Supporting Information for

Highly Efficient Synthesis of Cinnamamides from Methyl Cinnamates and Phenylethylamines Catalyzed by Lipozyme® TL IM under Continuous-Flow Microreactors

Li-Hua Du[1,*], Ling-Yan Zheng[1], Yue Pan[1], Zhi-Kai Sheng[1], Shi-Yi Zhang[1], Hang Lin[1], Ao-Ying Zhang[1], Han-Jia Xie[1] and Xi-Ping Luo[2,*]

[a]*College of Pharmaceutical Science, ZheJiang University of Technology, Zhejiang,Hangzhou, 310014, People's Republic of China*
[b]*Deparment of Environmental Science and Technology, Zhejiang A&F University, Zhejiang, Hangzhou, 311300, China*
[*] Corresponding author. Fax: +86 18969069399. E-mail: orgdlh@zjut.edu.cn; orgdlh@gmail.com; luoxiping@zafu.edu.cn

Materials

Unless otherwise stated, all chemicals were obtained from commercial sources and used without further purification. Lipozyme® TL IM from *Thermomyces lanuginosus* was purchased from Novo Nordisk. Methyl cinnamate, 5-methoxytryptamine was purchased from Shanghai bide Pharmaceutical Technology Co., Ltd. Methyl trans-p-Coumarate, tyramine was obtained from Aladdin. Methyl ferulat, phenylethylamine was obtained from Innochem. Methyl 4-chlorocinnamate was purchased from Macklin. Tryptamine was purchased from Rhawn. Harvard Apparatus PHD 2000 syringe pumps were purchased from Harvard.

Experimental setup

A continuous-flow microreactor device which was used for synthesis of cinnamamides from methyl cinnamates and phenylethylamines catalyzed by Lipozyme® TL IM from *Thermomyces lanuginosus* in figure S1. The device was composed of a syringe pump, syringes, a Y-shaped mixer, a reactor and a product collector. A syringe pump (Harvard Apparatus PHD 2000) was used to feed liquid reagents through two syringes connected to PFA tubings (2 mm I. D.), Reagent feed A (10 mL) with the methyl cinnamate derivatives in *tert*-amyl alcohol solution and reagent feed B (10 mL) with amine compounds in *tert*-amyl alcohol solution were fully mixed in Y-shaped mixer (Φ=1.8 mm;M). The reactor consists of a 100cm PFA tubing with an inner volume of 3.1 mL. The reactor was coiled which were filled with lipozyme® TL IM (catalyst reactivity: 250 IUN. g^{-1}) and submerged into a thermostatic water bath to control the temperature. Feed A and B were mixed together at a flow rate of 7.8 μL min^{-1} in a Y-mixer at 45°C and the resulting stream (15.6 μL min^{-1}) was connected to a sample vial which was used to collect the final mixture.

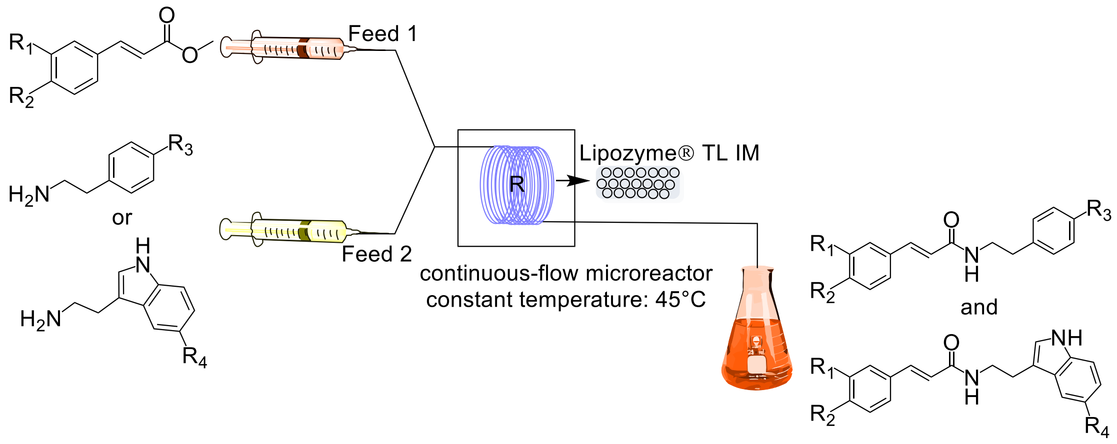


Figure S1. Equipment for the synthesis of cinnamamides from methyl cinnamates and phenylethylamines catalyzed by Lipozyme® TL IM under continuous-flow microreactors

General Procedure for the synthesis of cinnamamides from methyl cinnamates and phenylethylamines catalyzed by Lipozyme® TL IM under Continuous-Flow Microreactors

Method A: 5.0 mmol of the methyl cinnamate derivatives was dissolved in 10 mL *tert*-amyl alcohol (feed A, ~0.5 M) and 10.0 mmol amine compounds were dissolved in 10 mL *tert*-amyl alcohol (feed B; ~1.0 M). Lipozyme TL IM (0.87 g) were filled in PFA reactor coil (inner diameter ID= 2.0 mm, length = 100cm.). Streams A and B were mixed together at a flow rate of 7.8 μL min^{-1} in a Y-mixer at 45 °C and the resulting stream (15.6 μL min^{-1}) was connected to a sample vial which was used to collect the final mixture. The final mixture was then evaporated, and the residue was submitted to column chromatography on silica gel (200-300 mesh). The crude product was purified by silica gel column chromatography with a petroleum ether / ethyl acetate gradient from 10:1 to 2:1. The purification was monitored by TLC. The fractions containing the main products were pooled, the solvent evaporated, and the residue analyzed by ^{1}H NMR, and ^{13}C NMR.

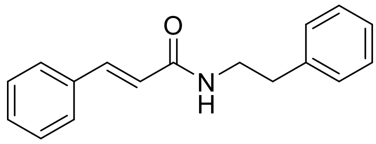
General Procedure for the synthesis of cinnamamides from methyl cinnamates and phenylethylamines catalyzed by Lipozyme® TL IM under Shaker Conditions

Method B: methyl cinnamate derivatives (5.0 mmol) and amine compounds (10.0 mmol) were added to 20 mL *tert*-amyl alcohol. The biocatalyst lipozyme TL IM (43.5 mg·mL^{-1}, 0.87 g) was then added and the suspension maintained at 45 °C for 24 h under Shaker Conditions (200 r·min^{-1}). The mixture was cooled and filtered. Then evaporated under reduced pressure and the residue was submitted to column chromatography on silica gel (200– 300 mesh). The crude product was purified by silica gel column chromatography with a petroleum ether /ethyl acetate gradient from 10:1 to 2:1. The purification was monitored by TLC. The fractions containing the main products were pooled, the solvent evaporated, and the residue analyzed by ^{1}H NMR, and ^{13}C NMR.

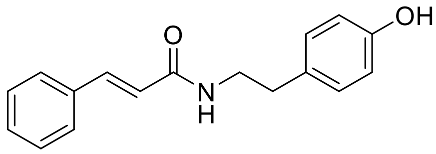
Thin-Layer Chromatography

Analytical TLC was performed on silica gel 60 plates (Merck) using petroleum ether / ethyl acetate from 6/1 (v/v) to 1/1 (v/v) as developing solvent. Spots weredetected by ultraviolet irradiation at 254 nm.

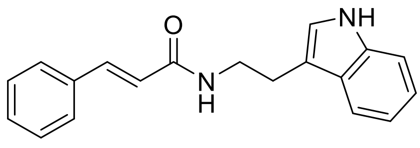
Characterization data for products



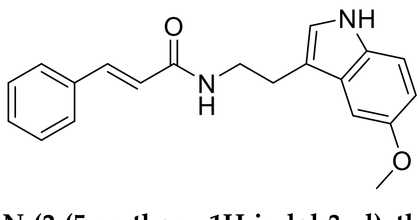
N-phenethylcinnamamide (3a)[1]. White power. ^{1}**H NMR** (400 MHz, DMSO-d_6) δ 8.21 (t, *J* = 5.6 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.43 – 7.14 (m, 9H), 6.59 (d, *J* = 15.9 Hz, 1H), 3.40 – 3.27 (m, 2H), 2.76 (t, *J* = 7.3 Hz, 2H).; ^{13}**C NMR** (101 MHz, DMSO) δ 165.16, 139.62, 138.82, 135.04, 129.66, 129.14, 128.84, 128.56, 127.71, 126.33, 122.31, 40.56, 35.30.



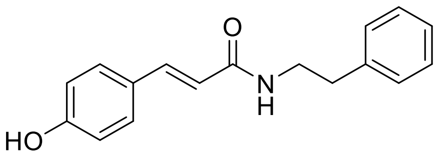
N-(4-hydroxyphenethyl)cinnamamide (3b)[2]. White powder. ^{1}**H NMR** (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.15 (t, *J* = 5.7 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.34 (m, 4H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.72 – 6.65 (m, 2H), 6.62 (d, *J* = 15.8 Hz, 1H), 3.34 – 3.32 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H).; ^{13}**C NMR** (101 MHz, DMSO) δ 165.06, 155.77, 138.65, 135.06, 129.60, 129.58, 129.46, 128.99, 127.58, 122.43, 115.27, 40.86, 34.48.



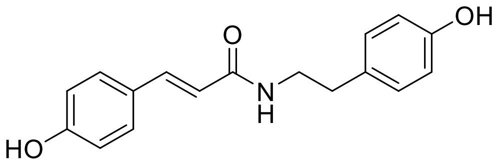
N-(2-(1H-indol-3-yl)ethyl)cinnamamide (3c)[3]. Orange yellow solid. ^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.81 – 10.77 (m, 1H), 8.20 (t, *J* = 5.7 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.44 – 7.27 (m, 5H), 7.13 (d, *J* = 2.3 Hz, 1H), 7.03 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 3.44 (td, *J* = 7.4, 5.7 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H).; ^{13}**C NMR** (101 MHz, DMSO) δ 165.01, 138.57, 136.36, 135.07, 129.50, 129.05, 127.60, 127.33, 122.79, 122.49, 121.05, 118.39, 118.35, 111.88, 111.49, 39.73, 25.35.



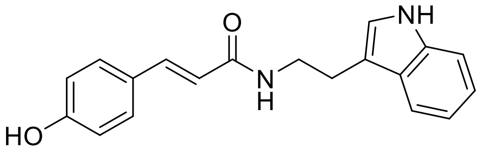
N-(2-(5-methoxy-1H-indol-3-yl)ethyl)cinnamamide (3d)[4]. Yellow powder. ^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.23 (q, *J* = 4.8, 4.2 Hz, 1H), 7.55 (ddd, *J* = 8.1, 3.4, 1.7 Hz, 2H), 7.48 – 7.34 (m, 4H), 7.25 – 7.19 (m, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.74 – 6.68 (m, 1H), 6.68 – 6.60 (m, 1H), 3.76 – 3.72 (m, 3H), 3.46 (td, *J* = 7.5, 4.2 Hz, 2H), 2.85 (td, *J* = 7.3, 2.5 Hz, 2H).; ^{13}**C NMR** (101 MHz, DMSO) δ 165.01, 153.08, 138.56, 135.07, 131.49, 129.50, 129.05, 127.67, 127.59, 123.47, 122.52, 112.13, 111.75, 111.21, 100.20, 55.39, 40.51, 25.35.



