Supporting Information

Dehydrogenative Heck coupling of biologically relevant N-heteroarenes with alkenes: discovery of fluorescent core frameworks

*Yumin Huang, Feijie Song, Zhen Wang, Peihua Xi, Ningjie Wu, Zhigang Wang, Jingbo Lan and Jingsong You**

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, PR China Fax: 86-28-85412203; E-mail: jsyou@scu.edu.cn

Table of contents

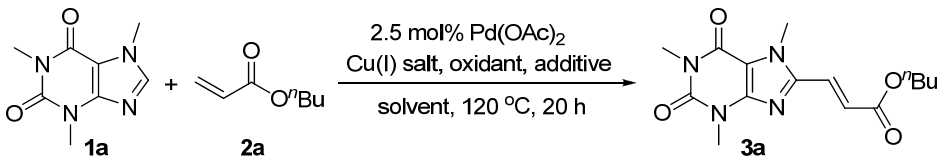
I. General Remarks

NMR spectra were obtained on a Bruker AMX-400 or a Bruker AMX-600. The ^{1}H NMR (400 MHz or 600 MHz) chemical shifts were measured using $CDCl_3$ or DMSO-d_6 as the internal reference ($CDCl_3$: δ = 7.26 ppm; DMSO-d_6: δ = 2.50 ppm). The ^{13}C NMR (100 MHz) chemical shifts are given using $CDCl_3$ or DMSO-d_6 as the internal standard ($CDCl_3$: δ = 77.16 ppm; DMSO-d_6: δ = 39.52 ppm). Low-resolution mass spectra (MS) were obtained by ESI-MS. High-resolution mass spectra (HR-MS) were obtained with a Waters-Q-TOF-Premier (ESI). Melting points were determined with XRC-1 and are uncorrected. Absorption spectra were obtained on a HITACHI U-2910 spectrometer. Fluorescence spectra were collected on a Horiba Jobin Yvon-Edison Fluoromax-4 fluorescence spectrometer. The photomultiplier voltage was 700 V. To reduce the fluctuation in the excitation intensity, the lamp was kept on for 1 hour prior to the experiment.

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. 1-Benzyl-3,7-dimethylxanthine, 7-butyl-1,3-dimethylxanthine, 1-allyl-3,7-dimethylxanthine,[1] 1,3-diethyl-7-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione,[2] other purine derivatives,[3] and indolizine[4] were prepared according to the literature procedures. Pyridine was dried over CaH_2 and freshly distilled prior to use. All solvents were purified and dried according to standard methods prior to use. Unless otherwise indicated, all reactions were carried out under N_2 atmosphere.

II. Optimization of the coupling reaction of caffeine 1a with *n*-butyl acrylate 2a

Table S1 Optimization results of the coupling reaction of caffeine **1a** with *n*-butyl acrylate **2a**[a]

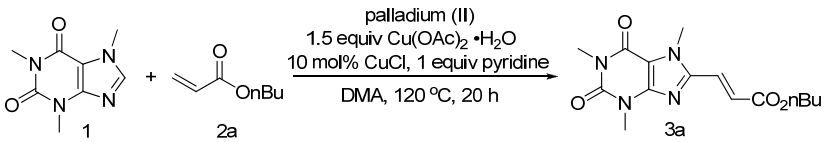


Entry	Oxidant	Cu(I) salts	Additive	Solvent	Yield (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	—	pyridine	DMA	29

2	$Cu(OAc)_2·H_2O$	CuBr (10 mol%)	pyridine	DMA	57
3	$Cu(OAc)_2·H_2O$	CuI (10 mol%)	pyridine	DMA	36
4	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	pyridine	DMA	67
5	$Cu(OAc)_2·H_2O$	CuCl (13 mol%)	pyridine	DMA	75
6	$Cu(OAc)_2·H_2O$	CuCl (15 mol%)	pyridine	DMA	81
7	$Cu(OAc)_2·H_2O$	CuCl (20 mol%)	pyridine	DMA	71
8	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	pyridine	DMF	62
9	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	pyridine	NMP	61
10	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	pyridine	DMSO	32
11	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	pyridine	dioxane	13
12	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	—	DMA	30
13	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	Et_3N	DMA	18
14	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	DABCO	DMA	23
15	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	2,6-lutidine	DMA	19
16	$Cu(OAc)_2·H_2O$	CuCl (10 mol%)	KOAc	DMA	57
17	$Cu(OAc)_2·H_2O$	CuCl (13 mol%)	pyridine	DMA	67[c]
18	$Cu(OAc)_2·H_2O$	CuCl (15 mol%)	pyridine	DMA	74[d]
19	$Cu(acac)_2$	CuCl (13 mol%)	pyridine	DMA	trace
20	Ag_2CO_3	CuCl (13 mol%)	pyridine	DMA	26

[a] The reactions were carried out using caffeine **1** (0.5 mmol), *n*-butyl acrylate **2a** (3.0 mmol), oxidant (0.75 mmol), additive (0.5 mmol), Cu(I) salt and $Pd(OAc)_2$ (0.0125 mmol, 2.5 mol%) in a 0.6 M solution. [b] Isolated yield. [c] *n*-Butyl acrylate **2a** (1.5 mmol) was used. [d] $Cu(OAc)_2·H_2O$ (1.0 mmol) was used.

Table S2 Optimization of palladium sources[a]



Entry	Palladium source	Yield (%)[b]
1	$PdCl_2$	68[c]
2	$Pd(OAc)_2$	67
3	$Pd(OAc)_2$	75[c]
4	$Pd(OAc)_2$	81[d]
5	$Pd(OAc)_2$	84[c,e]

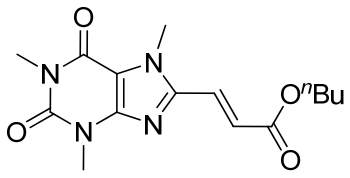
6	$Pd(acac)_2$	81[d]
7	$Pd(dppf)Cl_2$	76[d]
8	$Pd(PPh_3)_2Cl_2$	64
9	$Pd(PhCN)_2Cl_2$	66
10	$Pd(MeCN)_2Cl_2$	64

[a] Reactions were carried out using caffeine (0.5 mmol), palladium source (2.5 mol%), *n*-butyl acrylate **2a** (3.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.75 mmol), CuCl (10 mol%) and pyridine (0.5 mmol) in a 0.6 M DMA solution for 20 h at 120 °C. [b] Isolated yield. [c] 13 mol% CuCl was used. [d] 15 mol% CuCl was used. [e] 10 mol% $Pd(OAc)_2$ was used.

III. General procedure for the Pd/Cu co-catalyzed dehydrogenative Heck coupling reaction

A flame-dried Schlenk tube with a magnetic stirring bar was charged with $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), N-heterocycles (0.5 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) under N_2. After the mixture was stirred at room temperature for 5 min, alkene (3.0 mmol) was added. The resulting mixture was heated at 120 ºC for 20 h and then cooled to ambient temperature. The solvent was evaporated and the residue was diluted with 30 mL CH_2Cl_2, filtered through a Celite pad, and washed with CH_2Cl_2(10-20 mL). The combined organic phases were concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

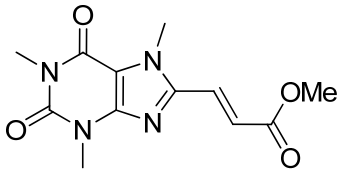
IV. Characterization of compounds 3a-3i, 4a-4m, CSC and KW6002



(*E*)-Butyl 3-(1,3,7-trimethyl-xanthine-8-yl) acrylate (3a)

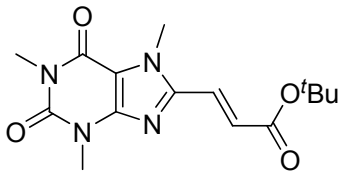
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3.0 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum

ether/acetone = 4/6/1, v/v) afforded the desired product as a pale yellow solid (81% yield). M.p.: 161-163 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.6 Hz, 3H), 1.41-1.47 (m, 2H), 1.68-1.72 (m, 2H), 3.42 (s, 3H), 3.59 (s, 3H), 4.09 (s, 3H), 4.25 (t, J = 6.4 Hz, 2H), 7.03 (d, J = 15.6 Hz, 1H), 7.51 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.2, 28.1, 29.8, 30.8, 32.0, 65.2, 109.3, 126.5, 126.5, 146.9, 148.5, 151.6, 155.4, 166.1 ppm. HRMS (ESI): calcd for $C_{15}H_{21}N_4O_4$ $[M+H]^+$ 321.1563, found 321.1508.



(*E*)-Methyl 3-(1,3,7-trimethyl-xanthine-8-yl) acrylate (3b)

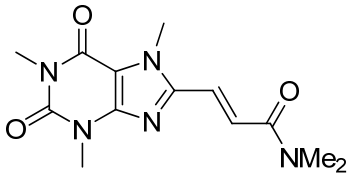
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), methyl acrylate (387.4 mg, 4.5 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum ether/acetone = 15/15/2, v/v) afforded the desired product as a pale yellow solid (66% yield). M.p.: 235-238 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.59 (s, 3H), 3.85 (s, 3H), 4.09 (s, 3H), 7.02 (d, J = 15.2 Hz, 1H), 7.51 (d, J = 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 29.9, 32.0, 52.3, 109.4, 125.9, 126.7, 146.7, 148.5, 151.6, 155.4, 166.4 ppm; HRMS (ESI): calcd for $C_{12}H_{15}N_4O_4$ $[M+H]^+$ 279.1093, found 279.1153.



(*E*)-*tert*-Butyl 3-(1,3,7-trimethyl-xanthine-8-yl) acrylate (3c)

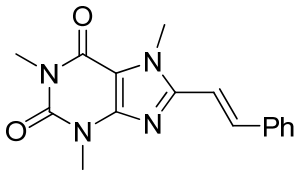
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4

mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), *tert*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/acetone = 8/1/0.4-6/1/0.4, v/v) afforded the desired product as a pale yellow solid (62% yield). M.p.: 214-216 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 9H), 3.40 (s, 3H), 3.57 (s, 3H), 4.06 (s, 3H), 6.96 (d, J = 15.6 Hz, 1H), 7.41 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 28.2, 29.8, 31.9, 81.7, 109.2, 125.6, 128.6, 147.2, 148.5, 151.7, 155.4, 165.2 ppm. HRMS (ESI): calcd for $C_{15}H_{21}N_4O_4$ $[M+H]^+$ 321.1563, found 321.1566.



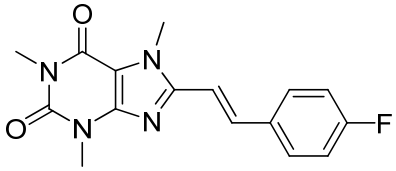
(*E*)-N,N**-Dimethyl-3-(1,3,7-trimethyl-xanthine-8-yl) acrylamide (3d)**

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), *N*,*N*-dimethylacrylamide (297.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum ether/acetone = 2/2/1, v/v) afforded the desired product as a pale yellow solid (84% yield). M.p.: 270-273 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.09 (s, 3H), 3.23 (s, 3H), 3.40 (s, 3H), 3.59 (s, 3H), 4.07 (s, 3H), 7.54 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 29.9, 31.9, 36.2, 37.6, 109.0, 124.7, 125.5, 147.8, 148.4, 151.7, 155.3, 165.2 ppm; HRMS (ESI): calcd for $C_{13}H_{18}N_5O_3$ $[M+H]^+$ 292.1410, found 292.1400.



(*E*)-1,3,7-Trimethyl-8-styryl-xanthine (3e)

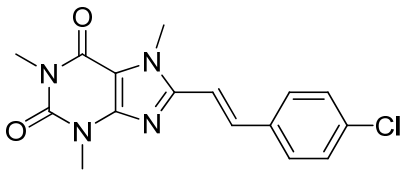
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), styrene (312.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum ether/acetone = 10/15/2, v/v) afforded the desired product as a white solid (68% yield). M.p.: 214-217 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 3H), 3.62 (s, 3H), 4.06 (s, 3H), 6.91 (d, J = 15.6 Hz, 1H), 7.36-7.42 (m, 3H), 7.57 (d, J = 7.2 Hz, 2H), 7.80 (d, J = 15.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 29.8, 31.6, 107.9, 111.2, 127.4, 129.0, 129.6, 135.5, 138.3, 148.6, 150.0, 151.7, 155.2 ppm; HRMS (ESI): calcd for $C_{16}H_{17}N_4O_2$ $[M+H]^+$ 297.1352, found 297.1361.



(*E*)-1,3,7-Trimethyl-8-(4-fluorostyryl)-xanthine (3f)

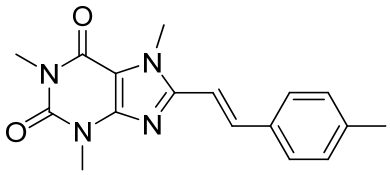
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), 4-fluorostyrene (366.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/acetone = 8/1/0.4-6/1/0.4, v/v) afforded the desired product as a pale yellow solid (82% yield). M.p.: 238-240 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.62 (s, 3H), 4.06 (s, 3H), 6.83 (d, J = 15.6 Hz, 1H), 7.10 (t, J = 8.8 Hz, 2H), 7.56 (dd, J = 5.6，8.4 Hz, 2H), 7.76 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 29.9,

31.6, 111.1, 116.1, 116.3, 129.2, 129.3, 131.9, 137.2, 148.7, 149.9, 151.8, 155.4 ppm. HRMS (ESI): calcd for $C_{16}H_{16}N_4O_2F$ $[M+H]^+$ 315.1257, found 315.1255.



(*E*)-1,3,7-Trimethyl-8-(4-chlorostyryl)-xanthine (3g)

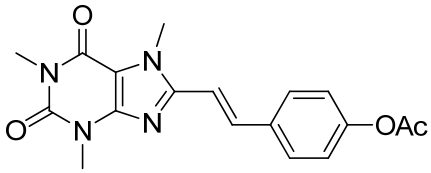
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), 4-chlorostyrene (415.8 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/acetone = 8/1/0.4-6/1/0.4, v/v) afforded the desired product as a pale yellow solid (70% yield). M.p.: 224-226 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.62 (s, 3H), 4.07 (s, 3H), 6.89 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 29.9, 31.6, 108.1, 111.8, 128.6., 129.3, 134.1, 135.4, 136.9, 148.6, 149.7, 151.8, 155.3 ppm. HRMS (ESI): calcd for $C_{16}H_{16}N_4O_2Cl$ $[M+H]^+$ 331.0962, found 331.0965.



(*E*)-1,3,7-Trimethyl-8-(4-methylstyryl)-xanthine (3h)

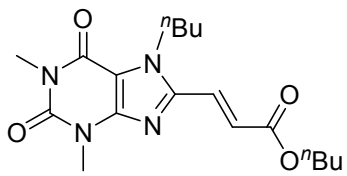
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), 4-methylstyrene (354.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum

ether/CH_2Cl_2/acetone = 8/1/0.4-6/1/0.4, v/v) afforded the desired product as a pale yellow solid (62% yield). M.p.: 199-201 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.39 (s, 3H), 3.61 (s, 3H), 4.03 (s, 3H), 6.84 (d, J = 15.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 16.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 28.0, 29.8, 31.5, 107.8, 110.2, 127.4, 129.7, 132.8, 138.4, 140.0, 148.6, 150.3, 151.8, 155.2 ppm. HRMS (ESI): calcd for $C_{17}H_{19}N_4O_2$ $[M+H]^+$ 311.1508, found 311.1512.



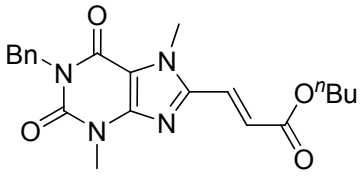
(*E*)-1,3,7-Trimethyl-8-(4-acetoxystyryl)-xanthine (3i)

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), 4-acetoxystyrene (486.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/ethyl acetate = 2/1/1-1/1/1, v/v) afforded the desired product as a pale yellow solid (58% yield). M.p.: 206-209 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 3.40 (s, 3H), 3.61 (s, 3H), 4.05 (s, 3H), 6.85 (d, J = 15.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 28.1, 29.9, 31.6, 108.1, 111.5, 122.3, 128.5, 133.3, 137.3, 148.6, 149.9, 151.6, 151.8, 155.3, 169.4 ppm. HRMS (ESI): calcd for $C_{18}H_{19}N_4O_4$ $[M+H]^+$ 355.1406, found 355.1391.



(*E*)-Butyl 3-(7-butyl-1,3-dimethyl-xanthine-8-yl) acrylate (4a)

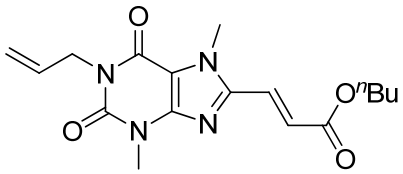
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 7-butyl-1,3-dimethyl-xanthine (118.1 mg, 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum ether/acetone = 5/10/1, v/v) afforded the desired product as a pale yellow solid (83% yield). M.p.: 81-84 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93-0.98 (m, 6H), 1.34-1.48 (m, 4H), 1.67-1.80 (m, 4H), 3.41 (s, 3H), 3.60 (s, 3H), 4.24 (t, J = 6.8 Hz, 2H), 4.43 (t, J = 7.2 Hz, 2H), 7.04 (d, J = 15.2 Hz, 1H), 7.48 (d, J = 15.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.8, 19.3, 19.8, 28.2, 29.8, 30.7, 33.7, 45.3, 65.2, 108.8, 126.4, 126.7, 146.3, 148.6, 151.6, 155.0, 166.2 ppm; HRMS (ESI): calcd for $C_{18}H_{27}N_4O_4$ $[M+H]^+$ 363.2032, found 363.2040.



(*E*)-Butyl 3-(1-benzyl-3,7-dimethyl-xanthine-8-yl) acrylate (4b)

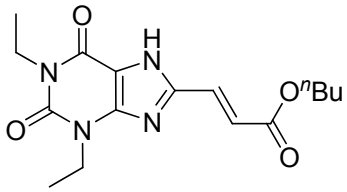
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 1-benzyl-3,7-dimethyl-xanthine (135.1 mg, 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3.0 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum ether/ethyl acetate = 15/20/4, v/v) afforded the desired product as a pale yellow solid (58% yield). M.p.: 172-174 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.2 Hz, 3H), 1.40-1.48 (m, 2H), 1.64-1.72 (m, 2H), 3.57 (s, 3H), 4.08 (s, 3H), 4.24 (t, J = 6.8 Hz, 2H), 5.19 (s, 2H), 7.02 (d, J = 15.6 Hz, 1H), 7.23-7.32 (m, 3H), 7.47-7.51 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.2, 29.9, 30.7, 32.0, 44.6, 65.2, 109.4, 126.4, 126.6, 127.7, 128.5, 128.9,

137.3, 147.0, 148.6, 151.5, 155.2, 166.1 ppm; HRMS (ESI): calcd for $C_{21}H_{25}N_4O_4$ $[M+H]^+$ 397.1876, found 397.1860.



(*E*)-Butyl 3-(1-allyl-3,7-dimethyl-xanthine-8-yl) acrylate (4c)

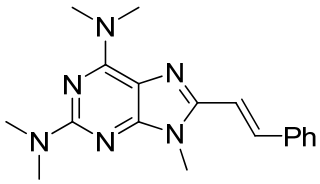
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 1-allyl-3,7-dimethylxanthine (110.1 mg, 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/acetone = 15/1/1, v/v) afforded the desired product as a green solid (51% yield). M.p.: 131-133 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.2 Hz, 3H), 1.36-1.48 (m, 2H), 1.65-1.72 (m, 2H), 3.58 (s, 3H), 4.08 (s, 3H), 4.24 (t, J = 6.8 Hz, 2H), 4.62 (d, J = 5.6 Hz, 2H), 5.18-5.28 (m, 2H), 5.86-5.96 (m, 1H), 7.03 (d, J = 15.2 Hz, 1H), 7.50 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.8, 19.2, 29.8, 30.8, 32.0, 43.5, 65.2, 109.4, 117.8, 126.5, 126.6, 132.3, 147.0, 148.7, 151.2, 155.0, 166.1 ppm; HRMS (ESI): calcd for $C_{17}H_{23}N_4O_4$ $[M+H]^+$ 347.1719, found 347.1718.



(*E*)-Butyl 3-(1,3-diethyl-xanthine-8-yl) acrylate (4d)

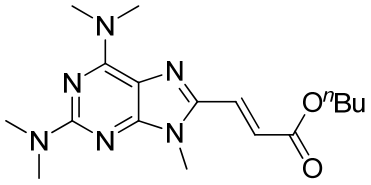
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 1,3-diethylxanthine (104.1 mg, 0.5 mmol), *n*-butyl acrylate (384.5

mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N, N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (CH_2Cl_2/petroleum ether/acetone = 5/10/2, v/v) afforded the desired product as white solid (71% yield). M.p.: 209.5-211 ºC; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.8 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.42-1.46 (m, 5H), 1.67-1.72 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.24 (t, J = 6.6 Hz, 2H), 4.47 (q, J = 7.2 Hz, 2H), 7.06 (d, J = 15.6 Hz, 1H), 7.48 (d, J = 15.0 Hz, 1H), 8.82 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 13.8, 17.0, 19.3, 30.8, 38.0, 40.7, 65.2, 109.0, 126.5, 126.9, 146.6, 150.1, 150.8, 154.7, 166.2 ppm. HRMS (ESI): calcd for $C_{16}H_{23}N_4O_4$ $[M+H]^+$ 335.1719, found 345.1723.



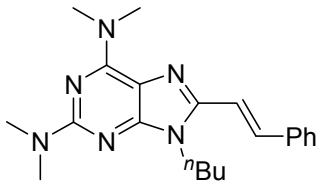
(*E*)-*N*^{2},*N*^{2},*N*^{6},*N*^{6},9-Pentamethyl-8-styryl-9*H*-purine-2,6-diamine (4e)

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 9-methyl-2,6-bis(dimethylamino)-purine (110.1 mg. 0.5 mmol), styrene (312.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/ethyl acetate = 15/3/1-12/3/1, v/v) afforded the desired product as a yellow solid (92% yield). M.p.: 154-156 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (s, 6H), 3.52 (s, 6H), 3.74 (s, 3H), 7.01 (d, J = 16.0 Hz, 1H), 7.27-7.31 (m, 1H), 7.37 (t, J =7.6 Hz , 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 16.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 37.5, 38.3, 114.2, 127.0, 128.5, 128.9, 133.3, 136.7, 144.1, 154.3, 158.7 ppm; HRMS (ESI): calcd for $C_{18}H_{23}N_6$ $[M+H]^+$ 323.1984, found 323.1983.



