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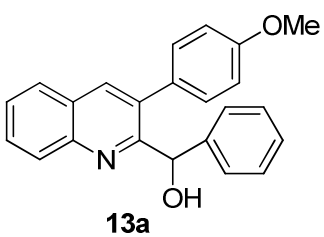
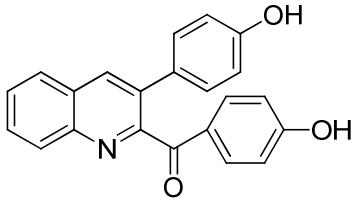
Graphical Abstract



13a



17

A number of 2-aroyl-3-arylquinoline derivatives were synthesized and evaluated for their anti-Dengue virus activity. Both **13a** and **17** were found to significantly inhibit the DENV2 RNA expression in Huh-7-DV-Fluc cells.

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Synthesis, Antiproliferative and Anti-Dengue Virus Evaluations of 2-Aroyl-3-arylquinoline Derivatives

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Abstract

A number of 2-aroyl-3-arylquinoline derivatives was synthesized and evaluated for their anti-Dengue virus activity. Both 2-(hydroxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (**13a**) and 2-(4-hydroxybenzoyl)-3-(4-hydroxyphenyl)quinoline (**17**) were found to significantly inhibit the DENV2 RNA expression in Huh-7-DV-Fluc cells with a potency approximately equal to that of ribavirin and the inhibition is in a dose-dependent manner. Compounds **13a** and **17** reduced DENV replication in both viral protein and mRNA levels, and no significant cell cytotoxicity was detected, with greater than 50% viability of Huh-7-DV-Fluc cells at a concentration of 100 μM. However, significant cytotoxicity was detected for the positive ribavirin. In addition, we performed infectious assay to further verify the inhibitory activity of **13a** and **17** on DENV replication in protein and RNA levels. On the other hand, compounds **19a - 19c** exhibited IC_{50} values ranged from 4.47 to 8.68 μM against A549, H1299, MCF-7, and Huh-7 which were approximately equal potent to the positive topotecan. Structural optimization of lead compounds, **13a** and **17**, and their detailed molecular mechanism of action are ongoing.

Keywords

2-Aroyl-3-arylquinoline; Ribavirin; Topotecan; Anti-Dengue virus; Antiproliferative

1. Introduction

Dengue virus (DENV) is a mosquito-borne human pathogen and belongs to the genus Flavivirus in the *Flaviviridae* family [1]. DENV has been identified as an etiological agent causing dengue hemorrhagic fever (DHF), dengue fever (DF), and dengue shock syndrome (DSS) [2]. In recent years, these members of the genus *Flavivirus* cause prominent morbidity and mortality, and DENV has become a serious public health threat worldwide. It is estimated that 40 to 80 million people are infected by DENV per year, particularly in the tropical Asia, Latin America, and the Caribbean, and infection with DENV lead to approximately 500,000 severe life-threatening cases and over 20,000 deaths [3, 4]. Unfortunately, there is no clinical approval vaccine to prevent DENV infection and effective antiviral therapy against DENV replication [5, 6]. Therefore, the development of safe and effective therapeutic agent is now urgent needed.

DENV is an enveloped RNA virus containing a positive-sense and single strand genome with an approximate 11 kilobases (kb) in the length [7]. Upon DENV entry into the target cells, the RNA genome is translated to a single polyprotein associated with the host endoplasmic reticulum (ER), on which members of Flavivirus are dependent for translation and replication [8]. The polyprotein is cleaved by host and viral proteases into three structural proteins (capsid [C], premembrane [prM], and envelope [E]) and seven non-structure proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). The structure proteins are important components for consisting of the functional virion to procceed virus entry, fusion and assembly, and the non-structure proteins are

essential components for virus replication [9]. Recently, a number of small molecule compounds were found to inhibit DENV replication significantly through different mechanisms, including the inhibition of virus entry [10], virus replication, or viral RNA dependent RNA polymerase [11].

Quinoline skeleton is one of the key building elements for a large number of natural and synthetic heterocycles which possess a wide variety of biological effects such as antimicrobial [12-16], anticancer [17-24], and antiviral activities [25-27]. Among these known antiviral quinoline derivatives, 4-[4-(2-chlorobenzyloxy)aniline]-6-ethoxy-2-methylquinoline (**1**, *Figure* 1) exhibited inhibitory activities against a DENV-2 sub-genomic replicon cell line with an IC_{50} value of 5 μM and against a WNV sub-genomic replicon cell line with an IC_{50} of 1.9 μM [27] while 3'-nitrophenylaminoquinoline (**2**) inhibited the growth of Hepatitis C virus with an EC_{50} value of 7.0 μM [24]. Certain quinoline derivatives are highly cytotoxic. For examples, compound **3** was active against the growth of H1299 and SKBR-3 with IC_{50} values of 1.41 and 0.70 μM respectively [22] while 6-fluoro-2,3-bis{4-[2-(piperidin-1-yl)ethoxy]phenyl}quinoline (**4**) was more active than tamoxifene against the growth of Hep 3B, H1299, and MDA-MB-231 with GI_{50} values of 0.71, 1.46, and 0.72 μM respectively [21].

The present study describes the preparation and anti-Dengue virus activities of certain 2-aroyl-3-arylquinoline derivatives whose structures are similar to compounds **1 - 4**. Structures of the target compounds can also be considered as derivatives of compound **3** in which the conjugated double bond bridge between quinoline and the carbonyl group is removed. Due to the significant

antiproliferative activities exhibited by compound **3**, these newly synthesized 2-aroyl-3-arylquinoline derivatives have also been evaluated for their cytotoxicities. Our aim is to identify potential anti-Dengue virus drug candidates with no significant cytotoxicity.

< **Insert Figure 1 here** >

2. Chemistry

The Pfitzinger reaction of indolin-2,3-dione (isatin, **5**) and 4-methoxyphenyacetone (**9**) under basic conditions gave 3-(4-methoxyphenyl)-2-methylquinoline-4-carboxylic acid (**10a**) [22, 28]. Accordingly, compounds **10b – 10e** were obtained from the starting materials **5** - **9** respectively under the same reaction conditions. Thermal decarboxylation of **10a – 10e** gave 3-(4-methoxyphenyl)-2-methylquinoline (**11a**) or its respective analogs **11b – 11e** in a yield of 70 – 78%. Oxidation of **11a – 11e** with selenium oxide afforded 3-(4-methoxyphenyl)quinoline-2-carbaldehyde (**12a**) or its analogs **12b – 12e** respectively in a yield of 70 – 87%. Treatment of **12a** with phenyl magnesium bromide (Grignard reagent) afforded 2-(hydroxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (**13a**) which was then oxidized with MnO_2 to gave 2-benzoyl-3-(4-methoxyphenyl)quinoline (**14a**) as described in *Scheme* 1. Accordingly, Grignard reaction of compounds **12b – 12e** afforded compounds **13b – 13e** respectively which was then oxidized with MnO_2 to give their respective carbonyl products **14b – 14e** under the same reaction conditions.

Treatment of **12a** with 4-methoxyphenyl magnesium bromide or 3,4,5-trimethoxyphenyl

magnesium bromide gave 2-(hydroxy-4-methoxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (**15a**) or its analog **15b** which was then oxidized with MnO_2 to afford 2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)quinoline (**16a**) or its analog **16b** respectively as described in *Scheme* 2. Demethylation of **16a** with 48% HBr gave 2-(4-hydroxybenzoyl)-3-(4-hydroxyphenyl)quinoline (**17**) which was then alkylated with *N*-(2-chloroethyl)pyrrolidine to give a mixture of the monoalkylated product **18a** and dialkylated product **19a** in the presence of NaH. The structural assignment of the monoalkylated products **18a** was determined by 2D Nuclear Overhauser Effect (2D NOESY) experiments, as shown in *Figure* 2. Compound **18a** was assigned as a monoalkylated product at the C-3 phenyl moiety by the correlation between OCH_2 (δ_H = 3.93 ppm) / *meta*-H of 3-phenyl (δ_H = 6.74 ppm), *meta*-H of 3-phenyl (δ_H = 6.74 ppm) / *ortho*-H of 3-phenyl (δ_H = 7.25 ppm), and *ortho*-H of 3-phenyl (δ_H = 7.25 ppm) / 4-H (δ_H = 8.20 ppm) were observed (*Figure* 2). Accordingly, compounds **18b, c** and **19b, c** were obtained by the alkylation of **17** with *N*-(2-chloroethyl)piperidine, and 3-chloro-*N,N*-dimethylpropanamine respectively as described in *Scheme* 3.

< **Insert Scheme 1-3 and Figure 2 here** >

3. Biological Results and Discussion

3.1. *Anti-DENV2 and Antiproliferative Activities*

The anti-DENV2 and cytotoxicities of 2-aroyl-3-arylquinoline derivatives are summarized in *Table* 1. Huh-7-DV-Fluc cells were treated with compounds **13** – **19** or the positive

ribavirin respectively at a concentration of 5 or 20 μM for three days. Cells were then analyzed through the firefly luciferase activity. Compounds which exhibited >50% inhibition of DENV at a concentration of 20 μM were considered as active. Results from *Table 1* indicated that 2-(hydroxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (**13a**) was more active than its fluoro-substituted counterparts, **13c** – **13e**. The anti-DENV2 activity was also slightly decreased by the substitution of a methoxy group at C-4 position in which **13a** was more active than **13b**. Oxidation of the secondary alcohol resulted in the lost of activity in which compound **14a** was inactive. The same SAR was observed since the secondary alcohol **15a** was more active than the oxo derivative **16a**. However, compound **17** was more active than its precursor **16a** thus indicating that the hydrogen bond donor groups are more favorable than that of hydrogen accepting groups. Among these 2-aroyl-3-arylquinoline derivatives, compounds **13a, 13b, 14b, 15a** and **17** exhibited more than 50% inhibition of DENV replication in the Huh-7-DV-Fluc cells at a concentration of 20 μM. The cell cytotoxicity of was determined by XTT assay in the Huh-7 cells after 3 days treatment with 20 and 100 μM of 2-aroyl-3-arylquinoline derivatives. Compounds **13a, 14b,** and **17** exhibited low cytotoxicity, with greater than 50% viability at a concentration of 100 μM. However, significant cytotoxicities were detected for compounds **13b**, **15a**, and the positive ribavirin. The concentration that inhibited 50% DENV replication (IC_{50}), the concentration that inhibited the growth of 50% cells (CC_{50}), and the selective index (SI : CC_{50}/IC_{50}) of compounds **13a, 13b, 14b, 15a** and **17** were determined as shown in *Table* 2. Results indicated that all the tested compounds

exhibited comparable anti-DENV2 actitity (IC_{50} ranged from 12.57 to 18.16 μM) to that of ribavirin (IC_{50} = 12.61 μM). However, compounds **13a, 14b,** and **17** demonstrated a good selectivity with SI value of greater than 7.96, 5.76, and 7.60 respectively which was higher than that of ribavirin (SI = 4.47).

Among these newly synthesized 2-aroyl-3-arylquinoline derivatives, compounds **18a** – **18c** and **19a** – **19c** exhibited significant cytotoxicities against Huh-7 cell with less than 20% viability at a concentration of 100 μM. These compounds were then evaluated for their antiproliferative activities against A549, H1299, MDA-MB231, MCF-7, and Huh-7 and the IC_{50} values are summarized in *Table 3*. Results indicated that diaminoalkoxy-substituted 2-aroyl-3-arylquinoline derivatives, **19a - 19c**, were more cytotoxic than their monoaminoalkoxy-substituted counterparts, **18a - 18c**. Compounds **19a - 19c** exhibited IC_{50} values ranged from 4.47 to 8.68 μM against A549, H1299, MCF-7, and Huh-7 which were approximatedly equal potent to the positive topotecan. However, topotecan was more active than compounds **19a - 19c** against MDA-MB231.