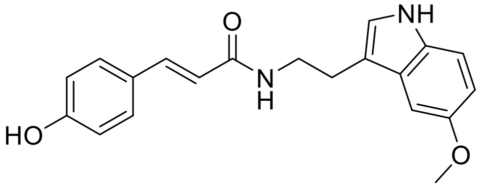
(E)-3-(4-hydroxyphenyl)-N-phenethylacrylamide **(3e)[1].** White powder**.** **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.07 (t, *J* = 5.7 Hz, 1H), 7.34 (dd, *J* = 24.1, 8.6 Hz, 3H), 7.28 – 7.17 (m, 5H), 6.80 – 6.73 (m, 2H), 6.37 (dd, *J* = 15.8, 1.1 Hz, 1H), 3.40 – 3.33 (m, 2H), 2.75 (t, *J* = 7.4 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.64, 159.00, 139.69, 138.92, 129.43, 128.83, 128.55, 126.30, 126.06, 118.76, 115.93, 40.53, 35.38.



(E)-N-(4-hydroxyphenethyl)-3-(4-hydroxyphenyl)acrylamide **(3f)[5].** White powder. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.15 (s, 1H), 7.99 (t, *J* = 5.7 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.30 (d, *J* = 15.7 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.81 – 6.74 (m, 2H), 6.71 – 6.63 (m, 2H), 6.38 (d, *J* = 15.7 Hz, 1H), 3.32 – 3.28 (m, 2H), 2.63 (t, *J* = 7.4 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.37, 158.86, 155.70, 138.63, 129.62, 129.55, 129.25, 126.01, 118.83, 115.81, 115.19, 40.75, 34.52.

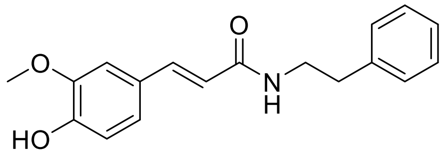


(E)-N-(2-(1H-indol-3-yl)ethyl)-3-(4-hydroxyphenyl)acrylamide **(3g)[3].** Orange yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.80 (d, *J* = 2.6 Hz, 1H), 9.82 (s, 1H), 8.08 (t, *J* = 5.8 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.40 – 7.28 (m, 4H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.05 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.96 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.40 (d, *J* = 15.8 Hz, 1H), 3.49 – 3.39 (m, 2H), 2.86 (t, *J* = 7.4 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.47, 158.89, 138.67, 136.36, 129.30, 127.34, 126.06, 122.76, 121.04, 118.93, 118.40, 118.34, 115.85, 111.95, 111.48, 39.67, 25.43.

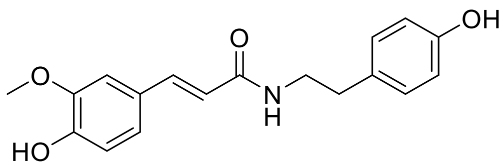


(E)-3-(4-hydroxyphenyl)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)acrylamide **(3h)[5].** Yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.64 – 10.60 (m, 1H), 9.81 (s, 1H), 8.06 (t, *J* = 5.8 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.28 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.79 – 6.72 (m, 2H), 6.67 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 3.71 (s, 3H), 3.39 (dd, *J* = 14.3, 7.6 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ

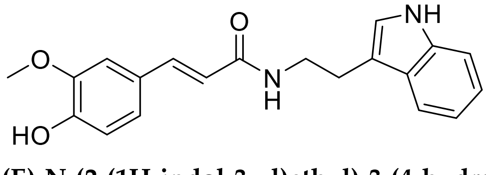
165.47, 158.87, 153.06, 138.64, 131.47, 129.27, 127.67, 126.06, 123.43, 118.96, 115.84, 112.10, 111.80, 111.19, 100.21, 55.39, 48.71, 25.42.



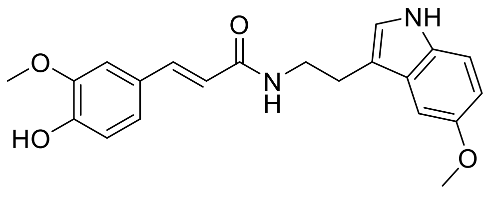
(E)-3-(4-hydroxy-3-methoxyphenyl)-N-phenethylacrylamide (3i)[6]. White solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.08 (t, *J* = 5.7 Hz, 1H), 7.37 (d, *J* = 15.7 Hz, 1H), 7.33 – 7.16 (m, 5H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 15.7 Hz, 1H), 3.81 (s, 3H), 3.47 – 3.40 (m, 2H), 2.79 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.62, 148.43, 147.98, 139.66, 139.19, 128.78, 128.48, 126.58, 126.23, 121.72, 119.09, 115.82, 110.90, 55.65, 40.49, 35.38.



(E)-3-(4-hydroxy-3-methoxyphenyl)-N-(4-hydroxyphenethyl)acrylamide (3j)[5]. White powder. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.13 (s, 1H), 7.94 (t, *J* = 5.7 Hz, 1H), 7.26 (d, *J* = 15.7 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.94 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.68 – 6.60 (m, 2H), 6.38 (d, *J* = 15.7 Hz, 1H), 3.76 (s, 3H), 3.28 (s, 2H), 2.60 (t, *J* = 7.4 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.85, 156.08, 148.72, 148.31, 139.37, 130.02, 129.92, 126.94, 121.99, 119.53, 116.15, 115.60, 111.31, 56.04, 41.12, 34.88.

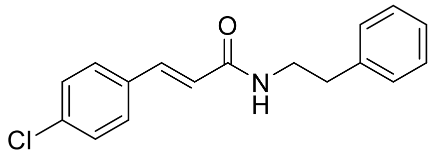


(E)-N-(2-(1H-indol-3-yl)ethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (3k)[1]. Orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.85 – 10.80 (m, 1H), 9.44 (s, 1H), 8.07 (t, *J* = 5.7 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.23 (m, 2H), 7.42 – 6.94 (m, 5H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 3.80 (s, 3H), 3.52 – 3.42 (m, 2H), 2.88 (t, *J* = 7.4 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.44, 148.31, 147.91, 138.95, 136.35, 127.33, 126.54, 122.75, 121.60, 121.03, 119.22, 118.38, 118.33, 115.73, 111.92, 111.47, 110.80, 55.60, 40.01, 25.40.

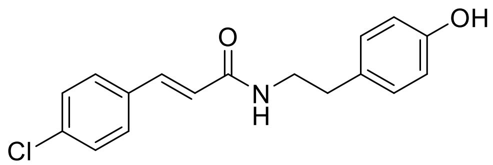


(E)-3-(4-hydroxy-3-methoxyphenyl)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)acrylamide (3l). Orange solid **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.64 – 10.60 (m, 1H), 9.40 (s, 1H), 8.04 (t, *J* = 5.7

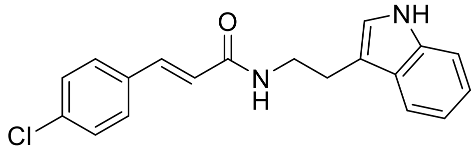
Hz, 1H), 7.30 (d, *J* = 15.6 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.08 (t, *J* = 2.7 Hz, 2H), 7.03 – 6.92 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.41 (q, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 165.48, 153.07, 148.31, 147.92, 138.94, 131.49, 127.69, 126.56, 123.44, 121.58, 119.26, 115.75, 112.11, 111.80, 111.19, 110.82, 100.23, 55.62, 55.41, 48.72, 25.42.



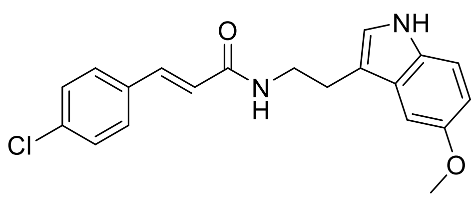
(E)-3-(4-chlorophenyl)-N-phenethylacrylamide (3m)[7]. White solid, **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 8.18 (t, *J* = 5.7 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.46 – 7.41 (m, 2H), 7.36 (d, *J* = 15.8 Hz, 1H), 7.30 – 7.13 (m, 5H), 6.58 (d, *J* = 15.8 Hz, 1H), 3.42 – 3.34 (m, 2H), 2.74 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 164.82, 139.53, 137.33, 133.99, 133.93, 129.33, 129.08, 128.75, 128.47, 126.24, 123.12, 40.47, 35.21.



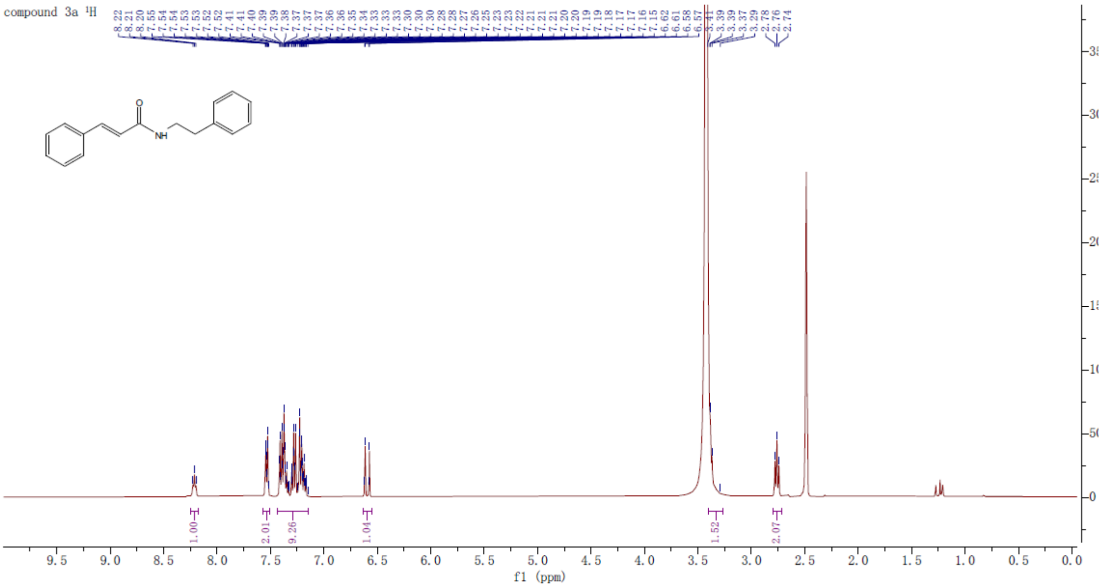
(E)-3-(4-chlorophenyl)-N-(4-hydroxyphenethyl)acrylamide (3n)[2]. White powder. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.18 (s, 1H), 8.16 (t, *J* = 5.7 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.50 – 7.42 (m, 2H), 7.38 (d, *J* = 15.8 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.71 – 6.63 (m, 2H), 6.61 (d, *J* = 15.8 Hz, 1H), 3.36 (s, 2H), 2.64 (t, *J* = 7.4 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 164.75, 155.76, 137.25, 134.01, 133.91, 129.60, 129.54, 129.32, 129.07, 123.19, 115.23, 40.83, 34.43.

