Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Synthesis and Antiviral Activity of Novel Myricetin Derivatives Containing a Ferulic Acid Amide Scaffolds

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Content

1.Experimental section

The melting points were determined by X-4B microscopic melting point meter (Shanghai Yi Dian Physical Optics Instrument Co., Ltd. China); proton nuclear magnetic resonance (NMR) spectra were obtained on JEOL-ECX500 NMR spectrometer (JEOL, Tokyo, Japan) and Bruker Ascend-400 spectrometer (Bruker, Germany) with DMSO or $CDCl_3$ as the solvent and TMS as the internal standard. High-resolution mass spectral (HRMS) data were performed with Thermo Scientific Q Exactive (Thermo Scientific, USA). The micro thermophoresis of the compound and TMV CP was determined by a micro thermophoresis instrument (NanoTemper Tchnologies GmbH, Germany); the fluorescence spectroscopy of the compound interacting with TMV-CP was determined by FluoroMax-4 fluorescence spectrometer (HORIBA Scientific, France). All reagents (analytical grade) were purchased from commercial suppliers.

2. Biological activities tests

2.1. Antiviral activities *in vivo*

2.1.1. Curative activity of the target compounds against TMV *in vivo*

Growing *N. tabacum* L. leaves of the same age were selected. The leaves were inoculated with TMV (concentration of 6×10^{-3} mg/mL) by dipping and brushing the whole leaves, which had previously been scattered with silicon carbide. The leaves were then washed with water after inoculation for 0.5 h. The compound solution was smeared on the left side of the leaves, and the solvent was smeared on the right side as the control. The number of local lesions was counted and recorded 3–4 d after inoculation. Three replicates were set up for each.

2.1.2. Protection activity of the target compounds against TMV *in vivo*

The compounds solutions were smeared on the left side of the *N. tabacum* L. leaves, and the solvents were smeared on the right side as the control sample for growing *N*. tabacum L. leaves. After 12 h, crude TMV (concentration of 6×10^{-3} mg/mL) was inoculated on whole leaves at the same concentration on each side of the leaves, which were previously scattered with silicon carbide. After 0.5 h, the leaves were washed with water and then dried. The number of local lesions was recorded 3–4 d after inoculation. Three replicates were used for each compound. The inhibitory rate (*I* %) of the compound was calculated according to the following formula:

$$(I\ \%) = (C_{num} - T_{num}) / C_{num} \times 100\ \%$$

T_{num}: average local lesion number smeared with drugs

C_{num}: average local lesion number of control(not treated with compounds)

2.2. Expression and purification of TMV-CP

The expression vector, pET28a-TMV-CP, containing the full-length TMV-CP gene, was stored at -80 °C in our lab. A freshly transformed overnight culture of *Escherichia coli* strain *BL21(DE3)* containing the plasmid pET28a-TMV-CP was transferred to 1 L Luria broth. The cells were grown at 37 °C in Luria-Bertani medium supplemented with 50 μg/mL kanamycin, and with an OD_{600} of 0.8. The cells were shaken at 200 rpm. Then protein expression was induced with 0.8 mM IPTG at 16 °C overnight. The cells were harvested by centrifugation and then stored at -80 °C. When analyzed, the cells were resuspended in lysis buffer (20 mM PB, 500 mM NaCl, 30 mM imidazole, 5 mMβ-mercaptoethanol and 5 % glycerol, pH=7.2) and then lysed at 4 °C by sonication. The lysate was clarified by centrifugation at 12, 000 g for 30 min at 4 °C, the soluble supernatants were loaded onto a 5 mL Ni-NTA column (GE Healthcare, USA), and the protein was eluted with a linear gradient of 30-350 mM imidazole (pH=7.2). The crude protein was performed at 4 °C using a desalting column (GE Healthcare, USA) attached to an AKTA purifier protein liquid chromatography system (GE Healthcare, USA), and the fractions containing target protein with His-tags were pooled, concentrated to a suitable concentration by ultrafiltration (10 kDa cut-off). The dealt protein concentration was determined using a Genequant100 (GE Healthcare, USA), and stored at -80 °C until further analysis.

2.3. Interaction studies 4l, 4m, myricetin and ningnanmycin to TMV-CP

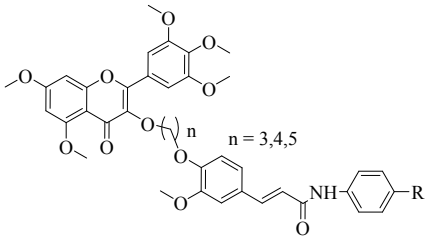
The binding was calculated for MST Monolith NT.115 (Nano Temper Technologies, Germany). A range of ligands from 0 to 5 μM were incubated with 0.5 μM of purified recombinant proteins for 5 min with a NT-647 dye (Nano Temper Technologies, Germany) and was used in the thermophoresis experiment at a final concentration of 20 nM. A 16 point dilution series was made for selected compounds in DMSO. Each compound dilution series was subsequently transferred to protein solutions in 10 mM Tris-HCl and 100 mM sodium chloride pH=7.5, 0.05 % Tween-20. After a 15 min incubation of the labeled TMV-CP with each dilution point (1:1 mix) at room temperature, samples were filled into standard capillaries (NanoTemper Technologies, Germany). Measurements were taken on a Monolith NT.115 microscale

thermophoresis system (NanoTemper Technologies, Germany) under a setting of 20 % LED and 40 % IR laser. Laser on time was set at 30 s, and laser-off time was set at 5 s. The Kd values were calculated from the duplicate reads of three separate experiments using the mass action equation in the Nano Temper software.

2.4. Molecular docking

The molecular docking was performed by using DS-CDocker implemented in Discovery Studio (version 4.5). The coat protein subunit amino acid sequence of tobacco mosaic virus (TMV) was searched by the UniProt database. The Protein BLAST server was used to search the template protein and the homologies of TMV-CP sequences were aligned. Homology modeling of TMV-CP was carried out using Create Homology Models, which is a module integrated in Discovery Studio. The obtained models were evaluated by Ramachandran plots. The 3D structures of the compounds were constructed using the Sketching module and optimized by the Full Minimization module. All parameters are default during the docking process.

3. The physical properties of compounds 4a-4v



Compounds **4a-4v**

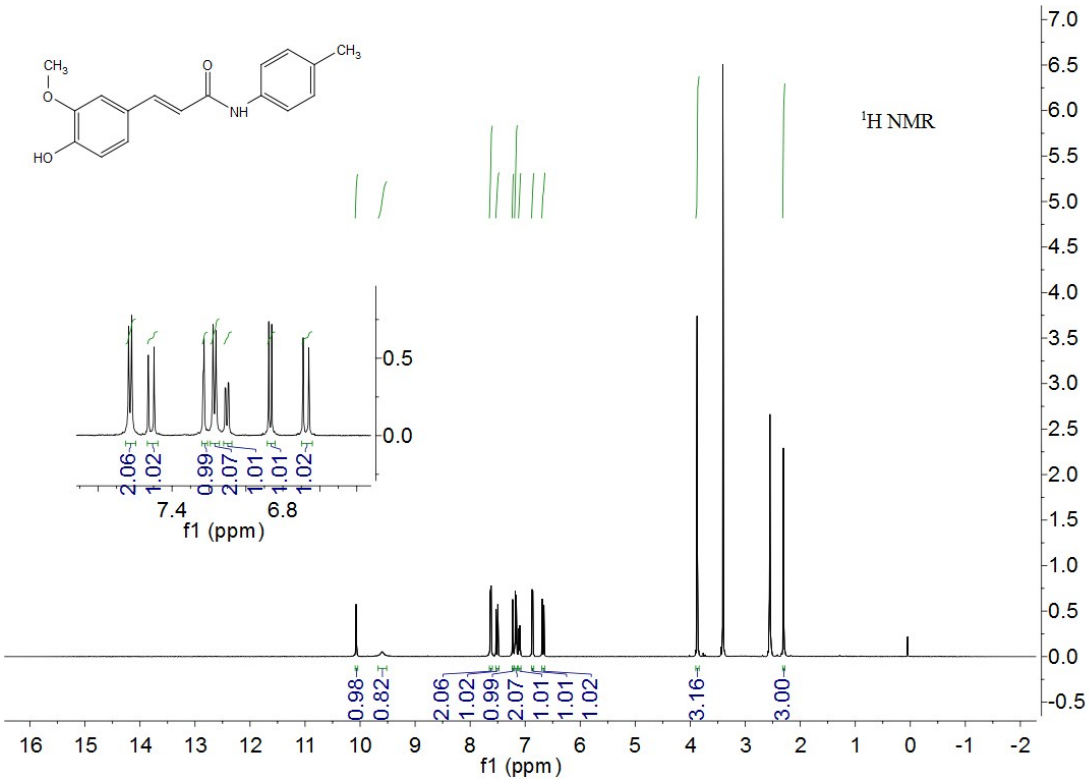
Table 1 The physical properties of compounds **4a**-**4v**

Compd.	R	n	Appearance	m.p./°C	Yield / %
4a	4-CH_3	3	Gray solid	215.4-215.5	58.6
4b	4-OCH_3	3	Gray solid	190.3-190.5	39.1
4c	4-CH_3	4	Gray solid	100.1-101.9	51.4
4d	4-OCH_3	4	Gray solid	108.6-109.8	63.6
4e	3-Cl	3	Yellow solid	187.2-187.5	49.6
4f	3-Cl	4	Gray solid	104.1-104.9	55.5
4g	4-Cl	4	Gray solid	103.3-104.8	62.0
4h	H	4	Yellow solid	116.4-116.7	60.3
4i	H	3	Yellow solid	242.5-242.9	49.7
4j	3,4-di-CH_3	3	Gray solid	202.5-202.9	83.9
4k	3,4-di-CH_3	4	Gray solid	107.3-108.1	48.3
4l	3,4-di-OCH_3	3	Green solid	118.0-118.7	65.3
4m	3,4-di-OCH_3	4	Green solid	95.3-96.1	59.6
4n	4-Br	3	Gray solid	208.4-209.6	67.9
4o	4-Br	4	Gray solid	180.3-181.6	58.2
4p	3,4-di-Cl	3	Yellow solid	118.6-119.3	65.5
4q	3,4-di-Cl	4	Gray solid	102.3-103.4	51.7
4r	4-Cl	5	Gray solid	112.3-112.9	58.2
4s	3-Cl	5	Gray solid	153.5-154.1	62.8
4t	4-OCH_3	5	Gray solid	123.6-124.7	64.7
4u	2-F	3	Gray solid	117.6-118.3	54.8
4v	2-F	4	Gray solid	162.3-163.6	66.7

4. Characterization of intermediate compounds 2a-2j

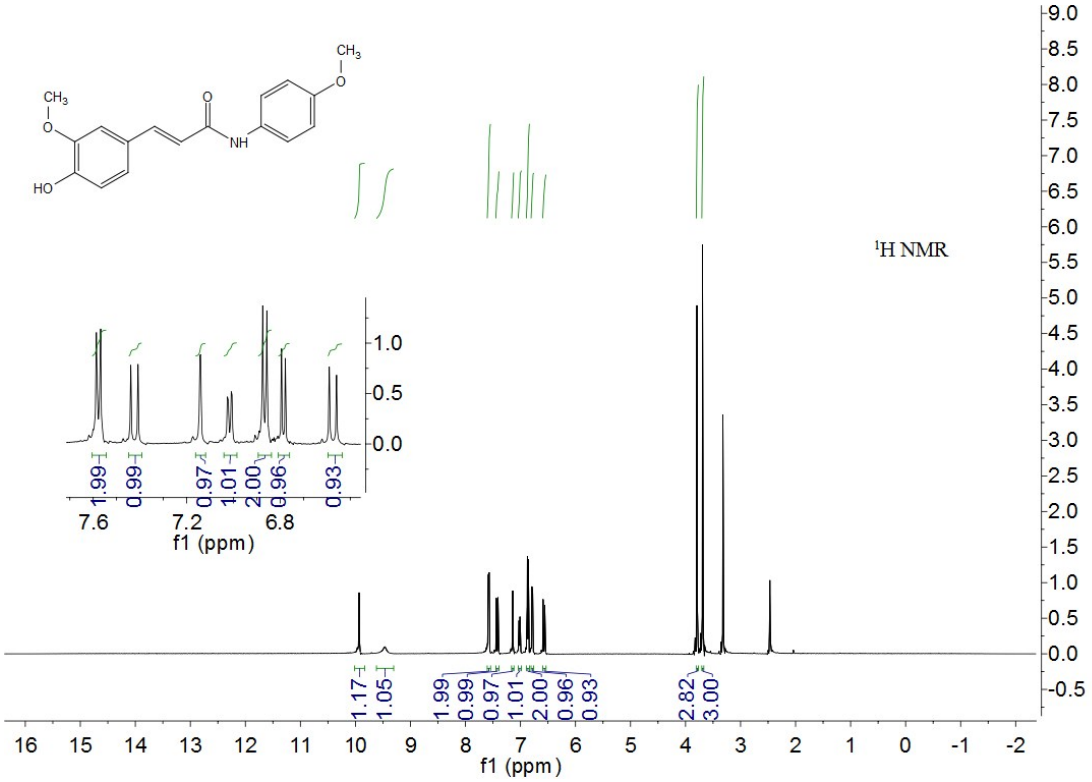
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(4-methylphenyl)acrylamide (**2a**): Yellow solid, yield: 62.14 %, m.p. 137.7 – 138.3, ^{1}H NMR (500 MHz, DMSO) δ 10.07 (s, 1H, OH), 9.60 (s, 1H, NH), 7.63 (d, J = 8.4 Hz, 2H, Ph-2H), 7.51 (d, J = 15.6 Hz, 1H, CO-C=CH), 7.22 (t, J = 5.0 Hz, 1H, CO-CH=), 7.17 (d, J = 8.3 Hz, 2H, Ph-2H), 7.10 (dt, J = 5.9, 2.9 Hz, 1H, Ph-H), 6.86 (t, J = 7.7 Hz, 1H, Ph-H), 6.67 (d, J = 15.6 Hz, 1H, Ph-H), 3.87 (s, 3H, OCH_3), 2.29 (d, J = 11.3 Hz, 3H, CH_3).

Figure S1. ^{1}H NMR spectrum of intermediate **2a**



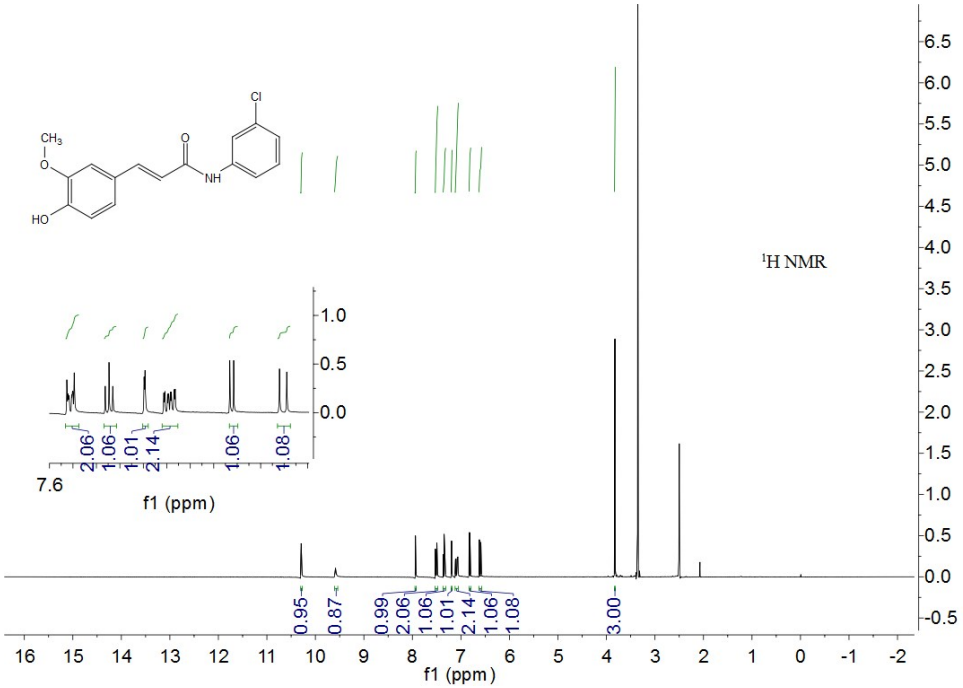
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(4-methoxyphenyl)acrylamide (**2b**): Gray solid, yield: 57.23 %, m.p. 163.1 – 163.7, ^{1}H NMR (500 MHz, DMSO) δ 10.01 – 9.83 (m, 1H, OH), 9.46 (s, 1H, NH), 7.60 – 7.54 (m, 2H, Ph-2H), 7.42 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.14 (d, *J* = 1.6 Hz, 1H, Ph-H), 7.01 (dt, *J* = 11.8, 5.9 Hz, 1H, CO-CH=), 6.89 – 6.84 (m, 2H, Ph-2H), 6.79 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.57 (d, *J* = 15.6 Hz, 1H, Ph-H), 3.79 (s, 3H, OCH_3), 3.68 (d, *J* = 10.1 Hz, 3H, OCH_3).

Figure S2. ^{1}H NMR spectrum of intermediate **2b**



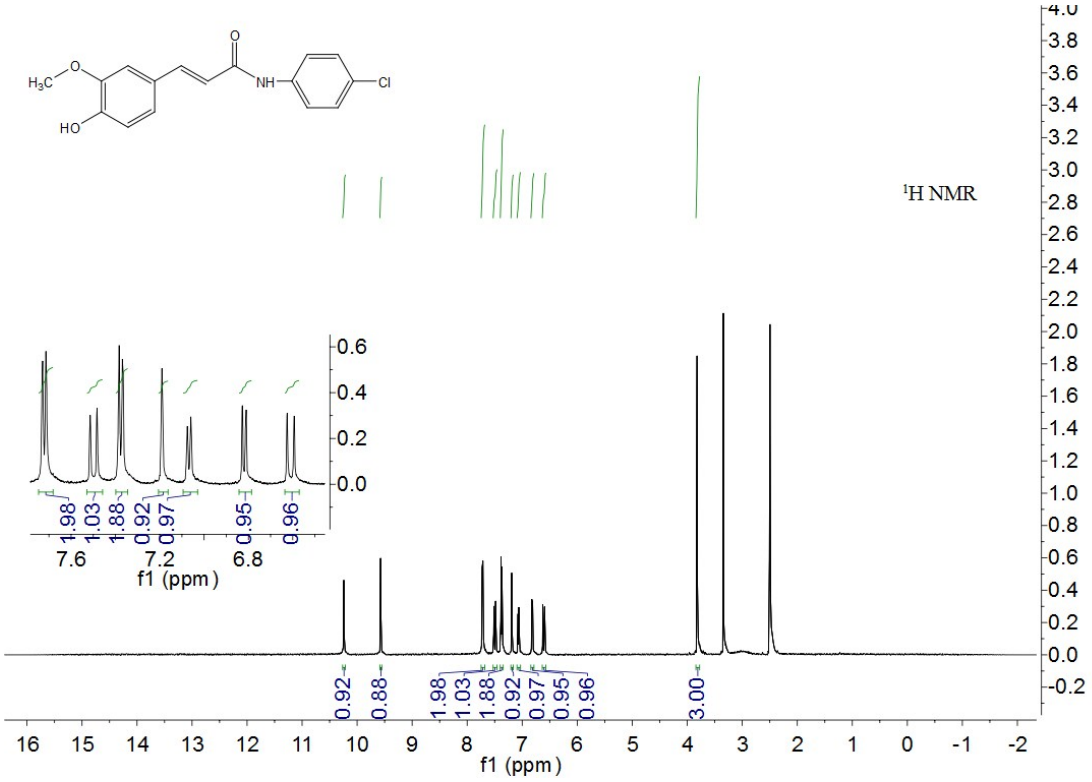
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(3-chlorophenyl)acrylamide (**2c**): Yellow solid, yield: 60.63 %, m.p. 172.3 – 173.2, ^{1}H NMR (500 MHz, DMSO) δ 10.29 (s, 1H, OH), 9.59 (s, 1H, NH), 7.94 (t, *J* = 2.0 Hz, 1H, Ph-H), 7.53 – 7.47 (m, 2H, Ph-2H), 7.35 (t, *J* = 8.1 Hz, 1H, CO-CH=CH), 7.19 (d, *J* = 1.9 Hz, 1H, CO-CH=), 7.12 – 7.05 (m, 2H, Ph-2H), 6.82 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.60 (d, *J* = 15.6 Hz, 1H, Ph-2H), 3.82 (s, 3H, OCH_3).

Figure S3. ^{1}H NMR spectrum of intermediate **2c**



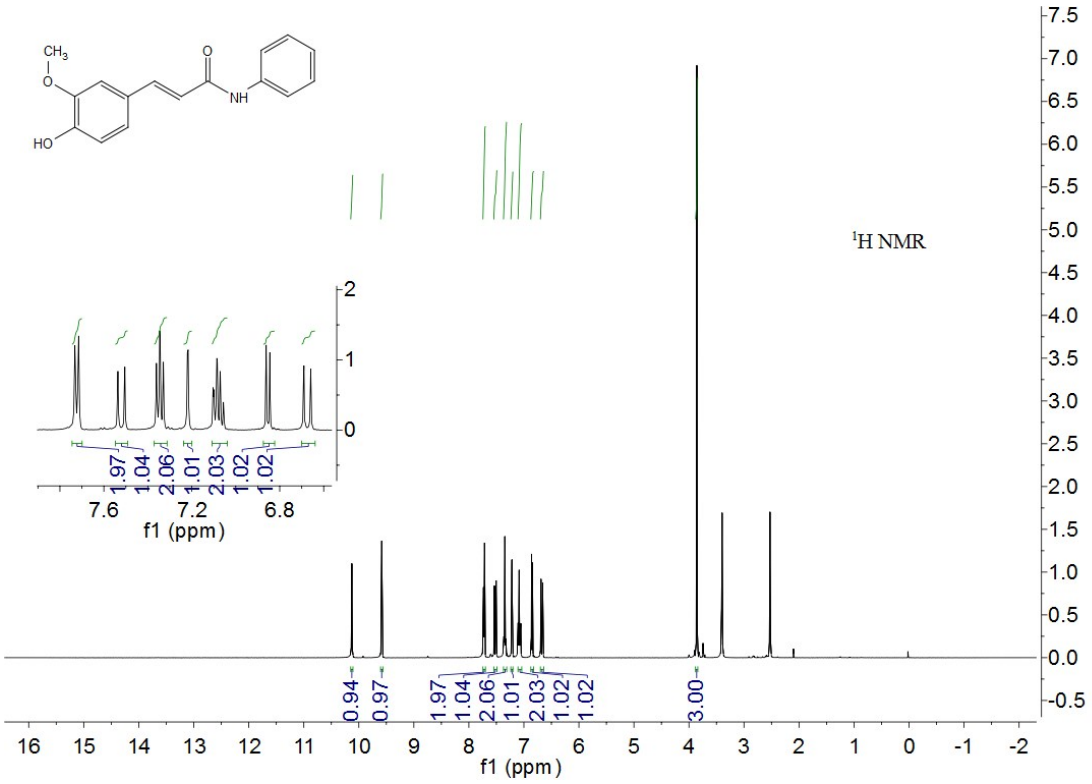
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(4-chlorophenyl)acrylamide (**2d**): Gray solid, yield: 56.92 %, m.p. 234.7 – 235.2, ^{1}H NMR (500 MHz, DMSO) δ 10.24 (s, 1H, OH), 9.57 (s, 1H, NH), 7.75 – 7.68 (m, 2H, Ph-2H), 7.50 (d, J = 15.4 Hz, 1H, CO-CH=CH), 7.40 – 7.34 (m, 2H, Ph-2H), 7.19 (s, 1H, Ph-H), 7.06 (t, J = 11.3 Hz, 1H, CO-CH=), 6.82 (dd, J = 8.1, 1.0 Hz, 1H, Ph-H), 6.64 – 6.57 (m, 1H, Ph-H), 3.81 (t, J = 7.8 Hz, 3H, OCH_3).

Figure S4. ^{1}H NMR spectrum of intermediate **2d**



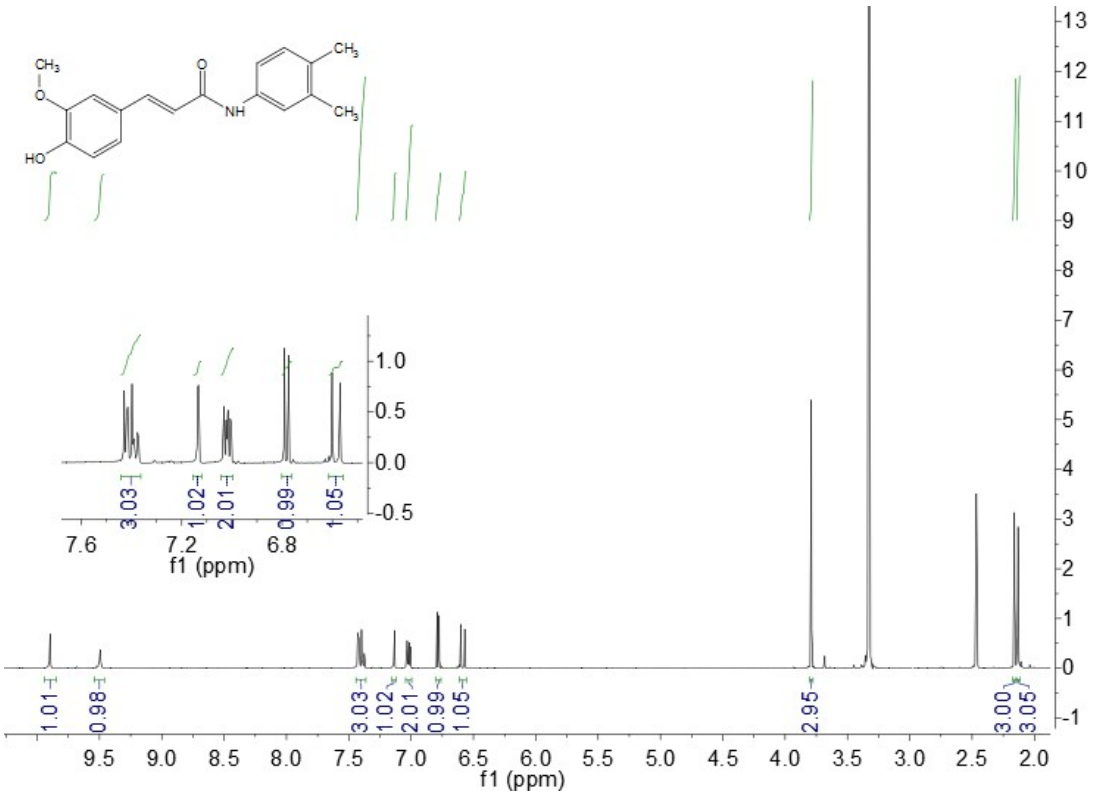
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-phenylacrylamide (**2e**): Yellow solid, yield: 63.74 %, m.p. 120.3 – 121.1, ^{1}H NMR (500 MHz, DMSO) δ 10.13 (s, 1H, OH), 9.58 (s, 1H, NH), 7.74 – 7.70 (m, 2H, Ph-2H), 7.52 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.34 (dd, *J* = 16.1, 8.0 Hz, 2H, Ph-2H), 7.22 (d, *J* = 1.8 Hz, 1H, CO-CH=), 7.11 – 7.04 (m, 2H, Ph-2H), 6.85 (dd, *J* = 11.1, 6.1 Hz, 1H, Ph-H), 6.67 (d, *J* = 15.6 Hz, 1H, Ph-H), 3.86 (s, 3H, OCH_3).

Figure S5. ^{1}H NMR spectrum of intermediate **2e**



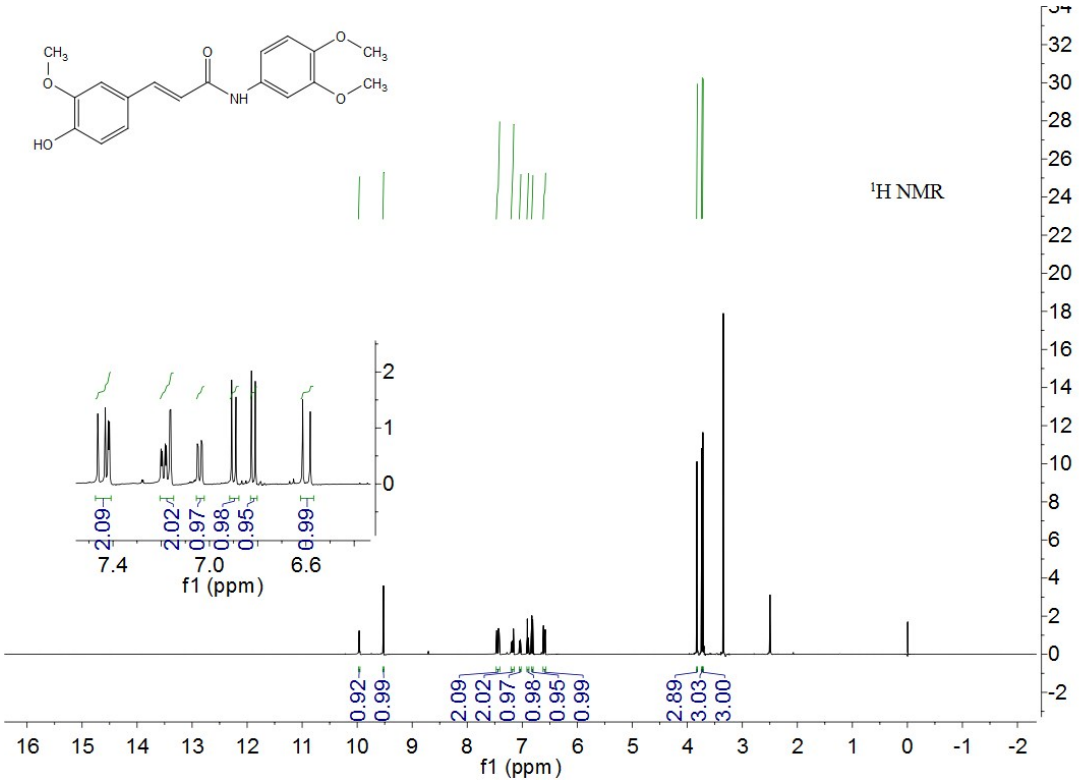
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(3,4-dimethylphenyl)acrylamide (**2f**): Gray solid, yield: 67.38 %, m.p. 182.4 – 183.6, ^{1}HNMR (500 MHz, DMSO) δ 9.90 (s, 1H), 9.49 (s, 1H), 7.40 (ddd, *J* = 10.2, 7.5, 3.6 Hz, 3H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.80 – 6.76 (m, 1H), 6.59 (dd, *J* = 16.0, 5.4 Hz, 1H), 3.79 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H).