< **Insert Table 1-3** >

3.2. *Compounds **13a** and **17** reduced DENV replication in DENV infected Huh-7 cells*

To confirm the results of dose-dependent decease luciferase activity representing the DENV replication in the Huh-7-DV-Fluc cells, we performed western blotting with anti-NS2B and anti-GAPDH and RT-qPCR with specific primers to determine the DENV NS2B protein expression and DENV NS5 mRNA expression. Both results of western blotting and RT-qPCR revealed that **13a** and **17** consistently reduced DENV replication in the Huh-7-DV-Fluc cells at the concentration

of 5 and 20 μM after 3 days treatment. Treatment of ribavirin was served as a positive control of the inhibition on DENV replication and 0.1% DMSO was served as mock control (*Figures* 3 and 4). Results from *Figure* 3 also indicated that compound **13a** was more active than **13b** which implied that the methoxy group substituted at C-6 position is unfavorable. Substitution of the methoxy group at the para-position of C-2 phenylmethyl group resulted in a decreased activity in which compound **15a** was less ative than **13a**. The inhibitory activities of compounds **13a** and **17** on DENV2 RNA expression in Huh-7-DV-Fluc cells were approximately equal to that of ribavirin and the inhibition is in a dose-dependent manner (*Figure* 4). Furthermore, compounds **13a** and **17** were inoculated with the Huh-7-DV-Fluc cells at various concentrations for 3 days, and then total protein and RNA were collected and analyzed through western blotting and RT-PCR. Results showed **13a** and **17** reduced DENV replication in the dose dependent manner in both viral protein and mRNA levels, and no significant cell cytotoxicity in Huh-7-DV cells was detected (*Figure 5*). In addition, we performed infectious assay to further verify the inhibitory activity of **13a** and **17** on DENV replication in protein and RNA levels (*Figure* 6). Results further confirmed that compounds **13a** and **17** were capable of reducing DENV replication in DENV infected Huh-7 cells in a concentration-dependent manner.

< **Insert Figure 3-6 here** >

4. Conclusion

A number of 2-aroyl-3-arylquinoline derivatives were synthesized and evaluated for

anti-Dengue virus activity against of DENV2. Among them, 2-(hydroxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (**13a**) and 2-(4-hydroxybenzoyl)-3-(4-hydroxyphenyl)quinoline (**17**) were found to significantly inhibit the DENV2 RNA expression in Huh-7-DV-Fluc cells with a potency approximately equal to that of ribavirin and the inhibition is in a dose-dependent manner. Compounds **13a** and **17** reduced DENV replication in both viral protein and mRNA levels, and no significant cell cytotoxicity was detected, with greater than 50% viability of Huh-7-DV-Fluc cells at a concentration of 100 μM. Both compounds were identified as novel type of structures for further development of anti-DENV agents.

5. Experimental

5.1. General

Melting points were determined on a Electrothermal IA9100 melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Varian Gemini 200 spectrometer or Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co.. Mass spectra were recorded on Bruker APEX II (ESI) mass spectrometer. The elemental analyses were performed in the Instrument Center of National Science Council at National Cheng-Kung University and National Taiwan University using Heraeus CHN-O Rapid EA, and all values are within ± 0.4% of the theoretical compositions.

5.2. General procedure for the preparation of 3-aryl-2-methylquinoline-4-carboxylic acids 10 [22]. A mixture of isatin **5**, **6**, or **7** (40 mmol), phenylacetone **8** or **9** (48 mmol) and KOH (6.74 g, 120 mmol) in EtOH was heated at 80 ^{o}C for 48 h (TLC monitoring). After cooling, the solvent was removed in vacuo and the residue dissolved in H_2O (50 mL), and the aqueous solution was washed twice with Et_2O (30 mL). The ice-cold aqueous phase was acidified to pH 1 with 37% HCl, and the precipitate was collected by suction filtration, washed with H_2O and recrystallized with EtOH to give 3-aryl-2-methylquinoline-4-carboxylic acids **10**.

5.2.1. 6-Fluoro-3-(4-methoxyphenyl)-2-methylquinoline-4-carboxylic acid (**10b**). Yield: 93% as a white solid. Mp. 269^{o}C (dec). ^{1}H NMR (DMSO-d_6): 2.45 (s, 3H, 2-Me), 3.83 (s, 3H, OMe), 7.05-7.08 (m, 2H, Ar-H), 7.29-7.32 (m, 2H, Ar-H), 7. 45 (dd, 1H, *J* = 9.6, 2.8 Hz, 5-H), 7.73 (ddd, 1H, *J* = 9.2, 8.4, 2.8 Hz, 7-H), 8.12 (dd, 1H, *J* = 9.2, 5.6 Hz, 8-H). ^{13}C NMR (DMSO-d_6): 24.43, 55.15, 108.07 (*J* = 23.5 Hz), 113.82 (2C), 119.78 (*J* = 25.7 Hz), 122.49 (*J* = 9.9 Hz), 128.17, 130.49 (2C), 131.27, 131.59 (*J* = 9.1 Hz), 139.65 143.39, 157.60 (*J* = 2.3 Hz), 159.03, 159.92 (*J* = 244 Hz), 167.79. Anal. calcd for $C_{18}H_{14}FNO_3$: C 69.45, H 4.53, N 4.50; found C 69.45, H 4.59, N 4.57.

5.2.2. 6-Methoxy-3-(4-methoxyphenyl)-2-methylquinoline-4-carboxylic acid (10c). Yield: 84% as a white solid. Mp. 279^{o}C (dec). ^{1}H NMR (DMSO-d_6): 2.72 (s, 3H, 2-Me), 3.82 (s, 3H, OMe), 3.87 (s, 3H, 6-OMe), 7.03-7.06 (m, 3H, Ar- & 5-H), 7.27-7.29 (m, 2H, Ar-H), 7.45 (dd, 1H, *J* = 8.4, 0.8 Hz, 7-H), 7.95 (d, 1H, *J* = 8.4 Hz, 8-H). ^{13}C NMR (DMSO-d_6): 24.16, 55.19, 55.51, 102.71, 113.81 (2C), 121.98, 122.80, 129.21, 130.22, 130.60 (2C), 139.38, 142.29, 155.06, 157.53, 158.95,

168.38. Anal. calcd for $C_{19}H_{17}NO_4 \cdot 0.25\ H_2O$: C 69.60, H 5.39, N 4.27; found C 69.78, H 5.44, N 4.16.

5.2.3. (4-Fluorophenyl)-2-methylquinoline-4-carboxylic acid (10d). Yield: 88% as a white solid. Mp. 348^{o}C (dec). ^{1}H NMR (DMSO-d_6): 2.43 (s, 3H, 2-Me), 7.31-7.44 (m, 4H, Ar-H), 7.63--7.83 (m, 3H, Ar-H), 8.04 (d, 1H, J = 8.4 Hz, 8-H). ^{13}C NMR (DMSO-d_6): 24.51, 115.28 (2C, J = 21.3 Hz), 121.64, 124.89, 127.09, 128.56, 129.43, 130.01, 131.53 (2C, J = 8.3 Hz), 133.19, 143.30, 157.46, 161.88 (J = 243.3 Hz), 168.01. Anal. calcd for $C_{17}H_{12}FNO_2 \cdot 0.2\ H_2O$: C 71.67, H 4.39, N 4.92; found C 71.80, H 4.46, N 4.88.

5.2.4. 6-Fluoro-3-(4-fluorophenyl)-2-methylquinoline-4-carboxylic acid (10e). Yield: 88% as a white solid. Mp. 279^{o}C (dec). ^{1}H NMR (DMSO-d_6): 2.44 (s, 3H, 2-Me), 7.32-7.50 (m, 5H, Ar- & 5-H), 7.74 (ddd, 1H, J = 9.2, 9.2, 2.8 Hz, 7-H), 7.13 (dd, 1H, J = 9.2, 5.6 Hz, 8-H). ^{13}C NMR (DMSO-d_6): 24.42, 108.21 (J = 23.5 Hz), 115.39 (2C, J = 22.0 Hz), 120.10 (J = 25.8 Hz), 122.40 (J = 9.9 Hz), 130.07, 131.46 (2C, J = 8.4 Hz), 131.66 (J = 9.1 Hz), 133.04 (J = 3.8 Hz), 139.68 (J = 5.3 Hz), 143.61, 157.18, 160.02 (J = 244.7 Hz), 162.00 (J = 243.3 Hz), 167.65. Anal. calcd for $C_{19}H_{17}NO_4 \cdot 0.25\ H_2O$: C 69.60, H 5.39, N 4.27; found C 69.78, H 5.44, N 4.16.

5.3. General procedure for the decarboxylation of acids 10 [22]. The suspension of quinoline-4-carboxylic acid **10** (5.0 mmol) in 10 mL dowtherm was heated to 280 ^{o}C for 4 h (TLC monitoring). After cooling, the reaction mixture was added *n*-hexane (50 mL) and the formed solid was collected by filtration, washed with *n*-hexane. The crude product was purified by flash

chromatography on silica gel (hexane/CH_2Cl_2 1/1) and recrystallized from EtOH to give compounds **11**.

5.3.1. 6-Fluoro-3-(4-methoxyphenyl)-2-methylquinoline (11b). Yield: 73% as a brown solid. Mp. 88-89°C. ^{1}H NMR ($CDCl_3$): 2.66 (s, 3H, 2-Me), 3.89 (s, 3H, OMe), 6.99-7.03 (m, 2H, Ar-H), 7.31-7.34 (m, 2H, Ar-H), 7.39 (dd, 1H, *J* = 9.2, 2.8 Hz, 5-H), 7.44 (ddd, 1H, *J* = 9.2, 8.8, 2.8 Hz, 7-H), 7.88 (s, 1H, 4-H), 8.05 (dd, 1H, *J* = 9.2, 5.2 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 24.48, 55.34, 110.29 (*J* = 21.2 Hz), 113.92 (2C), 119.23 (*J* = 25.8 Hz), 127.47 (*J* = 9.8 Hz), 130.28 (2C), 130.80 (*J* = 9.1 Hz), 131.81, 135.33 (*J* = 5.3 Hz), 136.20, 143.95, 157.04 (*J* = 3.1 Hz), 159.28, 160.18 (*J* = 244.8 Hz). Anal. calcd for $C_{17}H_{14}FNO$: C 76.39, H 5.28, N 5.24; found: C 76.25, H 5.38, N 5.18.

5.3.2. 6-Methoxy-3-(4-methoxyphenyl)-2-methylquinoline (11c). Yield: 70% as a brown solid. Mp. 209-210°C. ^{1}H NMR ($CDCl_3$): 2.69 (s, 3H, 2-Me), 3.88 (s, 3H, OMe), 3.92 (s, 3H, 6-OMe), 6.98-7.02 (m, 2H, Ar-H), 7.04 (d, 1H, *J* = 2.8 Hz, 5-H), 7.31-7.35 (m, 3H, Ar- & 7-H), 7.84 (s, 1H, 4-H), 7.95 (d, 1H, *J* = 9.2 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 24.22, 55.32, 55.48, 104.94, 113.81 (2C), 121.72, 127.77, 129.78, 130.31 (2C), 132.38, 135.02, 135.60, 142.95, 154.92, 157.38, 159.08. Anal. calcd for $C_{18}H_{17}NO_2 \cdot 0.3\ H_2O$: C 75.91, H 6.24, N 4.91; found C 75.63, H 6.21, N 4.82.

5.3.3. 3-(4-Fluorophenyl)-2-methylquinoline (11d). Yield: 75% as a brown oil. Mp. ^{1}H NMR ($CDCl_3$): 2.61 (s, 3H, 2-Me), 7.08-7.12 (m, 2H, Ar-H), 7.27-7.30 (m, 2H, Ar-H), 7.41-7.45 (m, 1H, 6-H), 7.61-7.64 (m, 1H, 7-H), 7.69 (dd, 1H, *J* = 8.4, 1.2 Hz, 5-H), 7.85 (s, 1H, 4-H), 8.05 (d, 1H, *J* = 8.4 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 24.27, 115.21 (2C, *J* = 21.3 Hz), 125.95, 126.57, 127.23, 128.16,

129.29, 130.65 (2C, *J* = 7.6 Hz), 134.46, 135.58 (*J* = 3.0 Hz), 135.99, 146.81, 156.99, 162.16 (*J* = 245.5 Hz),. Anal. calcd for $C_{16}H_{12}FN$: C 80.99, H 5.09, N 5.90; found C 80.69, H 5.23, N 5.82.

5.3.4. 6-Fluoro-3-(4-fluorophenyl)-2-methylquinoline (11e). Yield: 78% as a brown solid. Mp. 209-210^{o}C. ^{1}H NMR ($CDCl_3$): 2.63 (s, 3H, 2-Me), 7.14-7.20 (m, 2H, Ar-H), 7.34-7.49 (m, 4H,5-, 7-, and Ar-H), 7.88 (s, 1H, 4-H), 8.04 (dd, 1H, *J* = 8.8, 5.6 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 24.40, 110.35 (*J* = 21.3 Hz), 115.50 (2C, *J* = 21.3 Hz), 119.58 (*J* = 25.0 Hz), 127.29 (*J* = 9.9 Hz), 130.78 (2C, *J* = 7.6 Hz), 130.93, 135.45, 135.48, 135.53, 144.15, 156.60, 160.23 (*J* = 245.5 Hz), 162.46 (*J* = 245.5 Hz). Anal. calcd for $C_{18}H_{17}NO_2 \cdot 0.3\ H_2O$: C 75.91, H 6.24, N 4.91; found C 75.63, H 6.21, N 4.82.