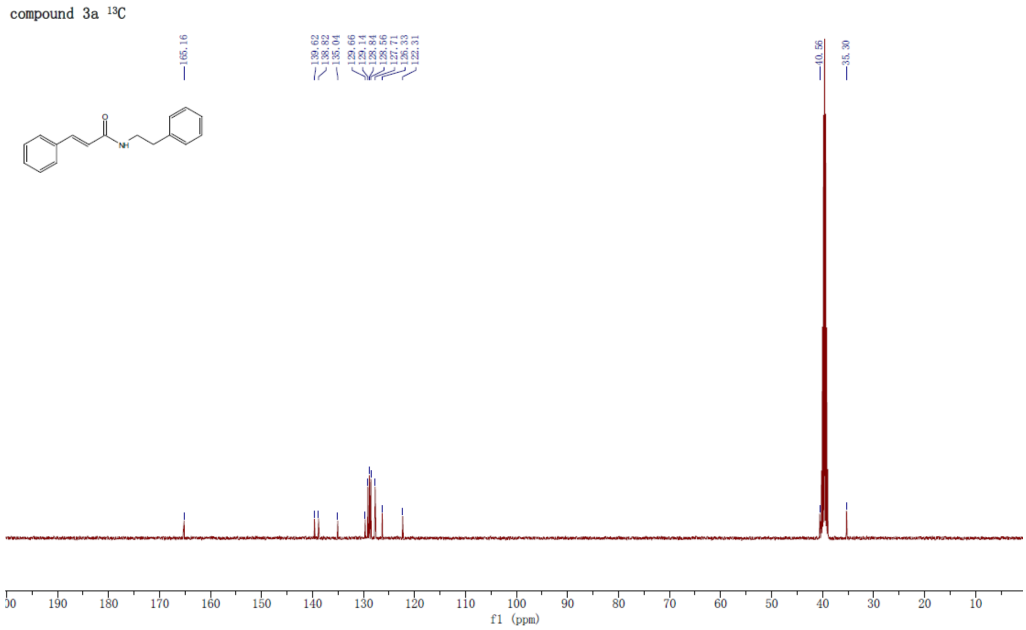


(E)-N-(2-(1H-indol-3-yl)ethyl)-3-(4-chlorophenyl)acrylamide (3o). Yellow solid. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 10.83 – 10.77 (m, 1H), 8.22 (t, *J* = 5.8 Hz, 1H), 7.55 (dd, *J* = 11.4, 8.2 Hz, 3H), 7.49 – 7.44 (m, 2H), 7.40 (d, *J* = 15.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.05 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.96 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 3.50 – 3.41 (m, 2H), 2.87 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 164.77, 137.20, 136.34, 134.04, 133.87, 129.28, 129.05, 127.30, 123.30, 122.77, 121.02, 118.36, 118.33, 111.83, 111.46, 39.71, 25.29.

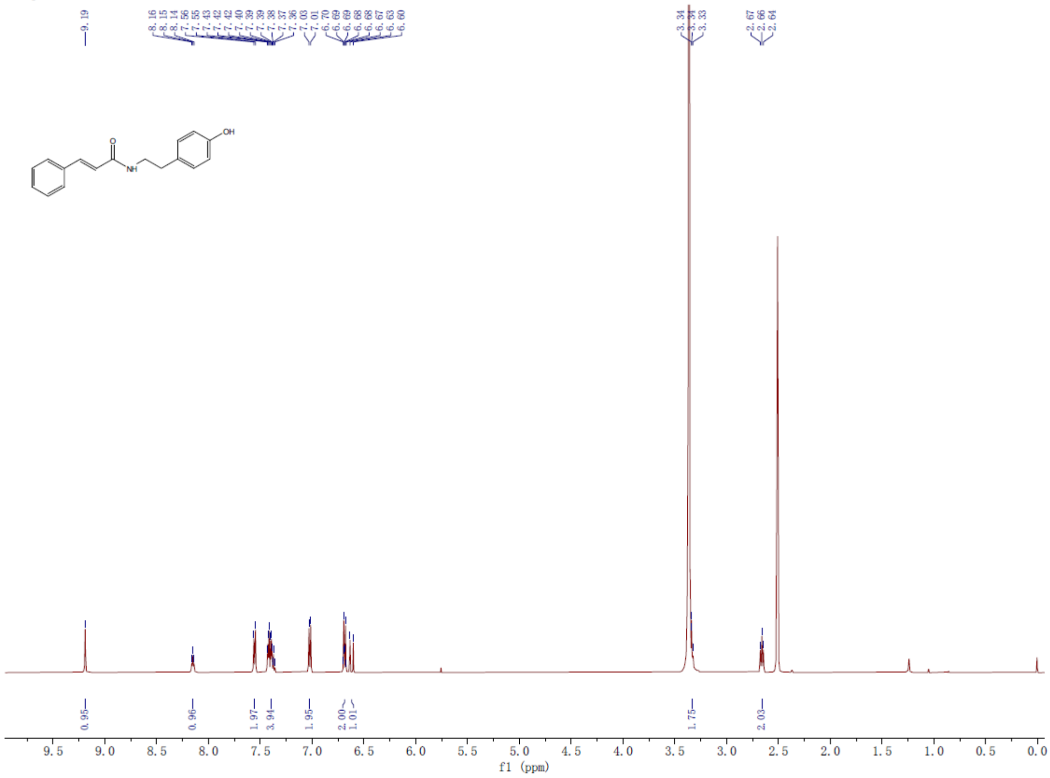


(E)-3-(4-chlorophenyl)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)acrylamide (3p)[8]. Yellow powder. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 10.62 (d, *J* = 2.3 Hz, 1H), 8.21 (t, *J* = 5.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.48 – 7.42 (m, 2H), 7.39 (d, *J* = 15.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 3.71 (s, 3H), 3.43 (q, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR** (101 MHz, DMSO) δ 164.81, 153.08, 137.21, 134.04, 133.89, 131.49, 129.29, 129.07, 127.66, 123.46, 123.32, 112.12, 111.71, 111.20, 100.22, 55.40, 40.02, 25.31.