Figure S6. ^{1}H NMR spectrum of intermediate **2f**



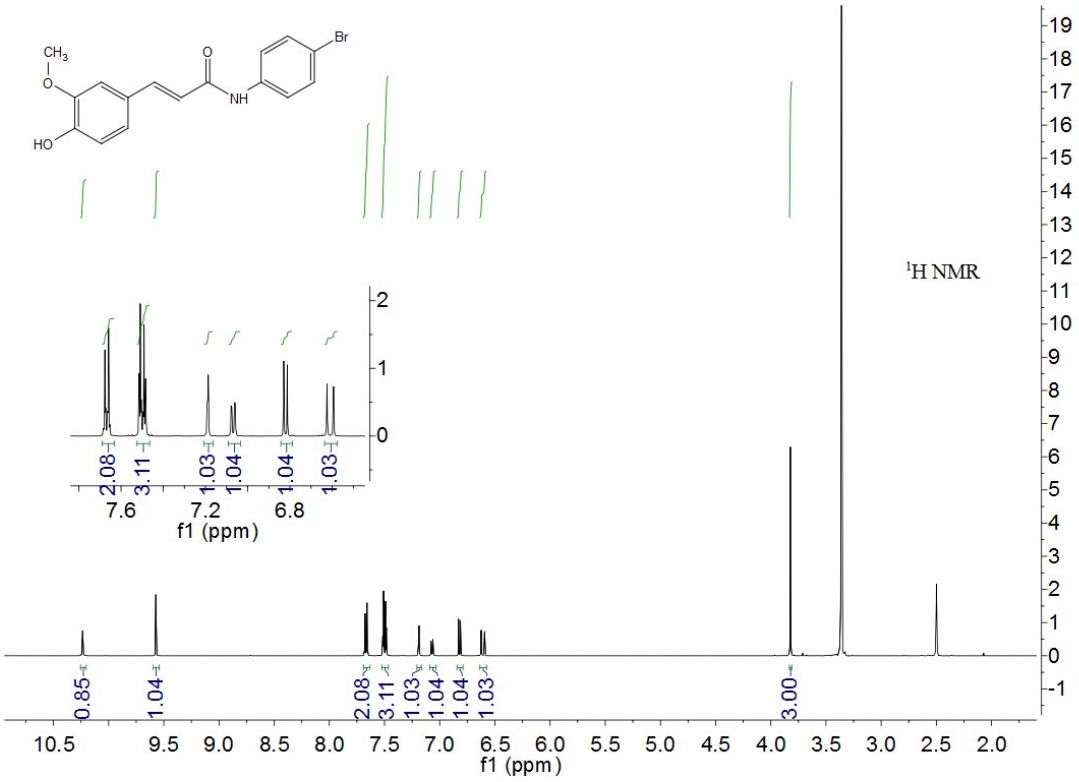
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(3,4-dimethoxyphenyl)acrylamide (**2g**): Purple solid, yield: 72.85 %, m.p. 91.2 – 91.7, ^{1}H NMR (500 MHz, DMSO) δ 9.96 (s, 1H, OH), 9.52 (s, 1H, NH), 7.43 (dd, J = 15.2, 9.0 Hz, 2H, Ph-2H), 7.21 – 7.15 (m, 2H, Ph-2H), 7.04 (dd, J = 8.2, 1.9 Hz, 1H, CO-CH=CH), 6.90 (d, J = 8.8 Hz, 1H, Ph-H), 6.83 – 6.80 (m, 1H, CO-CH=), 6.60 (d, J = 15.6 Hz, 1H, Ph-H), 3.82 (s, 3H, OCH3), 3.74 (s, 3H, OCH3), 3.72 (s, 3H, OCH3).

Figure S7. ^{1}H NMR spectrum of intermediate **2g**



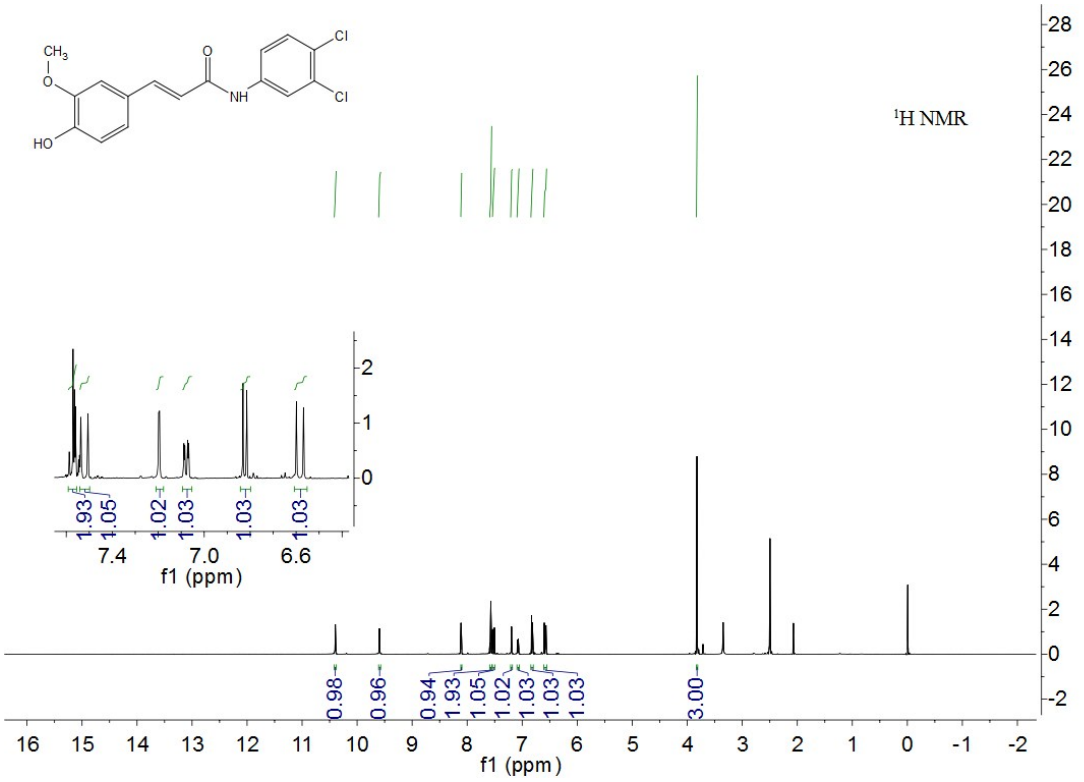
(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(4-bromophenyl)acrylamide (**2h**): Gray solid, yield: 54.73 %, m.p. 205.3 – 206.7, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H, OH), 9.57 (s, 1H, NH), 7.69 – 7.63 (m, 2H, Ph-2H), 7.52 – 7.46 (m, 3H, Ph-3H), 7.19 (d, *J* = 1.9 Hz, 1H, CO-CH=CH), 7.07 (dd, *J* = 8.2, 1.9 Hz, 1H, CO-CH=), 6.84 – 6.79 (m, 1H, Ph-H), 6.61 (d, *J* = 15.6 Hz, 1H, Ph-H), 3.82 (s, 3H, OCH_3).

Figure S8. ^{1}H NMR spectrum of intermediate **2h**



(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(3,4-dichlorophenyl)acrylamide (**2i**): Yellow solid, yield: 54.33 %, m.p. 224.4 – 224.9, ^{1}H NMR (500 MHz, DMSO*)* δ 10.40 (s, 1H, OH), 9.59 (s, 1H, NH), 8.11 (d, *J* = 2.1 Hz, 1H, Ph-H), 7.59 – 7.55 (m, 2H, Ph-2H), 7.52 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.20 (d, *J* = 1.9 Hz, 1H, Ph-H), 7.07 (dt, *J* = 6.8, 3.4 Hz, 1H, CO-CH=), 6.82 (t, *J* = 7.6 Hz, 1H, Ph-H), 6.58 (d, *J* = 15.6 Hz, 1H, Ph-H), 3.82 (s, 3H, OCH_3).

Figure S9. ^{1}H NMR spectrum of intermediate **2i**



(*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(2-fluorophenyl)acrylamide (**2j**): Yellow solid, yield: 73.34 %, m.p. 190.2-190. ^{1}H NMR (400 MHz, DMSO) δ 9.78 (s, 1H), 9.54 (s, 1H), 8.12 (td, *J* = 8.0, 1.6 Hz, 1H), 7.50 (d, *J* = 15.6 Hz, 1H), 7.27 (ddd, *J* = 11.2, 7.9, 1.6 Hz, 1H), 7.22 – 7.11 (m, 3H), 7.07 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.89 (d, *J* = 15.6 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 3H), ^{19}F NMR (376 MHz, DMSO) δ -125.57 (s).

Figure S10. ^{1}H NMR spectrum of intermediate **2j**

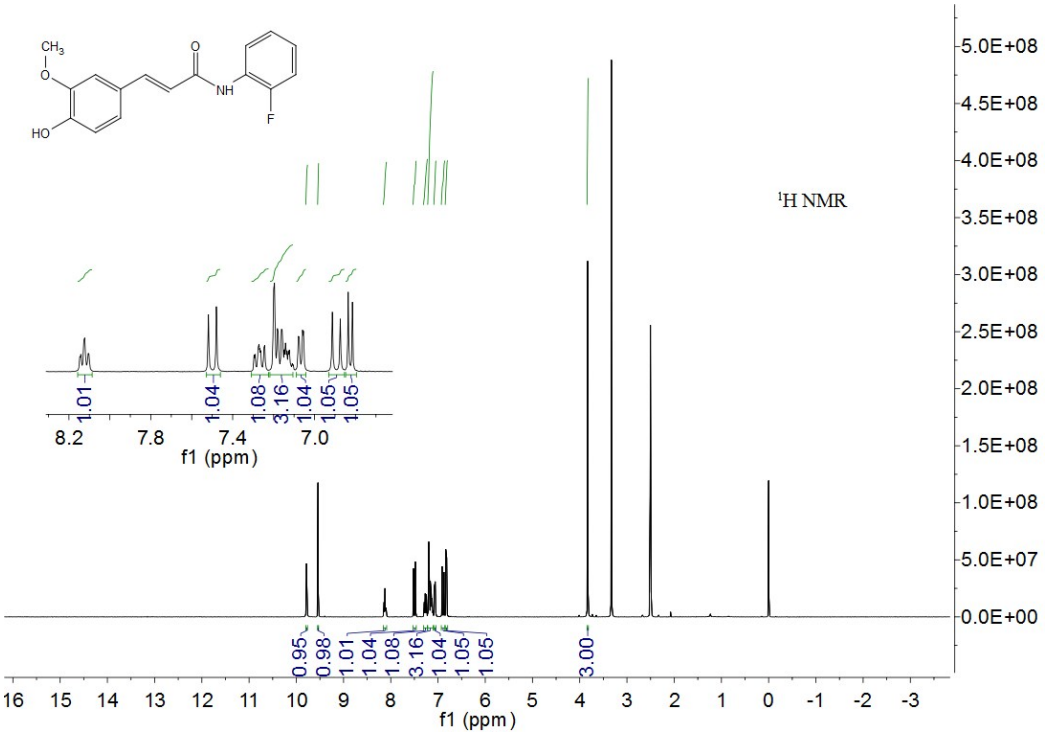
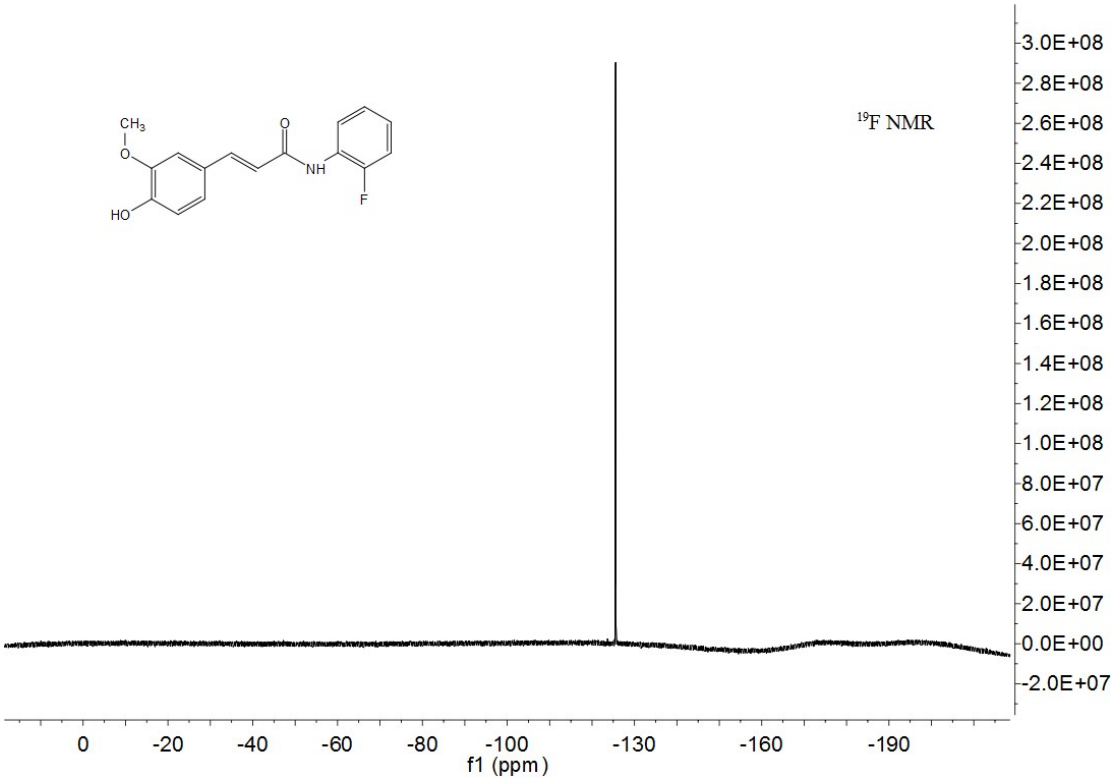


Figure S11. ^{19}F NMR spectrum of intermediate **2j**



5. Characterization of title compounds 4a-4v

(*E*)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)-*N*-(p-tolyl)acrylamide (**4a**): gray solid, m.p. 215.4-215.5, yield: 58.68 %, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, NH), 7.63 (t, *J* = 11.8 Hz, 1H, Ph-H), 7.57 (d, *J* = 7.1 Hz, 2H, Ph-2H), 7.32 (s, 2H, Ph-2H), 7.13 (d, *J* = 8.2 Hz, 2H, Ph-2H), 7.00 (d, *J* = 8.3 Hz, 1H, CO-CH=CH), 6.95 (s, 1H, Ph-H), 6.74 (d, *J* = 8.3 Hz, 1H, Ph-H), 6.51 (d, *J* = 2.1 Hz, 1H, Ph-H), 6.47 (s, 1H, CO-CH=), 6.36 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.23 (t, *J* = 5.9 Hz, 2H, CH_2), 4.18 (t, *J* = 6.7 Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 3.92 (d, *J* = 3.4 Hz, 6H, 2×OCH_3), 3.88 (s, 6H, 2×OCH_3), 3.77 (s, 3H, OCH_3), 2.31 (d, *J* = 9.9 Hz, 3H, CH_3), 2.25 (dd, *J* = 12.6, 6.3 Hz, 2H, CH_2), ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.07, 164.12, 163.82, 160.99, 158.83, 153.02, 152.77, 150.00, 149.22, 141.68, 140.56, 140.00, 129.51, 127.77, 125.94, 121.78, 119.88, 112.61, 110.41, 109.35, 105.91, 95.89, 92.49, 69.26, 66.00, 61.01, 56.38, 56.30, 55.86, 55.77, 30.13, 20.91, HRMS calcd for $C_{40}H_{42}NO_{11}[M+H]^+$: 712.2753, found 712.2752.

(*E*)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)-*N*-(4-methoxyphenyl)acrylamide (**4b**): gray solid, m.p. 190.3-190.5, yield: 39.19 %, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H, Ph-H), 7.67 (d, *J* = 5.0 Hz, 1H, Ph-H), 7.66 – 7.61 (m, 2H, Ph-2H), 7.35 (s, 2H, Ph-2H), 7.01 (d, *J* = 8.3 Hz, 1H, CO-CH=CH), 6.96 (s, 1H, Ph-H), 6.89 (d, *J* = 8.8 Hz, 2H, Ph-2H), 6.76 (d, *J* = 8.3 Hz, 1H, CO-CH=), 6.56 – 6.48 (m, 2H, Ph-2H), 6.38 (d, *J* = 2.0 Hz, 1H, Ph-H), 4.25 (t, *J* = 5.9 Hz, 2H, CH_2), 4.19 (t, *J* = 6.6 Hz, 2H, CH_2), 3.97 – 3.92 (m, 9H, 3×OCH_3), 3.90 (s, 6H, 2×OCH_3), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.34 – 2.20 (m, 2H, CH_2),^{13} C NMR (101 MHz, $CDCl_3$) δ 174.07, 164.36, 164.13, 160.97, 158.83, 156.20, 153.02, 152.79, 149.94, 149.20, 141.40, 140.56, 140.00, 131.82, 127.83, 125.93, 121.68, 121.52, 119.15, 114.14, 112.61, 110.44, 109.33, 105.90, 95.90, 92.50, 77.39, 77.07, 76.76, 69.27, 65.99, 61.01, 56.36, 56.30, 55.86, 55.75, 55.48, 30.14, HRMS calcd for $C_{40}H_{42}NO_{12}[M+H]^+$: 728.2702, found 728.2691.

(*E*)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)-*N*-(p-tolyl)acrylamide (**4c**): gray solid, m.p.100.1-101.9, yield: 51.49 %, ^{1}H NMR (400 MHz, DMSO) δ 10.05 (s, 1H, NH), 7.59 (d, J = 8.4 Hz, 2H, Ph-2H), 7.50 (d, J = 15.5 Hz, 1H, CO-CH=CH), 7.40 (s, 2H, Ph-2H), 7.20 (d, J = 1.8 Hz, 1H, Ph-H), 7.14 (dd, J = 8.5, 3.7 Hz, 2H, Ph-2H), 7.12 (s, 1H, CO-CH=), 6.98 (d, J = 8.4 Hz, 1H, Ph-H), 6.85 (d, J = 2.2 Hz, 1H, Ph-H), 6.68 (d, J =

15.6 Hz, 1H, Ph-H), 6.50 (d, J = 2.3 Hz, 1H, Ph-H), 4.05 – 3.96 (m, 4H, 2×CH_2), 3.90 (s, 3H, OCH_3), 3.87 (s, 6H, 2×OCH_3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 1.84 (s, 4H, 2×CH_2), ^{13}C NMR (126 MHz, DMSO) δ 172.74, 164.29, 164.17, 160.80, 158.70, 153.23, 152.11, 150.16, 149.56, 140.54, 140.45, 139.88, 137.49, 132.60, 129.70, 127.97, 126.15, 122.21, 120.40, 119.58, 113.18, 110.59, 108.97, 106.16, 93.62, 71.77, 68.26, 60.71, 56.61, 56.56, 55.89, 26.84, 25.91, 21.02, HRMS calcd for $C_{41}H_{44}NO_{11}[M+H]^+$: 726.2908, found 726.2904.

(*E*)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)-*N*-(4-methoxyphenyl)acrylamide (**4d**): gray solid, m.p. 108.6-109.8, yield: 63.54 %, ^{1}H NMR (400 MHz, DMSO) δ 10.01 (s, 1H, NH), 7.62 (d, J = 9.1 Hz, 2H, Ph-2H), 7.52 – 7.45 (m, 1H, CO-CH=CH), 7.40 (s, 2H, Ph-2H), 7.21 – 7.18 (m, 1H, Ph-H), 7.14 (dd, J = 8.4, 1.7 Hz, 1H, CO-CH=), 6.98 (d, J = 8.4 Hz, 1H, Ph-H), 6.93 – 6.87 (m, 2H, Ph-2H), 6.84 (t, J = 4.0 Hz, 1H, Ph-H), 6.67 (d, J = 15.6 Hz, 1H, Ph-H), 6.50 (d, J = 2.3 Hz, 1H, Ph-H), 4.01 (dd, J = 6.0, 3.2 Hz, 4H, 2×CH_2), 3.90 (s, 3H, OCH_3), 3.87 (s, 6H, 2×OCH_3), 3.84 (d, J = 3.1 Hz, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (d, J = 5.6 Hz, 6H, 2×OCH_3), 1.84 (s, 4H, 2×CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.68, 164.23, 163.86, 160.75, 158.64, 155.62, 153.17, 152.05, 150.06, 149.51, 140.39, 140.22, 139.84, 133.13, 127.97, 126.09, 122.09, 120.97, 120.40, 114.38, 113.16, 110.53, 108.92, 106.12, 96.39, 93.57, 71.72, 68.21, 60.65, 56.51, 55.84, 55.62, 26.78, 25.85, HRMS calcd for $C_{41}H_{44}NO_{12}[M+H]^+$: 742.2858, found 742.2840.

(*E*)-*N*-(3-chlorophenyl)-3-(3-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-4-methoxyphenyl)acrylamide (**4e**): yellow solid, m.p. 187.2-187.5, yield: 49.65 %, ^{1}H NMR (400 MHz, DMSO) δ 10.34 (s, 1H, NH), 7.97 (t, J = 2.0 Hz, 1H, Ph-H), 7.59 – 7.51 (m, 2H, Ph-2H), 7.40 – 7.34 (m, 3H, Ph-3H), 7.21 (t, J = 5.4 Hz, 1H, CO-CH=CH), 7.19 – 7.10 (m, 2H, Ph-2H), 6.90 (d, J = 8.4 Hz, 1H, CO-CH=), 6.84 (d, J = 2.2 Hz, 1H, Ph-H), 6.68 (d, J = 15.6 Hz, 1H, Ph-H), 6.50 (d, J = 2.3 Hz, 1H, Ph-H), 4.16 – 4.12 (m, 2H, CH_2), 4.09 (t, J = 6.4 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.86 (d, J = 1.7 Hz, 9H, 3×OCH_3), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.13 (p, J = 6.2 Hz, 2H, CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.66, 164.61, 164.23, 160.74, 158.64, 153.17, 152.07, 150.15, 149.50, 141.36, 140.37, 139.85, 133.58, 130.95, 127.85, 126.01, 123.31, 122.29, 119.81, 118.99, 117.95, 113.08, 110.72, 108.90, 106.18, 96.38, 93.55, 69.25, 65.71, 60.64, 56.54, 56.48, 55.85, 49.07, 30.11, HRMS calcd for $C_{39}H_{39}ClNO_{11}[M+H]^+$: 732.2206, found 732.2187.

(*E*)-*N*-(3-chlorophenyl)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-

chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)acrylamide (**4f**): gray solid, m.p. 104.1-104.9, yield : 55.55 %, ^{1}H NMR (400 MHz, DMSO) δ 10.33 (s, 1H, NH), 7.95 (t, J = 2.0 Hz, 1H, Ph-H), 7.54 (ddd, J = 6.7, 5.8, 4.2 Hz, 2H, Ph-2H), 7.40 (s, 2H, Ph-2H), 7.36 (t, J = 8.1 Hz, 1H, CO-CH=CH), 7.22 (d, J = 1.8 Hz, 1H, CO-CH=), 7.19 – 7.09 (m, 2H, Ph-2H), 6.99 (d, J = 8.4 Hz, 1H, Ph-H), 6.84 (d, J = 2.2 Hz, 1H, Ph-H), 6.67 (d, J = 15.6 Hz, 1H, Ph-H), 6.49 (d, J = 2.3 Hz, 1H, Ph-H), 4.06 – 3.96 (m, 4H, 2×CH_2), 3.90 (s, 3H, OCH_3), 3.87 (d, J = 5.8 Hz, 6H, 2×OCH_3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.84 (s, 4H, 2×CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.67, 164.63, 164.21, 160.74, 158.63, 153.17, 152.02, 150.32, 149.52, 141.43, 141.37, 140.39, 139.85, 133.58, 130.95, 127.68, 126.09, 123.30, 122.42, 119.71, 118.98, 117.94, 113.12, 110.62, 108.92, 106.12, 96.37, 93.55, 71.70, 68.22, 60.64, 56.53, 56.50, 55.86, 26.78, 25.85, HRMS calcd for $C_{40}H_{41}ClNO_{11}[M+H]^+$: 746.2362,found746.2345. (*E*)-*N*-(4-chlorophenyl)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)acrylamide (**4g**): gray solid, m. p. 103.3-104.8, yield: 62.00 %,

^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H, NH), 7.74 (d, *J* = 7.7 Hz, 2H, Ph-2H), 7.54 (d, *J* = 15.5 Hz, 1H, Ph-H), 7.41 (d, *J* = 1.2 Hz, 3H, Ph-3H), 7.39 (s, 1H, CO-CH=CH), 7.23 – 7.15 (m, 2H, Ph-2H), 7.00 (d, *J* = 7.9 Hz, 1H, CO-CH=), 6.87 (s, 1H, Ph-H), 6.68 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.51 (s, 1H, Ph-H), 4.05 – 3.98 (m, 4H, 2×CH_2), 3.91 (d, *J* = 1.0 Hz, 3H, OCH_3), 3.87 (d, *J* = 1.1 Hz, 6H, 2×OCH_3), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.75 (d, *J* = 1.3 Hz, 3H, OCH_3), 1.84 (s, 4H, 2×CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.68, 164.43, 164.24, 160.75, 158.65, 153.18, 152.06, 150.25, 149.51, 141.16, 140.39, 139.83, 138.88, 129.17, 127.74, 127.14, 126.09, 122.35, 121.06, 119.86, 113.13, 110.59, 108.91, 106.12, 96.41, 93.58, 71.72, 68.21, 60.66, 56.52, 55.85, 26.77, 25.84, HRMS calcd for $C_{40}H_{41}ClNO_{11}[M+H]^+$: 746.2362, found 746.2351.

(*E*)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)-*N*-phenylacrylamide (**4h**): yellow solid, m.p. 116.4-116.7, yield: 60.30 %, ^{1}H NMR (400 MHz, DMSO) δ 10.13 (s, 1H, NH), 7.71 (d, *J* = 7.6 Hz, 2H, Ph-2H), 7.53 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.41 (s, 2H, Ph-2H), 7.36 – 7.30 (m, 2H, Ph-2H), 7.22 (d, *J* = 1.8 Hz, 1H, CO-CH=), 7.16 (dd, *J* = 8.4, 1.8 Hz, 1H, Ph-H), 7.06 (t, *J* = 7.4 Hz, 1H, Ph-H), 6.99 (d, *J* = 8.4 Hz, 1H, Ph-H), 6.86 (d, *J* = 2.2 Hz, 1H, Ph-H), 6.71 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.51 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.07 – 3.96 (m, 4H, 2×CH_2), 3.91 (s, 3H, OCH_3), 3.87 (d, *J* = 7.5 Hz, 9H, 3×OCH_3), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.85 (s, 4H, 2×CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.68, 164.32, 164.24, 160.76, 158.65,

153.18, 152.07, 150.17, 149.53, 140.76, 140.39, 139.92, 139.88, 129.25, 127.88, 126.09, 123.63, 122.23, 120.25, 119.56, 113.19, 110.61, 108.93, 106.16, 96.40, 93.59, 71.74, 68.24, 60.66, 56.53, 55.87, 26.78, 25.85, HRMS calcd for $C_{40}H_{42}NO_{11}[M+H]^+$: 712.2752, found 712.2743.

(*E*)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)-*N*-phenylacrylamide (**4i**): yellow solid, m.p. 242.5-242.9, yield: 49.79 %, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 22.6 Hz, 1H, Ph-H), 7.70 – 7.62 (m, 3H, Ph-3H), 7.36 – 7.29 (m, 4H, Ph-4H)), 7.10 (t, *J* = 7.4 Hz, 1H, CO-CH=CH)), 7.01 (d, *J* = 8.3 Hz, 1H, CO-CH=), 6.95 (s, 1H, Ph-H), 6.75 (d, *J* = 8.3 Hz, 1H, Ph-H), 6.54 – 6.43 (m, 2H, Ph-2H), 6.35 (t, *J* = 4.8 Hz, 1H, Ph-H), 4.23 (t, *J* = 5.9 Hz, 2H, CH_2), 4.17 (t, *J* = 6.6 Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.88 (s, 6H, 2×OCH_3), 3.77 (s, 3H, OCH_3), 2.25 (p, *J* = 6.2 Hz, 2H, CH_2), ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.09, 164.55, 164.19, 161.09, 158.90, 153.11, 152.81, 150.20, 149.38, 142.05, 140.64, 140.17, 138.56, 129.07, 127.80, 126.01, 124.17, 121.91, 119.98, 118.99, 112.80, 110.60, 109.45, 106.08, 95.95, 92.58, 69.33, 66.12, 61.05, 56.43, 56.39, 55.89, 30.22, HRMS calcd for $C_{39}H_{40}NO_{11}[M+H]^+$: 696.2439, found 696.2459.

(*E*)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)-*N*-(3,4-dimethylphenyl)acrylamide (**4j**): gray solid, m.p. 202.5-202.9, yield: 83.97 %, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, Ph-H), 7.63 (d, *J* = 15.4 Hz, 1H, Ph-H), 7.47 (s, 1H, Ph-H), 7.39 (d, *J* = 6.7 Hz, 1H, Ph-H), 7.32 (s, 2H, Ph-2H), 7.07 (d, *J* = 8.1 Hz, 1H, CO-CH=CH), 7.00 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.94 (s, 1H, Ph-H), 6.73 (d, *J* = 8.3 Hz, 1H, CO-CH=), 6.50 (t, *J* = 7.7 Hz, 2H, Ph-2H), 6.35 (s, 1H, Ph-H), 4.23 (t, *J* = 5.7 Hz, 2H, CH_2), 4.17 (t, *J* = 6.5 Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.88 (s, 6H, 2×OCH_3), 3.75 (s, 3H, OCH_3), 2.26 (d, *J* = 6.2 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.07, 164.40, 164.11, 160.97, 158.82, 153.02, 152.76, 149.94, 149.18, 141.54, 140.56, 139.94, 137.18, 136.26, 132.42, 129.97, 127.80, 125.95, 121.77, 121.20, 119.19, 117.36, 112.54, 110.33, 109.33, 105.85, 95.89, 92.47, 69.25, 65.98, 61.02, 56.39, 56.29, 55.87, 55.74, 30.13, 19.96, 19.24, HRMS calcd for $C_{41}H_{44}NO_{11}[M+H]^+$:726.2908, found 726.2902.

(*E*)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)-*N*-(3,4-dimethylphenyl)acrylamide (**4k**): gray solid, m.p. 107.3-108.1, yield: 48.39 %, ^{1}H NMR (400 MHz, DMSO) δ 9.97 (s, 1H, NH), 7.49 (d, *J* = 15.6 Hz, 2H, Ph-2H), 7.43 (dd, *J* = 7.7, 5.9 Hz, 1H, CO-CH=CH), 7.41 (s, 2H, Ph-2H), 7.20 (d, *J* = 1.8 Hz, 1H, Ph-H), 7.14 (dd, *J* = 8.4,

1.7 Hz, 1H, Ph-H), 7.08 (d, *J* = 8.3 Hz, 1H, CO-CH=), 6.99 (d, *J* = 8.4 Hz, 1H, Ph-H), 6.85 (d, *J* = 2.0 Hz, 1H, Ph-H), 6.69 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.50 (d, *J* = 2.1 Hz, 1H, Ph-H), 4.03 (t, *J* = 9.7 Hz, 4H, 2×CH_2), 3.91 (s, 3H, OCH_3), 3.88 (s, 6H, 2×OCH_3), 3.85 (d, *J* = 7.1 Hz, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.76 (d, *J* = 4.7 Hz, 3H, OCH_3), 2.21 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.85 (s, 4H, 2×CH_2), ^{13} C NMR (101 MHz, DMSO) *δ* 172.68, 164.22, 164.05, 160.75, 158.63, 153.17, 152.03, 150.09, 149.52, 140.39, 140.35, 139.86, 137.68, 136.77, 131.37, 130.08, 127.96, 126.09, 122.09, 120.74, 120.47, 117.10, 113.17, 110.60, 108.92, 106.13, 96.38, 93.56, 71.72, 68.22, 60.65, 56.54, 56.51, 55.85, 26.79, 25.86, 20.16, 19.28, HRMS calcd for $C_{42}H_{46}NO_{11}[M+H]^+$:740.3065, found 740.3060.