(*E*)-Butyl 3-(2,6-bis(dimethylamino)-9-methyl-9*H*-purin-8-yl) acrylate (4f)

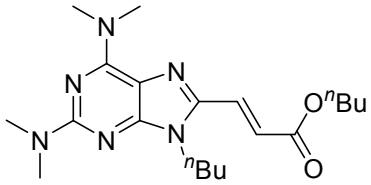
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (300 mg, 1.50 mmol), CuCl (7.4 mg, 0.075 mmol), 9-methyl-2,6-bis(dimethylamino)-purine (110.1 mg. 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/ethyl acetate = 15/3/1-12/3/1, v/v) afforded the desired product as a golden yellow solid (75% yield). M.p.: 92-94 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.2 Hz, 3H), 1.37-1.46 (m, 2H), 1.63-1.70 (m, 2H), 3.15 (s, 6H), 3.44 (s, 6H), 3.66 (s, 3H), 4.19 (t, J = 6.4 Hz, 2H), 6.80 (d, J = 15.6 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.2, 28.3, 30.8, 37.2, 38.2, 64.5, 115.6, 120.0, 129.8, 140.8, 154.7, 154.7, 159.6, 167.0 ppm; HRMS (ESI): calcd for $C_{17}H_{27}N_6O_2$ $[M+H]^+$ 347.2195, found 347.2204.



(*E*)-9-Butyl-N^2,N^2,N^6,N^6-tetramethyl-8-styryl-9*H*-purine-2,6-diamine (4g)

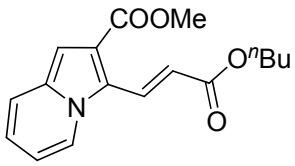
$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 9-butyl-2,6-bis(dimethylamino)-purine (131.2 mg. 0.5 mmol), styrene (312.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/ethyl acetate = 15/3/1-12/3/1, v/v) afforded the desired product as a yellow solid (90% yield). M.p.: 101-103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.2 Hz, 3H), 1.33-1.39 (m, 2H), 1.75-1.82 (m, 2H),

3.19 (s, 6H), 3.52 (s, 6H), 4.18 (t, J = 6.8 Hz, 2H), 6.98 (d, J = 15.6 Hz, 1H), 7.28-7.31 (m, 1H), 7.38 (t, J =7.2 Hz , 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.9, 32.3, 37.4, 38.3, 41.4, 114.2, 114.4, 127.0, 128.3, 128.9, 132.9, 136.9, 143.5, 154.4, 159.2 ppm; HRMS (ESI): calcd for $C_{21}H_{29}N_6$ $[M+H]^+$ 365.2454, found 345.2446.



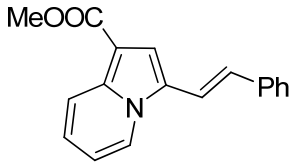
(*E*)-Butyl 3-(9-butyl-2,6-bis(dimethylamino)-9*H*-purin-8-yl) acrylate (4h)

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (300 mg, 1.50 mmol), CuCl (7.4 mg, 0.075 mmol), 9-butyl-2,6-bis(dimethylamino)-purine (131.2 mg. 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/ethyl acetate = 15/3/1-12/3/1, v/v) afforded the desired product as a golden yellow solid (75% yield). M.p.: 84-86 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (q, J = 7.6 Hz, 6H), 1.29-1.34 (m, 2H), 1.41-1.46 (m, 2H), 1.64-1.77 (m, 4H), 3.18 (s, 6H), 3.48 (s, 6H), 4.15 (t, J = 6.8 Hz, 2H), 4.22 (t, J = 6.8 Hz, 2H), 6.89 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.9, 19.3, 19.9, 30.9, 32.5, 37.3, 41.5, 64.6, 115.6, 120.3, 129.7, 140.5, 154.7, 154.8, 159.6, 167.2 ppm; HRMS (ESI): calcd for $C_{20}H_{33}N_6O_2$ $[M+H]^+$ 389.2665, found 389.2656.



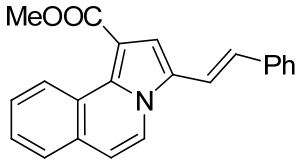
(*E*)-Methyl 3-(3-butoxy-3-oxoprop-1-enyl) indolizine-2-carboxylate (4i)

$Pd(dppf)Cl_2$ (9.2 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), methyl indolizine-2-carboxylate (87.6 mg, 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/ diethyl ether = 15/1-10/1, v/v) afforded the desired product as a yellow solid (60% yield). M.p.: 58-60 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.2 Hz, 3H), 1.43-1.48 (m, 2H), 1.68-1.75 (m, 2H), 3.92 (s, 3H), 4.24 (t, J = 6.8 Hz, 2H), 6.61 (d, J = 16.4 Hz, 1H), 6.78 (t, J = 6.8 Hz, 1H), 6.88-6.92 (m, 1H), 7.03 (s, 1H), 7.47 (d, J = 9.2 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 16.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 19.3, 31.0, 52.0, 64.6, 105.5, 114.3, 115.5, 120.7, 120.9, 121.7, 121.8, 124.9, 131.0, 135.2, 165.2, 168.1 ppm; HRMS (ESI): calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1392, found 302.1399.



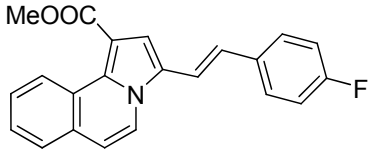
(*E*)-Methyl 3-styrylindolizine-1-carboxylate (4j)

$Pd(dppf)Cl_2$ (9.2 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), methyl indolizine-1-carboxylate (87.6 mg, 0.5 mmol), styrene (312.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-Dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/ethyl acetate/toluene = 25/2/1-20/2/1, v/v) afforded the desired product as a yellow solid (47% yield). M.p.: 109-112 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.82 (s, 3H), 6.99 (t, J = 6.4 Hz, 1H), 7.21-7.32 (m, 3H), 7.38 (t, J = 7.2 Hz, 2H), 7.64 (s, 1H), 7.69 (d, J = 8.4 Hz, 3H), 8.10 (d, J = 8.8 Hz, 1H), 8.88 (d, J = 6.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.8, 103.6, 112.7, 113.2, 114.8, 118.9, 123.2, 124.8, 125.0, 126.4, 127.3, 127.5, 128.6, 135.6, 137.4, 164.1 ppm; HRMS (ESI): calcd for $C_{18}H_{15}NNaO_2$ $[M+Na]^+$ 300.1000, found 300.1000.



(*E*)-Methyl 3-styryl pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (4k)

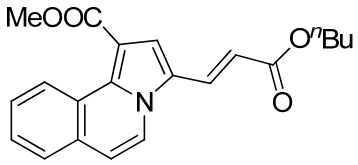
$Pd(dppf)Cl_2$ (9.2 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), methyl pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (112.6 mg, 0.5 mmol), styrene (312.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/ethyl ether/CH_2Cl_2 = 25/2/1-20/2/1, v/v) afforded the desired product as a yellow solid (64% yield). M.p.: 141-144 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.88 (s, 3H), 7.26-7.42 (m, 5H), 7.56-7.63 (m, 2H), 7.66 (s, 1H), 7.72-7.75 (m, 3H), 7.84 (d, J = 7.2 Hz, 1H), 8.72 (d, J = 7.6 Hz, 1H), 9.68 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 51.4, 108.7, 113.2, 113.5, 114.8, 122.6, 125.0, 126.2, 126.5, 126.6, 127.0, 127.4, 127.5, 127.7, 128.6, 128.8, 131.3, 137.2, 164.9 ppm; HRMS (ESI): calcd for $C_{22}H_{18}NO_2$ $[M+H]^+$ 328.1338, found 328.1333.



(*E*)-Methyl 3-(4-fluorostyryl) pyrrolo[2,1-a]isoquinoline-1-carboxylate (4l)

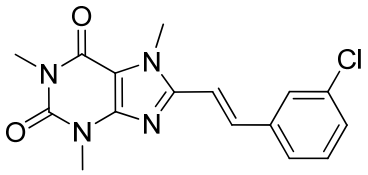
$Pd(dppf)Cl_2$ (9.2 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), methyl pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (112.6 mg, 0.5 mmol), 4-fluorostyrene (366.4 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/ethyl ether/CH_2Cl_2 = 35/2/1-25/2/1, v/v) afforded the desired product as a yellow solid (62% yield). M.p.: 165-168 ºC; ^{1}H NMR (400

MHz, $CDCl_3$): δ = 3.96 (s, 3H), 7.04-7.12 (m, 5H), 7.48-7.53 (m, 4H), 7.59-7.66 (m, 2H), 7.98 (d, J = 7.6 Hz, 1H), 9.80 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7, 109.3, 114.1, 114.3, 114.5, 114.5, 115.8, 116.0, 121.0, 125.9, 126.0, 126.8, 127.2, 127.8, 127.9, 128.0, 128.0, 128.5, 128.8, 132.9, 133.4, 133.5, 165.8 ppm; HRMS (ESI): calcd for $C_{22}H_{16}FNNaO_2$ $[M+Na]^+$ 348.1063, found 348.1069.



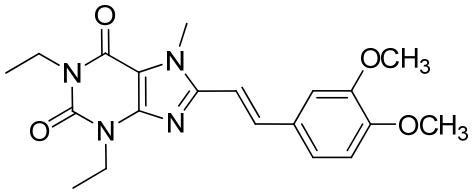
(*E*)-Methyl (3-butoxy-3-oxoprop-1-enyl) pyrrolo[2,1-*a*]isoquinoline-1-carboxy -late (4m)

$Pd(dppf)Cl_2$ (9.2 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (300 mg, 1.5 mmol), CuCl (7.4 mg, 0.075 mmol), methyl pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (112.6 mg, 0.5 mmol), *n*-butyl acrylate (384.5 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/ethyl ether = 50/1-20/1, v/v) afforded the desired product as a yellow solid (68% yield). M.p.: 102-105 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.2 Hz, 3H), 1.43-1.48 (m, 2H), 1.67-1.73 (m, 2H), 3.94 (s, 3H), 4.23 (t, J = 6.4 Hz, 2H), 6.44 (d, J = 15.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.53-7.71 (m, 4H), 7.91 (d, J = 15.6 Hz, 1H), 8.07 (d, J = 7.2 Hz, 1H), 9.77 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 19.4, 31.0, 51.8, 64.6, 110.6, 115.0, 115.8, 118.5, 120.9, 123.2, 125.7, 126.9, 127.6, 128.2, 129.3, 129.8, 134.7, 165.4, 167.5 ppm; HRMS (ESI): calcd for $C_{21}H_{22}NO_4$ $[M+H]^+$ 352.1549, found 352.1547.



(*E*)-1,3,7-Trimethyl-8-(3-chlorostyryl)-xanthine (CSC)

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), caffeine (97.1 mg, 0.5 mmol), 3-chlorostyrene (415.8 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/acetone = 8/1/1-6/1/1, v/v) afforded the desired product as a pale yellow solid (65% yield). M.p.: 195-197 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.62 (s, 3H), 4.08 (s, 3H), 6.92 (d, J = 15.6 Hz, 1H), 7.33 (d, J = 4.8 Hz, 2H), 7.43 (d, J = 4.0 Hz, 1H), 7.57 (s, 1H), 7.74 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 29.9, 31.7, 108.3, 112.7, 125.9, 127.0, 129.5, 130.3, 135.1, 136.8, 137.4, 148.6, 149.5, 151.8, 155.4 ppm. MS (ESI): calcd for $C_{16}H_{16}N_4O_2Cl$ $[M+H]^+$ 331.0, found 331.0.



(*E*)-8-(3,4-Dimethoxystyryl)-1,3-diethyl-7-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (KW6002)

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), $Cu(OAc)_2 \cdot H_2O$ (150 mg, 0.75 mmol), CuCl (7.4 mg, 0.075 mmol), 1,3-diethyl-7-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (111.1 mg, 0.5 mmol), 3,4-dimethoxystyrene (492.6 mg, 3 mmol), pyridine (39.6 mg, 0.5 mmol) and N,N-dimethylacetamide (0.6 mL) at 120 ºC for 20 h. Purification via silica gel column chromatography (petroleum ether/CH_2Cl_2/acetone = 6/1/0.4-8/1/1, v/v) afforded the desired product as a yellow solid (95% yield). M.p.: 209-211 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 6.8 Hz, 3H), 1.47 (t, J = 6.8 Hz, 3H), 3.42 (s, 3H), 3.93 (s,

3H), 3.96 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.49 (q, J = 7.2 Hz, 2H), 6.75 (d, J = 15.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 16.8, 27.9, 38.6, 40.0, 56.1, 56.1, 107.2, 109.3, 109.9, 111.4, 121.2, 128.8, 138.3, 148.5, 149.3, 149.6, 150.5, 151.3, 155.0 ppm. MS (ESI): calcd for $C_{20}H_{25}N_4O_4$ $[M+H]^+$ 385.2, found 385.2.

V. Absorption and fluorescence emission data of compounds 3a-3i and 4a-4m

Table S3 UV absorption and fluorescence emission maxima of N-heteroarenes **3** and **4** in DCM.

compd.	$\lambda_{abs}/\lambda_{em}$ [nm]	Stokes shift [nm]	compd.	$\lambda_{abs}/\lambda_{em}$ [nm]	Stokes shift [nm]
3a	353/422	69	**4c**	351/422	71
3b	353/423	70	**4d**	349/417	68
3c	348/420	72	**4e**	395/483	88
3d	348/402	54	**4f**	417/510	93
3e	354/417	63	**4g**	395/482	87
3f	353/417	64	**4h**	417/508	91
3g	358/423	65	**4i**	394/446	52
3h	355/418	63	**4j**	368/461	93
3i	356/421	65	**4k**	367/435	68
4a	349/421	72	**4l**	365/434	69
4b	353/421	68	**4m**	381/433	52

VI. Cell culture experiments, imaging of living-cells and cytotoxicity assays

The human hepatocellular carcinoma cell (SMMC-7721) lines were purchased from American Type Culture Collection. The cells were seeded in a 8-well tissue culture plate for one day and then cultured following ATCC protocols (The cells were maintained at 37 ºC, 5% CO_2 atmosphere in Dublecco's Minimum Essential Medium (DMEM) medium supplemented with 10% FBS, 2 mM L-glutamine, 100 units/mL of penicillin, and 100 mg/mL of streptomycin for overnight). For imaging experiments, live cells were coincubated with 5 μM **4f** in a physiological saline solution containing 1% DMSO for 40 min at 37 ºC. The cells were observed with a Fluorescence Inverted Microscope (IX71, OLYMPUS) and photographed by using Spot Flex.

Cytotoxicity assays

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay were performed to evaluate the cytotoxicity effect of 4e, 4f and 3g. HepG2 cells or A549 cells were incubated in a 96-well culture plates at a volume of 100 μL (5×10^4 cells/mL) for a stationary culture. This media were changed into fresh media with a final volume of 200 μL containing sample in the 2-fold down dilution series and then incubated for 24 hours. Then 20 μL of MTT (5 mg/mL in phosphate-buffered saline (PBS)) was added to each well, incubated for an additional 4 hours. After centrifuged at 1000 rpm for 5 min, the medium was removed. MTT formazan precipitate was dissolved in 150 μL of DMSO, shaken mechanically for 5 min and then absorbance readings at a wavelengthof 570 nm were taken on a spectrophotometer (Molecular Devices, Sunnyvale, USA). The cell viability was calculated by the following formula:

(mean optical density (OD) in treated wells/mean OD in control wells) × 100%.

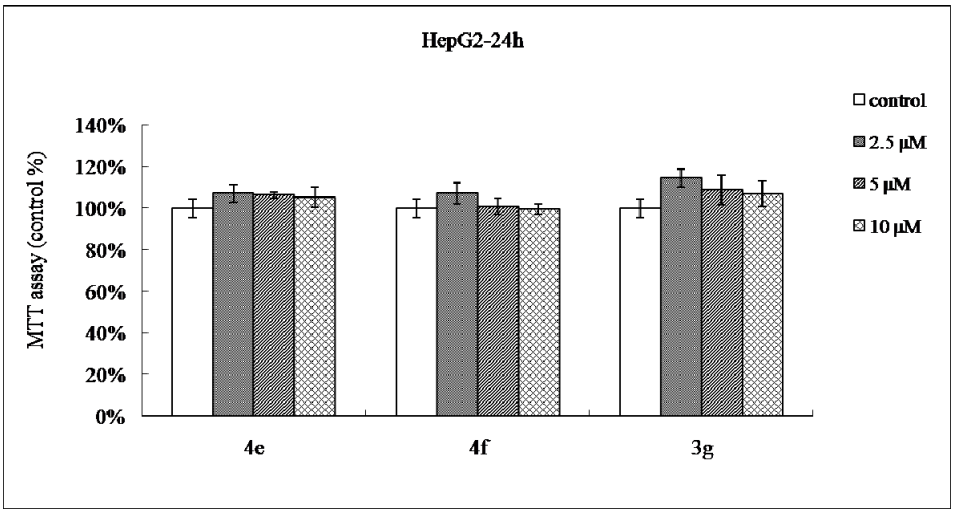


Fig. S1 Cell viability values (%) estimated by MTT assays on HepG2 cells, which were cultured in the presence of 2.5-10 μM of sample for 24 h at 37 °C.

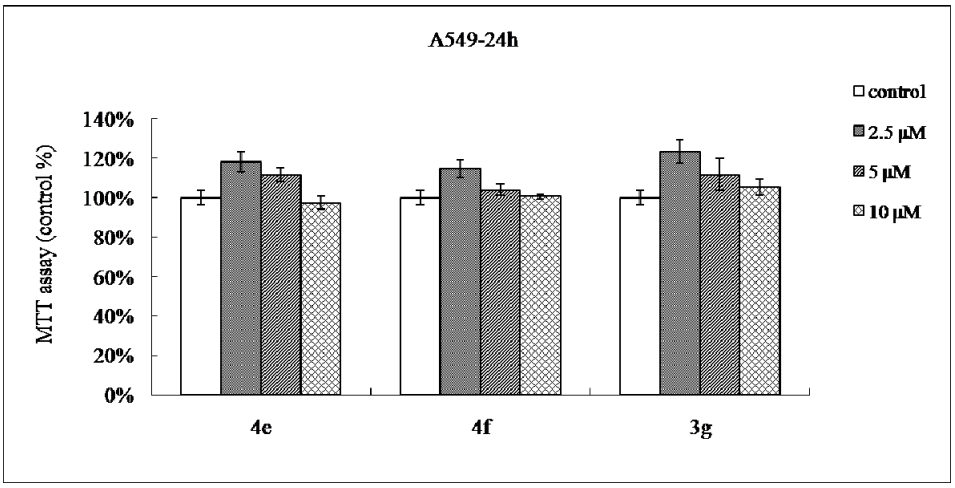


Fig. S2 Cell viability values (%) estimated by MTT assays on A549 cells, which were cultured in the presence of 2.5-10 μM of sample for 24 h at 37 °C.

VII. References

(1) J. W. Daly, W. L. Padgett and M. T. Shamim, *J. Med. Chem.*, 1986, **29**, 1305.

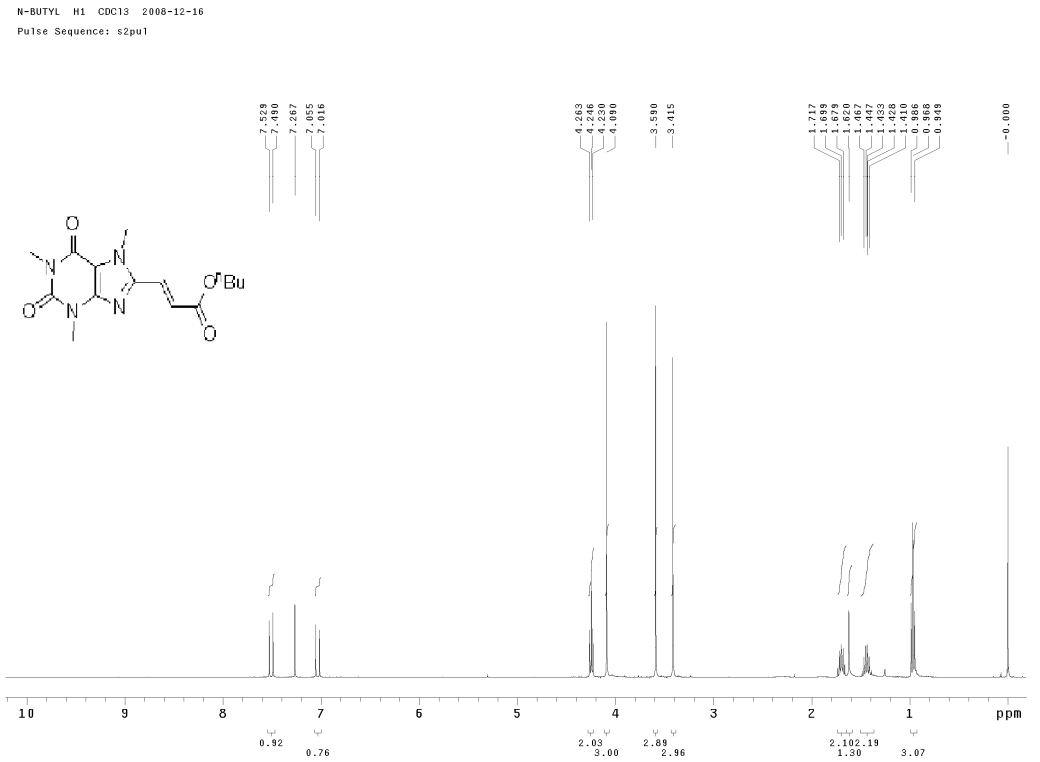
(2) (*a*) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.* 2010, **132**, 1822; (*b*) D. van den Berg, K. R. Zoellner, M. O. Ogunrombi, S. F. Malan, G. Terre'Blanche, N. Castagnoli, Jr., J. J. Bergh and J. P. Petzer, *Bioorg. Med.*

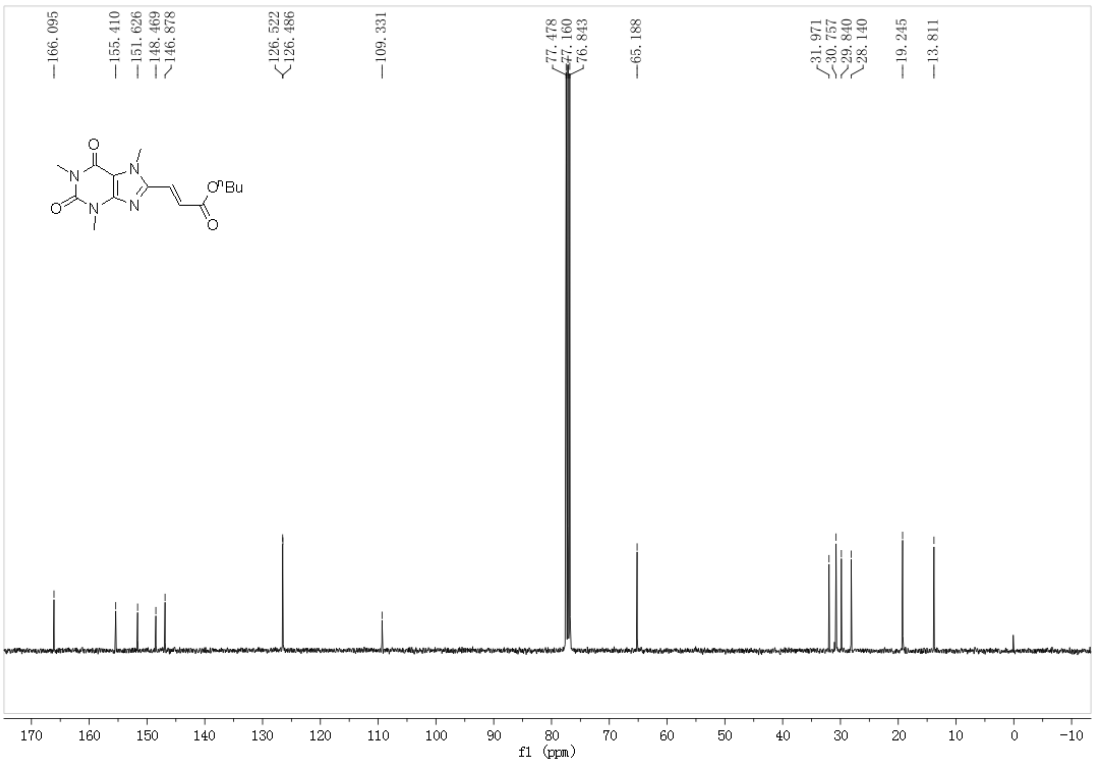
Chem. 2007, **15**, 3692.

