Electronic supplementary materials *Mendeleev Commun.*, 2026, **36**, 332–334

Design, synthesis and antitumor activity of new *s*-triazine–2-hydroxybenzophenone hybrids

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Table of content

Design considerations

1,3,5-Triazine (*s*-triazine) has three easily modifiable positions 2, 4 and 6, and is usually used to regulate its physicochemical and biological activities. 1,3,5-Triazine scaffolds provide resources for the design of biologically relevant molecules, which possess antibacterial, anti-cancer and anti-inflammatory activities. Hu *et al*.[S1] designed a novel covalent BTK (Core regulatory protein of B cell function) inhibitor compound **1** by replacing 1*H*-pyrazolo[3,4-*d*]pyrimidine (ibrutinib) with a 1,3,5-triazine skeleton containing a key acrylamide (Figure S1). Compound **1** showed potent BTK inhibitory activity, verifying the potential of 1,3,5-triazine skeleton as a new skeleton for the development of effective BTK inhibitors. Morpholine is a six-membered heterocyclic ring with both secondary amine and ether groups. In many cases, the presence of a morpholine ring in the heterocyclic system helps to enhance pharmacological activity. We found that the morpholine mono/disubstituted *s*-triazine structure has good antitumor activity. Toshiyuki *et al*.[S2] discovered compound **2** 2-(1-imidazolyl)-4,6-(dimorpholino)1,3,5-triazine (Figure S2) showed significant aromatase inhibitory activity and exhibited cytotoxicity against various human breast cancer cell lines (MCF-7) and murine leukaemia cell line, P388 leukemia. Moreover, the cytotoxic activity of compound **2** was higher than the hydroxylated metabolite of HMM (hexamethylmelamine) and its main active form HMPMM, which are clinically used to treat lung, ovarian, and breast cancers.

Aniline compounds have a wide range of biological activities, such as anti-tumor, anti-inflammatory, antibacterial, anti-epileptic and so on. We found that aniline monosubstituted *s*-triazine structure also has good anti-tumor activity. Zacharie *et al*.[S3] explored a series of 2-(fluorophenylamino)-4,6-disubstituted 1,3,5-triazine structure with anticancer activity, and tested the inhibitory effect of the compounds on the inhibition of TNF-a released by LPS induction from J774A.1 cells. Among them, the IC_{50} value of compound 3 (Figure S3) was 13 μM. The structure-activity relationship study showed that the direct connection of 3- or 4-fluorophenylaniline components to the triazine ring was crucial for good activity.

Thiophene, a five-membered sulfur-containing heterocycle, exhibits extensive biological activities, including antitumor, antibacterial, anti-inflammatory, and antidepressant properties. We found that the thiophene monosubstituted *s*-triazine structure also has good anti-tumor activity. For example, Zhu[S4] reported 2-(thiophen-2-yl)-1,3,5-triazine derivatives as PI3K and mTOR inhibitors in 2020. By experimental screening, compound 4 (Figure S4) showed excellent inhibition activity of cell proliferation against A549, MCF-7, and Hela cancer cell lines with IC_{50} values of 0.20±0.05 μM, 1.25±0.11 μM, and 1.03±0.24 μM.

The benzophenone scaffold serves as a ubiquitous motif in medicinal chemistry owing to its presence in numerous naturally occurring molecules endowed with diverse biological activities, such as anticancer, anti-inflammatory, antimicrobial, and antiviral activities. In 2016, Liu and Yao[S5] designed and synthesized some benzophenone-nucleoside derivatives based on the mechanism and structural similarity of telomerase reverse transcriptase (TERT) and HIV-1 reverse transcriptase, and tested their telomerase inhibitory activity. They expected that the presence of stavudine (an effective HIV-1 inhibitor) in the phenstatin portion (an effective anti-cancer agent) would play an important role in telomerase activity. Compound 5 (Figure S5) showed strong activity against HeLa, SMMC-7721 and SGC-7901 cell lines with IC_{50} values of 1.58±0.20, 0.82±0.11 and 0.77±0.33 μM, respectively.

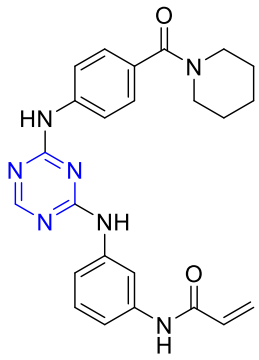


Figure S1 Compound **1**

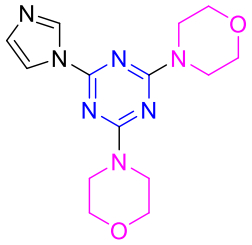


Figure S2 Compound **2**

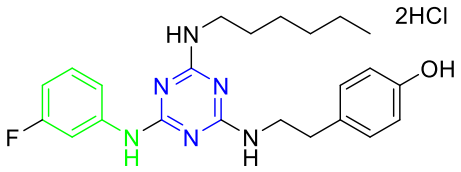


Figure S3 Compound **3**

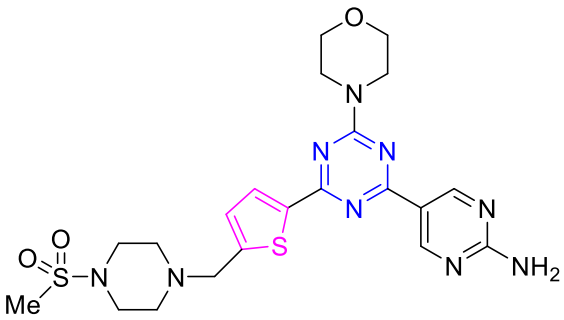


Figure S4 Compound **4**

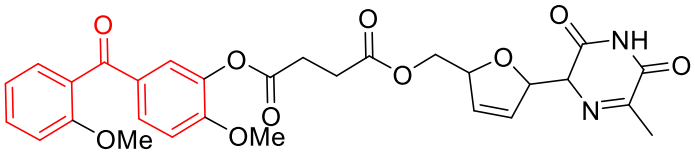


Figure S5 Compound **5**

Therefore, we adopted the principle of active substructure splicing to splice benzophenone derivatives with mono-/disubstituted cyanuric chlorides, morpholine, aniline, and thiophene moieties, aiming to obtain compounds with potent antitumor activity.

Materials and methods

The NMR spectra of the synthesized compounds were recorded using an AVANCE III NMR spectrometer from Bruker, Switzerland. Mass spectrometry was conducted on a Shimadzu Instruments (Suzhou) LCMS-IT-TOF mass spectrometer, equipped with an ESI source. Comprehensive characterization data for 16 target derivatives are included as supplementary material. All reagents and solvents utilized in the experimental procedures were procured from commercial suppliers and were of analytical grade, used without the need for additional purification or drying.

Cell lines and culture conditions: Human colon cancer cells SW620, human non-small cell lung cancer cells A549, human cervical cancer cells HeLa and human breast cancer cells MCF-7 were inoculated with 5000 cells per well in a 96-well cell culture plate, and cultured at 37 °C for 20 h in a 5 % CO_2 incubator.

Experimental

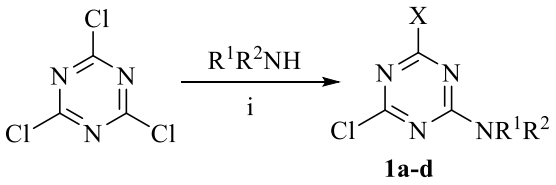
Preparation of intermediates 1a-d

2,4-Dichloro-6-morpholino-1,3,5-triazine **1a:** A mixture of morpholine (7.09 g, 81.34 mmol) and triethylamine (8.15 g, 81.34 mmol) was loaded into a constant pressure dropping funnel. At -45 ℃, the mixture was dropped into acetone (50 mL) containing cyanuric chloride (10.00 g, 54.23 mmol), placed in a 250 mL three-port flask, and stirred vigorously. Continue stirring at -45 ℃ for 2 h (TLC monitoring). Water (50 mL) was added, and the mixture was stirred at room temperature for 1 h to form a solid which was collected by filtration. Final drying (in vacuum) afforded 12.32 g (97%) of the title product as a white solid.

2-Chloro-4,6-dimorpholino-1,3,5-triazine **1b:** A mixture of morpholine (14.17 g, 162.69 mmol) and triethylamine (8.15 g, 81.34 mmol) was loaded into a constant pressure dropping funnel. At -25 ℃, the mixture was dropped into acetone (50 mL) containing cyanuric chloride (10.00 g, 54.23 mmol), placed in a 250 mL three-port flask, and stirred violently. Continue stirring at -25 ℃ for 2 h (TLC monitoring). Water (50 mL) was added, and the mixture was stirred at room temperature for 1 h to form a solid which was collected by filtration. Final drying (in vacuum) afforded 14.42 g (93%) of the title product as a white solid.

4,6-Dichloro-N-(2-thienylmethyl)-1,3,5-triazine-2-amine **1c:** A mixture of 2-(aminomethyl)thiophene (9.21 g, 81.34 mmol) and triethylamine (8.15 g, 81.34 mmol) was loaded into a constant pressure dropping funnel. At -10 ℃, the mixture was dropped into acetone (50 mL) containing cyanuric chloride (10.00 g, 54.23 mmol), placed in a 250 mL three-port flask, and stirred violently. Continue stirring at -15 ℃ for 2 h (TLC monitoring). Water (50 mL) was added, and the mixture was stirred at room temperature for 1 h to form a solid which was collected by filtration. Final drying (in vacuum) afforded 11.92 g (92%) of the title product as a white solid.

4,6-Dichloro-N-phenyl-1,3,5-triazine-2-amine **1d:** A mixture of aniline (7.58 g, 81.34 mmol) and triethylamine (8.15 g, 81.34 mmol) was loaded into a constant pressure dropping funnel. At -25 ℃, the mixture was dropped into acetone (50 mL) containing cyanuric chloride (10.00 g, 54.23 mmol), placed in a 250 mL three-port flask, and stirred violently. Continue stirring at -25 ℃ for 2 h (TLC monitoring). Water (50 mL) was added, and the mixture was stirred at room temperature for 2 h to form a solid which was collected by filtration. Final drying (in vacuum) afforded 12.17 g (90%) of the title product as a white solid.



1a-d

a X = Cl, NR^1R^2 = morpholin-4-yl
b X = NR^1R^2 = morpholin-4-yl
c X = Cl, R^1 = H, R^2 = 2-thienylmethyl
d X = Cl, R^1 = H, R^2 = Ph

Scheme S1 *Reagents and conditions:* i, Et_3N, Me_2CO, -45~ -10 °C, 2 h.

Preparation of intermediates 2a-f

The classic Friedel–Crafts acylation reaction[S6-S10] was used to synthesize intermediate **2a-f**: Polyhydroxy substituted benzene and benzoyl chloride were used as raw materials, anhydrous $AlCl_3$ was used as catalyst, dichloromethane was used as solvent, mixed below 0 °C, the ice bath was removed after dissolution, the reaction was stirred and refluxed for 2 h, and the reaction process was tracked by TLC. After the reaction was completed, it was quenched with ice water, and the stirring was continued until the solid appeared. After filtration, the yellow solid crude product was washed with saturated $NaHCO_3$ solution to obtain the target compounds **2a-f**.

2,4-Dihydroxybenzophenone **2a:** A mixture of anhydrous $AlCl_3$ (12.93 g, 97.01 mmol) and dichloromethane (50 mL) was loaded into a 250 mL three-port flask. At 0 ℃, benzoyl chloride (10.00 g, 71.14 mmol) was dropped with

a constant pressure dropping funnel. When $AlCl_3$ was completely dissolved, resorcinol (7.12 g, 64.67 mmol) was slowly added. After adding, stirring reflux reaction for 2 h (TLC monitoring), the ice water (50 mL) was added, and the mixture was stirred at for 1 h to form a yellow solid. Washed with saturated $NaHCO_3$ solution (25mL×2) which was collected by filtration. Final drying (in vacuum) afforded 12.86 g (93%) of the title product as a light yellow solid.

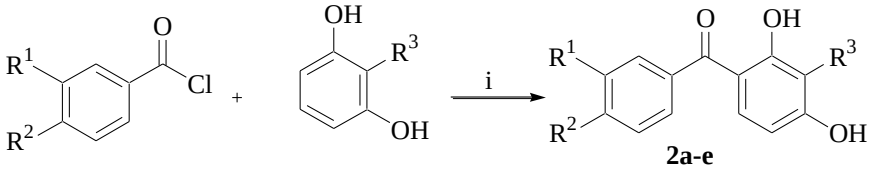
4'-Chloro-2,4-dihydroxybenzophenone **2b:** A mixture of anhydrous $AlCl_3$ (10.39 g, 77.92 mmol) and dichloromethane (50 mL) was loaded into a 250 mL three-port flask. At 0 ℃, *p*-chlorobenzoyl chloride (10.00 g, 57.14 mmol) was dropped with a constant pressure dropping funnel. When $AlCl_3$ was completely dissolved, resorcinol (5.72 g, 51.95 mmol) was slowly added. After adding, stirring reflux reaction for 2 h (TLC monitoring), the ice water (50 mL) was added, and the mixture was stirred at for 1 h to form a light yellow solid. Washed with saturated $NaHCO_3$ solution (25mL×2) which was collected by filtration. Final drying (in vacuum) afforded 12.03 g (93%) of the title product as a white solid.

4'-Methyl-2,4-dihydroxybenzophenone **2c:** A mixture of anhydrous $AlCl_3$ (11.76 g, 88.21 mmol) and dichloromethane (50 mL) was loaded into a 250 mL three-port flask. At 0 ℃, *p*-methylbenzoyl chloride (10.00 g, 64.69 mmol) was dropped with a constant pressure drip funnel. When $AlCl_3$ was completely dissolved, resorcinol (6.48 g, 58.81 mmol) was slowly added. After adding, stirring reflux reaction for 2 h (TLC monitoring), the ice water (50 mL) was added, and the mixture was stirred at for 1 h to form a gray-white solid. Washed with saturated $NaHCO_3$ solution (25 mL × 2) which was collected by filtration. Final drying (in vacuum) afforded 11.32 g (84%) of the title product as a white solid.

3'-Nitro-2,4-dihydroxybenzophenone **2d:** A mixture of anhydrous $AlCl_3$ (9.80 g, 73.49 mmol), resorcinol (5.39 g, 48.99 mmol) and chlorobenzene (50 mL) was loaded into a 250 mL three-port flask. After heating to 80 ℃, when $AlCl_3$ was completely dissolved, *m*-nitrobenzoyl chloride (10.00 g. 53.89 mmol) was slowly added. After adding, the reaction was heated to 110 ℃ and stirred at reflux for 5 h (TLC monitoring). The mixture was cooled to room temperature, 35% HCl (25 mL) was added, and the mixture was stirred at for 1 h to form a gray-white solid. This was washed with saturated $NaHCO_3$ solution (25 mL×2) and collected by filtration. Final drying (in vacuum) afforded 11.59 g (91%) of the title product as a white solid.

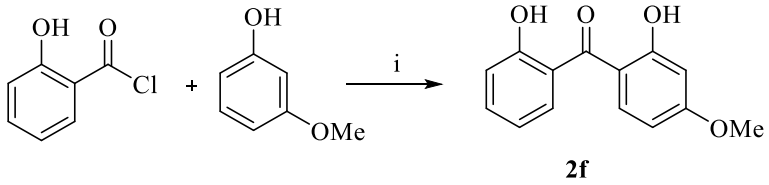
2,3,4-Trihydroxybenzophenone **2e:** A mixture of anhydrous $AlCl_3$ (12.93 g, 97.01 mmol) and dichloromethane (50 mL) was loaded into a 250 mL three-port flask. At 0 ℃, benzoyl chloride (10.00 g, 71.14 mmol) was dropped with a constant pressure dropping funnel. When $AlCl_3$ was completely dissolved, pyrogallol (8.16 g, 64.67 mmol) was slowly added. The mixture was stirred at reflux for 2 h (TLC monitoring), ice water (50 mL) was added, and the mixture was stirred for 1 h to form a yellow solid. This was washed with saturated $NaHCO_3$ solution (25mL×2) and collected by filtration. Final drying (in vacuum) afforded 13.46 g (90%) of the title product as a light yellow solid.

2,2'-Dihydroxy-4-methoxybenzophenone **2f:** A mixture of anhydrous $AlCl_3$ (10.66 g, 79.94 mmol), 3-methoxyphenol (7.36 g, 53.29 mmol) and chlorobenzene (50 mL) was loaded into a 250 mL three-port flask. After heating to 80 ℃, when $AlCl_3$ was completely dissolved, 2-hydroxybenzoyl chloride (10.00 g, 58.62 mmol) was slowly added. The mixture was heated to 110 ℃ and stirred at reflux for 5 h (TLC monitoring). The mixture was cooled to room temperature, 35% HCl (25 mL) was added, and the mixture was stirred at for 1 h to form a gray-white solid. This was washed with saturated $NaHCO_3$ solution (25 mL×2) and collected by filtration. Final drying (in vacuum) afforded 11.32 g (87%) of the title product as a white solid.



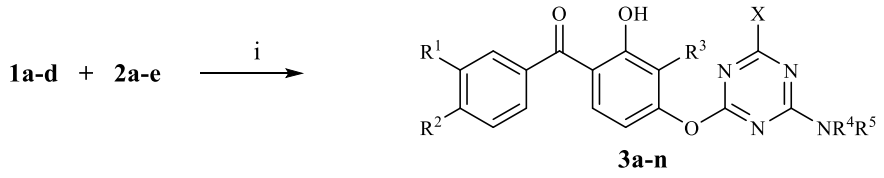
a $R^1 = R^2 = R^3 = H$
b $R^1 = R^3 = H$, $R^2 = Cl$
c $R^1 = R^3 = H$, $R^2 = Me$
d $R^1 = NO_2$, $R^2 = R^3 = H$
e $R^1 = R^2 = H$, $R^3 = OH$

Scheme S2 *Reagents and conditions:* i, $AlCl_3$, CH_2Cl_2, reflux.



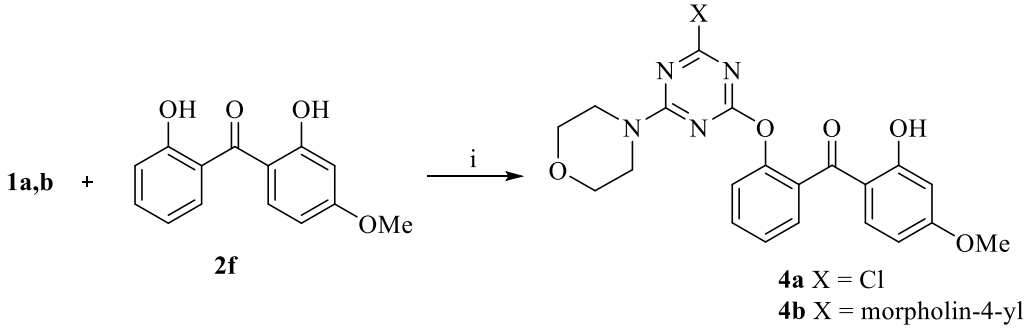
Scheme S3 *Reagents and conditions:* i, $AlCl_3$, CH_2Cl_2, reflux.

Synthesis of target compounds



3a $R^1 = R^2 = R^3 = H$, X = Cl, NR^4R^5 = morpholin-4-yl
3b $R^1 = R^3 = H$, R^2 = Cl, X = Cl, NR^4R^5 = morpholin-4-yl
3c $R^1 = R^3 = H$, R^2 = Me, X = Cl, NR^4R^5 = morpholin-4-yl
3d $R^1 = NO_2$, $R^2 = R^3 = H$, X = Cl, NR^4R^5 = morpholin-4-yl
3e $R^1 = R^2 = H$, R^3 = OH, X = Cl, NR^4R^5 = morpholin-4-yl
3f $R^1 = R^2 = R^3 = H$, X = NR^4R^5 = morpholin-4-yl
3g $R^1 = NO_2$, $R^2 = R^3 = H$, X = NR^4R^5 = morpholin-4-yl
3h $R^1 = R^2 = H$, R^3 = OH, X = NR^4R^5 = morpholin-4-yl
3i $R^1 = R^2 = R^3 = R^4 = H$, X = Cl, R^5 = 2-thienylmethyl
3j $R^1 = R^3 = R^4 = H$, R^2 = X = Cl, R^5 = 2-thienylmethyl
3k $R^1 = R^3 = R^4 = H$, R^2 = Me, X = Cl, R^5 = 2-thienylmethyl
3l $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$, X = Cl, R^5 = 2-thienylmethyl
3m $R^1 = R^2 = R^3 = R^4 = H$, X = Cl, R^5 = Ph
3n $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$, X = Cl, R^5 = Ph

Scheme S4 *Reagents and conditions:* i, Na_2CO_3, 1,4-dioxane, reflux.



