrier.

2.3.2. Bioactivity score prediction

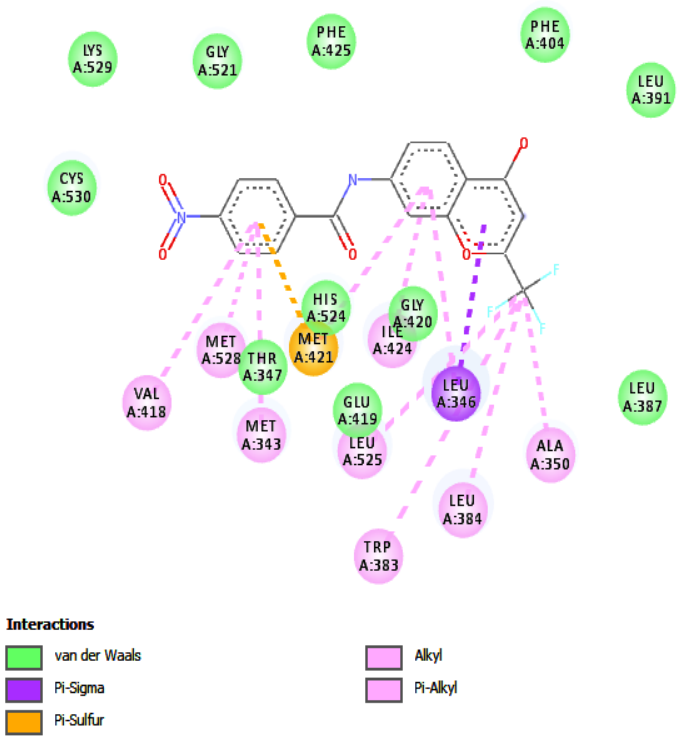
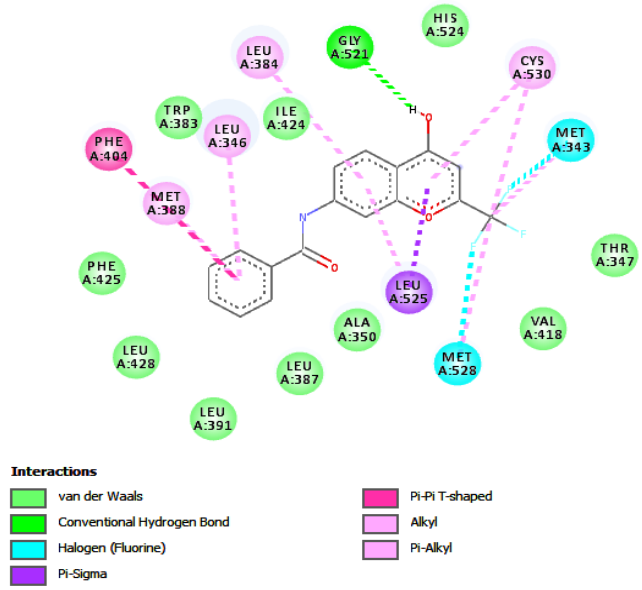
Table S2 summarises the computed bioactivity scores of the compounds that were screened for GPCR ligand, kinase, protease, and enzyme inhibitors. The synthesized compounds exhibited good to moderate behaviour towards inhibitors, as indicated by their bioactive score. The titled compounds exhibited high bioactivity scores of -0.12 to -0.38 towards enzyme inhibitors. It was observed from the bioactivity scores of compounds that were found within the range of -0.12 to -0.73.

Table S2. Prediction of molecular properties, bioactivity and drug likeness scores of title compounds.