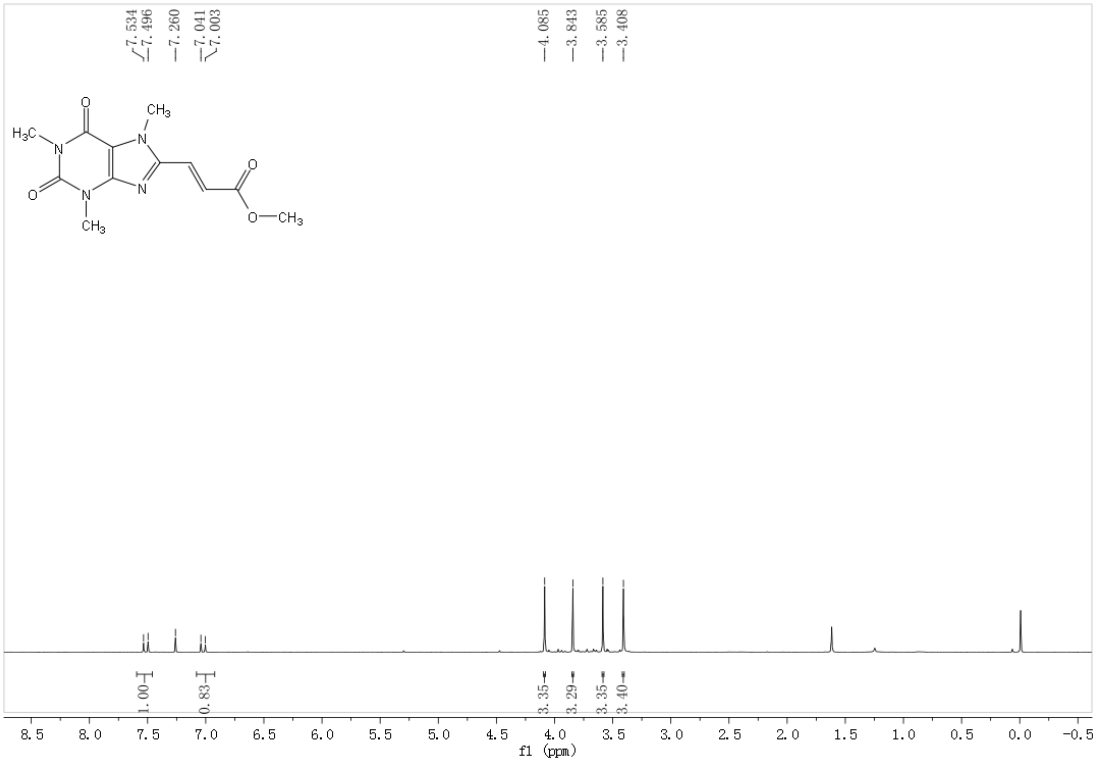
(3) R. S. Butler, P. Cohn, P. Tenzel, K. A. Abboud and R. K. Castellano, *J. Am. Chem. Soc.*, 2009, **131**, 623.

(4) (*a*) L. Zhang, F. Liang, L. Sun, Y. Hu and H. Hu, *Synthesis*, 2000, 1733. (*b*) M. L. Bode and P. T. Kaye, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1809.