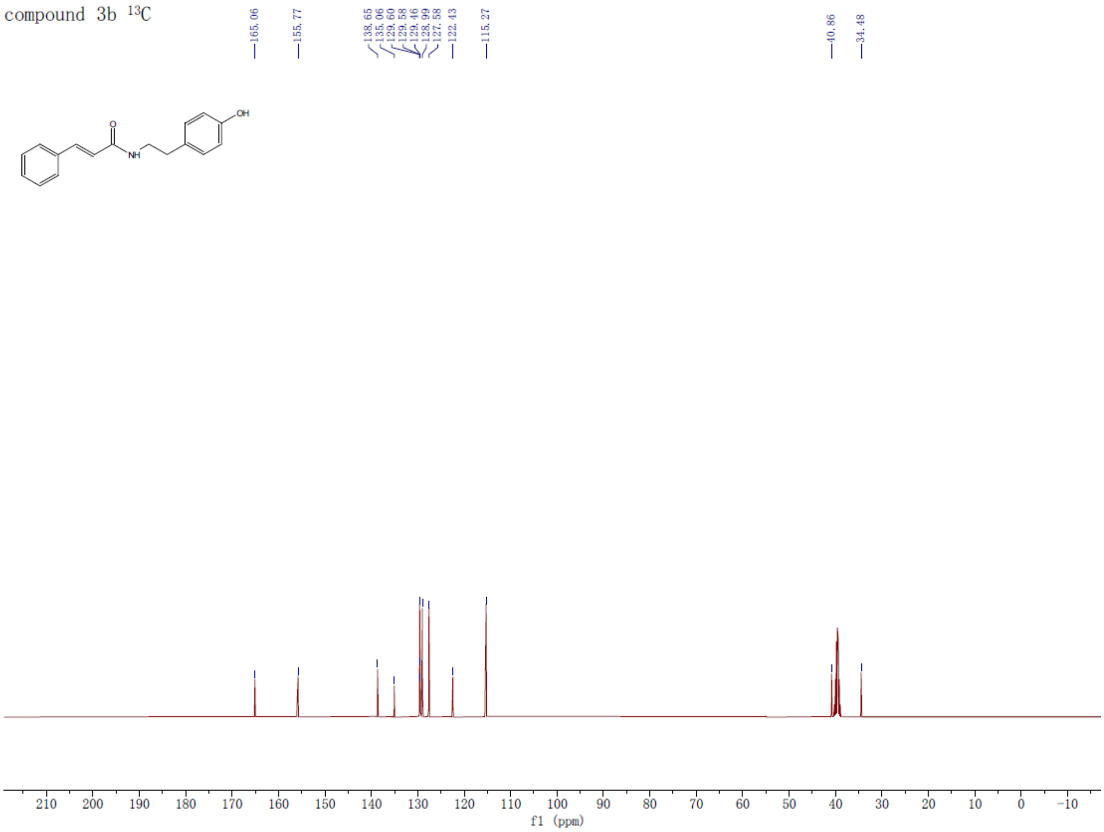


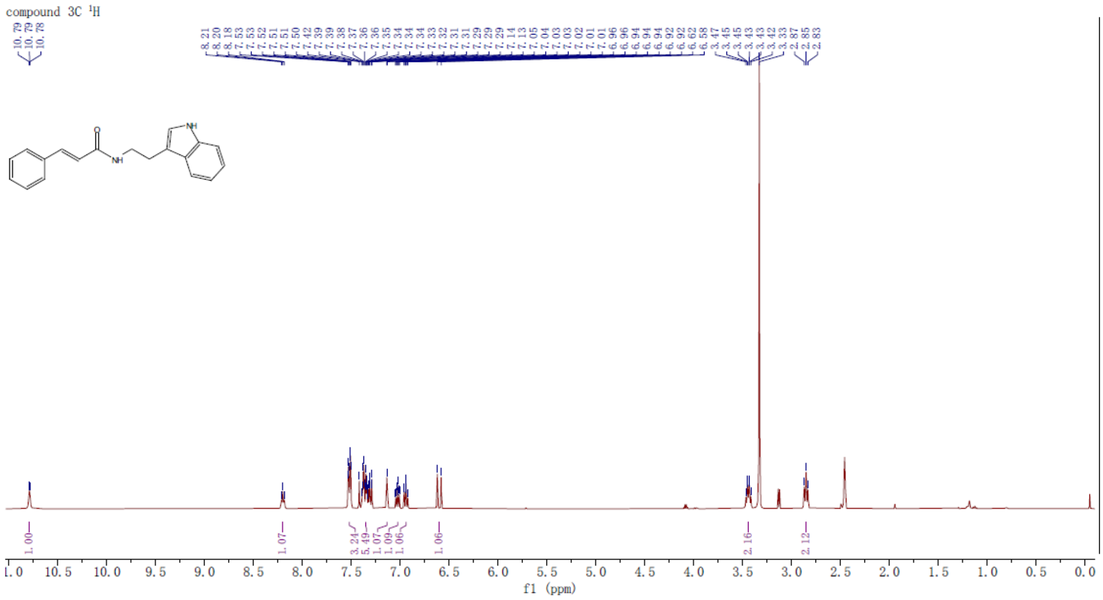


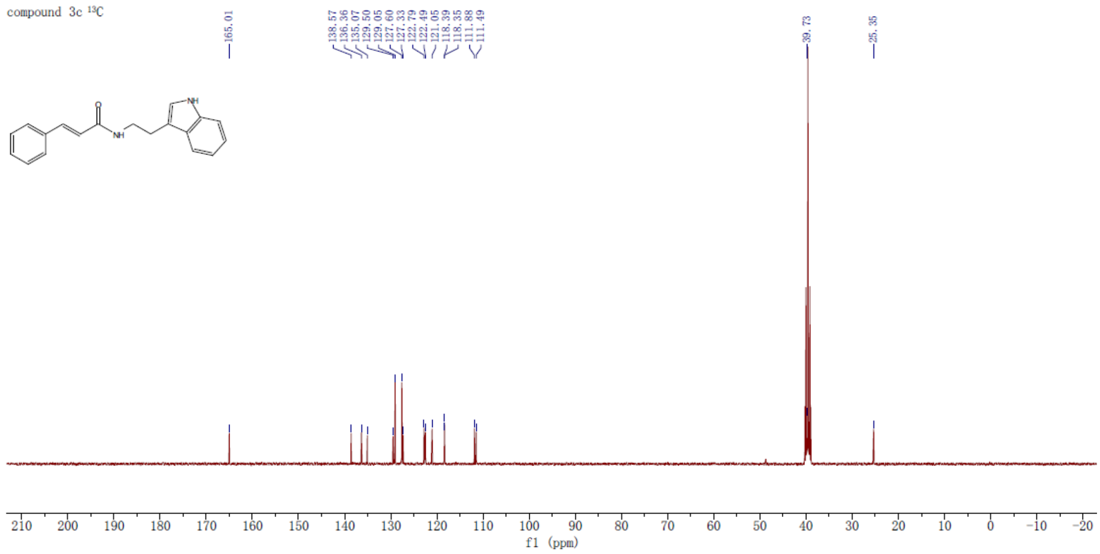
compound 3b ^{1}H



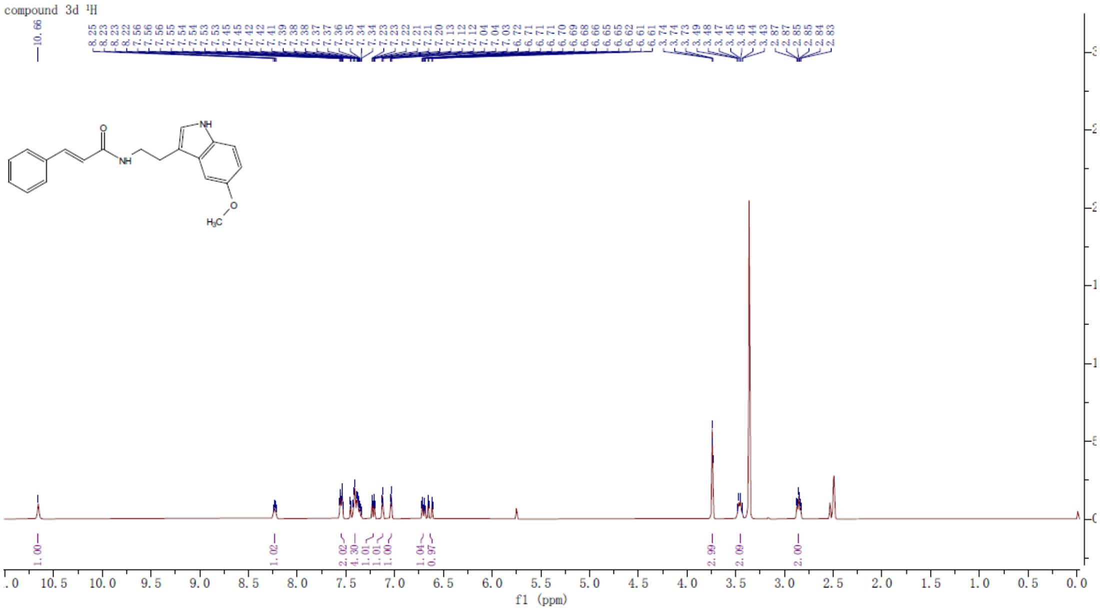
compound 3b ^{13}C



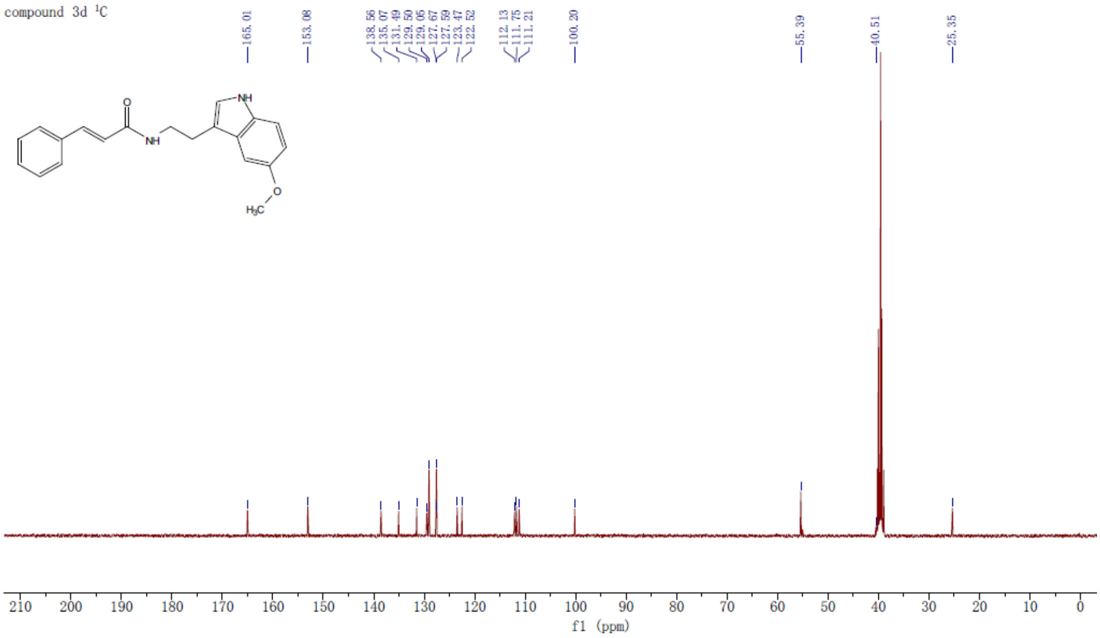

compound 3C ¹H
f1 (ppm)


compound 3c ¹³C
f1 (ppm)