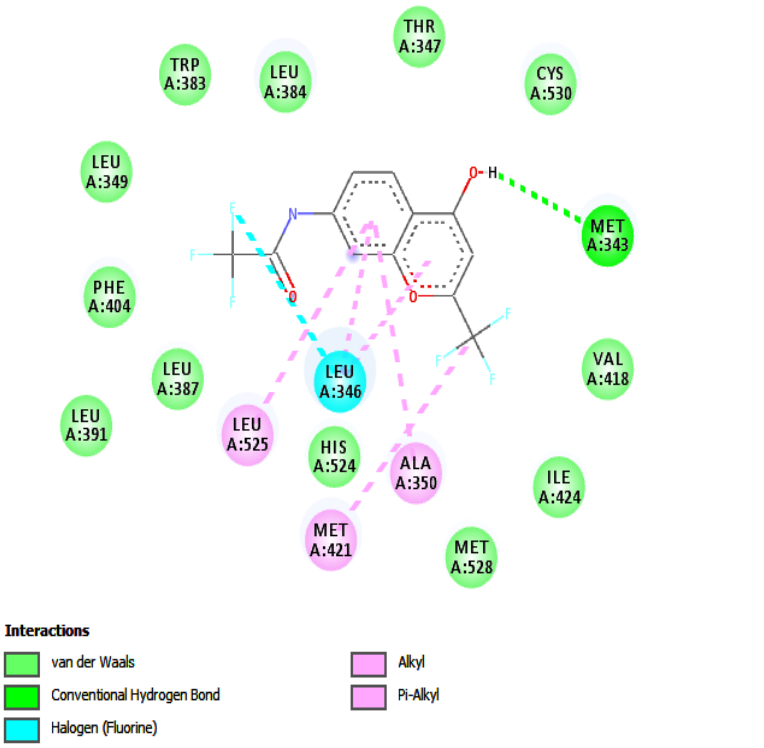
Comp	LogP	TPSA	No. of H-bond acceptors	No. of H-bond donors	No. of rotatable bonds	GPCR ligand	Kinase inhibitor	Protease inhibitor	Enzyme inhibitor	Druglikeness	Log BBB	% HIA
4a	5.74	101.73	7	0	6	-0.22	-0.20	-0.09	-0.14	-20.5	3.63647	98.582877
4b	3.78	105.13	7	1	4	-0.37	-0.31	-0.40	-0.28	-23.3	0.0222056	94.545202
4c	3.82	59.31	4	1	3	-0.26	-0.18	-0.31	-0.21	-11.3	0.135592	95.611921
4d	3.02	68.54	5	1	6	-0.39	-0.44	-0.37	-0.24	-17.35	0.104906	95.612031
4e	3.03	59.31	4	1	3	-0.34	-0.45	-0.39	-0.23	-31.7	0.766701	95.010104
4f	2.15	59.31	4	1	2	-0.49	-0.47	-0.63	-0.32	-11.5	0.628878	94.975635
4g	2.16	76.38	5	1	3	-0.26	-0.33	-0.30	-0.12	-10.6	0.620491	95.360538
4h	3.98	59.31	4	1	3	-0.24	-0.15	-0.32	-0.21	-10.3	0.191751	95.616308
4i	2.71	59.31	4	1	3	-0.69	-0.32	-0.73	-0.38	-11.5	0.657958	95.417777
4j	2.98	59.31	4	1	3	-0.41	-0.46	-0.56	-0.29	-10.6	0.208753	95.136674
4k	3.54	59.31	4	1	4	-0.33	-0.42	-0.42	-0.22	-13.4	0.212408	95.248380

- Molinspiration - log P- partition coefficient
- Druglikeness – yes/no
- No. of hydrogen bond acceptors
- PreADMET – ADME – BBB, % HIA
- No. of rotatable bonds
- Bioactivity score – GPCR ligand
- TPSA- Topological polar surface area
- No. of hydrogen bond donors
- Kinase inhibitor
- Protease inhibitor
- Enzyme inhibitor

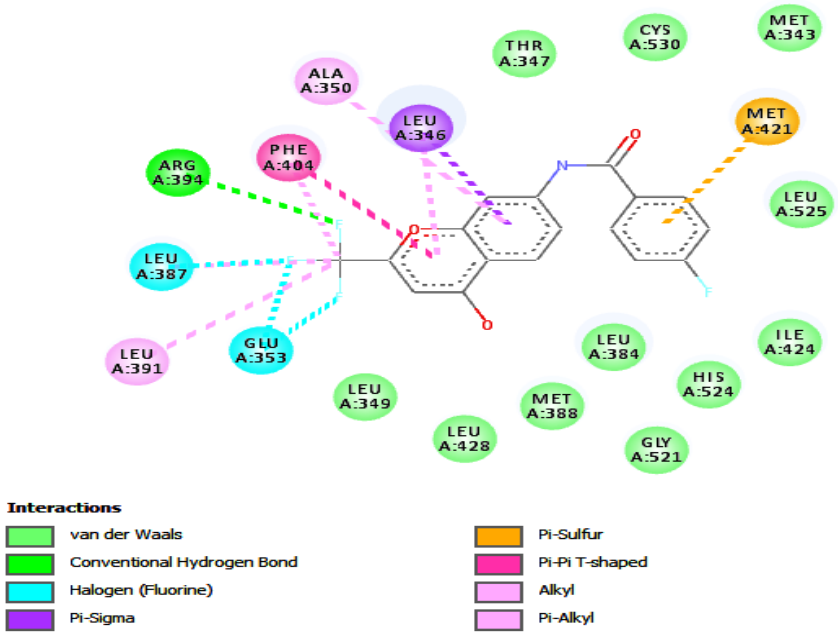
Figure S1. Diagrammatic representation of 2D modelled binding modes of the lead compounds with the binding domain of Human estrogen receptor alpha protein.