4a X = Cl
4b X = morpholin-4-yl

Scheme S5 *Reagents and conditions:* i, Na_2CO_3, 1,4-dioxane, reflux

(4-((4-Chloro-6-morpholino-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(phenyl)methanone **3a**: A mixture of intermediate **1a** (3.80 g, 17.73 mmol) and 1,4-dioxane (50 mL) was loaded into a 150 mL three-port flask. After stirring and dissolving, intermediate **2a** (5.00 g, 21.27 mmol) and sodium carbonate (1.50 g, 14.18 mmol) were added. After adding, stirring reflux reaction for 12 h (TLC monitoring). The solvent was removed, the residuewas purified by silica gel column chromatography. The eluent was petroleum ether/ethyl acetate = 1:6. Final drying (in vacuum) afforded 6.85 g (93%) of the title product as a white solid. m.p.: 160.0~161.2 °C. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 10.91 (s, 1H), 7.74~7.44 (m, 6H), 6.87~6.84 (m, 2H), 3.76~3.64 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.5, 170.7, 170.2, 165.4, 159.3, 155.5, 137.9, 133.2, 132.5, 129.3, 129.0, 122.4, 113.1, 110.3, 66.1, 44.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}ClN_4O_4$: 413.1011, found: 413.1002.

(4-((4-Chloro-6-morpholino-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(4-chlorophenyl)methanone **3b:** White solid, yield 85%, m.p.: 203.1~203.8 °C. 1H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J=8.0 Hz, 2H), 7.70 (d, J=8.0 Hz, 2H), 7.56~7.52 (m, 1H), 7.32 (s, 1H), 7.26~7.22 (m, 2H), 3.74~3.61 (m, 8H). 13C NMR (101 MHz, DMSO-d6) δ 170.8, 170.5, 165.3, 164.1, 152.4, 151.4,139.6, 132.2, 130.6, 129.7, 128.1, 120.0, 119.8, 116.5, 66.1, 44.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{16}Cl_2N_4O_4$: 447.0621, found: 447.0621.

(4-((4-Chloro-6-morpholino-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(p-tolyl)methanone **3c:** White solid, yield 84%, m.p.: 183.4~184.8 °C. 1H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J=8.0 Hz, 2H), 7.55~7.51 (m, 1H), 7.42 (d, J=8.0 Hz, 2H), 7.29 (s, 1H), 7.24~7.20 (m 2H), 3.74~3.61 (m, 8H), 2.43 (s, 3H). 13C NMR (101 MHz, DMSO-d6) δ 170.7, 170.5, 165.3, 164.8, 152.4, 151.5, 145.2, 130.6, 130.4, 130.0, 126.4, 120.1, 119.6, 116.6, 66.1, 44.3, 21.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}ClN_4O_4$: 427.1168, found: 427.1171.

(4-((4-Chloro-6-morpholino-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(3-nitrophenyl)methanone **3d:** White solid, yield 89%, m.p.: 210.6~211.2°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.49~8.42 (m, 2H), 8.16 (d, *J*=4.0 Hz, 1H), 7.86~7,83 (m, 1H), 7.53 (d, *J*=8.0 Hz, 1H), 6.88 (s, 2H), 3.76~3.64 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.7, 170.7, 170.2, 165.4, 158.8, 155.8, 148.2, 139.3, 135.7, 132.6, 130.9, 127.5, 124.0, 122.2, 113.5, 110.3, 66.0, 44.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{16}ClN_5O_6$: 458.0862, found: 458.0857.

(4-((4-Chloro-6-morpholino-1,3,5-triazin-2-yl)oxy)-2,3-dihydroxyphenyl)(phenyl)methanone **3e:** White solid, yield 90%, m.p.: 219.5~220.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 11.13 (s, 1H), 7.68~7.54(m, 5H), 7.35 (d, *J*=8.0 Hz, 1H), 6.58 (d, *J*=8.0 Hz, 1H), 3.76~3.64 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 199.5, 170.7, 170.4, 165.5, 156.7, 156.3, 138.1, 132.3, 132.2, 129.3, 128.9, 127.6, 113.5, 108.6, 66.1, 44.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}ClN_4O_5$: 429.0960, found: 429.0953.

(4-((4,6-Dimorpholino-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(phenyl)methanone **3f:** White solid, yield 89%, m.p.: 190.5~191.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.71~7.67 (m, 2H), 7.65~7.63 (m, 1H), 7.56~7.52 (m 2H), 7.42 (d, *J*=8.0 Hz, 1H), 6.82~6.77 (m, 2H), 3.71~3.57 (m, 16H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.9, 170.4, 166.0, 159.8, 156.8, 138.1, 133.1, 132.5, 129.6, 129.0, 120.8, 113.3, 110.2, 66.8, 43.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{25}N_5O_5$: 464.1928 found: 464.1924.

(4-((4,6-Dimorpholino-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(3-nitrophenyl)methanone **3g:** White solid, yield 84%, m.p.: 220.1~220.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.48~8.39 (m, 2H), 8.15 (d, J=4.0 Hz, 1H), 7.86~7.82 (m, 1H), 7.48 (d, *J*=8.0 Hz, 1H), 6.82 (s, 2H), 3.71~3.60 (m, 16H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.8, 170.5, 166.0, 159.0,157.1, 148.2, 139.5, 135.5, 132.4, 130.8, 127.4, 124.1, 121.0, 113.7, 110.3, 66.3, 43.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}N_6O_7$: 509.1779, found: 509.1778.

(4-((4,6-Dimorpholino-1,3,5-triazin-2-yl)oxy)-2,3-dihydroxyphenyl)(phenyl)methanone **3h:** White solid, yield 85%, m.p.: 251.4~252.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 10.87 (s, 1H), 7.64~7.56 (m, 5H), 7.28 (d, *J*=4.0 Hz, 1H), 6.53 (d, *J*=8.0 Hz, 1H), 3.68~3.57 (m, 16H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 199.6, 170.5, 166.2, 157.2, 156.9, 138.2, 132.2, 131.5, 129.2, 128.9, 128.2, 113.2, 108.4, 66.3, 43.8. HRMS (ESI) *m/z*$[M+H]^+$ calcd for $C_{24}H_{25}N_5O_6$: 480.1878, found: 480.1878.

(4-((4-Chloro-6-((thiophen-2-ylmethyl)amino)-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(phenyl)methanone **3i:** White solid, yield 85%, m.p.: 139.5~142.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 9.28 (d, *J*=24.0 Hz, 1H), 7.73~7.53 (m, 3H), 7.51~7.40 (m, 4H), 7.02~6.87 (m, 4H), 4.59 (d, *J*=40.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.4, 171.0, 170.5, 170.3, 166.9, 159.2, 155.5, 141.1, 137.8, 133.3, 132.5, 129.7, 129.0, 127.2, 126.9, 126.7, 126.0, 122.7, 122.6, 113.3, 110.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{15}ClN_4O_3S$: 439.0626, found: 439.0628.

(4-((4-Chloro-6-((thiophen-2-ylmethyl)amino)-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(4-chlorophenyl)methanone **3j:** White solid, yield 80%, m.p.: 156.2~156.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27~9.23 (m, 1H), 8.14~8.12 (m, 2H), 7.71~7.69 (m, 2H), 7.68~7.35 (m, 1H), 7.34~7.27 (m, 4H), 7.25~6.82 (m, 2H), 4.60 (d, *J*=4.0 Hz, 1H),

4.50 (d, *J*=4.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.9, 170.7, 170.3, 166.9, 164.0, 152.4, 151.4, 141.1, 140.9, 139.6, 132.2, 129.7, 127.1, 126.9, 125.9, 120.1, 116.6, 39.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{14}Cl_2N_4O_3S$: 473.0236, found: 473.0238.

(4-((4-Chloro-6-((thiophen-2-ylmethyl)amino)-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(p-tolyl)methanone **3k:** White solid, yield 81%, m.p.: 131.4~133.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29~9.22 (m, 1H), 8.02 (d, *J*=8.2 Hz, 2H), 7.54~7.52 (m, 1H), 7.43~7.22 (m, 6H), 7.00~6.81 (m, 2H),4.62 (d, *J*=8.0 Hz, 1H),4.50 (d, *J*=4.0 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz,DMSO-d_6) δ 170.7, 170.3, 166.9, 164.8, 152.5, 151.6, 145.1, 140.9, 130.6, 130.4, 130.0, 127.1, 126.9, 126.7, 126.4, 125.9, 120.1, 119.8, 116.6, 39.2, 21.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}ClN_4O_3S$: 453.0783, found: 453.0783.

(4-((4-Chloro-6-((thiophen-2-ylmethyl)amino)-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(3-nitrophenyl)methanone **3l:** White solid, yield 84%, m.p.: 186.4~187.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 9.31~9.25 (m, 1H), 8.44~8.44 (m, 2H), 8.13~8.13 (m, 1H), 7.84~7.80 (m, 1H), 7.54~7.37 (m, 2H), 6.93~6.86 (m, 4H), 4.60 (d, *J*=4.0 Hz, 1H), 4.54 (d, *J*=8.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.7, 170.9, 170.3, 166.9, 158.8, 155.9, 148.2, 140.8, 139.3, 135.7, 130.9, 127.5, 127.2, 126.9, 126.0, 123.9, 122.3, 113.8, 110.6, 39.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{14}ClN_5O_5S$: 484.0477, found: 484.0479.

(4-((4-Chloro-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(phenyl)methanone **3m:** Faint yellow solid, yield 84%, m.p.: 157.3~158.8 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88~10.67 (m, 2H), 7.78 (d, *J*=8.0 Hz, 2H), 7.72~7.69 (m, 1H), 7.58~7.56 (m, 3H), 7.52~7.51 (m, 2H), 7.42~7.38 (s, 1H), 7.27~7.23 (m, 1H), 7.13~7.09 (m, 1H), 6.95~6.93 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.1, 171.0, 170.3, 165.1, 158.7, 155.4, 138.0, 137.8, 133.4, 132.1, 129.7, 129.2, 129.0, 124.5, 123.3, 122.0, 121.1, 113.4, 110.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{15}ClN_4O_3$: 419.0905, found: 418.0904.

(4-((4-Chloro-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-2-hydroxyphenyl)(3-nitrophenyl)methanone **3n:** White solid, yield 82%, m.p.: 183.4~184.0 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 10.65 (s, 1H), 8.51~8.47 (m, 2H), 8.18~8.13 (m, 1H), 7.86~7.82 (m, 1H), 7.61~7.35 (m, 4H), 7.23~7.19 (m, 1H), 7.07~7.03 (m, 1H), 6.97~6.93 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.6, 170.9, 170.3, 165.1, 158.7, 156.0, 148.3, 139.3, 138.0, 135.8, 130.8, 129.0, 127.6, 124.5, 123.9, 121.1, 113.9, 110.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{14}ClN_5O_5$: 464.0756, found: 464.0758.

(2-((4-Chloro-6-morpholino-1,3,5-triazin-2-yl)oxy)phenyl)(2-hydroxy-4-methoxyphenyl)methanone **4a:** White solid, yield 89%, m.p.: 144.3~145.8 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 7.68~7.40 (m, 4H), 7.24 (d, *J*=8.0 Hz, 1H), 6.52 (s, 1H), 6.45 (d, *J*=12.0 Hz, 1H), 3.82 (s, 3H), 3.69~3.52 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.8, 170.5, 170.2, 166.5, 165.0, 164.5, 148.6, 135.2, 132.5, 131.5, 129.9, 126.5, 123.4, 114.4, 107.9, 101.4, 66.1, 56.3, 44.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}ClN_4O_5$: 443.1117, found: 443.1117.

(2-((4,6-Dimorpholino-1,3,5-triazin-2-yl)oxy)phenyl)(2-hydroxy-4-methoxyphenyl)methanone **4b:** White solid, yield 88%，m.p.: 155.2~156.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.60~7.24 (m, 5H), 6.51 (s, 1H), 6.42 (d, *J*=8.0 Hz, 1H), 3.81 (s, 3H), 3.62~3.46 (m, 16H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.6, 170.5, 166.4, 165.7, 164.8, 149.3, 135.4, 132.1, 131.8, 129.5, 125.7, 123.6, 114.1, 107.8, 101.2, 66.3, 56.3, 43.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{27}N_5O_6$: 494.2034, found: 494.2036.