5.4. General procedure for the preparation of quinoline-2-carbaldehydes 12 [22]. A mixture **11** (3.0 mmol) and selenium dioxide (0.66 g, 6.0 mmol) in 1,4-dioxane (50 mL) was heated to 100 ^{o}C for 2 h (TLC monitoring). The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O followed by brine, dried with $MgSO_4$ and evaporated. The crude product was recrystallized with EtOH to give quinoline-2-carbaldehydes **12.**

5.4.1. 6-Fluoro-3-(4-methoxyphenyl)quinoline-2-carbaldehyde (12b). Yield: 73% as a yellow solid. Mp. 116-117^{o}C. ^{1}H NMR ($CDCl_3$): 3.89 (s, 3H, OMe), 7.01-7.05 (m, 2H, Ar-H), 7.34-7.38 (m, 2H, Ar-H), 7.49 (dd, 1H, *J* = 8.4, 2.8 Hz, 5-H), 7.58 (ddd, 1H, *J* = 9.2, 8.4, 2.8 Hz, 7-H), 8.13 (s, 1H, 4-H), 8.33 (dd, 1H, *J* = 9.2, 5.6 Hz, 8-H), 10.24 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): 55.37,

110.43 (*J* = 22.0 Hz), 114.08 (2C), 121.02 (*J* = 26.5 Hz), 128.65, 129.94 (*J* = 10.6 Hz), 130.78 (2C), 133.33 (*J* = 9.8 Hz), 136.32, 137.72 (*J* = 6.1 Hz), 144.06, 149.43, 159.88, 162.23 (*J* = 251.6 Hz), 192.23. Anal. calcd for $C_{17}H_{12}FNO_2$: C 72.59, H 4.30, N 4.98; found C 72.82, H 4.45, N 4.76.

5.4.2. 6-Methoxy-3-(4-methoxyphenyl)quinoline-2-carbaldehyde (12c). Yield 70% as a yellow solid. Mp. 100-102°C. ^{1}H NMR ($CDCl_3$): 3.89 (s, 3H, OMe), 3.97 (s, 3H, 6-OMe), 7.01-7.05 (m, 2H, Ar-H), 7.10 (d, 1H, *J* = 2.8 Hz, 5-H), 7.35-7.39 (m, 2H, Ar-H), 7.45 (dd, 1H, *J* = 9.2, 2.8 Hz, 7-H), 8.05 (s, 1H, 4-H), 8.20 (d, 1H, *J* = 9.2 Hz, 8-H), 10.22 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): 55.35, 55.70, 104.30, 113.93 (2C), 123.81, 129.28, 130.57, 130.77 (2C), 132.09, 136.25, 136.86, 143.23, 147.59, 159.66, 160.12, 192.37. Anal. calcd for $C_{18}H_{15}NO_3$: C 73.69, H 5.16, N 4.91; found C 73.63, H 4.91, N 4.70.

5.4.3. 3-(4-Fluorophenyl)quinoline-2-carbaldehyde (12d). Yield 87% as a yellow solid. Mp. 155-156°C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.20 (m, 2H, Ar-H), 7.37-7.41 (m, 2H, Ar-H), 7.68-7.85 (m, 2H, 6-, and 7-H), 7.88 (d, 1H, *J* = 8.4 Hz, 5-H), 8.17 (s, 1H, 4-H), 8.36 (d, 1H, *J* = 8.4 Hz, 8-H), 10.26 (s, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): 115.43 (2C, *J* = 22.0 Hz), 127.58, 128.80, 129.64, 130.39, 130.60, 131.10 (2C, *J* = 8.4 Hz), 133.17 (*J* = 3.0 Hz), 134.38, 138.74, 147.06, 149.75, 162.76 (*J* = 246.4 Hz), 192.64. Anal. calcd for $C_{16}H_{10}FNO \cdot 0.2\ H_2O$: C 75.40, H 4.11, N 5.50; found: C 75.65, H 4.03, N 5.46.

5.4.4. 3-(4-Fluorophenyl)-6-floroquinoline-2-carbaldehyde (12e). Yield 81% as a yellow solid. Mp. 154-156°C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.16-7.21 (m, 2H, Ar-H), 7.37-7.40 (m, 2H, Ar-H),

7.51 (dd, 1H, *J* = 8.4, 2.8 Hz), 7.60 (ddd, 1H, *J* = 9.2, 8.4, 2.8 Hz, 7-H), 8.11 (s, 1H, 4-H), 8.33 (dd, 1H, *J* = 9.2, 5.2 Hz, 8-H), 10.23 (s, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): 110.56 (*J* = 21.2 Hz), 115.43 (2C, *J* = 22.0 Hz), 121.28 (*J* = 26.5 Hz), 129.78 (*J* = 10.6 Hz), 131.06 (2C, *J* = 8.3 Hz), 133.23 (*J* = 9.8 Hz), 132.77 (*J* = 3.0 Hz), 135.12, 137.96, 138.02, 144.20, 162.36 (*J* = 252.3 Hz), 162.86 (*J* = 247.1 Hz), 192.26. Anal. calcd for $C_{16}H_9F_2NO$: C 71.37, H 3.37, N 5.20; found: C 71.39, H 7.70, N 5.17.

5.5. General procedure for the preparation of 2-(hydroxyphenylmethyl)-3-phenylquinoline compounds 13a-e, 15a and 15b. A mixture of 3-phenylquinoline-2-carbaldehyde **12a** (0.23 g, 1.0 mmol), phenyl magnesium bromide (3 mmol, 3 mL of a 1 M solution in THF), and THF (30 mL) was stirded at 0^{o}C for 12 h (TLC monitoring). The reaction was quenched by addition of water (3 mL) and partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic layer was washed with brine and dried over $MgSO_4$ and removal of the volatiles in vacuo provided a residue, which was purified by flash chromatography on silica gel (*n*-hexane : CH_2Cl_2 = 3/2) and recrystallized from EtOH to give compounds **13a.** Accordingly, compounds **13b-e**, **15a,** and **15b** were obtained in this manner.

5.5.1. 2-(Hydroxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (13a). Yield 58% as a white solid. Mp. 113-114^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.86 (s, 3H, OCH_3), 5.98 (d, 1H, *J* = 6.0 Hz, CH), 6.31 (d, 1H, *J* = 6.0 Hz, OH), 6.78-6.81 (m, 2H, Ar-H), 6.84-6.86 (m, 2H, Ar-H), 6.93- 6.96 (m, 2H, Ar-H) 7.03-7.11 (m, 3H, Ar-H), 7.56-7.60 (m, 1H, 6-H), 7.75-7.83 (m, 2H, 7- and 5-H),

7.91 (s, 1H, 4-H), 8.20 (dd, 1H, *J* = 8.4, 1.2 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.37, 72.86, 113.75 (2C), 126.86, 127.26, 127.45, 127.60 (2C), 127.95 (2C), 128.66, 129.68, 130.15, 130.51(2C), 133.95, 137.54, 142.35, 145.11, 159.10, 159.35. Anal. calcd for $C_{23}H_{19}NO_2 \cdot 0.1\ H_2O$: C 80.49, H 5.64, N 4.08; found: C 80.21, H 5.59, N 4.00.

5.5.2. 2-(Hydroxyphenylmethyl)-3-(4-methoxyphenyl)-6-methoxyquinoline (13b). Yield 51% as a white solid. Mp. 170-171^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.86 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.94 (s, 1H, CH), 6.22 (br s, 1H, OH), 6.78-6.80 (m, 2H, Ar-H), 6.84-6.86 (m, 2H, Ar-H), 6.93-6.95 (m, 2H, Ar-H), 7.03-7.10 (m, 4H, 5- and Ar-H), 7.42 (dd, 1H, *J* = 9.2, 2.8 Hz, 7-H), 7.81 (s, 1H, 4-H), 8.09 (d, 1H, *J* = 9.2 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.35, 55.59, 72.69, 104.96, 113.72 (2C), 122.31, 127.17, 127.55 (2C), 127.92 (2C), 128.56, 130.07, 130.34, 130.47 (2C), 134.19, 136.43, 141.16, 142.67, 156.48, 158.11, 159.30. Anal. calcd for $C_{24}H_{21}NO_3 \cdot 0.2\ H_2O$: C 76.86, H 5.75, N 3.73; found: C 76.53, H 5.65, N 3.68.

5.5.3. 6-Fluoro-2-(hydroxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (13c). Yield 53% as a white solid. Mp. 124-125^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.86 (s, 3H, OCH_3), 5.97(s, H, CH), 6.16 (br s, 1H, OH), 6.77-6.80 (m, 2H, Ar-H), 6.84-6.87 (m, 2H, Ar-H), 6.92-6.96 (m, 2H, Ar-H), 7.04-7.12 (m, 3H, Ar-H), 7.43 (dd, 1H, *J* = 8.8, 2.8 Hz, 5-H), 7.53 (ddd, 1H, J = 9.2, 8.4, 2.8 Hz, 7-H), 7.86 (s, 1H, 4-H), 8.20 (dd, 1H, J = 9.2, 5.2 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.37, 72.84, 110.51 (*J* = 21.3 Hz), 113.82 (2C), 119.87 (*J* = 25.8 Hz), 127.36, 127.55 (2C), 128.01 (2C), 128.23 (*J* = 9.9 Hz), 129.72, 130.43 (2C), 131.06 (*J* = 9.1 Hz), 134.82, 136.96, 142.14, 142.18,

158.62 (*J* = 3.0 Hz), 159.50, 160.73 (*J* = 247.2 Hz). Anal. calcd for $C_{23}H_{16}FNO_2 \cdot 0.5\ H_2O$: C 75.40, H 4.68, N 3.82; found: C 75.72, H 4.94, N 3.81.

5.5.4. 3-(4-Fluorophenyl)-2-(hydroxyphenylmethyl)quinoline (13d). Yield 60% as a white solid. Mp.: 145-146°C. ^{1}H NMR (400 MHz, $CDCl_3$): 5.91 (s, 1H, CH), 6.33 (br s, 1H, OH), 6.75-6.78 (m, 2H, 2-H), 6.93-7.12 (m, 7H, Ar-H), 7.57-7.62 (m, 1H, 6-H), 7.77-7.84 (m, 2H, 7- and 5-H), 7.91 (s, 1H, 4-H), 8.22 (dd, 1H, *J* = 8.4, 1.2 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 73.00, 115.26 (2C, *J* = 21.2 Hz), 127.07, 127.42, 127.48, 127.66 (2C), 128.06 (2C), 128.68, 130.01, 131.03 (2C, *J* = 7.6 Hz), 133.20, 133.75 (*J* = 3.8 Hz), 137.65, 142.04, 145.16, 158.63, 162.49 (*J* = 246.3 Hz). Anal. calcd for $C_{22}H_{16}FNO \cdot\ 0.1\ H_2O$: C 79.79, H 4.93, N 4.23; found: C 79.60, H 4.79, N 4.21.

5.5.5. 6-Fluoro-2-(hydroxyphenylmethyl)-3-(4-fluorophenyl)quinoline (13e). Yield 52% as a white solid. Mp.: 154-155°C. ^{1}H NMR (400 MHz, $CDCl_3$): 5.90 (s, 1H, CH), 6.18 (br s, 1H, OH), 6.74-6.77 (m, 2H, ArH), 6.93-7.13 (m, 7H, Ar-H), 7.44 (dd, 1H, *J* = 8.8, 2.8 Hz, 5-H), 7.56 (ddd, 1H, *J* = 9.2, 8.4, 2.8 Hz, 7-H), 7.87 (s, 1H, 4-H), 8.22 (dd, 1H, *J* = 9.2, 5.2 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 72.97, 110.58 (*J* = 22.0 Hz), 115.35 (2C, *J* = 22.0 Hz), 120.18 (*J* = 25.7 Hz), 127.57 (*J* = 9.1 Hz), 127.61 (2C), 128.13 (2C), 130.95 (2C, *J* = 8.3 Hz), 131.16 (*J* = 9.0 Hz), 133.39 (*J* = 3.8 Hz), 134.06, 136.99, 137.05, 141.88, 142.29, 158.16 (*J* = 3.1 Hz), 160.81 (*J* = 247.8 Hz), 162.59 (*J* = 246.3 Hz). Anal. calcd for $C_{22}H_{15}F_2NO \cdot 0.1\ H_2O$: C 75.68, H 4.39, N 4.01; found: C 75.63, H 4.20, N 4.05.

