Supporting Information

The First Total Synthesis of 4,5-Didehydroguadiscine, the Potent Melanogenesis Inhibitor Isolated from a Brazilian Medicinal Herb, *Hornschuchia obliqua*

Genzoh Tanabe,[†] Youta Sugano,[†] Miki, Shirato,[†] Naoki Sonoda,[†] Nozomi Tsutsui,[†] Toshio Morikawa,[§] Kiyofumi Ninomiya,[§] and Osamu Muraoka[*†]

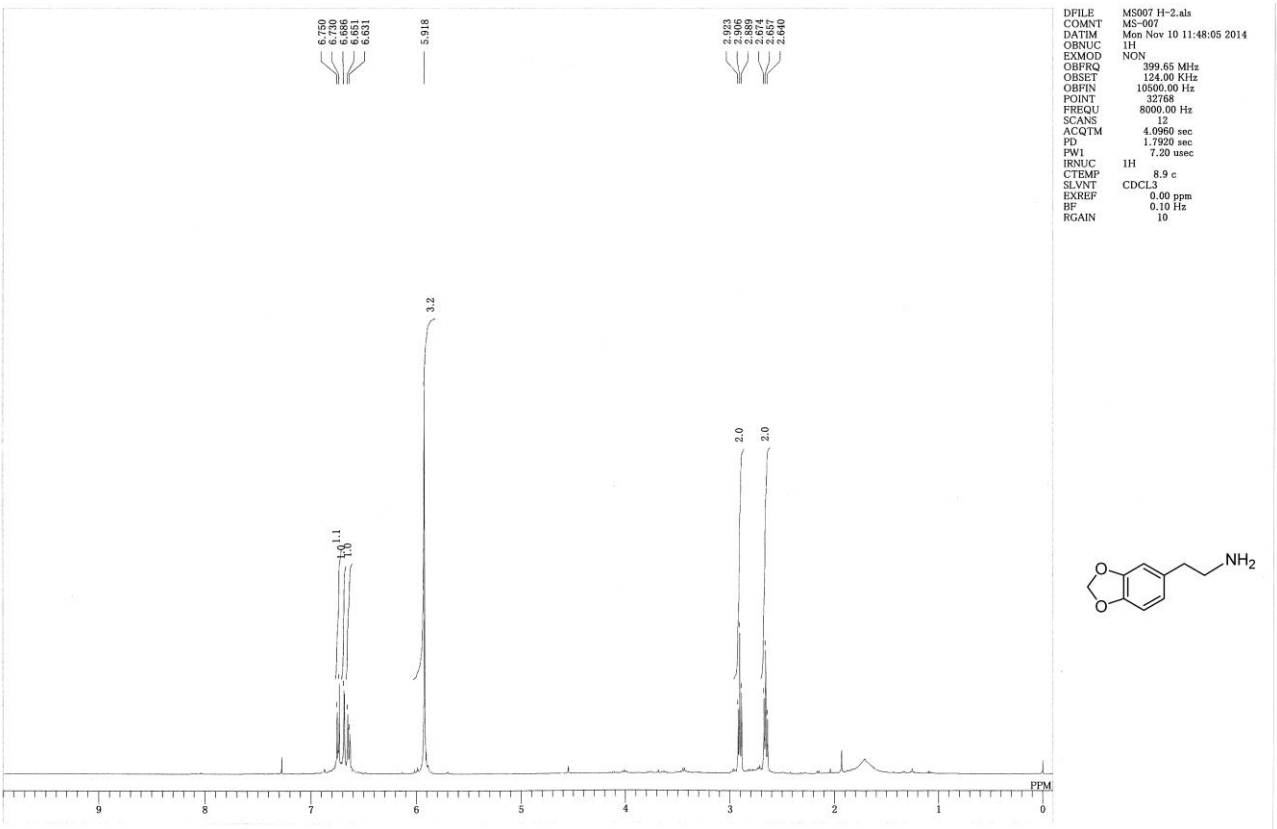
[†]Faculty of Pharmacy and [§]Pharmaceutical Research and Technology Institute, Kinki University, Higashi-osaka, Osaka 577-8502, Japan

Table of Contents

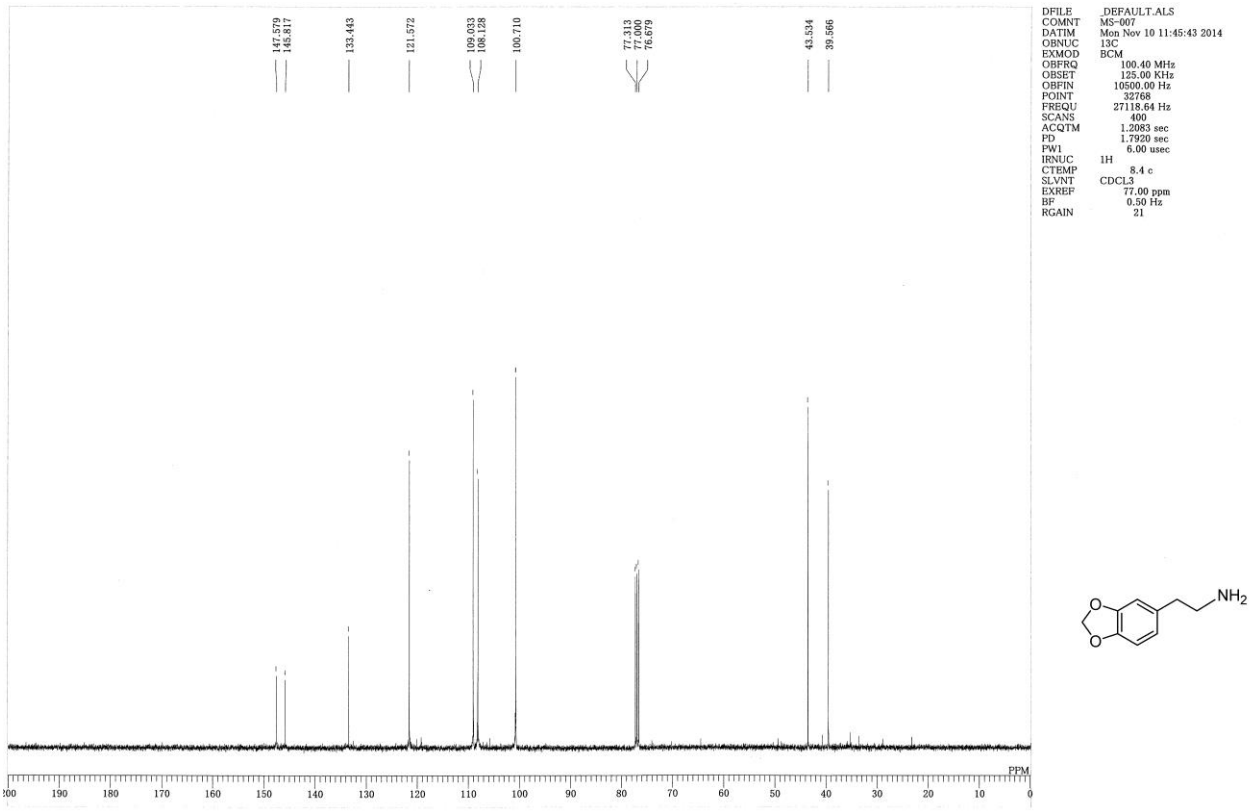
^{1}H and ^{13}C NMR spectra of homopiperonylamine (**7**) • 2
^{1}H and ^{13}C NMR spectra of (5-methoxy-2-nitrophenyl)acetic acid (**12**) • 3
^{1}H and ^{13}C NMR spectra of methyl (5-methoxy-2-nitrophenyl)acetate (**13**) • • • • • • • • • • • • • • • • • • 4
^{1}H and ^{13}C NMR spectra of methyl 2-(5-methoxy-2-nitrophenyl)-2-methylpropionate (**14**) • • • • • • • 5
^{1}H and ^{13}C NMR spectra of methyl (5-methoxy-2-nitrophenyl)propionate (**15**) • • • • • • • • • • • • • • • 6
^{1}H and ^{13}C NMR spectra of methyl 2-hydroxy-2-(5-methoxy-2-nitrophenyl)propionate (**16**) • • • • • • 7
^{1}H and ^{13}C NMR spectra of methyl 2-methoxy-2-(5-methoxy-2-nitrophenyl)propionate (**17**) • • • • • • 8
^{1}H and ^{13}C NMR spectra of 2-methyl-2-(5-methoxy2-nitrophenyl)propionic acid (**8**) • • • • • • • • • • • • 9
^{1}H and ^{13}C NMR spectra of *N*-homopiperonyl-2-methyl-2-(5-methoxy-2-nitrophenyl)propionamide (**19**) • • • • • • • • • • • • 10
^{1}H and ^{13}C NMR spectra of 3,4-dihydro-1-[1,1-dimethyl-1-(5-methoxy-2-nitrophenyl)-methyl]-6,7-methylenedioxyisoquinoline (**20**) • • • • • • • • • • • • 11
^{1}H and ^{13}C NMR spectra of 1-[1-Methyl-1-(5-methoxy-2-nitrophenyl)ethyl]-6,7-methylenedioxyisoquinoline (**21**) • • • • • • • • • • • • 12
^{1}H and ^{13}C NMR spectra of 1-[1-Methyl-1-(5-methoxy-2-aminophenyl)ethyl]-6,7-methylenedioxyisoquinoline (**22**) • • • • • • • • • • • • 13
^{1}H and ^{13}C NMR spectra of 4,5-didehydroguadiscine (**6**) • 14
HMBC spectrum ($J_{C–H}$ = 8 Hz) of 4,5-didehydroguadiscine (**6**) • 15
HMBC spectrum ($J_{C–H}$ = 35 Hz) of 4,5-didehydroguadiscine (**6**) • 16
^{1}H and ^{13}C NMR spectra of 1-[1-methyl-1-(5-methoxyphenyl)ethyl]-6,7-methylenedioxyisoquinoline (**24**) • • • • • • • • • • • • 17

Table 1. Inhibitory Effects of Aporphinoids **1**, **2**, **3**, **4**, **5**, **6** and Arbutin on Theophylline-stimulated Melanogenesis in B16 Melanoma 4A5 Cells • • • • • • 18

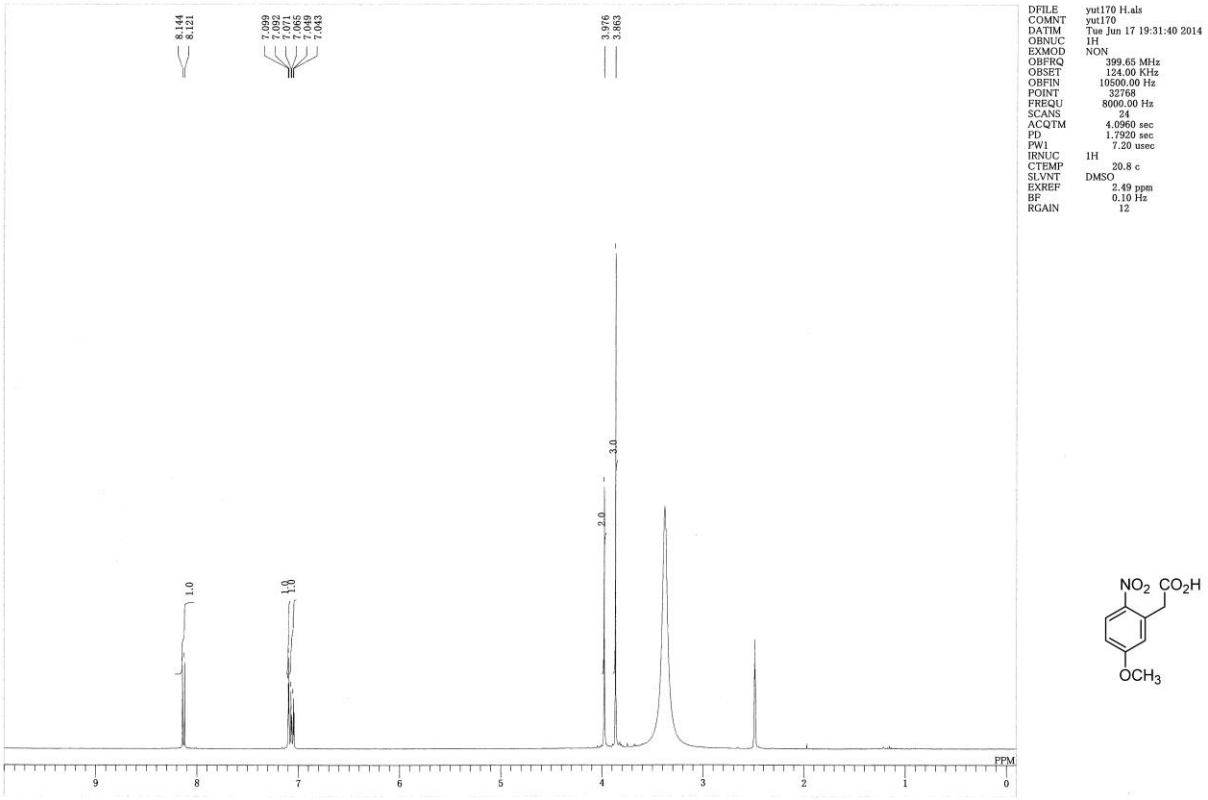
^{1}H NMR spectrum (400 MHz, in $CDCl_3$) of homopiperonylamine (**7**)



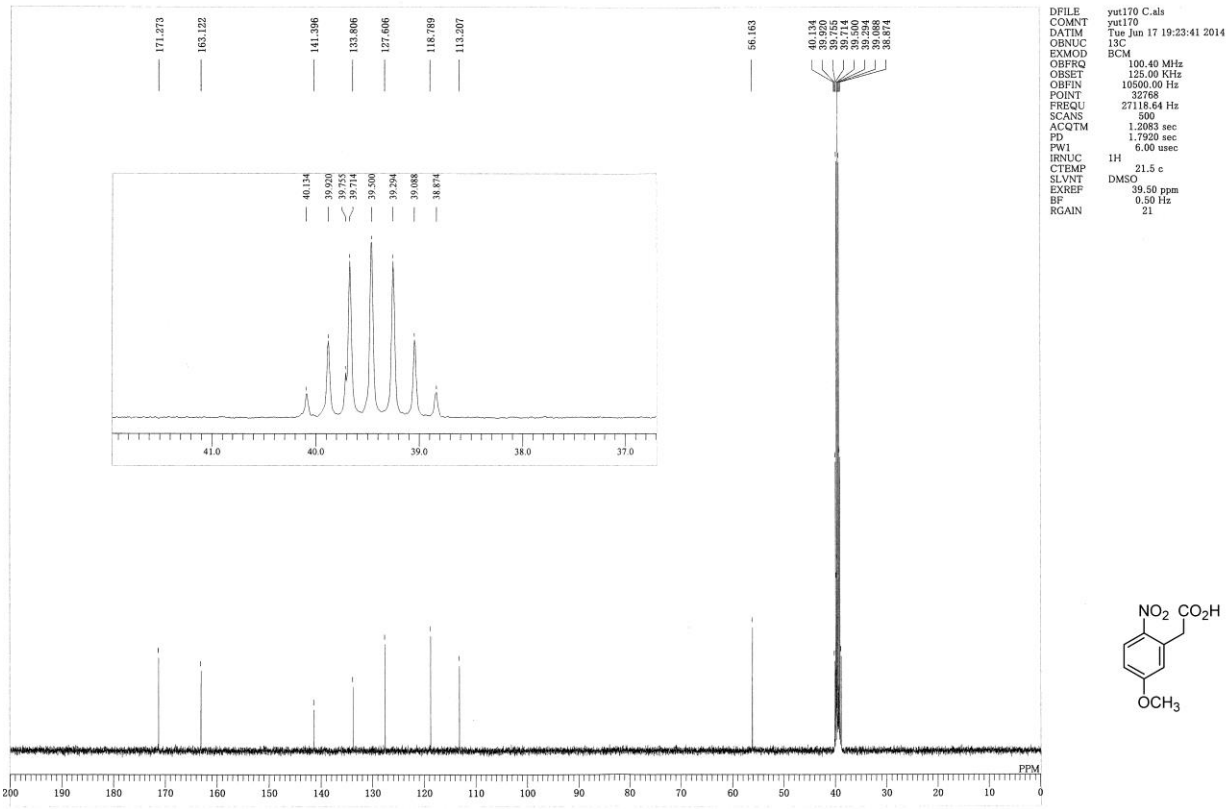
^{13}C NMR spectrum (100 MHz, in $CDCl_3$) of homopiperonylamine (**7**)