(*E*)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)-*N*-(3,4-dimethoxyphenyl)acrylamide (**4l**): green solid, m.p. 118.0-118.7, yield: 65.33 %, ^{1}H NMR (400 MHz, DMSO) *δ* 10.03 (s, 1H, NH), 7.47 (dd, *J* = 21.3, 8.8 Hz, 2H, Ph-2H), 7.36 (d, *J* = 14.3 Hz, 2H, Ph-2H), 7.26 – 7.16 (m, 2H, Ph-2H), 7.13 (d, *J* = 8.3 Hz, 1H, CO-CH=CH), 6.97 – 6.77 (m, 3H, Ph-2H, CO-CH=), 6.68 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.51 (d, *J* = 2.1 Hz, 1H, Ph-H), 4.11 (dt, *J* = 19.2, 6.1 Hz, 4H, 2×CH_2), 3.91 (d, *J* = 7.0 Hz, 3H, OCH_3), 3.85 (t, *J* = 7.1 Hz, 9H, 3×OCH_3), 3.81 (s, 3H, OCH_3), 3.79 – 3.70 (m, 9H, 3×OCH_3), 2.12 (dd, *J* = 12.5, 6.3 Hz, 2H, CH_2), ^{13} C NMR (101 MHz, DMSO) *δ* 172.67, 164.24, 163.90, 160.76, 158.65, 153.17, 152.09, 149.92, 149.52, 149.02, 145.29, 140.37, 140.21, 139.88, 133.57, 128.13, 126.01, 121.99, 120.52, 113.17, 112.61, 111.48, 110.65, 108.91, 106.21, 104.69, 96.39, 93.57, 69.28, 65.73, 60.65, 56.50, 56.19, 55.85, 55.80, 30.12, HRMS calcd for $C_{41}H_{44}NO_{13}[M+H]^+$:756.2650, found 756.2675.

(*E*)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)-*N*-(3,4-dimethoxyphenyl)acrylamide (**4m**): green solid, m.p. 95.3-96.1, yield: 59.67 %, ^{1}H NMR (400 MHz, DMSO) *δ* 10.01 (s, 1H, NH), 7.49 (d, *J* = 15.5 Hz, 1H, CO-CH=CH), 7.43 (t, *J* = 3.9 Hz, 1H, Ph-H), 7.41 (s, 2H, Ph-2H), 7.24 – 7.18 (m, 2H, Ph-2H), 7.14 (dd, *J* = 8.4, 1.7 Hz, 1H, CO-CH=), 6.99 (d, *J* = 8.4 Hz, 1H, Ph-H), 6.92 (d, *J* = 8.9 Hz, 1H, Ph-H), 6.85 (d, *J* = 2.2 Hz, 1H, Ph-H), 6.67 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.50 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.02 (dd, *J* = 6.0, 3.1 Hz, 4H, 2×CH_2), 3.91 (s, 3H, OCH_3), 3.88 (s, 6H, 2×OCH_3), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.76 (s, 6H, 2×OCH_3), 3.74 (s, 3H), 1.85 (s, 4H, 2×CH_2), ^{13} C NMR (101 MHz, DMSO) *δ* 172.68, 164.22, 163.91, 160.75, 158.64, 153.17, 152.04, 150.09, 149.53, 149.01, 145.27, 140.39, 140.24, 139.85, 133.58, 127.96, 126.09, 122.11, 120.43, 113.18, 112.59, 111.45, 110.54, 108.92, 106.14, 104.67,

96.38, 93.57, 71.72, 68.23, 60.65, 56.54, 56.51, 56.18, 55.85, 55.79, 26.78, 25.85, HRMS calcd for $C_{42}H_{46}NO_{13}[M+H]^+$:772.2963, found 772.2972.

(*E*)-N-(4-bromophenyl)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)acrylamide (**4n**): gray solid, m.p. 208.4-209.6, yield: 67.92 %,[1] H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H, NH), 7.61 (dd, *J* = 19.4, 12.0 Hz, 3H, Ph-3H), 7.42 (d, *J* = 8.7 Hz, 2H, Ph-2H), 7.32 (s, 2H, Ph-2H), 7.03 – 6.88 (m, 2H, Ph-2H), 6.73 (d, *J* = 8.3 Hz, 1H, CO-CH=CH), 6.50 (d, *J* = 2.2 Hz, 1H, Ph-H), 6.46 (d, *J* = 15.5 Hz, 1H, CO-CH=), 6.35 (d, *J* = 2.1 Hz, 1H, Ph-H), 4.19 (dt, *J* = 13.2, 6.2 Hz, 4H, 2×CH_2), 3.92 (t, *J* = 5.5 Hz, 9H, 3×OCH_3), 3.87 (s, 6H, 2×OCH_3), 3.75 (s, 3H, OCH_3), 2.33 – 2.17 (m, 2H, CH_2), [13] C NMR (101 MHz, $CDCl_3$) δ 174.08, 164.51, 164.18, 160.99, 158.85, 153.06, 152.85, 150.21, 149.30, 142.30, 140.56, 140.14, 137.73, 131.92, 127.63, 125.91, 121.82, 121.39, 118.62, 116.53, 112.71, 110.63, 109.35, 106.02, 95.93, 92.55, 69.29, 66.03, 60.99, 56.33, 55.84, 55.80, 30.16, HRMS calcd for $C_{39}H_{39}BrNO_{11}[M+H]^+$: 776.1701, found 776.1682.

(*E*)-*N*-(4-bromophenyl)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)acrylamide (**4o**): yellow solid, m.p. 180.3-181.6, yield: 58.25 %, [1] H NMR (400 MHz, DMSO) δ 10.30 (s, 1H, NH), 7.72 (d, *J* = 8.9 Hz, 2H, Ph-2H), 7.56 (t, *J* = 7.7 Hz, 2H, Ph-2H), 7.53 (s, 1H, CO-CH=CH), 7.43 (s, 2H , Ph-2H), 7.22 (dd, *J* = 19.9, 5.0 Hz, 2H, Ph-2H), 7.02 (d, *J* = 8.3 Hz, 1H, CO-CH=), 6.88 (t, *J* = 2.1 Hz, 1H, Ph-H), 6.71 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.53 (d, *J* = 1.9 Hz, 1H, Ph-H), 4.08 – 4.01 (m, 4H, 2×CH_2), 3.94 (s, 3H, OCH_3), 3.90 (s, 6H, 2×OCH_3), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 1.87 (s, 4H, 2× CH_2), [13] C NMR (101 MHz, DMSO) δ 172.68, 164.46, 164.23, 160.75, 158.64, 153.17, 152.04, 150.27, 149.52, 141.19, 140.39, 139.86, 139.28, 132.06, 127.75, 126.09, 122.34, 121.46, 119.87, 115.18, 113.15, 110.63, 108.92, 106.14, 96.39, 93.57, 71.72, 68.23, 60.65, 56.51, 55.86, 26.78, 25.84, HRMS calcd for $C_{40}H_{41}BrNO_{11}$ $[M+H]^+$:790.1857, found 790.1853.

(*E*)-*N*-(3,4-dichlorophenyl)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)acrylamide (**4p**): yellow solid, m.p. 118.6-119.3, yield: 65.55 %, [1] H NMR (400 MHz, DMSO) δ 10.45 (s, 1H, NH), 8.13 (d, *J* = 1.9 Hz, 1H, Ph-H), 7.60 – 7.57 (m, 2H, Ph-2H), 7.57 – 7.53 (m, 1H, CO-CH=CH), 7.37 (d, *J* = 2.7 Hz, 2H, Ph-2H), 7.23 – 7.13 (m, 2H, Ph-2H), 6.87 (dd, *J* = 18.4, 5.3 Hz, 2H, Ph-2H), 6.65 (d, *J* = 15.6 Hz, 1H, CO-CH=), 6.51 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.16 – 4.03 (m, 4H, 2×CH_2), 3.91 (s, 3H, OCH_3), 3.88 – 3.83 (m, 9H, 3×OCH_3),

3.79 (s, 3H, OCH_3), 3.74 (d, *J* = 2.5 Hz, 3H, OCH_3), 2.18 – 2.05 (m, 2H, CH_2), ^{13}C NMR (101 MHz, DMSO) *δ* 172.66, 164.70, 164.25, 160.76, 158.66, 153.18, 152.11, 150.23, 149.51, 141.70, 140.37, 140.00, 139.87, 131.48, 131.21, 127.76, 126.01, 125.00, 122.37, 120.69, 119.62, 119.53, 113.11, 110.78, 108.91, 106.21, 96.42, 93.59, 69.27, 65.72, 60.65, 56.50, 55.87, 30.10, HRMS calcd for $C_{39}H_{38}Cl_2NO_{11}$ $[M+H]^+$:766.1816, found 766.1801.

(*E*)-*N*-(3,4-dichlorophenyl)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)acrylamide (**4q**): grey solid, m.p. 102.3-103.4, yield: 51.70 %, ^{1}H NMR (400 MHz, DMSO) *δ* 10.42 (s, 1H, NH), 8.13 (s, 1H, Ph-H), 7.59 (s, 2H, Ph-2H), 7.55 (s, 1H, CO-CH=CH), 7.41 (s, 2H, Ph-2H), 7.24 – 7.14 (m, 2H, Ph-2H), 7.00 (d, *J* = 8.4 Hz, 1H, CO-CH=), 6.84 (d, *J* = 2.2 Hz, 1H, Ph-H), 6.65 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.50 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.06 – 3.99 (m, 4H, 2×CH_2), 3.92 (s, 3H, OCH_3), 3.88 (s, 6H, 2×OCH_3), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 1.85 (s, 4H, 2×CH_2), ^{13}C NMR (101 MHz, DMSO) *δ* 172.68, 164.71, 164.22, 160.77, 158.63, 153.18, 152.02, 150.43, 149.57, 141.71, 140.39, 140.00, 139.94, 131.48, 131.15, 127.65, 126.09, 125.00, 122.47, 120.71, 119.61, 119.47, 113.21, 110.78, 108.95, 106.22, 96.37, 93.58, 71.73, 68.29, 60.65, 56.54, 56.49, 55.91, 26.79, 25.86, HRMS calcd for $C_{40}H_{40}Cl_2NO_{11}$ $[M+H]^+$:780.1972, found 780.1976.

(*E*)-*N*-(4-chlorophenyl)-3-(4-((5-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)pentyl)oxy)-3-methoxyphenyl)acrylamide (**4r**): grey solid, m.p. 112.3-112.9, yield: 58.23 %, ^{1}H NMR (400 MHz, DMSO) *δ* 10.28 (s, 1H, NH), 7.75 (d, *J* = 8.6 Hz, 2H, Ph-2H), 7.55 (d, *J* = 15.6 Hz, 1H, Ph-H), 7.41 (s, 3H, Ph-3H), 7.39 (s, 1H, CO-CH=CH), 7.23 (s, 1H, Ph-H), 7.18 (d, *J* = 8.5 Hz, 1H, Ph-H), 7.00 (d, *J* = 8.3 Hz, 1H, Ph-H), 6.85 (s, 1H, Ph-H), 6.69 (d, *J* = 15.6 Hz, 1H, CO-CH=), 6.51 (s, 1H, Ph-H), 3.98 (t, *J* = 6.2 Hz, 4H, 2×CH_2), 3.92 (s, 3H, OCH_3), 3.87 (d, *J* = 6.0 Hz, 9H, 3×OCH_3), 3.83 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 1.75 (dd, *J* = 13.6, 6.7 Hz, 4H, 2×CH_2), 1.59 – 1.48 (m, 2H, CH_2), ^{13}C NMR (101 MHz, DMSO) *δ* 172.68, 164.44, 164.21, 160.76, 158.63, 153.15, 152.01, 150.32, 149.52, 141.15, 140.46, 139.86, 138.88, 129.15, 127.75, 127.14, 126.12, 122.37, 121.07, 119.88, 113.12, 110.61, 108.94, 106.20, 96.38, 93.56, 71.94, 68.54, 60.65, 56.52, 55.88, 29.86, 28.83, 22.66, HRMS calcd for $C_{41}H_{43}ClNO_{11}$$[M+H]^+$:760.2519, found 760.2507.

(*E*)-*N*-(3-chlorophenyl)-3-(4-((5-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)pentyl)oxy)-3-methoxyphenyl)acrylamide (**4s**): grey solid, m.p. 153.5-154.1, yield: 62.87 %, ^{1}H NMR (400 MHz, DMSO) *δ* 10.31 (s, 1H, NH), 7.95 (d, *J* = 1.5 Hz, 1H, Ph-H), 7.53 (dd, *J* = 11.1,

8.8 Hz, 2H, Ph-2H), 7.39 (d, *J* = 1.8 Hz, 2H, Ph-H), 7.34 (dd, *J* = 8.1, 1.6 Hz, 1H, Ph-H), 7.21 (s, 1H, Ph-H), 7.17 (d, *J* = 8.2 Hz, 1H, CO-CH=CH), 7.11 (d, *J* = 7.9 Hz, 1H, Ph-H), 6.99 (d, *J* = 7.1 Hz, 1H, Ph-H), 6.83 (s, 1H, Ph-H), 6.67 (d, *J* = 15.6 Hz, 1H, CO-CH=), 6.49 (s, 1H, Ph-H), 3.96 (t, *J* = 5.6 Hz, 4H, 2×CH_2), 3.90 (d, *J* = 1.5 Hz, 3H, OCH_3), 3.88 – 3.83 (m, 9H, 3×OCH_3), 3.81 (d, *J* = 1.5 Hz, 3H, OCH_3), 3.75 (d, *J* = 1.9 Hz, 3H, OCH_3), 1.73 (d, *J* = 6.3 Hz, 4H, 2×CH_2), 1.52 (d, *J* = 6.8 Hz, 2H, CH_2), ^{13}C NMR (101 MHz, DMSO) δ^{13}C NMR (101 MHz, DMSO) δ 172.69, 164.63, 164.20, 160.76, 158.63, 153.15, 152.00, 150.39, 149.53, 141.43, 141.37, 140.46, 139.87, 133.58, 130.94, 127.68, 126.12, 123.30, 122.45, 119.72, 118.99, 117.95, 113.12, 110.64, 108.95, 106.21, 96.37, 93.56, 71.94, 68.55, 60.65, 56.53, 56.49, 55.89, 29.86, 28.83, 22.66, HRMS calcd for $C_{41}H_{43}ClNO_{11}$ $[M+H]^+$:760.2519, found 760.2507.

(*E*)-3-(4-((5-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)pentyl)oxy)-3-methoxyphenyl)-*N*-(4-methoxyphenyl)acrylamide (**4t**): grey solid, m.p. 123.6-124.7, yield: 64.75 %, ^{1}H NMR (400 MHz, DMSO) δ 9.99 (s, 1H, NH), 7.61 (d, *J* = 9.0 Hz, 2H, Ph-2H), 7.48 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.38 (s, 2H, Ph-2H), 7.19 (d, *J* = 1.6 Hz, 1H, Ph-H), 7.14 (dd, *J* = 8.3, 1.6 Hz, 1H, Ph-H), 6.97 (d, *J* = 8.4 Hz, 1H, Ph-H), 6.90 (d, *J* = 9.1 Hz, 2H, Ph-2H), 6.83 (d, *J* = 2.2 Hz, 1H, Ph-H), 6.66 (d, *J* = 15.6 Hz, 1H, CO-CH=), 6.48 (d, *J* = 2.2 Hz, 1H, Ph-H), 3.95 (dt, *J* = 12.4, 6.2 Hz, 4H, 2×CH_2), 3.89 (s, 3H, OCH_3), 3.87 – 3.82 (m, 9H, 3×OCH_3), 3.80 (s, 3H, OCH_3), 3.73 (d, *J* = 5.1 Hz, 6H, 2×OCH_3), 1.73 (dq, *J* = 12.8, 6.3 Hz, 4H, 2×CH_2), 1.56 – 1.46 (m, 2H, CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.69, 164.21, 163.87, 160.76, 158.63, 155.63, 153.15, 152.01, 150.13, 149.52, 140.46, 140.22, 139.86, 133.13, 127.97, 126.12, 122.12, 120.99, 120.41, 114.39, 113.15, 110.55, 108.94, 106.20, 96.37, 93.56, 71.94, 68.54, 60.65, 56.52, 56.50, 55.87, 55.62, 29.86, 28.84, 22.66, HRMS calcd for $C_{42}H_{46}NO_{12}[M+H]^+$:756.3014, found 756.2999.

(*E*)-3-(4-(3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propoxy)-3-methoxyphenyl)-*N*-(2-fluorophenyl)acrylamide (**4u**): grey solid, m.p. 117.6-118.3, yield: 54.83 %, ^{1}H NMR (400 MHz, DMSO) δ 9.85 (s, 1H, NH), 8.18 – 8.10 (m, 1H, Ph-H), 7.54 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.37 (s, 2H, Ph-2H), 7.29 (ddd, *J* = 11.1, 7.9, 1.6 Hz, 1H, Ph-2H), 7.20 (dd, *J* = 5.5, 1.6 Hz, 2H, Ph-2H), 7.19 – 7.11 (m, 3H, Ph-3H), 6.97 (d, *J* = 15.6 Hz, 1H, Ph-H), 6.89 (d, *J* = 8.4 Hz, 1H, Ph-H), 6.85 (d, *J* = 2.2 Hz, 1H, CO-CH=), 6.51 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.10 (dt, *J* = 17.9, 6.2 Hz, 4H, 2×CH_2), 3.91 (s, 3H, OCH_3), 3.86 (d, *J* = 3.9 Hz, 9H, 3×OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.12 (p, *J* = 6.1 Hz, 2H, CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.66,

164.69, 164.25, 160.76, 158.66, 153.18, 152.11, 150.08, 149.49, 141.25, 140.37, 139.87, 128.04, 127.12, 127.00, 126.02, 124.88, 123.89, 122.23, 119.92, 115.96, 115.77, 113.12, 110.71, 108.91, 106.21, 96.42, 93.58, 69.28, 65.71, 60.65, 56.58, 56.50, 55.84, 30.11, ^{19}F NMR (376 MHz, DMSO) δ -125.55 (s), HRMS calcd for $C_{39}H_{39}FNO_{11}$ $[M+H]^+$:716.2501, found 716.2494.

(*E*)-3-(4-(4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)butoxy)-3-methoxyphenyl)-*N*-(2-fluorophenyl)acrylamide (**4v**): grey solid, m.p. 162.3-163.6, yield: 66.77 %,^{1}H NMR (400 MHz, DMSO) δ 9.86 (s, 1H, NH), 8.19 – 8.12 (m, 1H, Ph-H), 7.55 (d, *J* = 15.6 Hz, 1H, CO-CH=CH), 7.42 (s, 2H, Ph-2H), 7.33 – 7.25 (m, 1H, Ph-H), 7.25 – 7.13 (m, 4H, Ph-4H), 6.99 (t, *J* = 11.5 Hz, 2H, Ph-2H), 6.86 (d, *J* = 2.2 Hz, 1H, CO-CH=), 6.51 (d, *J* = 2.2 Hz, 1H, Ph-H), 4.07 – 3.98 (m, 4H, 2×CH_2), 3.92 (s, 3H, OCH_3), 3.89 (s, 6H, 2×OCH_3), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 1.86 (s, 4H, 2×CH_2), ^{13}C NMR (101 MHz, DMSO) δ 172.68, 164.71, 164.23, 160.74, 158.64, 154.84, 153.17, 152.42, 152.05, 150.24, 149.49, 141.29, 140.39, 139.84, 127.86, 127.13, 127.01, 126.09, 124.84, 123.85, 122.35, 119.82, 115.95, 115.76, 113.12, 110.59, 108.91, 106.12, 96.39, 93.56, 71.71, 68.21, 60.65, 56.54, 56.51, 55.82, 49.07, 26.78, 25.84, ^{19}F NMR (376 MHz, DMSO) δ -125.58 (s), HRMS calcd for $C_{40}H_{41}FNO_{11}$$[M+H]^+$: 730.2658, found 730.2653.

6. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS spectrum of the title compounds 4a-4v