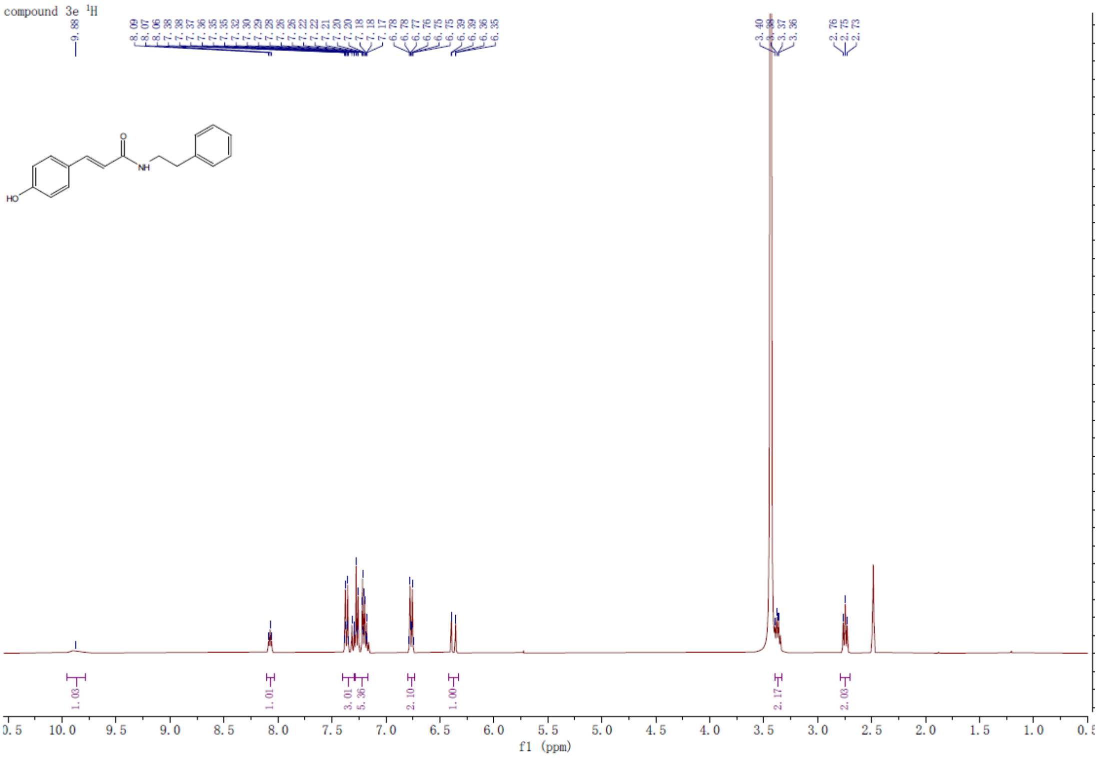
compound 3d ^{1}H



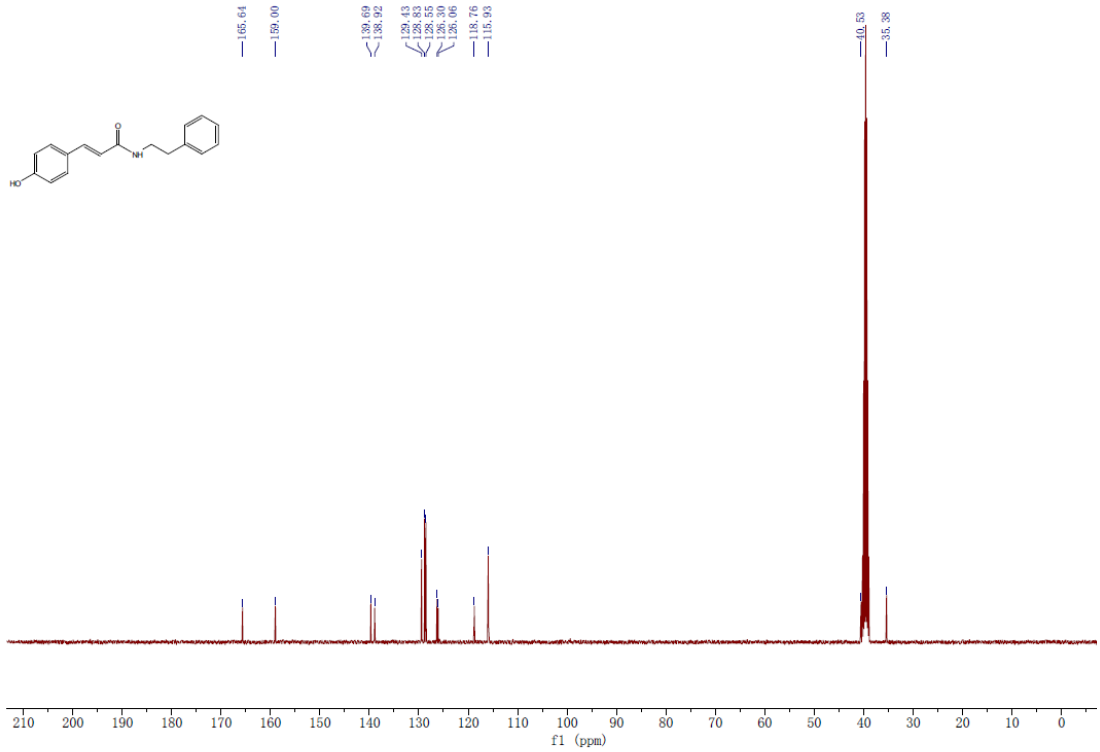
compound 3d ^{13}C



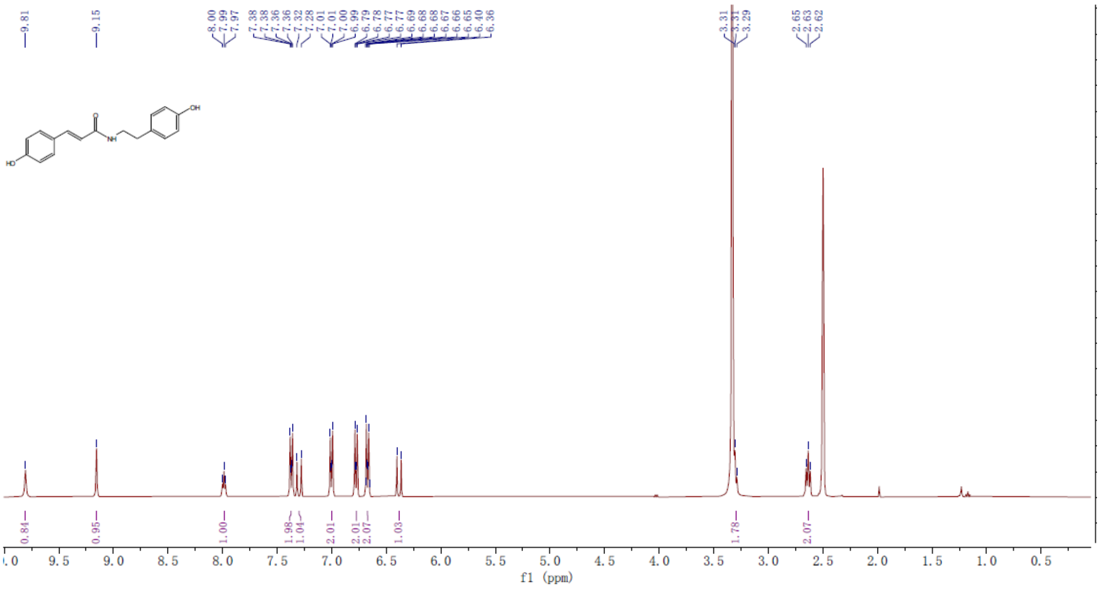
compound 3e ^{1}H



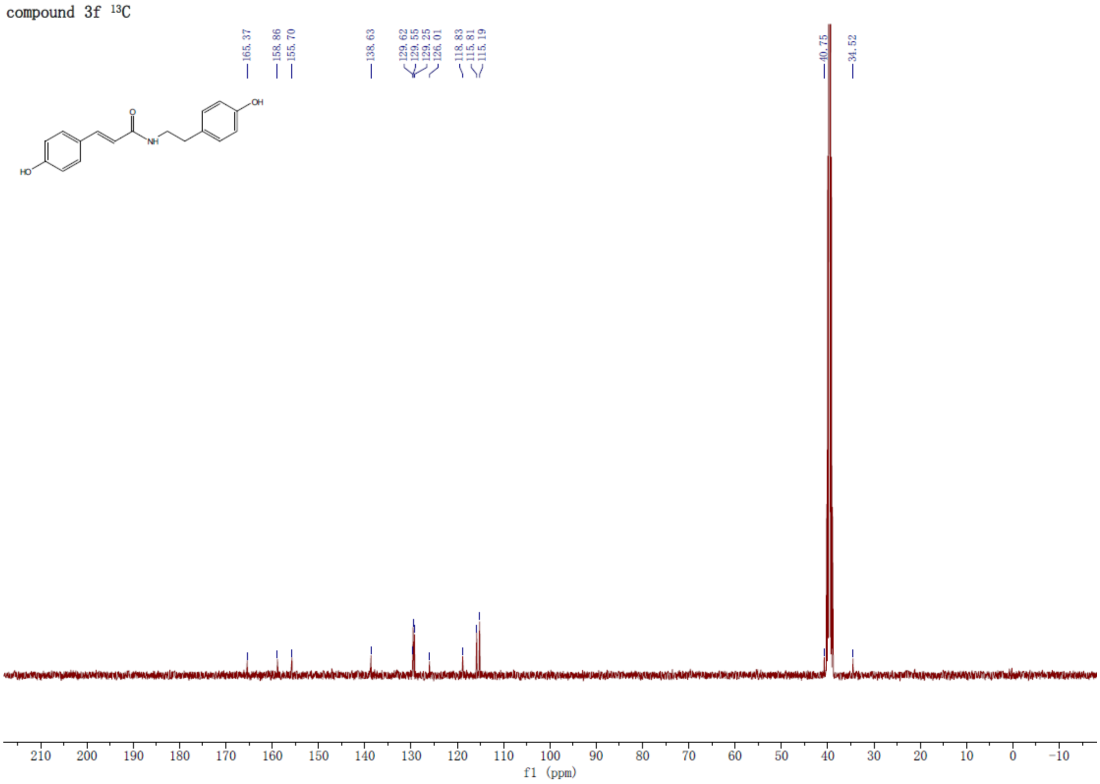
compound 3e ^{13}C



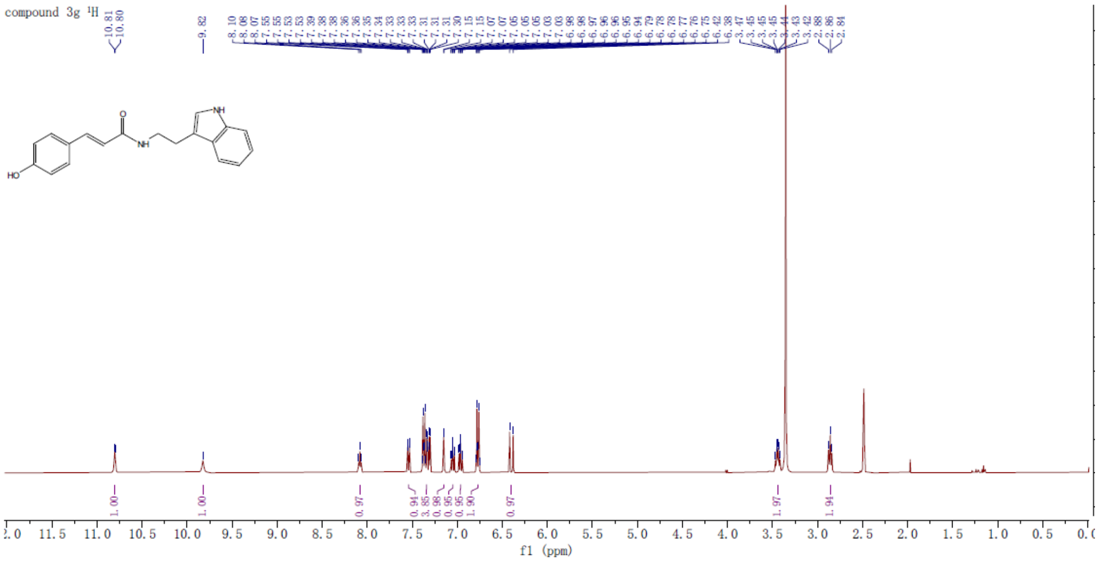
compound 3f ^{1}H



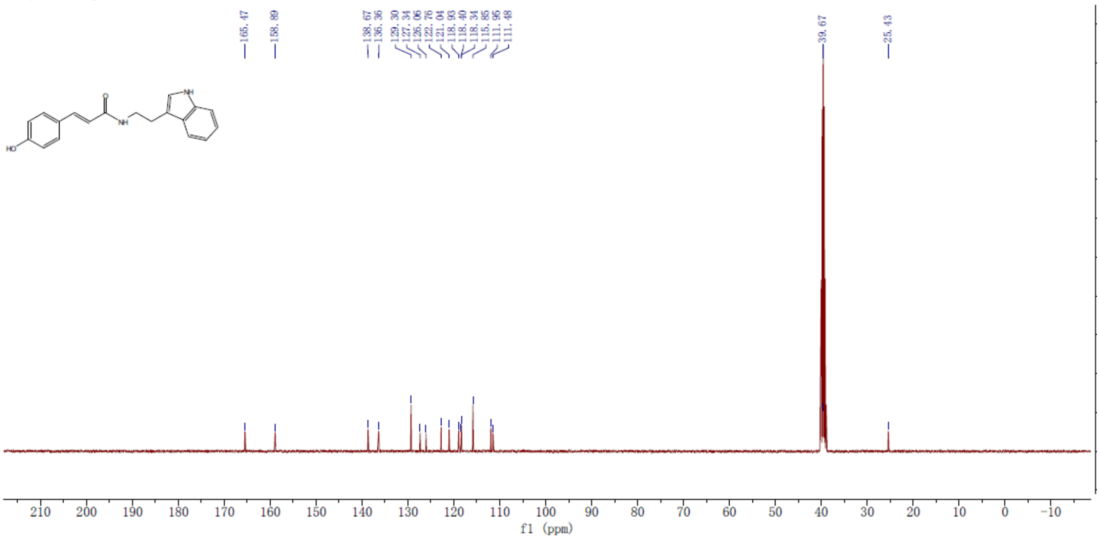
compound 3f ^{13}C



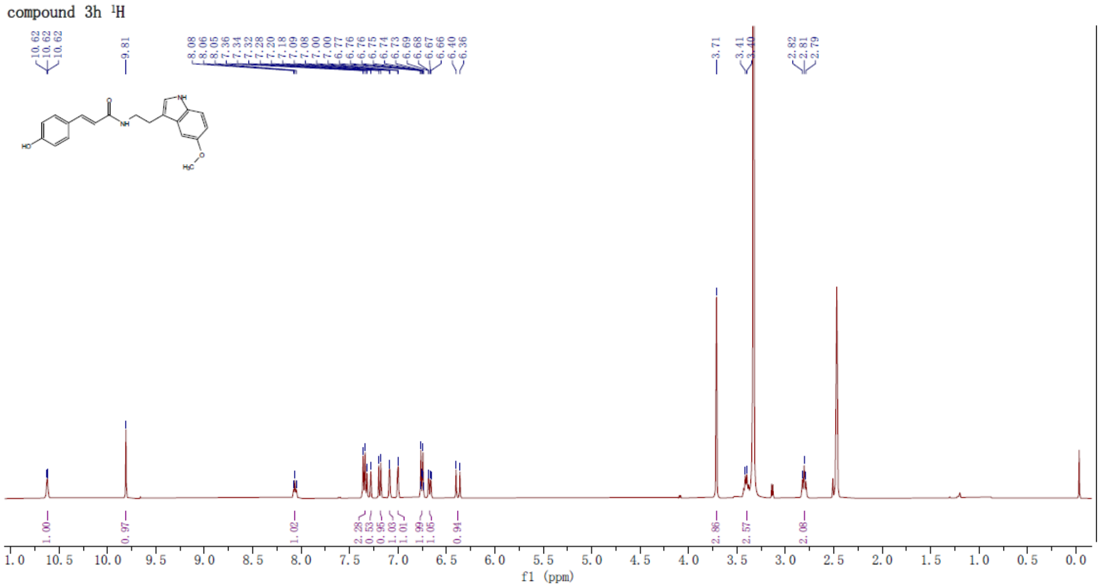