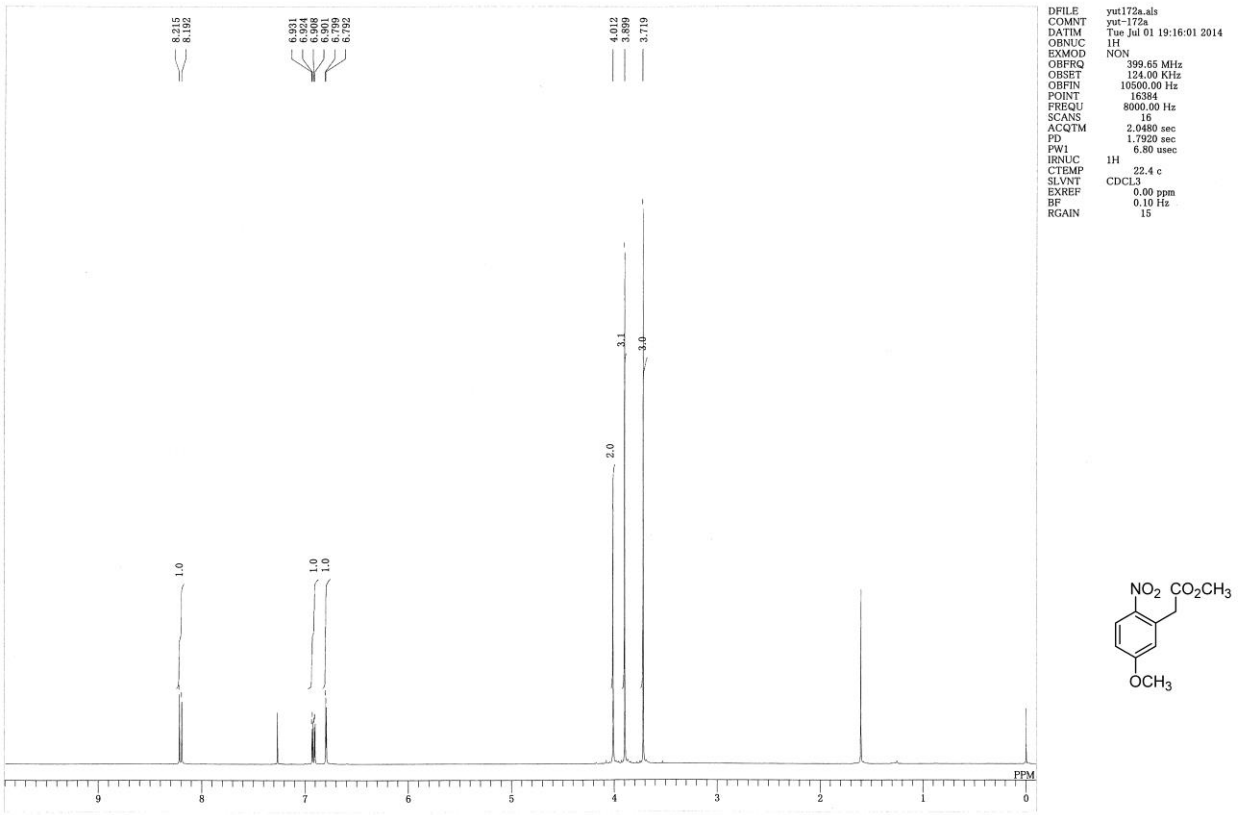
^{1}H NMR spectrum (400 MHz, in DMSO-d_6) of (5-methoxy-2-nitrophenyl)acetic acid (**12**)



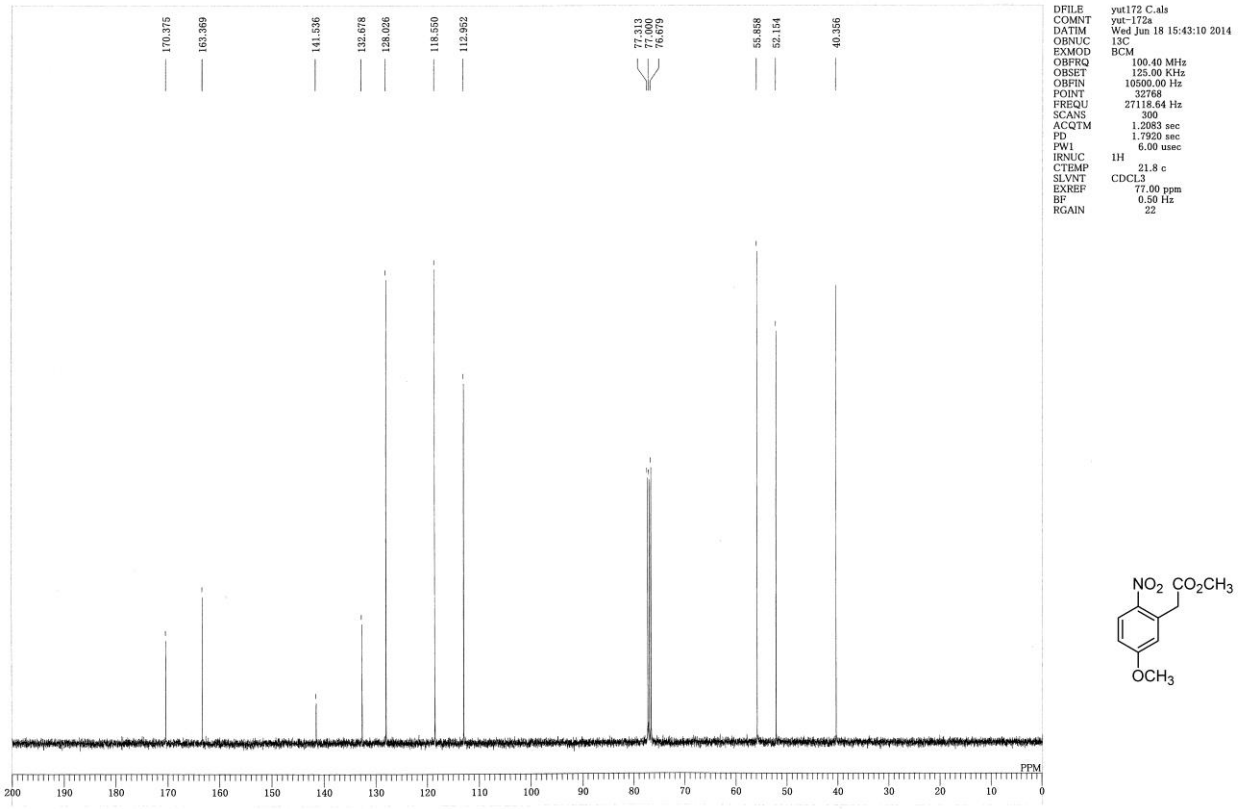
^{13}C NMR spectrum (100 MHz, in DMSO-d_6) of (5-methoxy-2-nitrophenyl)acetic acid (**12**)



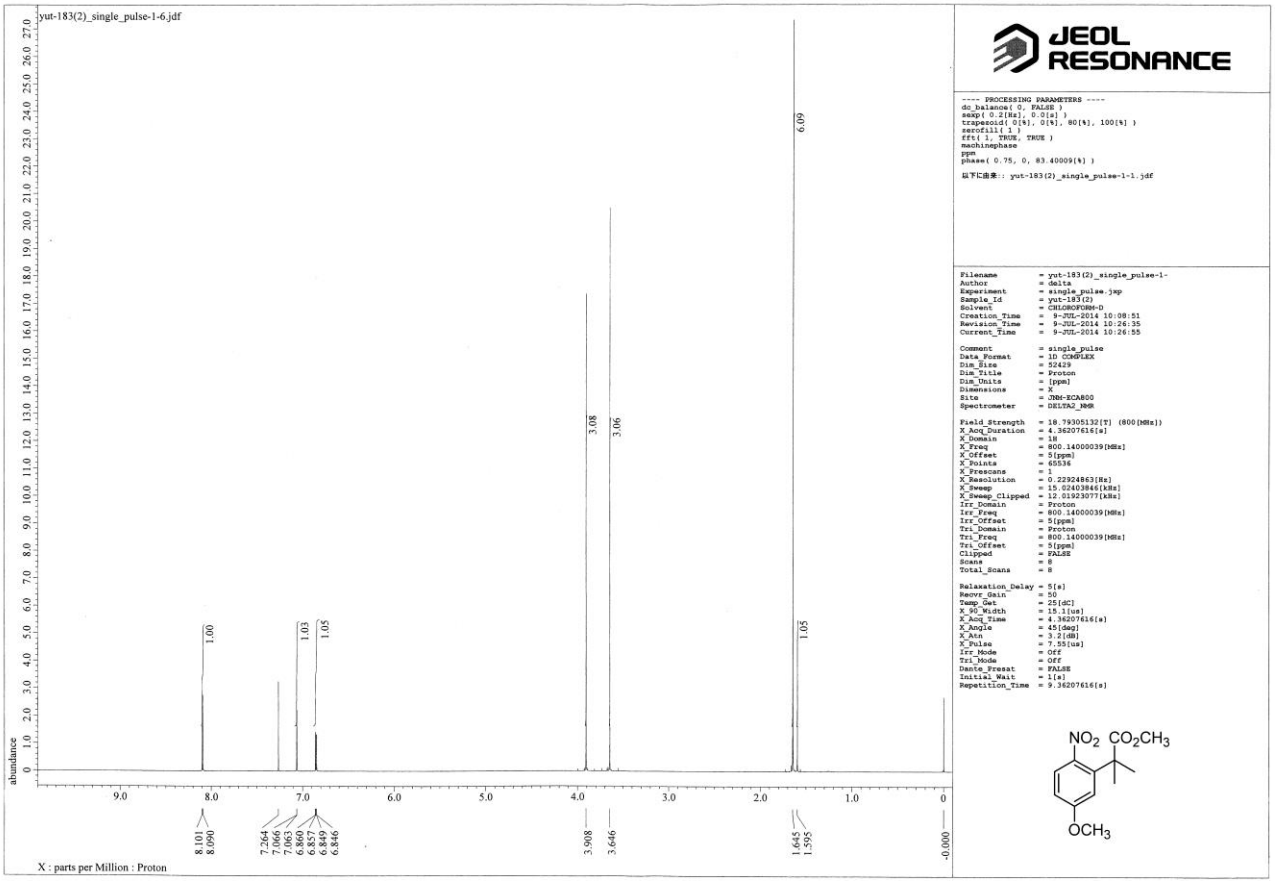
^{1}H NMR spectrum (400 MHz, in $CDCl_3$) of methyl (5-methoxy-2-nitrophenyl)acetate (**13**)



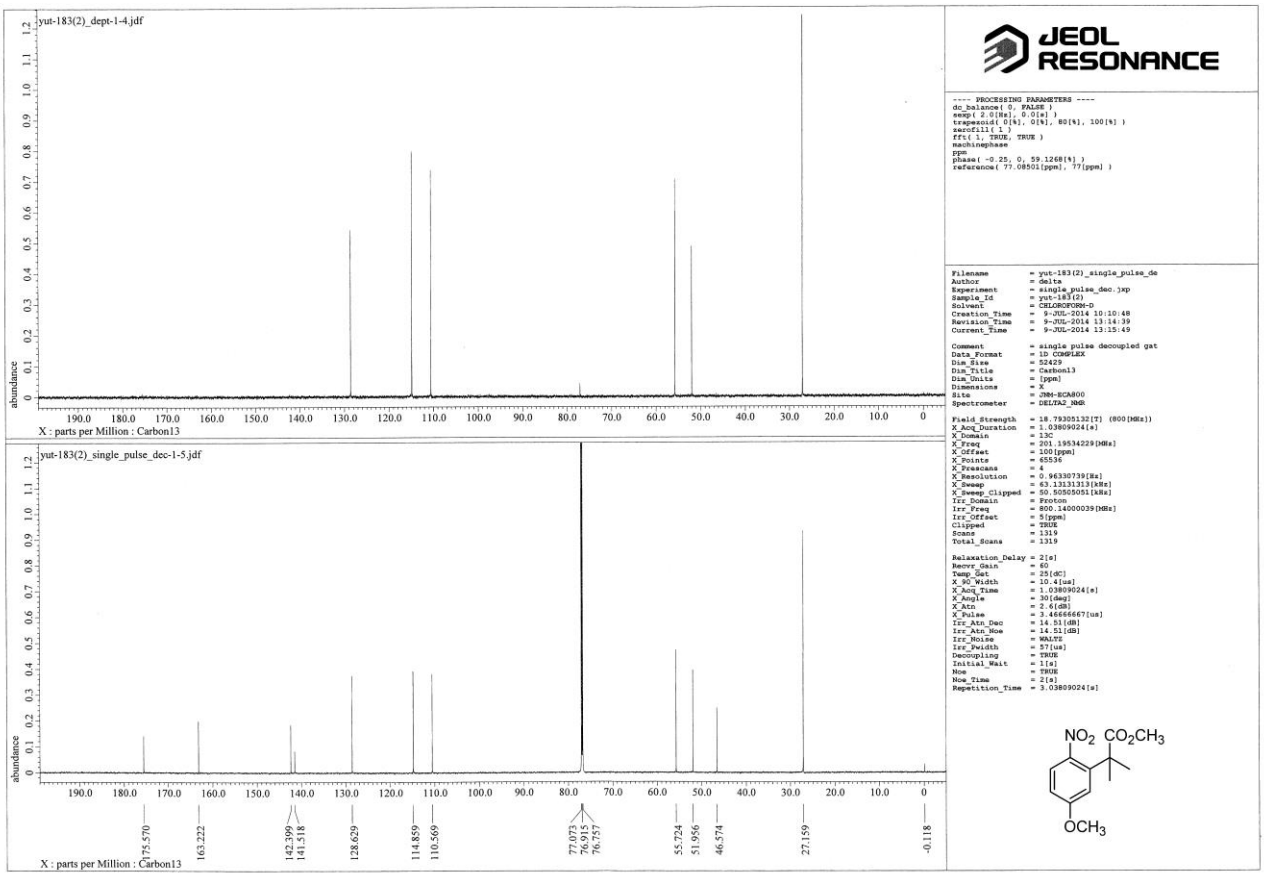
^{13}C NMR spectrum (100 MHz, in $CDCl_3$) of methyl (5-methoxy-2-nitrophenyl)acetate (**13**)