5.5.6. 2-(hydroxy-4-methoxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (15a). Yield 54% a

yellow solid. Mp. 129-130°C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.71 (s, 3H, OMe), 3.86 (s, 3H, OMe), 5.95 (s, 1H, CH), 6.60-6.62 (m, 2H, Ar-H), 6.73-6.75 (m, 2H, Ar-H), 6.86-6.88 (m, 2H, Ar-H), 6.95-6.97 (m, 2H, Ar-H), 7.57-7.62 (m, 1H, 6-H), 7.77-7.86 (m, 2H, 5- and 7-H), 7.95 (s, 1H, 4-H), 8.27 (d, 1H, *J* = 8.4 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.17, 55.37, 72.42, 113.45 (2C), 113.74 (2C), 127.05, 127.46, 127.53 (2C), 128.14, 128.85 (2C), 129.80, 129.91, 130.00, 130.51 (2C), 134.00, 138.08, 158.83, 159.36, 159.45. Anal. calcd for $C_{24}H_{21}NO_3$: C 77.61, H 5.70, N 3.77; found: C 77.65, H 5.81, N 3.56.

5.5.7. 2-(Hydroxy-3,4,5-trimethoxyphenylmethyl)-3-(4-methoxyphenyl)quinoline (15b). Yield 54% a yellow solid. Mp. 143-144°C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.61 (s, 6H, OMe), 3.74 (s, 3H, OMe), 3.78 (s, 3H, OMe), 5.95 (s, 1H, CH), 6.04 (s, 2H, Ar-H), 6.88-6.89 (m, 2H, Ar-H), 6.99-7.03 (m, 2H, Ar-H), 7.60-7.64 (m, 1H, 6-H), 7.79-7.87 (m, 2H, 5- and 7-H), 7.98 (s, 1H, 4-H), 8.30 (d, 1H, *J* = 8.4 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.31, 55.77 (2C), 60.69, 73.21, 104.53 (2C), 113.82 (2C), 114.19, 127.25, 127.54 (2C), 127.58, 128.04, 129.96, 130.20, 130.63 (2C), 133.92, 137.17, 137.43, 138.37, 152.82, 158.99, 159.39. Anal. calcd for $C_{26}H_{25}NO_5$: C 72.37, H 5.84, N 3.25; found: C 72.24, H 5.90, N 3.14.

5.6. General procedure for preparation of 2-benzoyl-3-phenylquinoline derivatives: 14a-e, 16a and 16b. A mixture of **13a** (0.34 g, 1 mmol) and MnO_2 (0.87 g, 10 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 12 h (TLC monitoring). The reaction mixture was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic layer was washed with brine and dried

over $MgSO_4$ and removal of the volatiles in vacuo provided a residue, which was crystallized from MeOH to give compounds **14a.** Accordingly, compounds **14b-e**, **16a,** and **16b** were obtained in this manner.

5.6.1. 2-Benzoyl-3-(4-methoxyphenyl)quinoline (14a). Yield 93% a white solid. Mp. 124-125^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (s, 3H, OCH_3), 6.83-6.87 (m, 2H, Ar-H), 7.30-7.34 (m, 2H, Ar-H) 7.38-7.42 (m, 2H, Ar-H), 7.52-7.56 (m, 1H, Ar-H), 7.62-7.66 (m, 1H, 6-H), 7.74-7.78 (m, 1H, 7-H), 7.85-7.88 (m, 2H, Ar-H), 7.91 (dd, 1H, *J* = 8.0, 1.2 Hz, 5-H), 8.16 (dd, 1H, *J* = 8.4, 0.8 Hz, 8-H), 8.24 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.21, 114.13 (2C), 127.64, 127.86, 128.16, 128.41 (2C), 129.61, 129.87, 129.98, 130.21 (2C), 130.43 (2C), 133.53, 133.57, 136.13, 136.77, 145.87, 156.44, 159.40, 195.35. Anal. calcd for $C_{23}H_{17}NO_2 \cdot 0.2\ H_2O$: C 80.54, H 5.11, N 4.08; found: C 80.83, H 5.02, N 4.06.

5.6.2. 2-Benzoyl-6-methoxy-3-(4-methoxyphenyl)quinoline (14b). Yield 89% a white solid. Mp: 122-123^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.82-6.86 (m, 2H, Ar-H), 7.14 (d, 1H, *J* = 2.8 Hz, 5-H), 7.29-7.32 (m, 2H, Ar-H) 7.37-7.41 (m, 3H, 7- and Ar-H), 7.51-7.55 (m, 1H, Ar-H), 7.86-7.88 (m, 2H, Ar-H), 8.04 (d, 1H, *J* = 9.2 Hz, 8-H), 8.11 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.19, 55.62, 104.78, 114.07 (2C), 122.85, 128.34 (2C), 129.41, 130.12 (2C), 130.24, 130.46 (2C), 131.07, 133.37, 134.01, 135.51, 136.35, 141.93, 153.81, 158.89, 159.32, 195.42. Anal. calcd for $C_{24}H_{19}NO_3 \cdot 0.2\ H_2O$: C 77.28, H 5.24, N 3.75; found: C 77.09, H 5.19, N 3.70.

5.6.3. 2-Benzoyl-6-fluoro-3-(4-methoxyphenyl)quinoline (14c). Yield 90% a white solid. Mp. 157-158°C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (s, 3H, OCH_3), 6.83-6.87 (m, 2H, Ar-H), 7.29-7.32 (m, 2H, Ar-H), 7.38-7.42 (m, 2H, Ar-H), 7.49-7.57 (m, 3H, 5-, 7-, and Ar-H), 7.84-7.87 (m, 2H, Ar-H), 8.15 (dd, 1H, J = 9.6, 5.2 Hz, 8-H), 8.17 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.21, 110.55 (*J* = 21.9 Hz), 114.18 (2C), 120.22 (*J* = 25.7 Hz), 128.44 (2C), 128.94 (*J* = 9.9 Hz), 129.56, 130.16 (2C), 130.38 (2C), 132.20 (*J* = 9.1 Hz), 133.61, 134.39, 136..03, 136.08, 142.89, 155.79 (*J* = 3.0 Hz), 159.54, 161.31 (*J* = 248.6 Hz), 195.35. Anal. calcd for $C_{23}H_{16}FNO_2 \cdot 0.2\ H_2O$: C 76.53, H 4.58, N 3.88; found: C 76.51, H 4.49, N 3.82.

5.6.4. 2-Benzoyl-3-(4-fluorophenyl)quinoline (14d). Yield 91% a white solid. Mp. 103-104°C. ^{1}H NMR (400 MHz, $CDCl_3$): 6.95-7.01 (m, 2H, Ar-H), 7.31-7.40 (m, 4H, Ar-H), 7.50-7.54 (m, 1H, Ar-H), 7.60-7.64 (m, 1-H, 6-H), 7.72-7.77 (m, 1H, 7-H), 7.84-7.90 (m, 3H, 5- and Ar-H), 8.16 (d, 1H, *J* = 8.8 Hz, 8-H), 8.21 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 115.54 (2C, *J* = 22.0 Hz), 127.63, 127.90, 128.02, 128.41 (2C), 129.51, 130.16, 130.32 (2C), 130.64 (2C, *J* = 8.3 Hz), 132.83, 133.61, 133.66 (*J* = 3.0 Hz), 135.95, 137.08, 145.93, 156.02, 162.45 (*J* = 245.6 Hz), 194.96. Anal. calcd for $C_{22}H_{14}FNO \cdot 0.2\ H_2O$: C 79.84, H 4.38, N 4.23; found: C 79.83, H 4.46, N 4.11.

5.6.5. 2-Benzoyl-6-fluoro-3-(4-fluorophenyl)quinoline (14e). Yield 91% a white solid. Mp. 118-119°C. ^{1}H NMR (400 MHz, $CDCl_3$): 6.99-7.04 (m, 2H, Ar-H), 7.32-7.37 (m, 2H, Ar-H) 7.39-7.44 (m, 2H, Ar-H), 7.51-7.58 (m, 3H, 5-, 7-, and Ar-H), 7.84-7.87 (m, 2H, Ar-H), 8.16-8.19

(m, 2H, 4-H and 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 110.54 (*J* = 21.2 Hz), 115.72 (2C, *J* = 22.0 Hz), 120.61 (*J* = 25.7 Hz), 128.51 (2C), 128.80 (*J* = 9.9 Hz), 130.40 (2C), 130.69 (2C, *J* = 8.4 Hz), 132.31 (*J* = 9.1 Hz), 133.39 (*J* = 3.1 Hz), 133.75, 135.94, 136.41, 136.47, 143.10, 155.51 (*J* = 2.2 Hz), 161.43 (*J* = 248.6 Hz), 162.67 (*J* = 246.2 Hz), 194.74. Anal. calcd for $C_{22}H_{13}F2NO$: C 76.51, H 3.79, N 4.06; found: C 76.37, H 3.67, N 4.05.

5.6.6. 2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)quinoline (16a). Yield 89% a yellow solid. Mp. 135-137^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.84-6.88 (m, 4H, Ar-H), 7.32-7.35 (m, 2H, Ar-H), 7.60-7.65 (m, 1H, 6-H), 7.73-7.77 (m, 1H, 7-H), , 7.82-7.86 (m, 2H, Ar-H), 7.89 (d, 1H, *J* = 8.4 Hz, 5-H), 8.15 (d, 1H, *J* = 8.4 Hz, 8-H), 8.23 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.19, 55.46, 113.74 (2C), 114.08 (2C), 127.61, 127.72, 129.08, 129.22, 129.53, 129.79, 130.07, 130.14 (2C), 132.82 (2C), 133.45, 136.71, 145.84, 156.79, 159.34, 163.90, 194.04. Anal. calcd for $C_{24}H_{19}NO_3$: C 78.03, H 5.18, N 3.79; found: C 77.64, H 5.27, N 3.66.

5.6.7. 2-(3,4,5-Trimethoxybenzoyl)-3-(4-methoxyphenyl)quinoline (16b). Yield 82% as a yellow solid. Mp. 161-1623^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.79 (s, 6H, OMe), 3.80(s, 3H, OMe), 3.92 (s, 3H, OMe), 6.88-6.90 (m, 2H, Ar-H), 7.17 (s, 2H, Ar-H), 7.32-7.36 (m, 2H, Ar-H), 7.64-7.68 (m, 1H, 6-H), 7.75-7.79 (m, 1H, 7-H) 7.93 (d, 1H, *J* = 8.4 Hz, 5-H), 8.18 (d, 1H, *J* = 8.4 Hz, 8-H), 8.26 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.23, 56.23 (2C), 60.92, 108.06 (2C), 114.22 (2C), 127.66 (2C), 127.94, 128.16, 129.55, 129.96, 130.03, 130.09 (2C), 130.78, 131.10, 133.66, 136.84, 145.79, 152.92, 156.24, 159.45, 194.09. Anal. calcd for $C_{26}H_{23}NO_5$: C 71.09, H 6.71, N 10.36;

found: C 71.09, H 6.76, N 10.41.

5.7. 2-(4-Hydroxybenzoyl)-3-(4-hydroxyphenyl)quinoline (17). A solution of **16a** (0.37 g, 1.0 mmol) in 48% HBr (5 mL) was heated at reflux for 48 h. The mixture was cooled and evaporated *in vacuo* to give a residue which was treated with H_2O (50 mL). The crude product was collected and crystallized from MeOH to give **17** (0.31 g, 90%) as a green solid. Mp. 173-174^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.73-6.76 (m, 2H, Ar-H), 6.82-6.84 (m, 2H, Ar-H), 7.22-7.24 (m, 2H, Ar-H), 7.61-7.63 (m, 2H, Ar-H), 7.69-7.73 (m, 1H, 6-H), 7.80-7.83 (m, 1H, 7-H), 8.05 (d, 1H, *J* = 8.4 Hz, 5-H), 8.11 (d, 1H, *J* = 8.4 Hz, 8-H), 8.48 (s, 1H, 4-H), 9.64 (br s, 1H, OH), 10.58 (br s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 115.46 (2C), 115.52 (2C), 127.48, 127.70, 127.78, 127.96, 128.12, 128.61, 130.04 (2C), 132.59 (2C), 132.81, 136.53, 145.01, 156.83, 157.31, 162.74 (2C), 193.25. Anal. calcd for $C_{22}H_{15}NO_3 \cdot 1.3\ H_2O$: C 72.44, H 4.86, N 3.84; found: C 72.49, H 4.75, N 3.84.