compound 3g ¹H



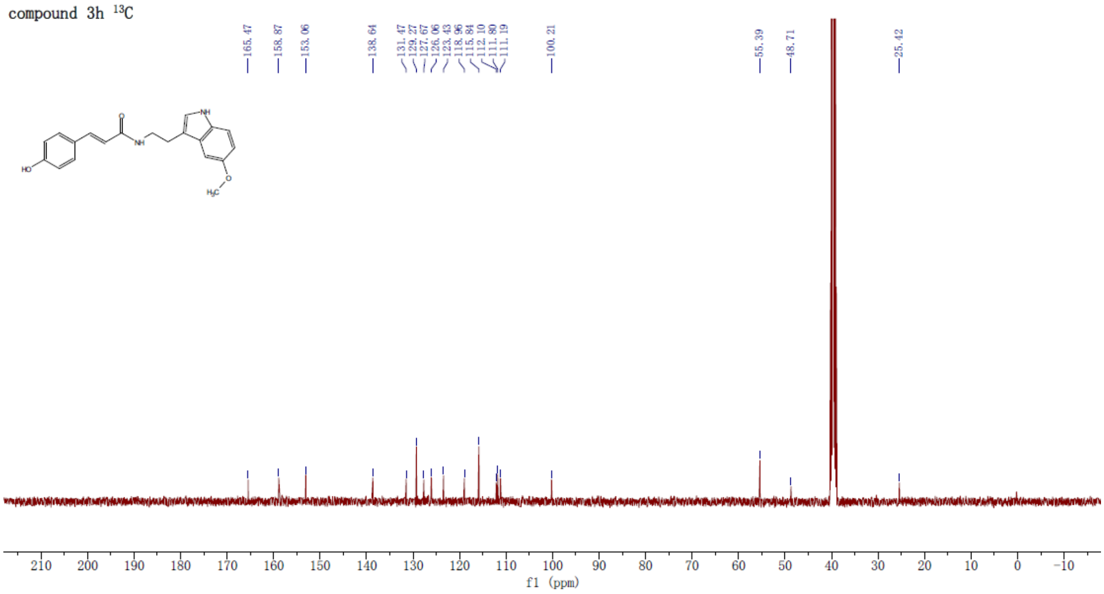
compound 3g ¹³C



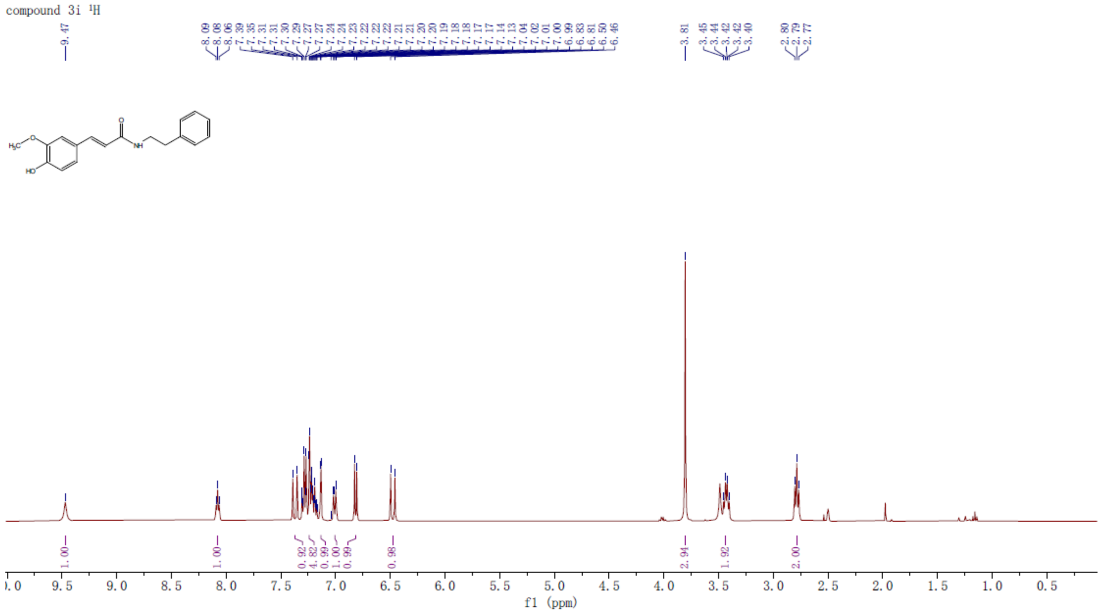
compound 3h ¹H



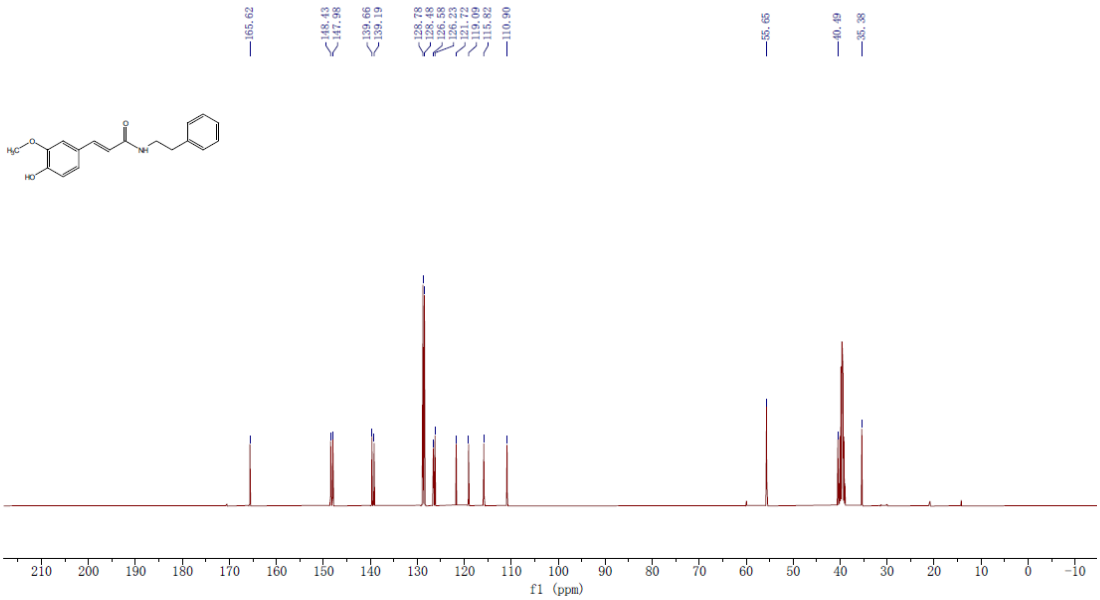
compound 3h ^{13}C



compound 3i ^{1}H



compound 3i ^{13}C



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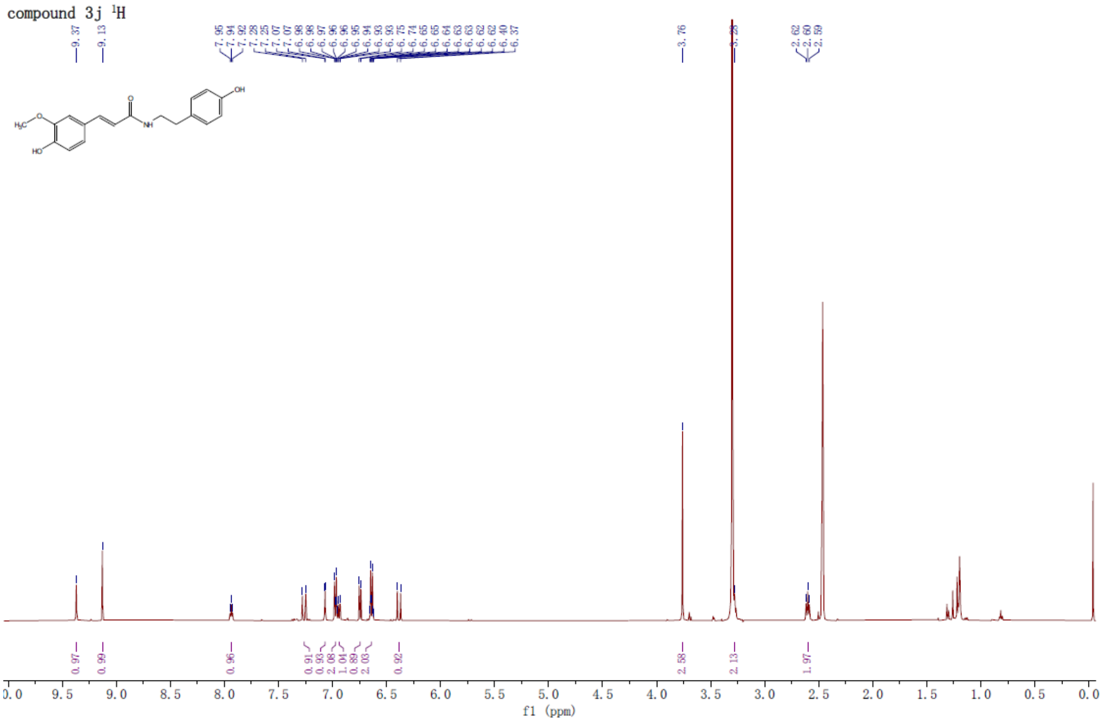
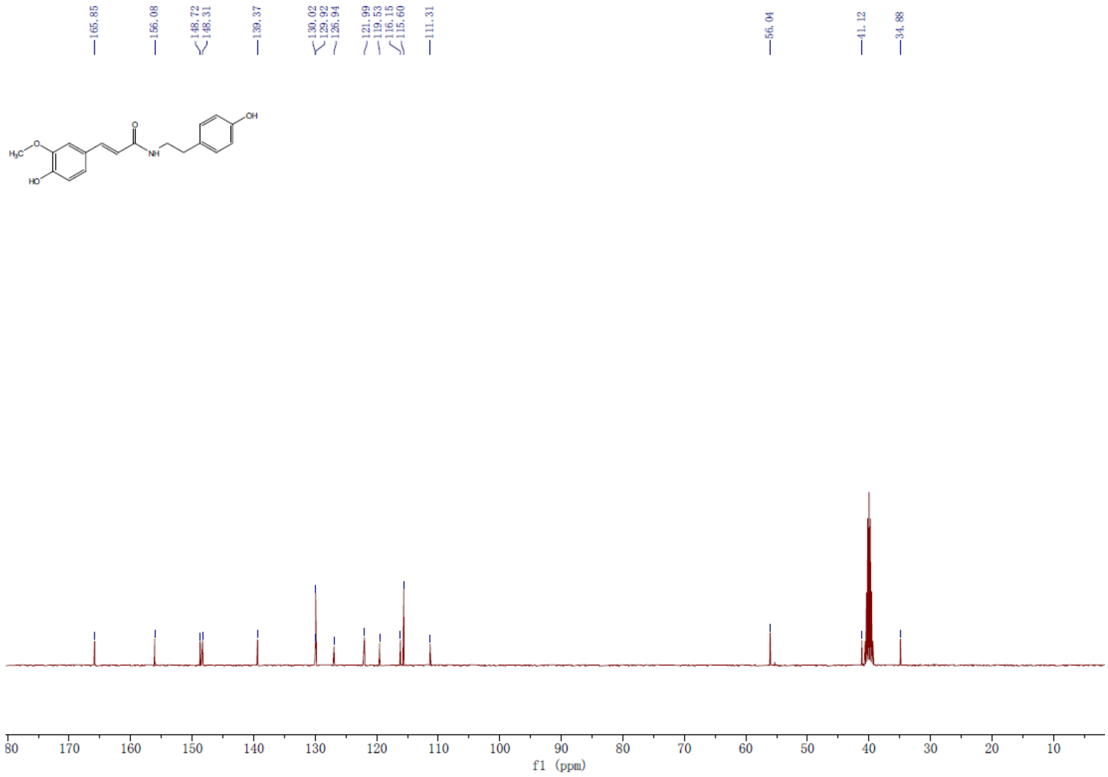
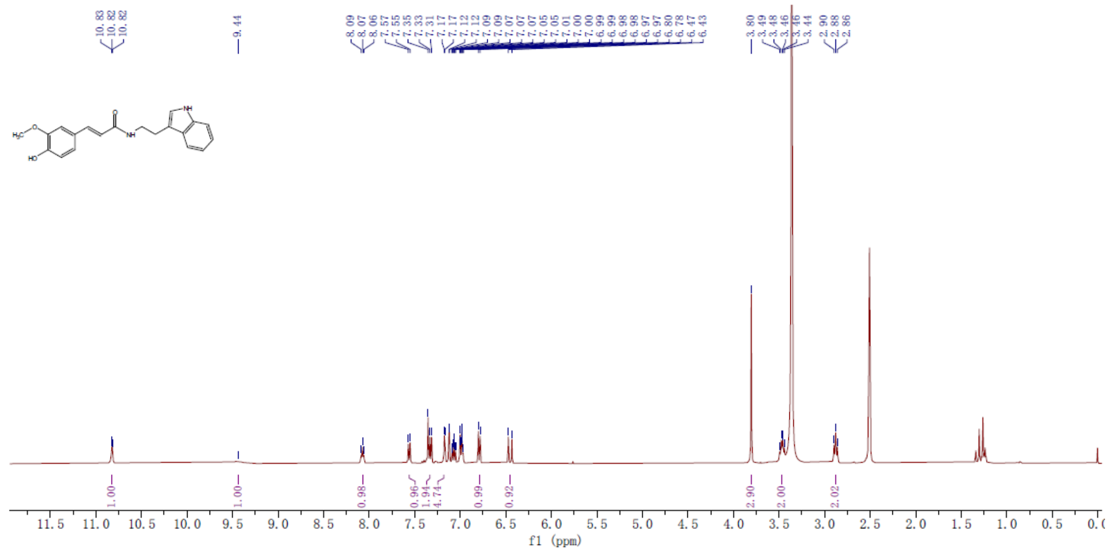