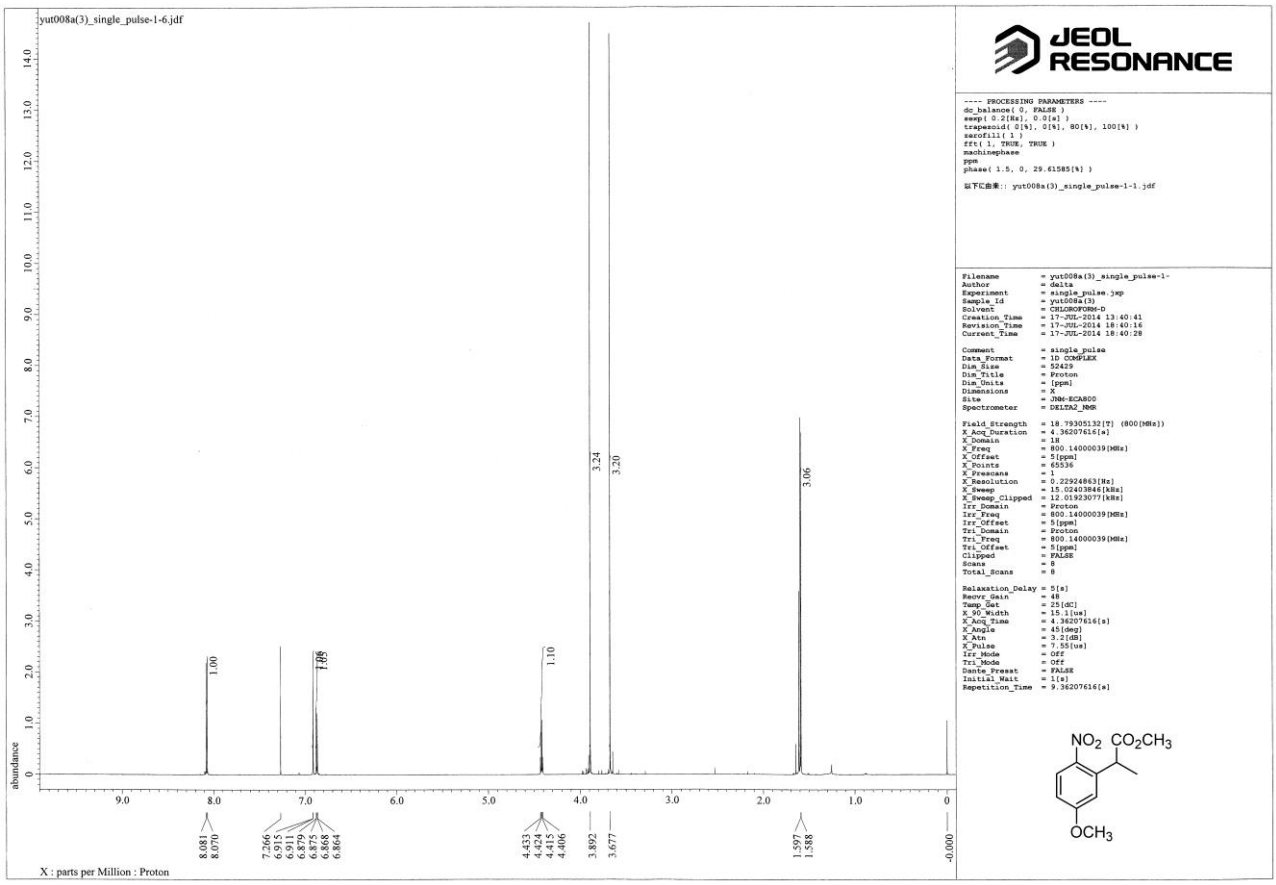
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of methyl 2-(5-methoxy-2-nitrophenyl)-2-methylpropionate (**14**)



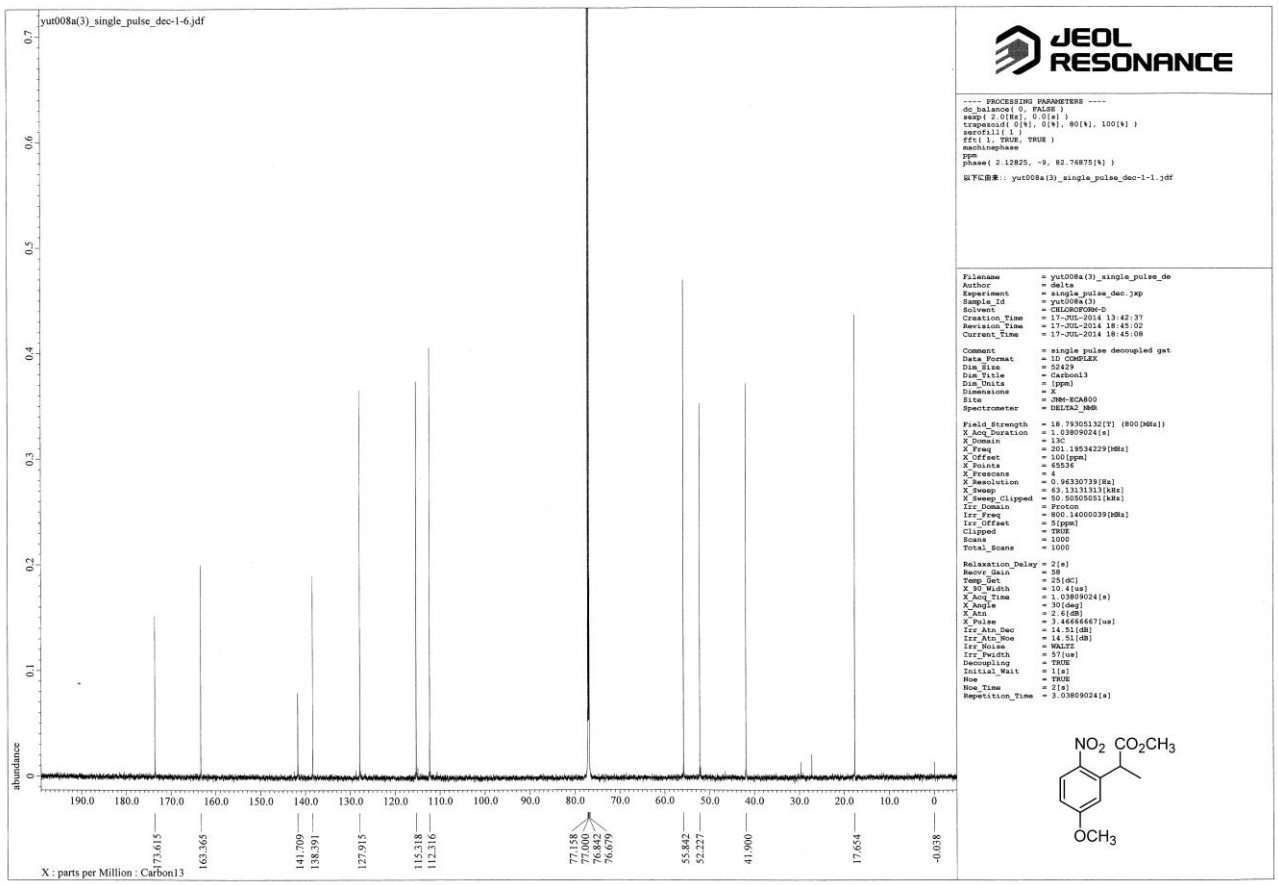
^{13}C NMR spectrum (200 MHz, in $CDCl_3$) of methyl 2-(5-methoxy-2-nitrophenyl)-2-methylpropionate (**14**)



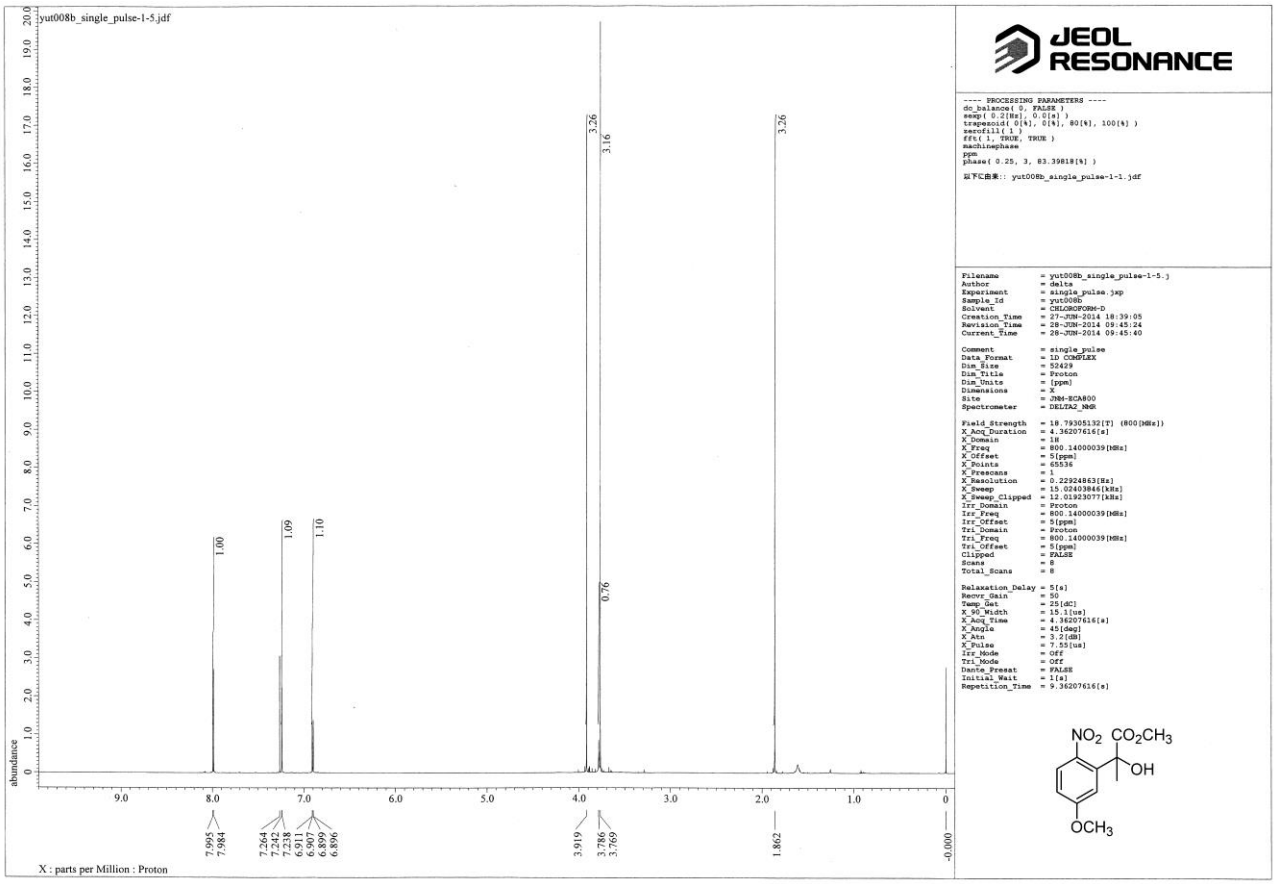
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of methyl (5-methoxy-2-nitrophenyl)propionate (**15**)



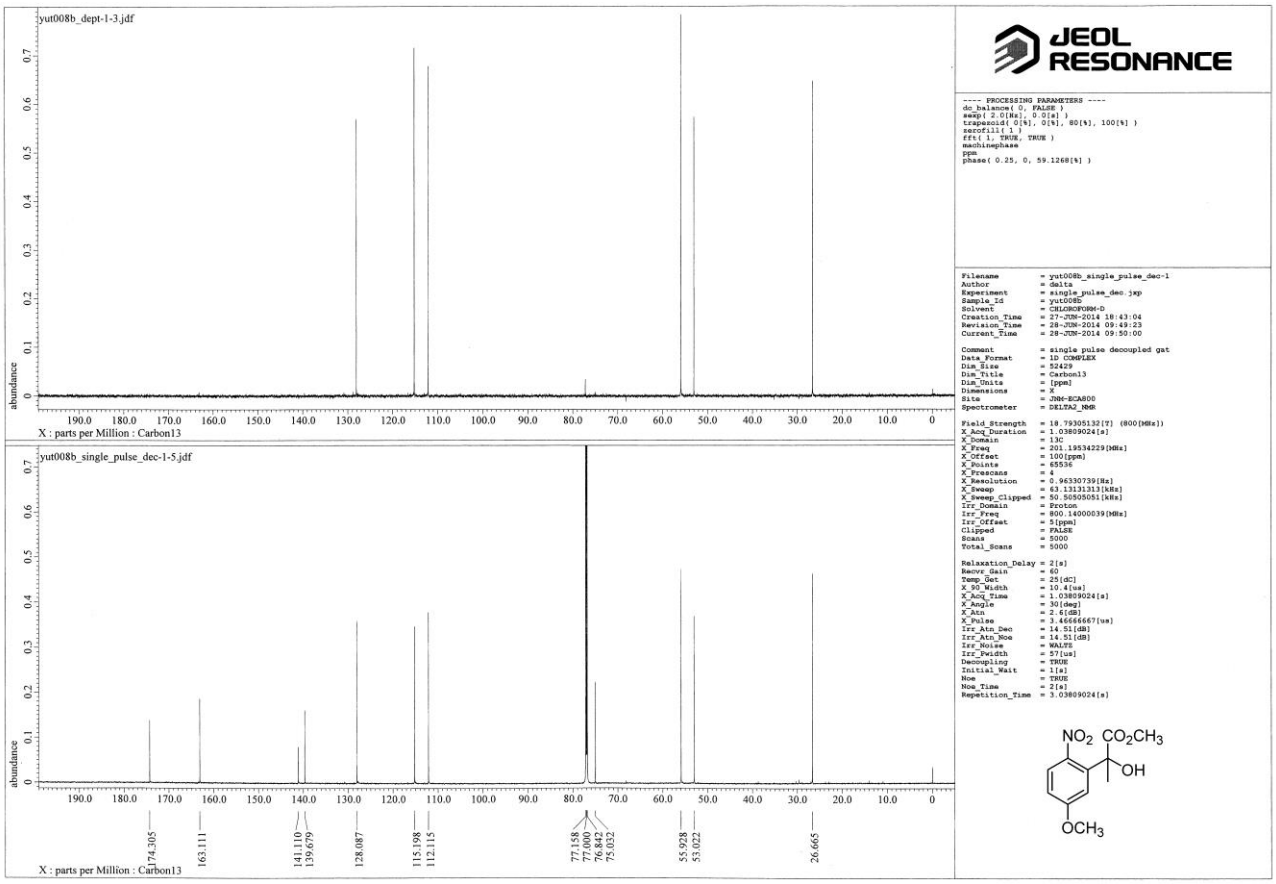
^{13}C NMR spectrum (800 MHz, in $CDCl_3$) of methyl (5-methoxy-2-nitrophenyl)propionate (**15**)