5.8. General procedure for preparation of aminoalkylated derivatives and disubstituted derivatives: 18a-19c. To a stirred solution of **17** (1.0 mmol) in dry DMF (20 mL) was added NaH (60% in oil, 0.50 g) at 0^{o}C for 1 h. An appropriate tertiary-aminoalkyl halide (3 mmol) was added and stirred at room temperature for 4 h (TLC monitoring). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuo. Crude product was purified by flash chromatography on silica gel, using a gradient of MeOH/CH_2Cl_2 (1/30 to 1/10) to give the **18a-19c**.

5.8.1. 2-(4-hydroxybenzoyl)-3-{4-[3-(dimethylamino)propoxyl]phenyl}quinoline (18a) and 2-{4-[3-(dimethylamino)propoxy]benzoyl}-3-{4-[3-(dimethylamino)propoxyl]phenyl}quinoline (19a). Compound 18c was obtained in 26 % yield (0.11 g) as a green liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.89-1.96 (m, 2H, $OCH_2C\underline{H_2}CH_2N$), 2.35 (s, 6H, NMe_2), 2.56-2.60 (m, 2H, $OCH_2CH_2C\underline{H_2}N$), 3.93 (t, 2H, *J* = 5.6 Hz, $OC\underline{H_2}CH_2CH_2N$), 6.23-6.28 (m, 4H, Ar-H), 7.57-7.62 (m, 3H, 6- and Ar-H), 7.72 (m, 1H, 7-H), 7.89 (d, 1H, *J* = 8.0 Hz, 5-H), 8.14 (d, 1H, *J* = 8.4Hz, 8-H), 8.22 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 26.36, 44.68 (2C), 56.01, 65.68, 114.75 (2C), 155.93 (2C), 127.68, 127.71, 127.86, 128.10, 129.24, 129.93, 130.19, 130.28 (2C), 132.97 (2C), 133.37, 136.68, 145.84, 157.18, 158.31, 163.03, 194.31. ESIMS $[M+H]^+$: 427.2.

Compound **19a** was obtained in 43% yield (0.22 g) as a green liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.00-2.07 (m, 4H, $OCH_2C\underline{H_2}CH_2N$), 2.34 and 2.38 (two s, 12H, NMe_2), 2.56-2.65 (m, 4H, $OCH_2CH_2C\underline{H_2}N$), 3.99 and 4.07 (two t, 4H, *J* = 5.6 Hz, $OC\underline{H_2}CH_2CH_2N$), 6.82-6.88 (m, 4H, Ar-H), 7.27-7.33 (m, 2H, Ar-H), 7.63 (m, 1H, 6-H), 7.75 (m, 1H, 7-H), 7.80-7.83 (m, 2H, Ar-H), 7.92 (d, 1H, *J* = 8.0 Hz, 5-H), 8.16 (d, 1H, *J* = 8.4 Hz, 8-H), 8.22 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 26.65, 26.72, 44.72 (2C), 44.91 (2C), 55.95, 56.07, 65.77, 66.17, 114.20 (2C), 114.61 (2C), 127.62, 127.73, 128.09, 129.23, 129.54, 129.71, 129.82, 130.16 (2C), 132.81 (2C), 133.43, 136.70, 145.88, 156.81, 158.63, 163.26, 194.03. ESIMS $[M+H]^+$: 512.3.

5.8.2. 2-(4-Hydroxybenzoyl)-3-{4-[2-(piperidin-1-yl)ethoxy]phenyl}quinoline (18b) and 2-{4-[2-(piperidin-1-yl)ethoxy]benzoyl}-3-{4-[2-(piperidin-1-yl)ethoxy]phenyl}quinoline

(19b). Compound **18b** was obtained in 24 % yield (0.11 g) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.57-1.59 (m, 2H, piperidinyl-H), 1.81-1.84 (m, 4H, piperidinyl-H), 2.86-2.88 (m, 4H, piperidinyl-H), 3.05(t, 2H, *J* = 5.6 Hz, $OCH_2C\underline{H_2}N$), 4.24 (t, 2H, *J* = 5.6 Hz, $OC\underline{H_2}CH_2N$), 6.72-6.77 (m, 4H, Ar-H), 7.26-7.28 (m, 2H, Ar-H), 7.60-7.65 (m, 3H, Ar-H and 6-H), 7.75 (m, 1H, 7-H), 7.91 (d, 1H, *J* = 8.0 Hz, 5-H), 8.17 (d, 1H, *J* = 8.4 Hz, 8-H), 8.21 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.35, 25.05 (2C), 54.22 (2C), 57.02, 65.08, 114.16 (2C), 115.08 (2C), 127.22 (2C), 127.44 (2C), 128.52 (2C), 129.43, 129.58 (2C), 132.28 (2C), 132.50, 136.18, 145.06, 156.41, 157.93, 162.54, 193.04. Anal. calcd for $C_{29}H_{28}N_2O_3 \cdot 0.4\ H_2O \cdot 0.5$ HCl: C 72.85, H 6.19, N 5.86; found: C 72.91, H 6.23, N 5.58.

Compound **19b** was obtained in 53 % yield (0.30 g) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44-1.46 (m, 4H, piperidinyl-H), 1.60-1.68 (m, 8H, piperidinyl-H), 2.53-2.57 (m, 8H, piperidinyl-H), 2.79-2.83 (m, 4H, $OCH_2C\underline{H_2}N$), 4.10-4.18 (m, 4H, $OC\underline{H_2}CH_2N$), 6.83-6.88 (m, 4H, Ar-H), 7.30-7.32 (m, 2H, Ar-H), 7.63 (m, 1H, 6-H), 7.75 (m, 1H, 7-H), 7.80-7.83 (m, 2H, Ar-H), 7.92 (d, 1H, *J* = 8.0 Hz, 5-H), 8.16 (d, 1H, *J* = 8.4Hz, 8-H), 8.22 (s, 1H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.90, 23.98, 25.54 (2C), 25.69 (2C), 54.90 (2C), 54.99 (2C), 57.57, 57.67, 65.54, 66.30, 114.30 (2C), 114.73 (2C), 127.62, 127.72, 128.09, 129.27, 129.56, 129.80, 130.15 (2C), 130.25, 132.80 (2C), 133.43, 136.70, 145.88, 156.79, 158.46, 163.10, 194.02. Anal. calcd for $C_{36}H_{41}N_3O_3 \cdot 0.6\ H_2O$: C 75.25, H 7.40, N 7.31; found: C 75.04, H 7.52, N 7.23.

5.8.3. 2-(4-Hydroxybenzoyl)-3-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}quinoline (18c) and

2-{4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl-3-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}quinoline (19c). Compound **18c** was obtained in 29% yield (0.13 g) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.82-1.84 (m, 4H, pyrrolidinyl-H), 2.87-2.89 (m, 4H, pyrrolidinyl-H), 2.99 (t, 2H, *J* = 5.6 Hz, $OCH_2C\underline{H_2}N$), 4.07 (t, 2H, *J* = 5.6 Hz, $OC\underline{H_2}CH_2N$), 6.65-6.74 (m, 4H, Ar-H), 7.23-7.28 (m, 2H, Ar-H), 7.56-7.72 (m, 4H, 6-, 7-, and Ar-H), 7.85 (d, 1H, *J* = 8.0 Hz, 5-H),8.12 (d, 1H, *J* = 8.4 Hz, 8-H), 8.17 (s, 1H, 4-H). ^{13}C NMR(100MHz, $CDCl_3$): 23.17 (2C), 54.38 (2C), 54.66, 65.58, 114.58 (2C), 115.87 (2C), 127.61, 127.69, 128.05, 129.18, 129.90, 130.18 (2C), 130.44, 133.10 (2C), 133.30, 136.82, 145.71, 157.10, 158.09, 163.36, 194.06. Anal. calcd for $C_{28}H_{26}N_2O_3 \cdot 2.25\ H_2O$: C 70.19, H 6.43, N 5.85; found: C 70.54, H 6.83, N 5.53.

Compound **19c** was obtained in 57 % yield (0.31 g) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89-1.95 (m, 8H, pyrrolidinyl-H), 2.82-2.92 (m, 8H, pyrrolidinyl-H), 3.06 and 3.11 (two t, 4H, *J* = 5.6 Hz, $OCH_2C\underline{H_2}N$), 4.22-4.27 (m, 4H, $OC\underline{H_2}CH_2N$), 6.84-6.89 (m, 4H, Ar-H), 7.30-7.34 (m, 2H, Ar-H), 7.62 (m, 1H, 6-H), 7.75 (m, 1H, 7-H), 7.80-7.84 (m, 2H, Ar-H), 7.91 (d, 1H, *J* = 8.0 Hz, 5-H),8.15 (d, 1H, *J* = 8.4Hz, 8-H), 8.22 (s, 1H, 4-H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.36 (2C), 23.40 (2C), 54.52 (2C), 54.62 (2C), 65.62, 66.37, 77.21 (2C), 114.32 (2C), 114.76 (2C), 127.65, 127.77, 128.08, 129.50, 129.55, 129.87, 130.23 (2C), 130.61, 132.81 (2C), 133.32, 136.76, 145.91, 156.71, 158.06, 162.77, 193.98. ESIMS $[M+H]^+$: 536.3.

5.9. Cytotoxicity and antiviral activity assays

5.9.1. Compounds

Compounds were dissolved in DMSO at 10 mM and then diluted in culture medium.

5.9.2. Cells and virus

Cancer cells (A549, H1299, MCF-7, MDA-MB-231 and Huh-7) were purchased from Bioresources Collection and Research Center, Taiwan. Huh-7-DV-Fluc cells and C6/36 cells were kindly provided by Dr Huey Nan Wu, Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan, ROC. The DENV-2 strain 16681 was isolated from a patient with dengue hemorrhage fever (DHF) from Thailand [29], and was amplified in C6/36 mosquito cells.

5.9.3. Cytotoxicity assays

For cytotoxicity tests, run in parallel with antiviral assays, plates at an initial density of (5×10^3 cells/well), in maintenance medium, with or without serial dilutions of test compounds. Cell viability was determined after 72 h at 37 ^{o}C in a humidified CO_2 (5%) atmosphere by the (2,3-bis [2-methyloxy-4-nitro-5-sulfophenyl]-2*H*-tetrazolium-5-carboxanilide) (XTT) method [30].

5.9.4. Analysis of luciferase activity

Huh-7-DV-Fluc cells were seeded in 24-well plates at a density of 2×10^4 cells per well, and treated with the 2-aroyl-3-arylquinoline compounds at two concentrations (5 and 20 μM) or 0.1% DMSO as control. After 72 h of incubation, the luciferase activity assay was performed using the Bright-Glo Luciferase assay system (Promega) according to the manufacturer's instructions.

5.9.5. Immunoblot analysis

The standard procedure was followed to perform western blotting as described previously [31]. The

membranes were incubated overnight with rabbit polyclonal antibodies against NS2B (1：3000, Genetex, Irvine, CA, USA) and GAPDH (1：10000, Genetex, Irvine, CA, USA) serving as loading control.

5.9.6. Quantification of DENV RNA

Total cellular RNA was extracted after 3 days compounds treatment through Total RNA Miniprep Purification Kit (GMbiolab, Taiwan) according to the manufacturer's instructions. The expression of DENV NS5 mRNA level was determine through quantification real-time RT-PCR (RT-PCR) with specific primers corresponding to the DENV NS5 gene：Forward primer, 5-AAG GTG AGA AGC AAT GCA GC-3；reverse primer, 5-CCA CTC AGG GAG TTC TCT CT-3. The copy number of NS5 in each sample was normalized to cellular endogenous reference gene glyceraldehydes-3-phosphate dehydrogenase (gapdh)；Forward primer: 5-GTC TTC ACC ACC ATG GAG AA-3 and Reverse primer: 5-ATG GCA TGG ACT GTG GTC AT-3. The CT value of each sample was determined by the ABI Step One Real-Time PCR-System (ABI Warrington, UK).

5.9.7. DENV infection assay

Huh-7 cells were seeded at the density of 4 X 10^4 cells/well in the 24 well culture plate for 16-20 hours and then infected with DENV-2 (16681 strain) at an MOI of 0.1 for 2 hours at 37 ℃. Cells were washed with PBS once and then re-filled with DMEM-2% FBS medium containing various indicating concentration of **13a** and **17**.