Figure S12. ^{1}H NMR spectrum of compound **4a**

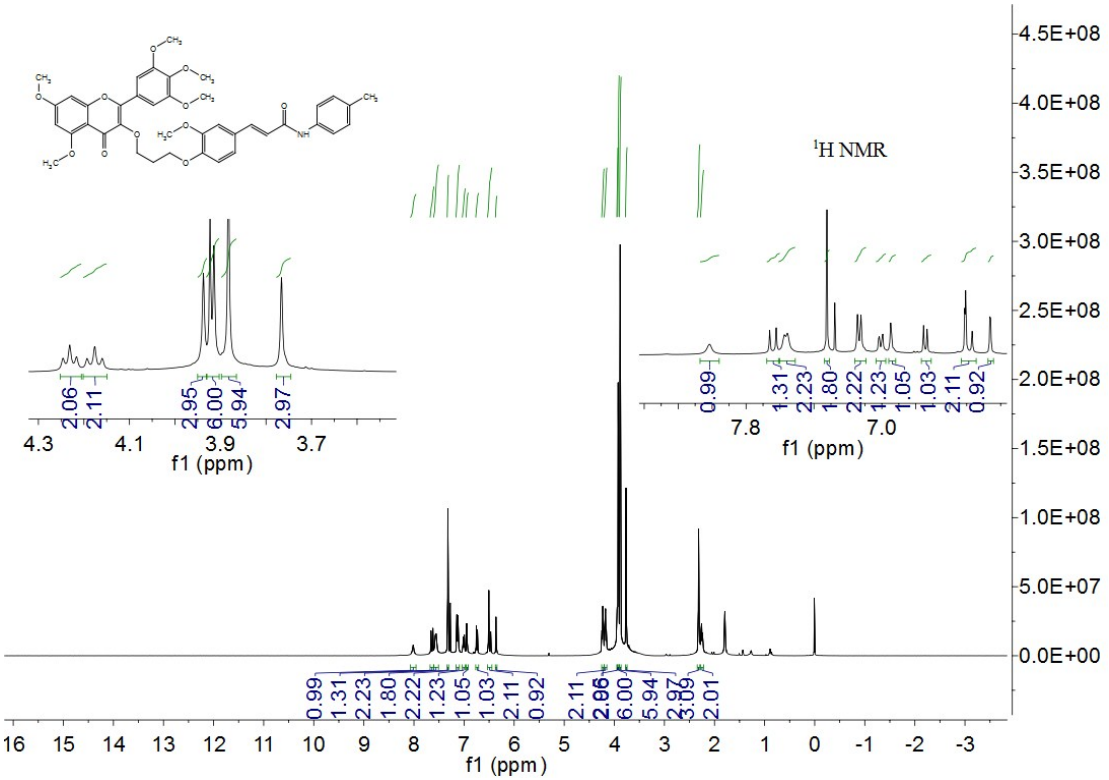


Figure S13. ^{13}C NMR spectrum of compound **4a**

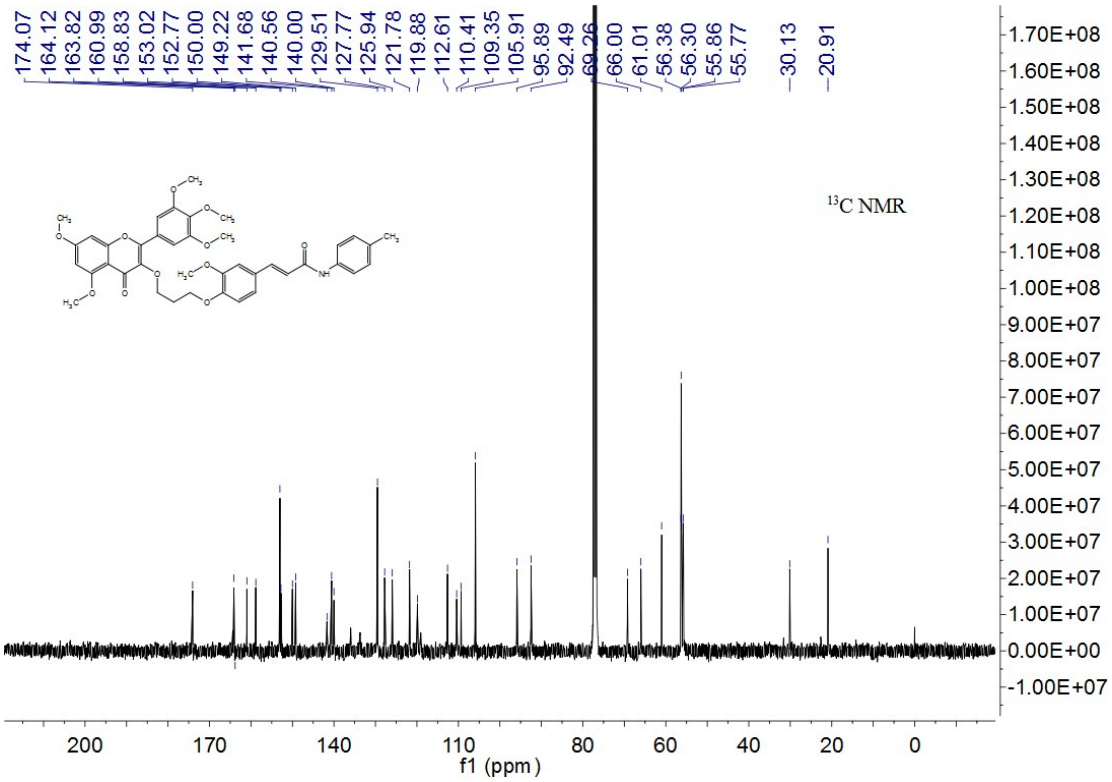


Figure S14. HRMS spectrum of compound **4a**

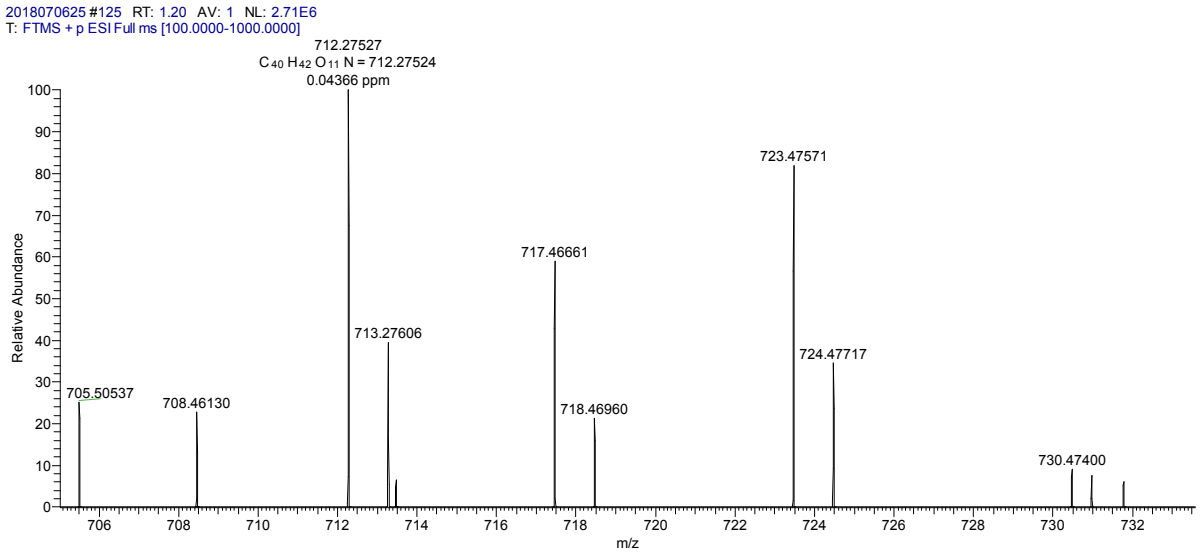


Figure S15. ^{1}H NMR spectrum of compound **4b**

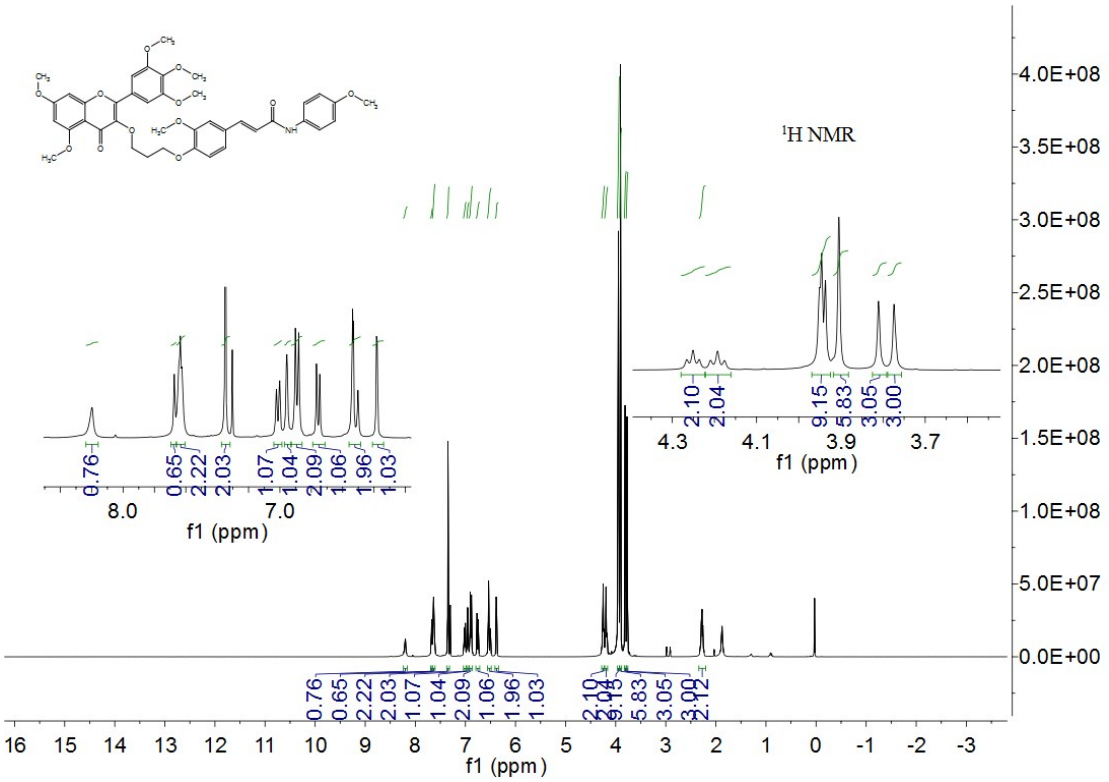


Figure S16. ^{13}C NMR spectrum of compound **4b**

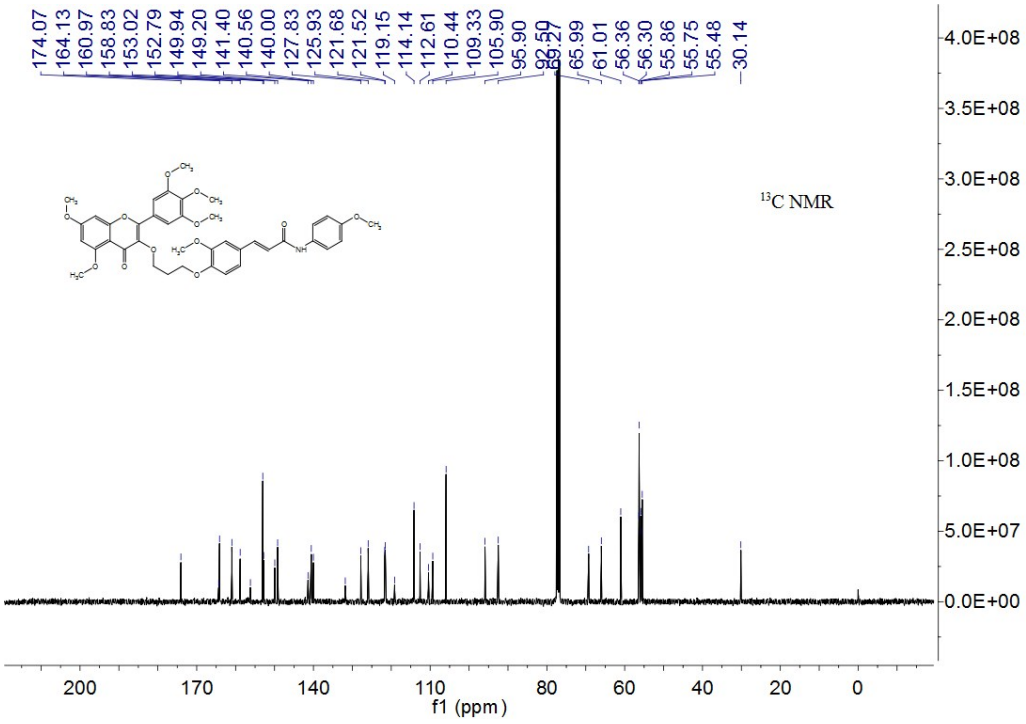


Figure S17. HRMS spectrum of compound **4b**

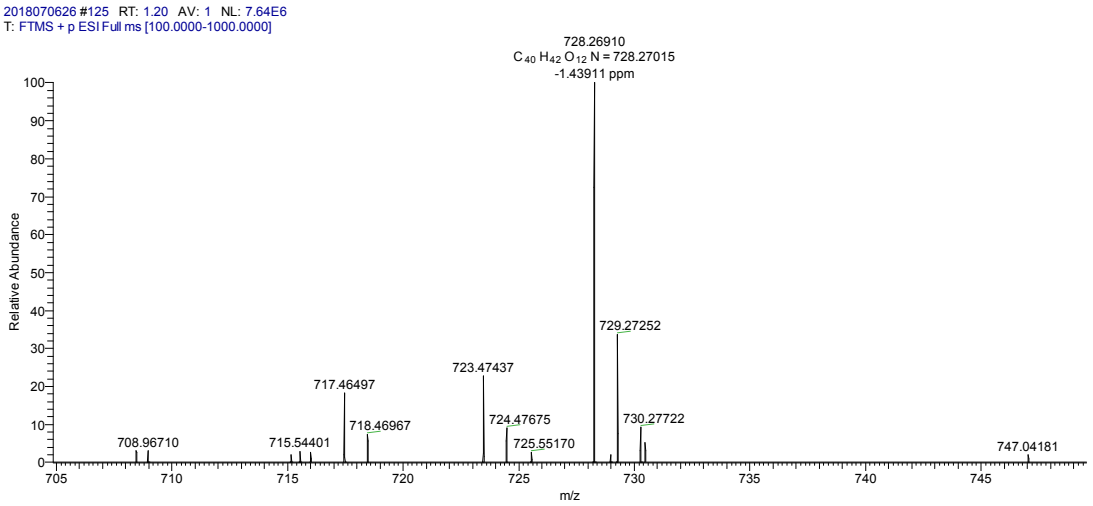


Figure S18. ^{1}H NMR spectrum of compound **4c**

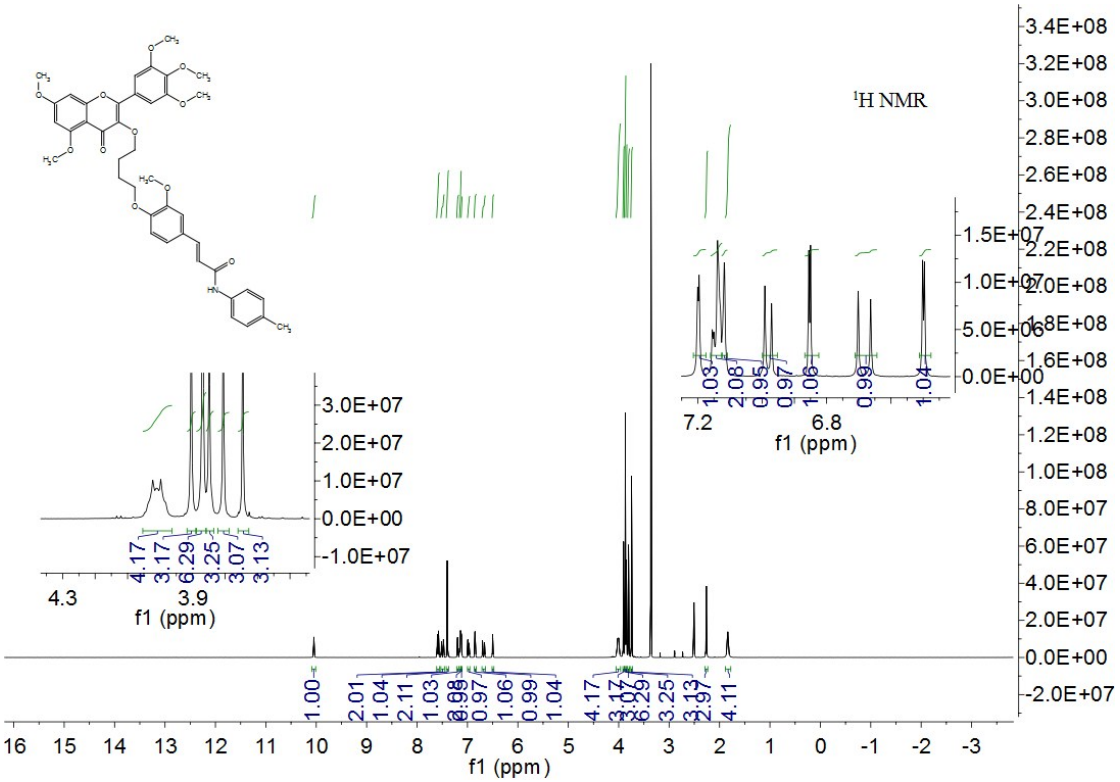


Figure S19. ^{13}C NMR spectrum of compound **4c**

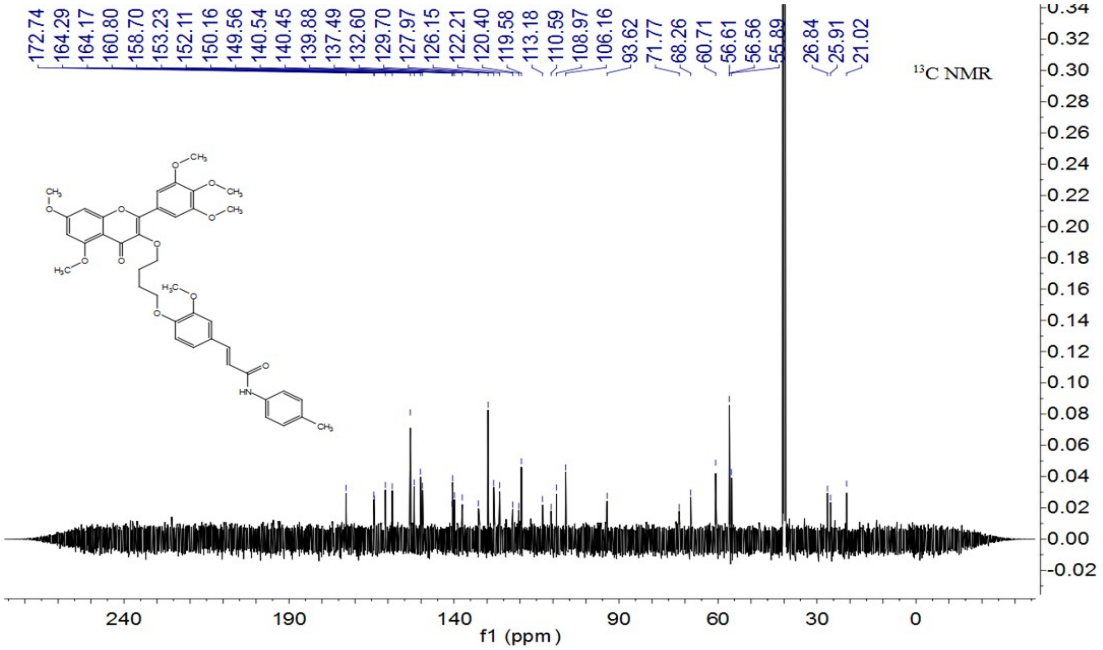


Figure S20. HRMS spectrum of compound **4c**

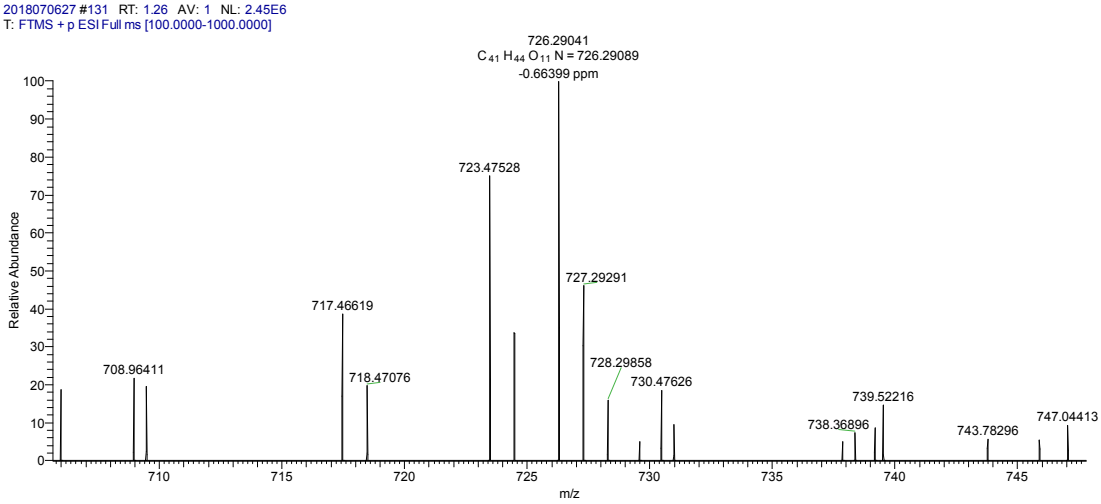


Figure S21. [1] H spectrum of compound **4d**

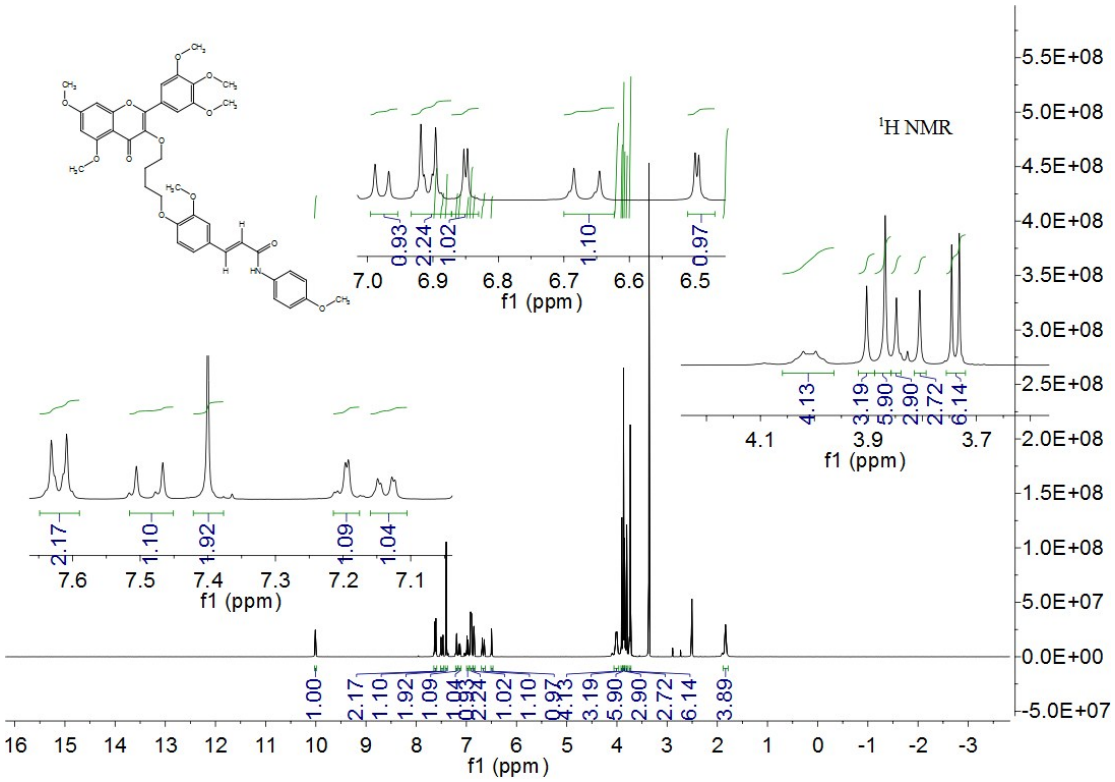


Figure S22. [13] C NMR spectrum of compound **4d**

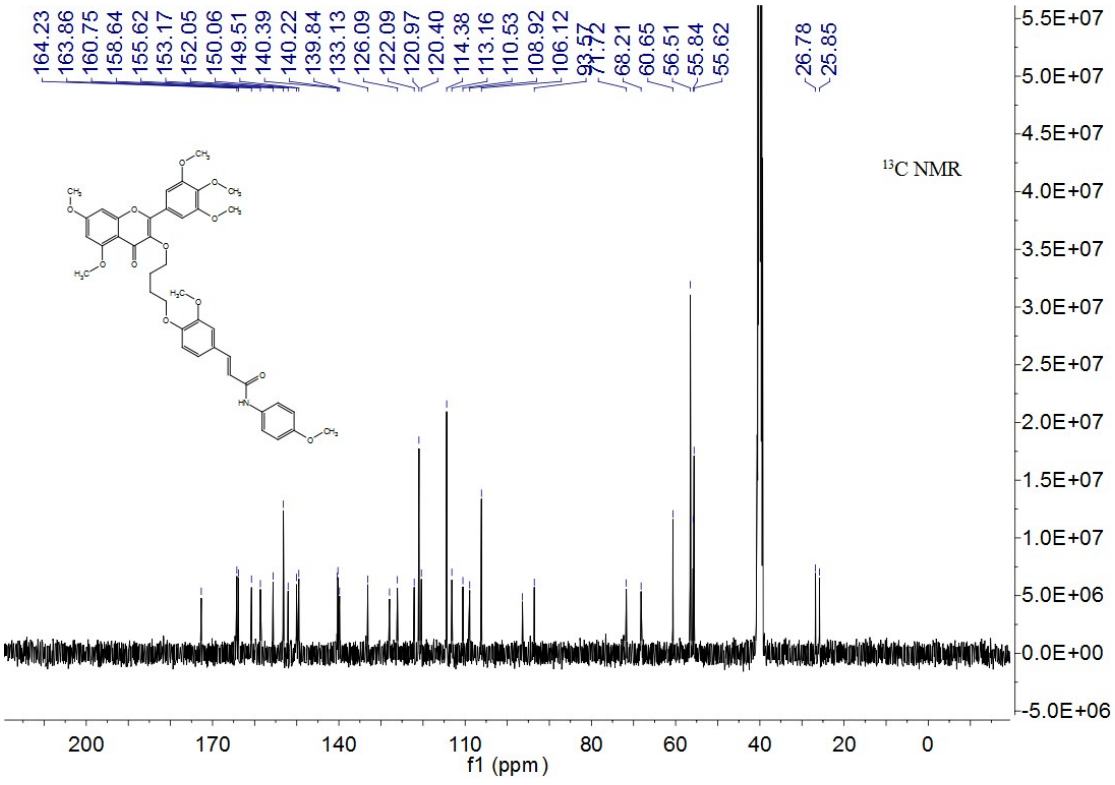


Figure S23. HRMS spectrum of compound **4d**

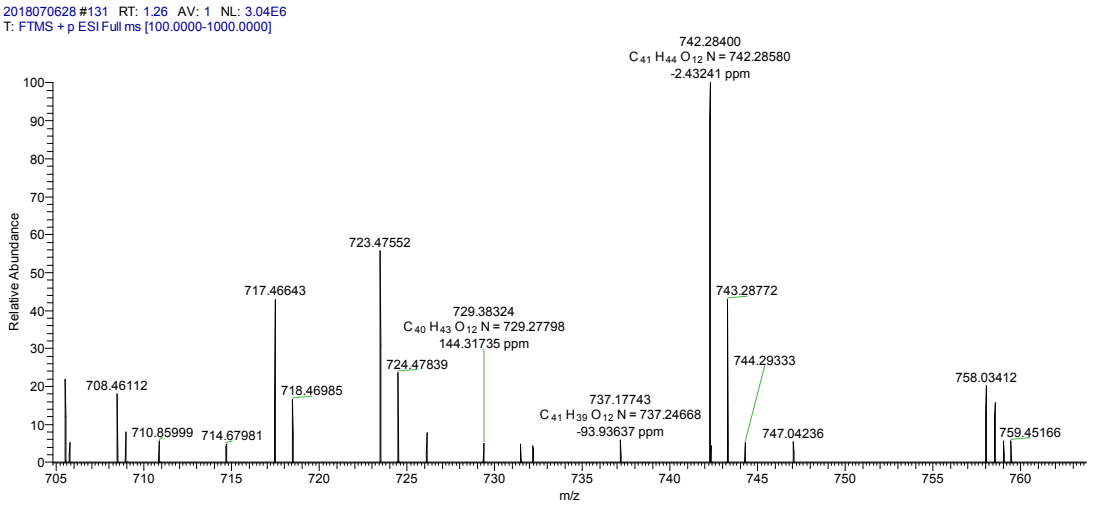


Figure S24. [1] HNMR spectrum of compound **4e**

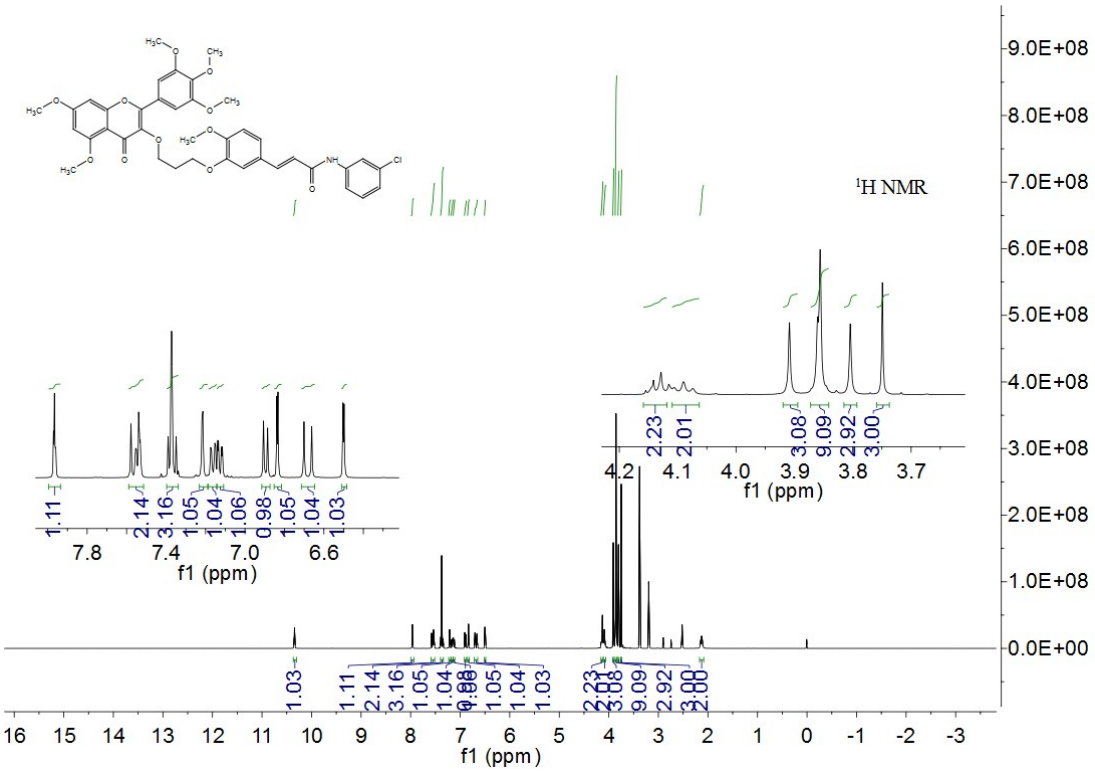


Figure S25.[13] C NMR spectrum of compound **4e**