NMR spectra

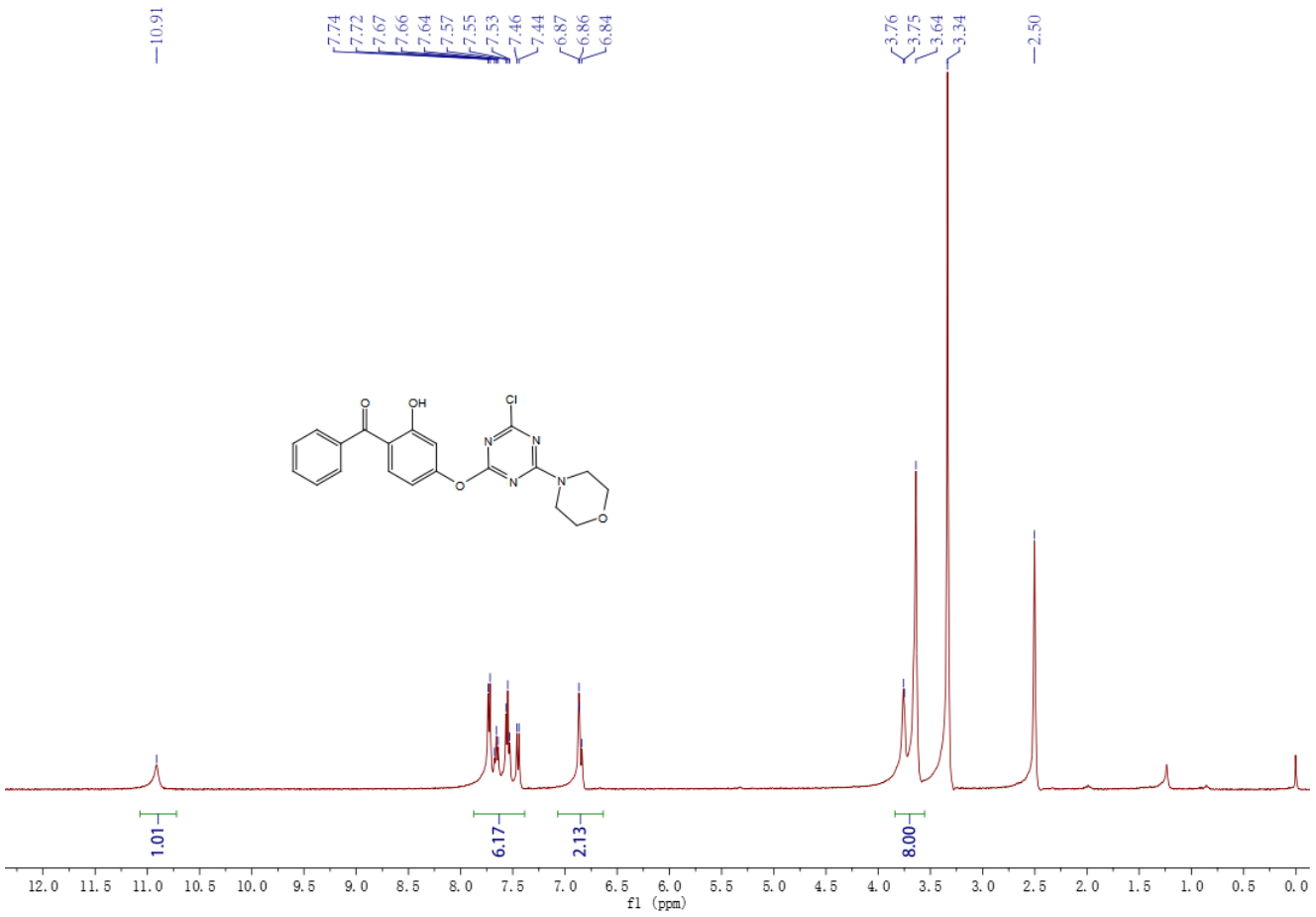


Figure S6-1 ^{1}H-NMR spectrum of compound **3a**

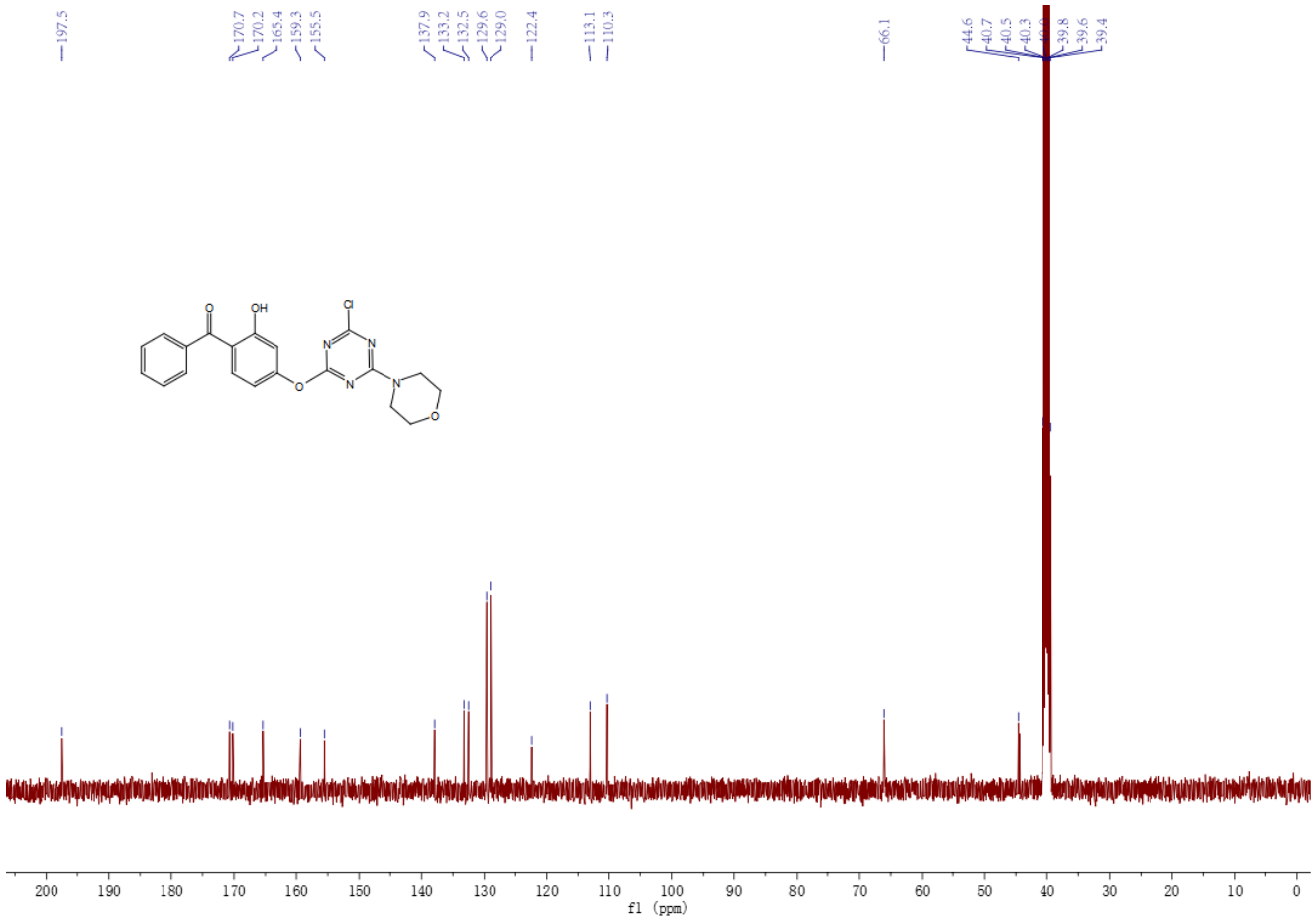


Figure S6-2 ^{13}C-NMR spectrum of compound **3a**

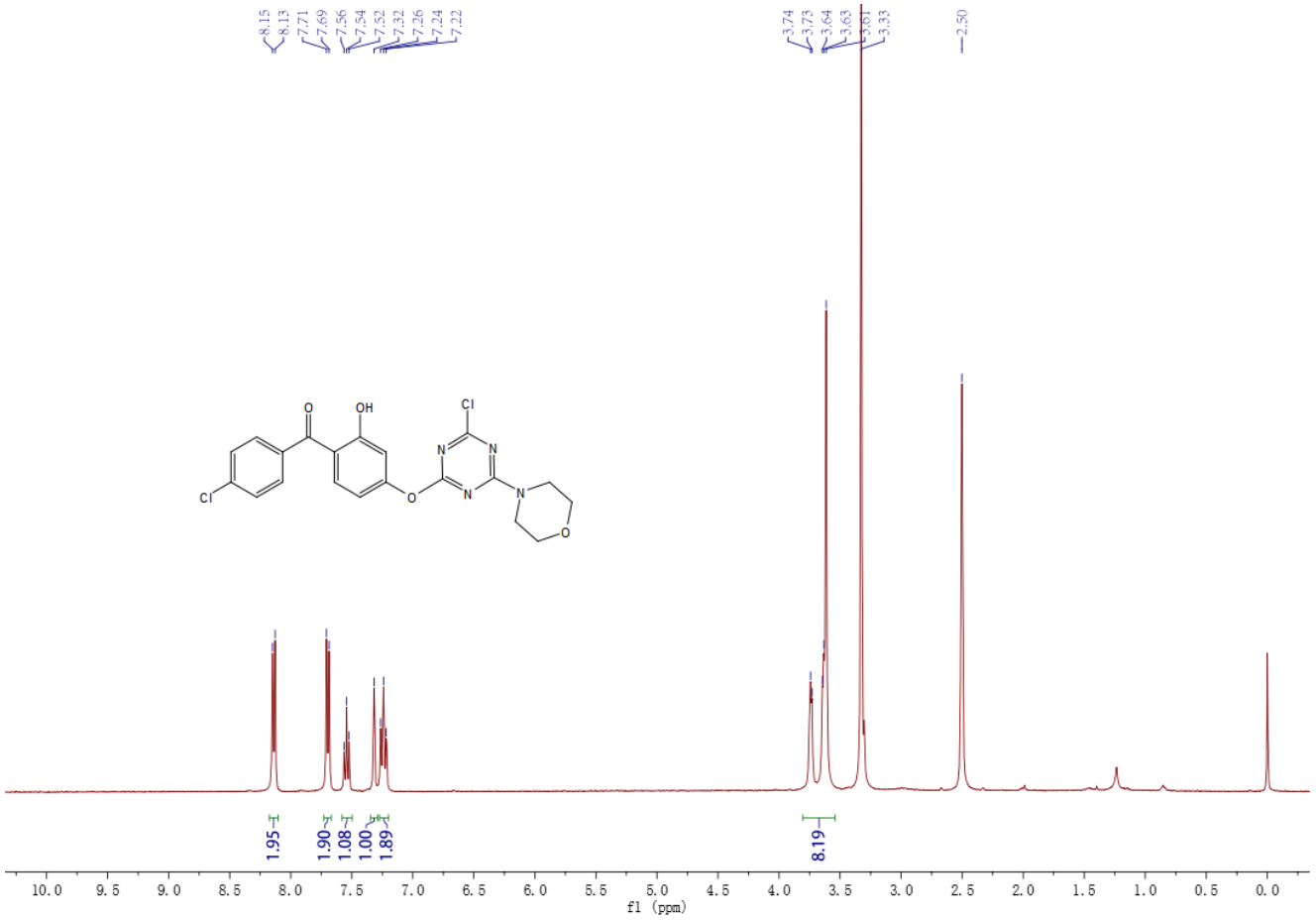


Figure S7-1 ^{1}H-NMR spectrum of compound **3b**

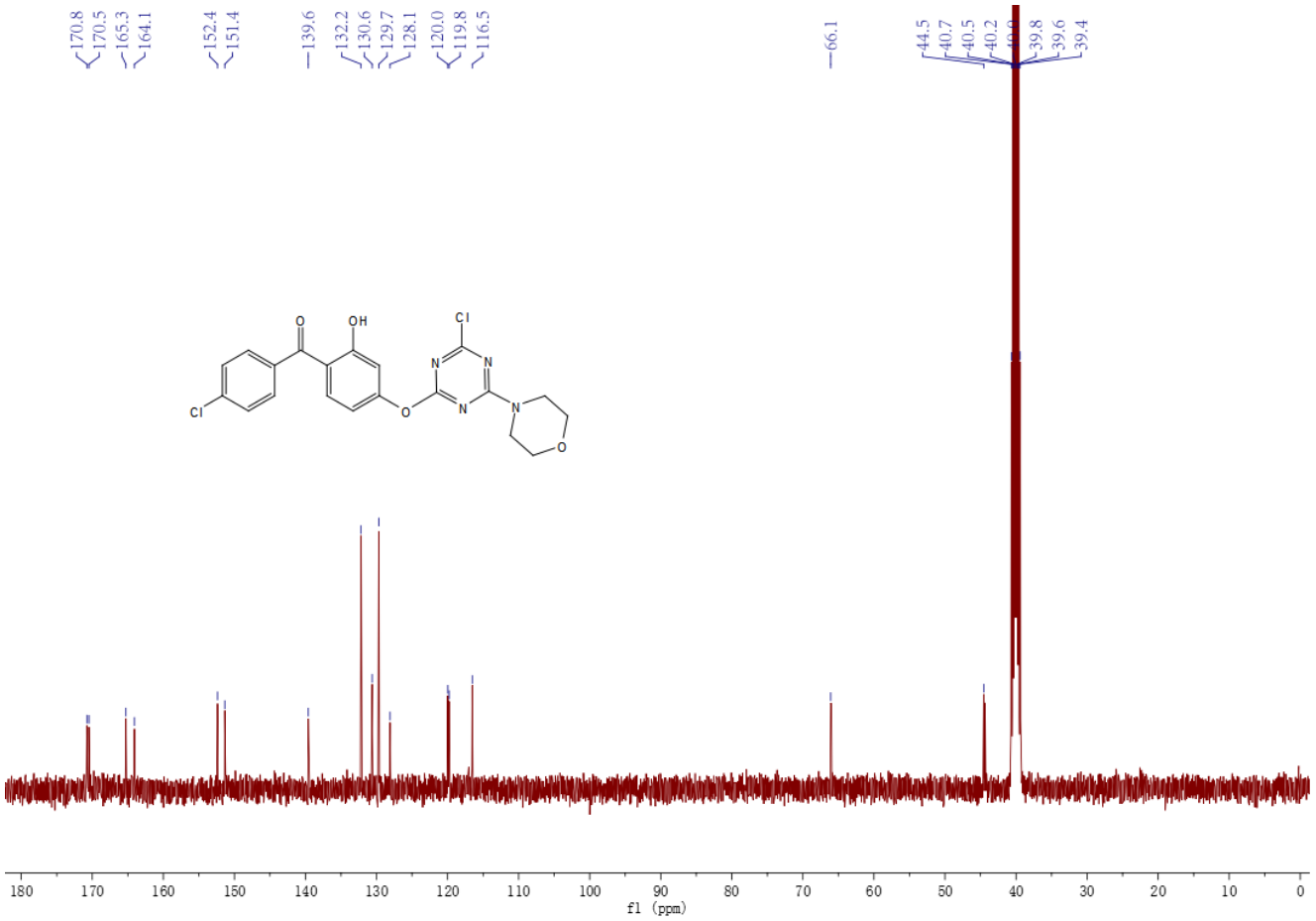


Figure S7-2 ^{13}C-NMR spectrum of compound **3b**

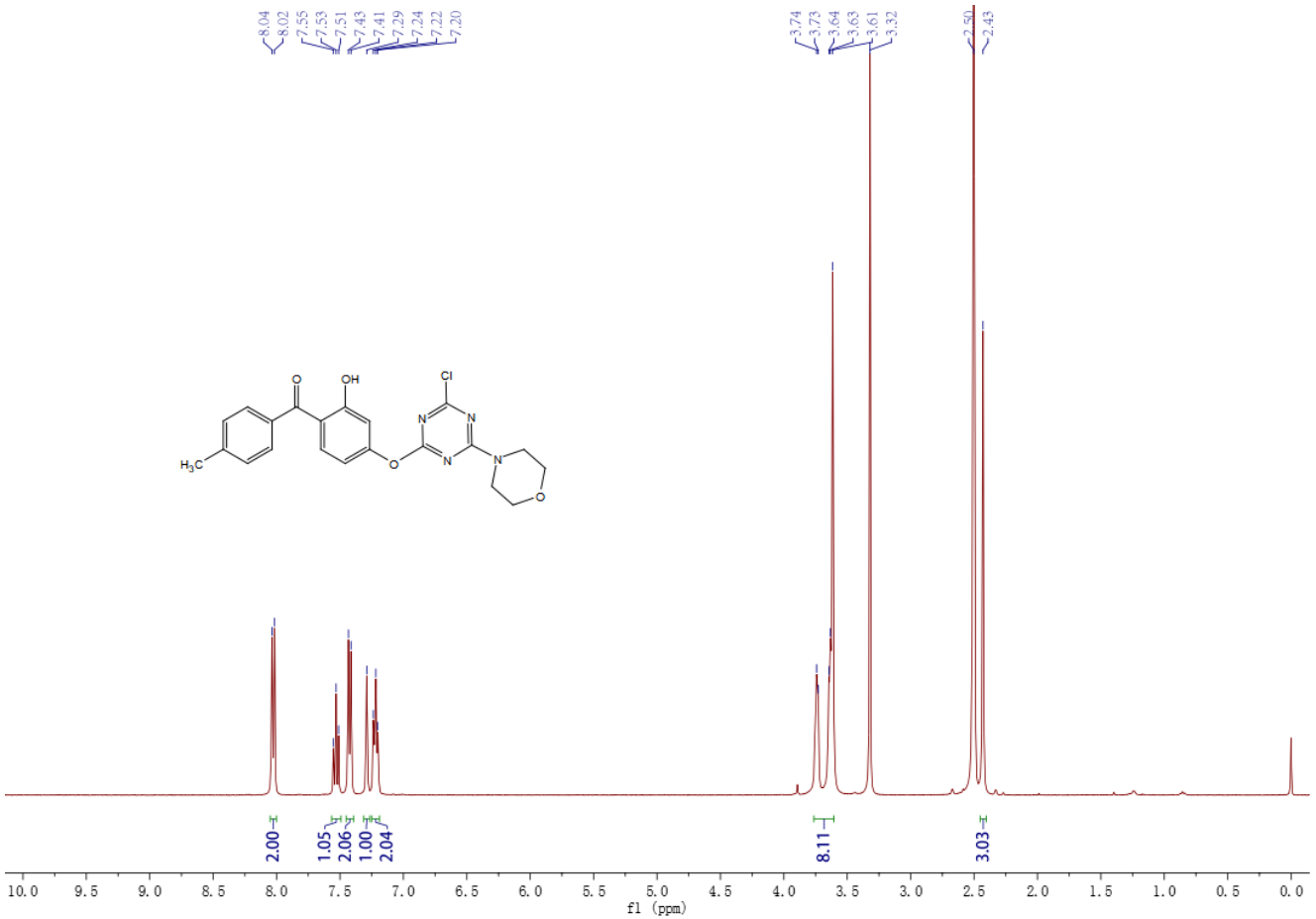


Figure S8-1 ^{1}H-NMR spectrum of compound **3c**

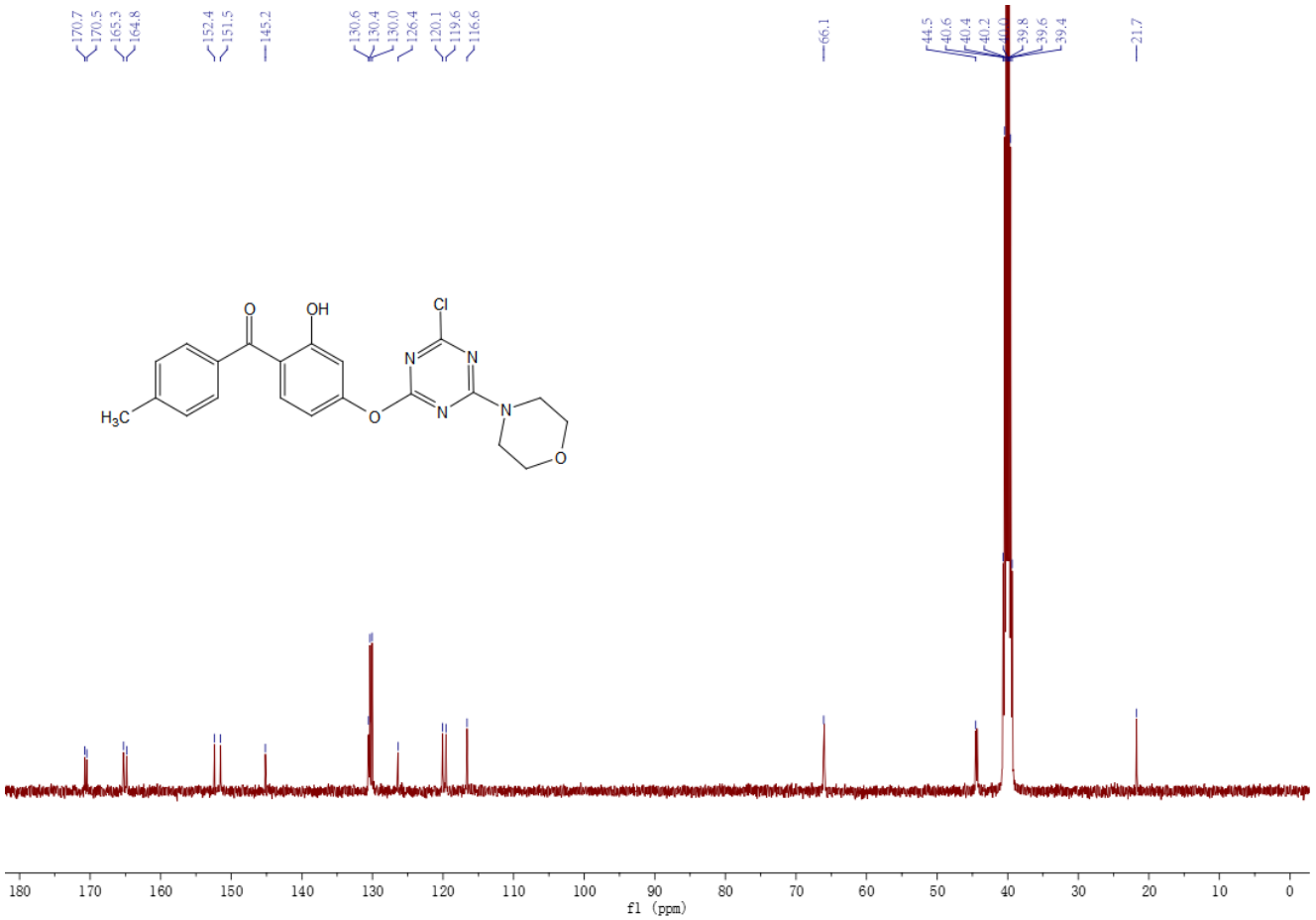


Figure S8-2 ^{13}C-NMR spectrum of compound **3c**

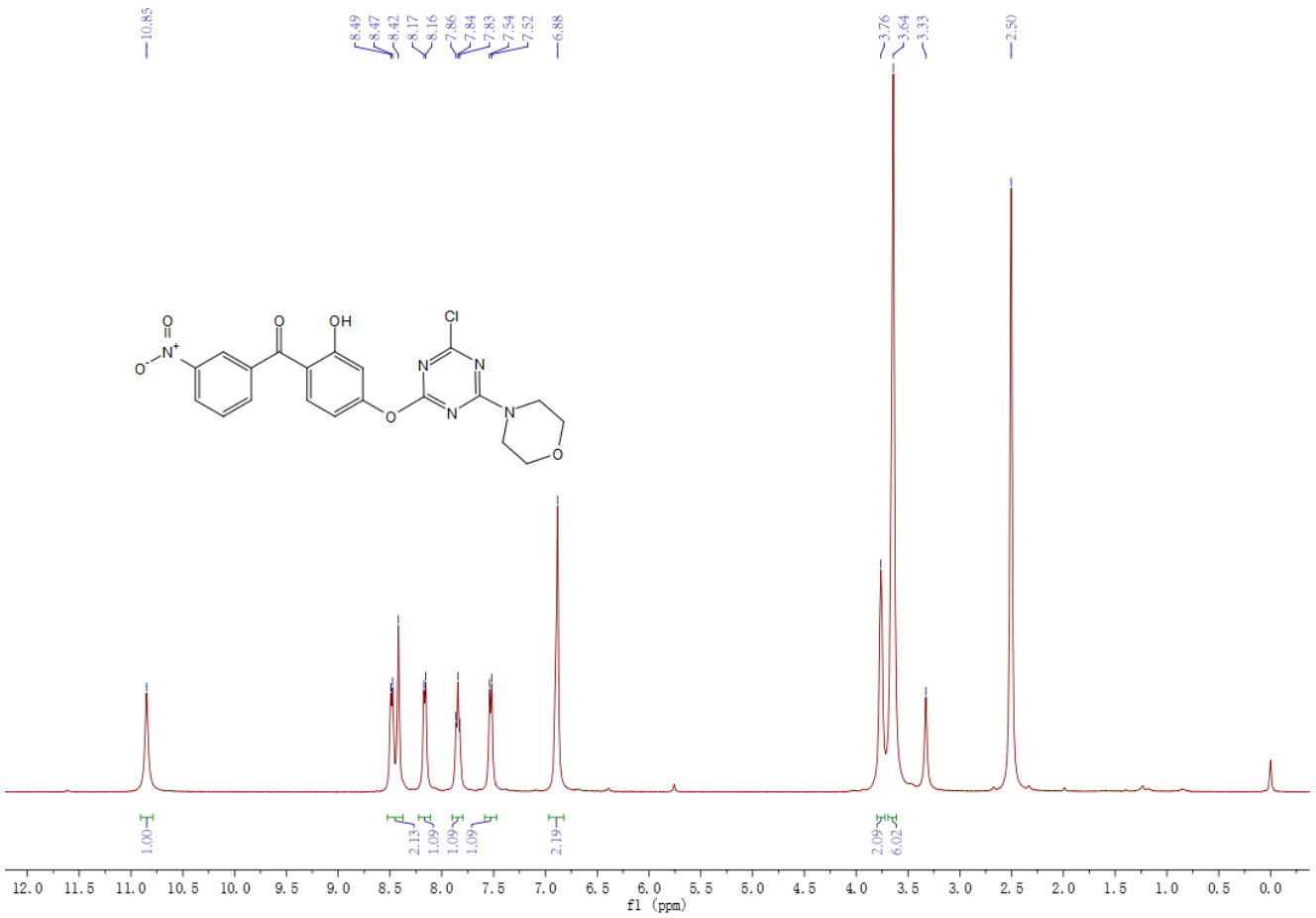


Figure S9-1 ^{1}H-NMR spectrum of compound **3d**

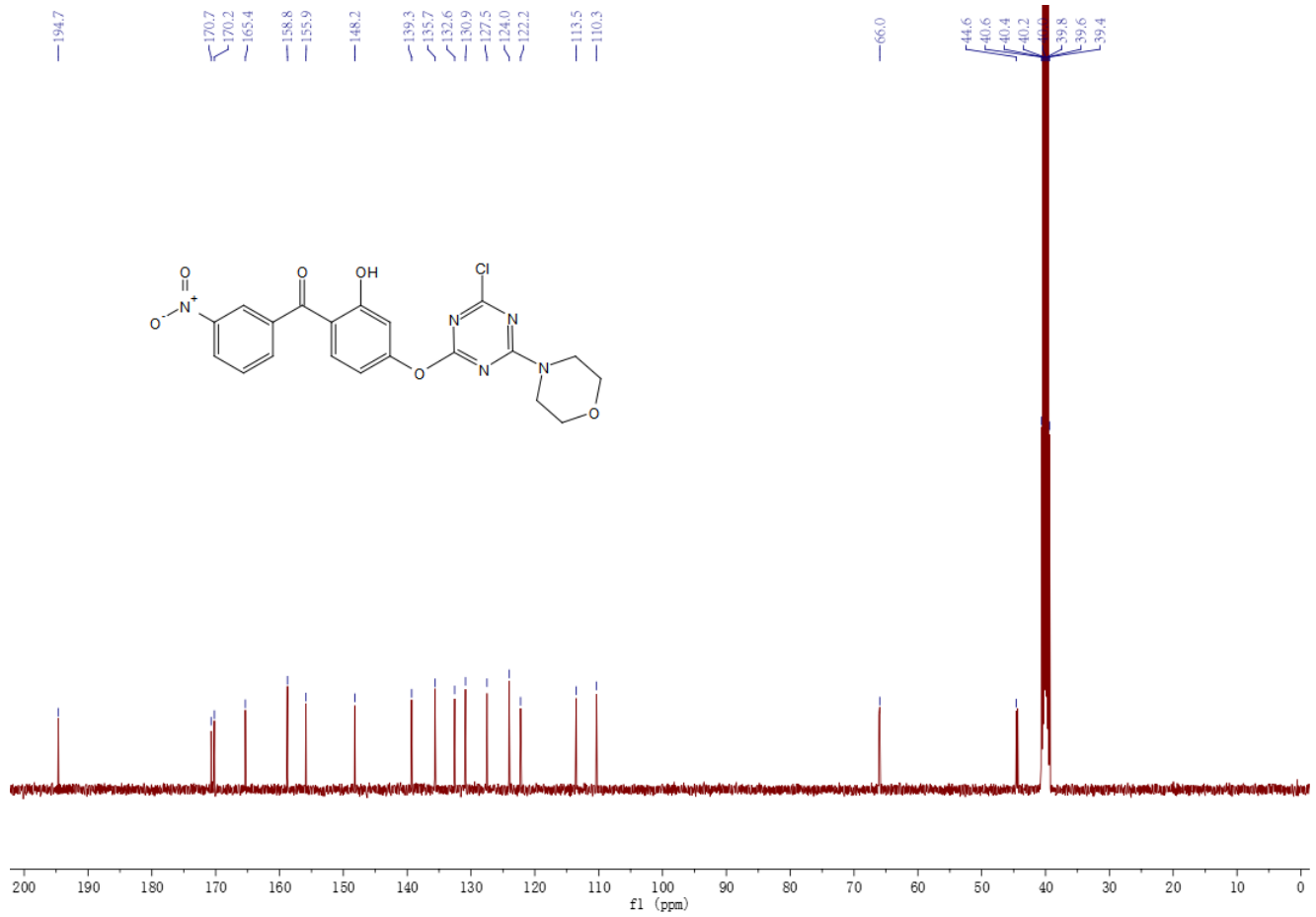


Figure S9-2 ^{13}C-NMR spectrum of compound **3d**

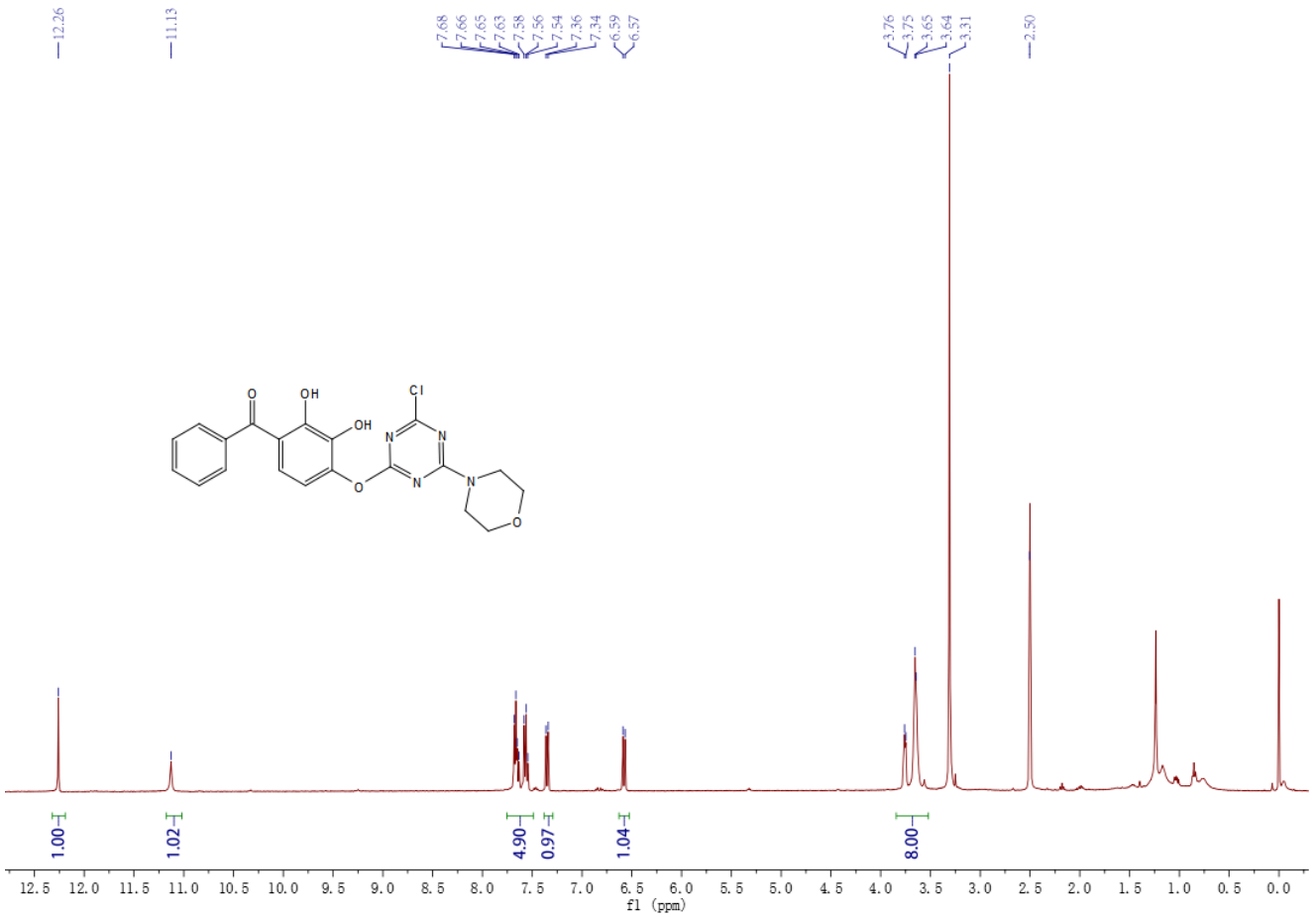


Figure S10-1 ^{1}H-NMR spectrum of compound **3e**

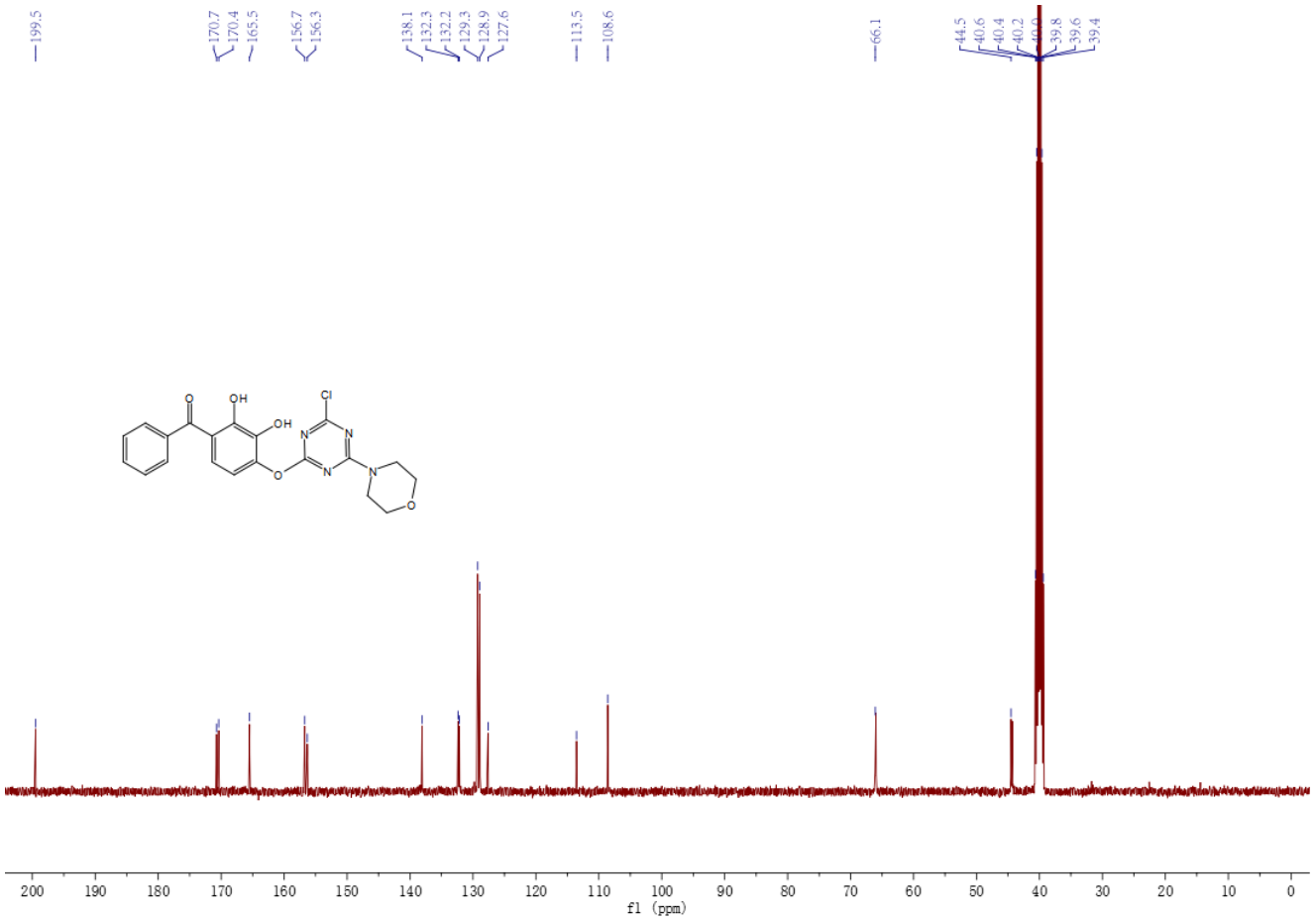