Entry	2D modelled binding modes
4b	
4c	

4e


THR A:347
TRP A:383
LEU A:384
CYS A:530
LEU A:349
MET A:343
PHE A:404
LEU A:387
LEU A:346
VAL A:418
LEU A:391
LEU A:525
HIS A:524
ALA A:350
ILE A:424
MET A:421
MET A:528
Interactions
van der Waals
Conventional Hydrogen Bond
Halogen (Fluorine)
Alkyl
Pi-Alkyl

4h


ALA A:350
THR A:347
CYS A:530
MET A:343
LEU A:346
MET A:421
PHE A:404
ARG A:394
LEU A:525
LEU A:387
GLU A:353
LEU A:391
LEU A:384
ILE A:424
HIS A:524
LEU A:349
MET A:388
LEU A:428
GLY A:521
Interactions
van der Waals
Conventional Hydrogen Bond
Halogen (Fluorine)
Pi-Sigma
Pi-Sulfur
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

4k

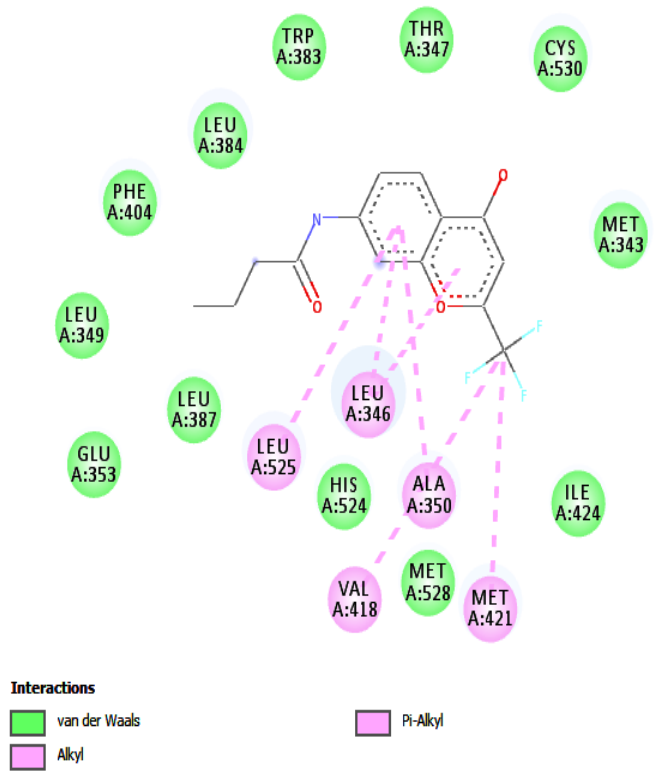
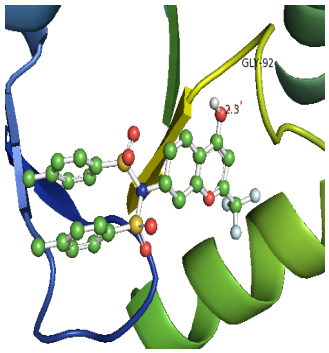
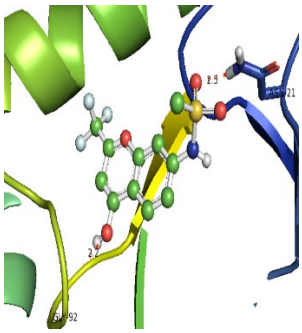
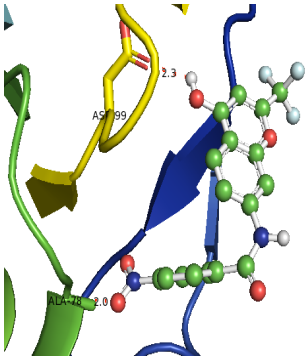
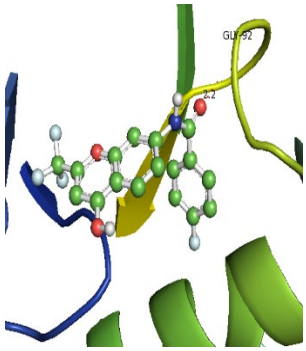
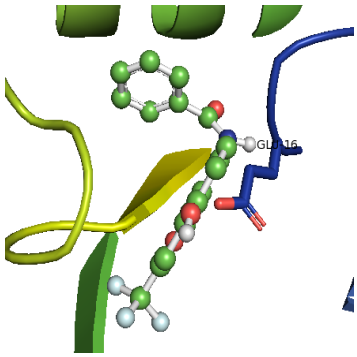
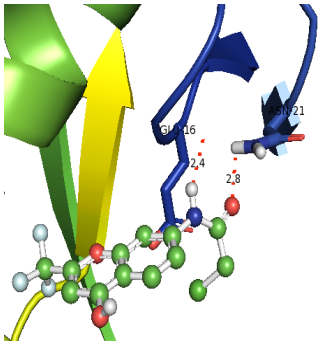
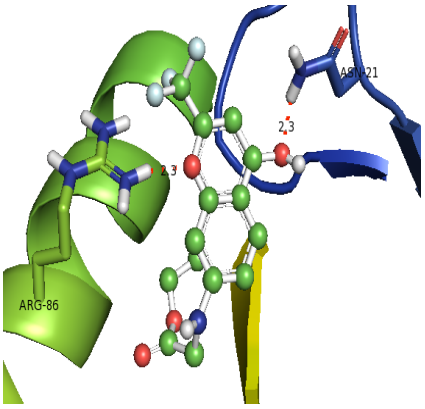