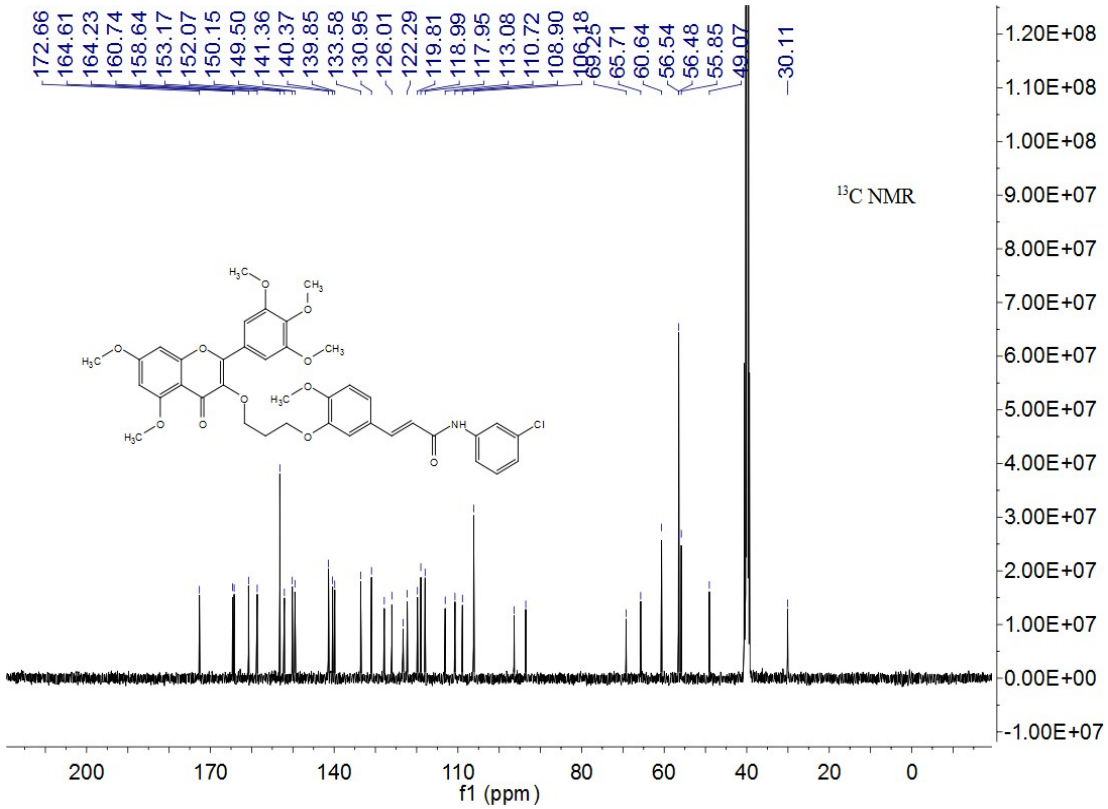


Figure S26. HRMS spectrum of compound **4e**

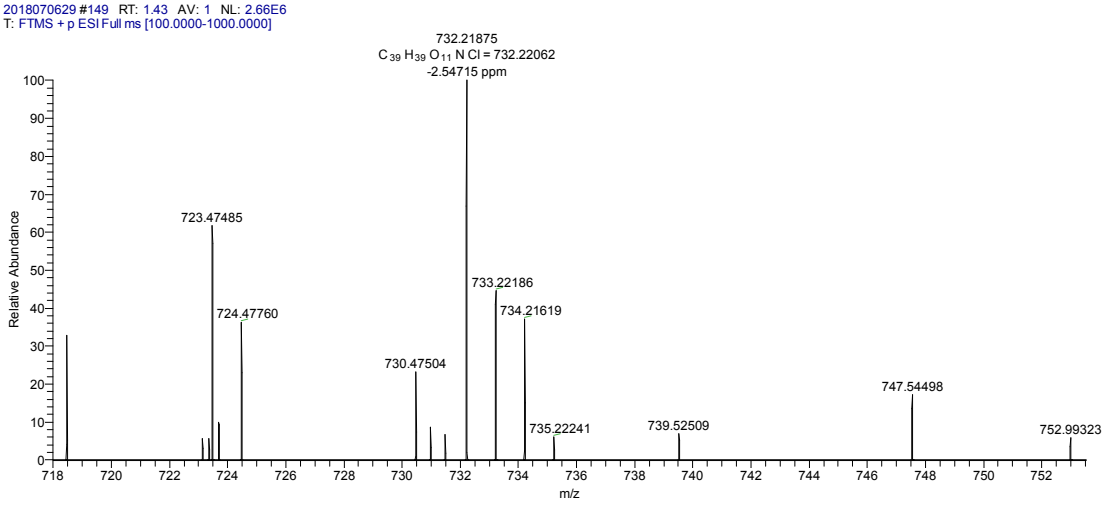


Figure S27. ^{1}H NMR spectrum of compound **4f**

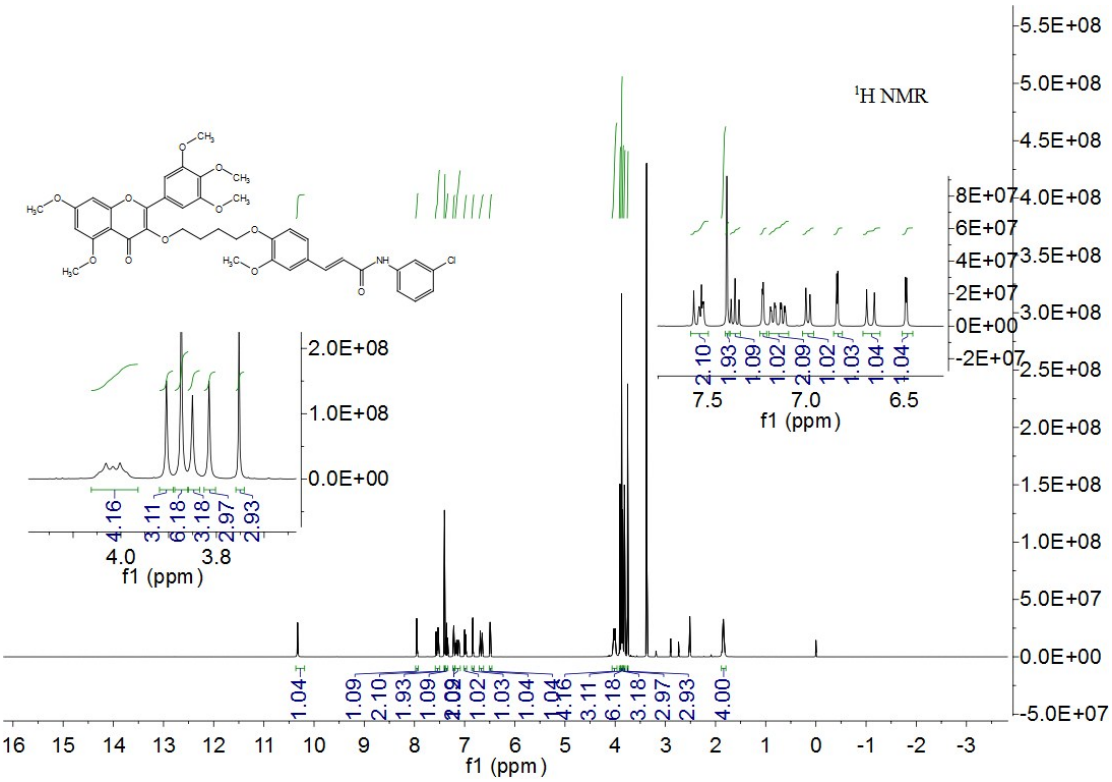


Figure S28. ^{13}C NMR spectrum of compound **4f**

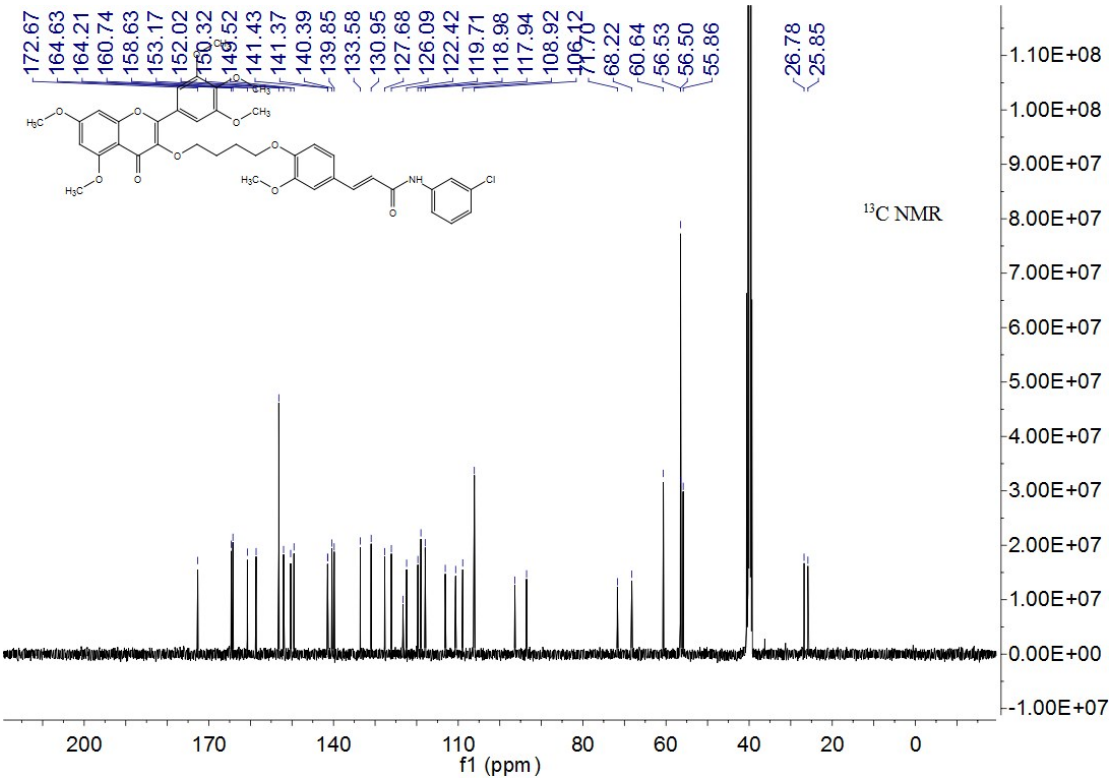


Figure S29. HRMS spectrum of compound **4f**

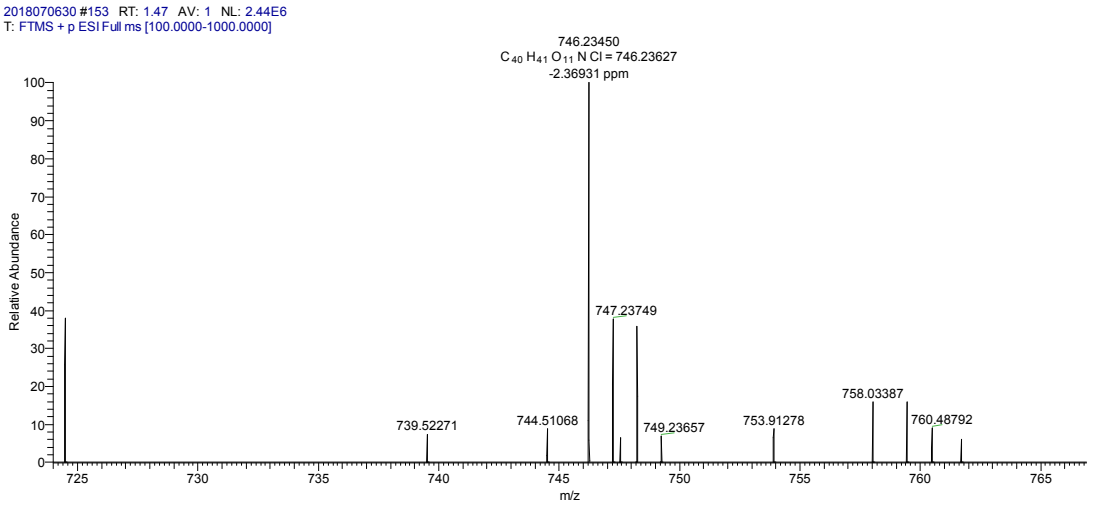


Figure S30. ^{1}H NMR spectrum of compound **4g**

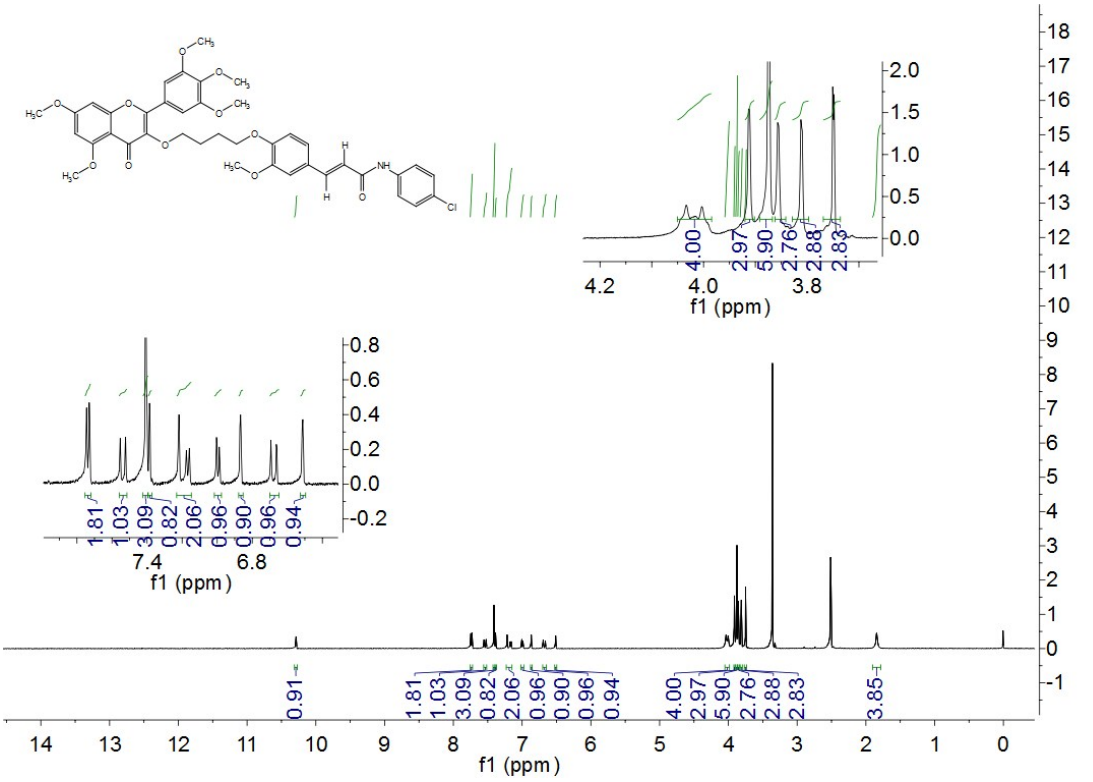


Figure S31.[13] C NMR spectrum of compound **4g**

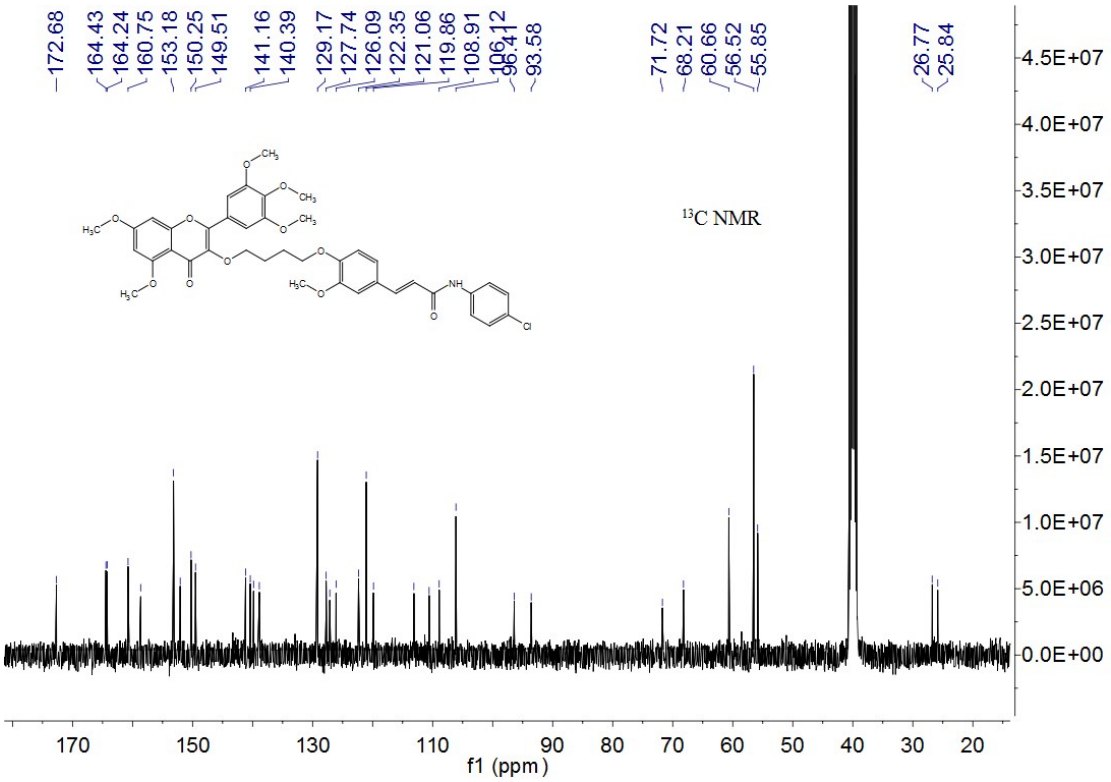


Figure S32. HRMS spectrum of compound **4g**

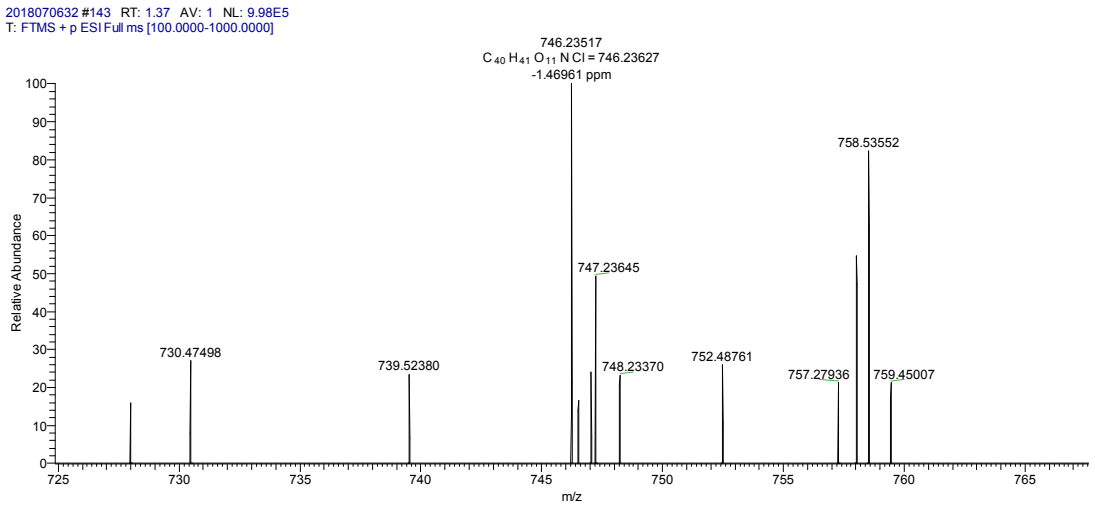


Figure S33. [1] H NMR spectrum of compound **4h**

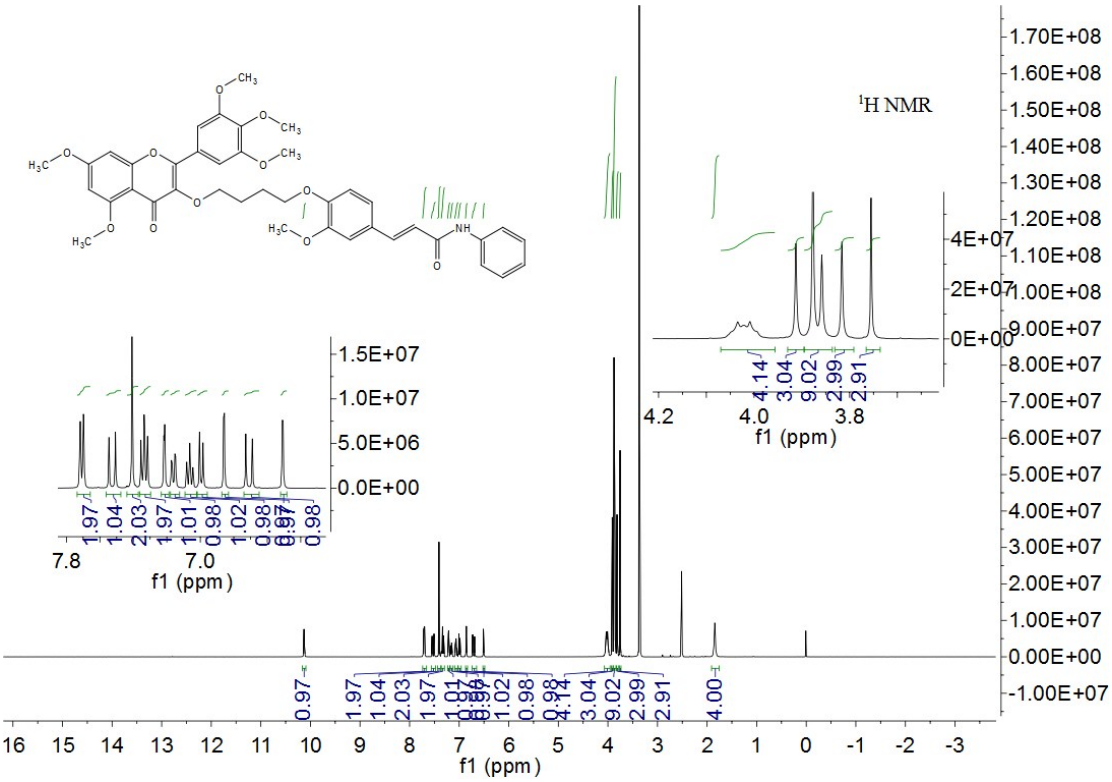


Figure S34. [13] C NMR spectrum of compound **4h**

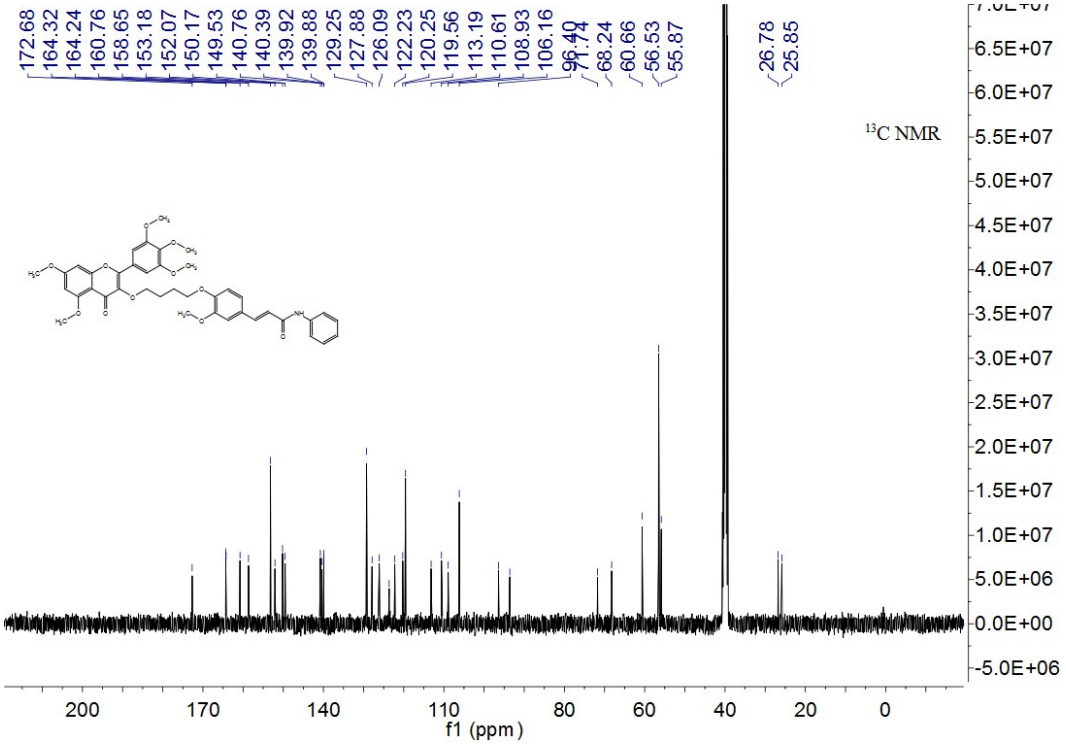


Figure S35. HRMS spectrum of compound **4h**

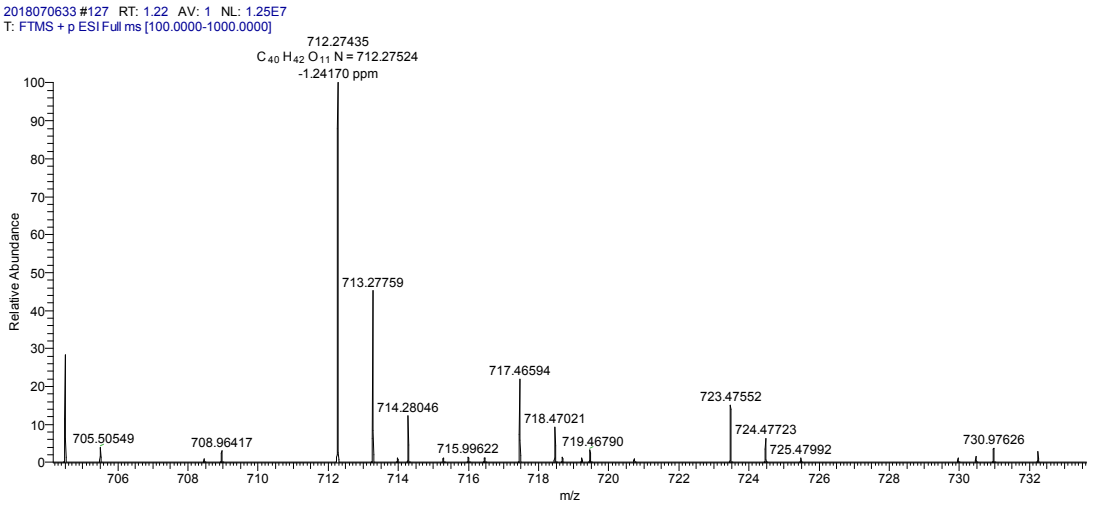


Figure S36.[1] H NMR spectrum of compound **4i**

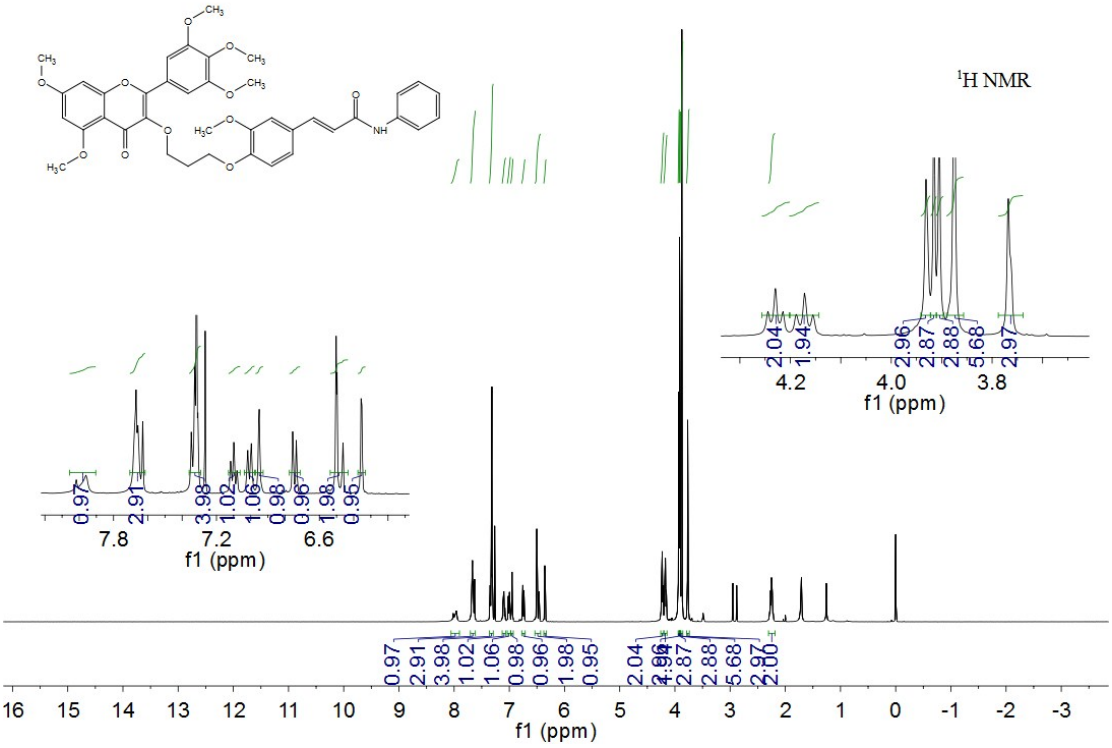


Figure S37.[13] C NMR spectrum of compound **4i**

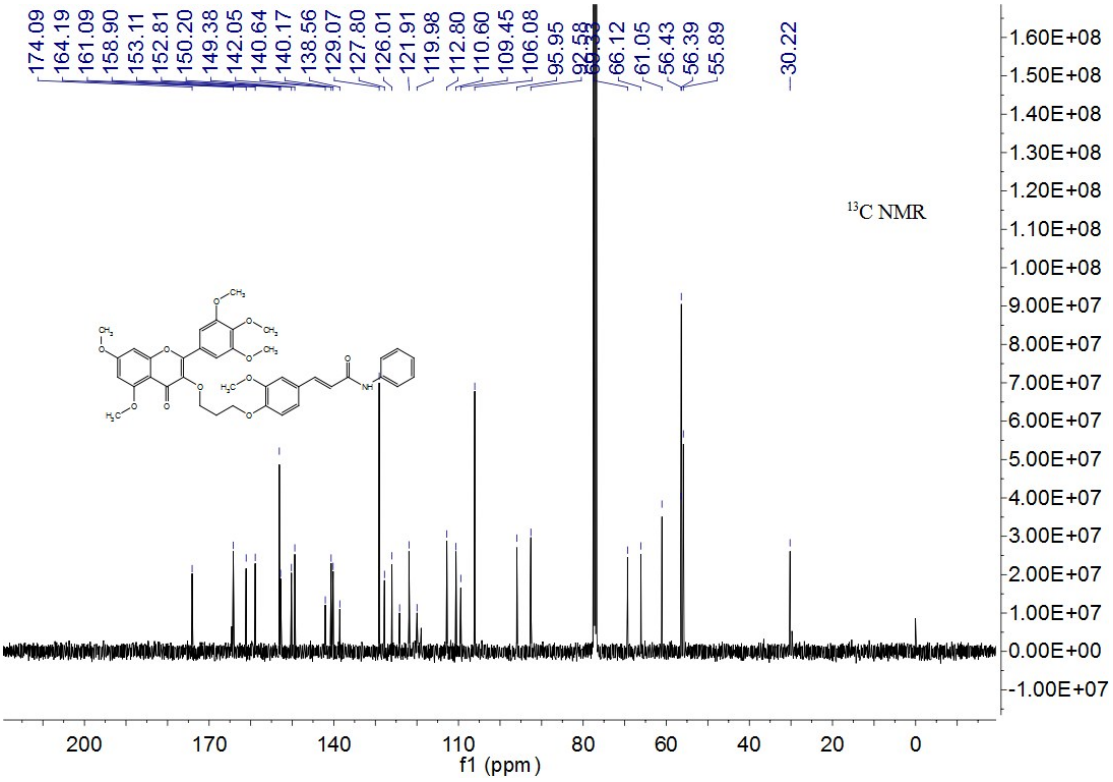


Figure S38. HRMS spectrum of compound **4i**

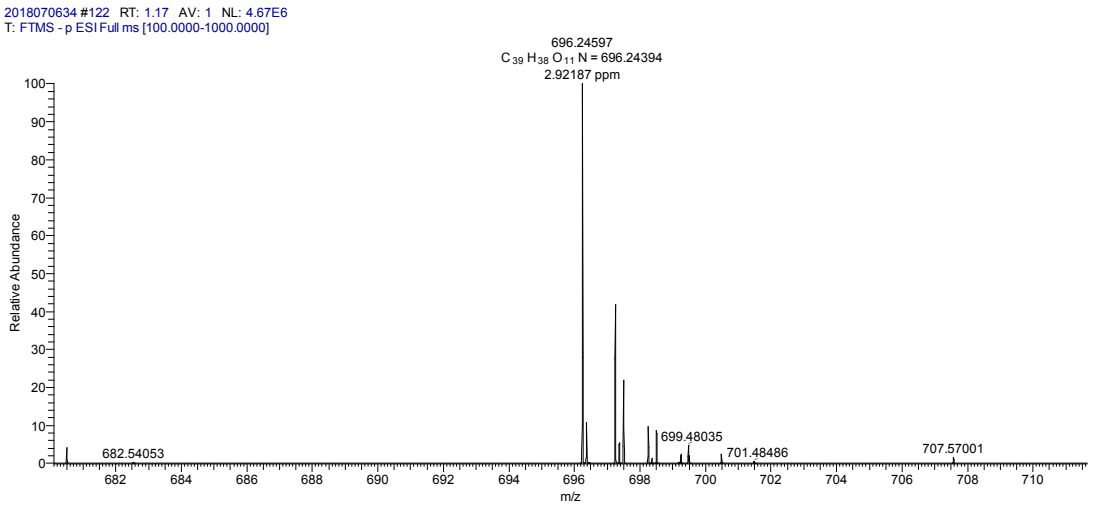