Figure S10-2 ^{13}C-NMR spectrum of compound **3e**

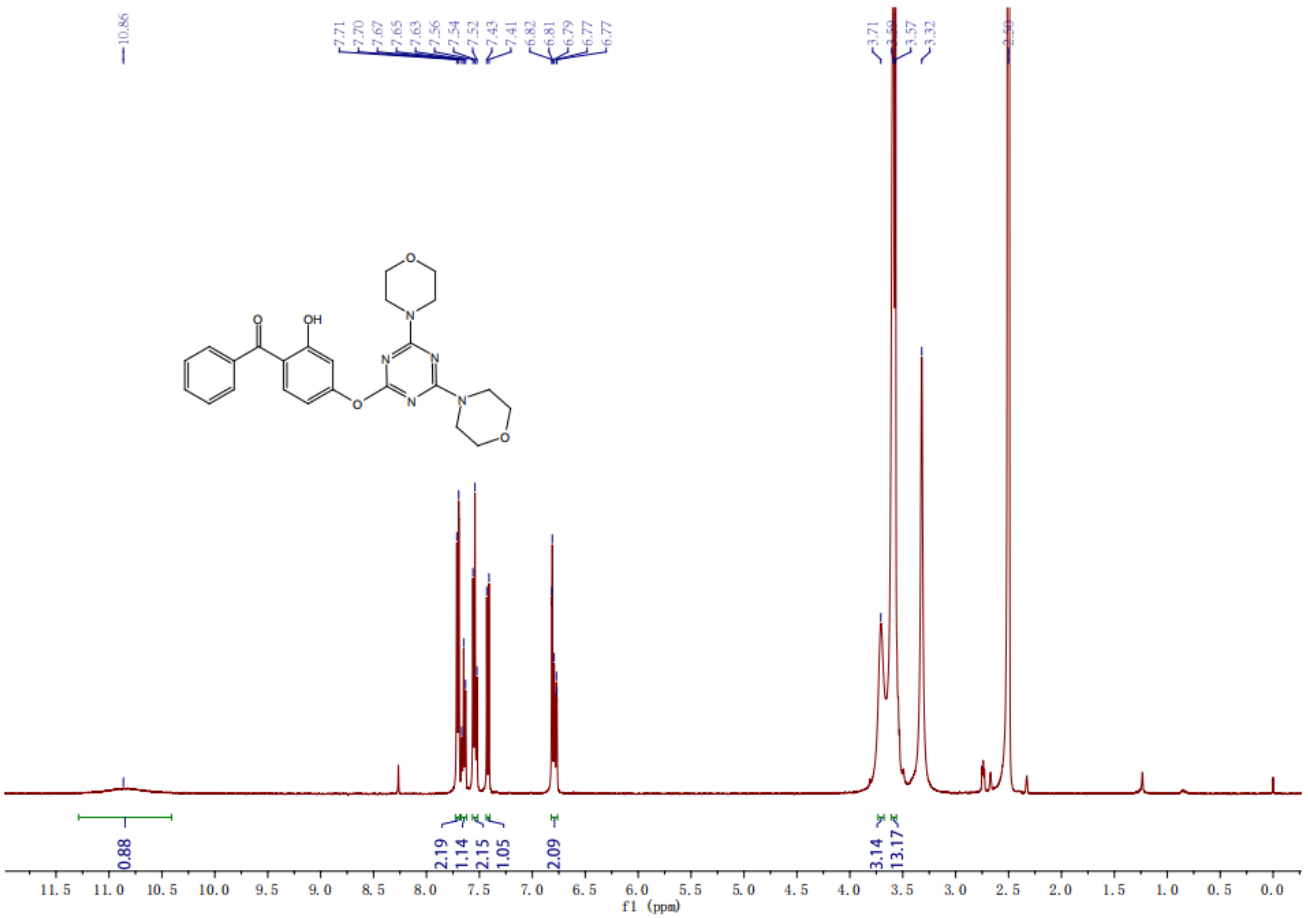


Figure S11-1 ^{1}H-NMR spectrum of compound **3f**

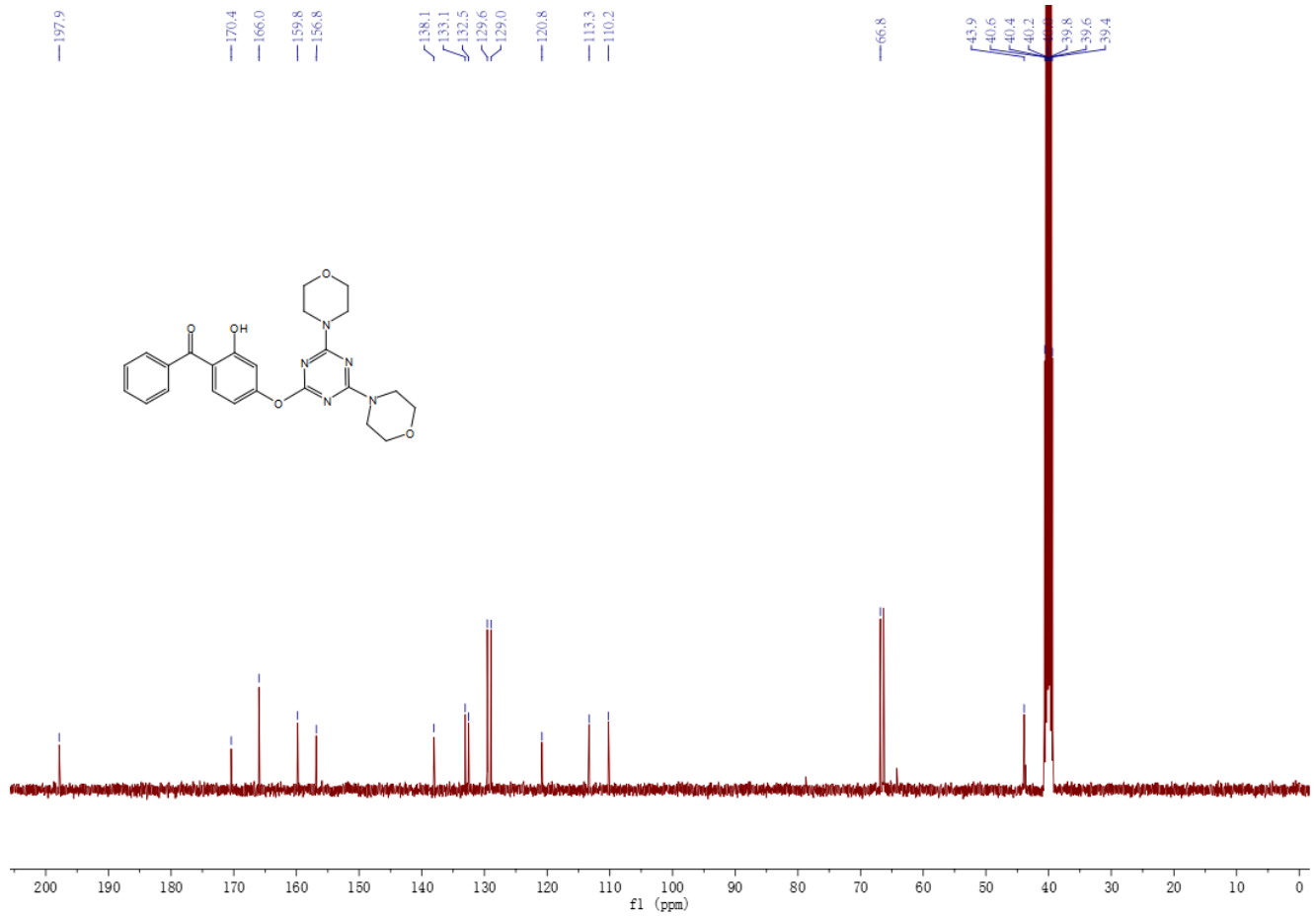


Figure S11-2 ^{13}C-NMR spectrum of compound **3f**

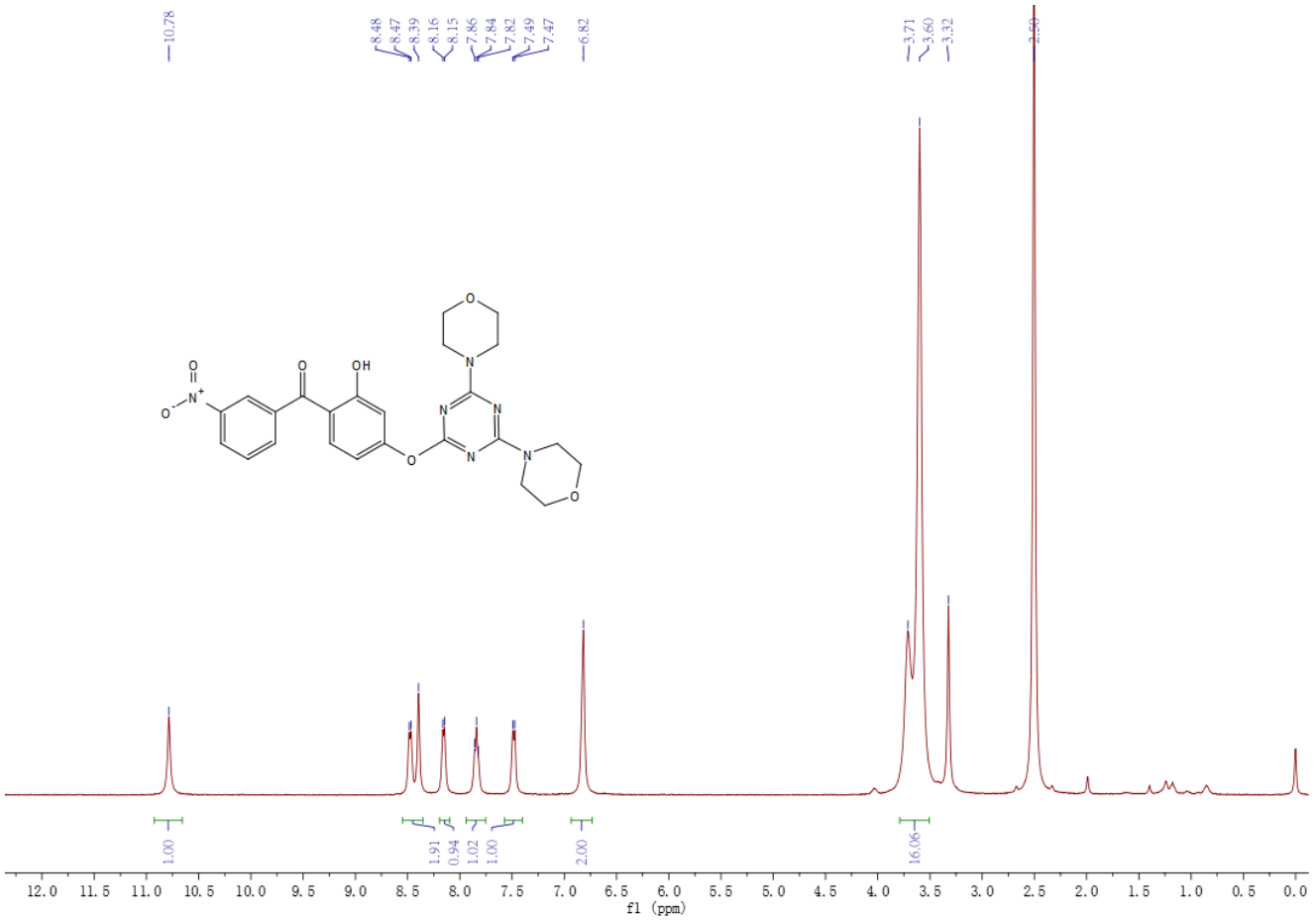


Figure S12-1 ^{1}H-NMR spectrum of compound **3g**

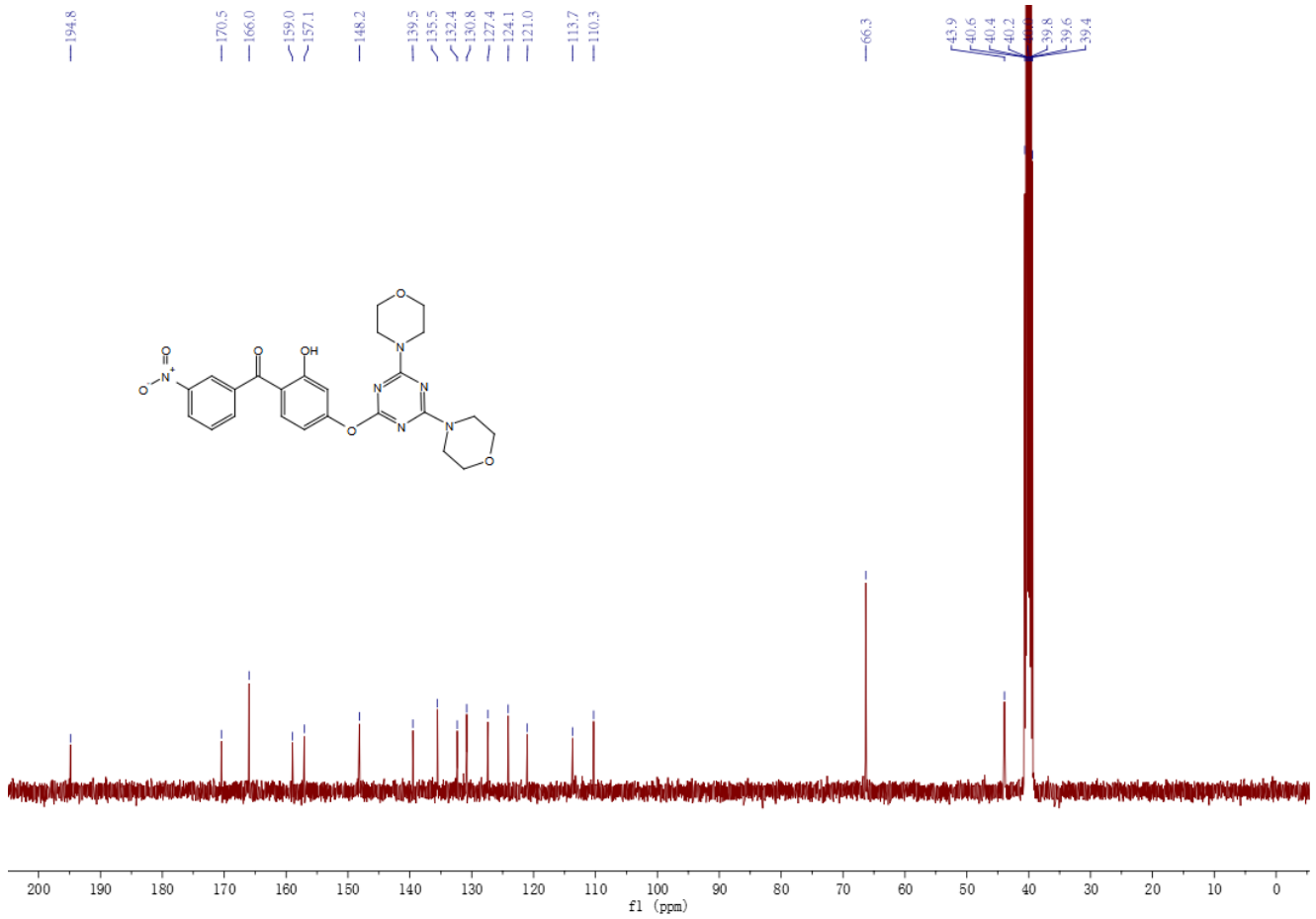


Figure S12-2 ^{13}C-NMR spectrum of compound **3g**

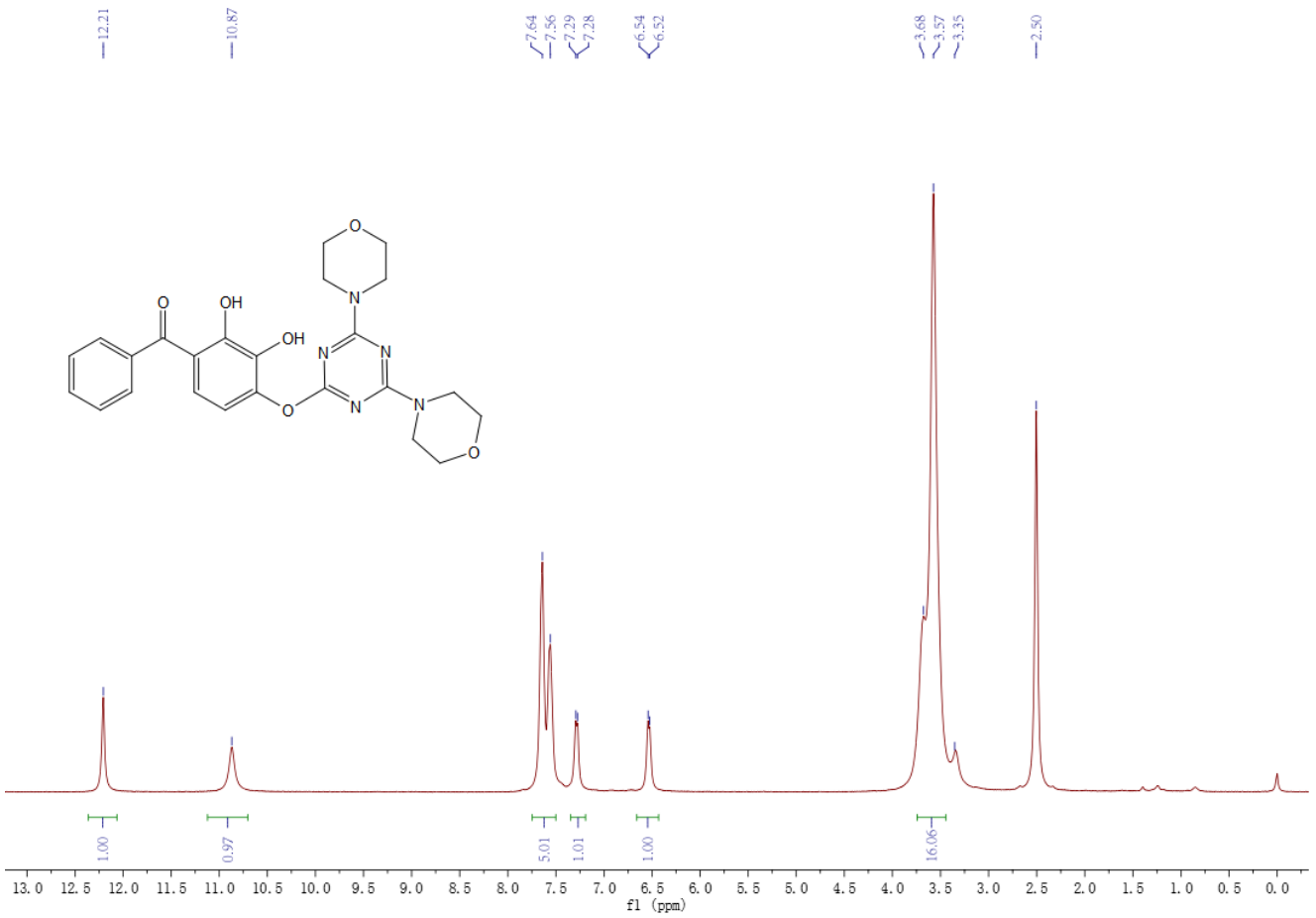


Figure S13-1 ^{1}H-NMR spectrum of compound **3h**

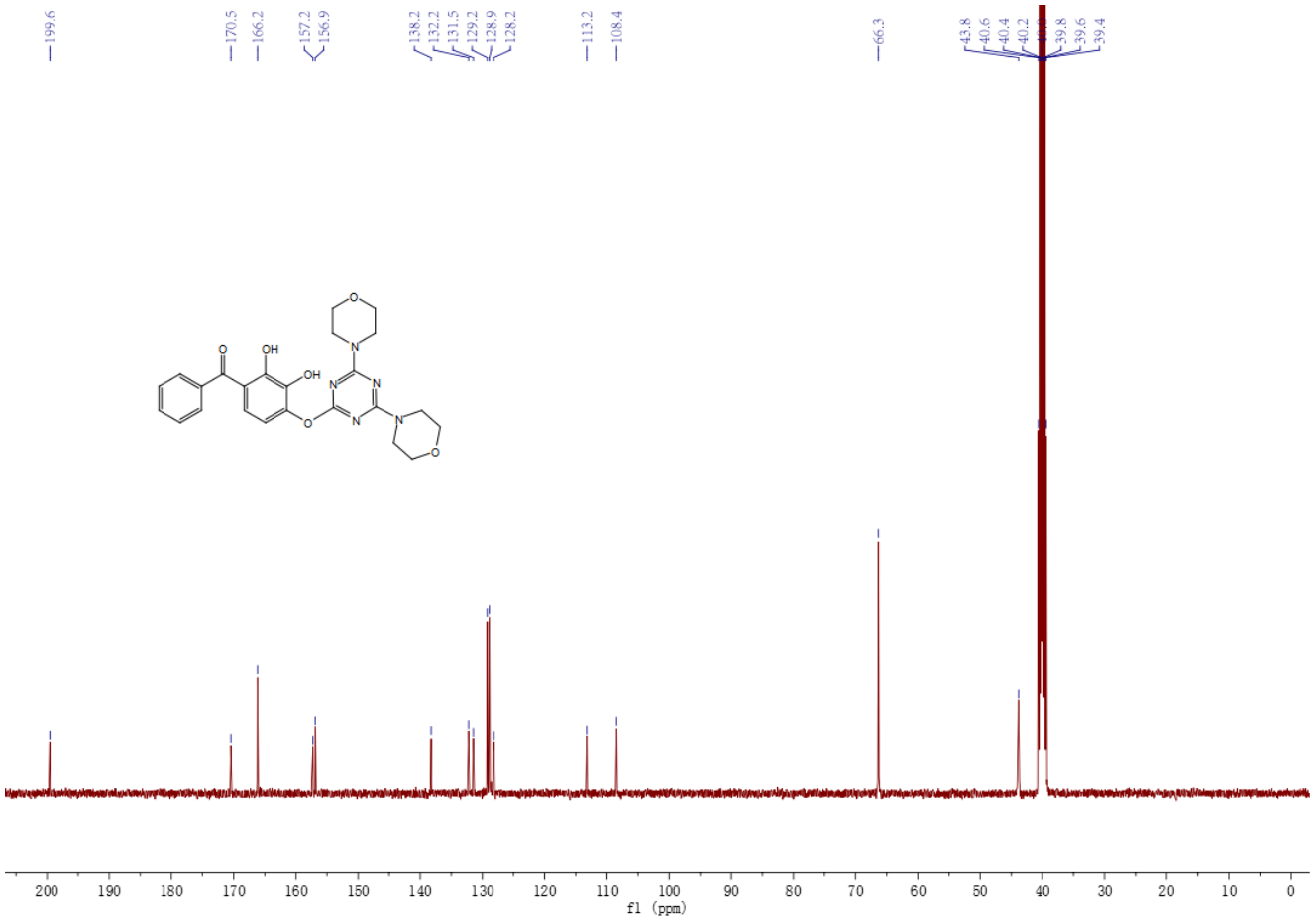


Figure S13-2 ^{13}C-NMR spectrum of compound **3h**

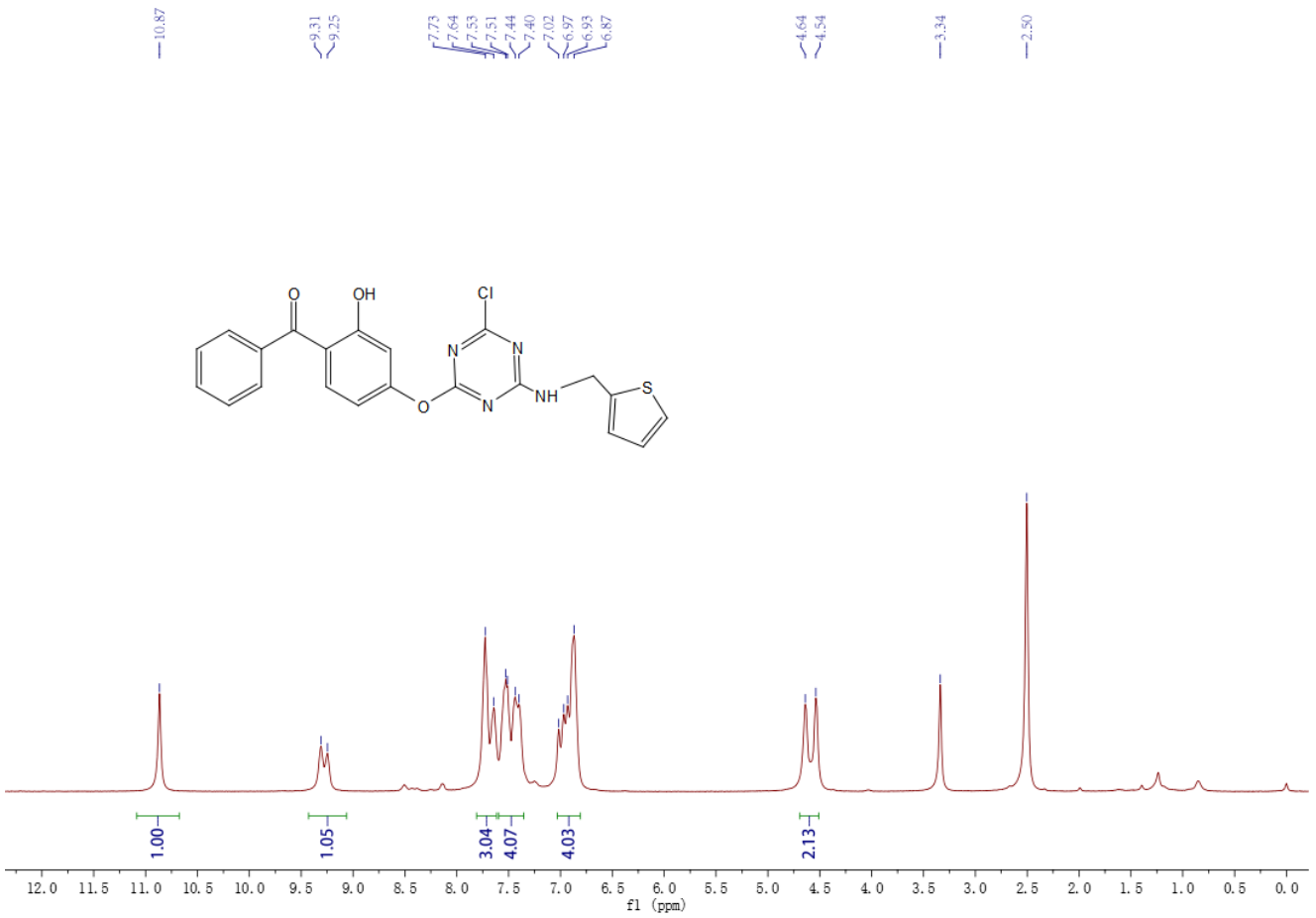


Figure S14-1 ^{1}H-NMR spectrum of compound **3i**

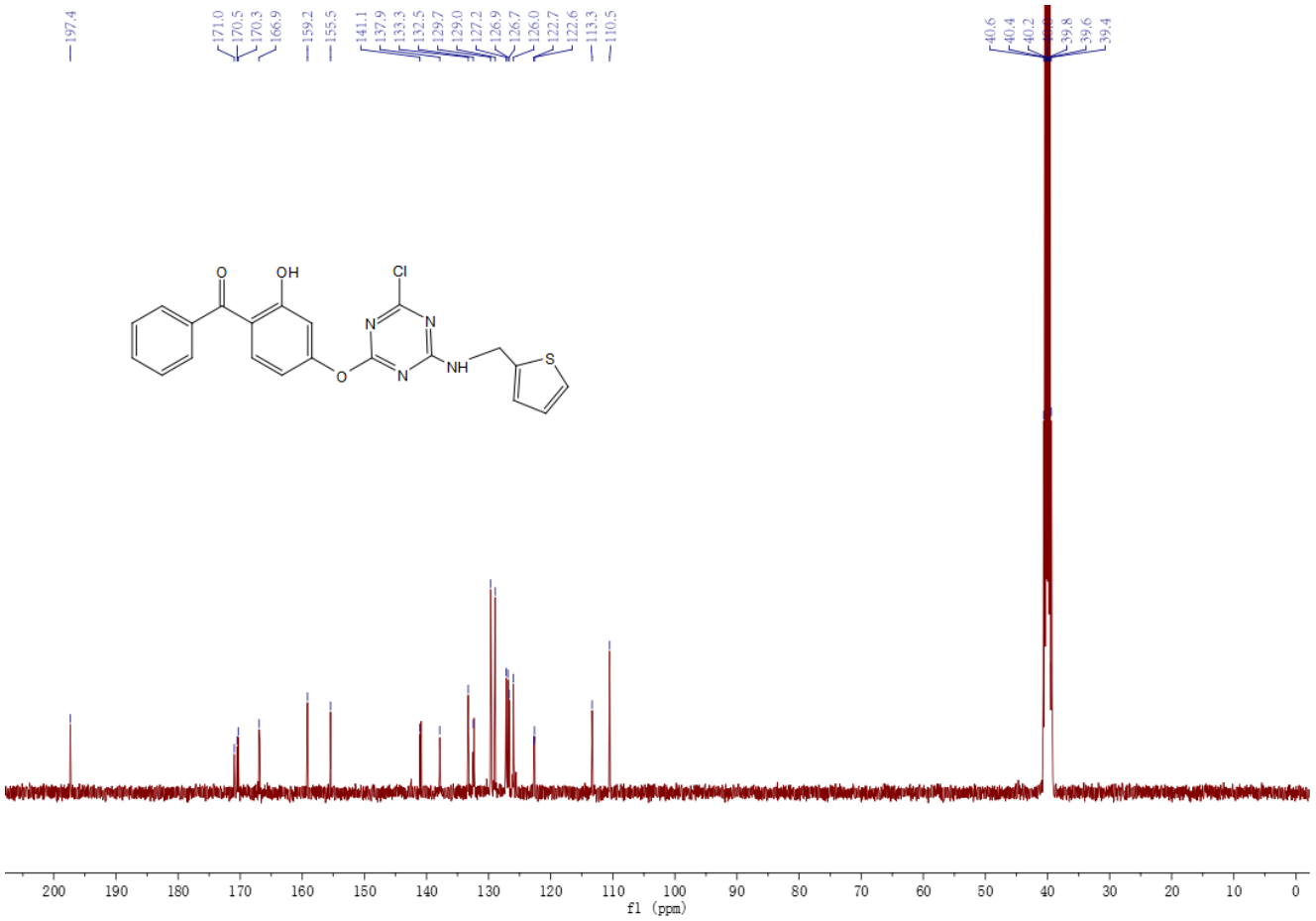


Figure S14-2 ^{13}C-NMR spectrum of compound **3i**

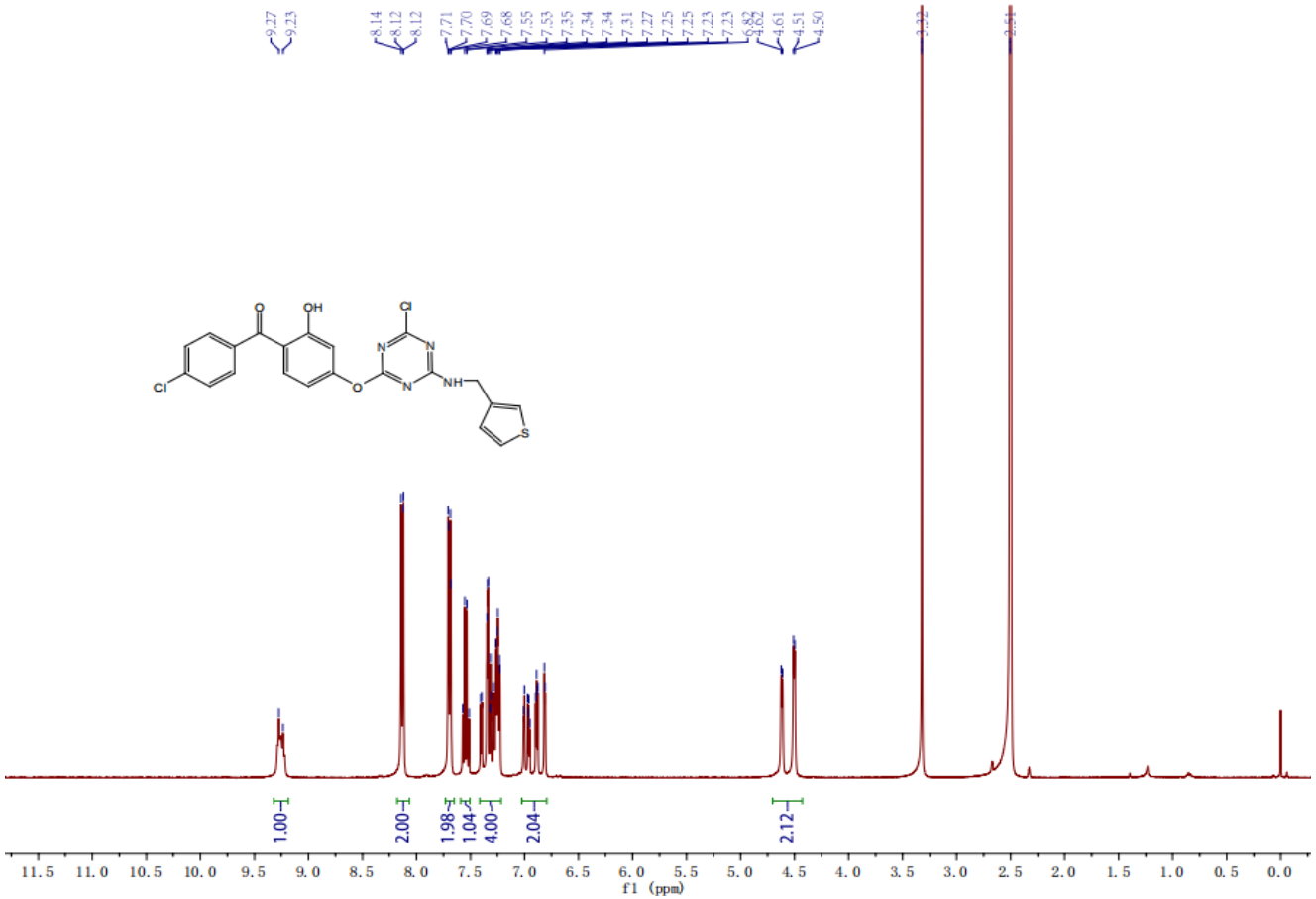


Figure S15-1 ^{1}H-NMR spectrum of compound **3j**

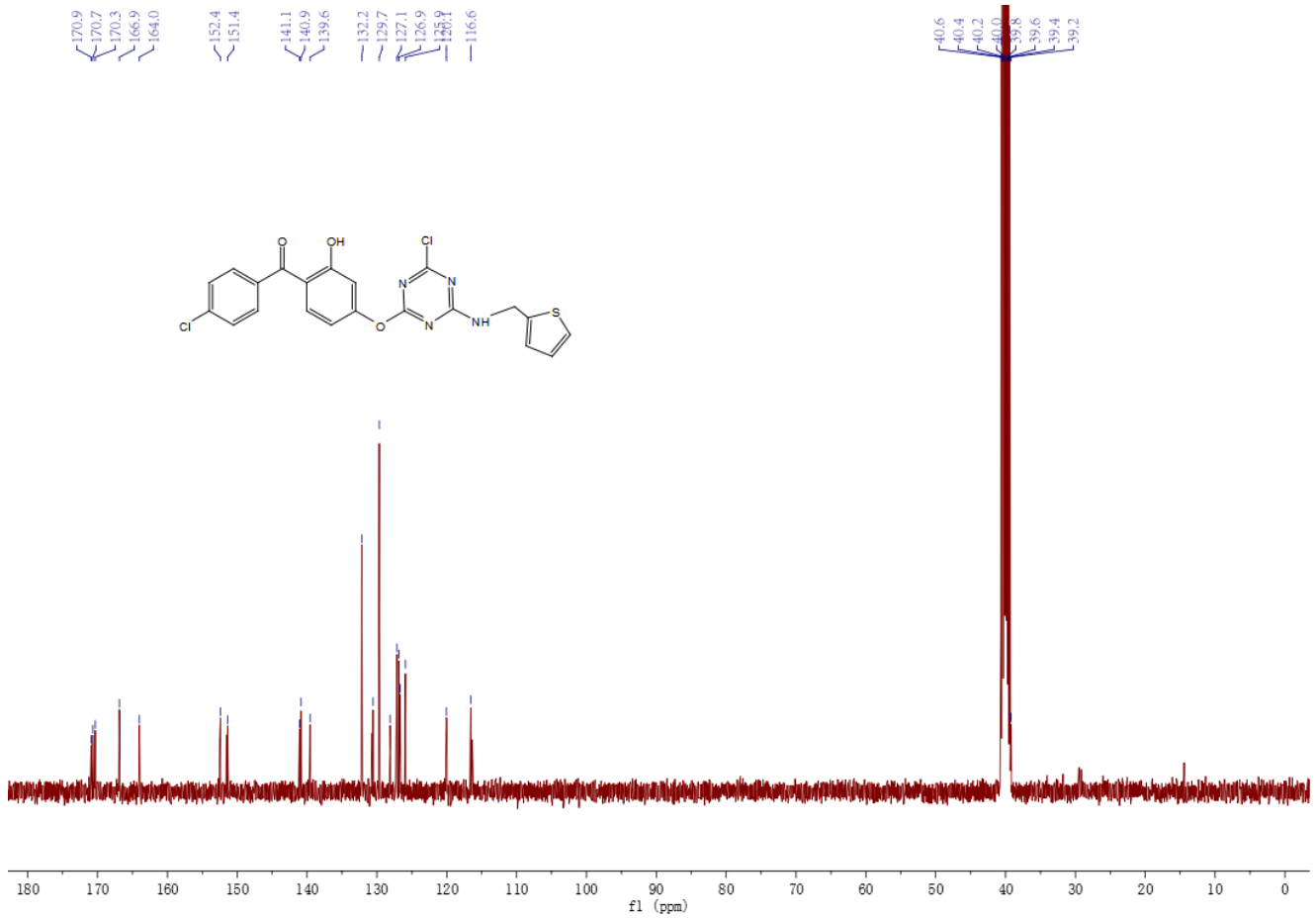