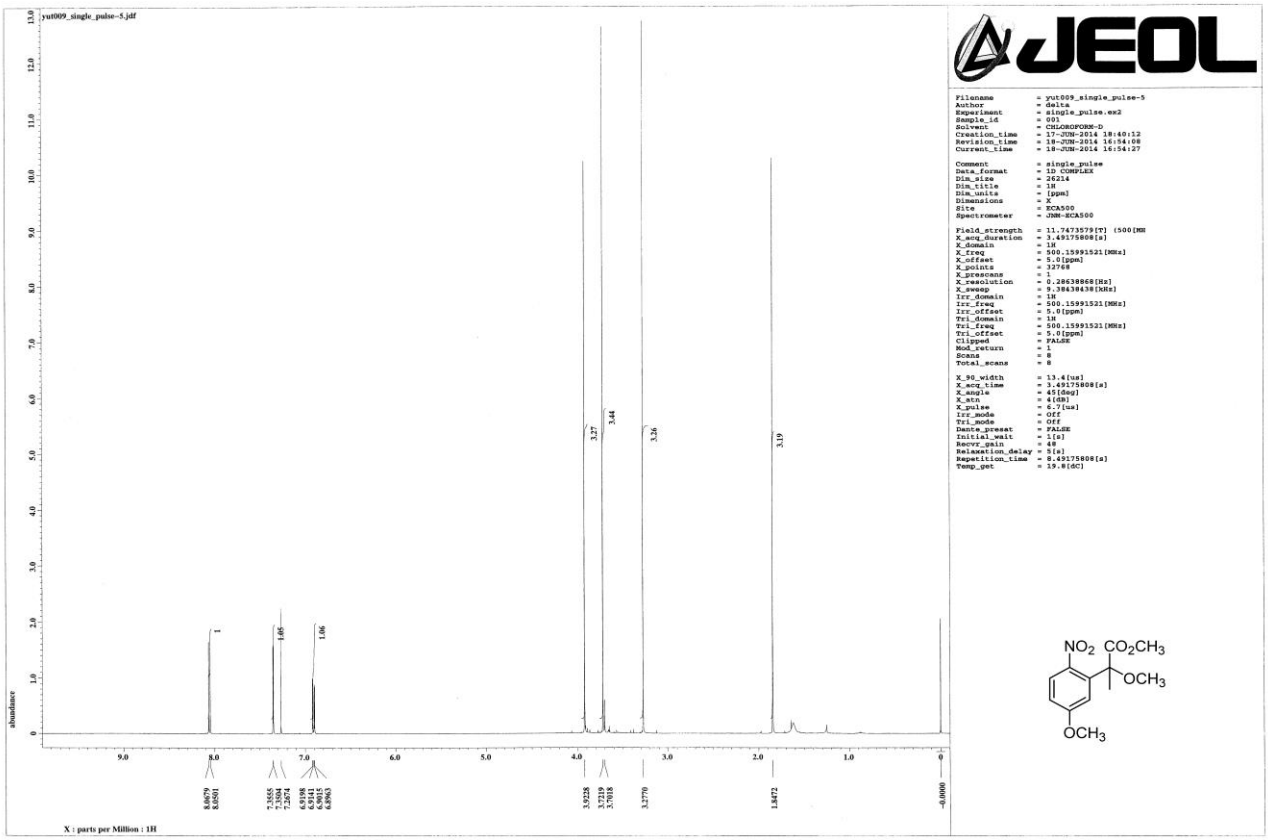
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of methyl 2-hydroxy-2-(5-methoxy-2-nitrophenyl)propionate (**16**)



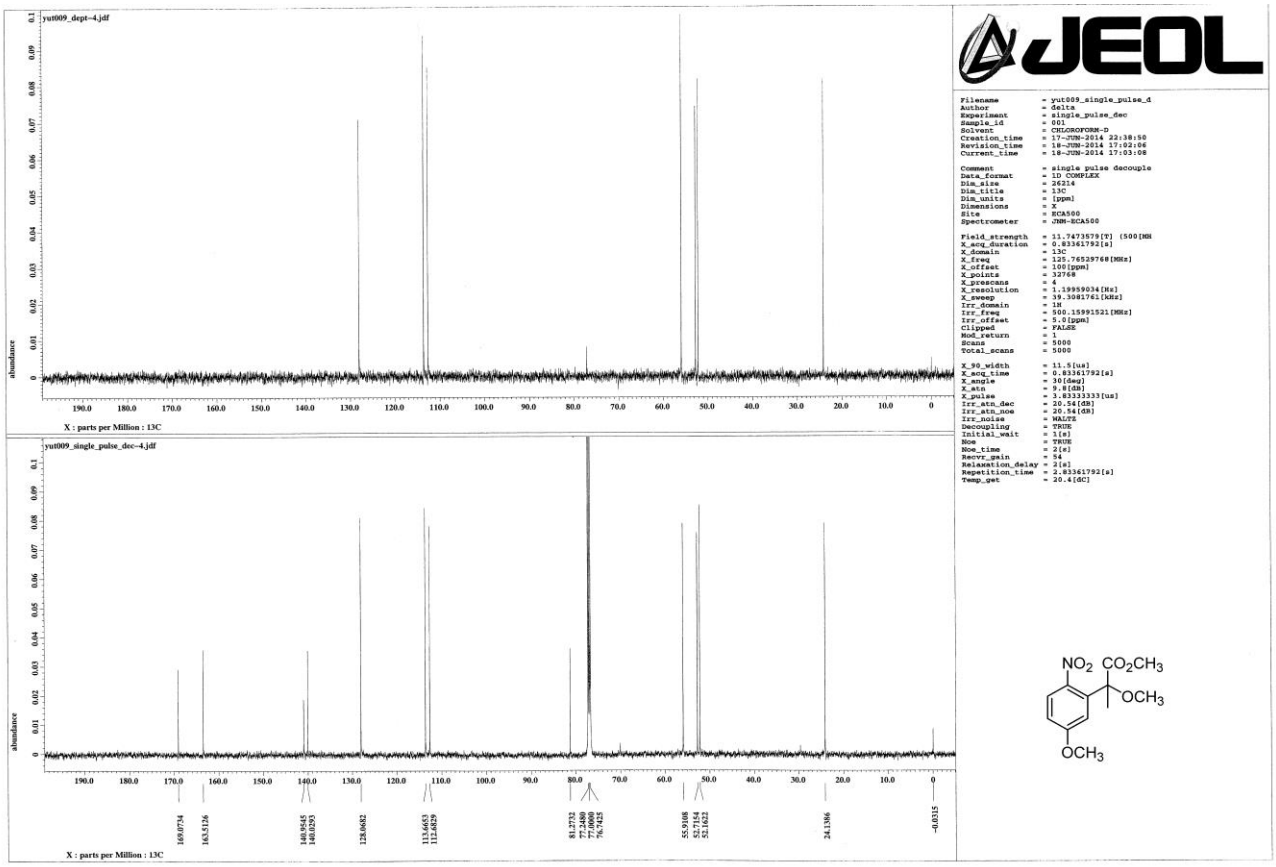
^{13}C NMR spectrum (200 MHz, in $CDCl_3$) of methyl 2-hydroxy-2-(5-methoxy-2-nitrophenyl)propionate (**16**)



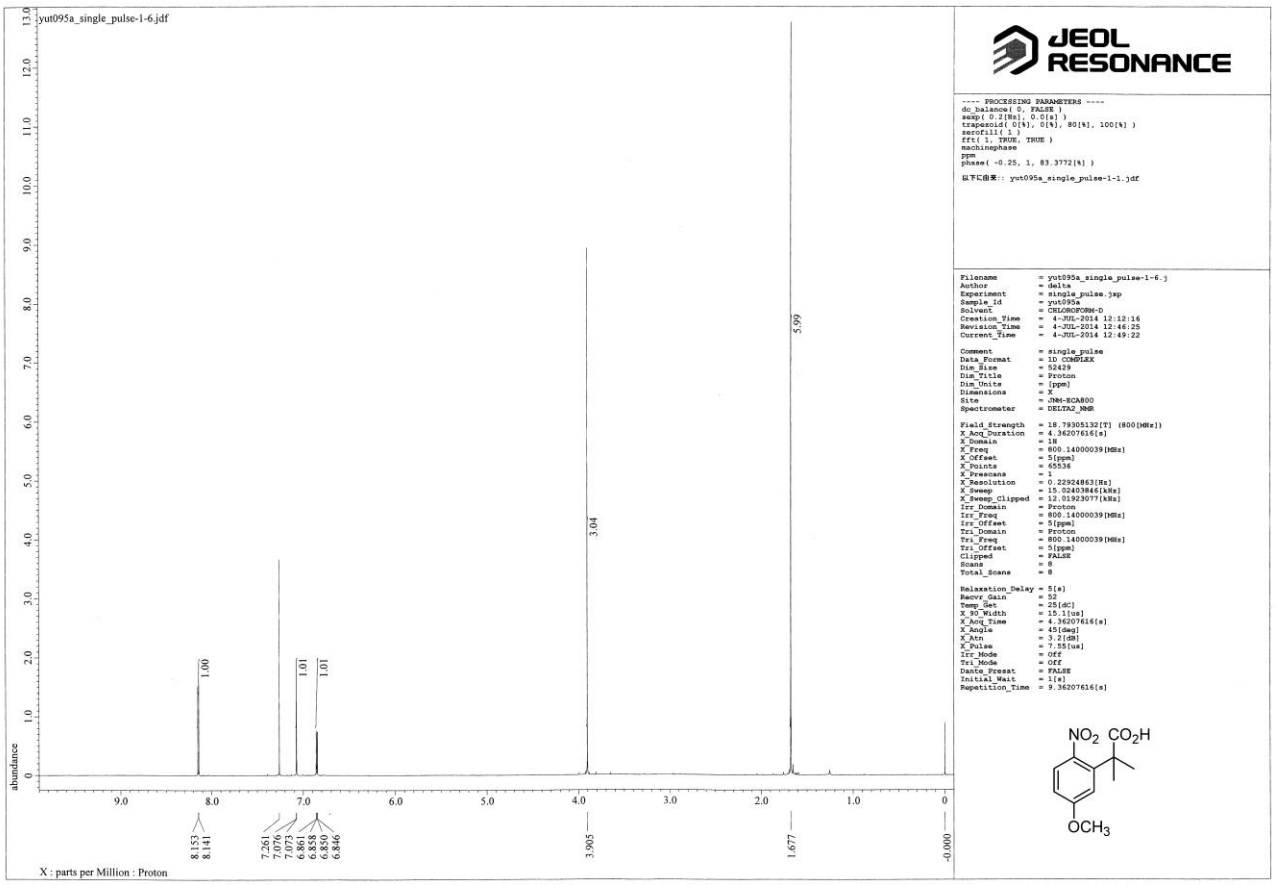
^{1}H NMR spectrum (500 MHz, in $CDCl_3$) of methyl 2-methoxy-2-(5-methoxy-2-nitrophenyl)propionate (**17**)



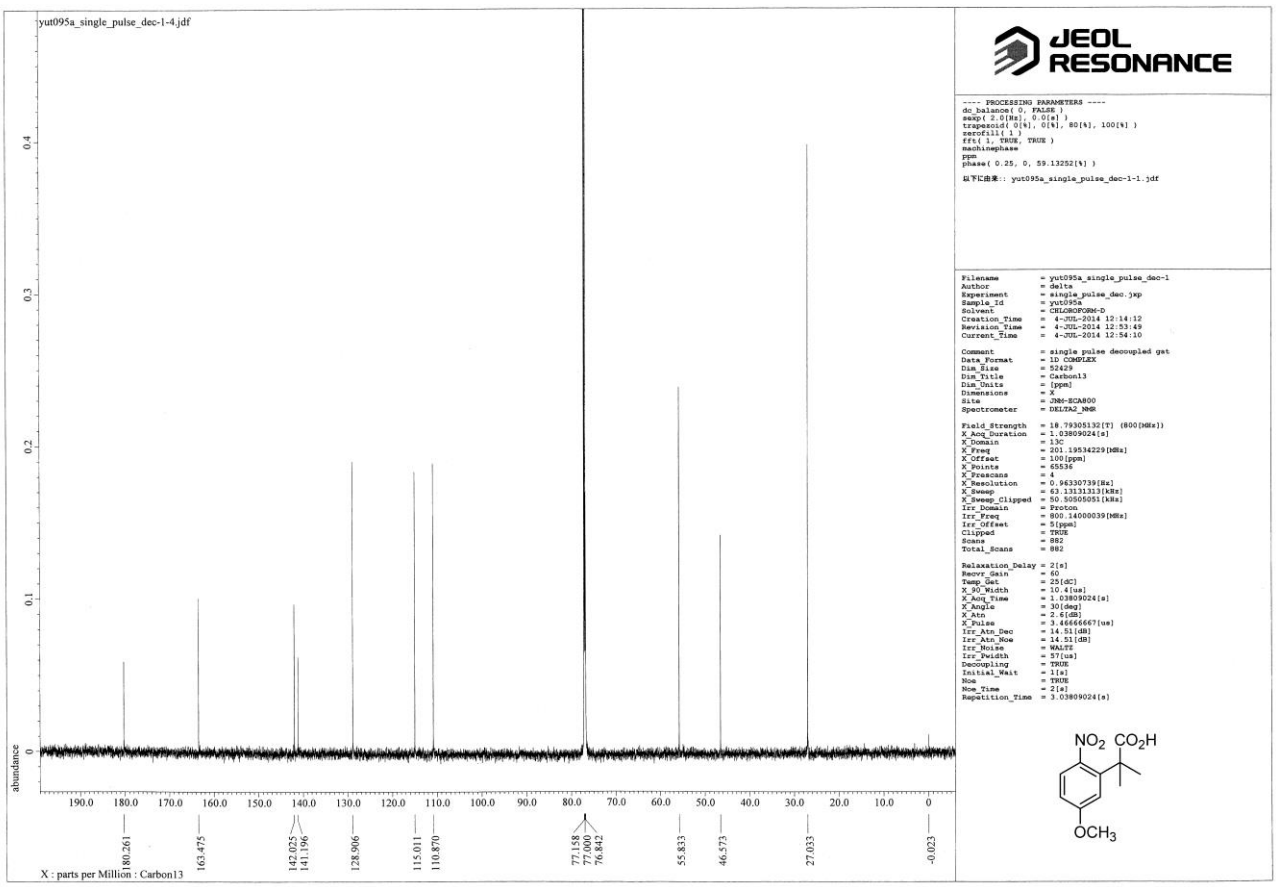
^{13}C NMR spectrum (125 MHz, in $CDCl_3$) of methyl 2-methoxy-2-(5-methoxy-2-nitrophenyl)propionate (**17**)