5.9.8. Statistical analysis

The results were expressed as means±S.D. Differences in mean values between groups were

analyzed by a one-way analysis of variance (ANOVA) and Student's t-test. For the septic shock assay, we used the log-rank test. Statistical significance was assessed as $p<0.05$ [*$p<0.05$; **$p<0.01$].

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Figure captions:

Figure 1. Structures of 4-[4-(2-chlorobenzyloxy)aniline]-6-ethoxy-2-methylquinoline (**1**), 3'-nitrophenylaminoquinoline (**2**), (*E*)-3-[3-(4-methoxyphenyl)quinolin-2-yl]-1-phenylprop-2-en-1-one (**3**), 6-fluoro-2,3-bis{4-[2-(piperidin-1-yl)ethoxy]phenyl}quinoline (**4**) and target compounds.

Figure 2. The 2D NOESY spectrum of monoalkylated compound **18a**.

Figure 3. Inhibition of DENV2 RNA expression in Huh-7-DV-Fluc cells by 2-aroyl-3-arylquinoline derivatives and ribavirin. Huh-7 cells were incubated with tested compounds and ribavirin at the indicated concentrations (5 and 20 μM). After three days of incubation, total RNA was extracted and quantified DENV2 RNA levels by RT-qPCR. DENV2 RNA expression was normalized by cellular GAPDH mRNA. Treatment with 0.1% DMSO served as a mock control. The results are expressed as the means ± standard deviations (error bars) of triplicate experiments. *P,0.05; **P,0.01

Figure 4. Inhibition of DENV2 protein expression in Huh-7-DV-Fluc cells by 2-aroyl-3-arylquinoline derivatives and ribavirin. Huh-7 cells were incubated with tested compounds and ribavirin at the indicated concentrations (5 and 20 μM). After three days of incubation, cell lysates were extracted and analyzed by western blotting with anti-NS2B and anti-GAPDH antibody (a loading control).

Figure 5. Inhibition of DENV2 protein and RNA expression in compound **13a** and **17**-treated Huh-7-DV-Fluc cells. Huh-7-DV-Fluc cells were incubated with compound **13a** and **17** respectively at the indicated concentration (from 5 to 40 μM) for 3 days. Total protein and RNA were extracted as decribed in Method and analyzed by western blotting with anti-NS2B and anti-GAPDH antibody (a loading control). DMSO (0.1%) treatment served as the mock controls. Error bars represent the SD from three experiments. *P,0.05; **P,0.01

Figure 6. Concentration-dependent inhibition of compounds **13a** and **17** in DENV-infected Huh-7 cells. Huh-7 cells were infected with DENV-2 (16681 strain) for 2 hours, and then re-fed with DMEM-2% FBS containing compounds **13a** and **17** at indicated concentration for 3 days. Total protein and RNA were collected and subjected to western blotting and qRT-PCR. DMSO (0.1%) treatment served as the mock controls. Error bars represent the SD from three experiments. *P,0.05; **P,0.01

Table 1. Antiviral activities and cytotoxicities of 2-aroyl-3-arylquinoline derivatives

compounds	DENV2		Huh-7 cell	
	% Inhibition at 5 μM	% Inhibition at 20 μM	% viability at 20 μM	% viability at 100 μM
13a	45.31 ± 7.0	65.11 ± 10.4	96.62 ± 8.78	68.07 ± 4.73
13b	38.02 ± 8.2	61.16 ± 18.4	87.65 ± 0.84	26.01 ± 0.15
13c	16.13 ± 7.2	19.13 ± 7.3	87.37 ± 4.08	30.70 ± 1.74
13d	13.10 ± 7.1	10.21 ± 9.4	109.19 ± 12.20	90.92 ± 11.50
13e	22.17 ± 8.3	23.14 ± 7.2	129.47 ± 19.92	92.26 ± 8.81
14a	3.12 ± 1.25	6.93 ± 1.27	93.11 ± 8.48	87.78 ± 4.16
14b	36.19 ± 5.3	53.10 ± 13.6	87.61 ± 1.46	84.32 ± 3.62
14c	7.24 ± 3.3	5.11 ± 3.2	95.95 ± 6.20	89.66 ± 2.66
14d	20.11 ± 8.7	14.10 ± 7.2	74.80 ± 2.03	45.92 ± 1.77
14e	32.12 ± 4.1	9.13 ± 3.3	96.29 ± 14.31	75.06 ± 1.20
15a	33.50 ± 9.9	58.51 ± 5.6	71.14 ± 7.26	31.89 ± 1.33
15b	22.30 ± 1.2	38.20 ± 4.8	93.56 ± 13.35	62.45 ± 12.76
16a	10.11 ± 7.3	14.12 ± 2.9	96.14 ± 2.27	68.25 ± 12.04
16b	CT[a]	CT	74.06 ± 1.29	35.10 ± 0.81
17	38.70 ± 4.9	62.15 ± 8.9	90.28 ± 2.62	65.11 ± 11.35
18a	CT	CT	80.42 ± 1.47	16.76 ± 0.27
18b	CT	CT	77.52 ± 0.25	19.51 ± 2.34
18c	CT	CT	91.03 ± 6.96	18.10 ± 1.38
19a	CT	CT	17.64 ± 0.28	19.21 ± 1.84
19b	CT	CT	18.36 ± 0.13	15.84 ± 2.14
19c	CT	CT	15.46 ± 0.36	16.60 ± 0.85
ribavirin	32.03 ± 2.14	67.47 ± 1.9	71.37 ± 1.31	26.78 ± 1.59

[a]CT: Cytotoxicity.

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Table 2. Antiviral activities [IC_{50} (μM)][a] of the compounds tested

Compounds	IC_{50}[a]	CC_{50}[b]	SI[c]
13a	12.57 ± 2.16	> 100	> 7.96
13b	14.13 ± 1.21	68.86 ± 2.17	4.87
14b	17.35 ± 1.18	> 100	> 5.76
15a	18.16 ± 1.14	63.09 ± 5.21	3.47
17	13.16 ± 1.23	> 100	> 7.60
ribavirin	12.61 ± 1.17	56.31 ± 2.32	4.47

[a] The IC_{50} is the concentration of the compound resulting in a 50% inhibition in virus production.

[b] The CC_{50} is the concentration of the compound causing a 50% growth inhibition of uninfected Huh-7 cells.

[c]SI: selectivity index. SI = CC_{50}/IC_{50}.

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Table 3. Antiproliferative activity of 2-aroyl-3-arylquinoline derivatives (**16b**, **18a-19c**)

Compounds	IC_{50} (μM)				
	A549	H1299	MDA-MB231	MCF-7	Huh-7
16b	> 10	> 10	> 10	> 10	> 10
18a	> 10	> 10	> 10	> 10	> 10
18b	> 10	> 10	> 10	> 10	> 10
18c	> 10	> 10	> 10	> 10	> 10
19a	6.35 ± 0.12	4.98 ± 0.21	7.14 ± 0.14	4.47 ± 0.07	6.44 ± 0.21
19b	6.53 ± 0.44	6.18 ± 0.36	7.99 ± 0.11	4.66 ± 0.36	6.59 ± 0.14
19c	7.38 ± 0.51	5.68 ± 0.43	8.42 ± 0.35	4.59 ± 0.03	8.68 ± 0.29
topotecan	4.81 ± 0.72	6.02 ± 0.20	< 0.1	5.97 ± 1.03	8.61 ± 1.14

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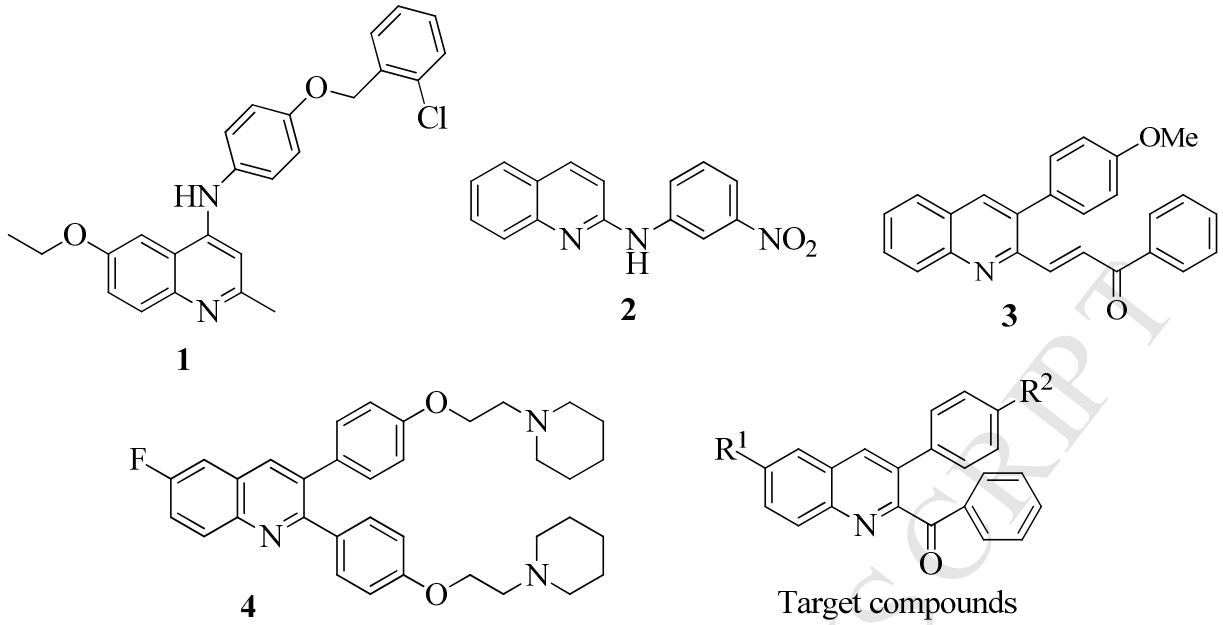

Figure 1.

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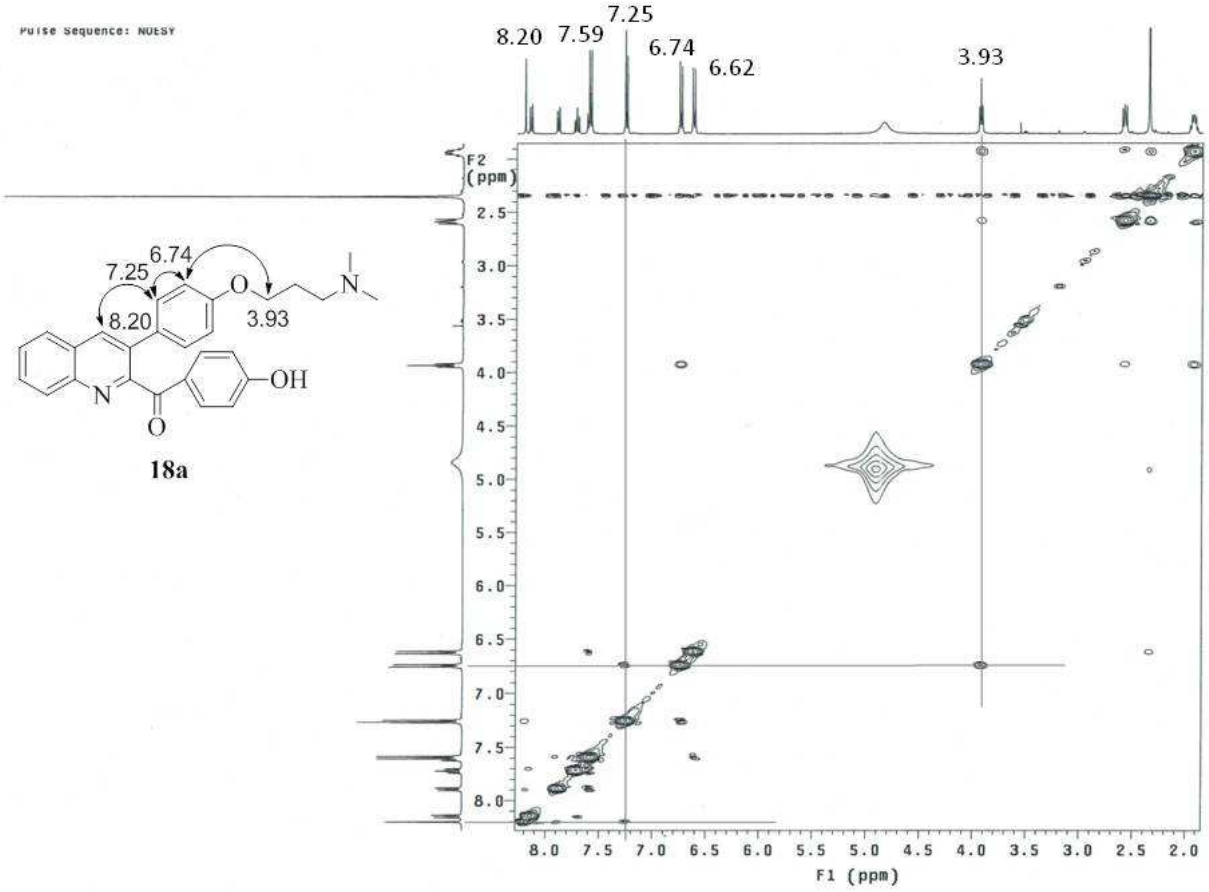


Figure 2.