VIII. ^{1}H and ^{13}C NMR spectra of compounds 3a-3i, 4a-4m, CSC and KW6002



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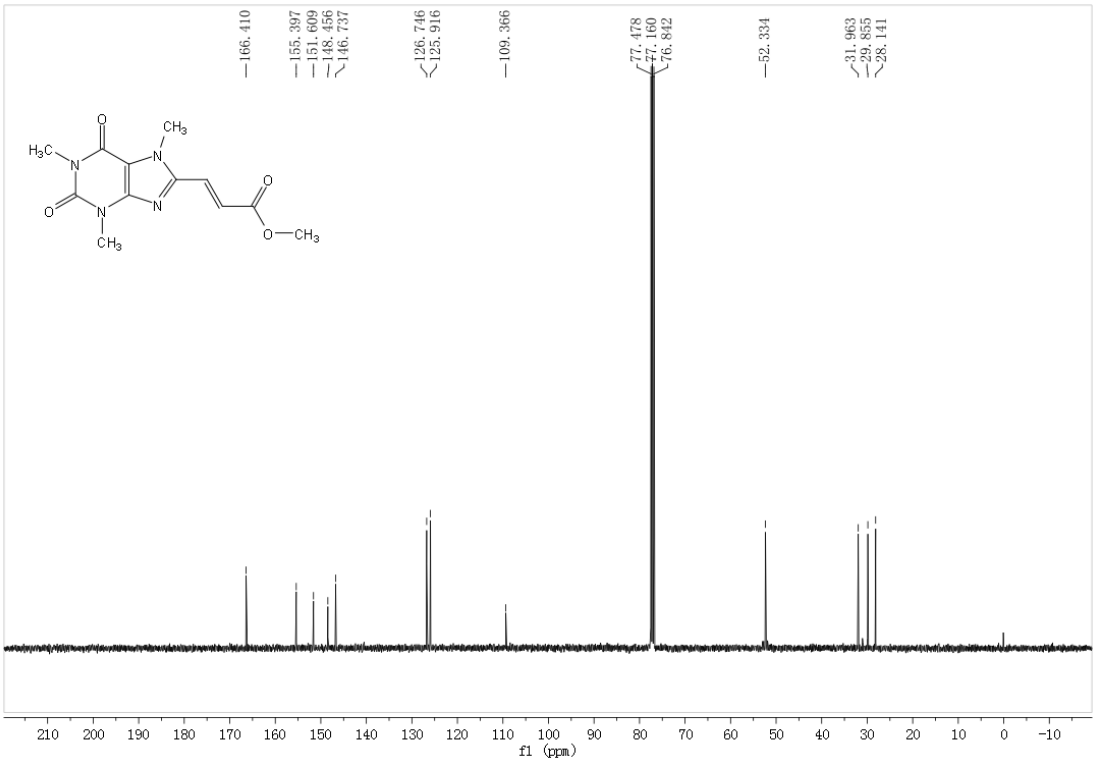
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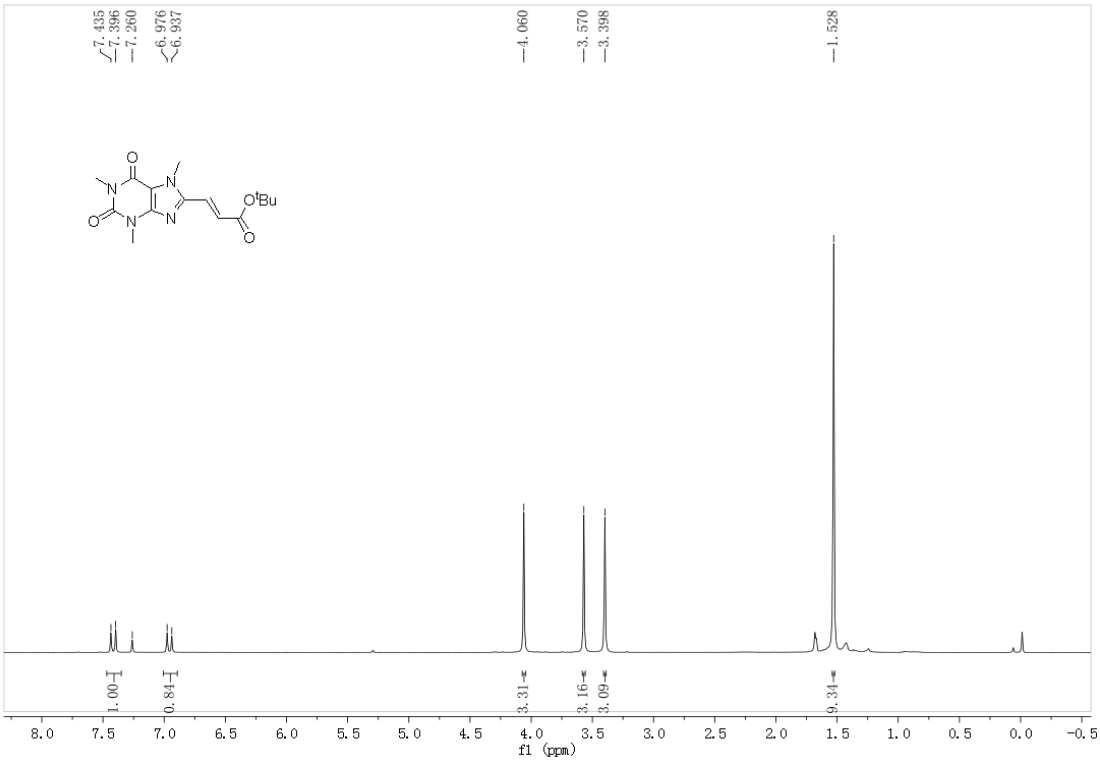
f1 (ppm)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O
tBu
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0.84
3.31
3.16
3.09
9.34
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.0
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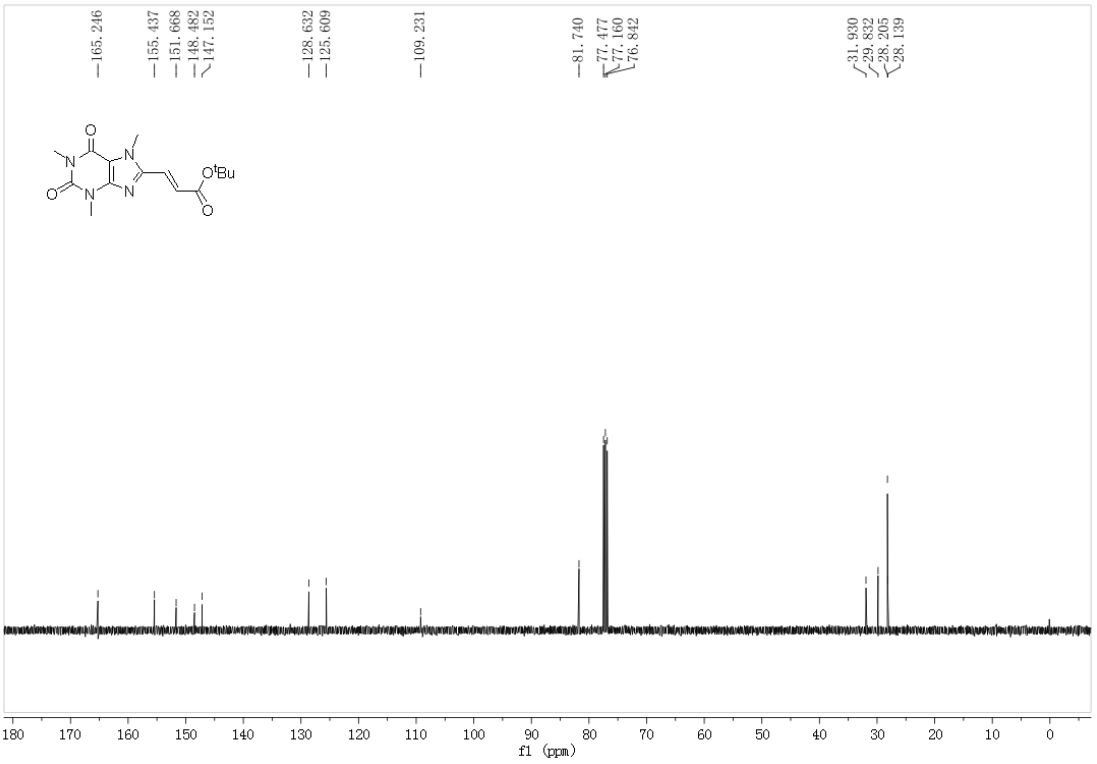
f1 (ppm)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28.205
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O
N
N
O
O
tBu
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50
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10
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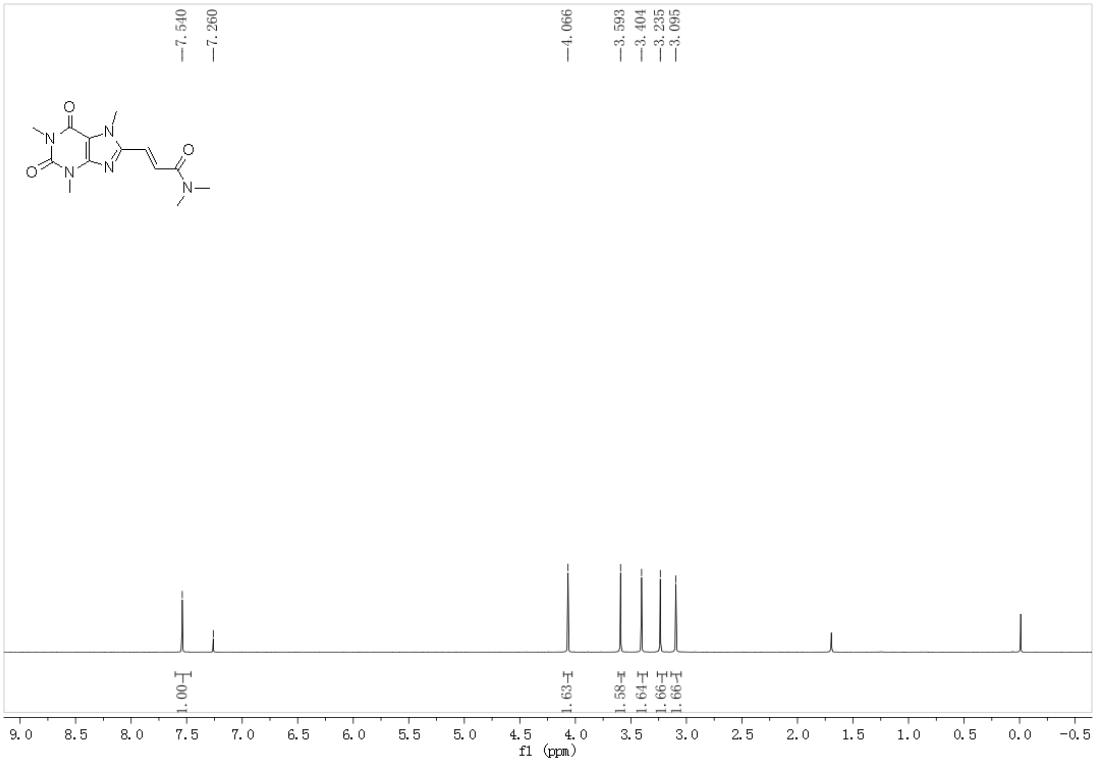
f1 (ppm)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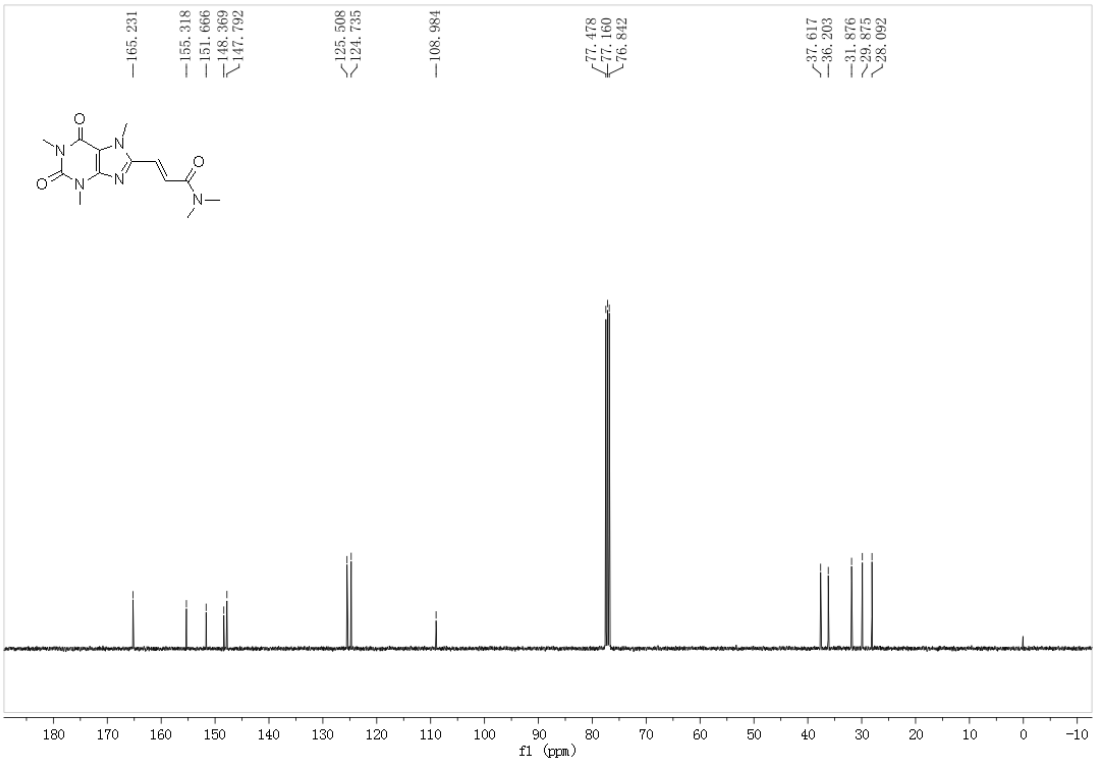
f1 (ppm)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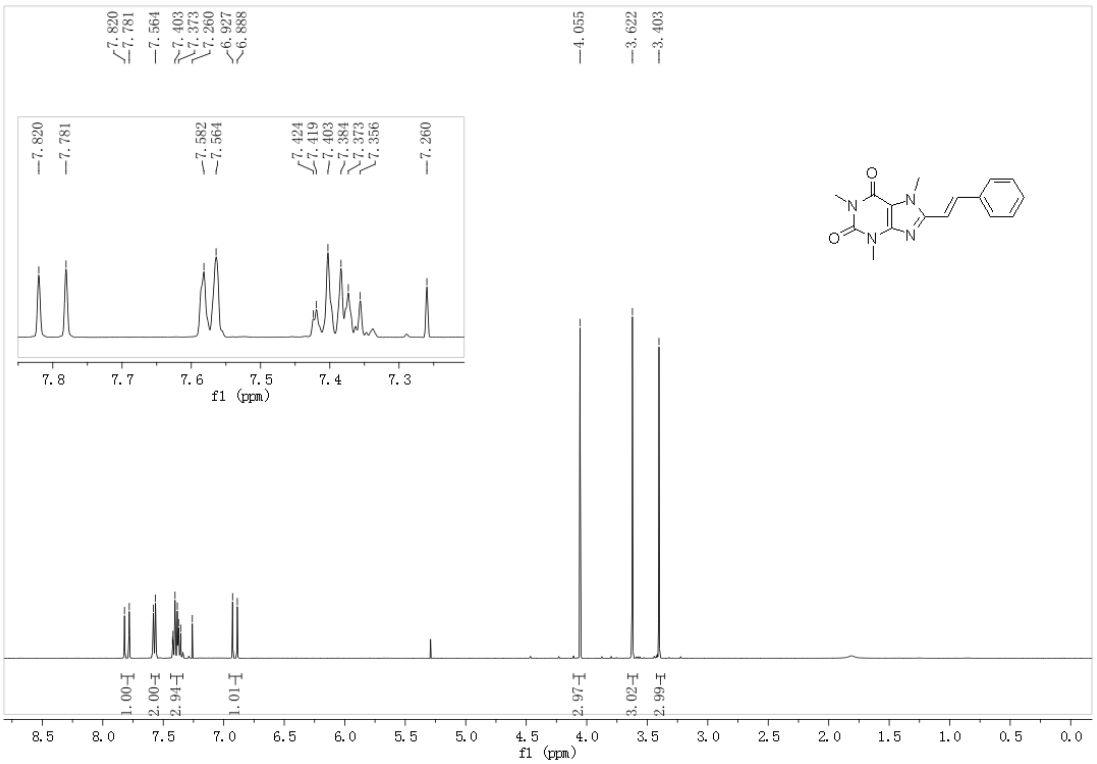
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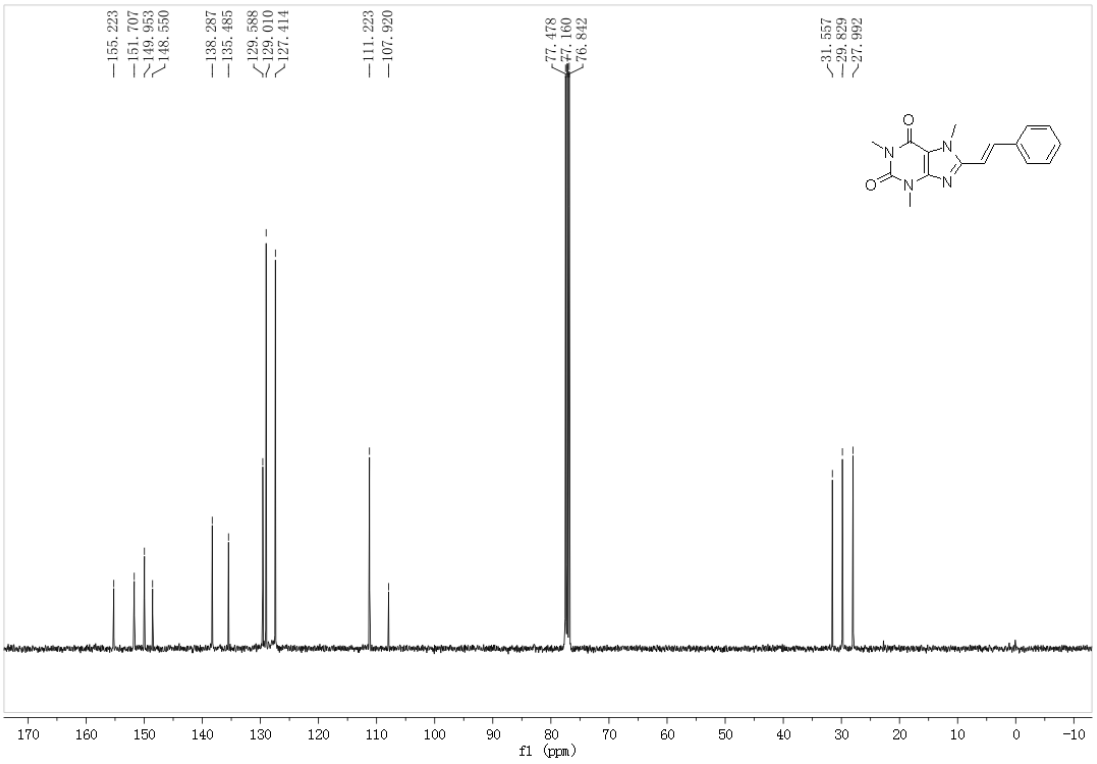
2.99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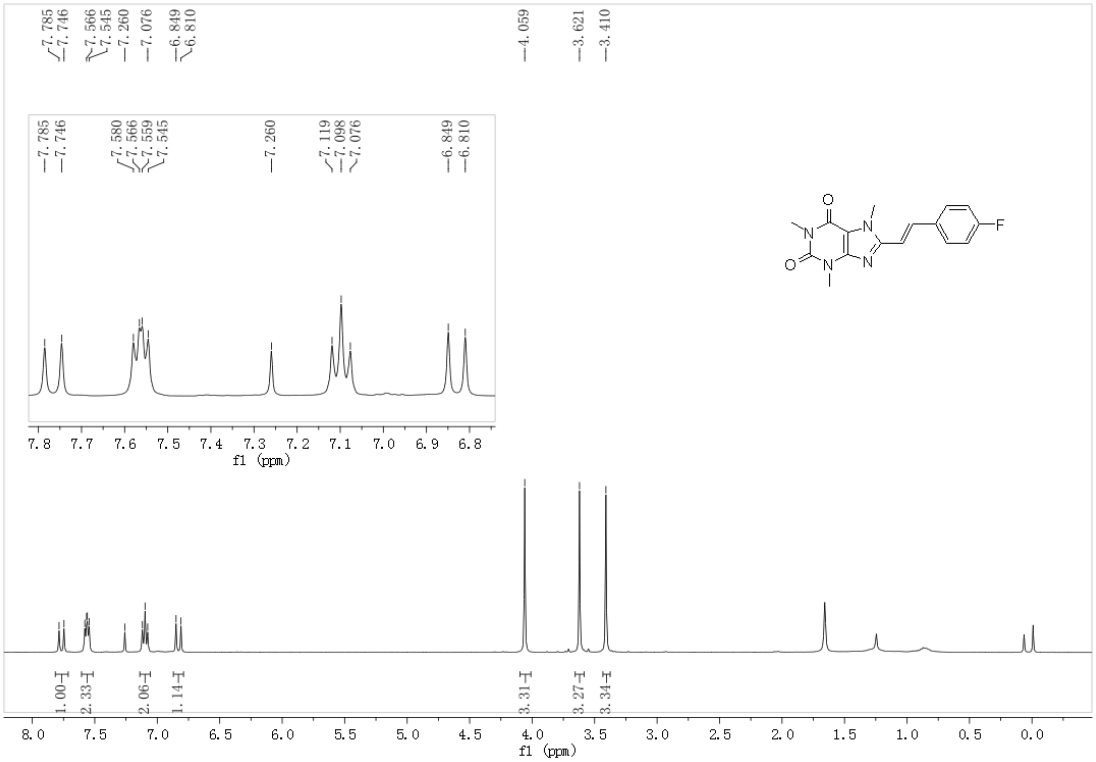
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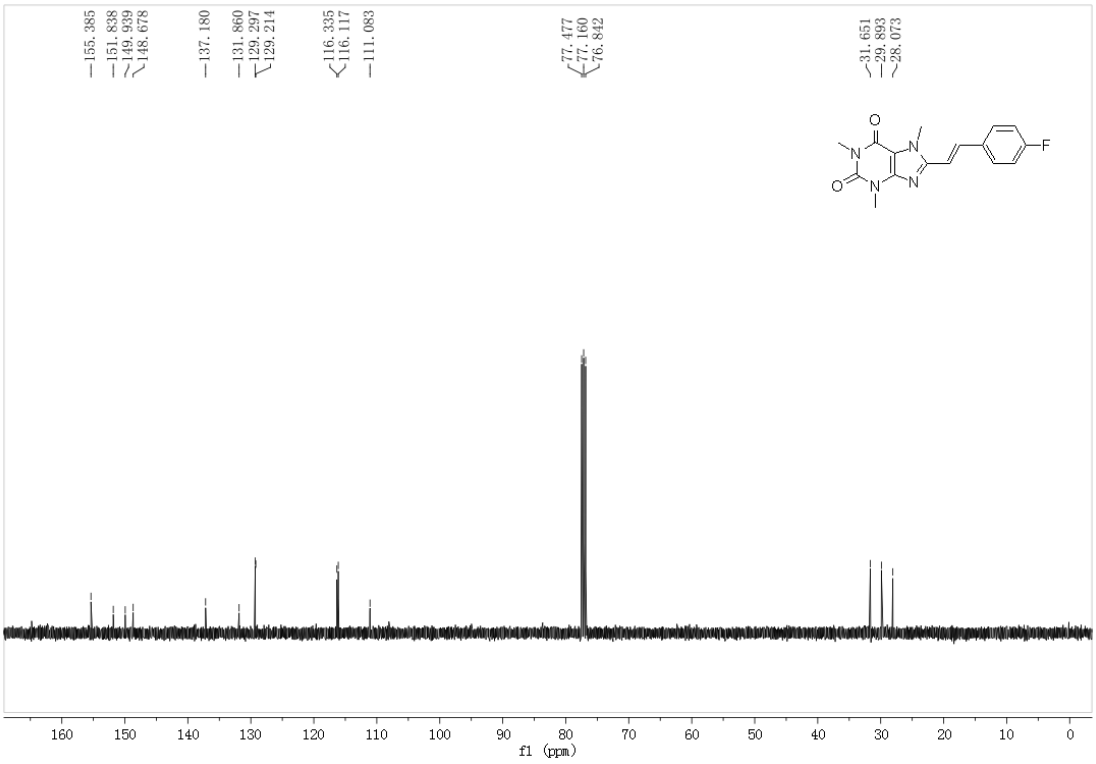
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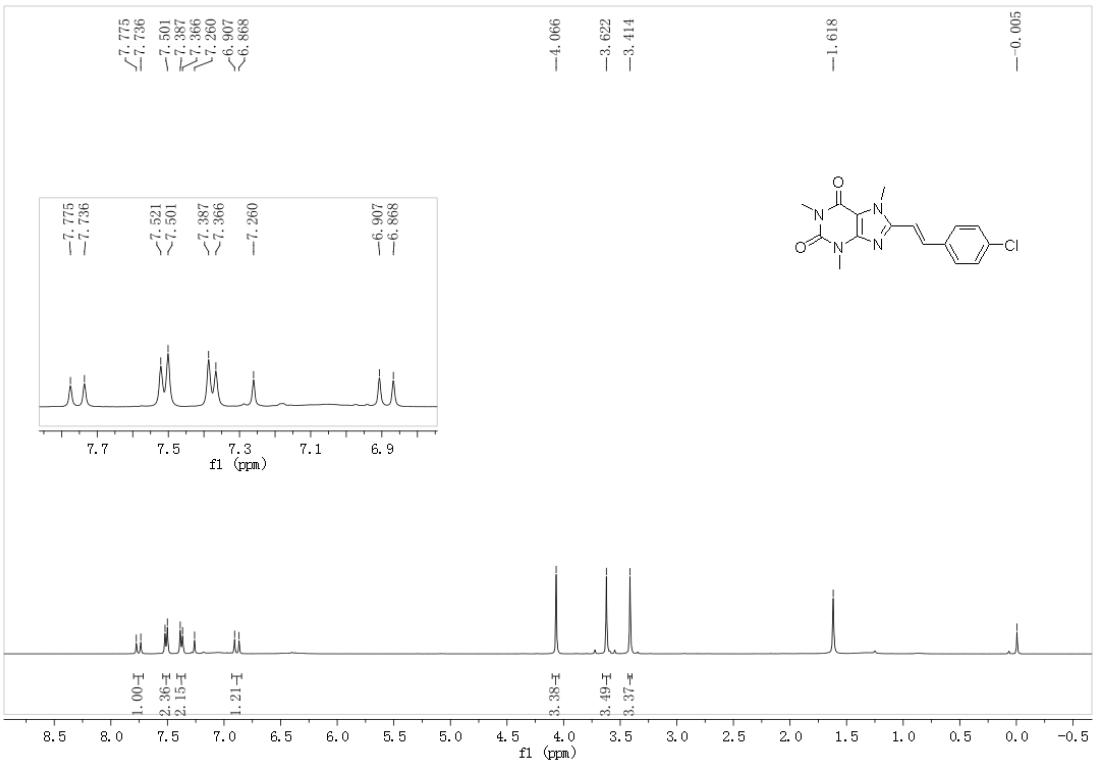
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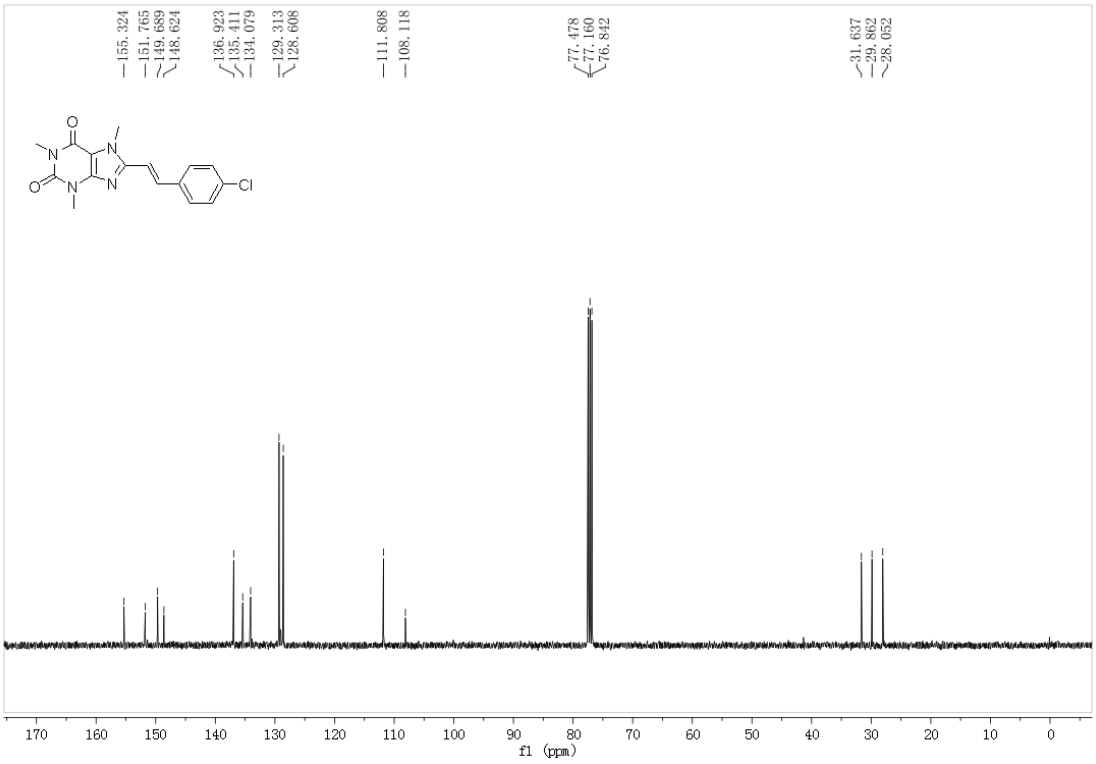
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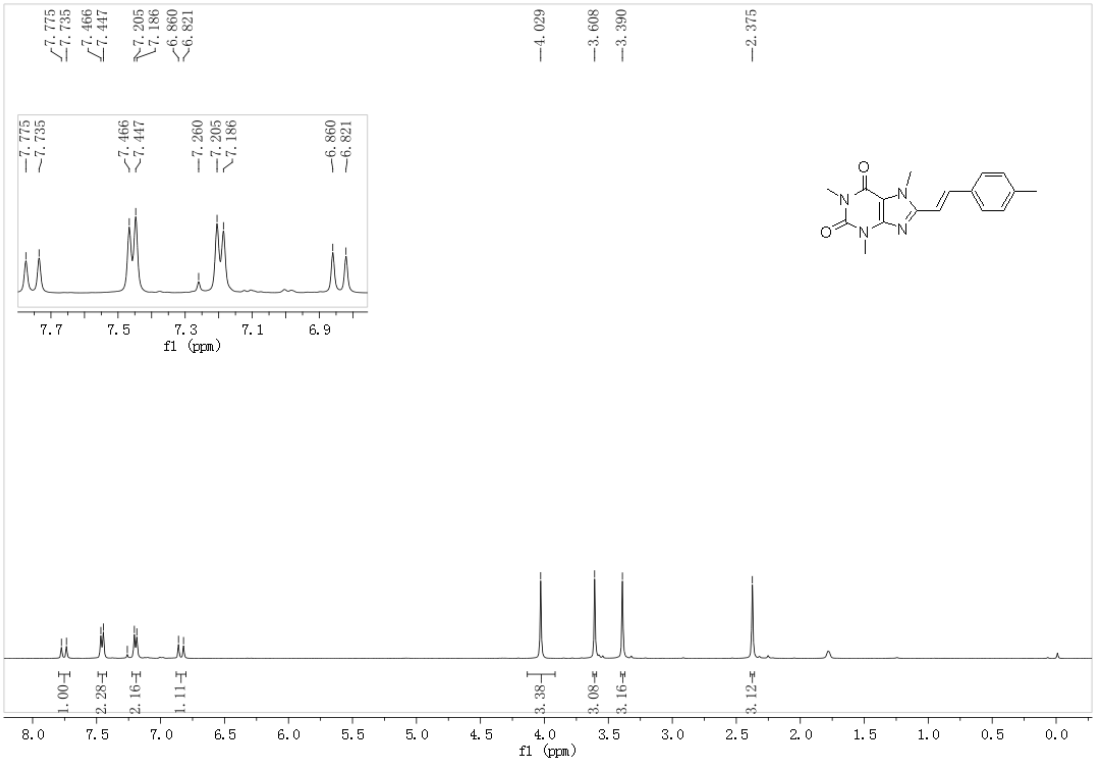
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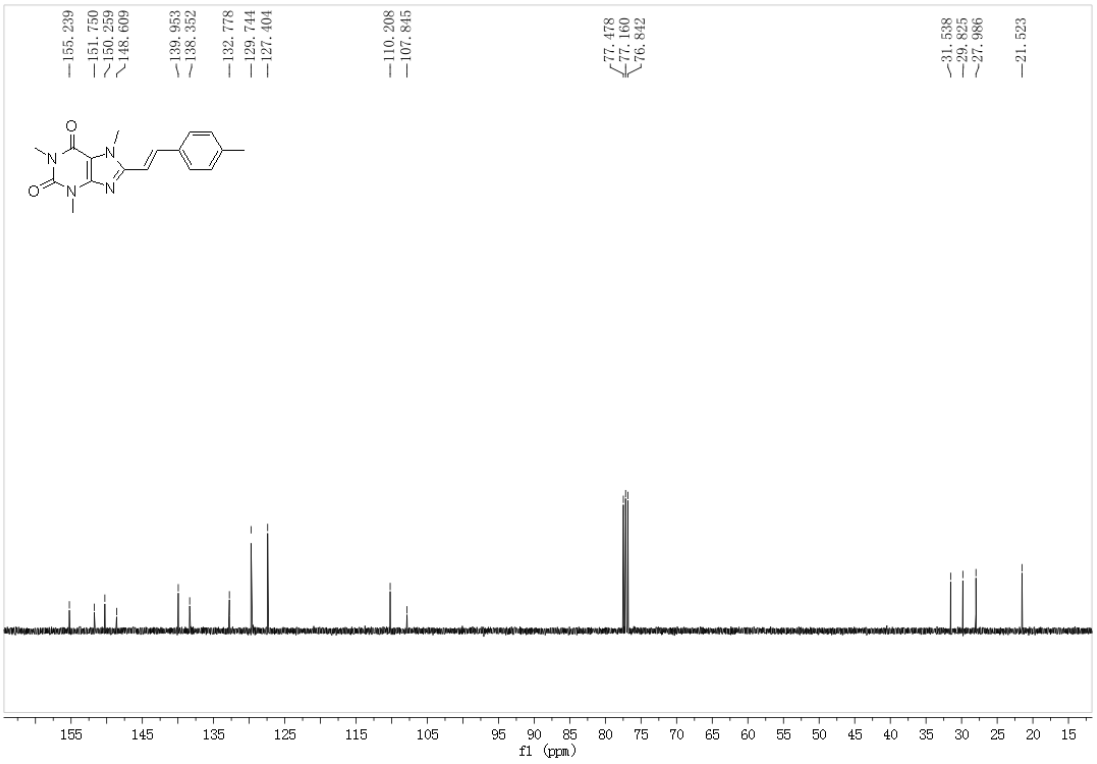
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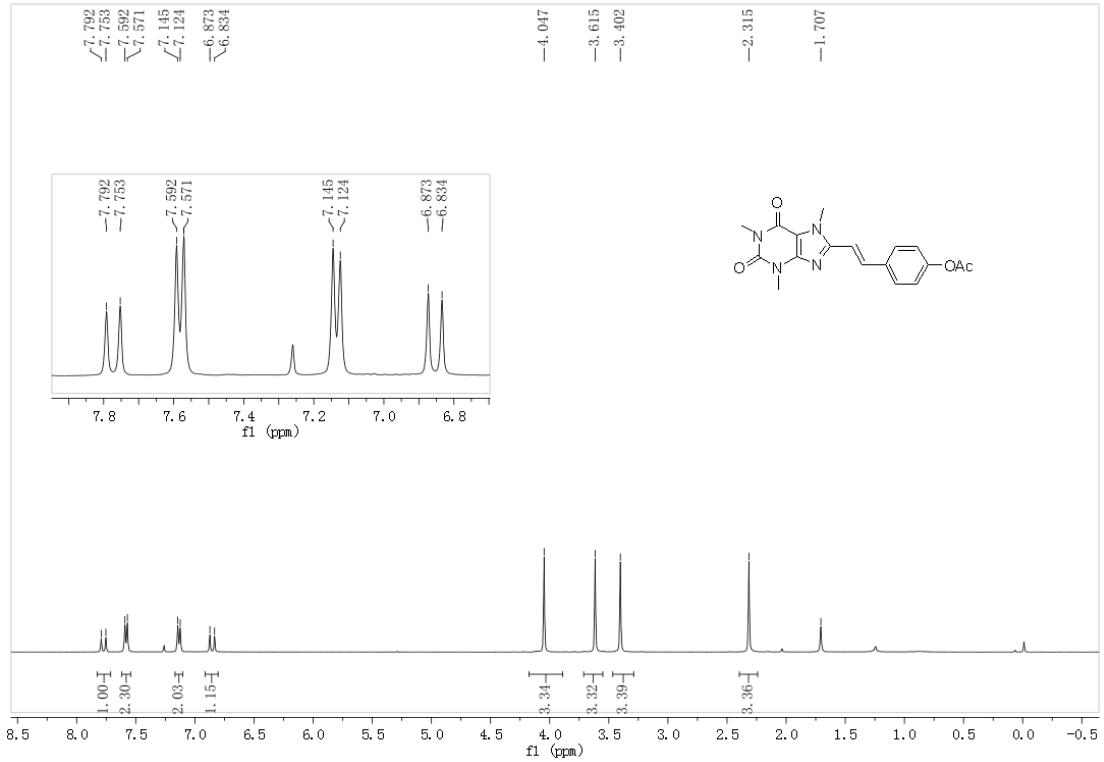
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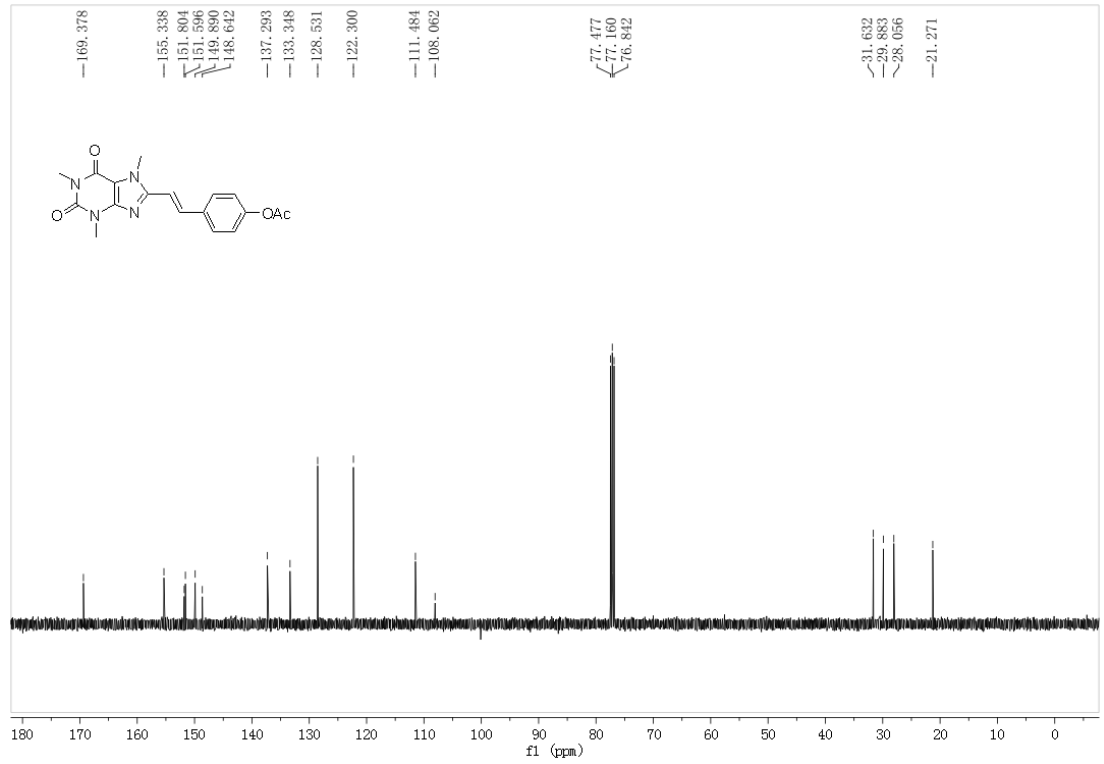
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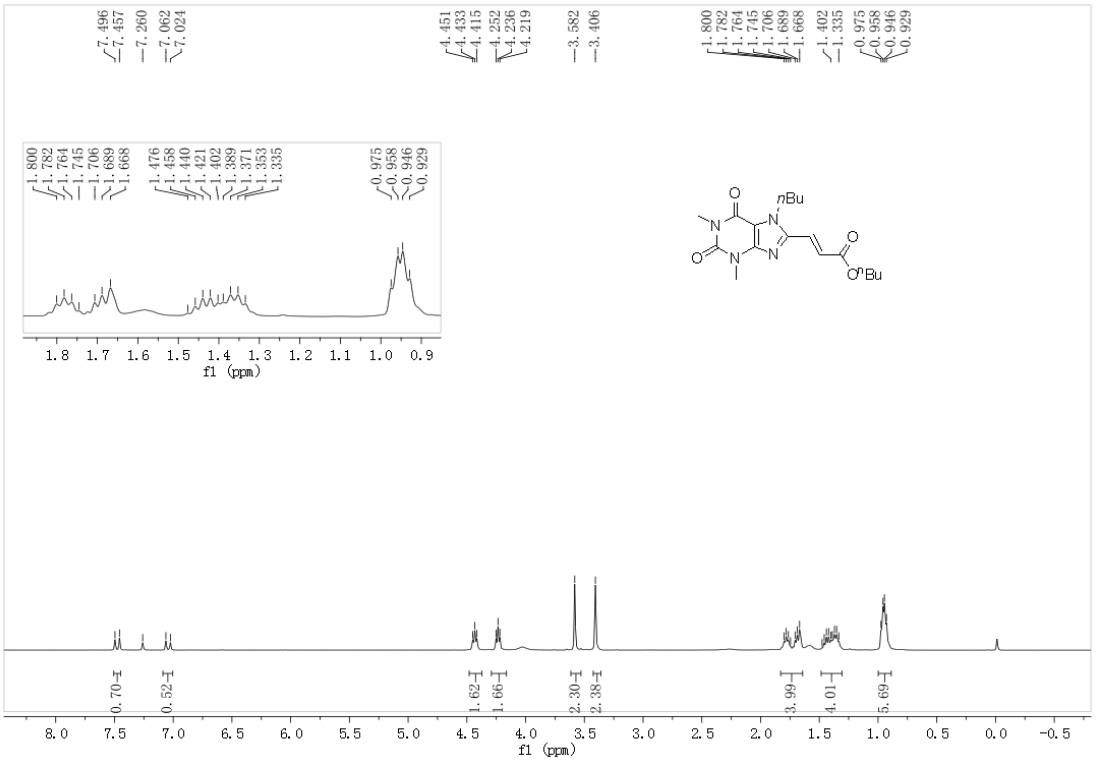
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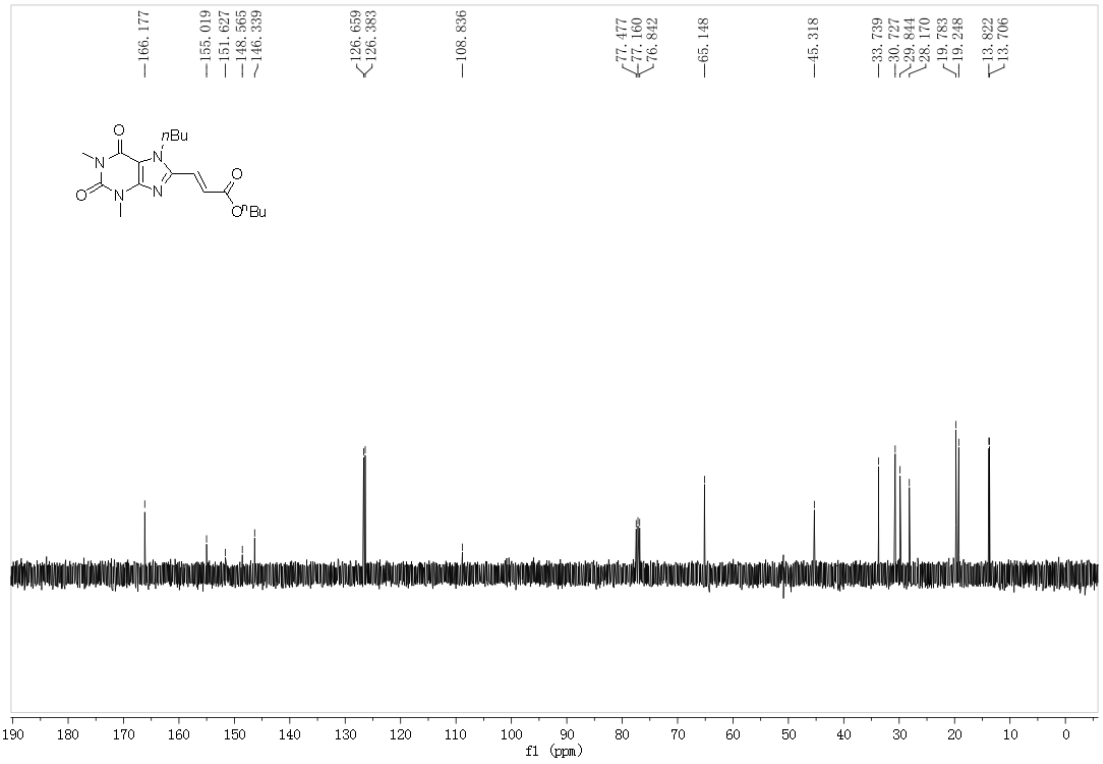
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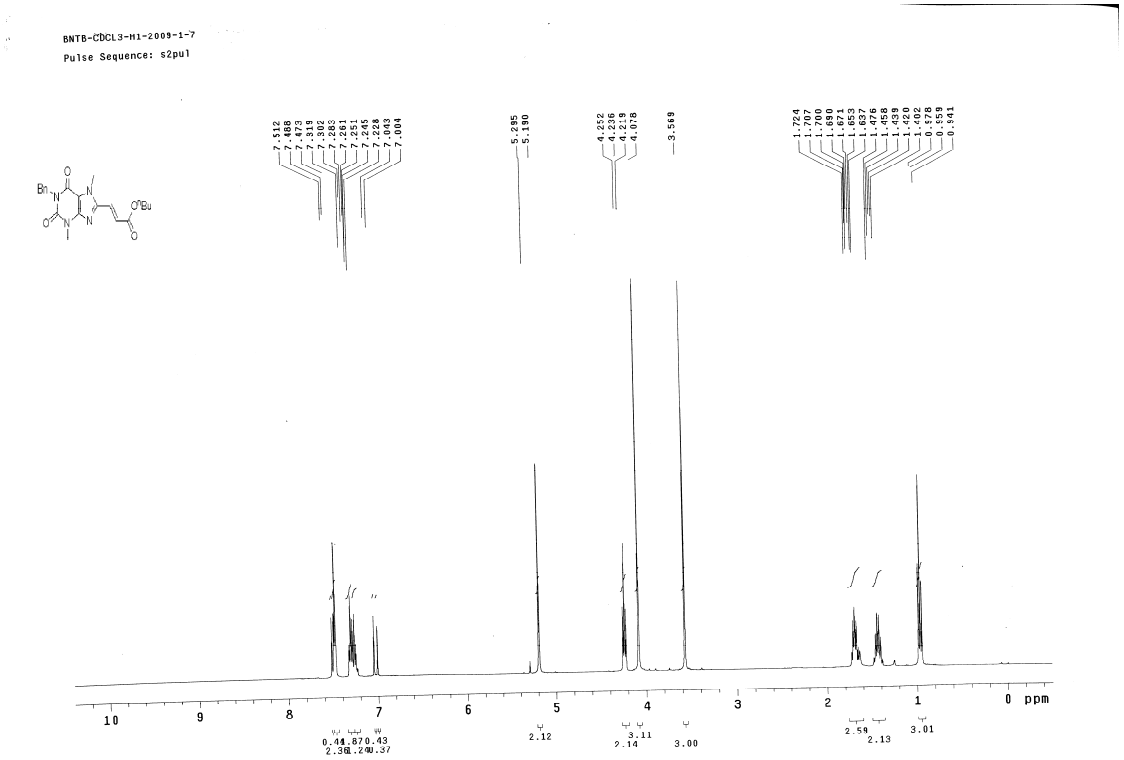
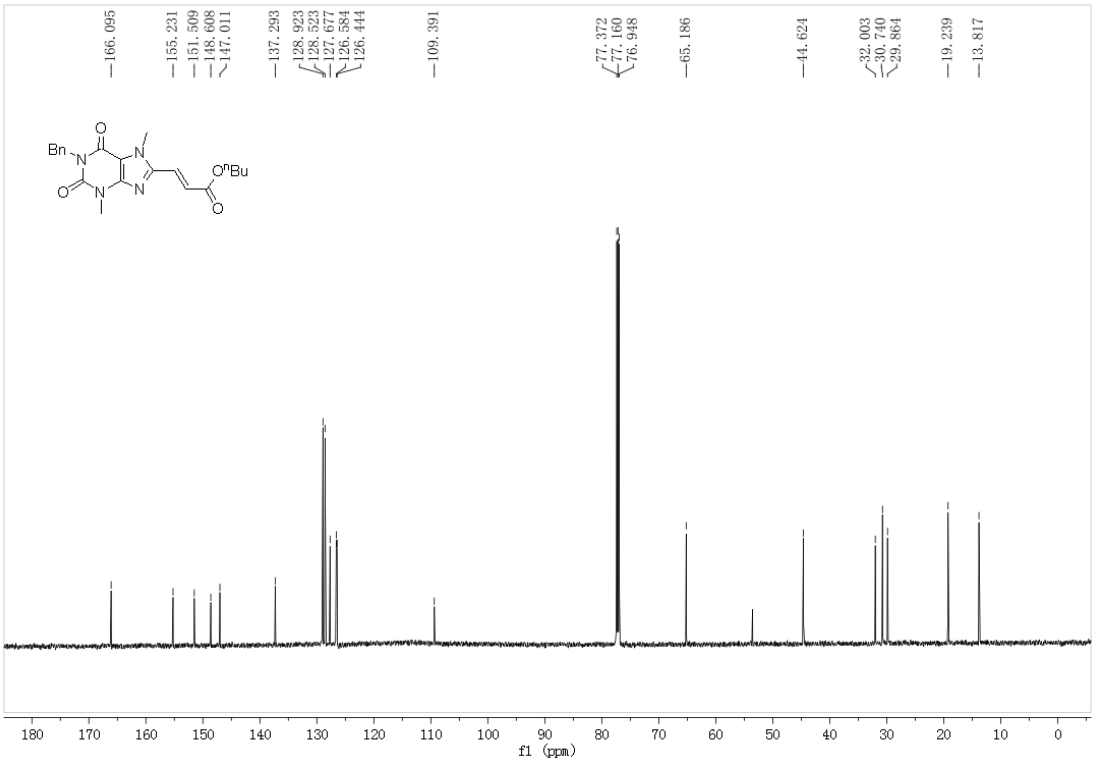
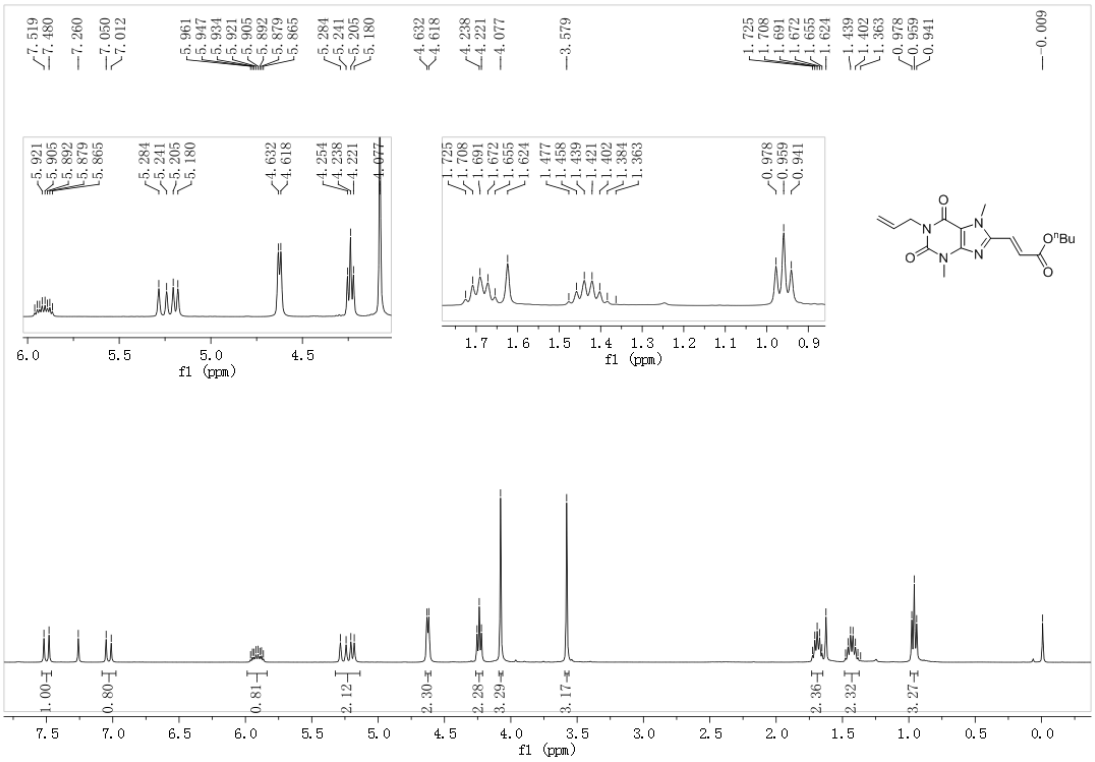
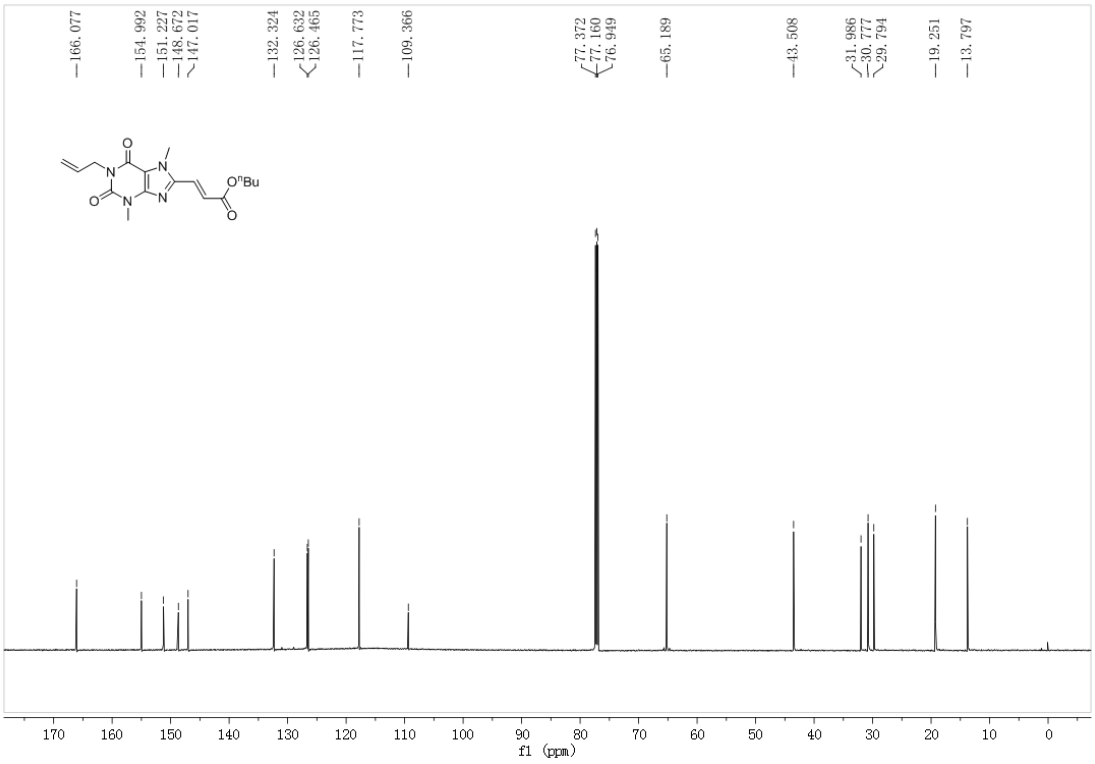
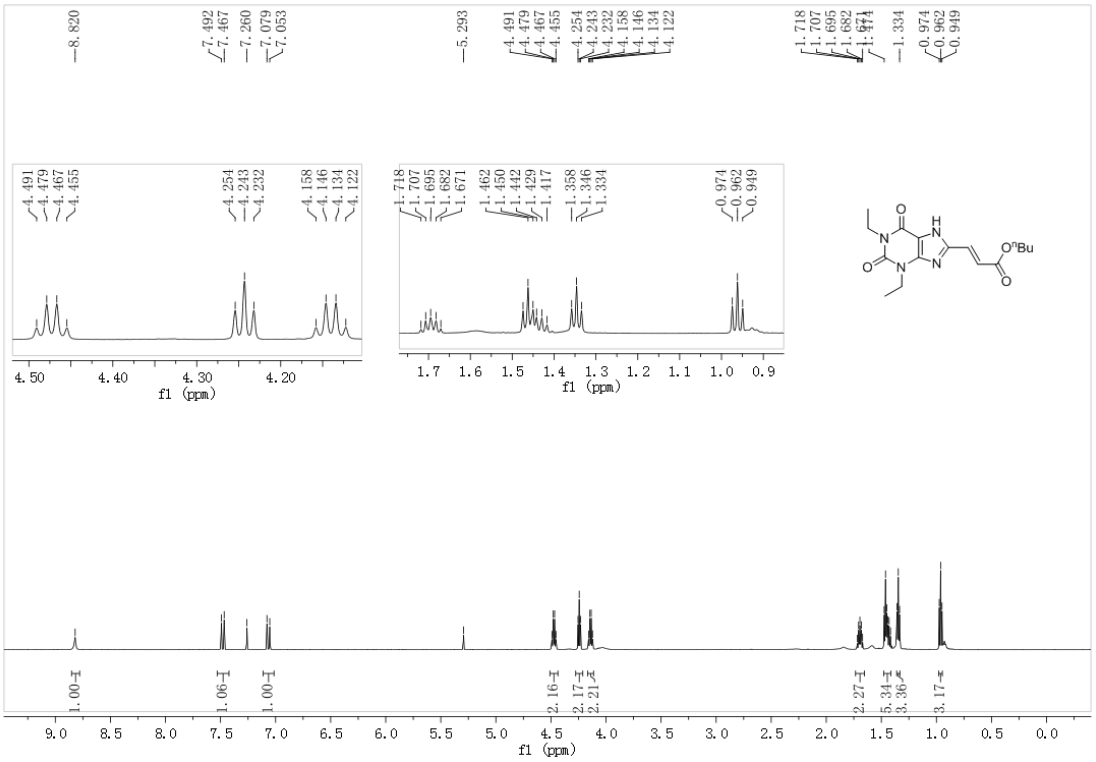
28.170
19.783
19.248
13.822
13.706
nBu
O
N
O
nBu
f1 (ppm)