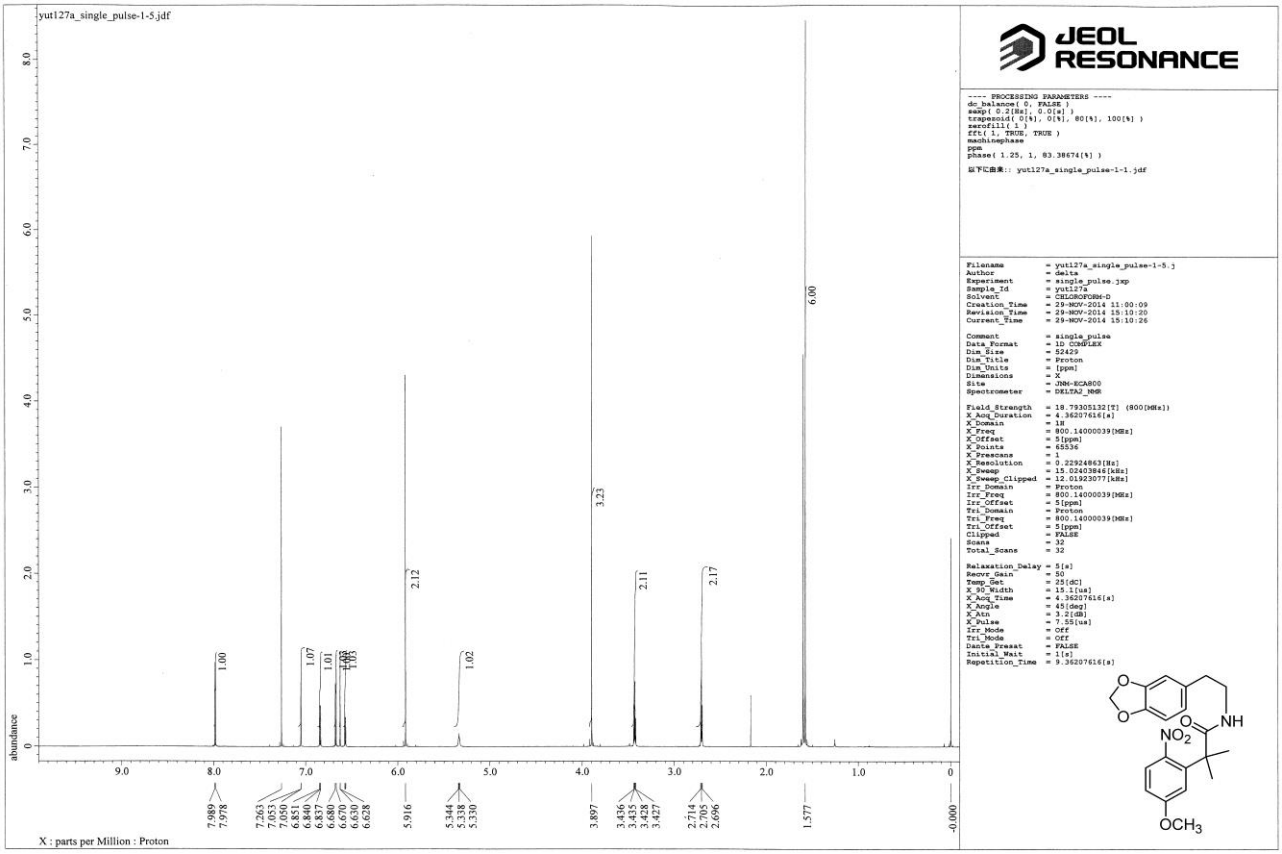
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of 2-methyl-2-(5-methoxy2-nitrophenyl)propionic acid (**8**)



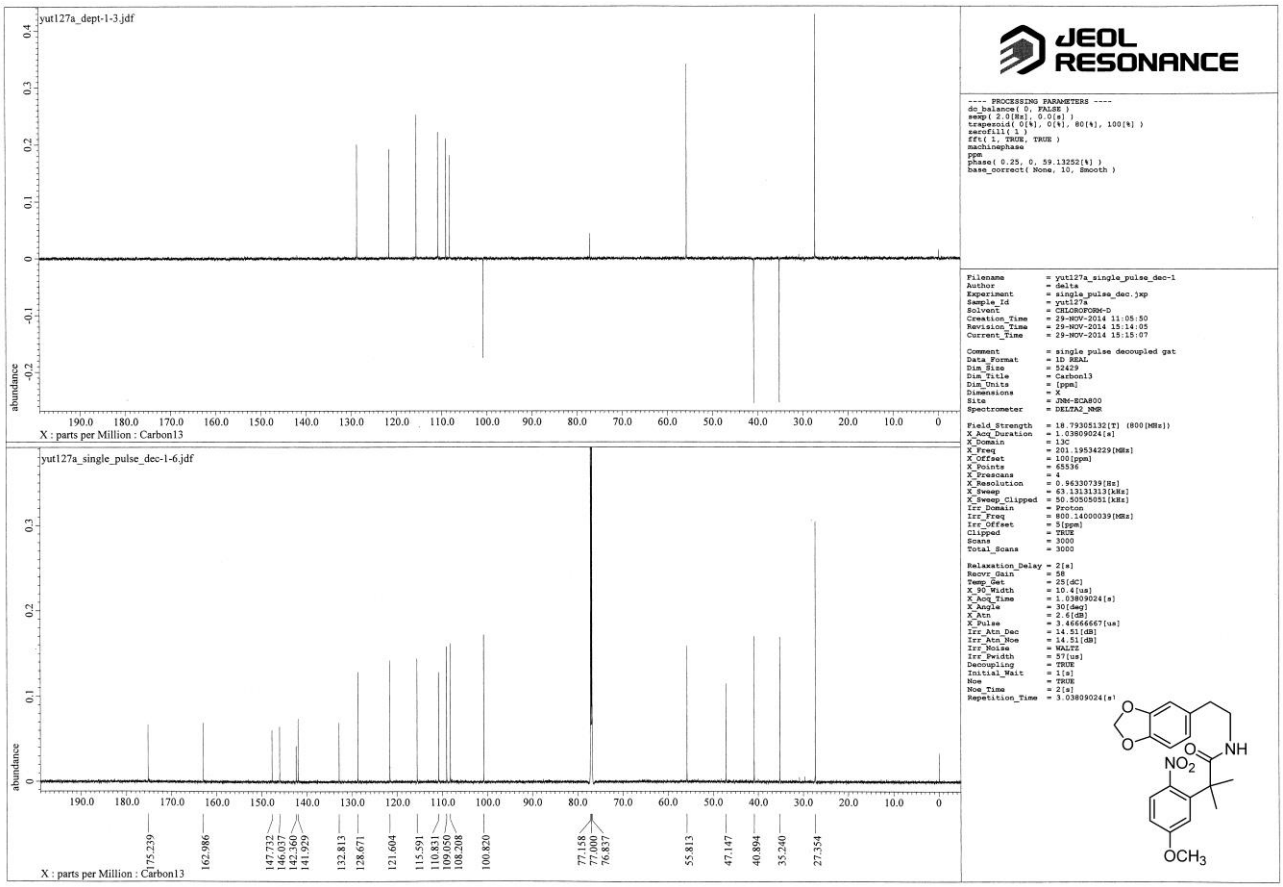
^{13}C NMR spectrum (200 MHz, in $CDCl_3$) of 2-methyl-2-(5-methoxy2-nitrophenyl)propionic acid (**8**)



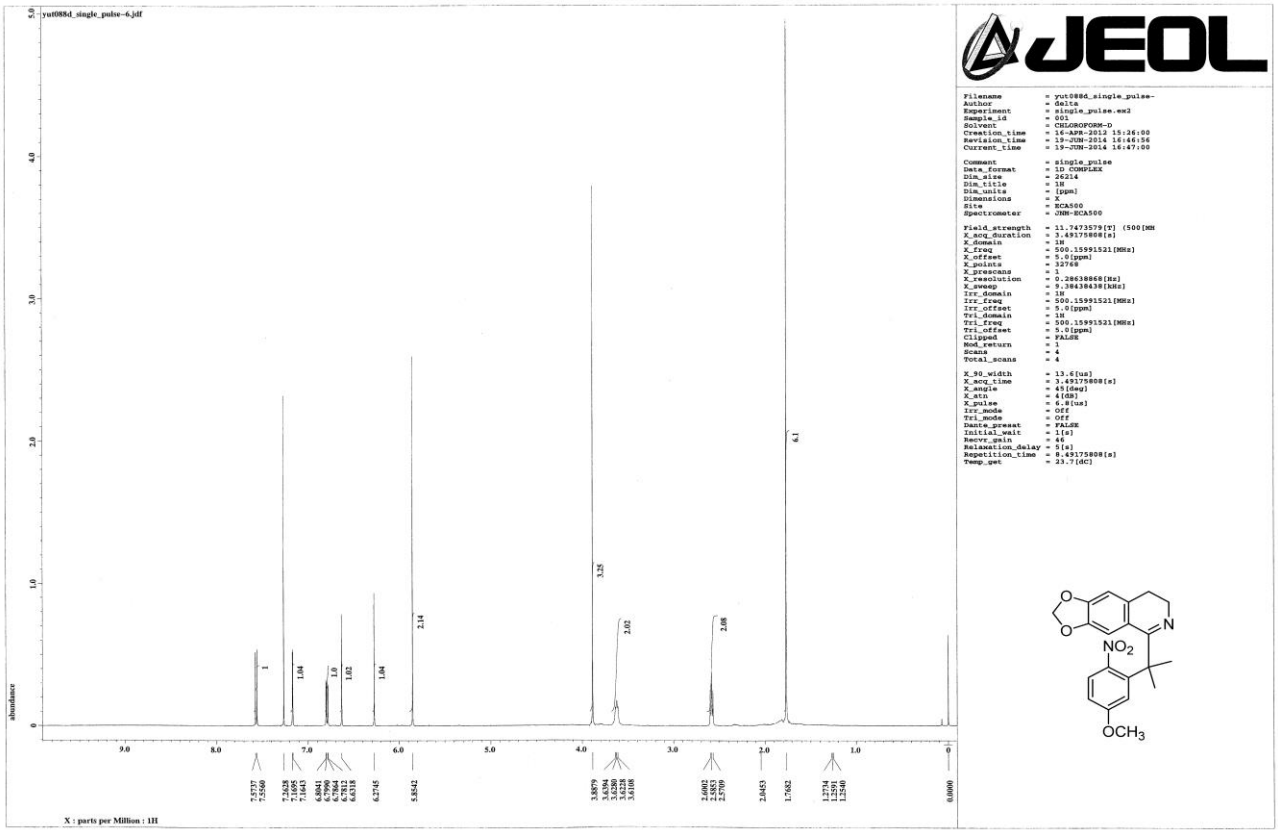
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of *N*-homopiperonyl-2-methyl-2-(5-methoxy-2-nitrophenyl)-propionamide (**19**)



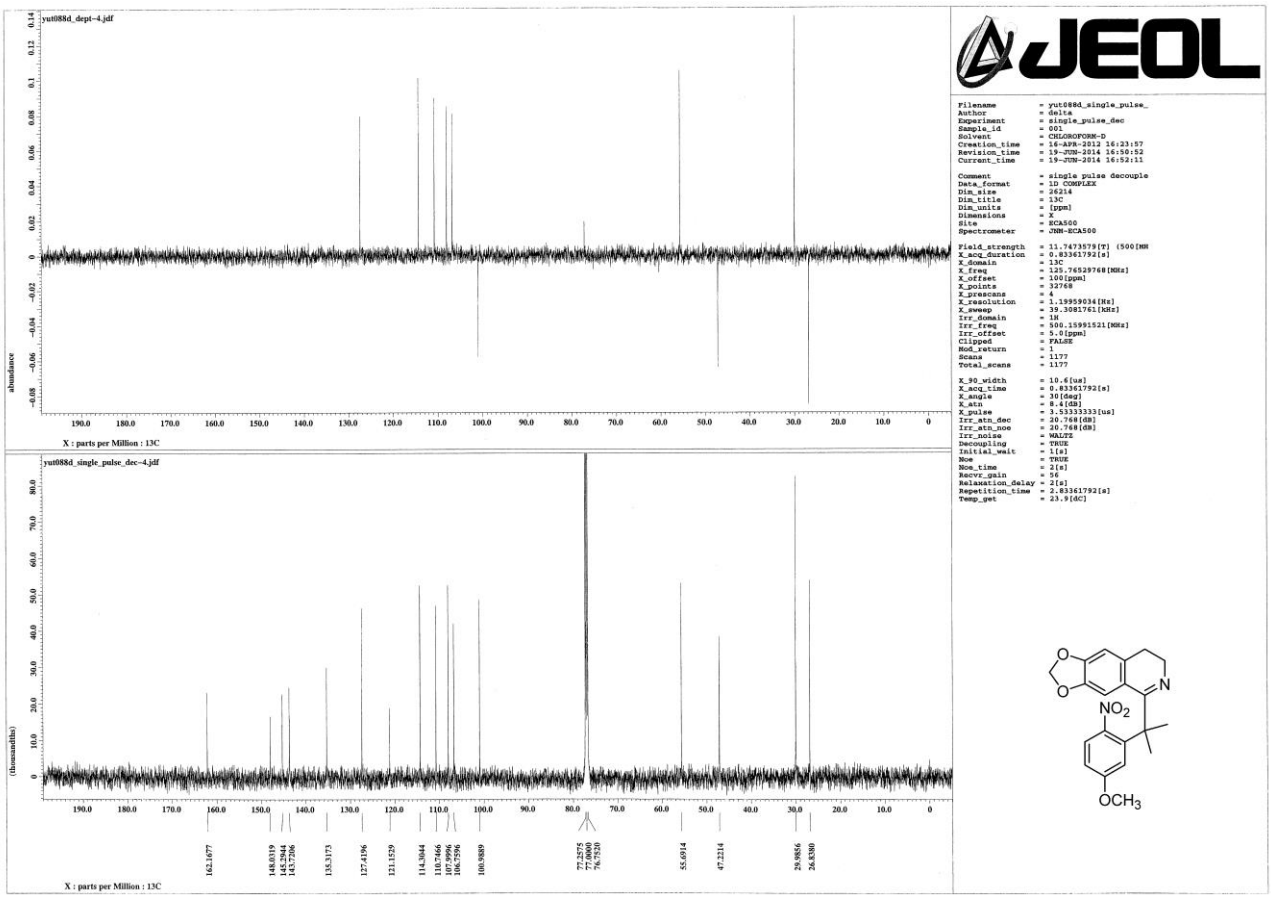
^{13}C NMR spectrum (200 MHz, in $CDCl_3$) of *N*-homopiperonyl-2-methyl-2-(5-methoxy-2-nitrophenyl)-propionamide (**19**).