Figure S39. [1] H NMR spectrum of compound **4j**

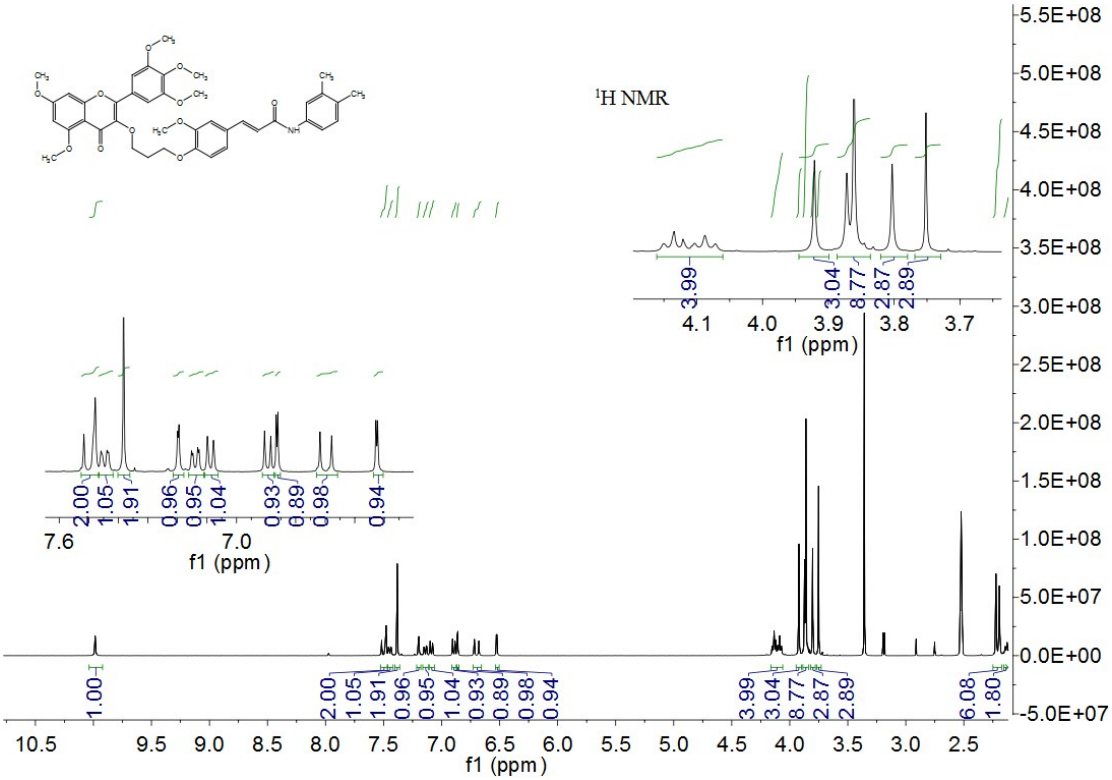


Figure S40. [13] C NMR spectrum of compound **4j**

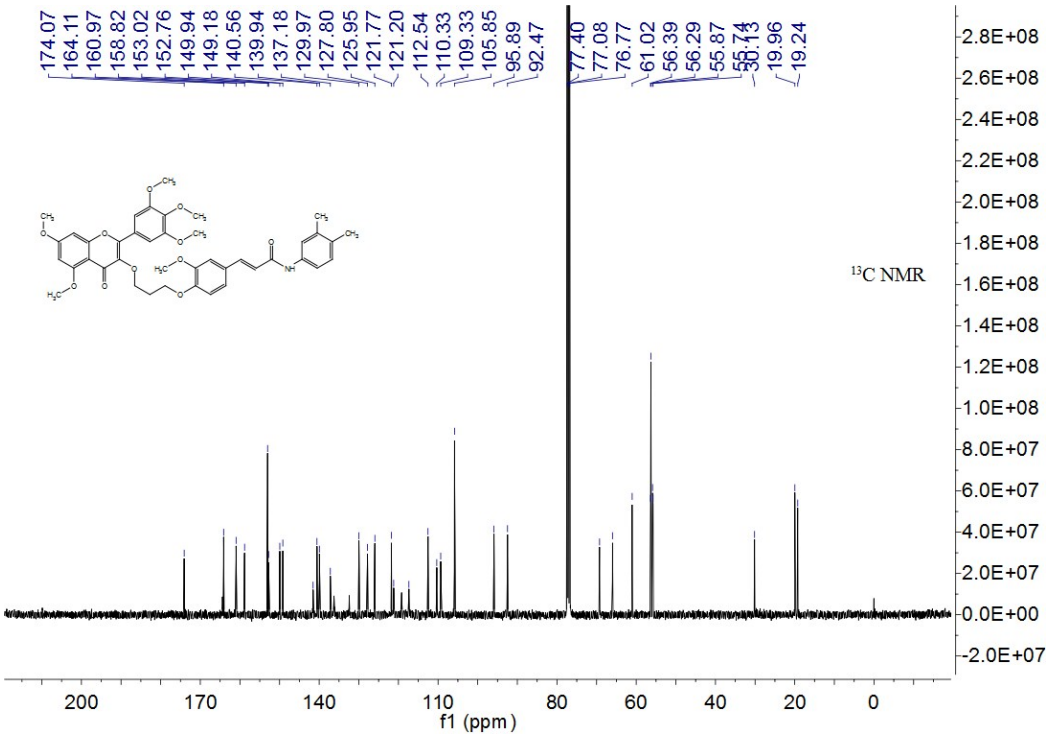


Figure S41. HRMS spectrum of compound **4j**

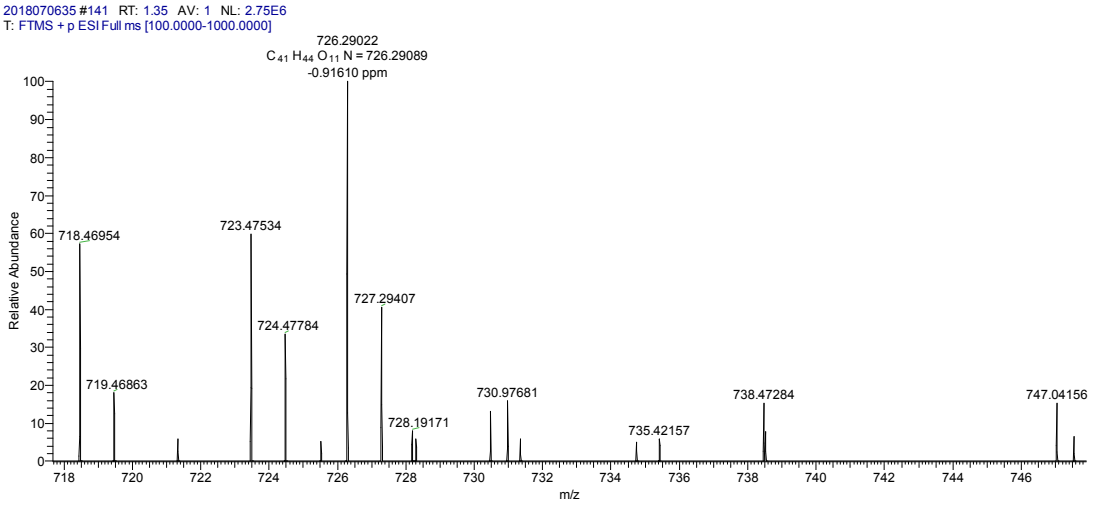


Figure S42. ^{1}H NMR spectrum of compound **4k**

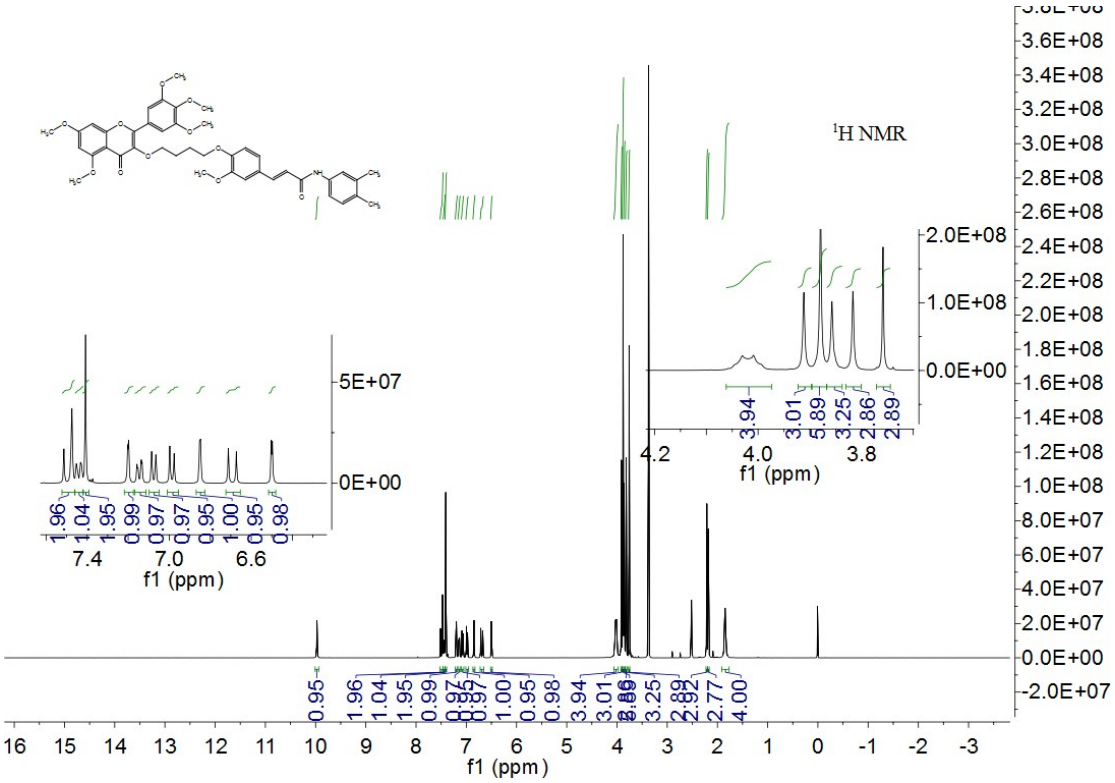


Figure S43. ^{13}C NMR spectrum of compound **4k**

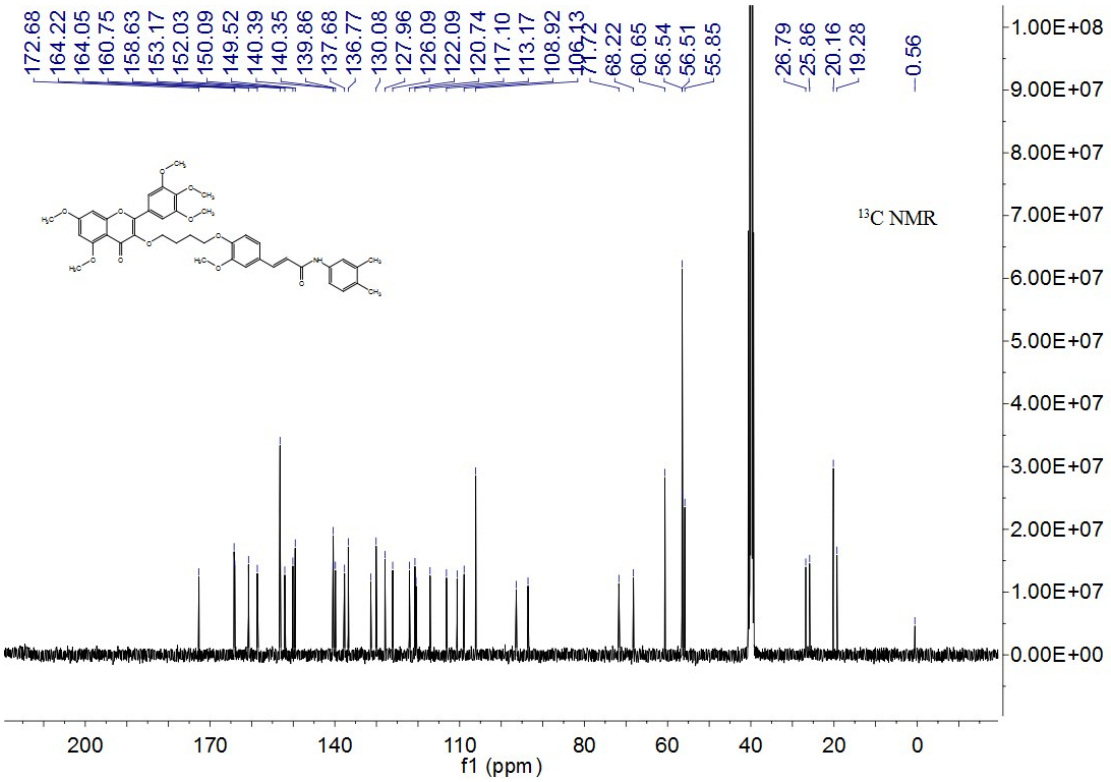


Figure S44. HRMS spectrum of compound **4k**

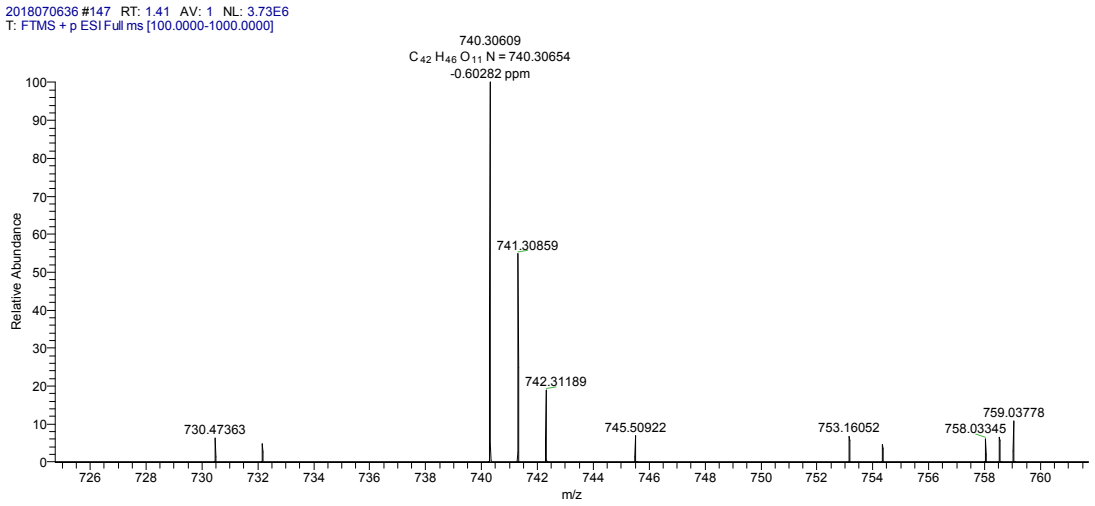


Figure S45. [1] H NMR spectrum of compound **4l**

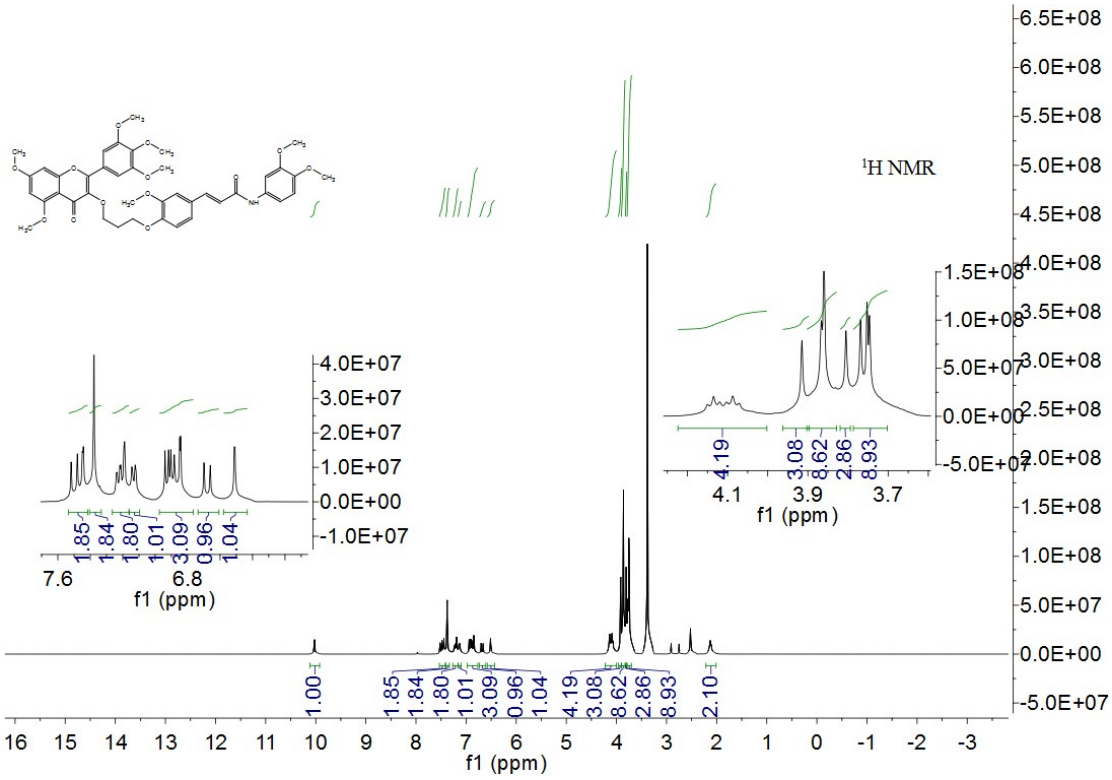


Figure S46. [13] C NMR spectrum of compound **4l**

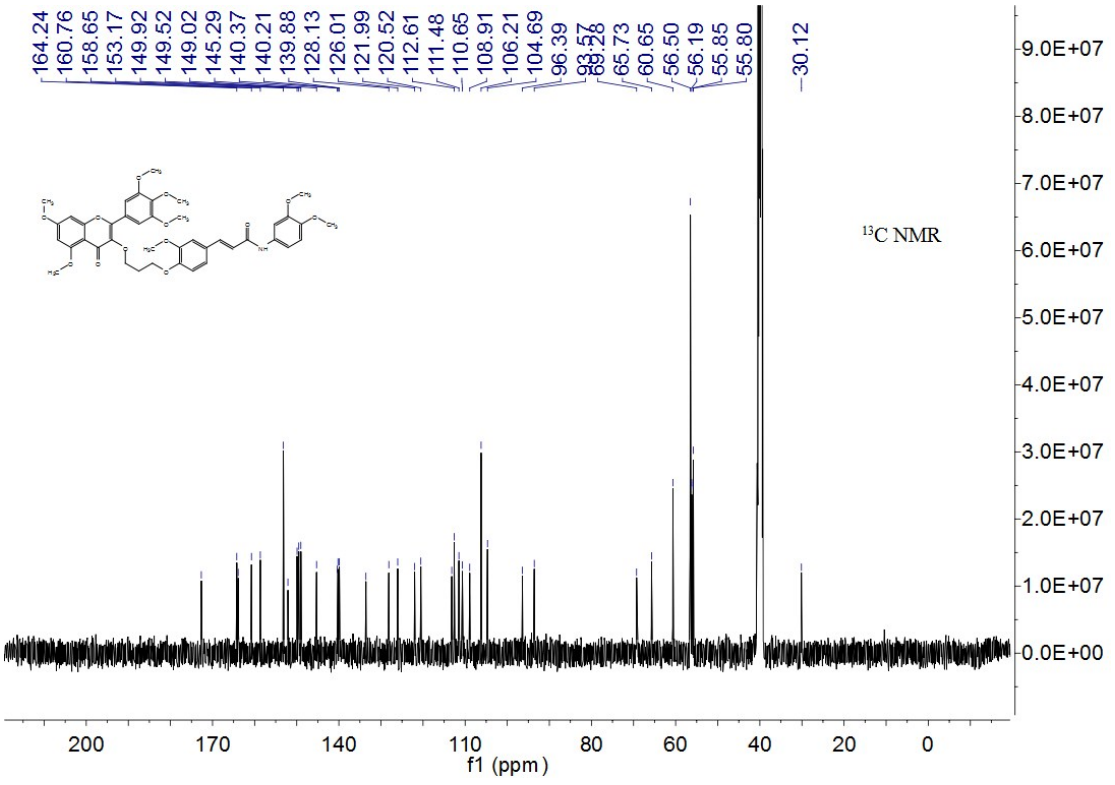


Figure S47. HRMS spectrum of compound **4l**

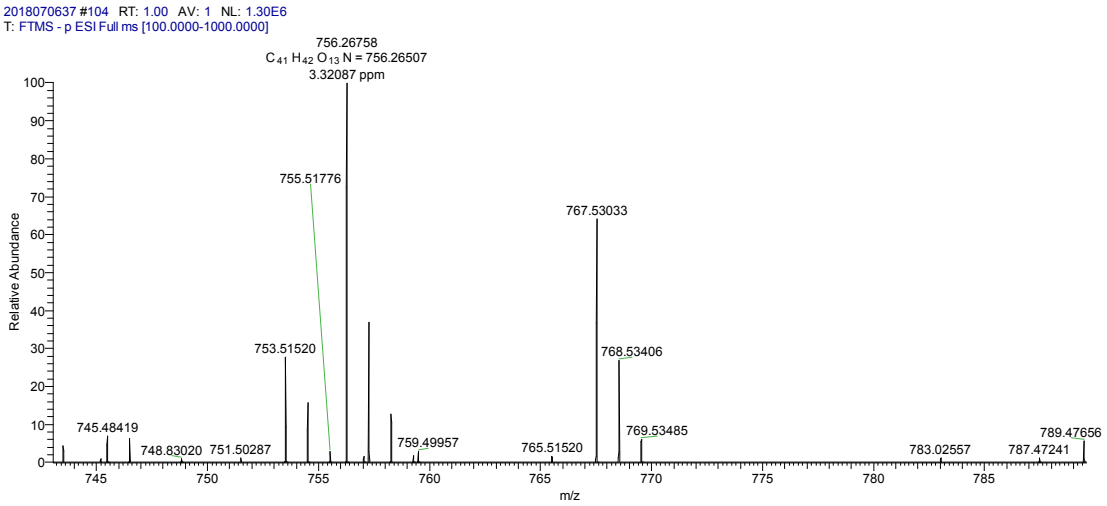


Figure S48. ^{1}H NMR spectrum of compound **4m**

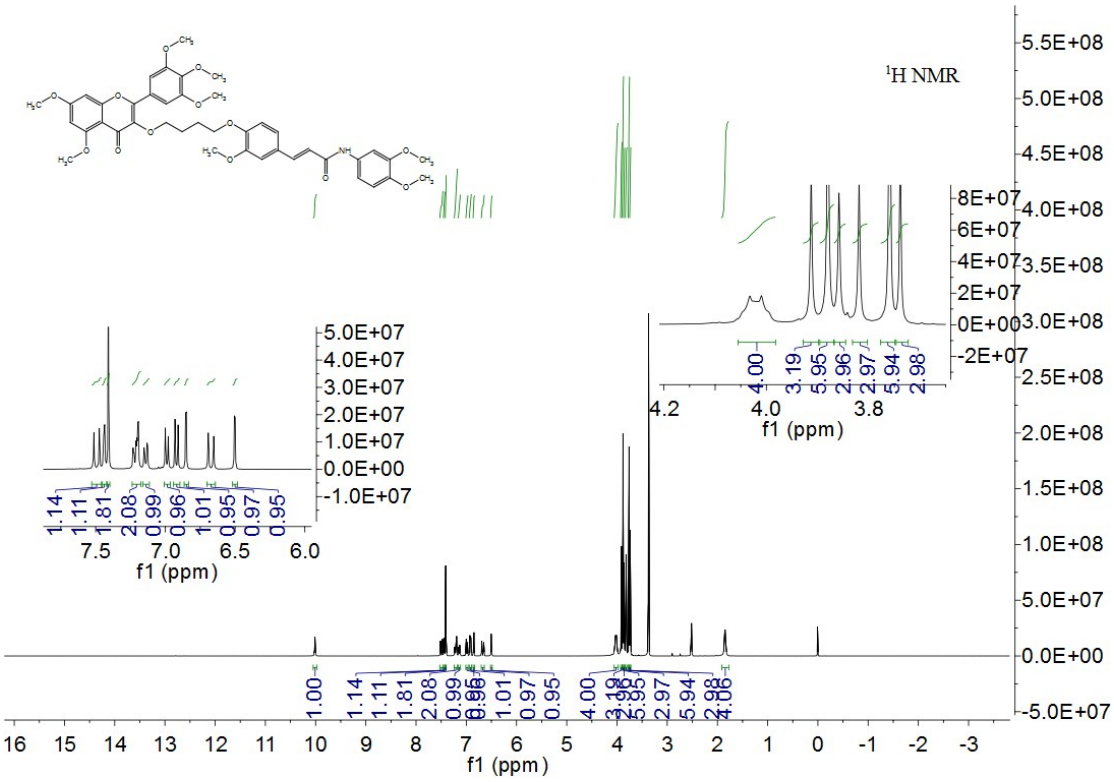


Figure S49. ^{13}C NMR spectrum of compound **4m**

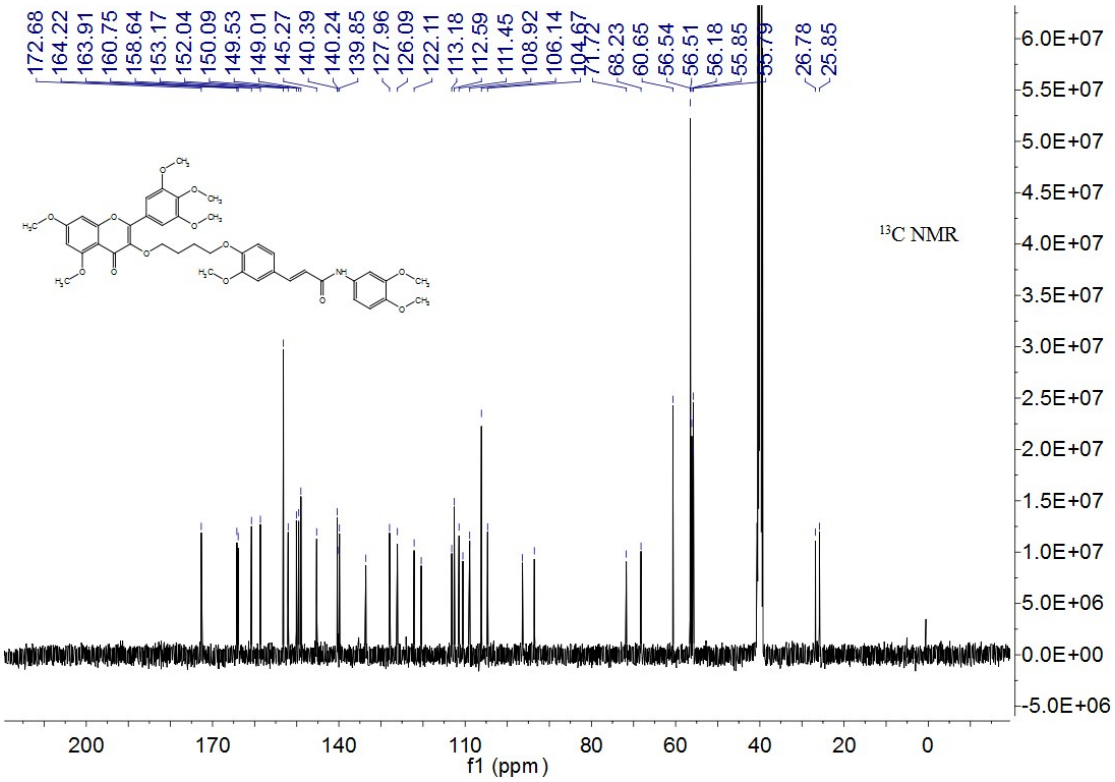


Figure S50. HRMS spectrum of compound **4m**

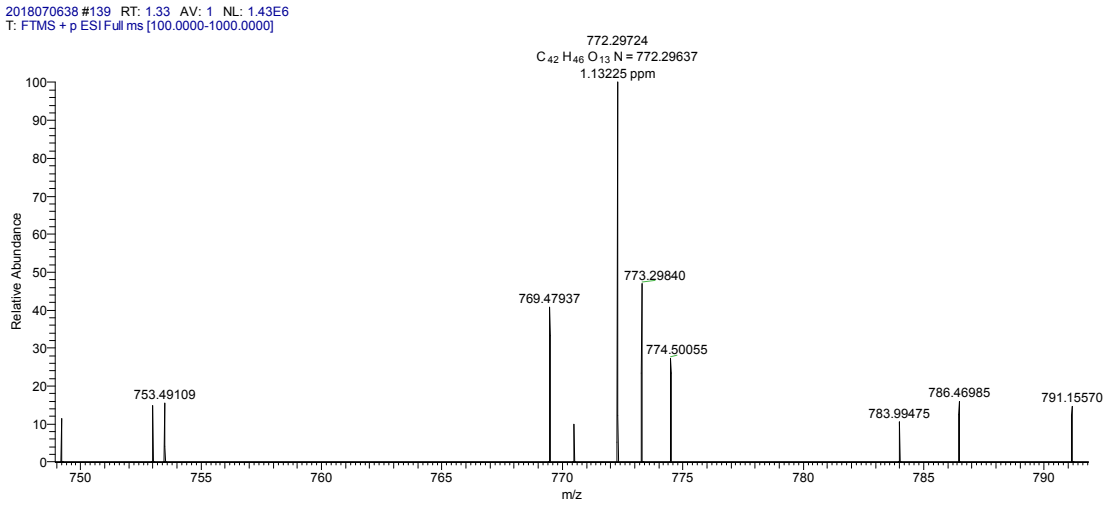


Figure S51. ^{1}H NMR spectrum of compound **4n**

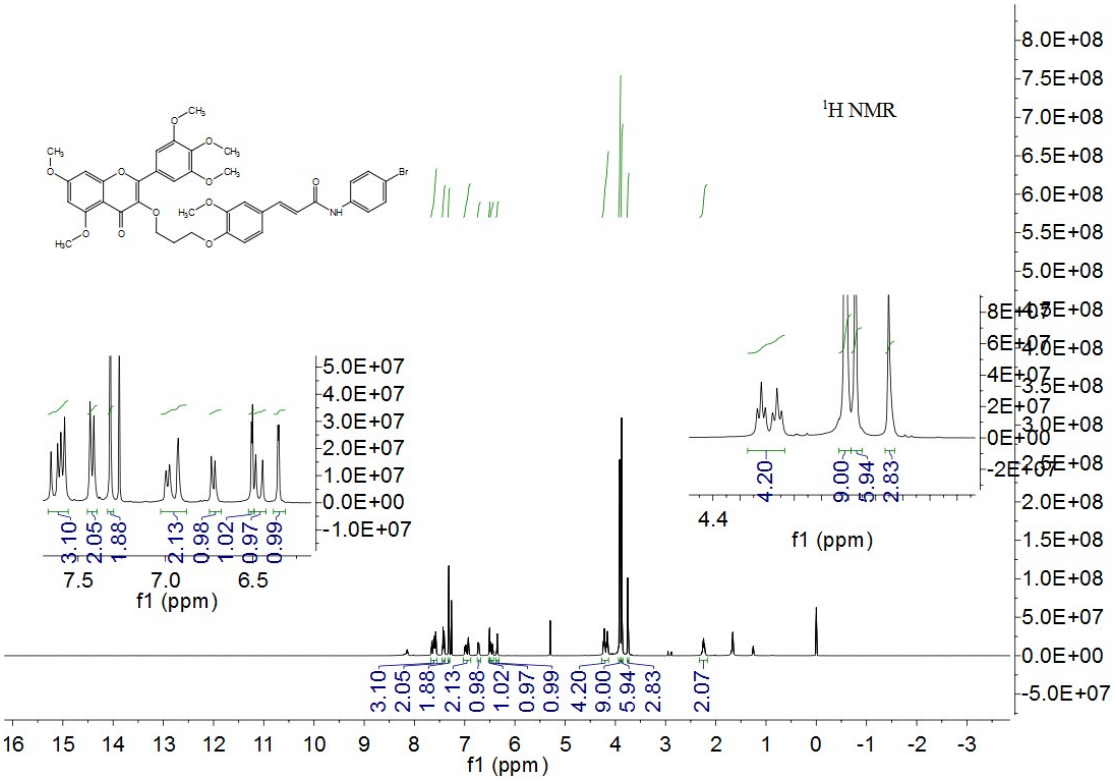


Figure S52. ^{13}C NMR spectrum of compound **4n**