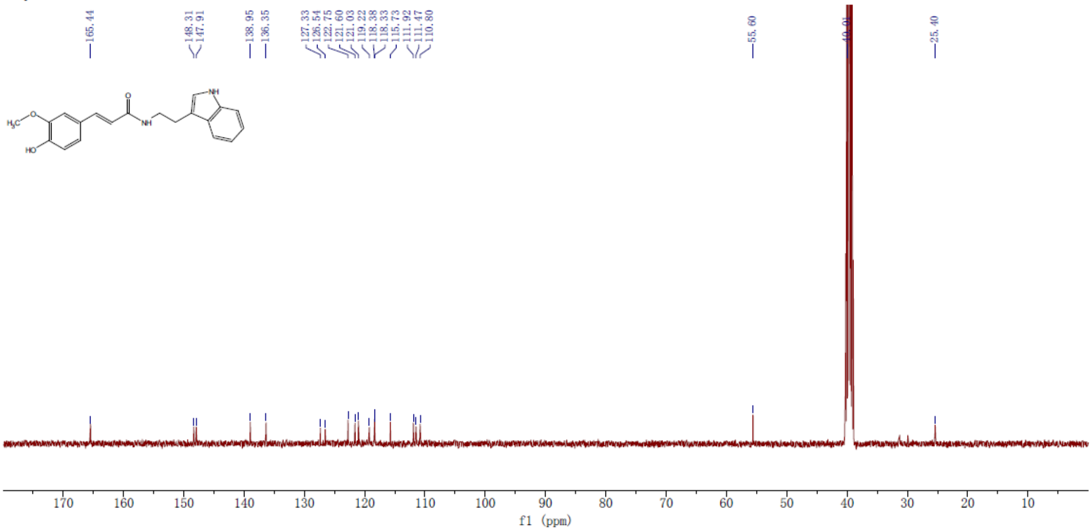
compound 3j ^{13}C



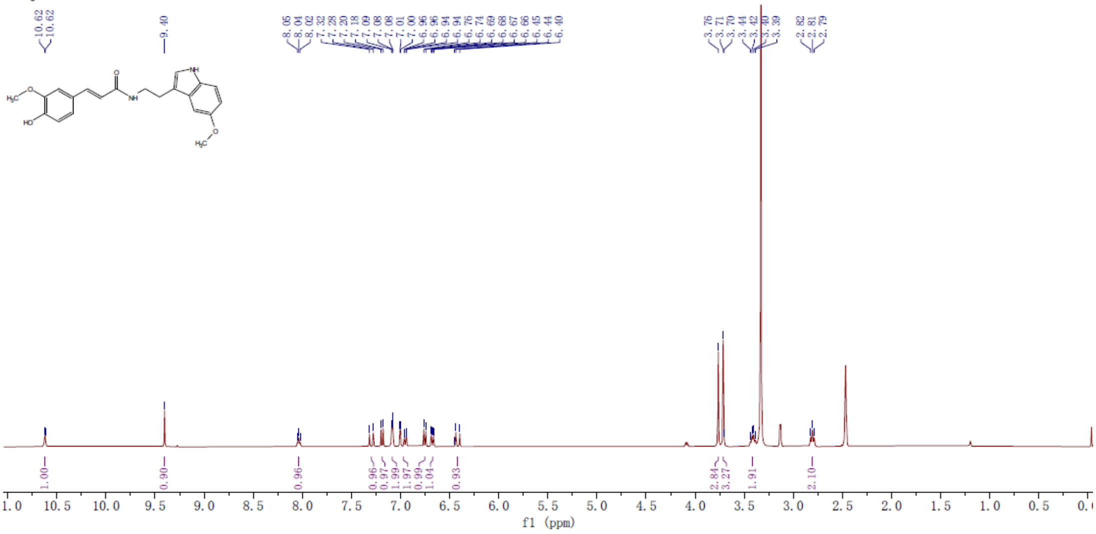
compound 3k ^{1}H



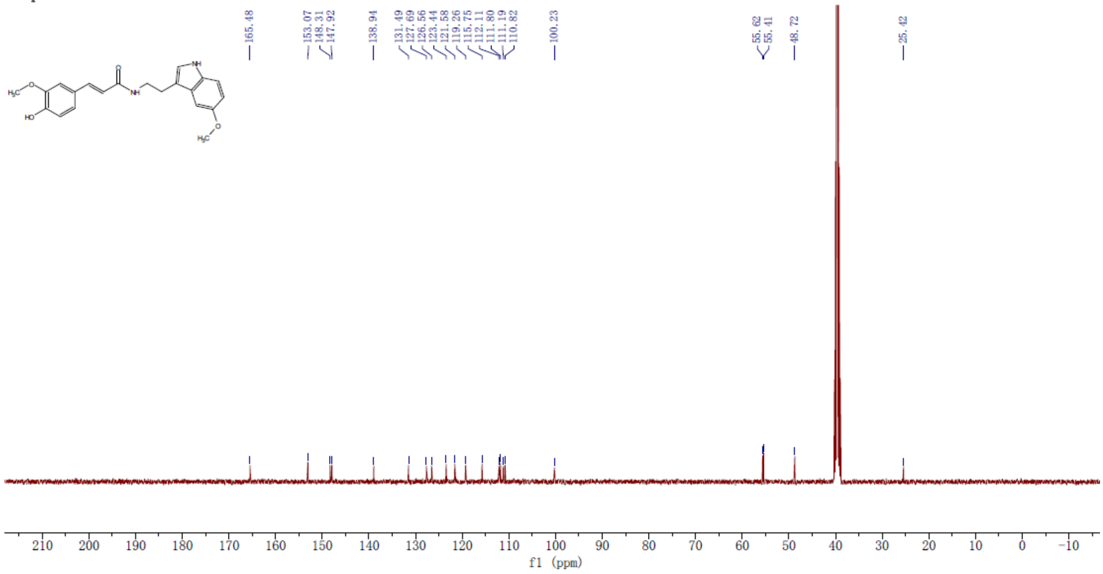
compound 3k ^{13}C



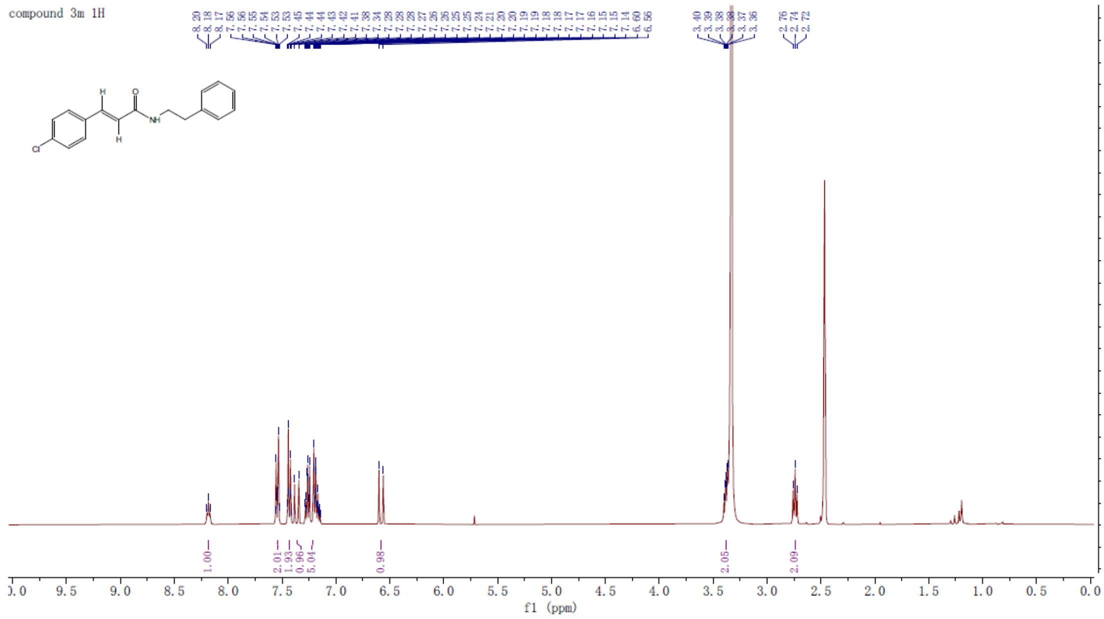
compound 31 ^{1}H



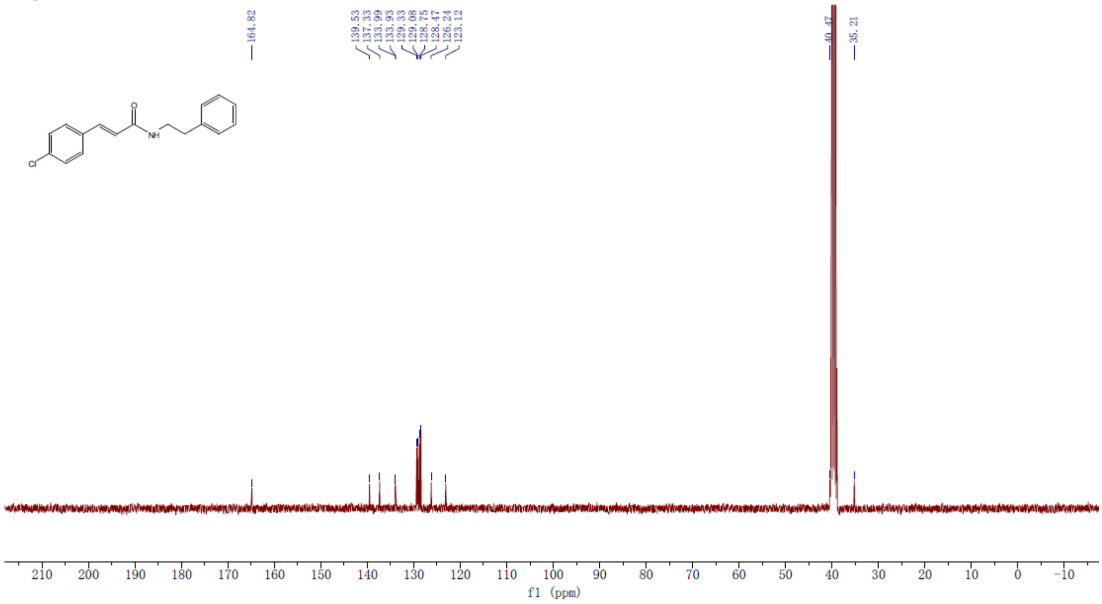
compound 3l ^{13}C



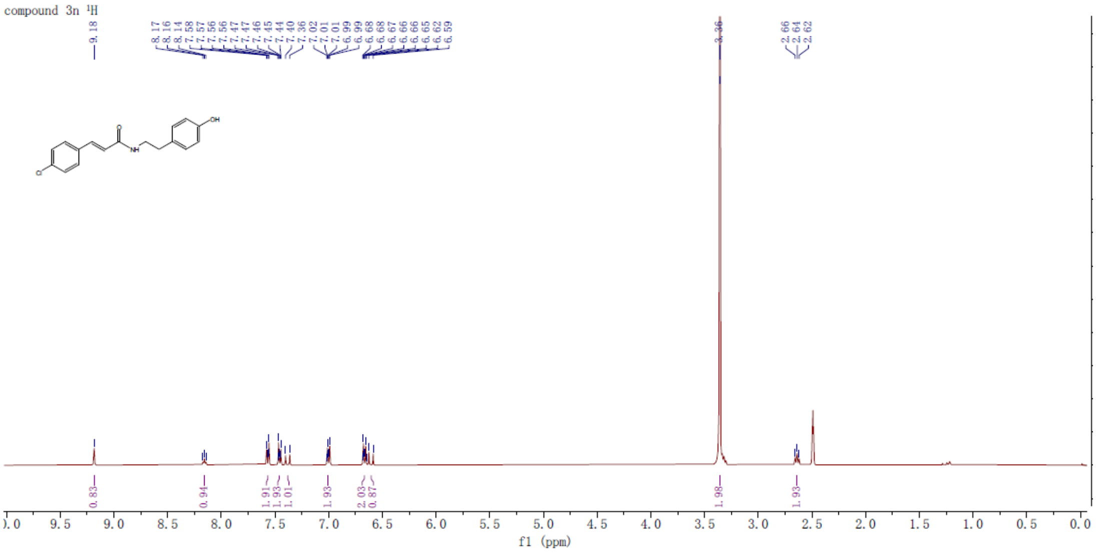
compound 3m 1H