ACCEPTED

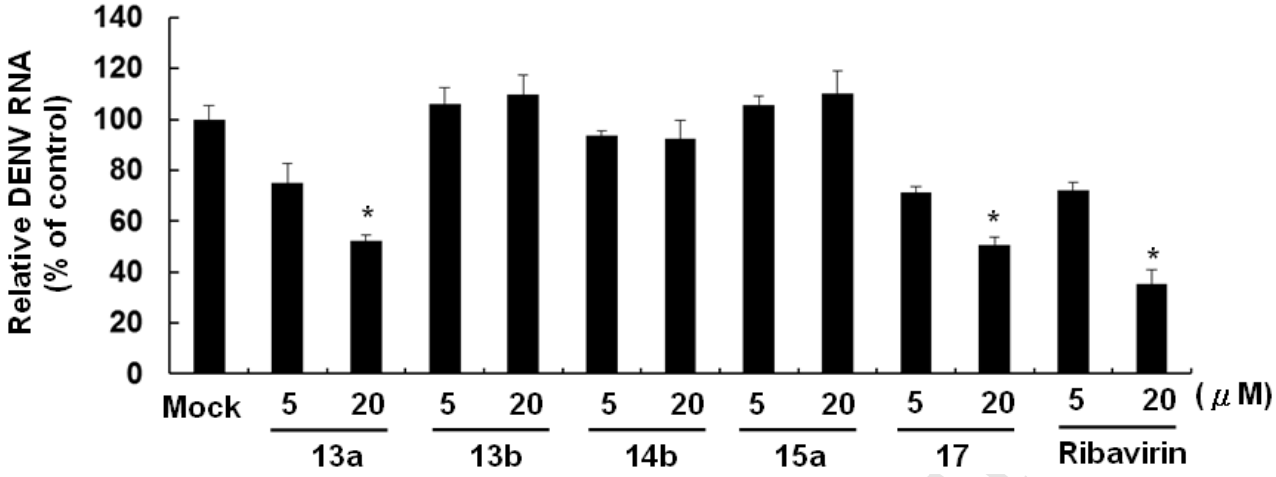


Figure 3.

ACCEPTED MANUSCRIPT

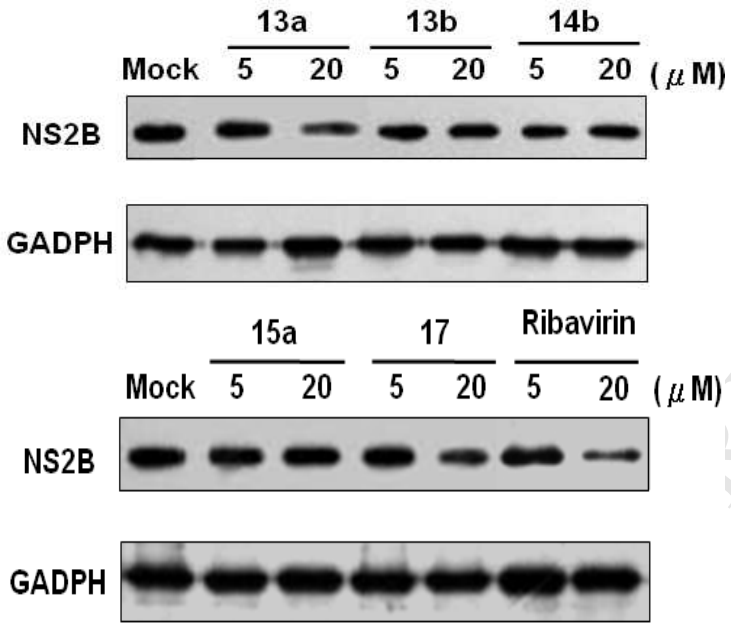


Figure 4.

ACCEPTED MANUSCRIPT

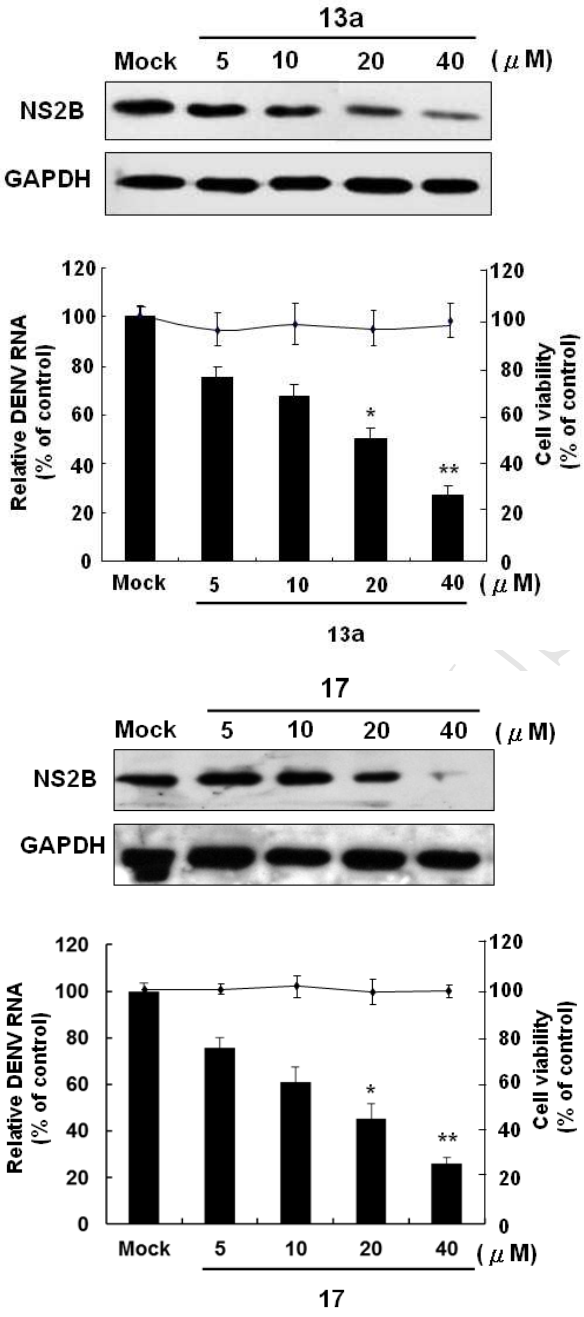

13a
Mock
5
10
20
40
(μM)
NS2B
GAPDH
Relative DENV RNA (% of control)
Cell viability (% of control)
120
100
80
60
40
20
0
*
**
13a
17
17

Figure 5.

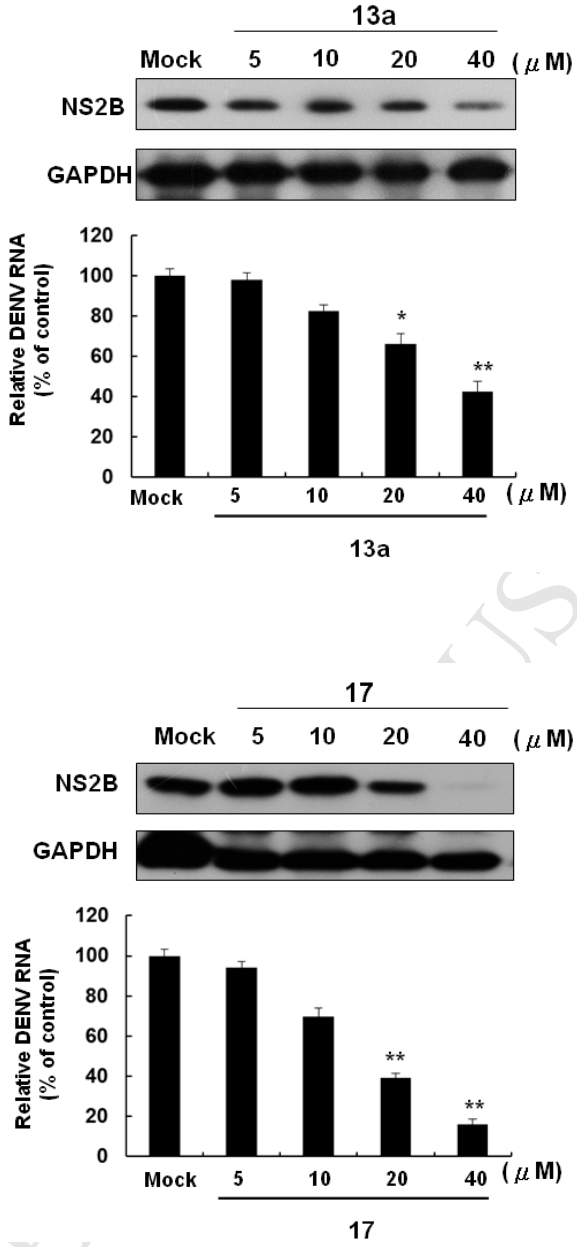
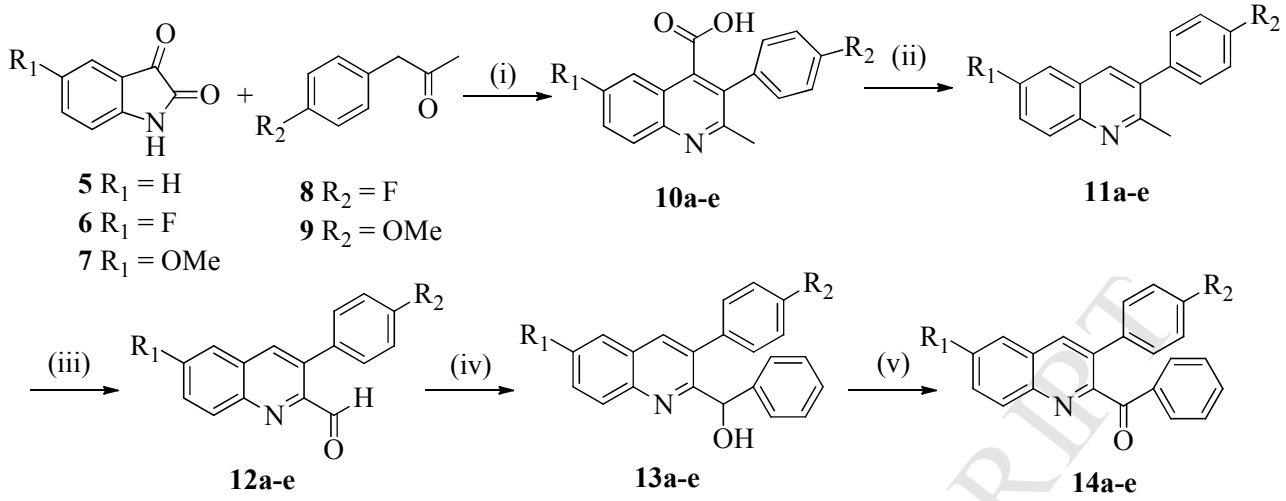

13a
Mock
5
10
20
40
(μM)
NS2B
GAPDH
Relative DENV RNA (% of control)
120
100
80
60
40
20
0
*
**
Mock
5
10
20
40
(μM)
13a
17
Mock
5
10
20
40
(μM)
NS2B
GAPDH
Relative DENV RNA (% of control)
120
100
80
60
40
20
0
**
**
Mock
5
10
20
40
(μM)
17

Figure 6.



5 R_1 = H
6 R_1 = F
7 R_1 = OMe

8 R_2 = F
9 R_2 = OMe

10a-e

11a-e

12a-e

13a-e

14a-e

a R_1 = H, R_2 = OMe; **b** R_1 = OMe, R_2 = OMe; **c** R_1 = F, R_2 = OMe; **d** R_1 = H, R_2 = F; **e** R_1 = F, R_2 = F

Scheme 1: Reagents and condictions: (i) KOH, EtOH, 80°C, 48h (84-93%); (ii) Dowtherm A, 280°C, 4hr (70-78%); (iii) SeO_2, 90°C, 2hr (70-87%); (iv) phenyl magnesium bromide, THF, 0°C, 12hr (51-61%); (v) MnO_2, CH_2Cl_2, rt, 12hr (89-93%).