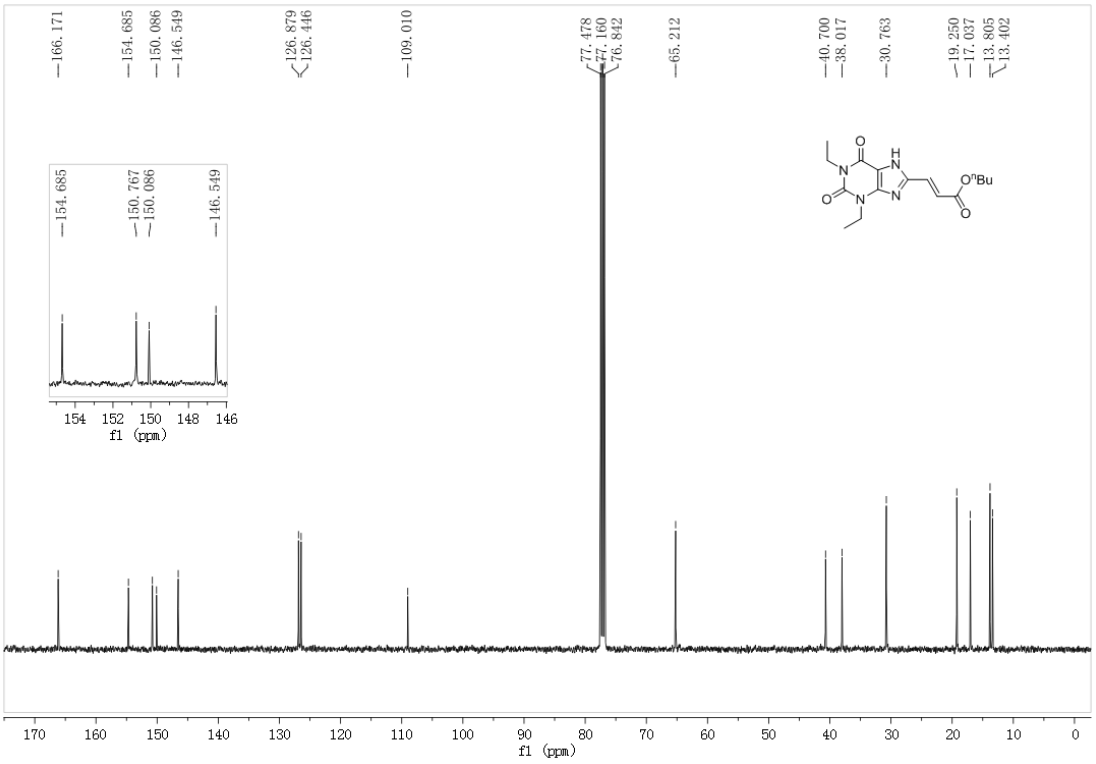

BNTB-CDCL3-H1-2009-1-7
Pulse Sequence: s2pul
7.512
7.488
7.473
7.319
7.303
7.288
7.261
7.251
7.245
7.228
7.043
7.004
5.295
5.190
4.252
4.236
4.219
4.078
3.569
1.724
1.707
1.700
1.680
1.671
1.655
1.637
1.476
1.458
1.439
1.420
1.402
0.578
0.559
0.541
Bn
O
N
OnBu
10
9
8
7
6
5
4
3
2
1
0 ppm
0.44
4.87
2.50
1.20
0.43
0.37
2.12
3.11
2.14
3.00
2.59
2.13
3.01