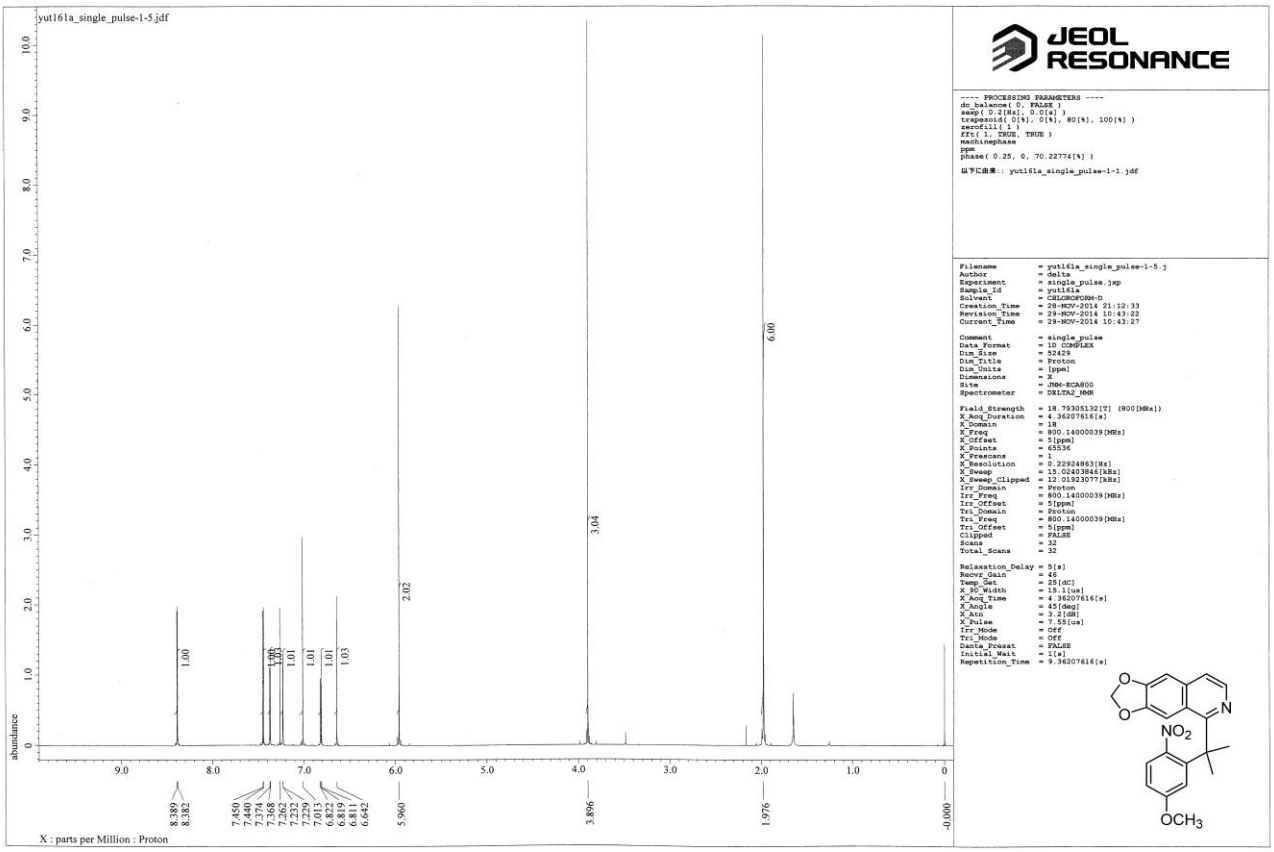
^{1}H NMR spectrum (500 MHz, in $CDCl_3$) of 3,4-dihydro-1-[1,1-dimethyl-1-(5-methoxy-2-nitrophenyl)-methyl]-6,7-methylenedioxyisoquinoline (**20**)



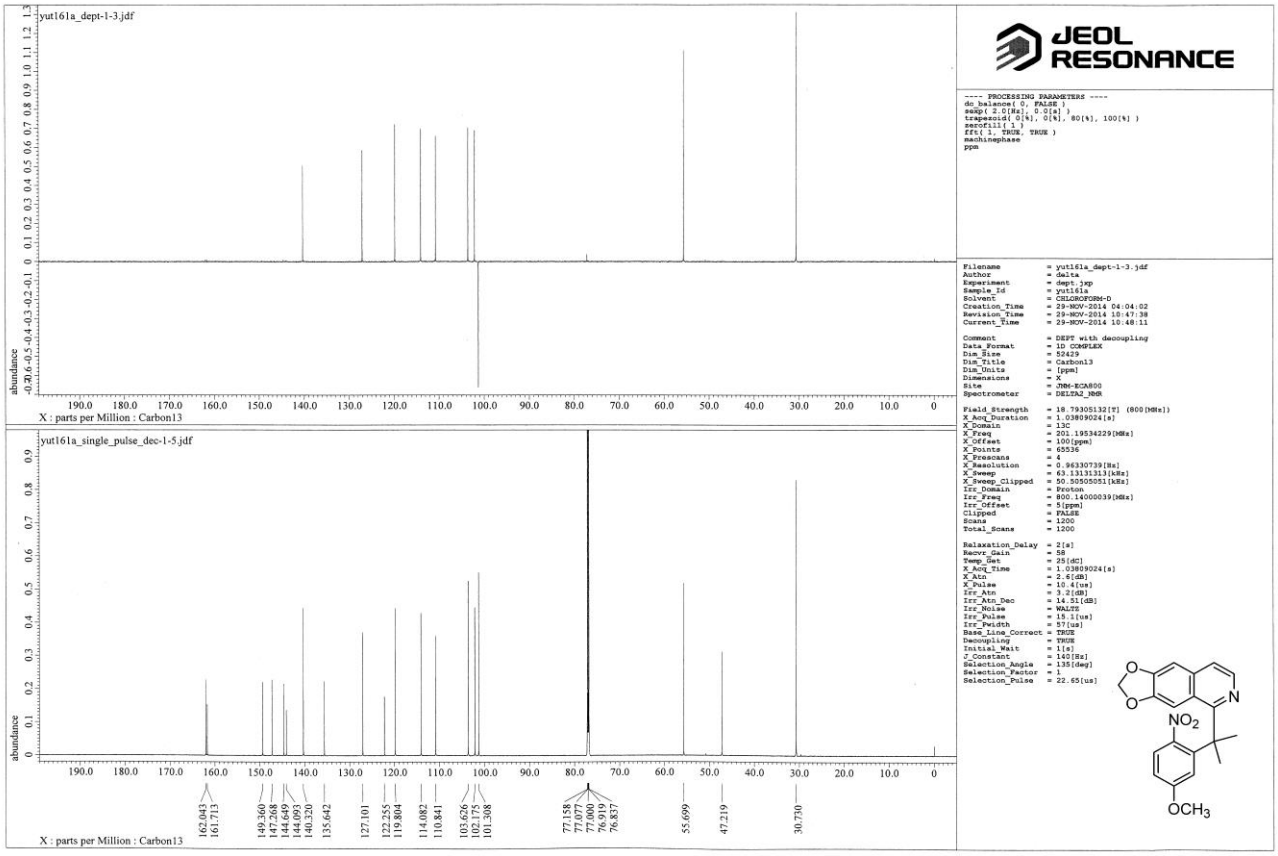
^{13}C NMR spectrum (125 MHz, in $CDCl_3$) of 3,4-dihydro-1-[1,1-dimethyl-1-(5-methoxy-2-nitro-phenyl)methyl]-6,7-methylenedioxyisoquinoline (**20**)



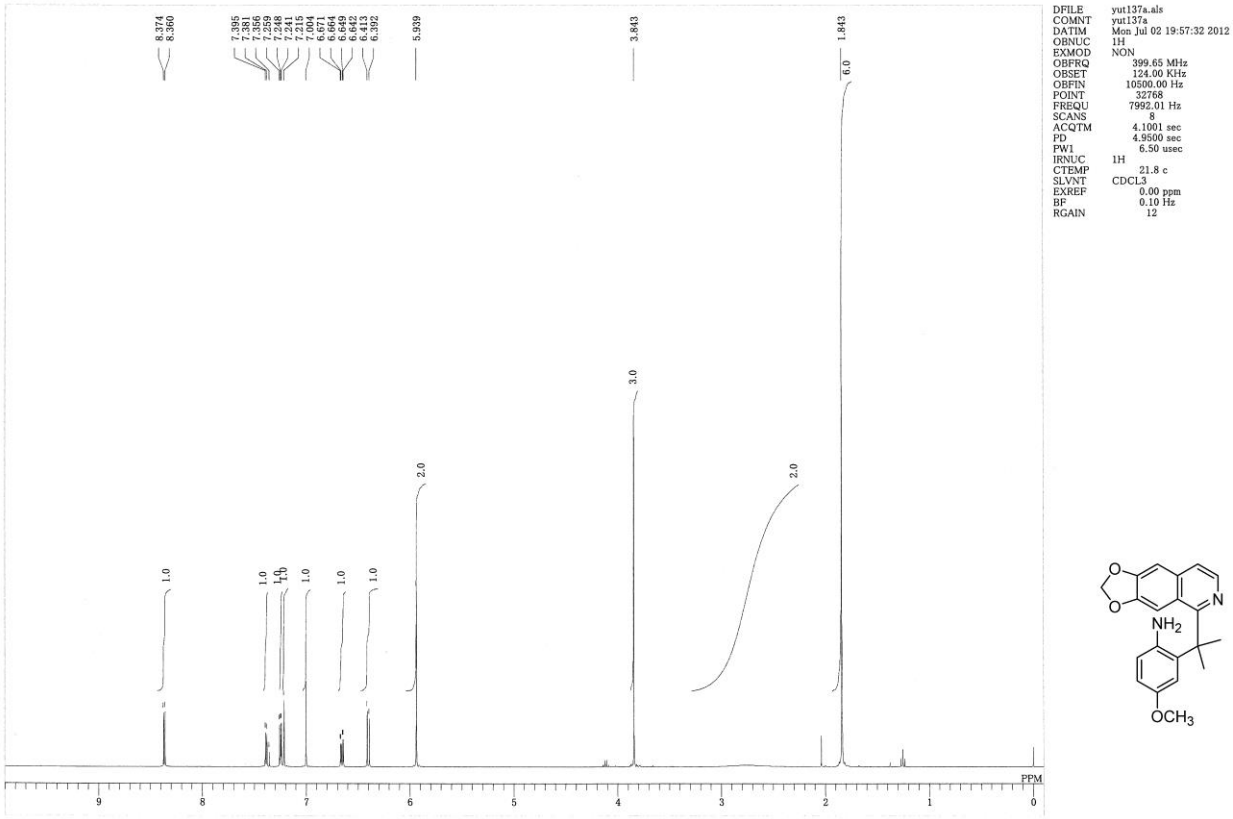
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of 1-[1-Methyl-1-(5-methoxy-2-nitrophenyl)ethyl]-6,7-methylenedioxyisoquinoline (**21**)



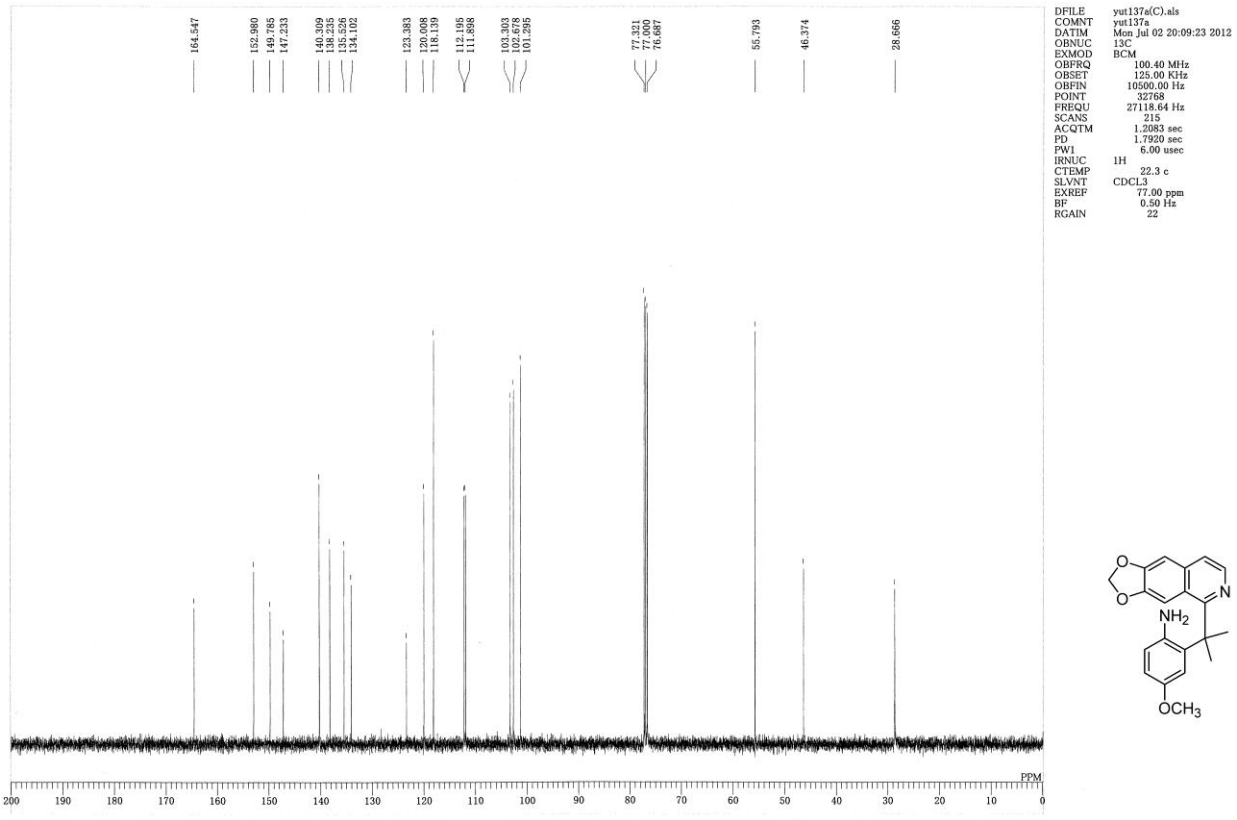
^{13}C NMR spectrum (200 MHz, in $CDCl_3$) of 1-[1-Methyl-1-(5-methoxy-2-nitrophenyl)ethyl]-6,7-methylenedioxyisoquinoline (**21**)