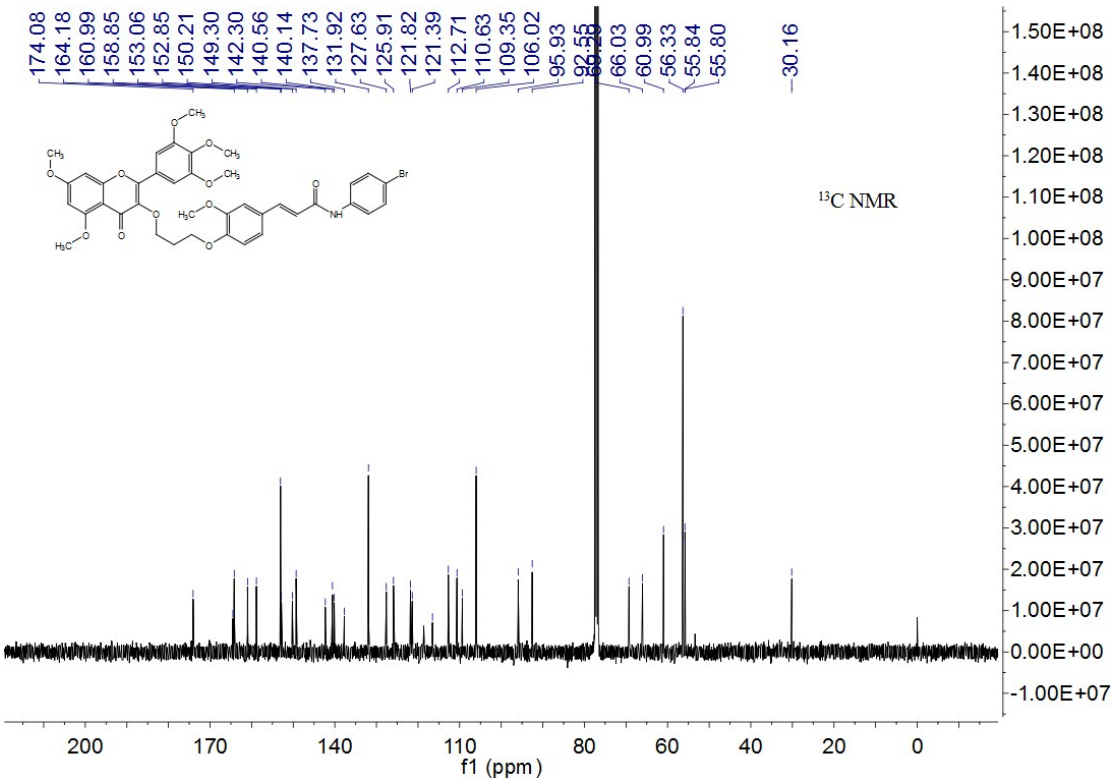


Figure S53. HRMS spectrum of compound **4n**

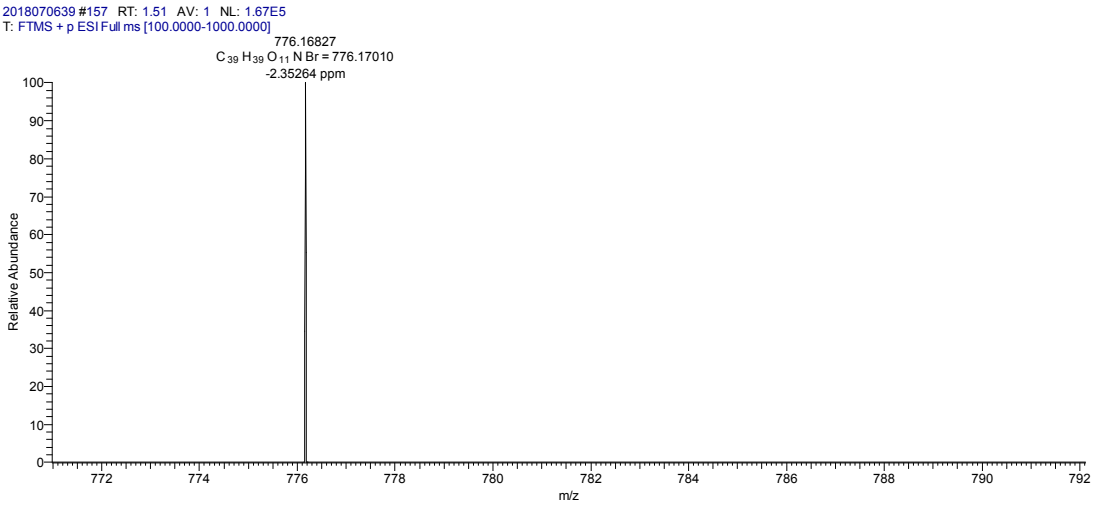


Figure S54. ^{1}H NMR spectrum of compound **4o**

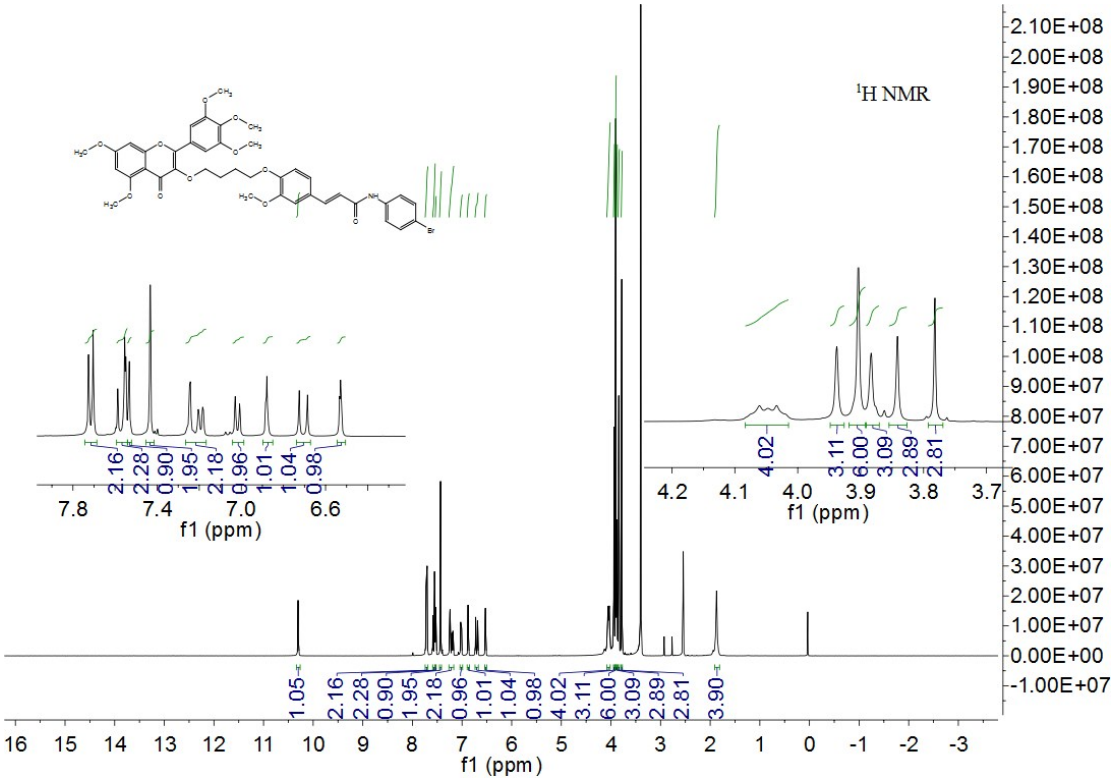


Figure S55. ^{13}C NMR spectrum of compound **4o**

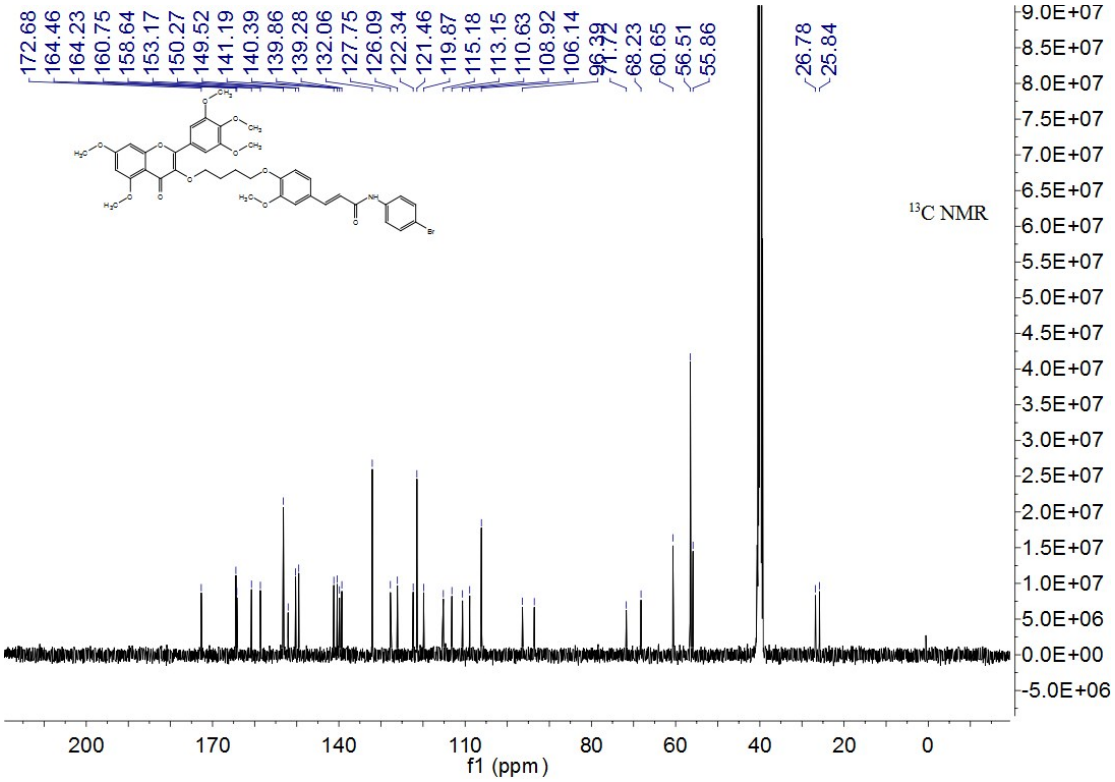


Figure S56. HRMS spectrum of compound **4o**

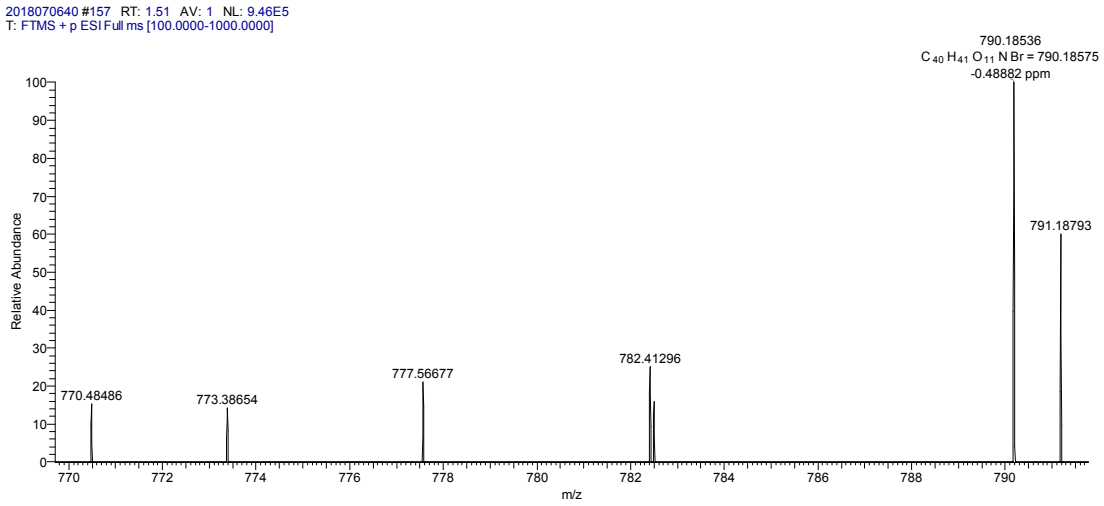


Figure S57. [1] H NMR spectrum of compound **4p**

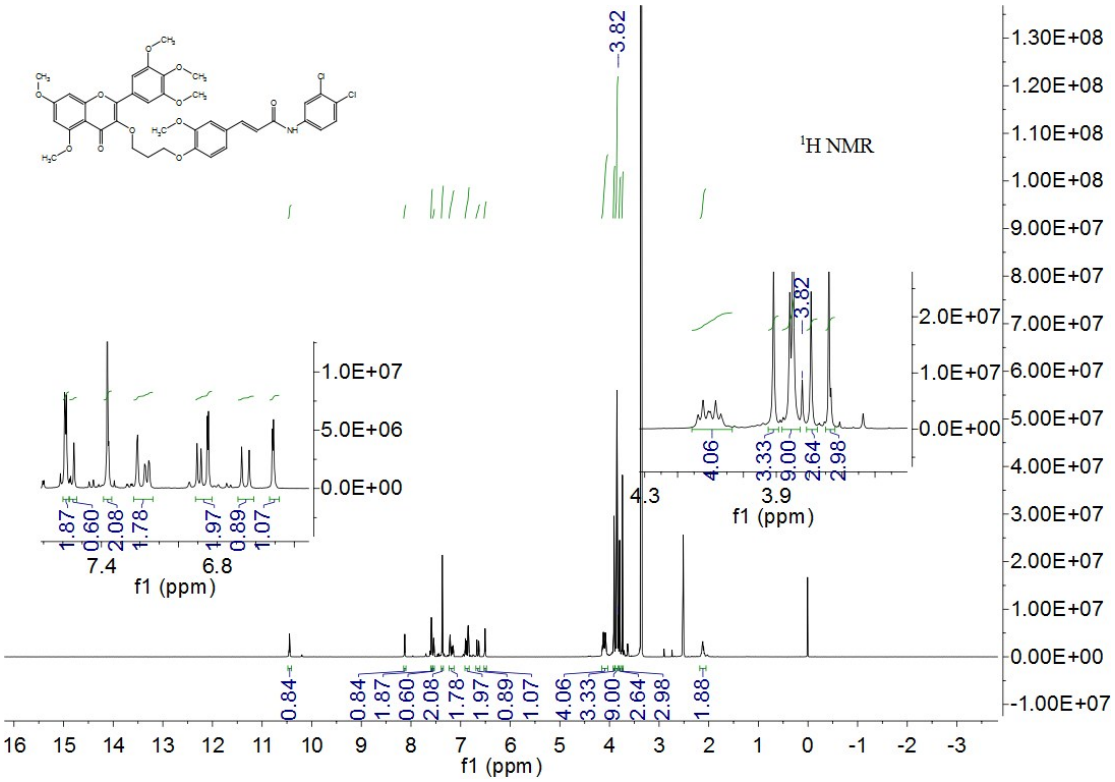


Figure S58. [13] C NMR spectrum of compound **4p**

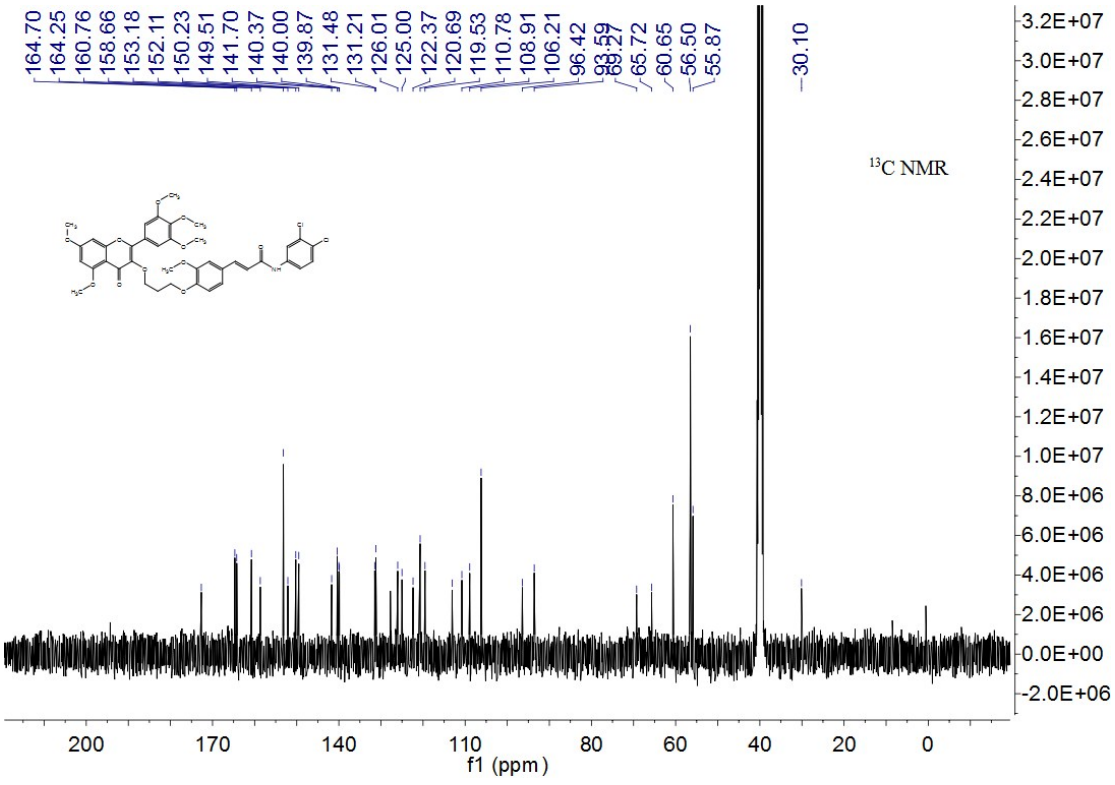


Figure S59. HRMS spectrum of compound **4p**

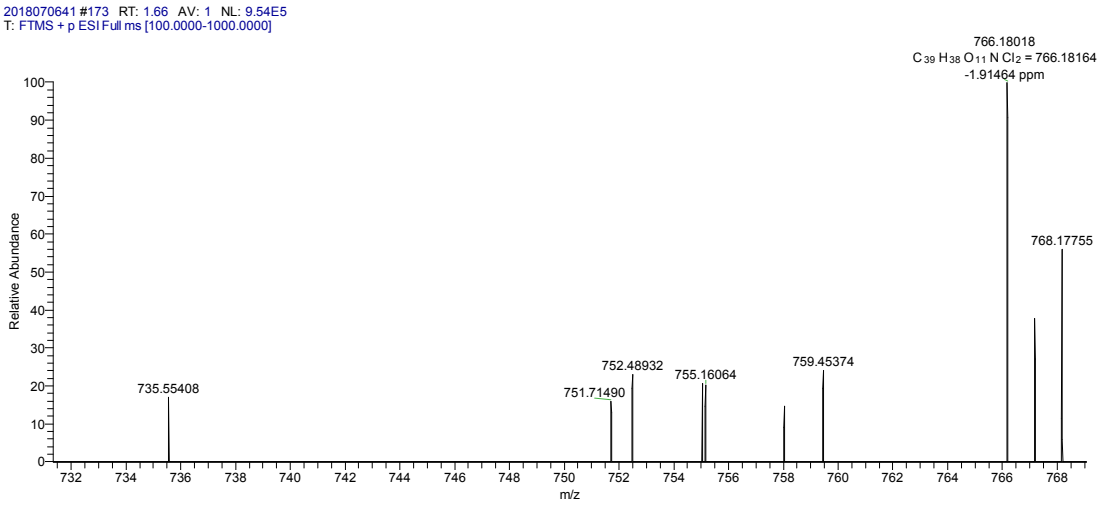


Figure S60. [1] H NMR spectrum of compound **4q**

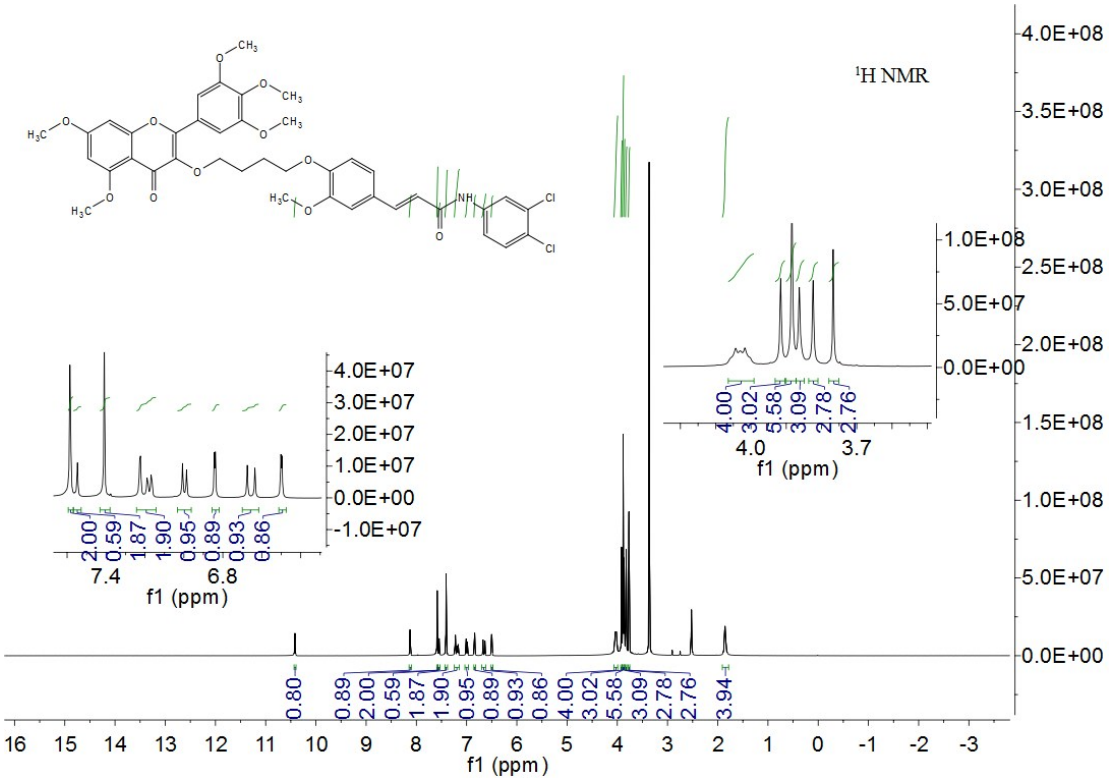


Figure S61. ^{13}C NMR spectrum of compound **4q**

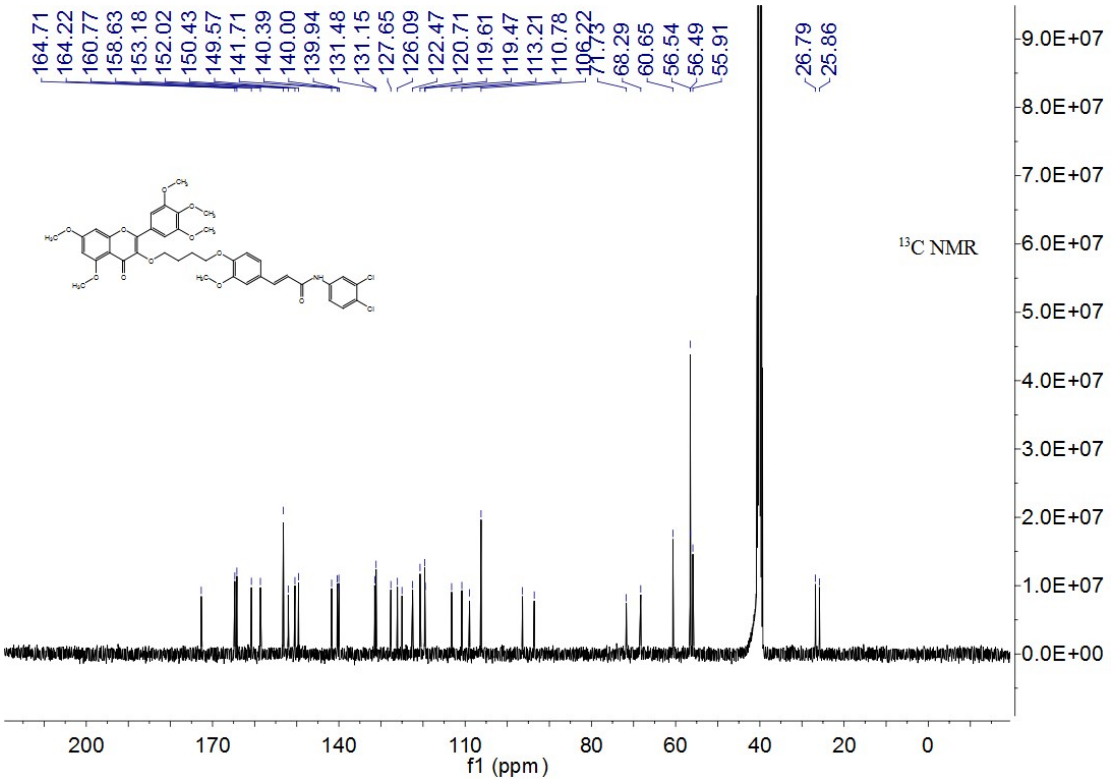


Figure S62. HRMS spectrum of compound **4q**

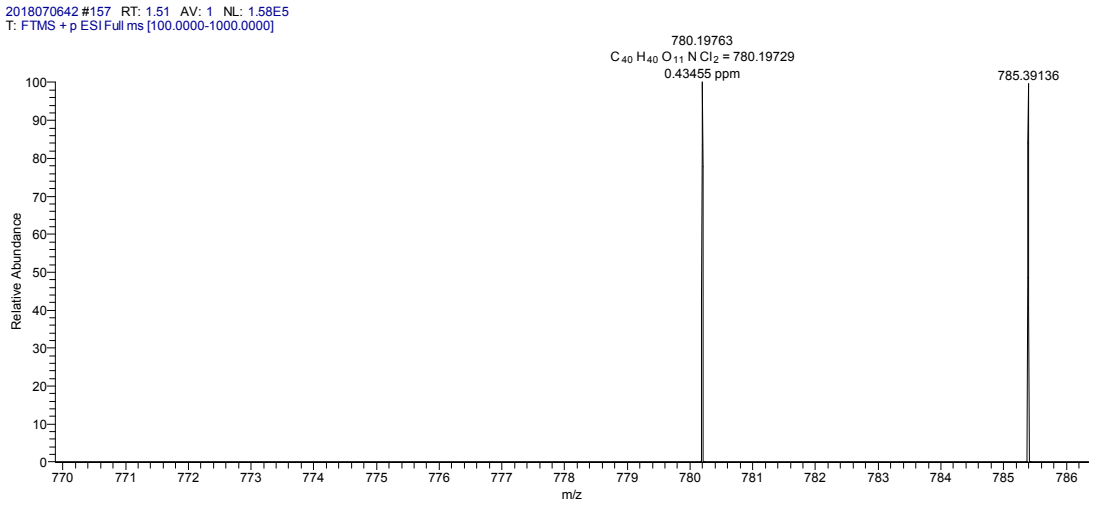


Figure S63. ^{1}H NMR spectrum of compound **4r**

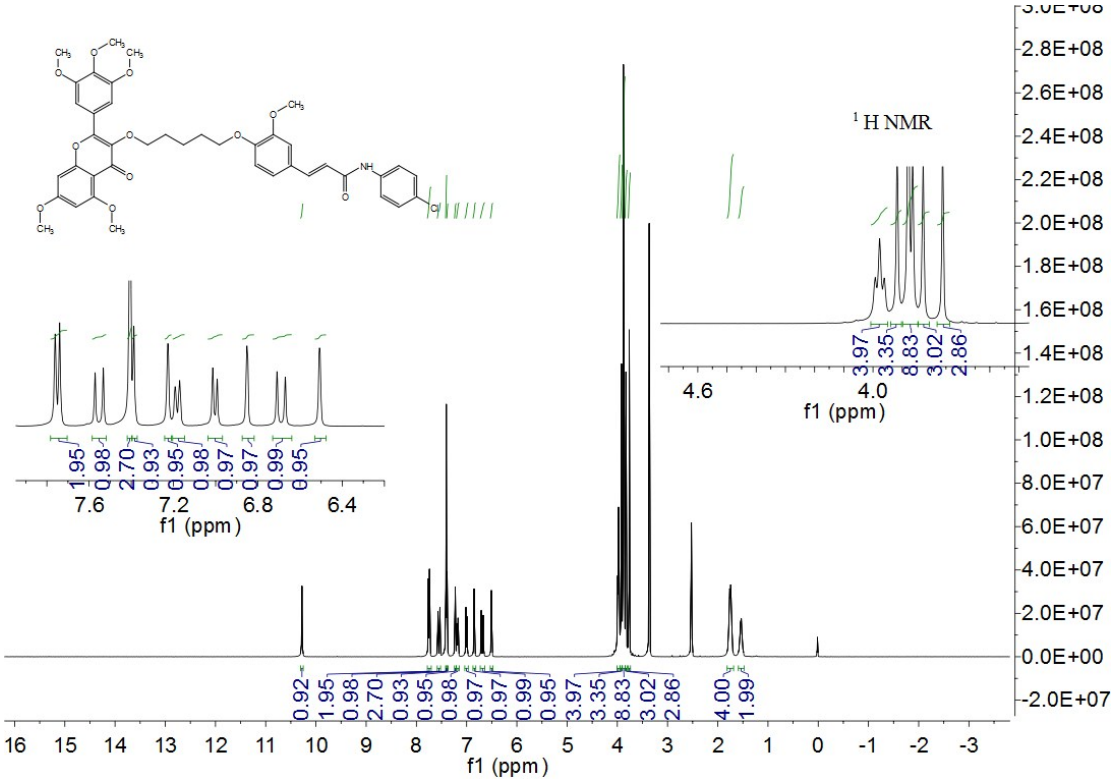


Figure S64. ^{13}C NMR spectrum of compound **4r**

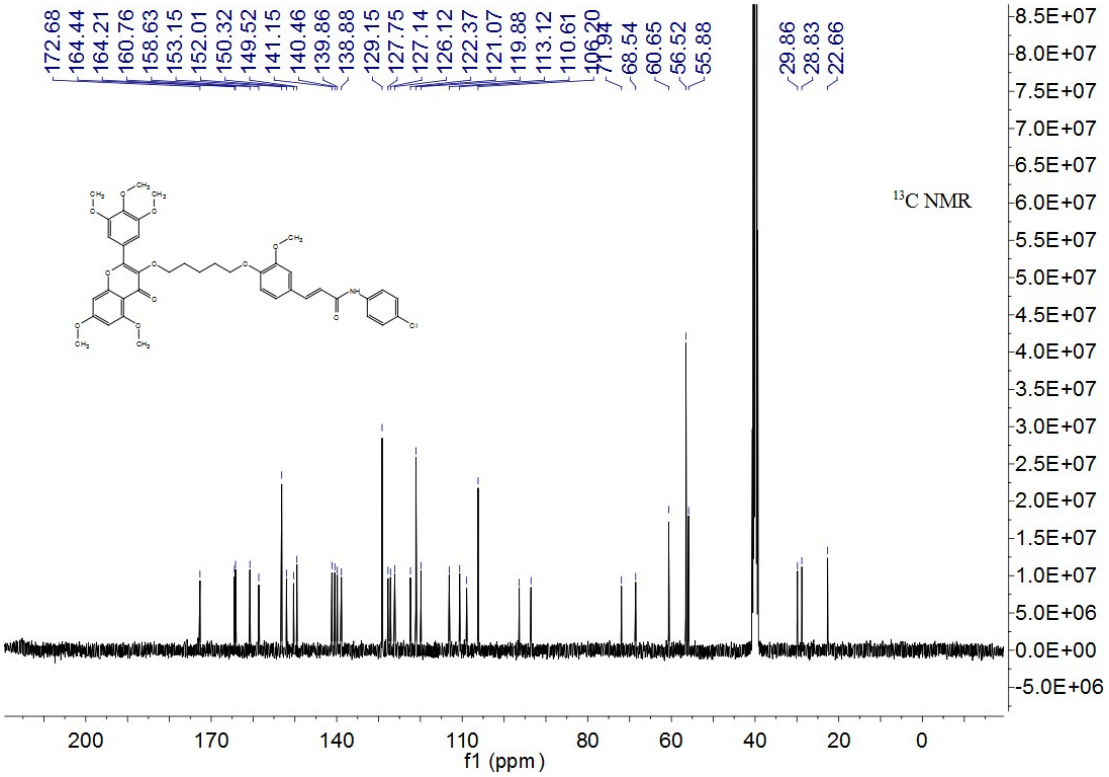


Figure S65. HRMS spectrum of compound **4r**

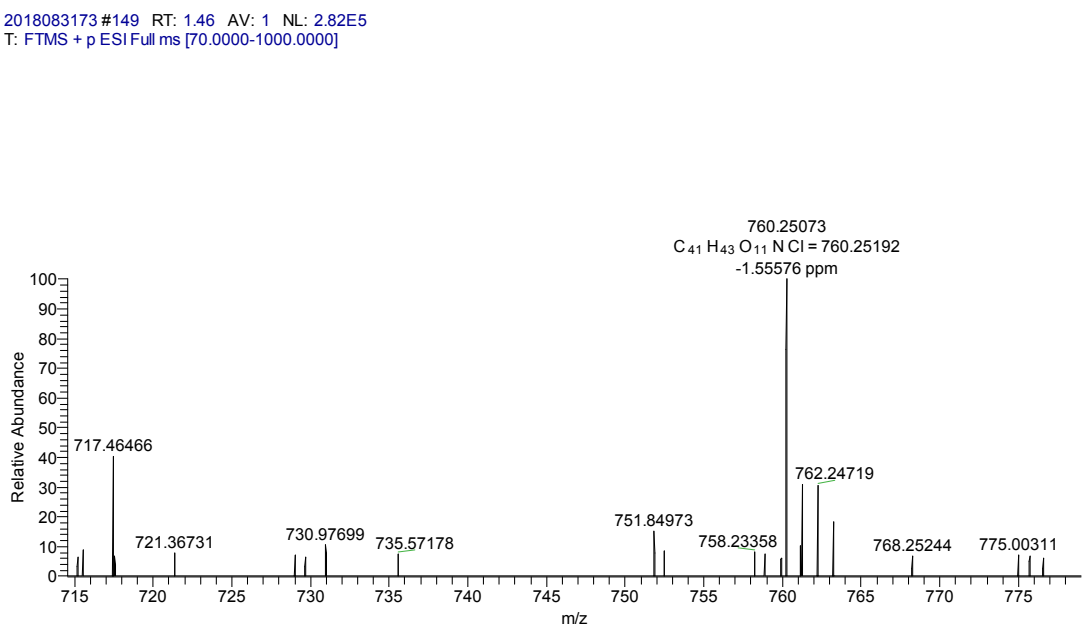