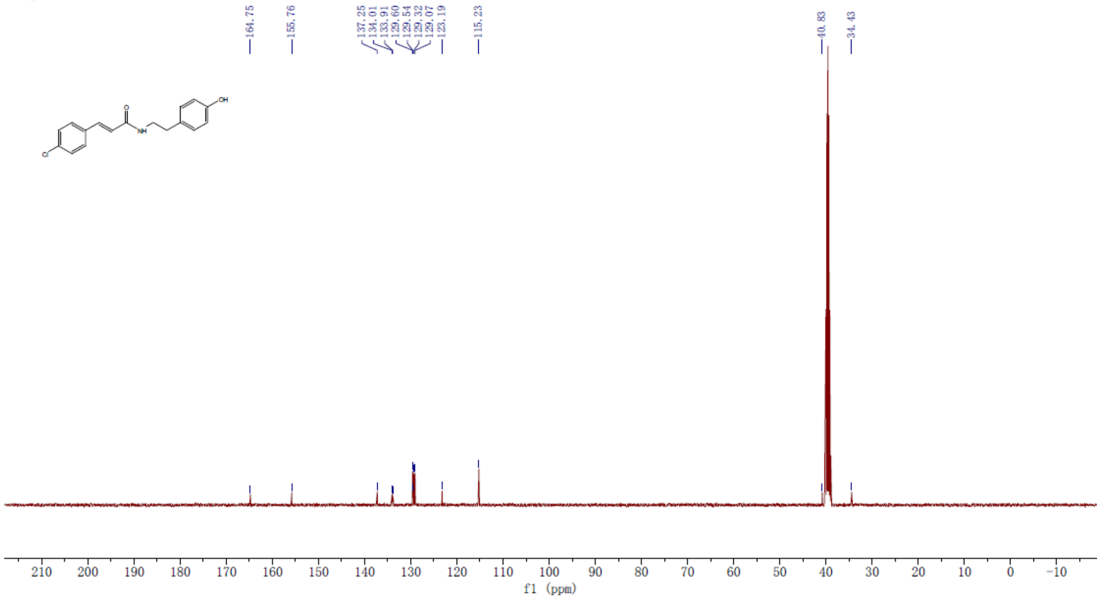
compound 3m ^{13}C



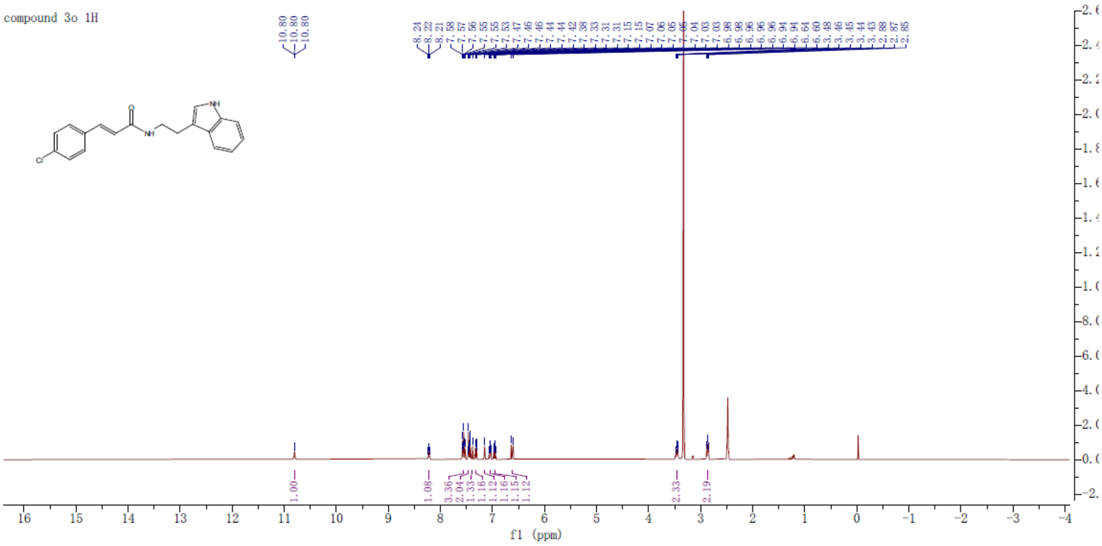
compound 3n ^{1}H



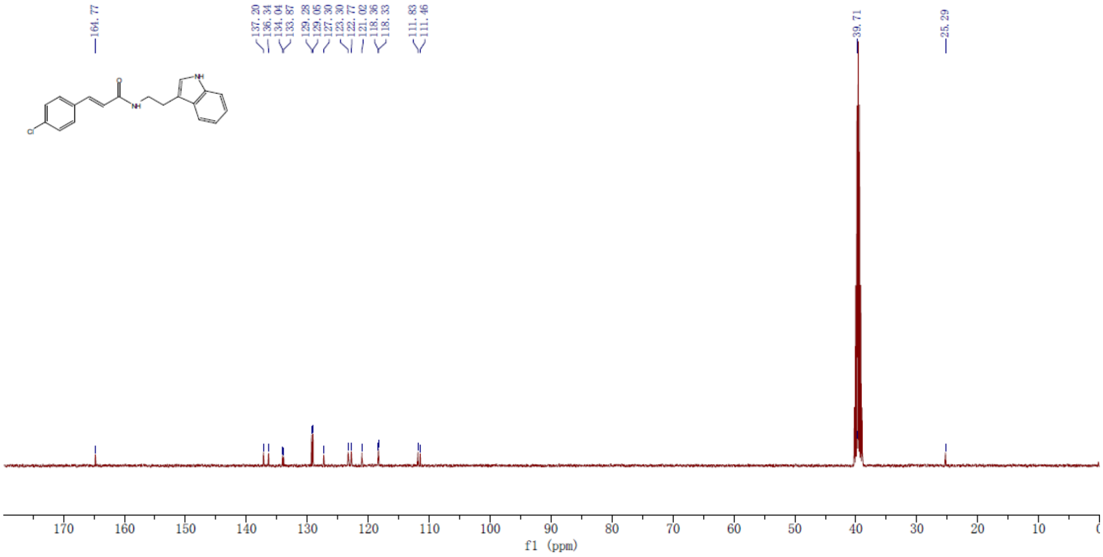
compound 3n ^{13}C



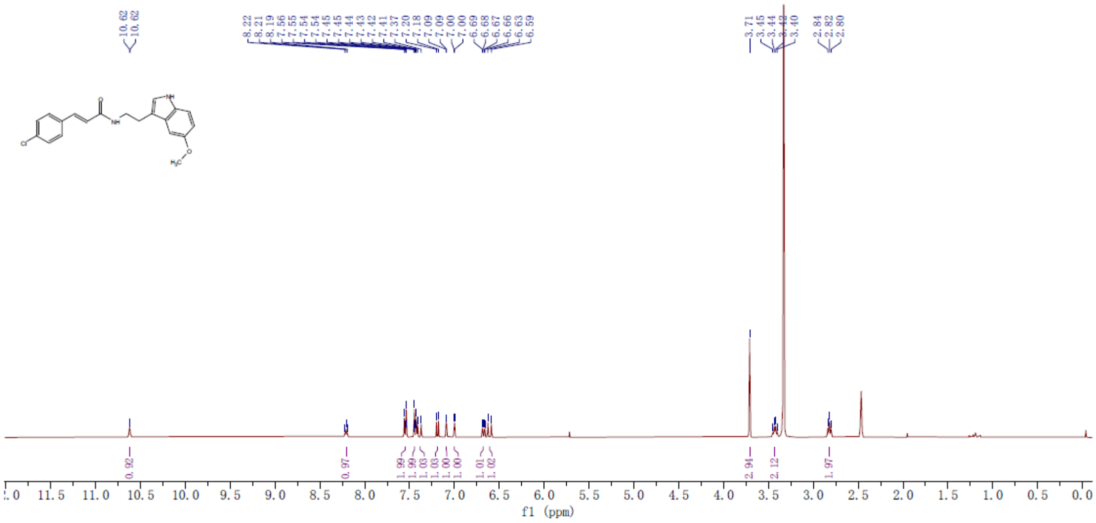
compound 3o 1H

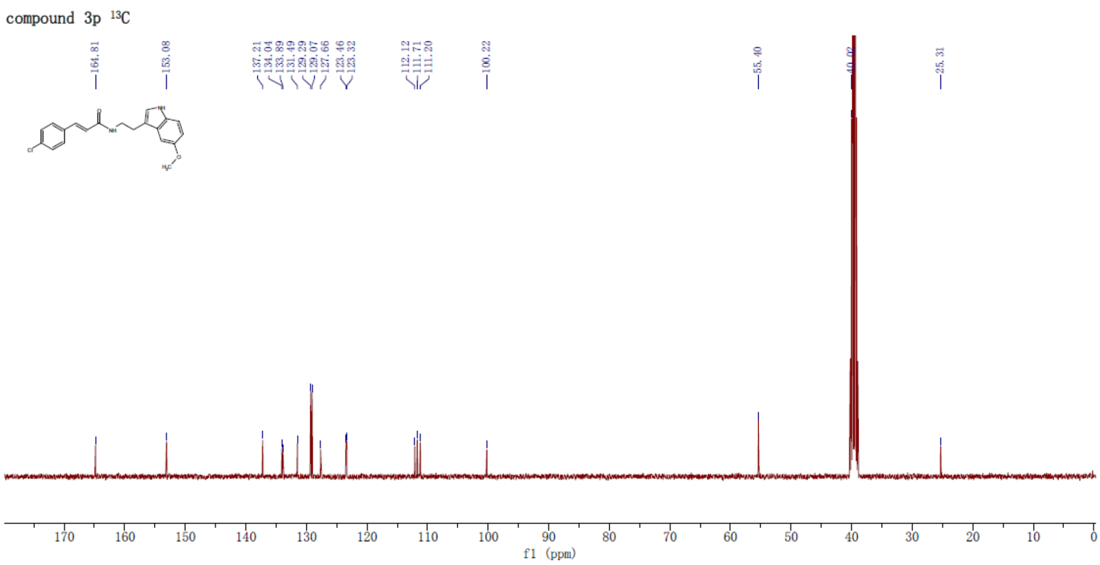


compound 3o ^{13}C



compound 3p ^{1}H





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