TRP A:383
THR A:347
CYS A:530
LEU A:384
PHE A:404
MET A:343
LEU A:349
LEU A:387
LEU A:346
LEU A:525
GLU A:353
HIS A:524
ALA A:350
ILE A:424
VAL A:418
MET A:528
MET A:421
Interactions
van der Waals
Alkyl
Pi-Alkyl

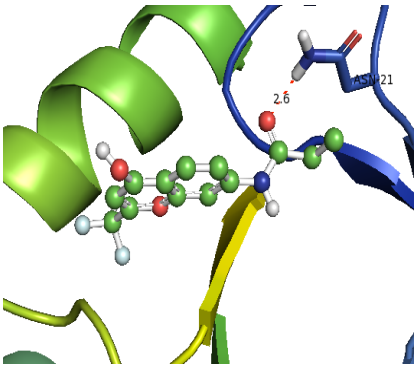
Figure S2. 3D binding domains of synthesized compounds (**4a-k**) and standards against 3MNG protein.

Entry	3D modelled binding modes	Entry	3D modelled binding modes
4a		**4g**	
4b		**4h**	
4c		**4i**	

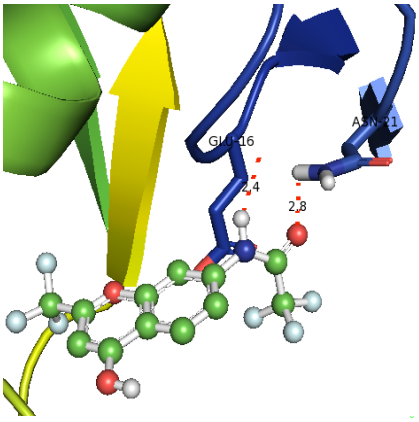
d



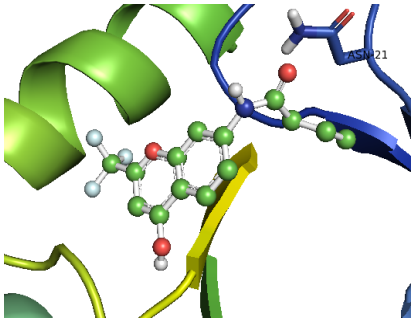
4j



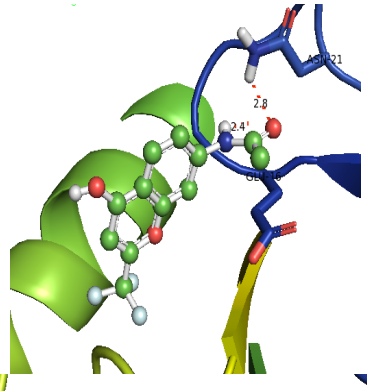
4e

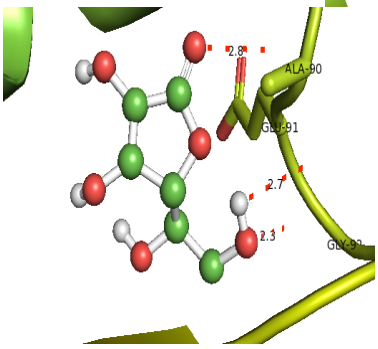


4k

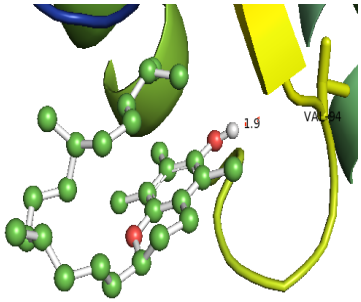


4f





Ascorbic acid



Tocopherol