Figure S66. ^{1}H NMR spectrum of compound **4s**

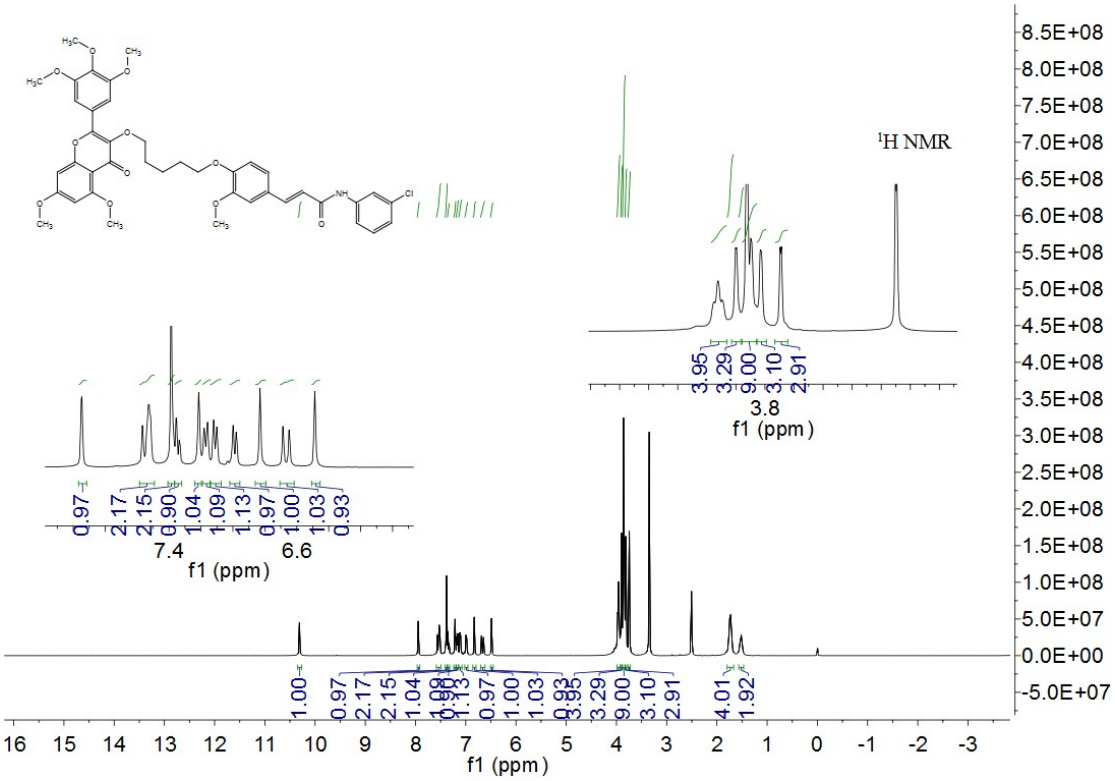


Figure S67. ^{13}C NMR spectrum of compound **4s**

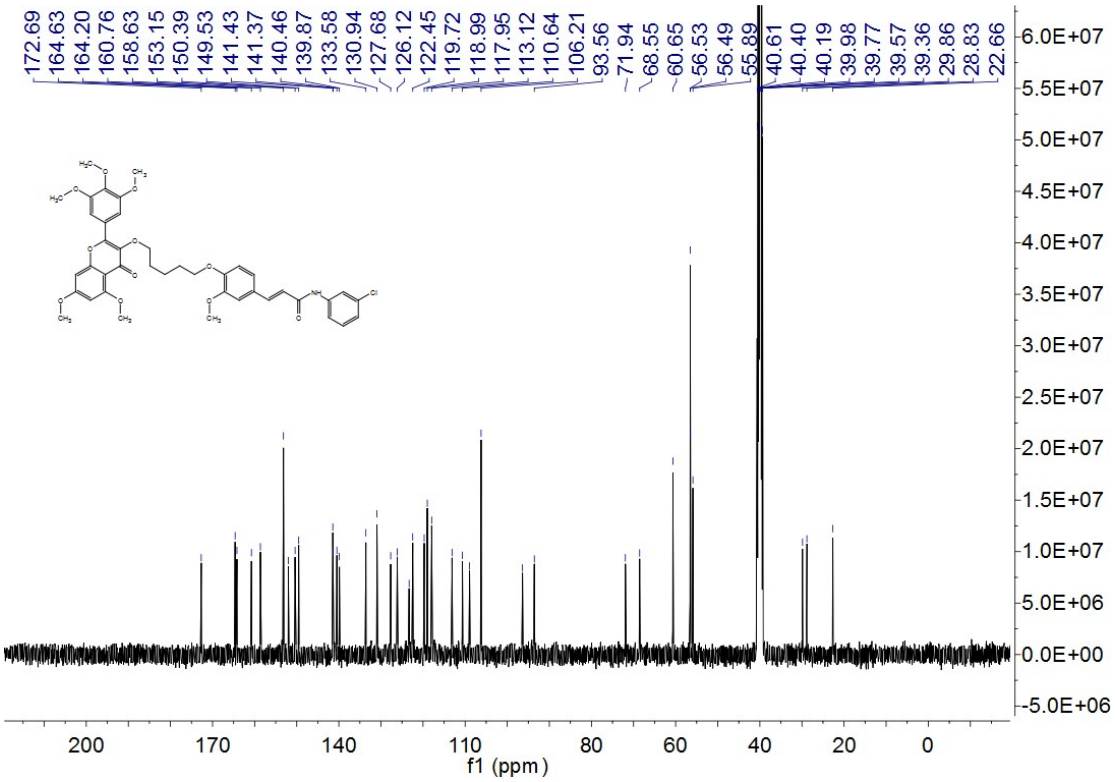


Figure S68. HRMS spectrum of compound **4s**

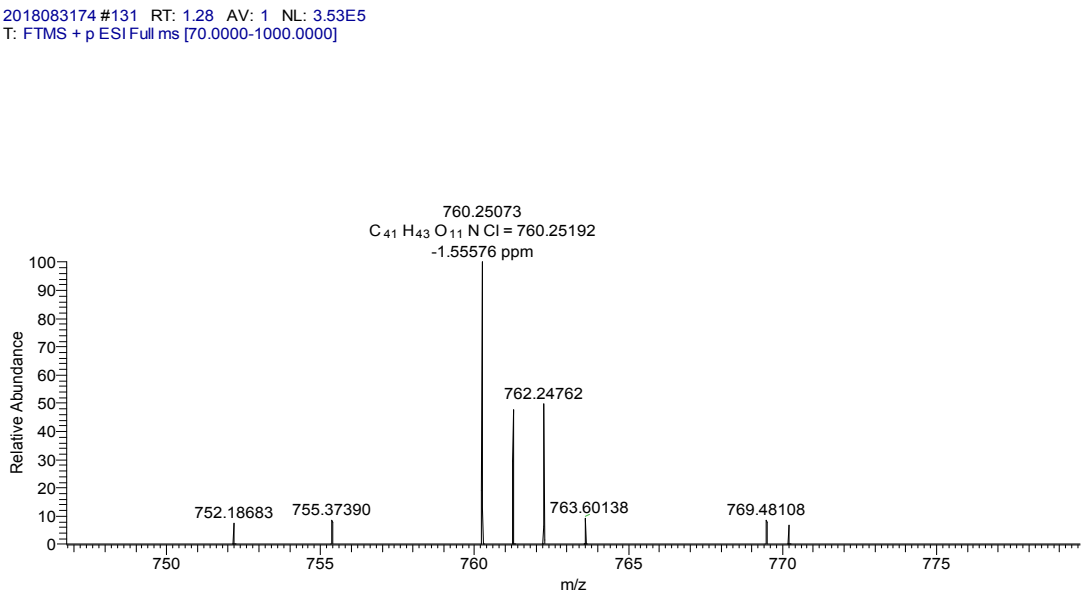


Figure S69. ^{1}H NMR spectrum of compound **4t**

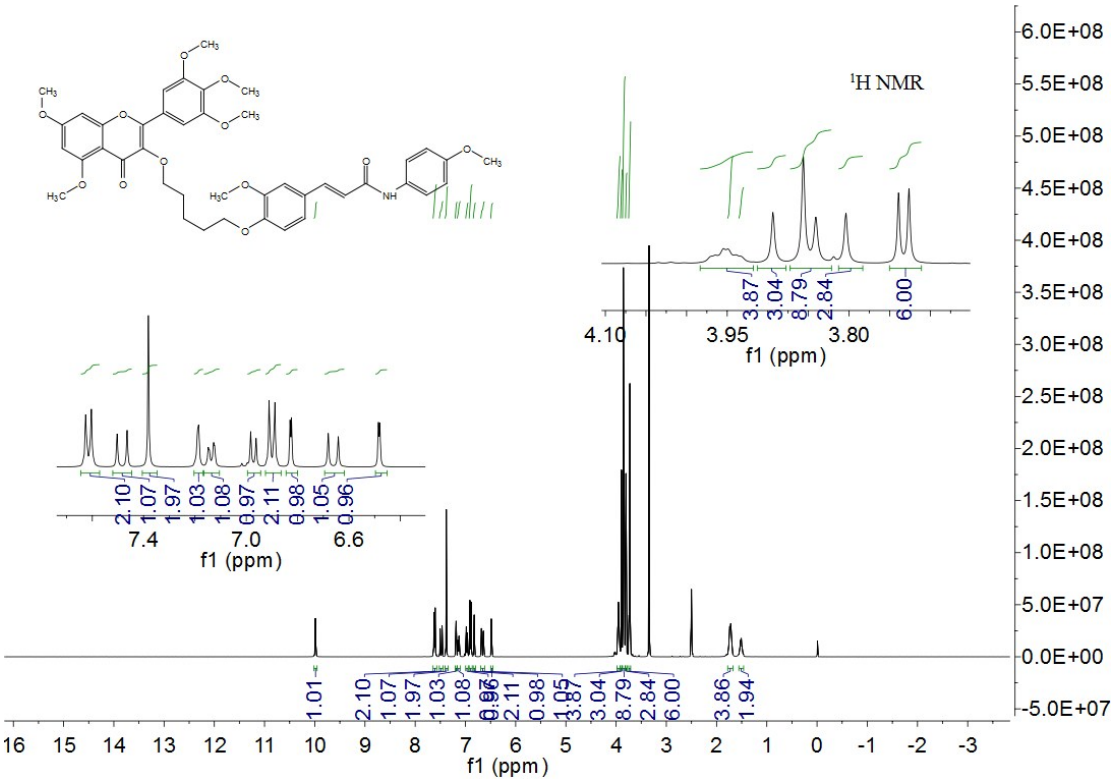


Figure S70. ^{13}C NMR spectrum of compound **4t**

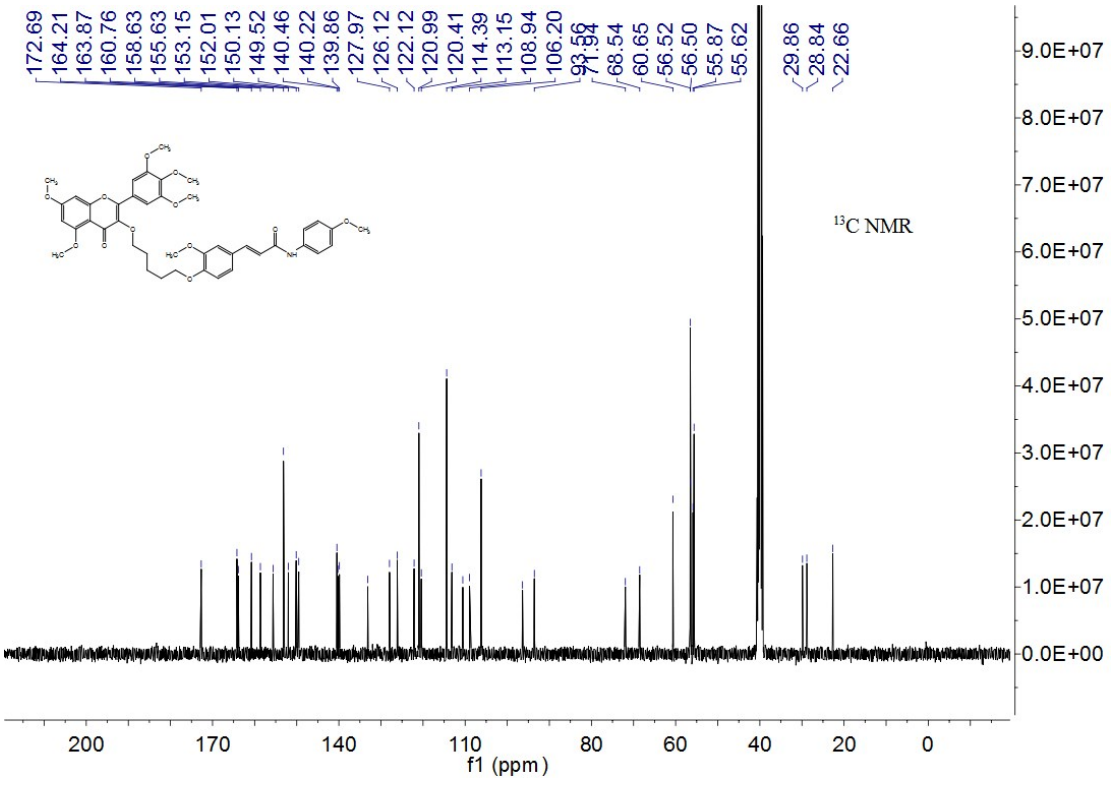


Figure S71. HRMS spectrum of compound **4t**

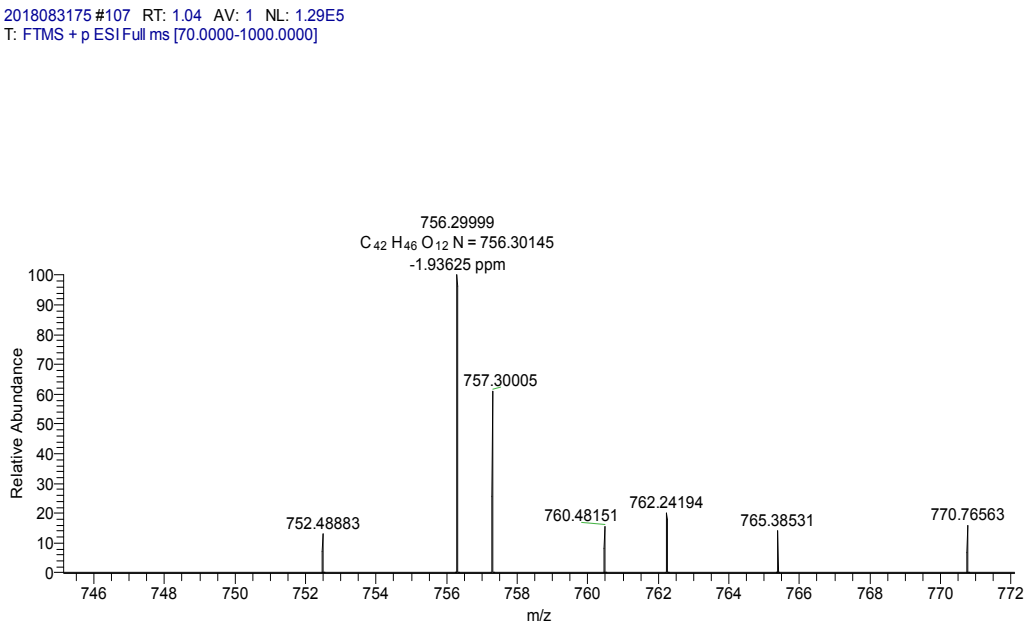


Figure S72. ^{1}H NMR spectrum of compound **4u**

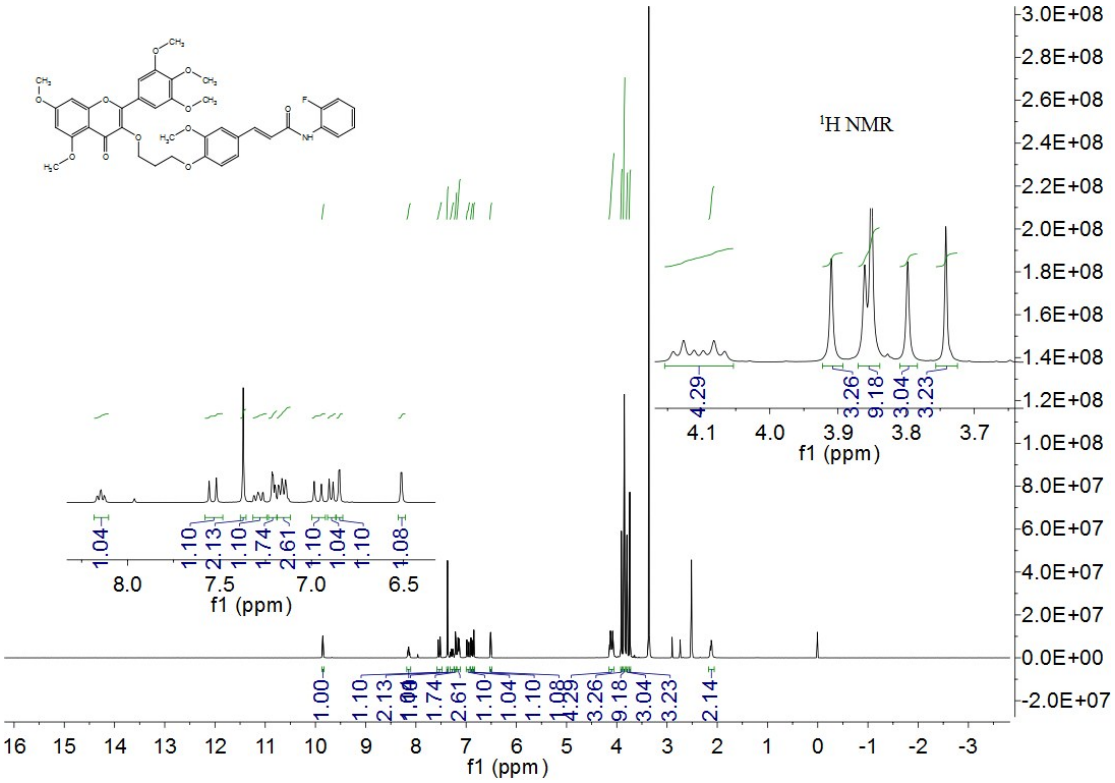


Figure S73. ^{13}C NMR spectrum of compound **4u**

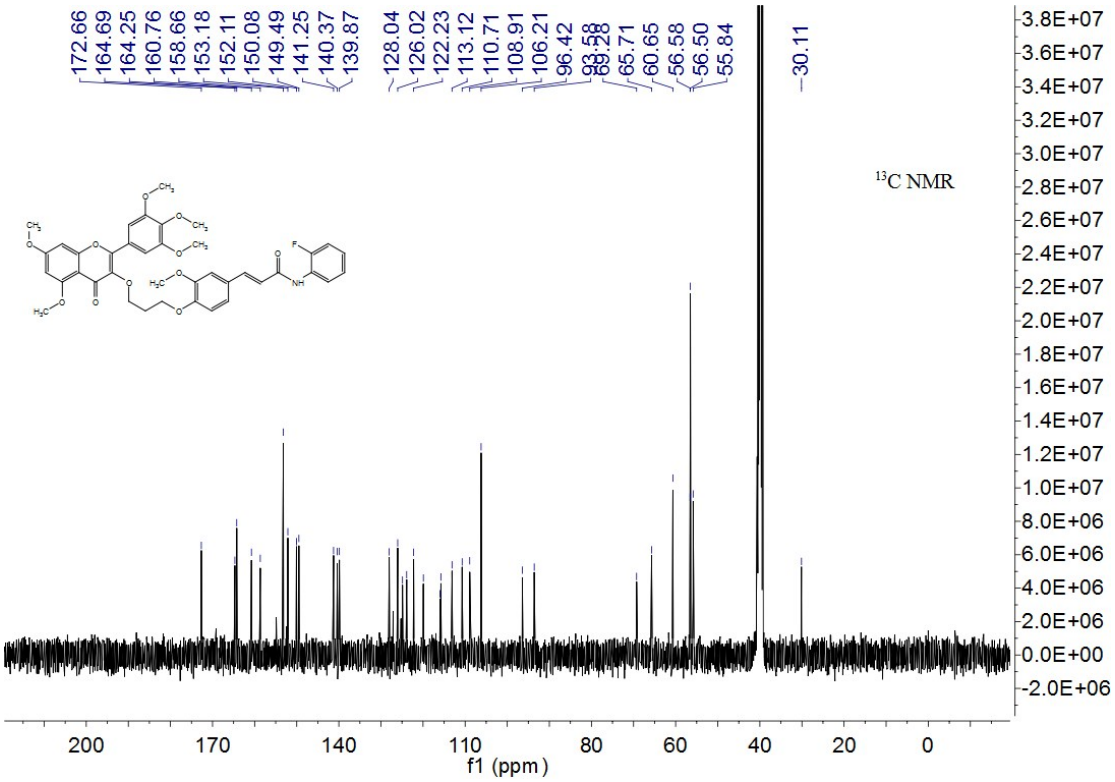


Figure S74. ^{19}F NMR spectrum of compound **4u**

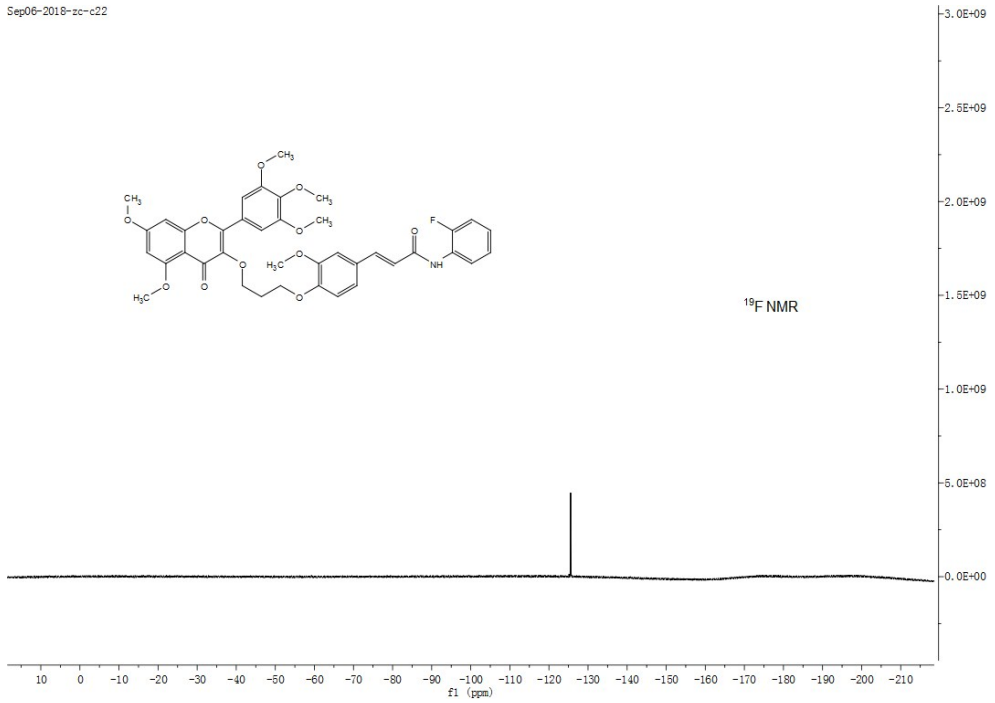


Figure S75. HRMS spectrum of compound **4u**

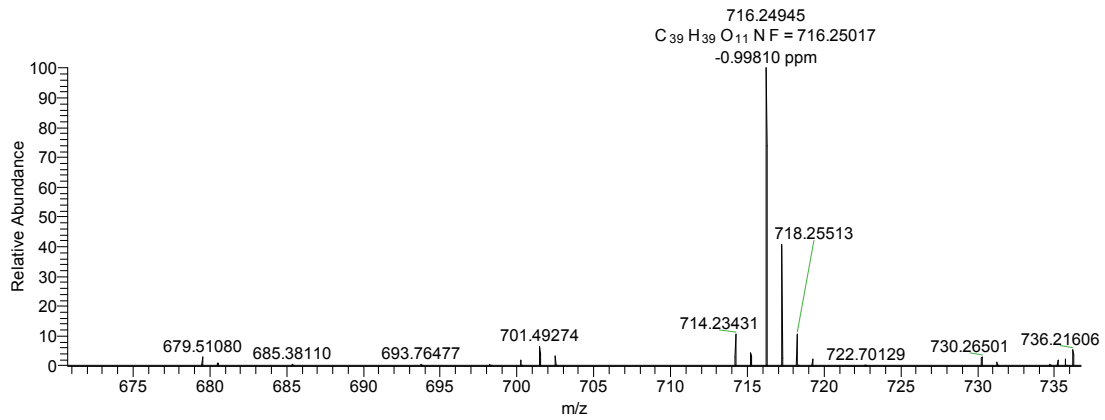


Figure S76. [1] H NMR spectrum of compound **4v**

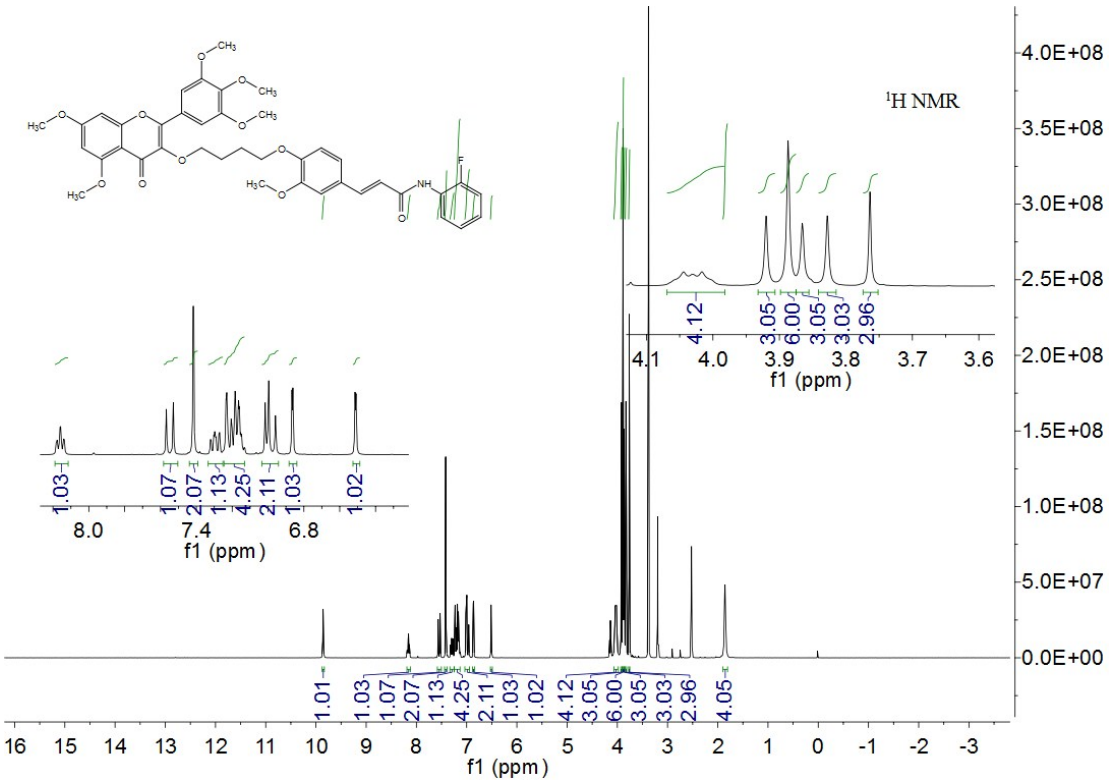


Figure S77. ^{13}C NMR spectrum of compound **4v**

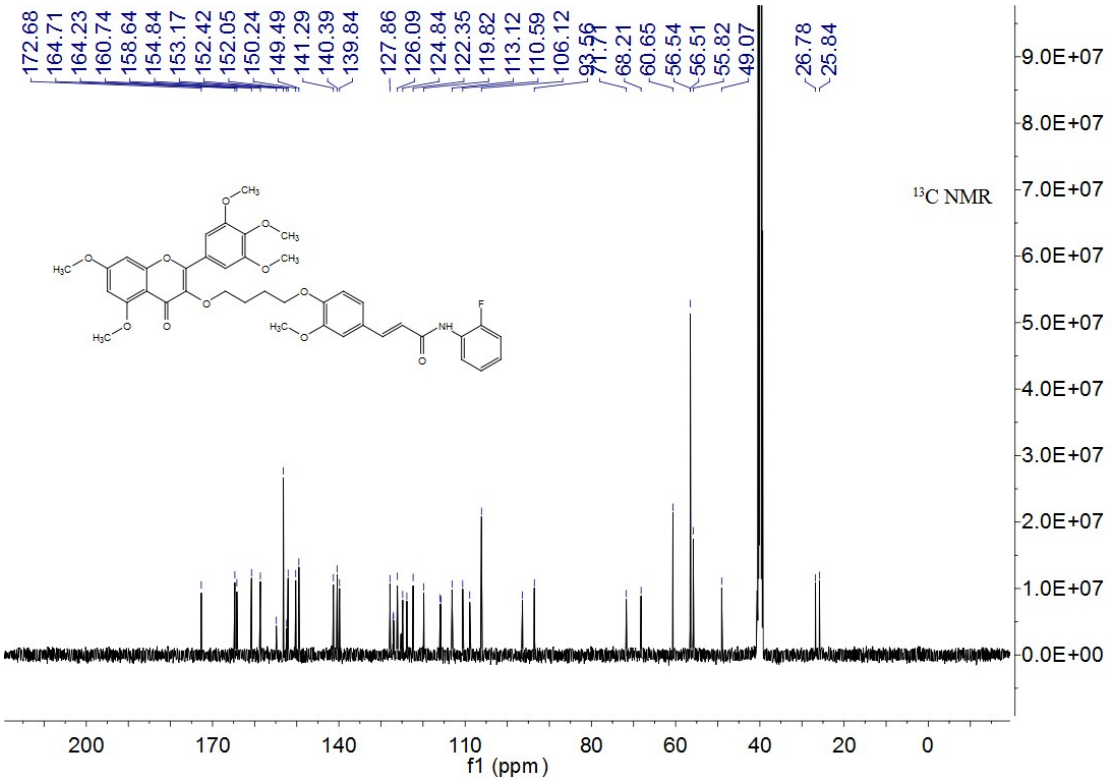


Figure S78. ^{19}F NMR spectrum of compound **4v**

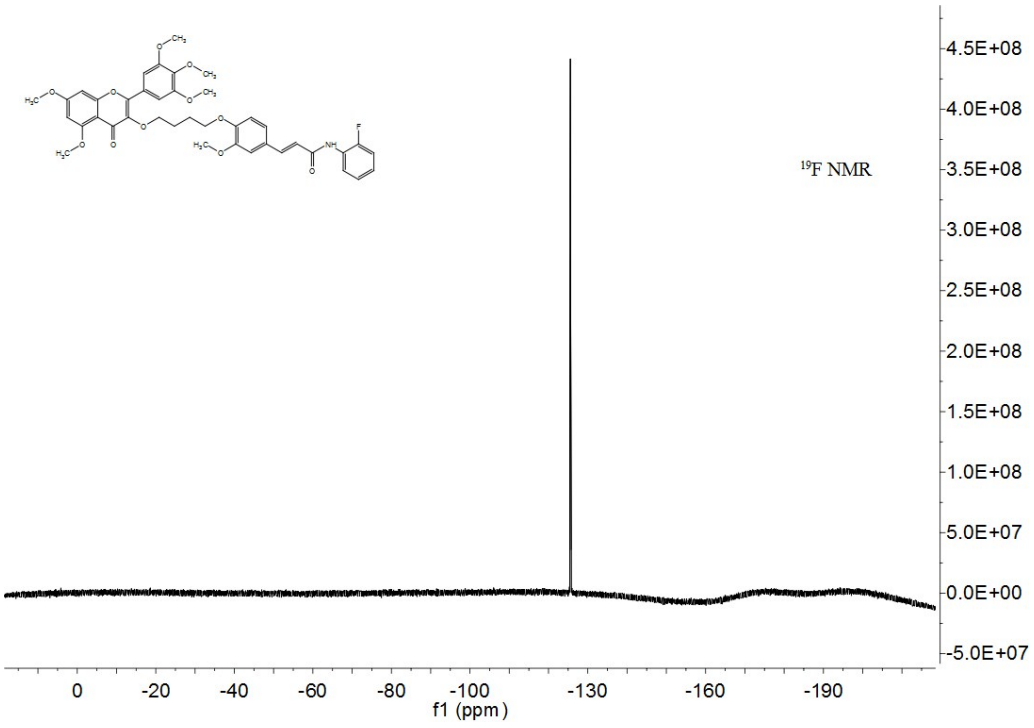


Figure S79. HRMS spectrum of compound **4v**