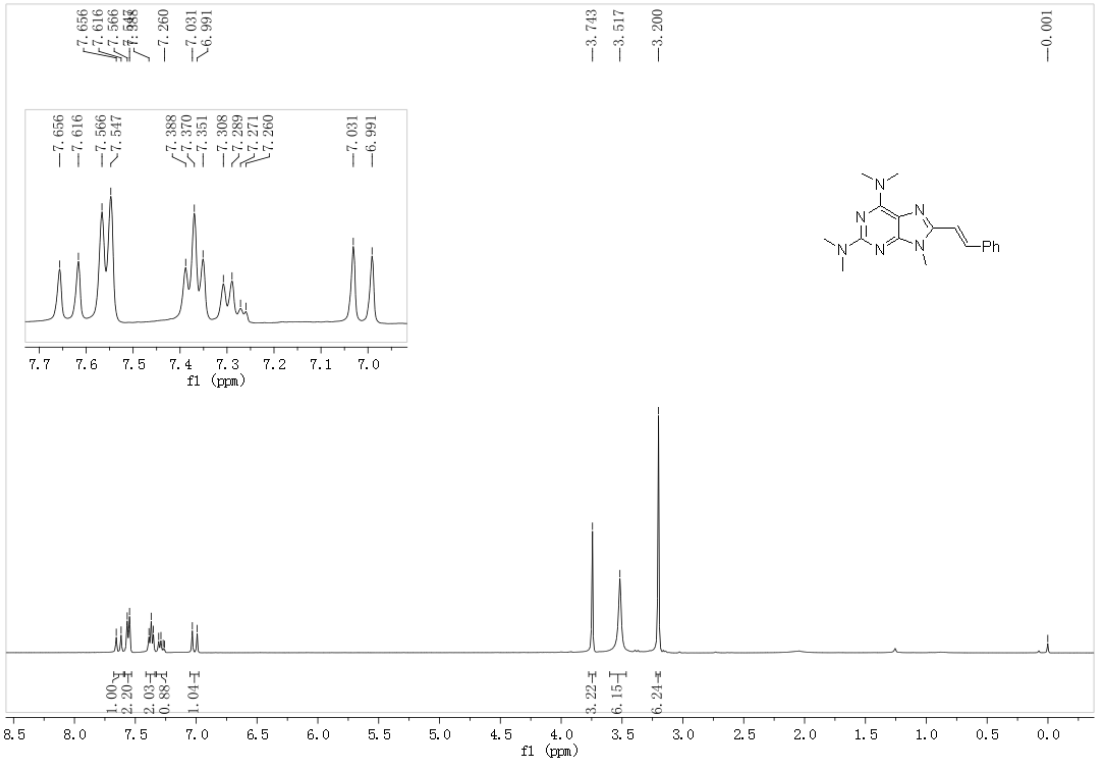

166.095
155.231
151.509
148.608
147.011
137.293
128.923
128.523
127.677
126.584
126.444
109.391
77.372
77.160
76.948
65.186
44.624
32.003
30.740
29.864
19.239
13.817
Bn
O
N
OnBu
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

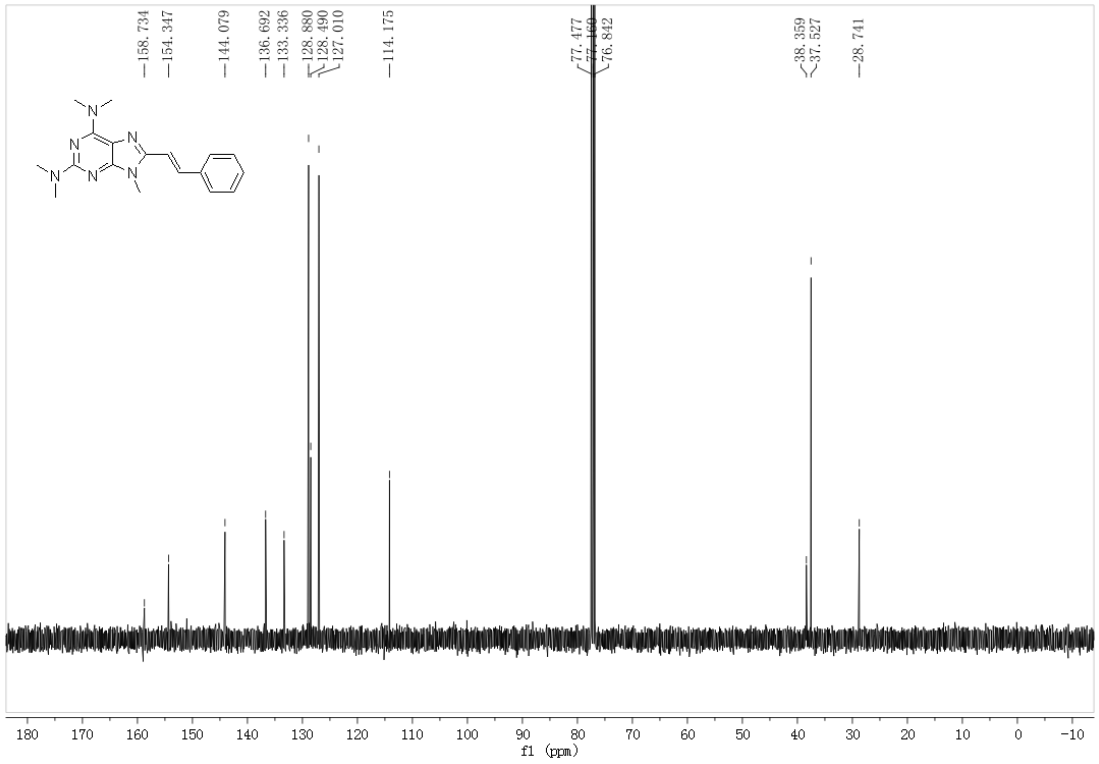

7.519
7.480
7.260
7.050
7.012
5.961
5.947
5.934
5.921
5.905
5.892
5.879
5.865
5.284
5.241
5.205
5.180
4.632
4.618
4.238
4.221
4.077
3.579
1.725
1.708
1.691
1.672
1.655
1.624
1.439
1.402
1.363
0.978
0.959
0.941
0.009
f1 (ppm)
1.00
0.80
0.81
2.12
2.30
2.28
3.29
3.17
2.36
2.32
3.27
OnBu

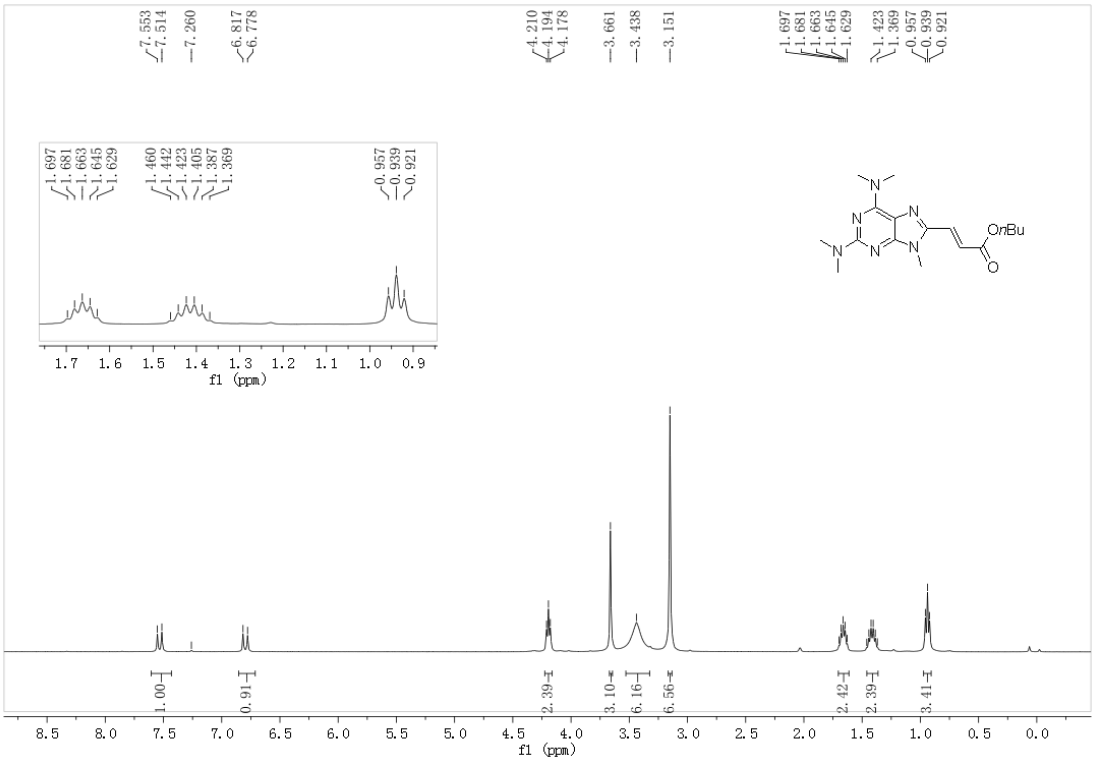

166.077
154.992
151.227
148.672
147.017
132.324
126.632
126.465
117.773
109.366
77.372
77.160
76.949
65.189
43.508
31.986
30.777
29.794
19.251
13.797
OnBu
f1 (ppm)

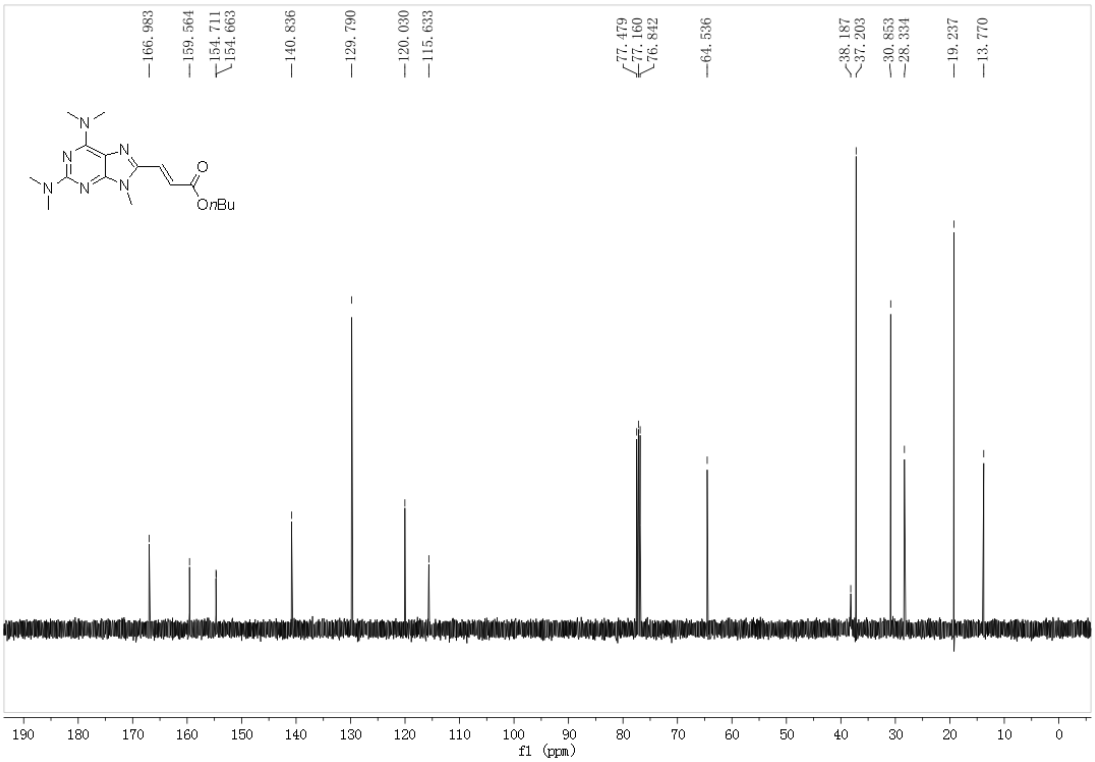

8.820
7.492
7.467
7.260
7.079
7.053
5.293
4.491
4.479
4.467
4.455
4.254
4.243
4.232
4.158
4.146
4.134
4.122
1.718
1.707
1.695
1.682
1.671
1.462
1.450
1.442
1.429
1.417
1.358
1.346
1.334
0.974
0.962
0.949
O^{n}Bu
f1 (ppm)
1.00
1.06
1.00
2.16
2.17
2.21
2.27
5.34
3.36
3.17

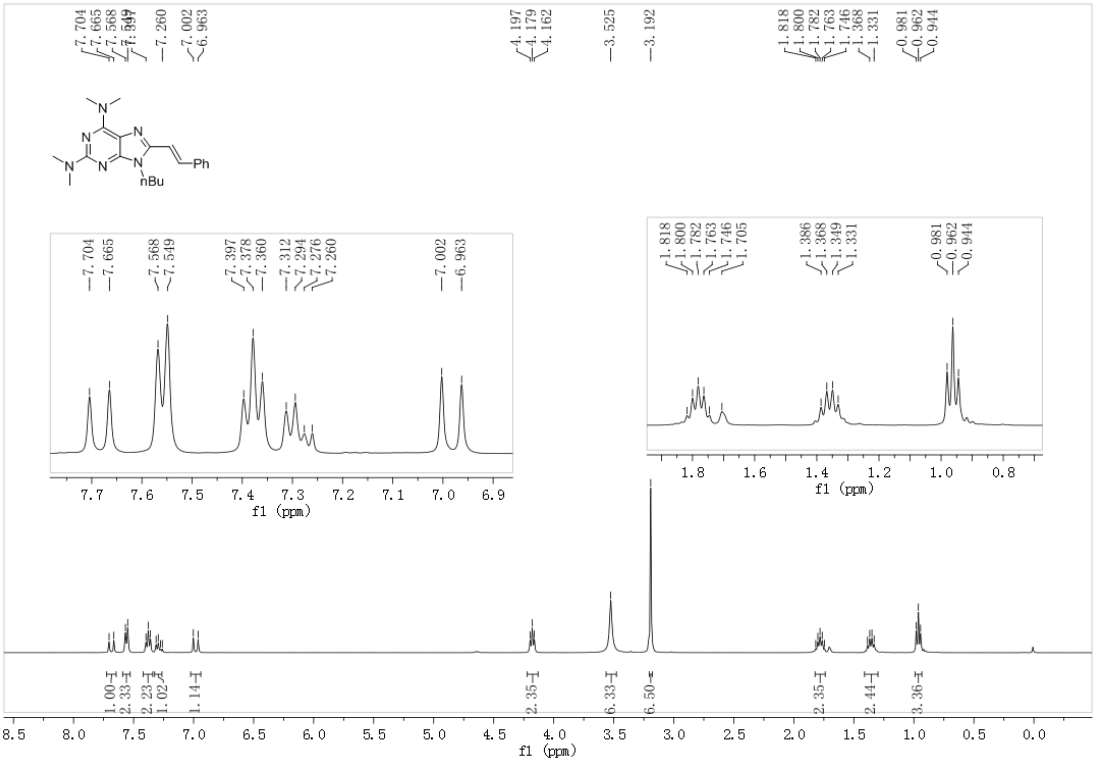

166.171
154.685
150.086
146.549
126.879
126.446
109.010
77.478
77.160
76.842
65.212
40.700
38.017
30.763
19.250
17.037
13.805
13.402
150.767
O^{n}Bu
f1 (ppm)

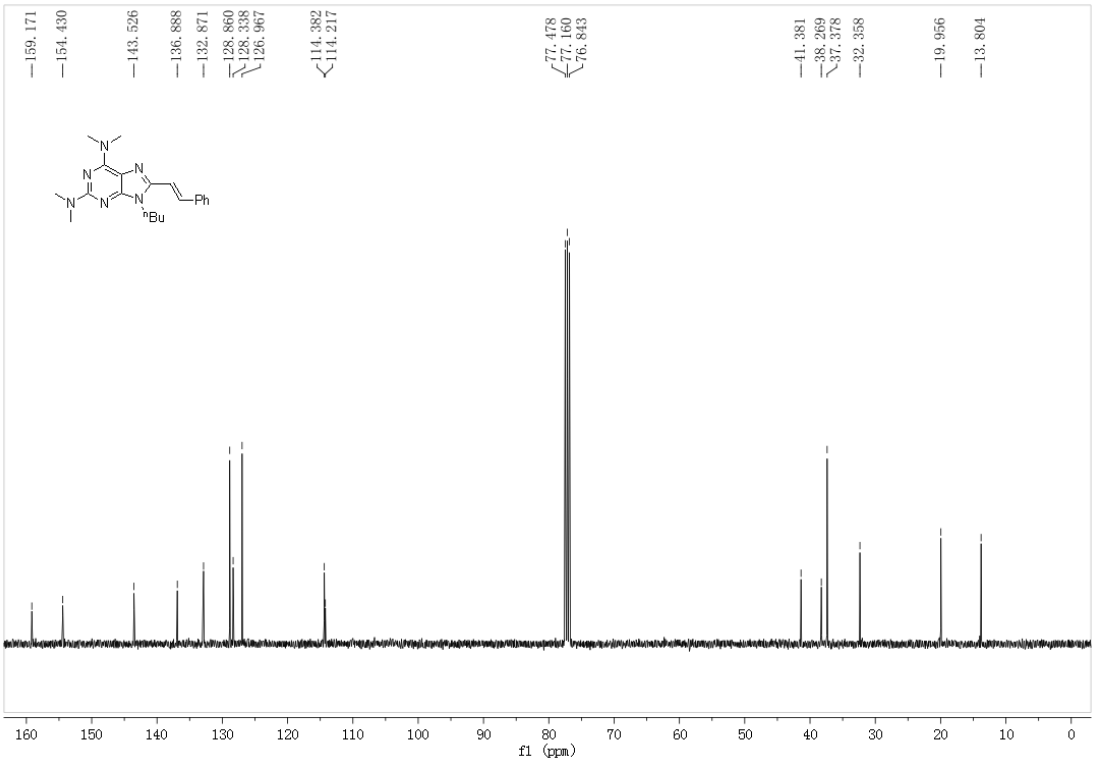

7.656
7.616
7.566
7.547
7.260
7.031
6.991
3.743
3.517
3.200
0.001
7.388
7.370
7.351
7.308
7.289
7.271
7.260
Ph
f1 (ppm)

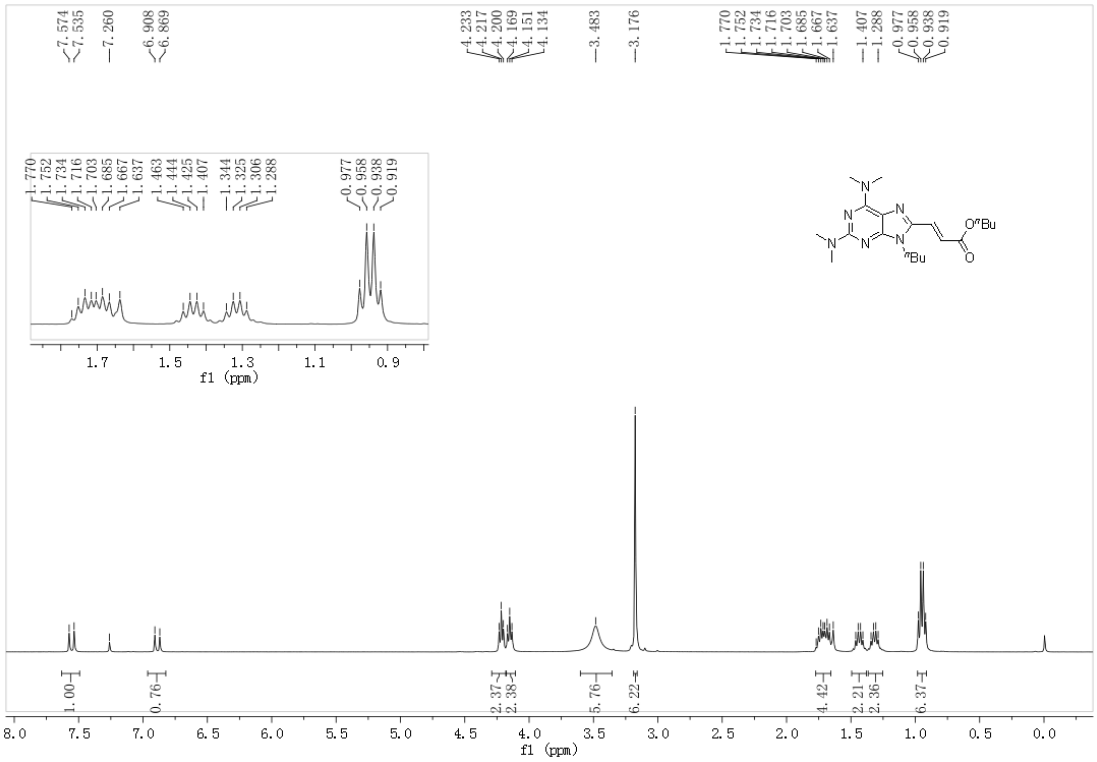

158.734
154.347
144.079
136.692
133.336
128.880
128.490
127.010
114.175
77.477
76.842
38.359
37.527
28.741
f1 (ppm)