Figure S15-2 ^{13}C-NMR spectrum of compound **3j**

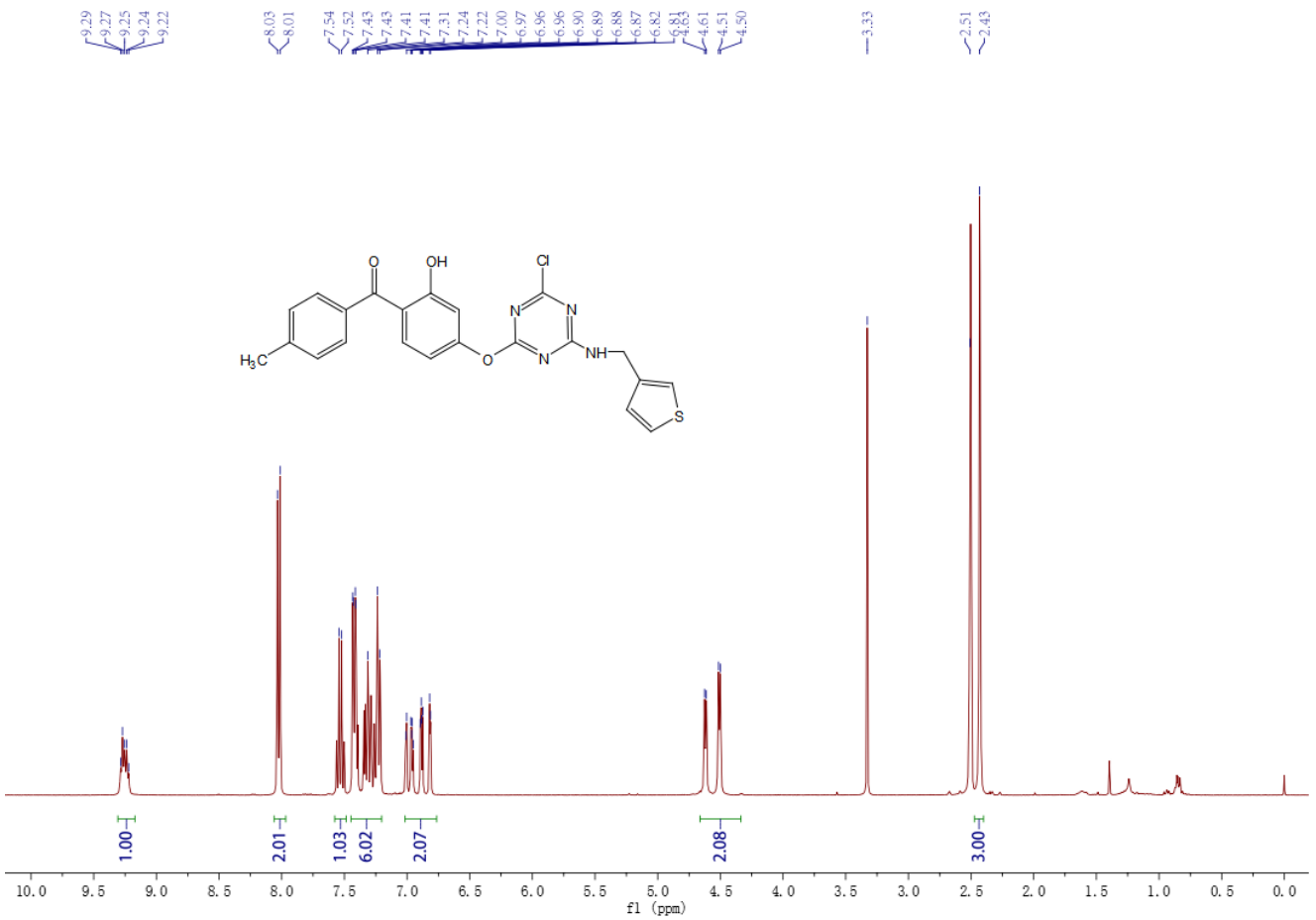


Figure S16-1 ^{1}H-NMR spectrum of compound **3k**

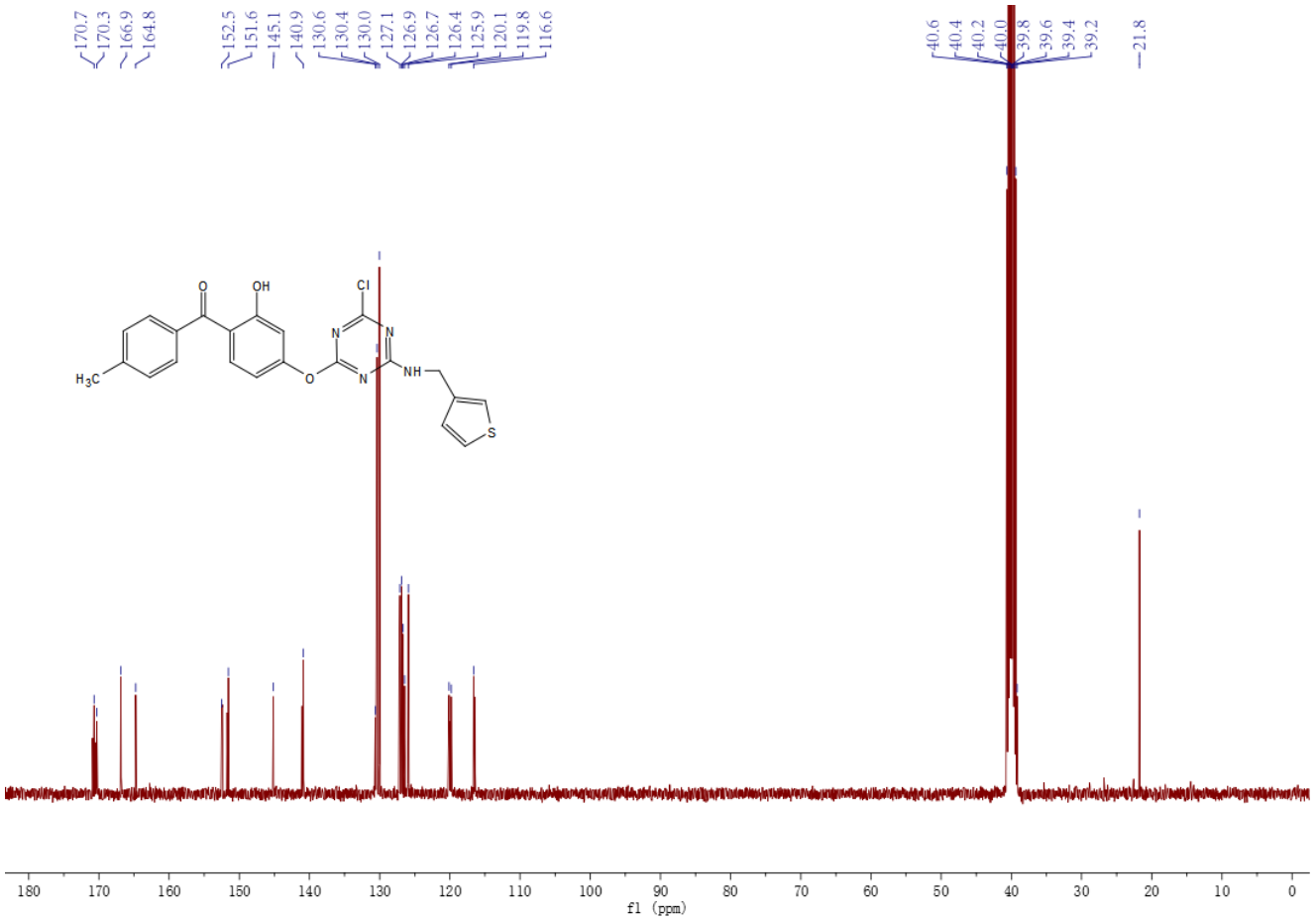


Figure S16-2 ^{13}C-NMR spectrum of compound **3k**

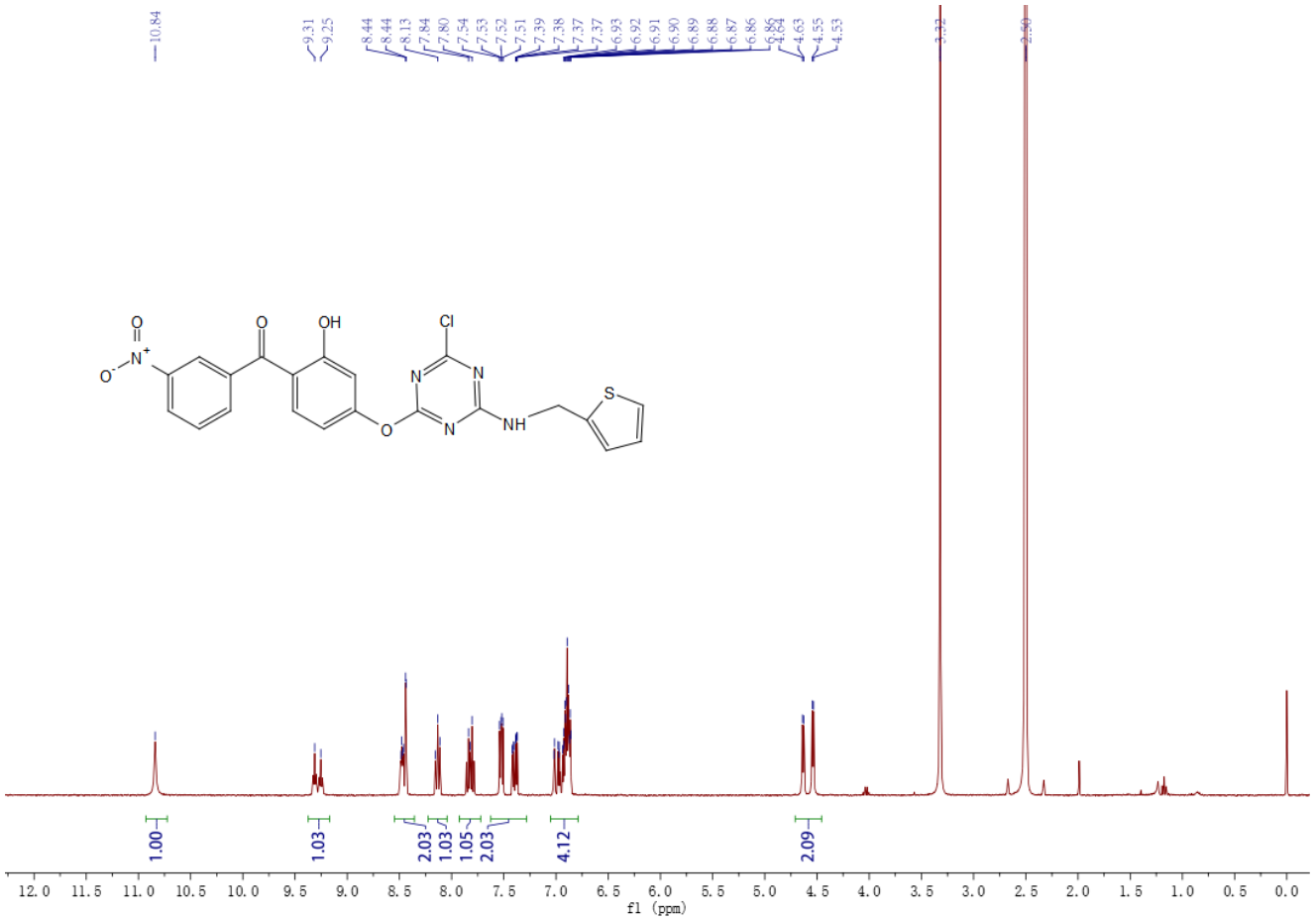


Figure S17-1 ^{1}H-NMR spectrum of compound **3l**

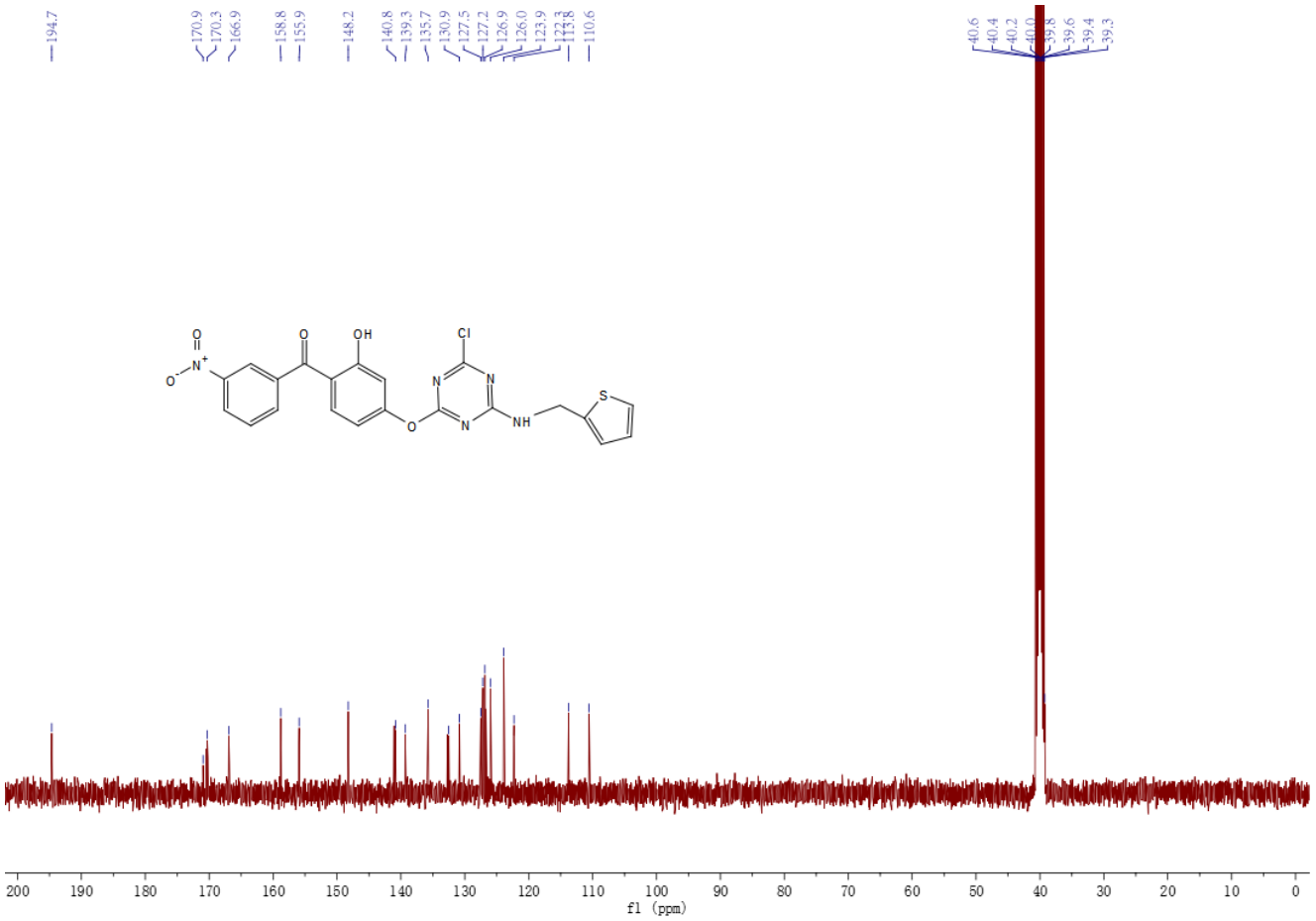


Figure S17-2 ^{13}C-NMR spectrum of compound **3l**

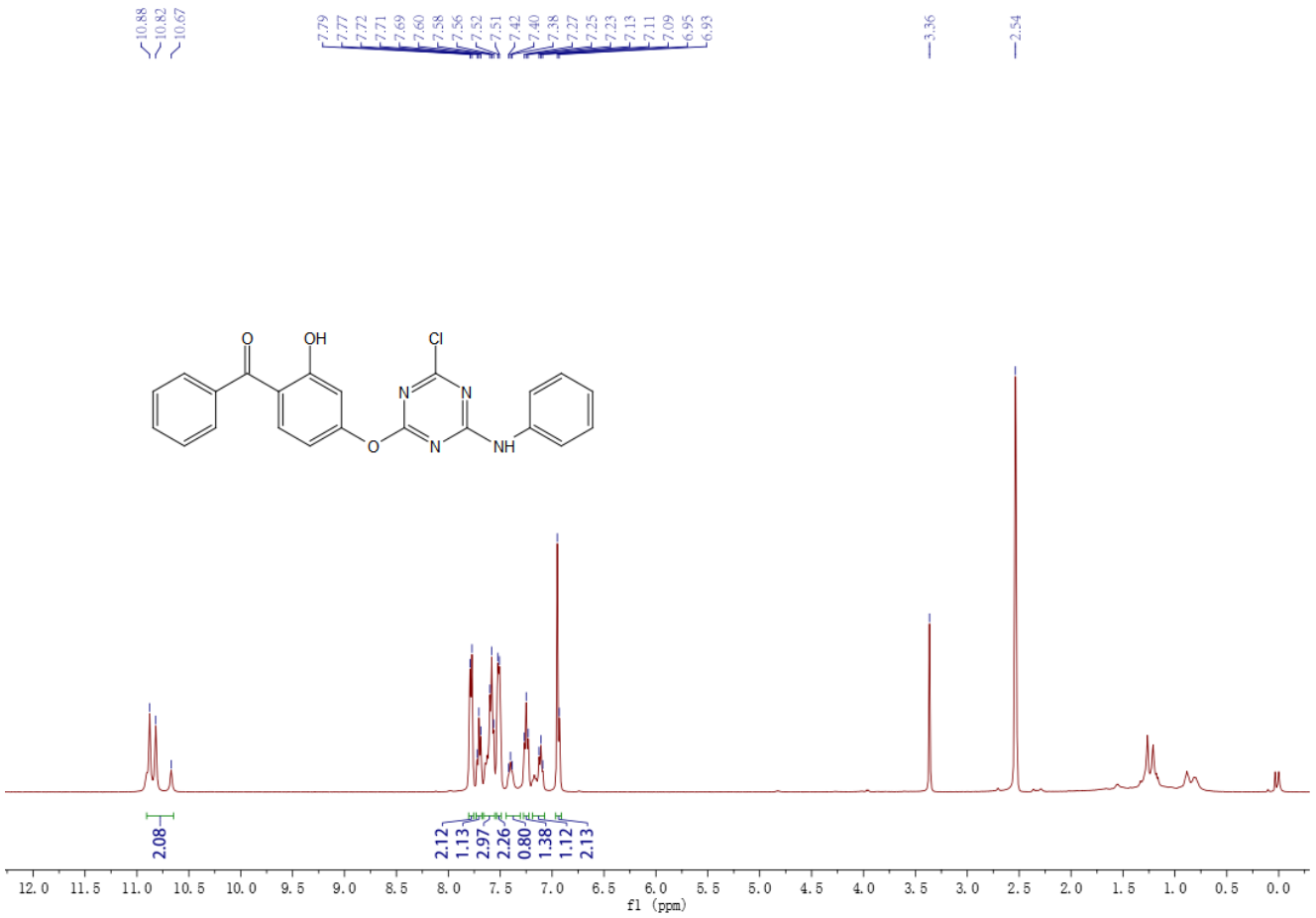


Figure S18-1 ^{1}H-NMR spectrum of compound **3m**

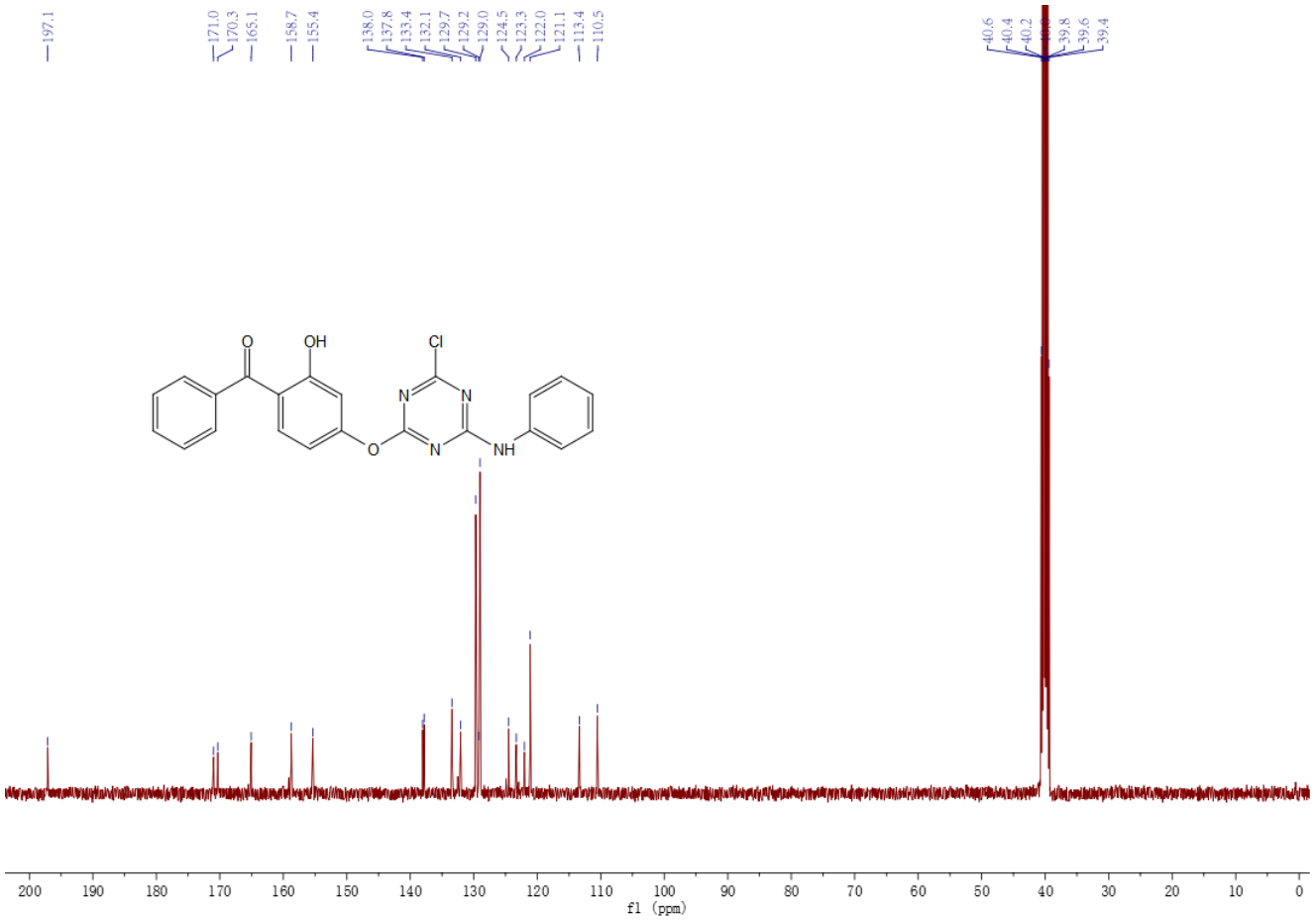


Figure S18-2 ^{13}C-NMR spectrum of compound **3m**

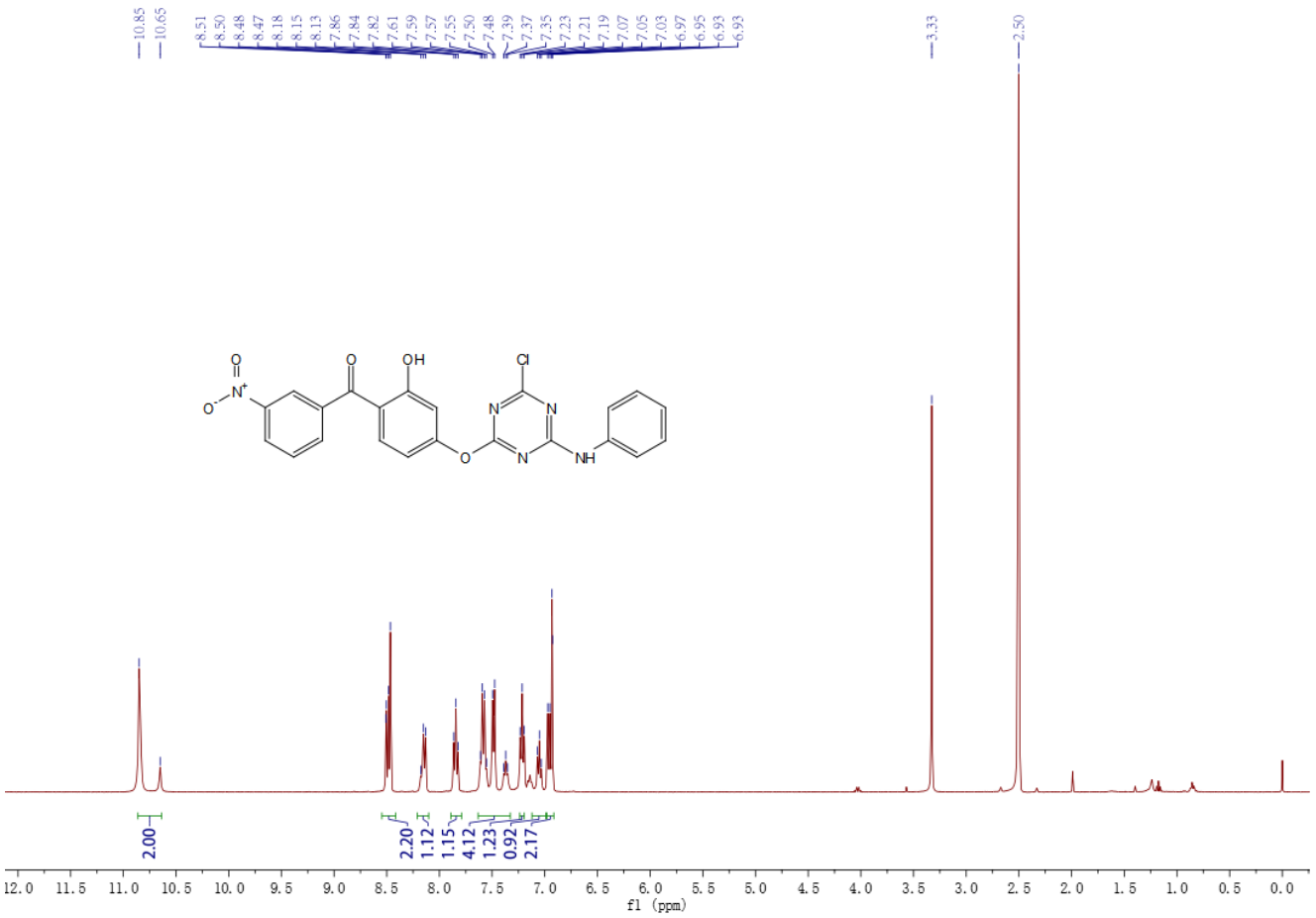


Figure S19-1 ^{1}H-NMR spectrum of compound **3n**

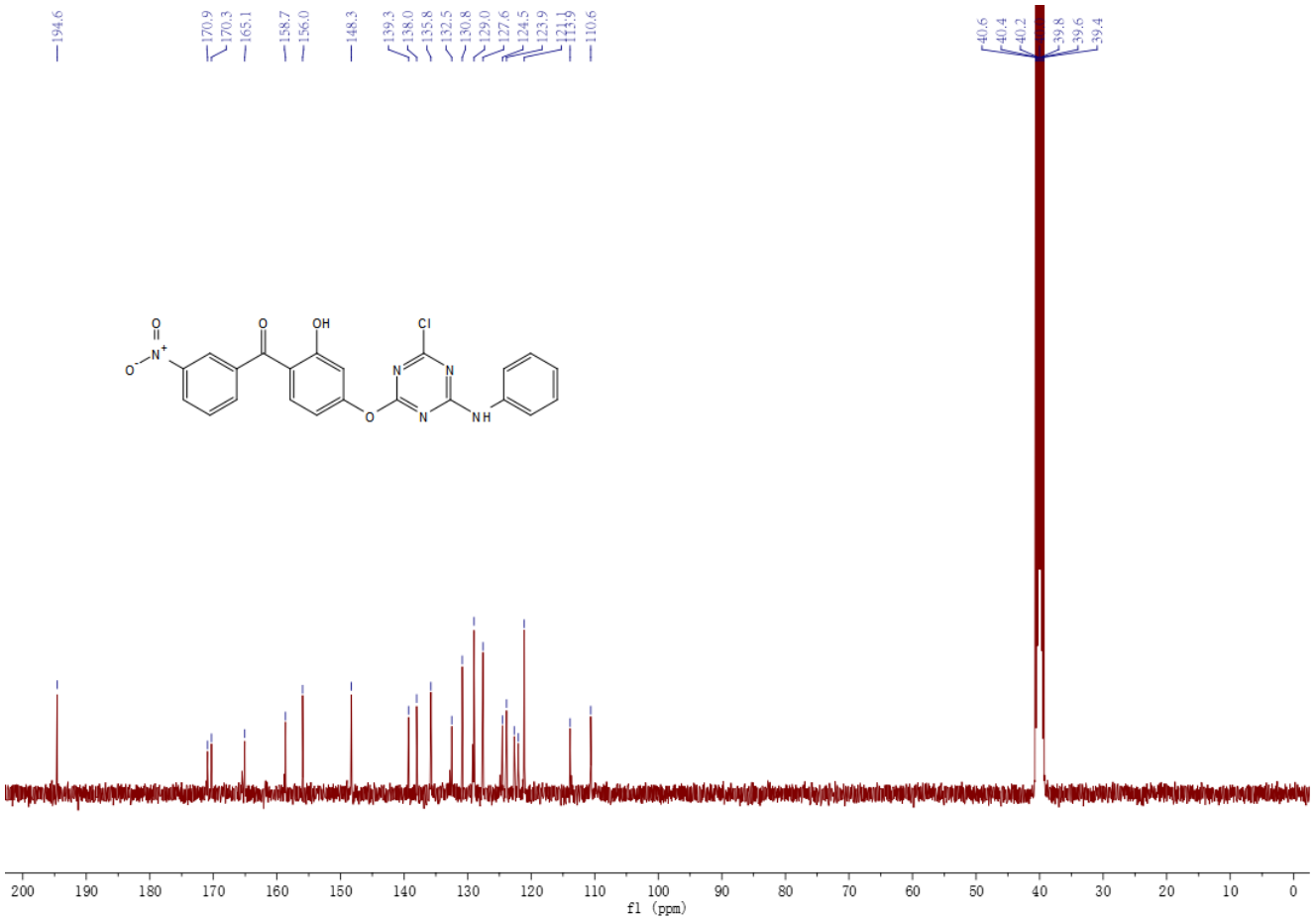


Figure S19-2 ^{13}C-NMR spectrum of compound **3n**

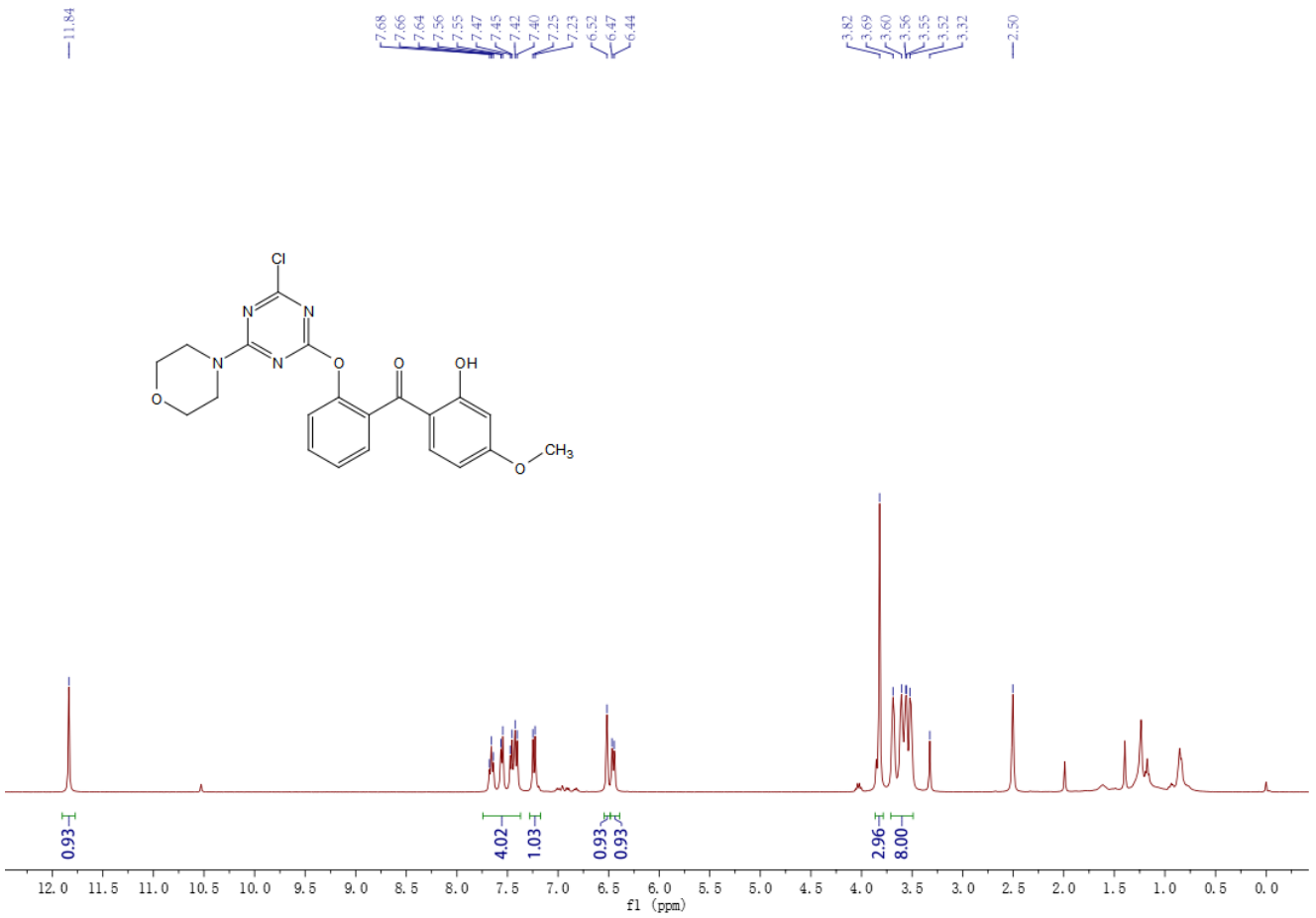


Figure S20-1 ^{1}H-NMR spectrum of compound **4a**