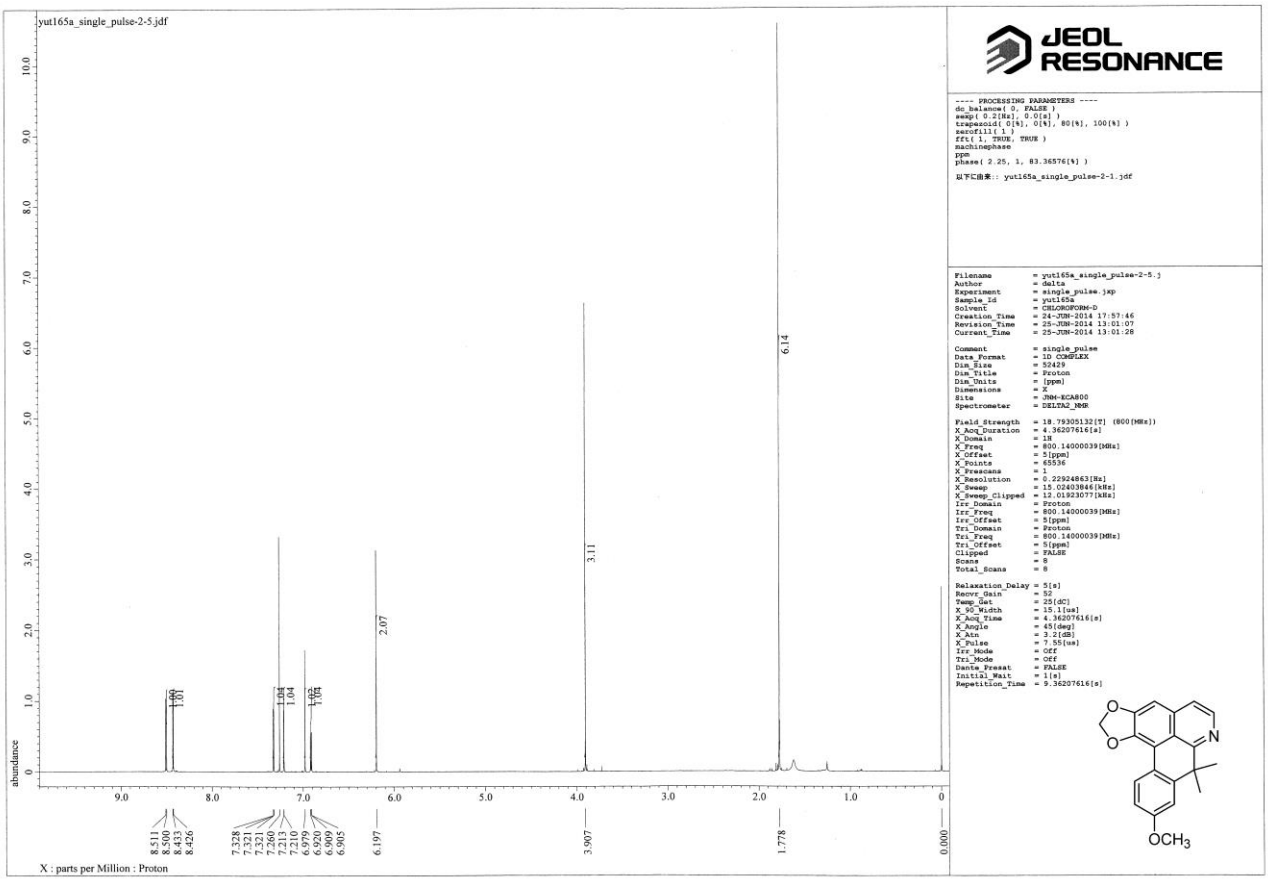
^{1}H NMR spectrum (400 MHz, in $CDCl_3$) of 1-[1-Methyl-1-(5-methoxy-2-aminophenyl)ethyl]-6,7-methylenedioxyisoquinoline (**22**)



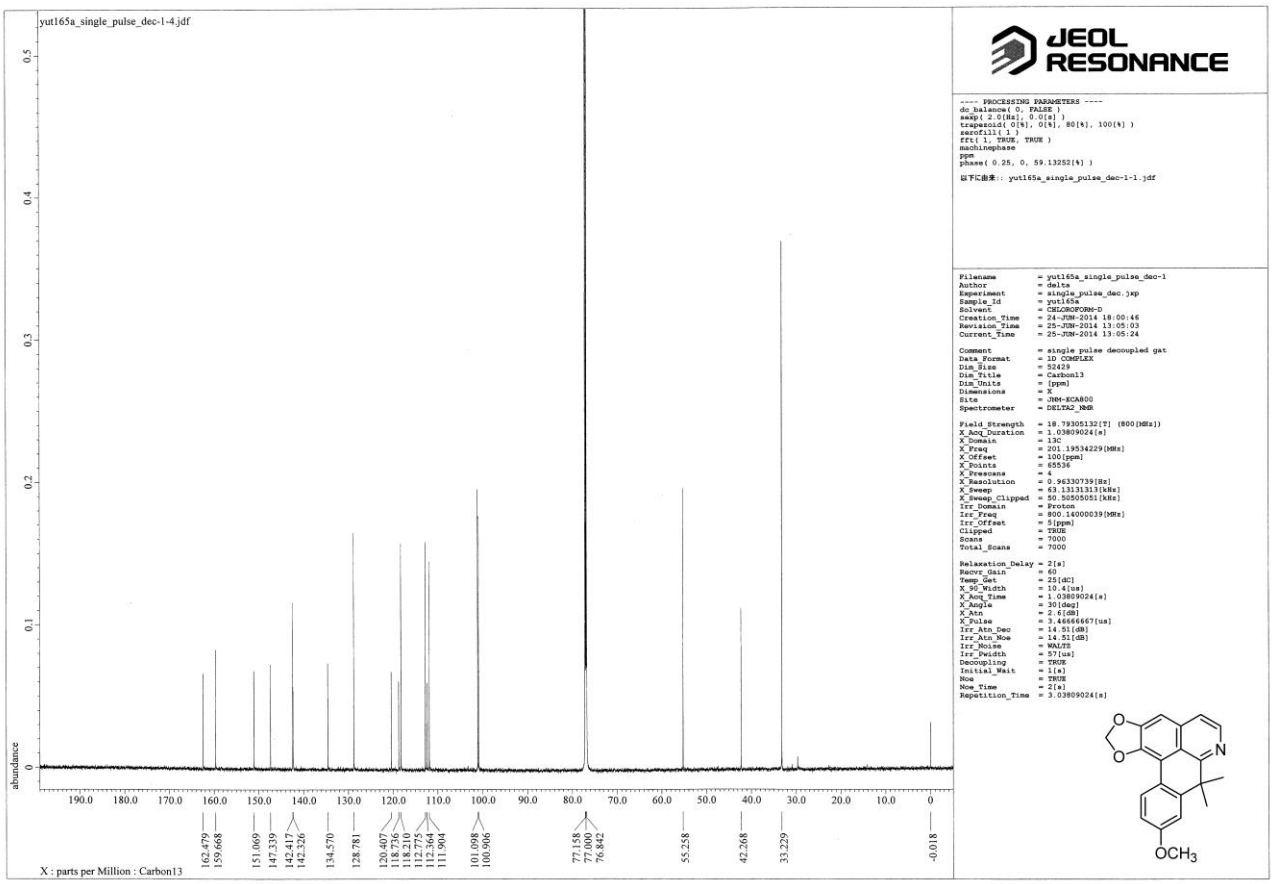
^{13}C NMR spectrum (100 MHz, in $CDCl_3$) of 1-[1-Methyl-1-(5-methoxy-2-aminophenyl)ethyl]-6,7-methylenedioxyisoquinoline (**22**)



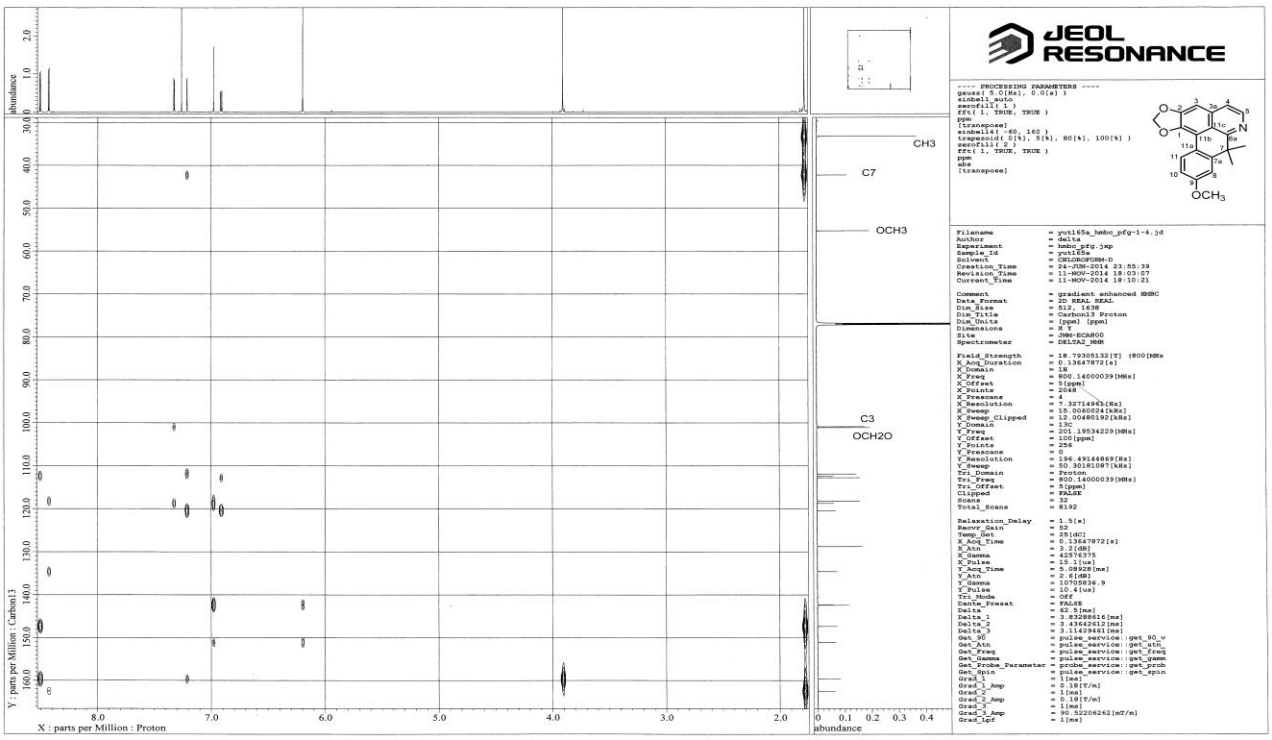
^{1}H NMR spectrum (800 MHz, in $CDCl_3$) of 4,5-didehydroguadiscine (**6**)

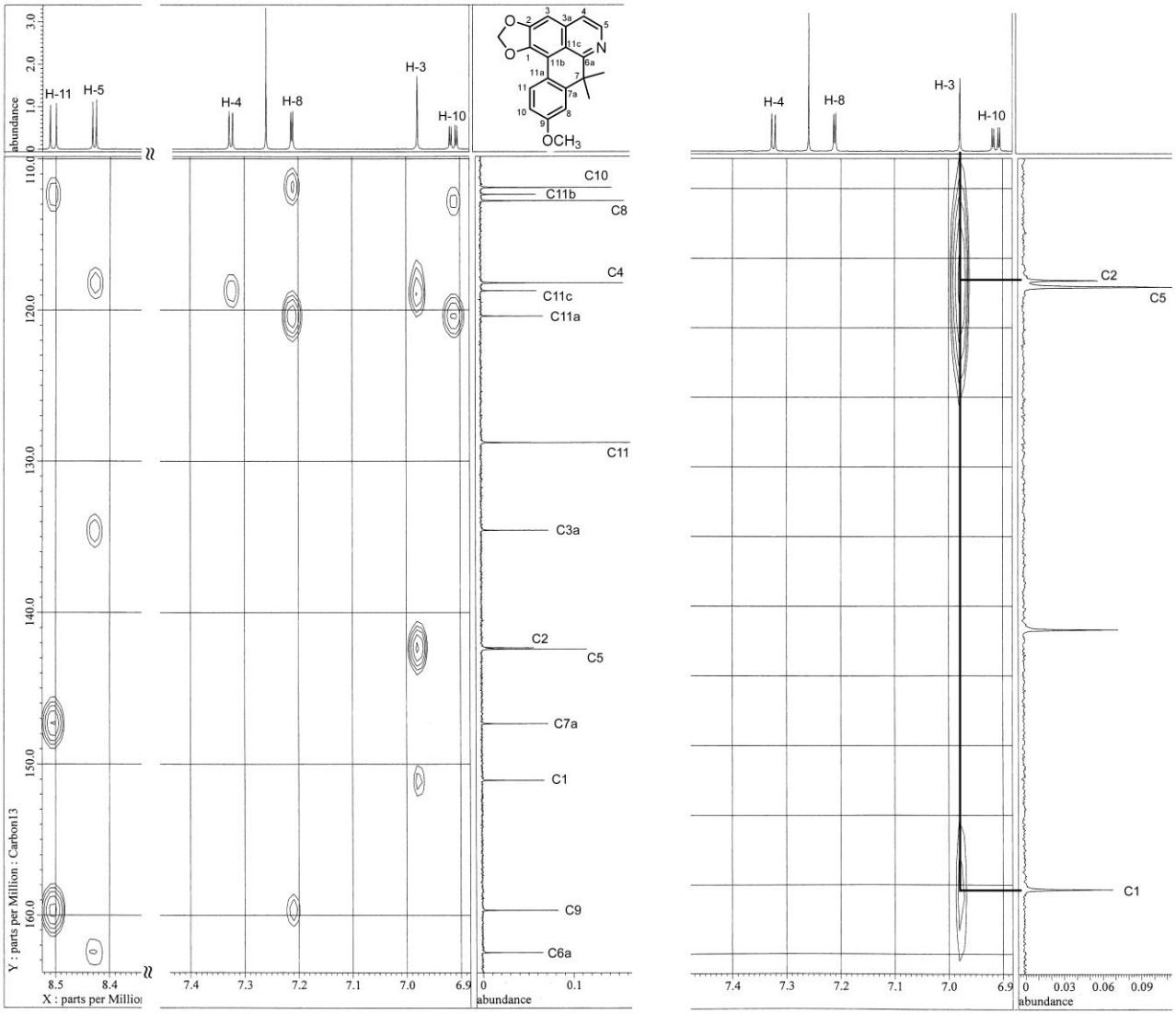


^{13}C NMR spectrum (200 MHz, in $CDCl_3$) of 4,5-didehydroguadiscine (**6**)