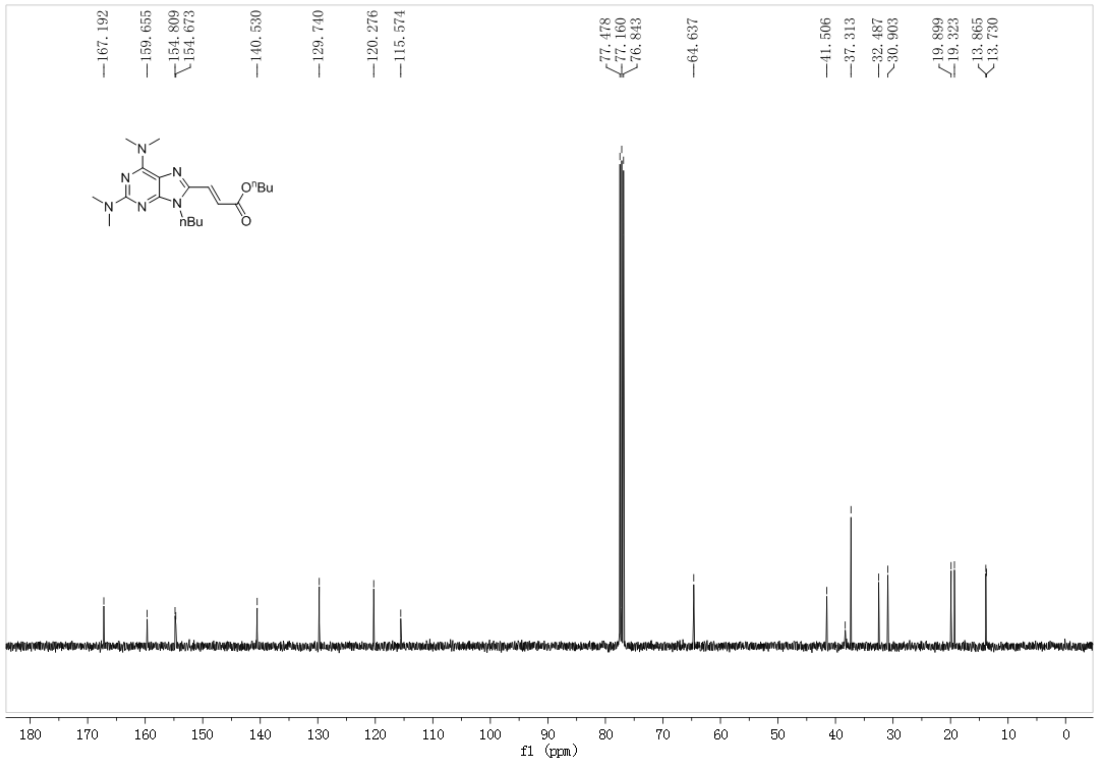

7.553
7.514
7.260
6.817
6.778
4.210
4.194
4.178
3.661
3.438
3.151
1.697
1.681
1.663
1.645
1.629
1.460
1.442
1.423
1.405
1.387
1.369
0.957
0.939
0.921
OnBu
f1 (ppm)
1.00
0.91
2.39
3.10
6.16
6.56
2.42
2.39
3.41

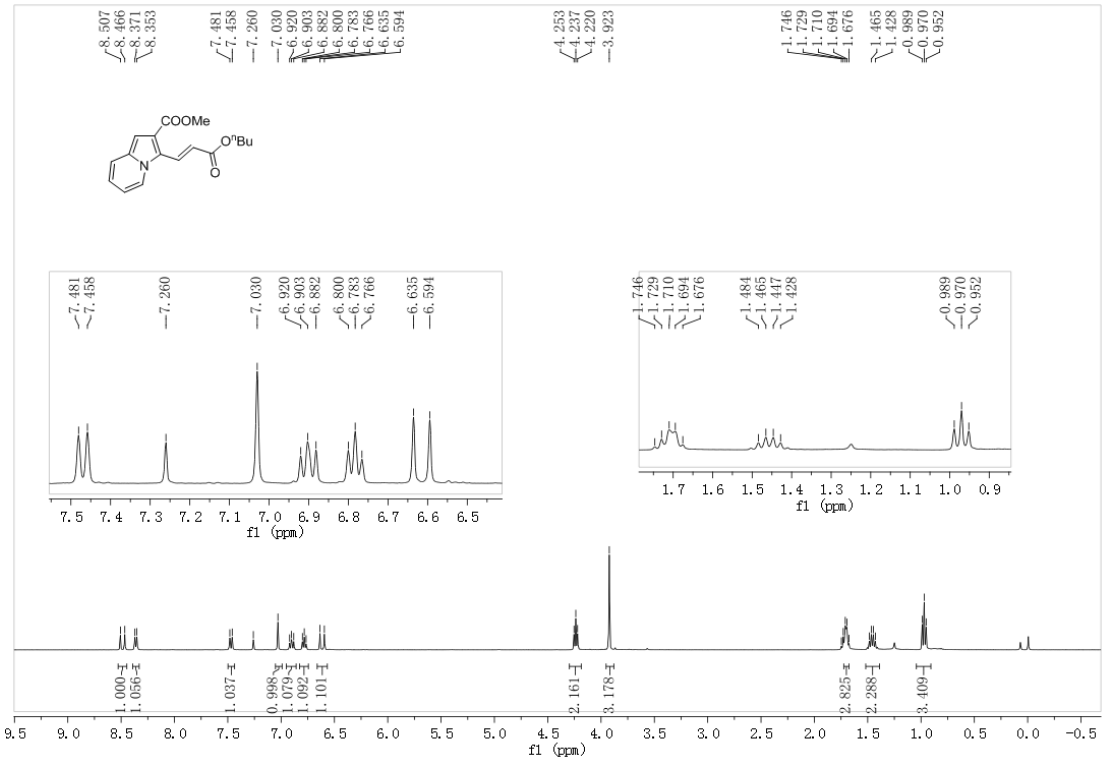

166.983
159.564
154.711
154.663
140.836
129.790
120.030
115.633
77.479
77.160
76.842
64.536
38.187
37.203
30.853
28.334
19.237
13.770
OnBu
f1 (ppm)

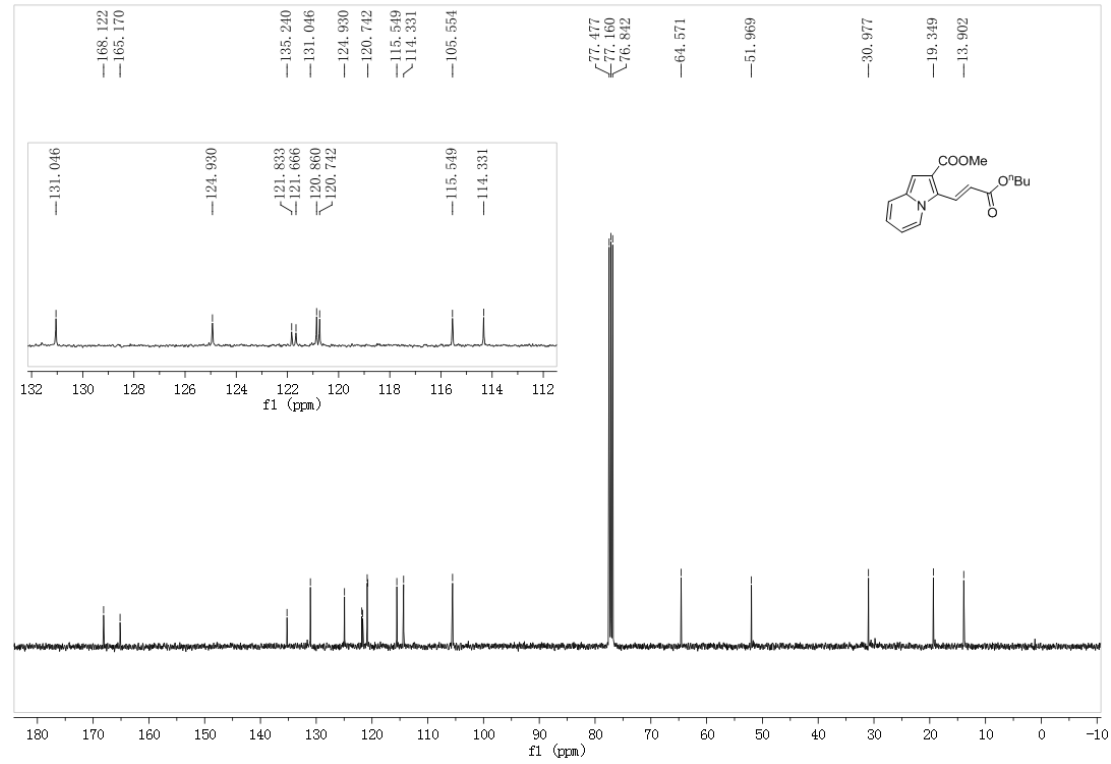

7.704
7.665
7.568
7.549
7.260
7.002
6.963
4.197
4.179
4.162
3.525
3.192
1.818
1.800
1.782
1.763
1.746
1.705
1.386
1.368
1.349
1.331
0.981
0.962
0.944
nBu
Ph
f1 (ppm)
1.00
2.33
2.23
1.02
1.14
2.35
6.33
6.50
2.35
2.44
3.36

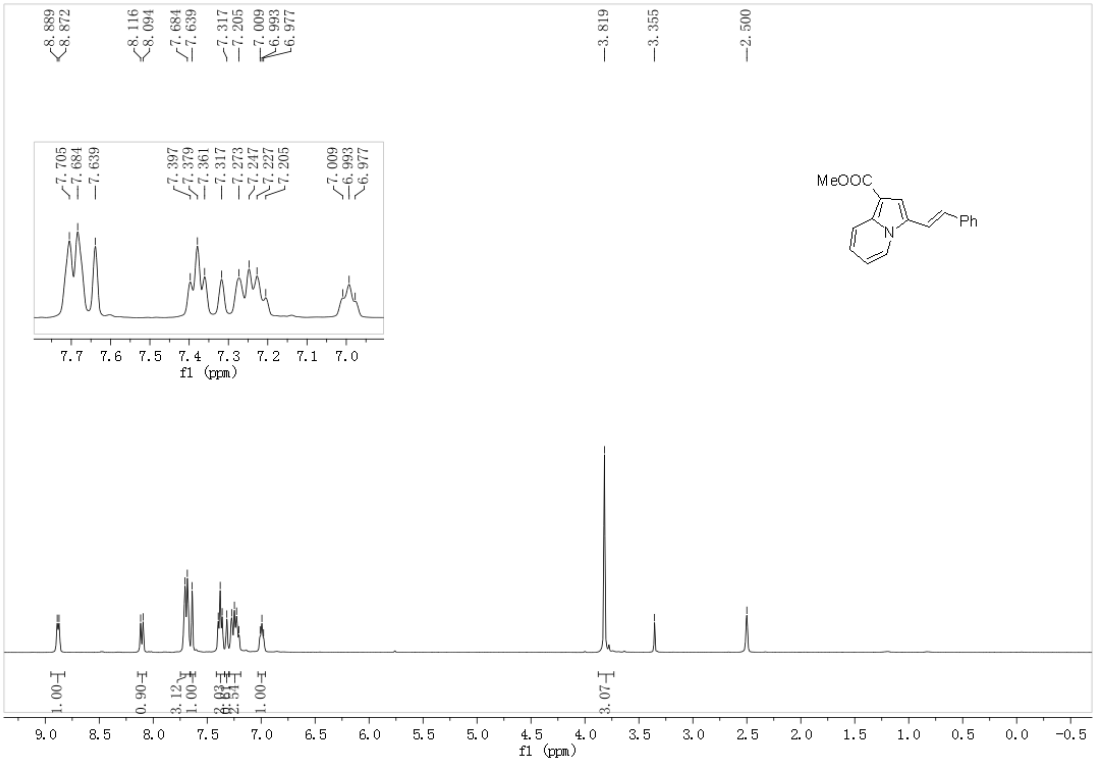

159.171
154.430
143.526
136.888
132.871
128.860
128.338
126.967
114.382
114.217
77.478
77.160
76.843
41.381
38.269
37.378
32.358
19.956
13.804
nBu
Ph
f1 (ppm)

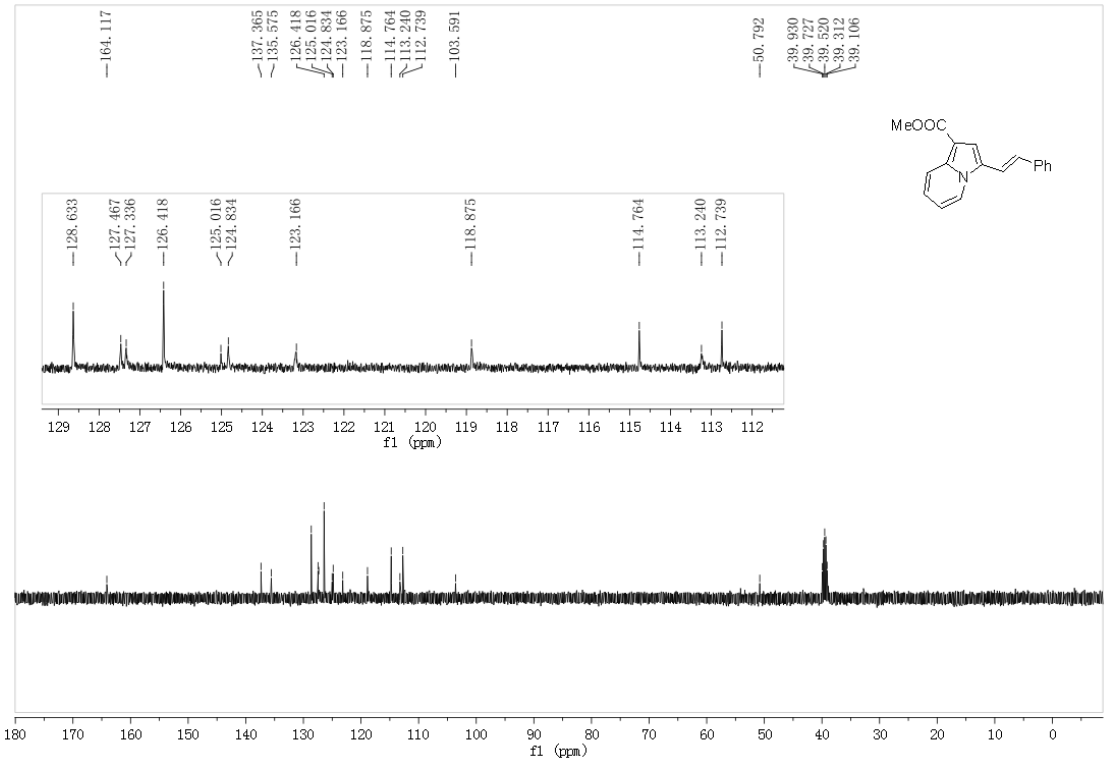

7.574
7.535
7.260
6.908
6.869
4.233
4.217
4.200
4.169
4.151
4.134
3.483
3.176
1.770
1.752
1.734
1.716
1.703
1.685
1.667
1.637
1.407
1.288
0.977
0.958
0.938
0.919
1.463
1.444
1.425
1.344
1.325
1.306
f1 (ppm)
O^{n}Bu
^{n}Bu
1.00
0.76
2.37
2.38
5.76
6.22
4.42
2.21
2.36
6.37
f1 (ppm)

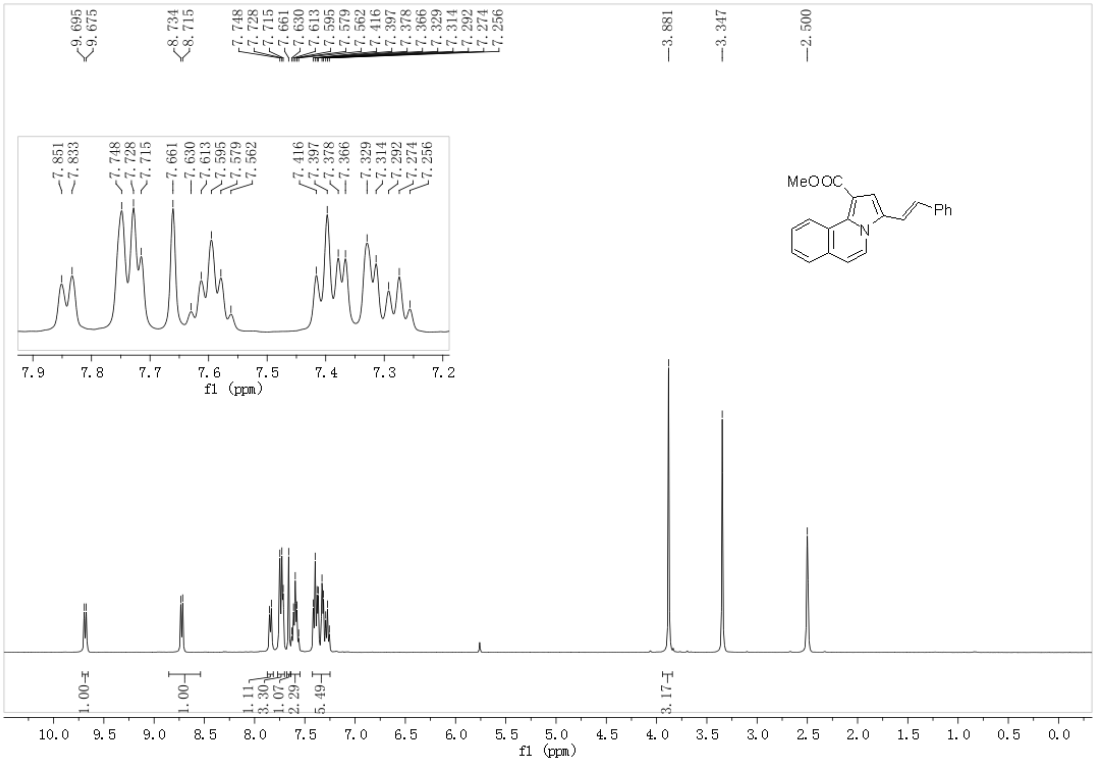

167.192
159.655
154.809
154.673
140.530
129.740
120.276
115.574
77.478
77.160
76.843
64.637
41.506
37.313
32.487
30.903
19.899
19.323
13.865
13.730
O^{n}Bu
nBu
f1 (ppm)

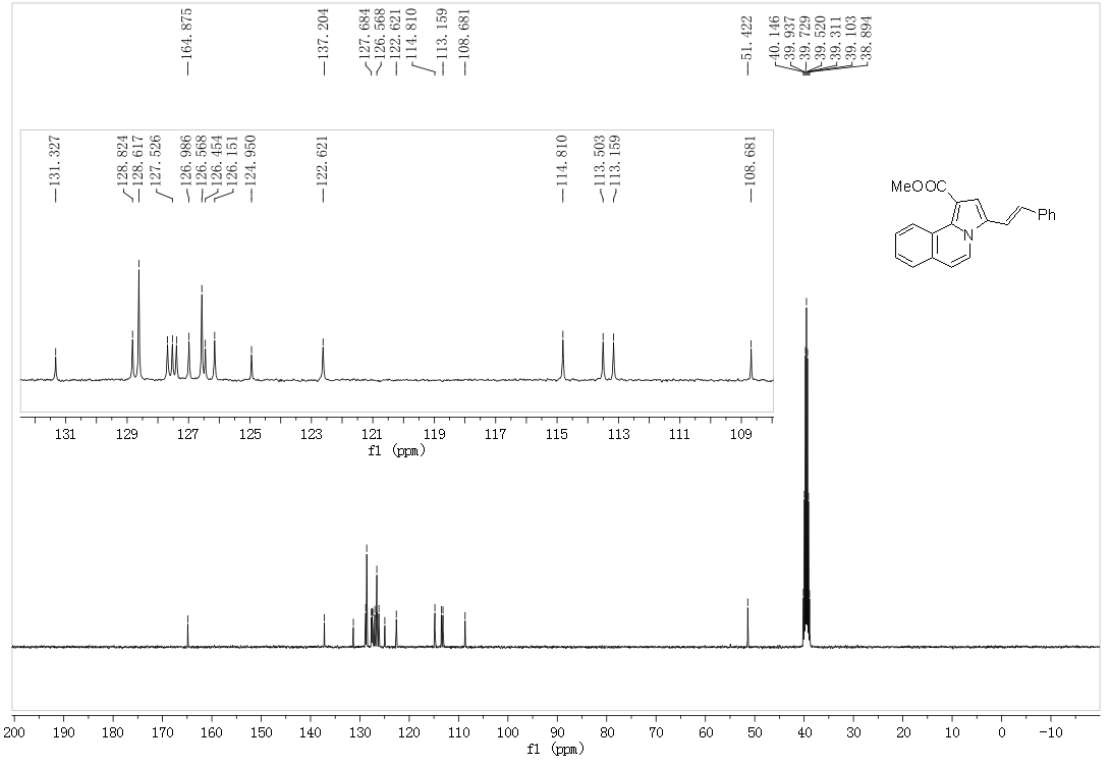

8.507
8.466
8.371
8.353
7.481
7.458
7.260
7.030
6.920
6.903
6.882
6.800
6.783
6.766
6.635
6.594
4.253
4.237
4.220
3.923
1.746
1.729
1.710
1.694
1.676
1.465
1.428
0.989
0.970
0.952
COOMe
O^{n}Bu
f1 (ppm)
1.000
1.056
1.037
0.998
1.079
1.092
1.101
2.161
3.178
2.825
2.288
3.409

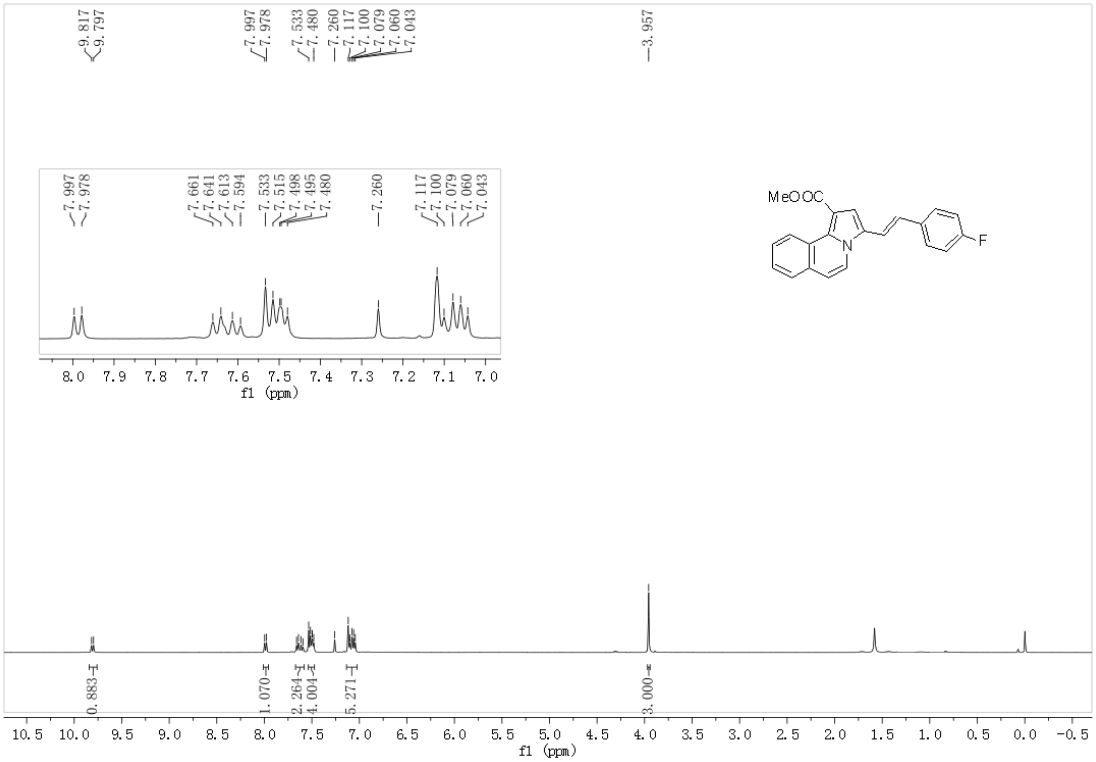

168.122
165.170
135.240
131.046
124.930
120.742
115.549
114.331
105.554
77.477
77.160
76.842
64.571
51.969
30.977
19.349
13.902
121.833
121.666
120.860
120.742
COOMe
O^{n}Bu
f1 (ppm)