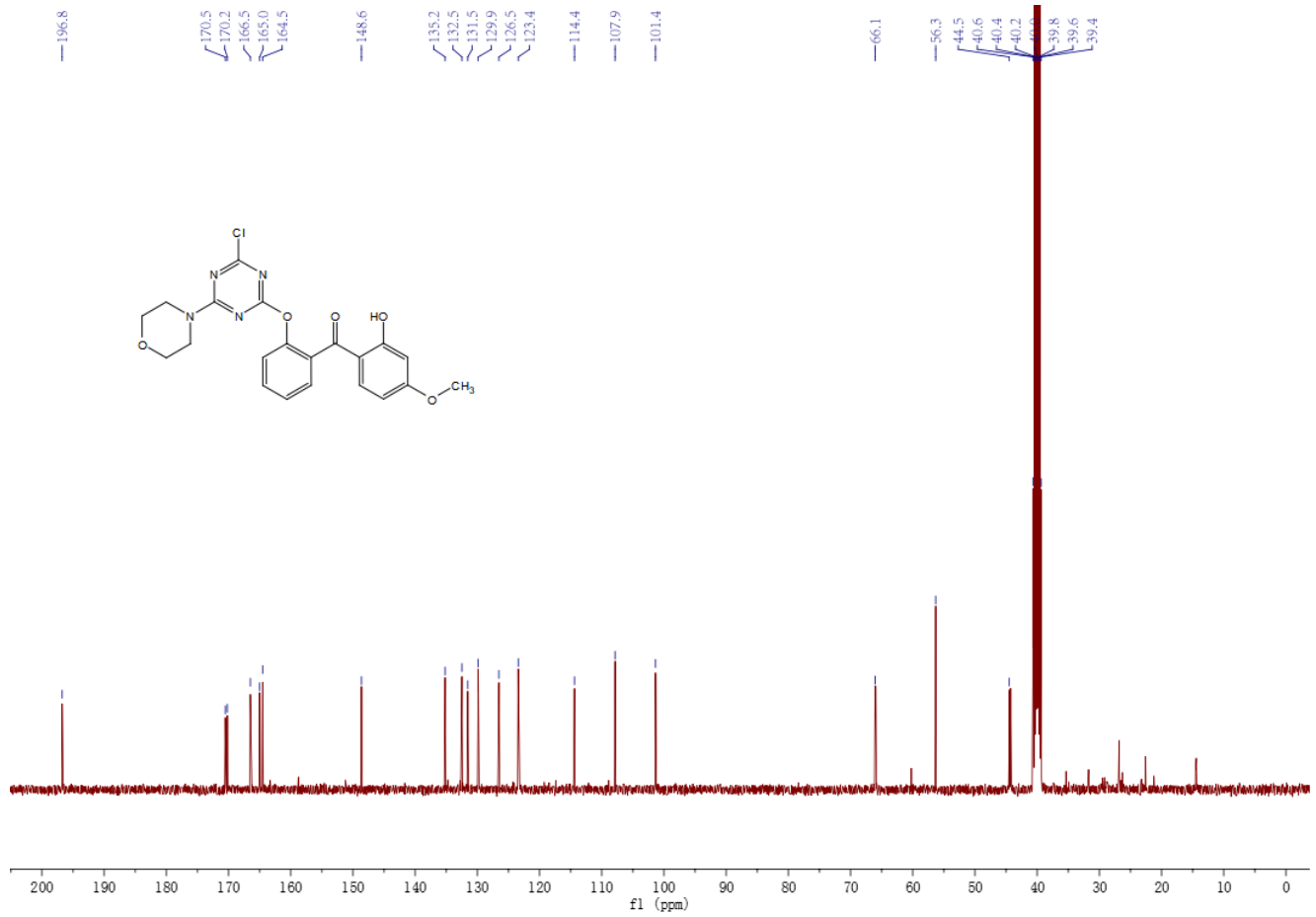


Figure S20-2 ^{13}C-NMR spectrum of compound **4a**

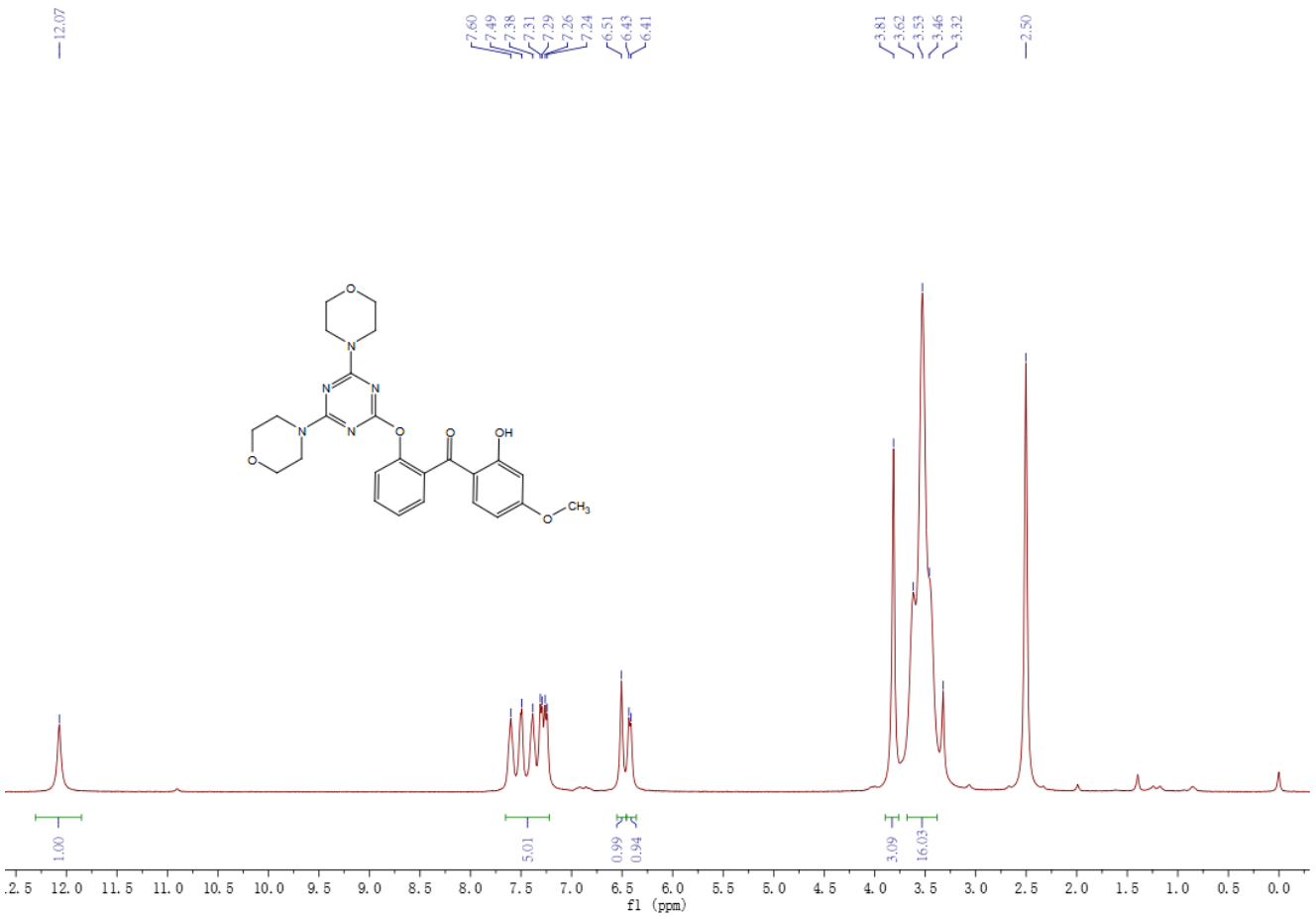


Figure S21-1 ^{1}H-NMR spectrum of compound **4b**

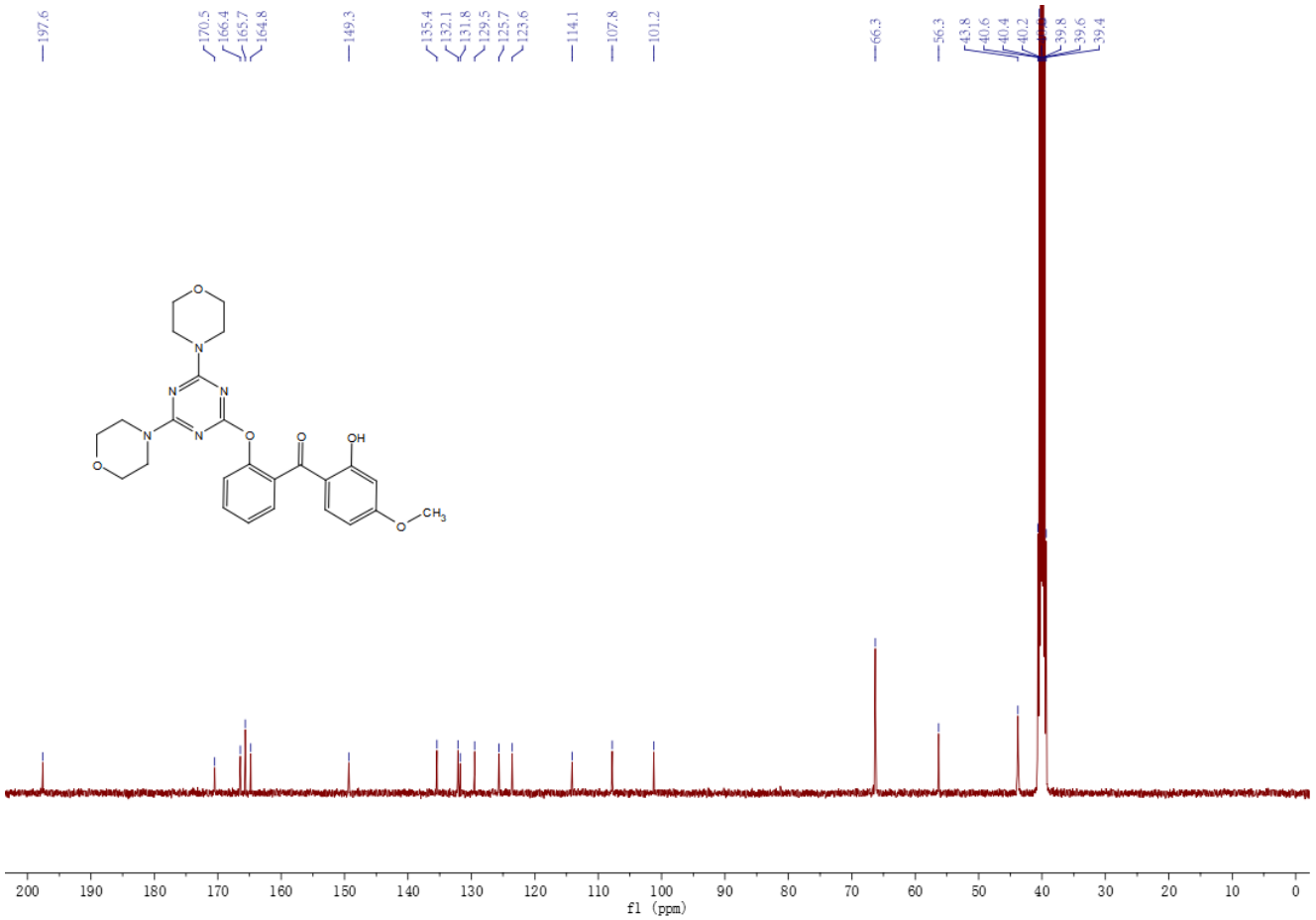


Figure S21-2 ^{13}C-NMR spectrum of compound **4b**

MTT test

Based on the methyl thiazolyl tetrazolium (MTT) method, Cisplatin was used as the positive control. The *in vitro* anti-proliferative activity of the designed and synthesized novel *s*-triazine derivatives against human non-small cell lung cancer cells (A549), cervical cancer cells (Hela), human breast cancer epithelial cells (MCF-7), and human colon cancer cells (SW620) was tested. The absorbance value (OD value) was measured at 490 nm wavelength by microplate reader. The cell growth inhibition rate and IC_{50} value were calculated by OD value.