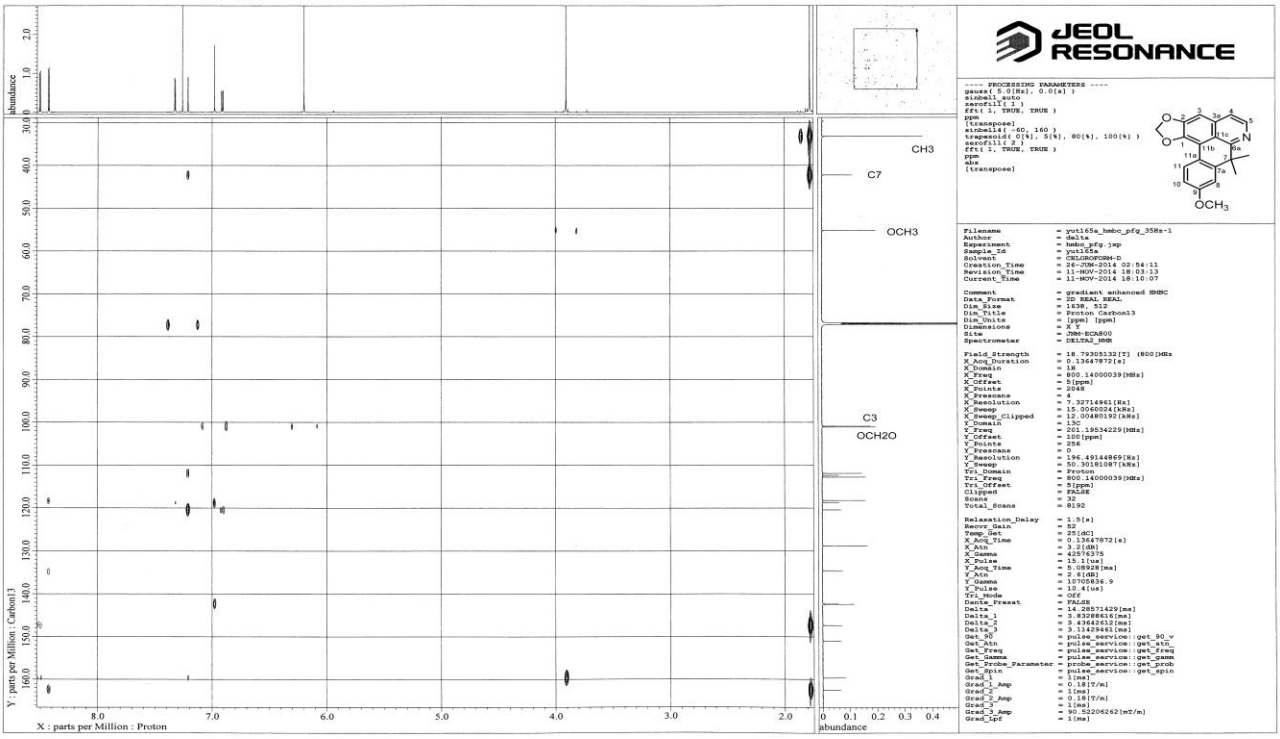


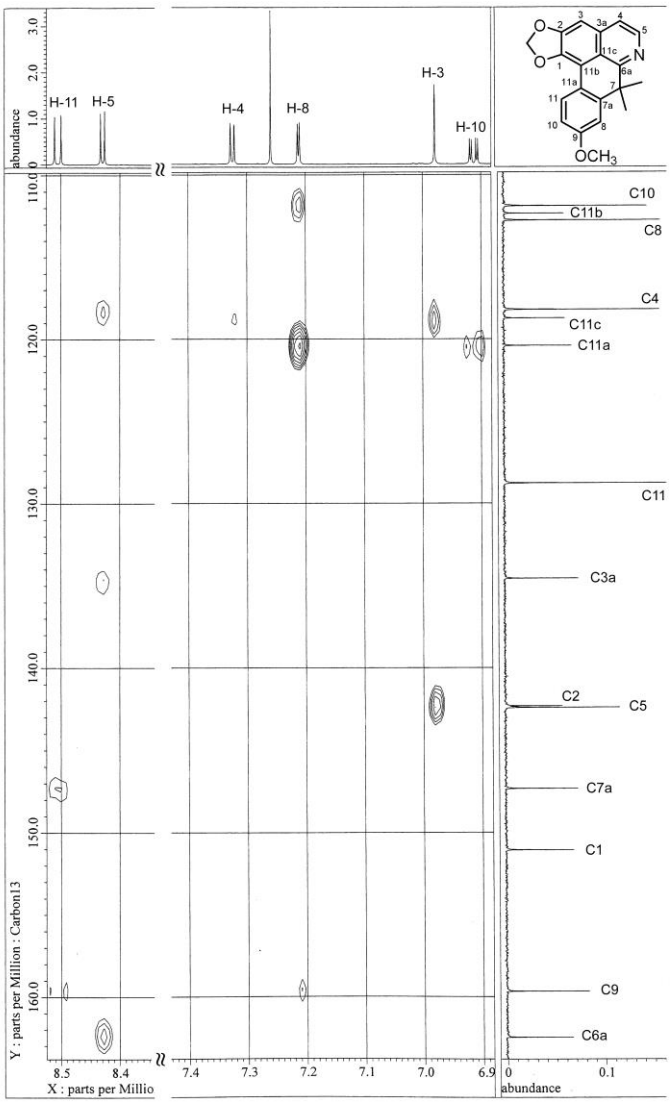
HMBC spectrum ($J_{C–H}$ = 8 Hz) of 4,5-didehydroguadiscine (**6**)

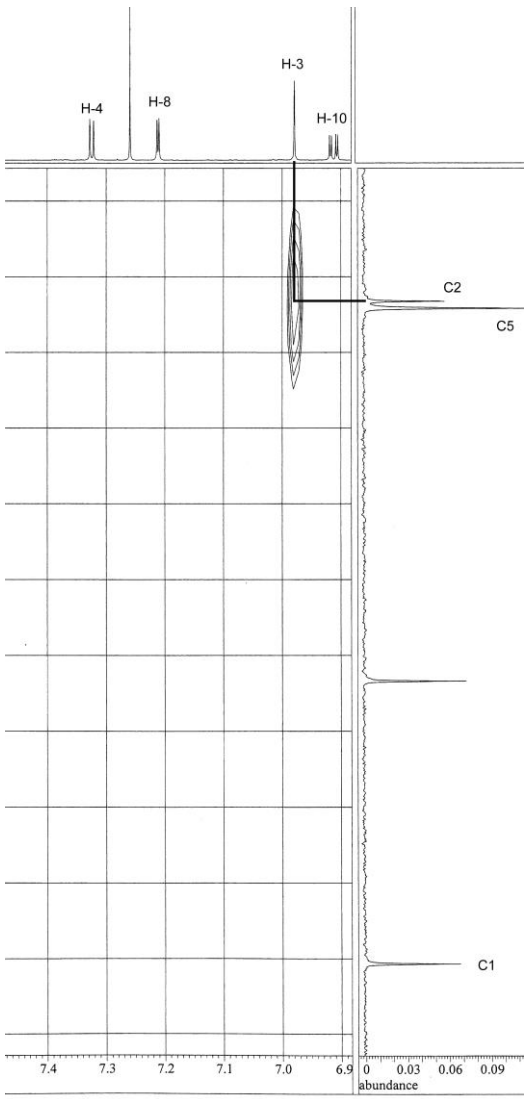




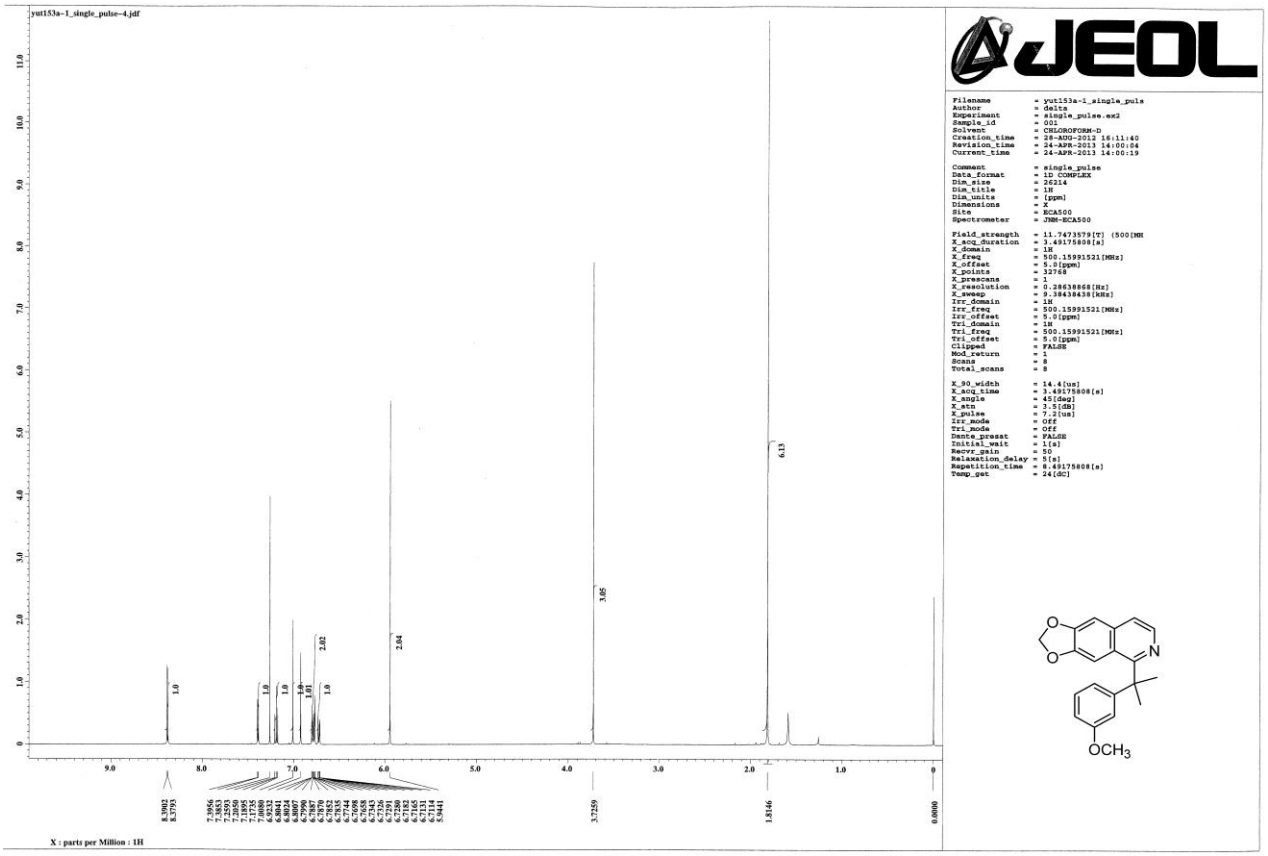
HMBC spectrum ($J_{C–H}$ = 35 Hz) of 4,5-didehydroguadiscine (**6**)







^{1}H NMR spectrum (500 MHz, in $CDCl_3$) of 1-[1-methyl-1-(5-methoxyphenyl)ethyl]-6,7-methylenedioxy-isoquinoline (**24**)



^{13}C NMR spectrum (125 MHz, in $CDCl_3$) of 1-[1-methyl-1-(5-methoxyphenyl)ethyl]-6,7-methylenedioxy-isoquinoline (**24**)

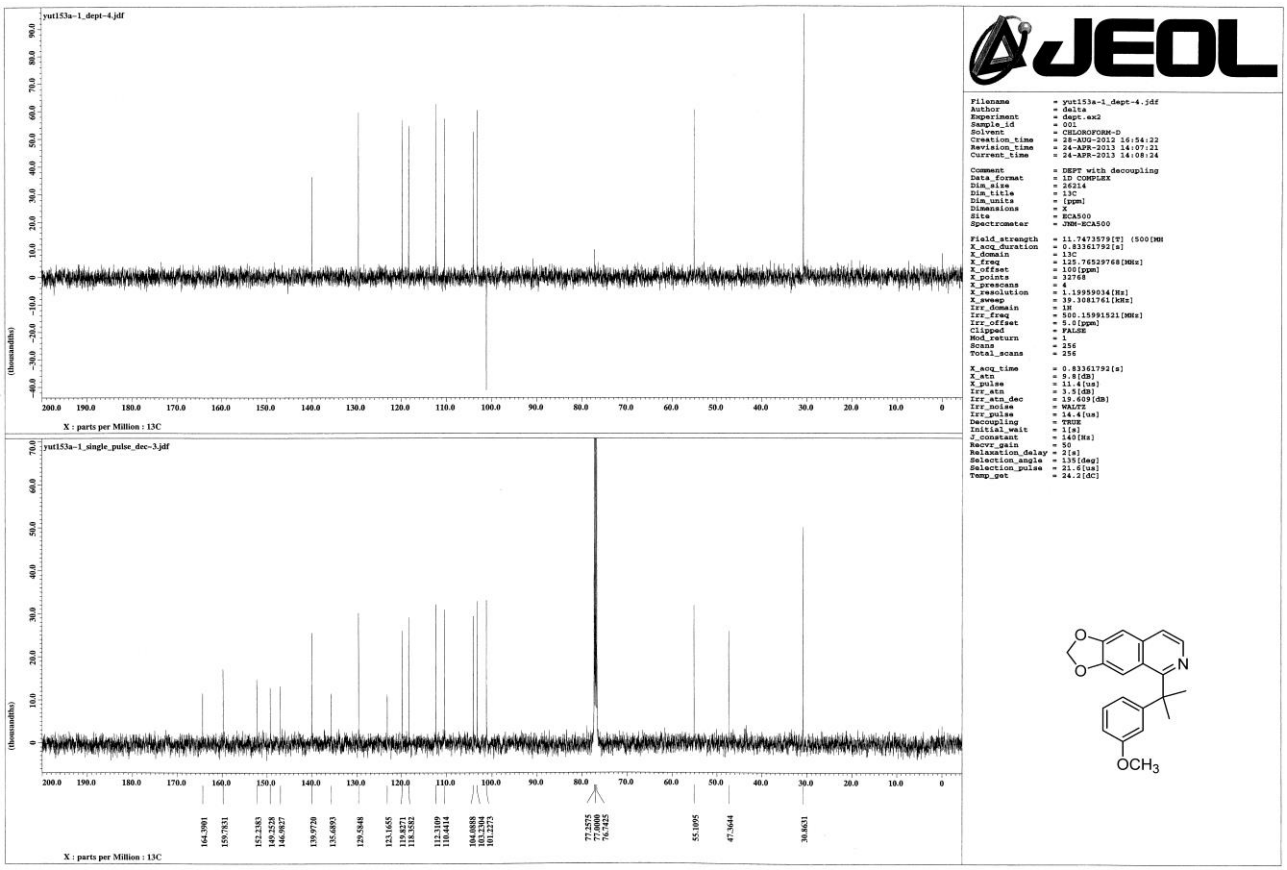


Table 1. Inhibitory Effects of Aporphinoids **1**, **2**, **3**, **4**, **5**, **6** and Arbutin on Theophylline-stimulated Melanogenesis in B16 Melanoma 4A5 Cells

	Inhibition (%)					IC_{50} (μM)
	0 μM	3 μM	10 μM	30 μM		
6[a]	0.0 ± 2.3	33.2 ± 3.4*	80.4 ± 7.2*	87.7 ± 5.6*		4.7
1[b]	0.0 ± 2.9	16.5 ± 1.7*	32.1 ± 1.5*	72.3 ± 2.8*		15.8
2[b]	0.0 ± 1.9	19.7 ± 2.5*	37.9 ± 1.7*	70.6 ± 1.0*		14.5
3[b]	0.0 ± 2.8	11.1 ± 2.0*	27.3 ± 1.1*	65.9 ± 0.7*		19.3
4[b]	0.0 ± 1.9	13.2 ± 3.3*	37.6 ± 2.7*	87.4 ± 5.0*		13.3
5[c]	0.0 ± 6.0	8.7 ± 3.7	–1.5 ± 2.0	65.3 ± 0.9*		–
	Inhibition (%)					IC_{50} (μM)
	0 μM	30 μM	100 μM	300 μM	1000 μM	
Arbutin[d]	0.0 ± 1.4	20.4 ± 0.5*	38.1 ± 0.9*	61.5 ± 0.6*	83.7 ± 0.5*	174

Each value represents the mean ± SEM ($N = 4$). Significantly different from the control, *$p < 0.01$. [a]The cell viabilities at 3, 10, and 30 μM were 96, 87, and 60%, respectively. [b]The cell viability at 30 μM was greater than 86%.[1] [c]The cell viability at 30 μM was greater than 69%.[1] [d]The cell viabilities at 30, 100, 300, and 1000 μM were 82, 78, 80, and 53%, respectively.[2]

References

(1) Nakamura, S.; Nakashima, S.; Tanabe, G.; Oda, Y.; Yokota, N.; Fujimoto, K.; Matsumoto, T.; Sakuma, R.; Ohta, T.; Ogawa, K.; Nishida, S.; Miki, H.; Matsuda, H.; Muraoka, O.; Yoshikawa, M. *Bioorg. Med. Chem.* **2013**, *21*, 779–787.

(2) Morikawa, T.; Nakanishi, Y.; Ninomiya, K.; Matsuda, H.; Nakashima, S.; Miki, H.; Miyashita, Y.; Yoshikawa, M.; Hayakawa, T.; Muraoka, O. *J. Nat. Med.* **2014**, *68*, 539–549.