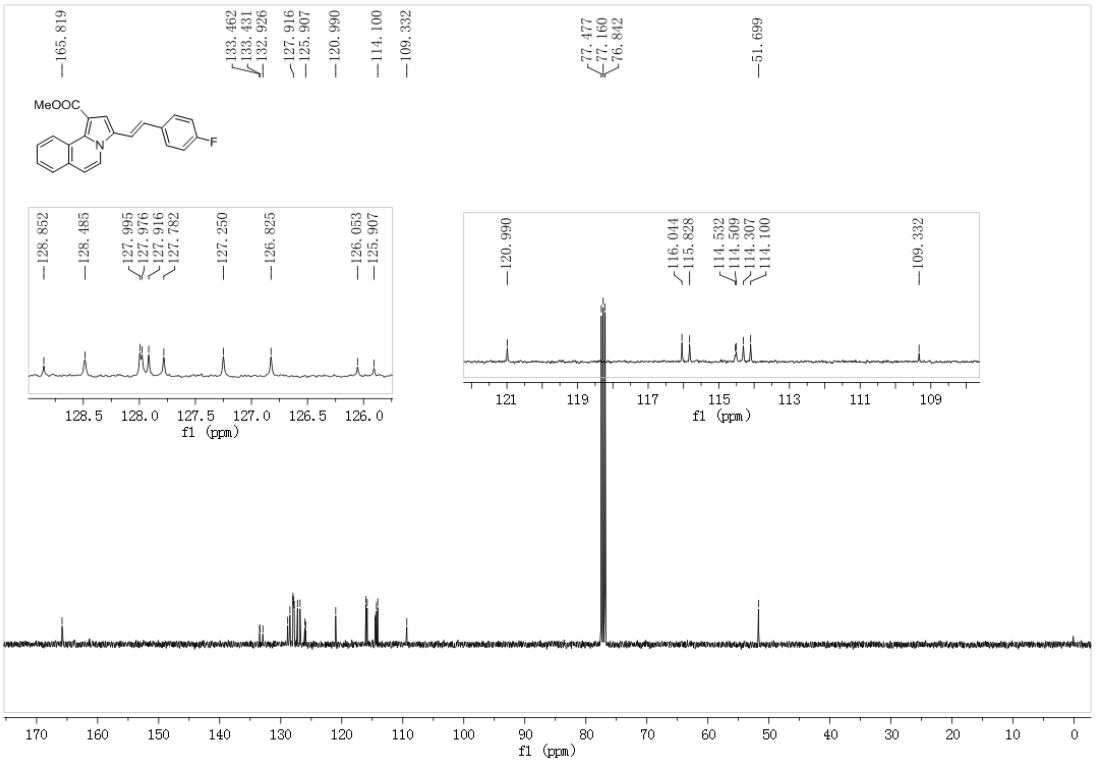

8.889
8.872
8.116
8.094
7.684
7.639
7.317
7.205
7.009
6.993
6.977
3.819
3.355
2.500
MeOOC
Ph
N
f1 (ppm)

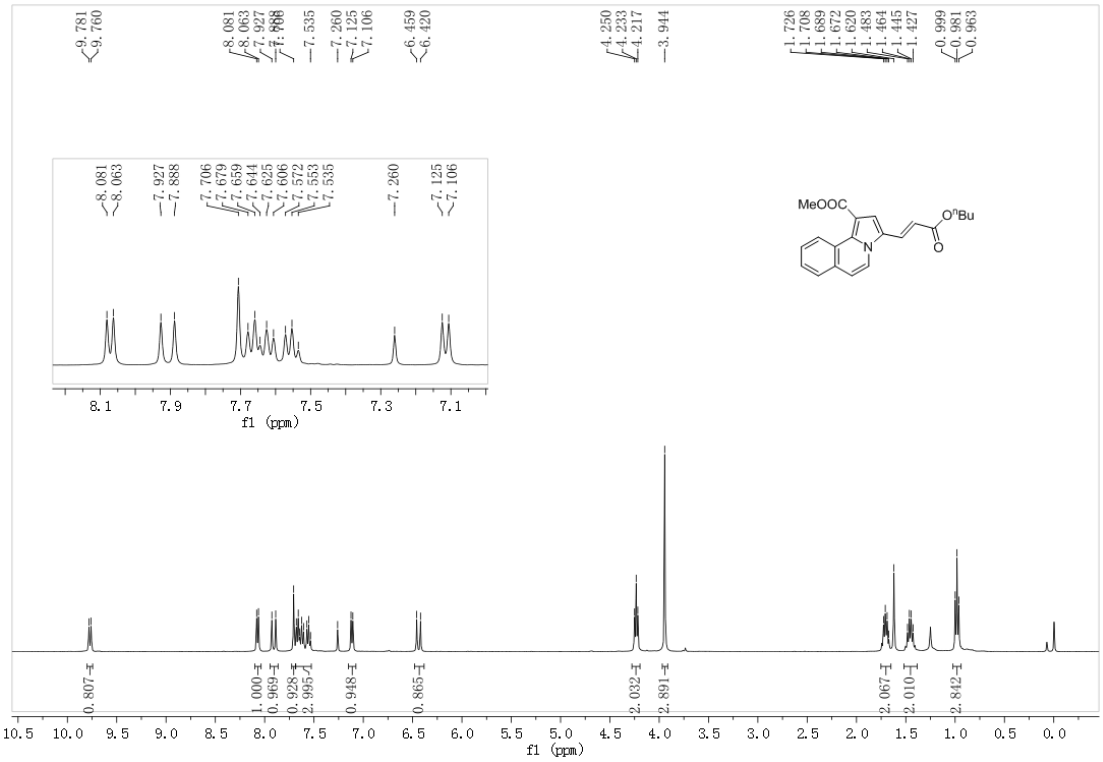

164.117
137.365
135.575
126.418
125.016
124.834
123.166
118.875
114.764
113.240
112.739
103.591
50.792
39.930
39.727
39.520
39.312
39.106
MeOOC
Ph
N
f1 (ppm)

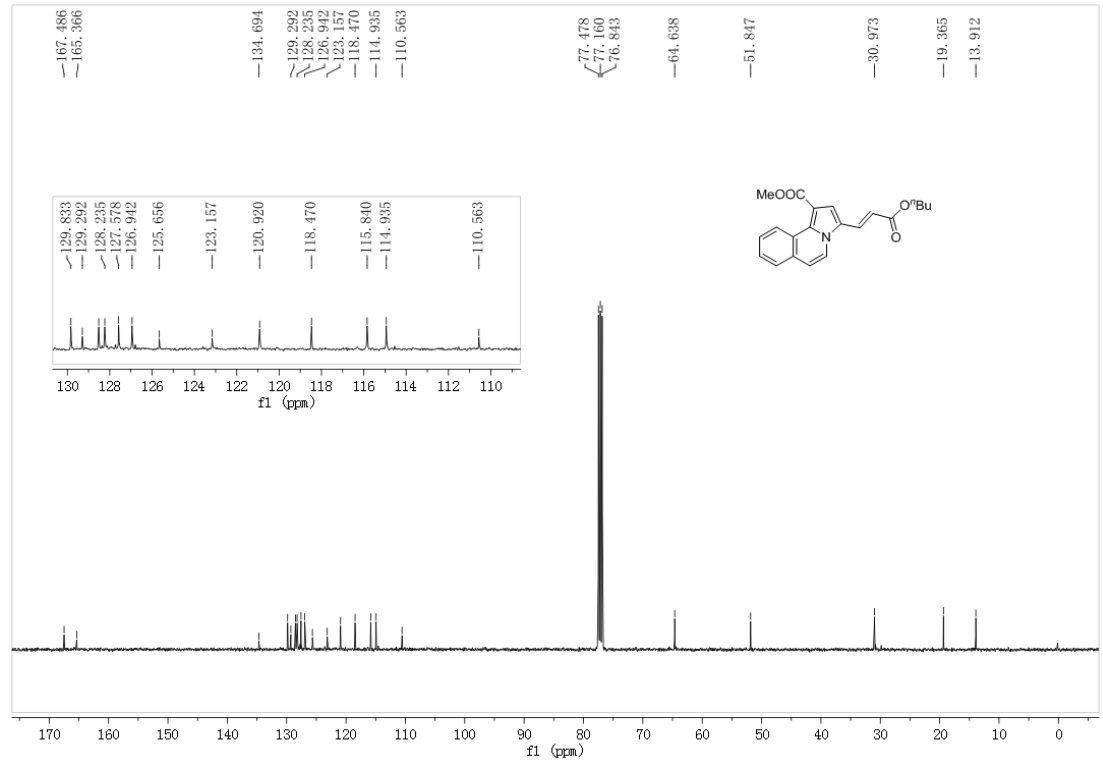

9.695
9.675
8.734
8.715
7.748
7.728
7.715
7.661
7.630
7.613
7.595
7.579
7.562
7.416
7.397
7.378
7.366
7.329
7.314
7.292
7.274
7.256
3.881
3.347
2.500
MeOOC
Ph
N
f1 (ppm)

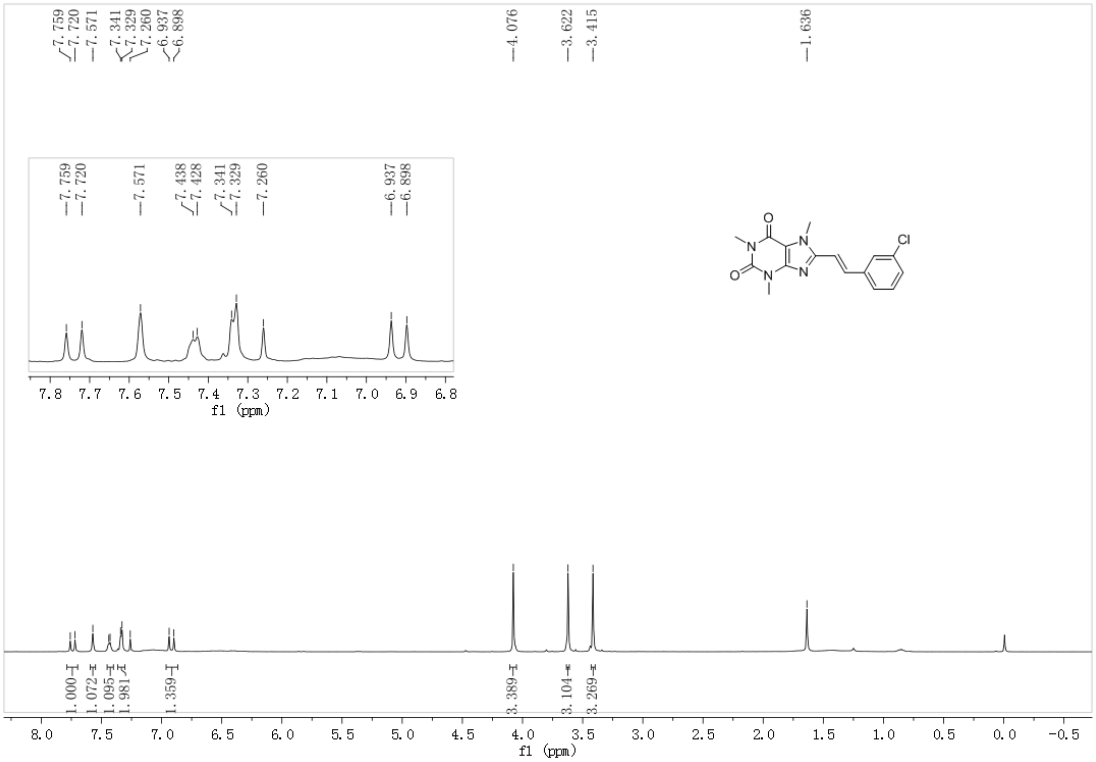

164.875
137.204
127.684
126.568
122.621
114.810
113.159
108.681
51.422
40.146
39.937
39.729
39.520
39.311
39.103
38.894
131.327
128.824
128.617
127.526
126.986
126.568
126.454
126.151
124.950
MeOOC
Ph
N
f1 (ppm)

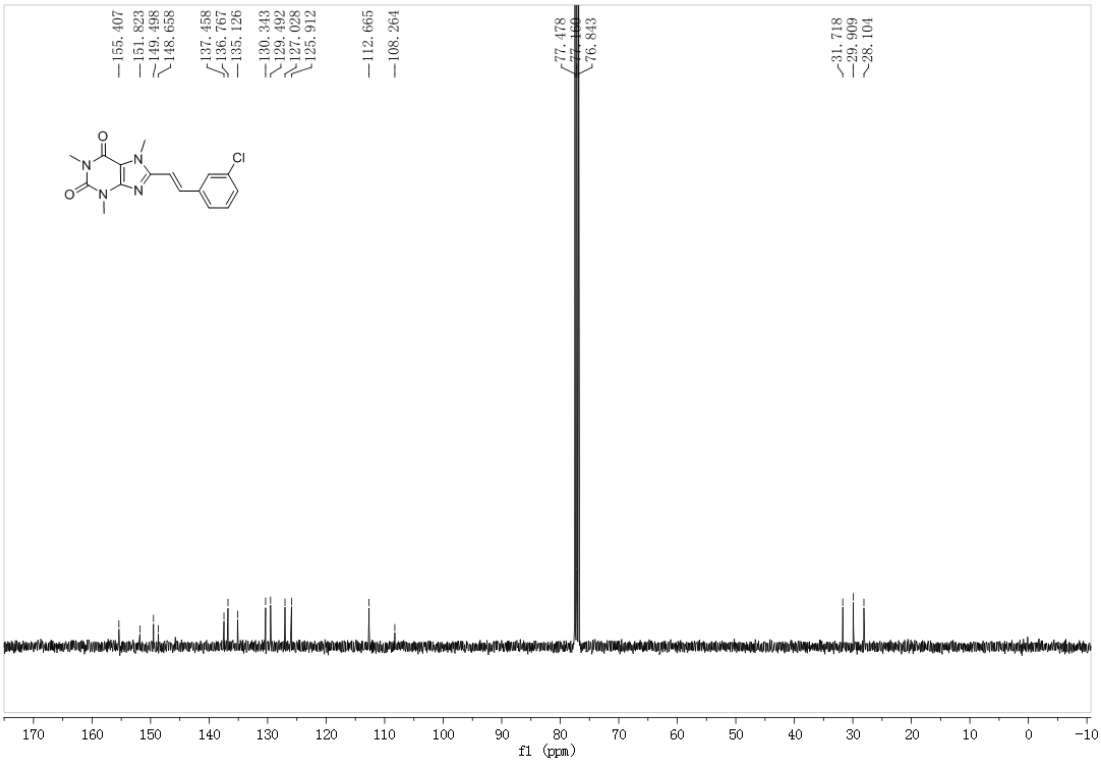

9.817
9.797
7.997
7.978
7.533
7.480
7.260
7.117
7.100
7.079
7.060
7.043
3.957
MeOOC
F
N
0.883
1.070
2.264
4.004
5.271
3.000
f1 (ppm)

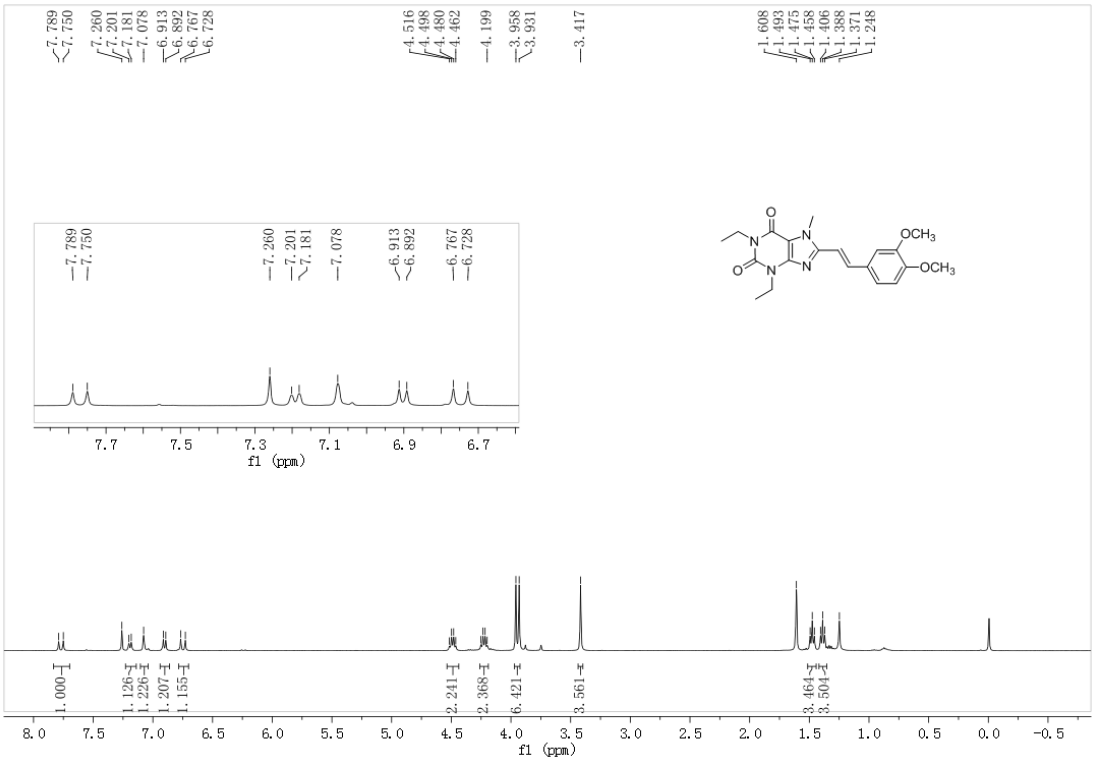

165.819
133.462
133.431
132.926
127.916
125.907
120.990
114.100
109.332
77.477
77.160
76.842
51.699
MeOOC
F
N
128.852
128.485
127.995
127.976
127.916
127.782
127.250
126.825
126.053
125.907
116.044
115.828
114.532
114.509
114.307
114.100
f1 (ppm)

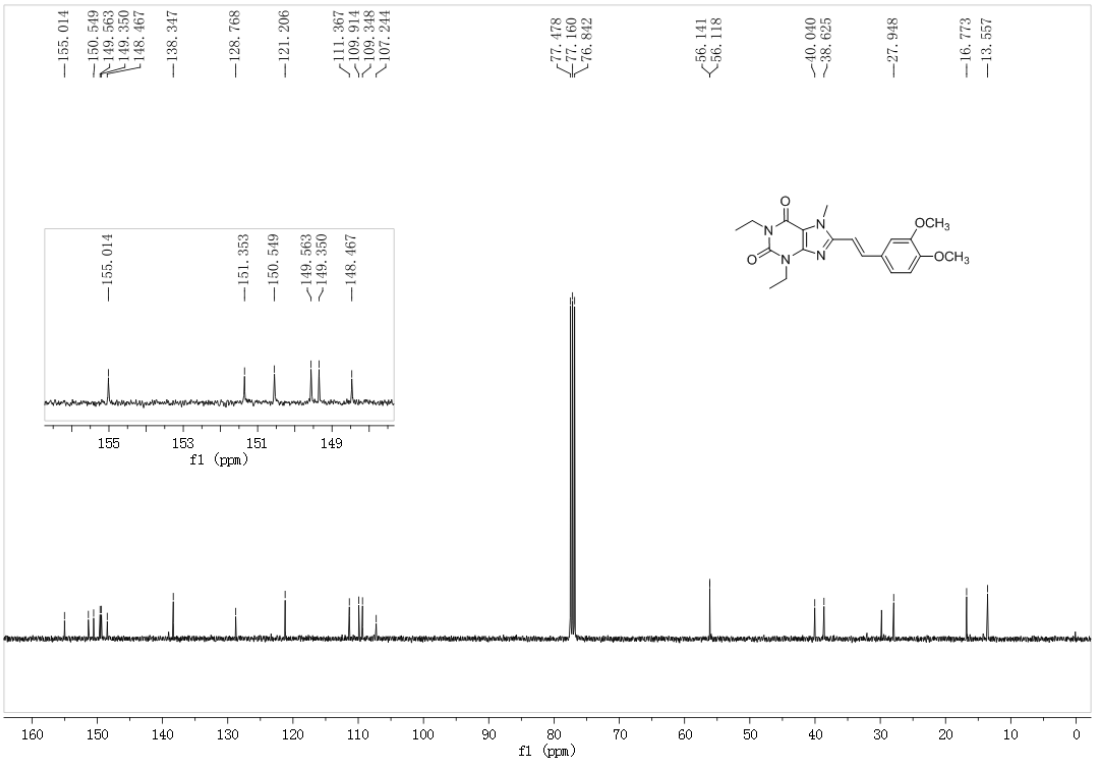

9.781
9.760
8.081
8.063
7.927
7.888
7.706
7.679
7.659
7.644
7.625
7.606
7.572
7.553
7.535
7.260
7.125
7.106
6.459
6.420
4.250
4.233
4.217
3.944
1.726
1.708
1.689
1.672
1.620
1.483
1.464
1.445
1.427
0.999
0.981
0.963
MeOOC
O^{n}Bu
f1 (ppm)
0.807
1.000
0.969
0.928
2.995
0.948
0.865
2.032
2.891
2.067
2.010
2.842


167.486
165.366
134.694
129.292
128.235
126.942
123.157
118.470
114.935
110.563
77.478
77.160
76.843
64.638
51.847
30.973
19.365
13.912
MeOOC
O^{n}Bu
f1 (ppm)


7.759
7.720
7.571
7.341
7.329
7.260
6.937
6.898
4.076
3.622
3.415
1.636
7.438
7.428
f1 (ppm)
1.000
1.072
1.095
1.981
1.359
3.389
3.104
3.269


155.407
151.823
149.498
148.658
137.458
136.767
135.126
130.343
129.492
127.028
125.912
112.665
108.264
77.478
77.160
76.843
31.718
29.909
28.104
f1 (ppm)


7.789
7.750
7.260
7.201
7.181
7.078
6.913
6.892
6.767
6.728
4.516
4.498
4.480
4.462
4.199
3.958
3.931
3.417
1.608
1.493
1.475
1.458
1.406
1.388
1.371
1.248
OCH3
OCH3
f1 (ppm)
1.000
1.126
1.226
1.207
1.155
2.241
2.368
6.421
3.561
3.464
3.504


155.014
150.549
149.563
149.350
148.467
138.347
128.768
121.206
111.367
109.914
109.348
107.244
77.478
77.160
76.842
56.141
56.118
40.040
38.625
27.948
16.773
13.557
OCH3
OCH3
151.353
f1 (ppm)