Operation method: The compounds to be tested and the positive control were accurately weighed, dissolved in 0.5 mL DMSO and diluted with medium to prepare solutions with concentrations of 40 μmol/L, 20 μmol/L, 10 μmol/L, 5 μmol/L and 2.5 μmol/L, respectively. A549, Hela, MCF-7, SW620 cells in logarithmic growth phase were collected, digested and counted, and inoculated into 96-well plates at a cell density of 4×103 cells/well, 100 μL per well, and 100 μL of paraformaldehyde (PBS) was added to the edge hole. Incubation in a 37 °C, 5 % CO_2 incubator for 12 h. After the adherent cells were completed, the culture medium in the original hole was sucked away, and 100 μL of the solution to be tested was added to each hole, and 4 duplicate holes were set for each concentration. The blank group was added with 100 μL of medium containing 0.1 % DMSO, and the positive control group was added with 100 μL of Cisplatin solution, and continued to be cultured for 24 h. Each well was added with 20 μL MTT (5 mg/mL, dissolved in PBS). After 4h, the supernatant was removed, and 150 μL DMSO was added to each well. The formed formazan crystal was completely dissolved by shaking for 15 min at room temperature. The absorbance value (OD value) was measured at 490 nm wavelength with a microplate reader. The cell growth inhibition rate and IC_{50} value were calculated by OD value.

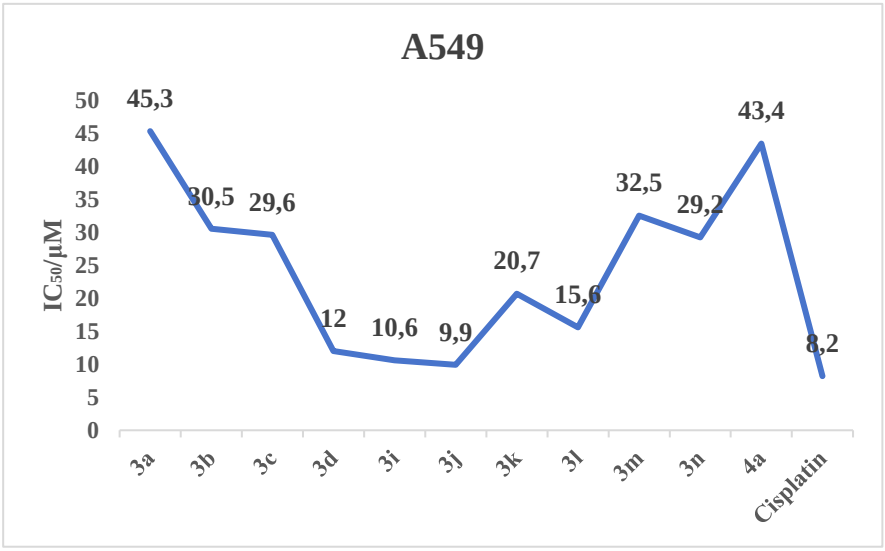
$$Growth\ inhibition\ \%=\left(1-\frac{OD(experimental\ \ group)-OD(blank\ \ control\ \ group)}{OD(normal\ \ contral\ \ group)-OD(blank\ \ control\ \ group)}\right)\times 100\%$$

Triazine is monosubstituted

3a 3b 3c 3d 3e 3i 3j 3k 3l 3m 3n 4a

3f 3g 3h 4b

Triazine is doubly substituted



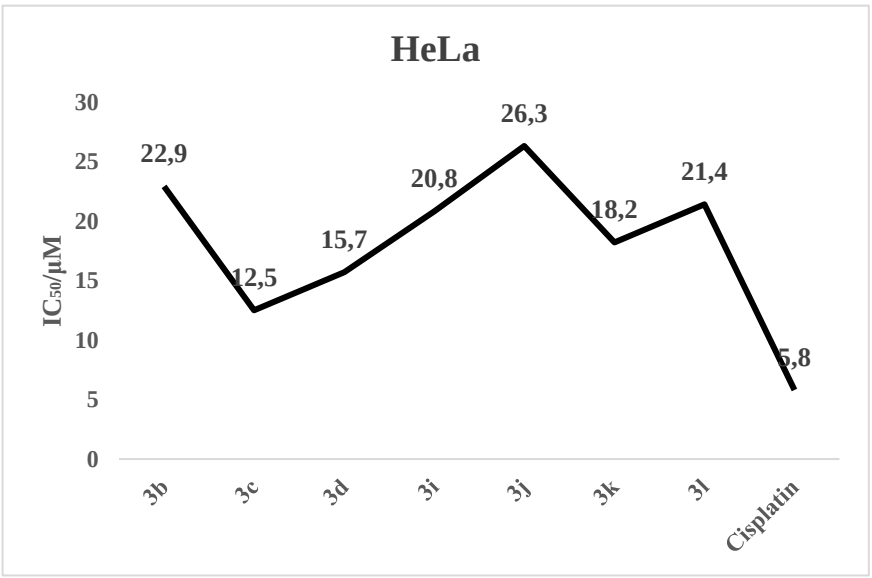


Figure S22 Comparison of growth inhibition of new *s*-triazine – 2-hydroxybenzophenone hybrids on various tumor cell lines

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