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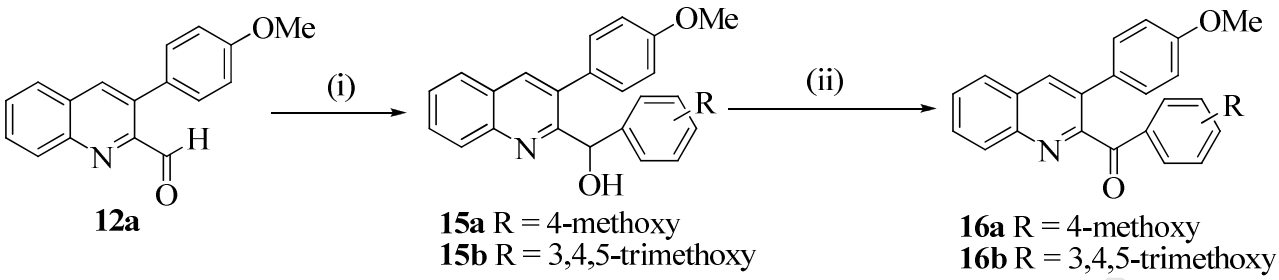

12a

15a R = 4-methoxy
15b R = 3,4,5-trimethoxy

16a R = 4-methoxy
16b R = 3,4,5-trimethoxy

Scheme 2: Reagents and condictions: (i) 4-methoxyphenyl magnesium bromide or 3,4,5-trimethoxyphenyl magnesium bromide, THF, 0°C, 12hr; (ii) MnO_2, CH_2Cl_2, rt, 12hr.

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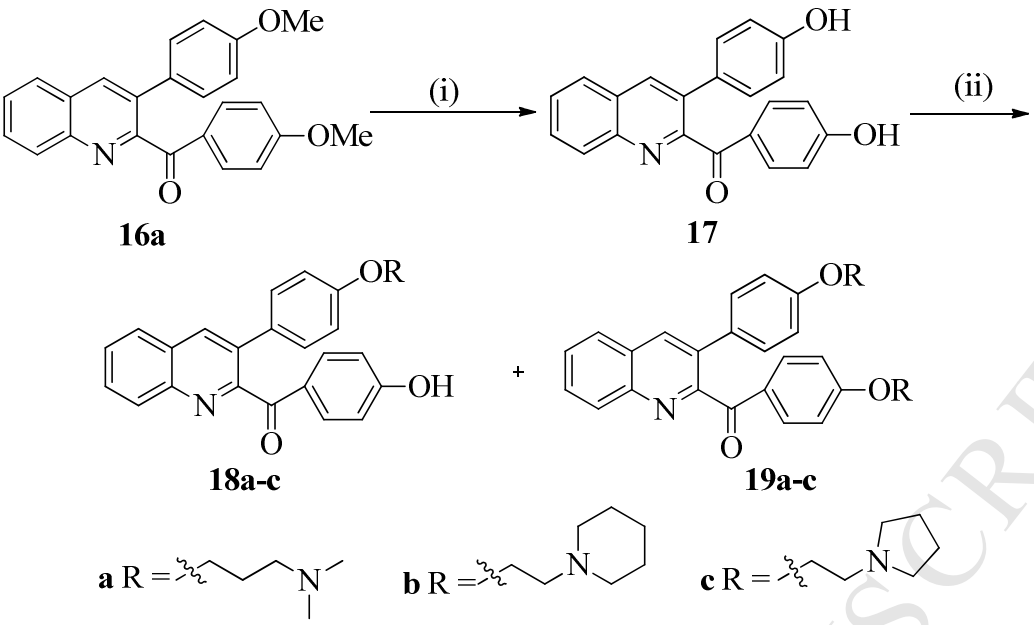

Scheme 3: Reagents and condictions: (i) 48% HBr, HOAc, reflux, 48 h; (ii) NaH, alkyl halides, DMF, rt, 4hr.

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Highlights

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1. A series of 2-aroyl-3-arylquinoline derivatives were synthesized.
2. **13a** and **17** inhibit the DENV2 RNA expression with potency approximately equal to that of ribavirin.
3. Compounds **19a - 19c** showed potent cytotoxicity as that of topotecan.

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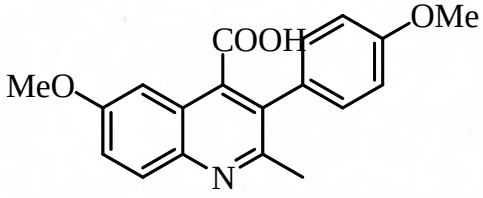
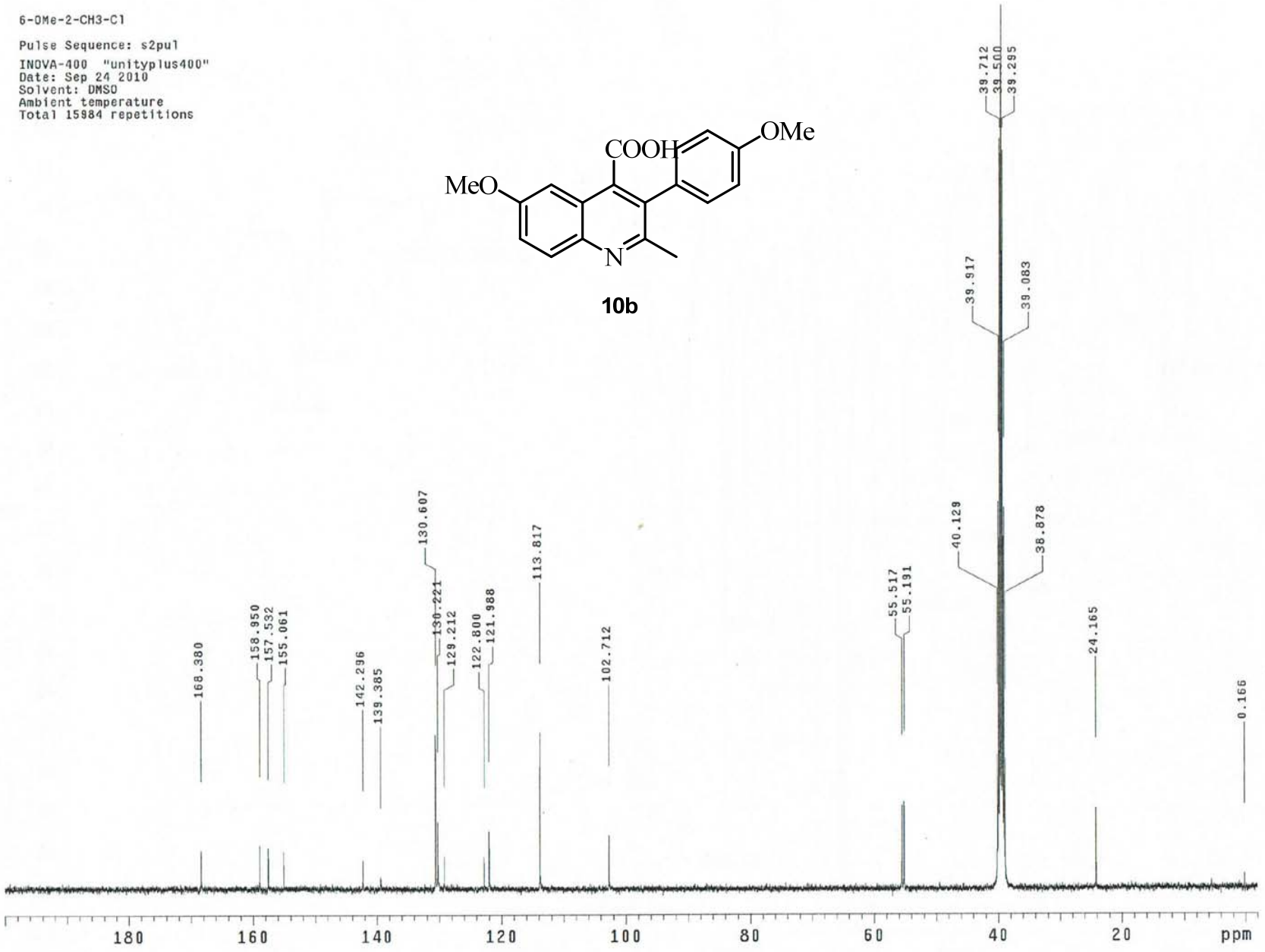
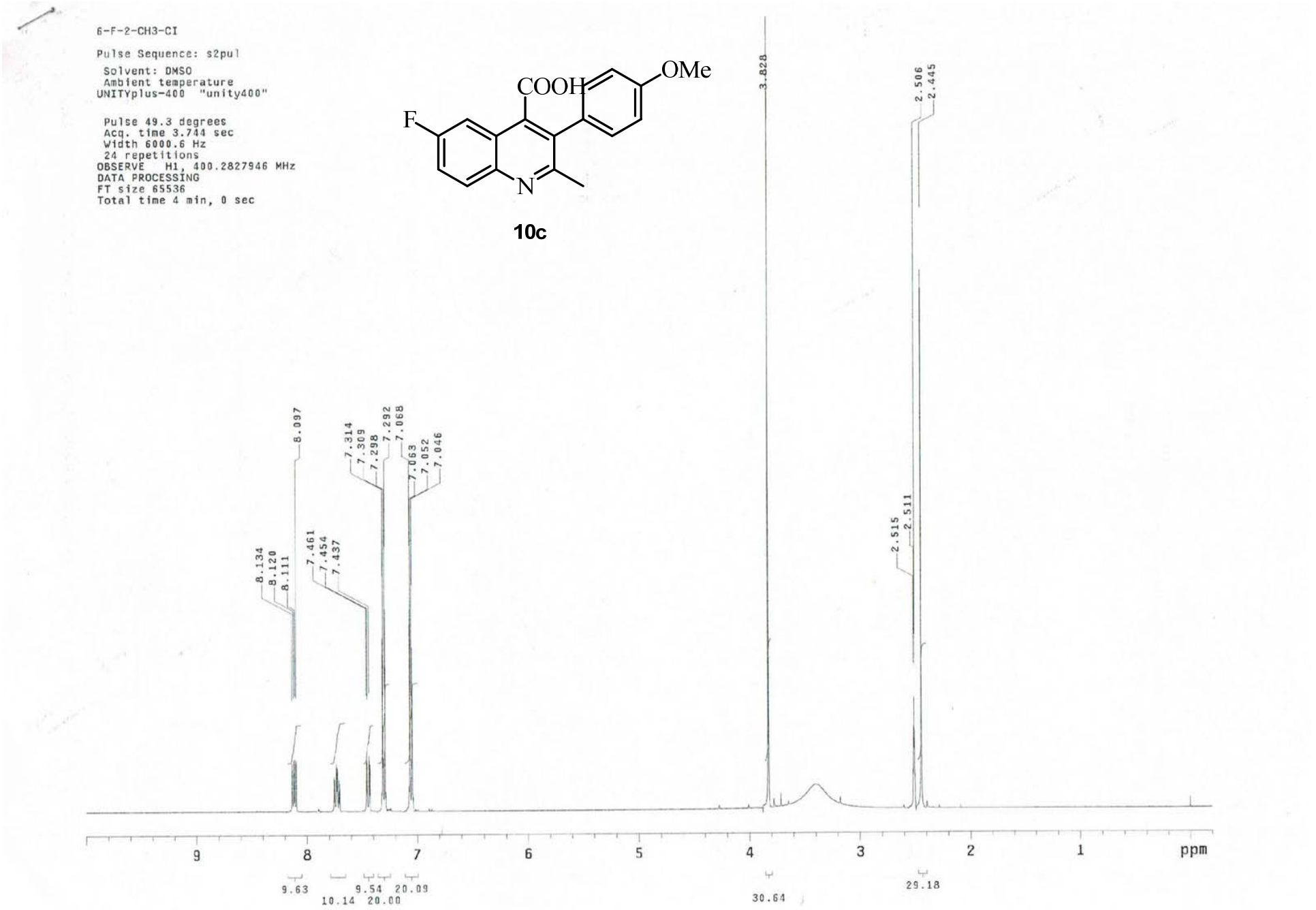
Solvent: DMSO
Ambient temperature
Total 64 repetitions



10b

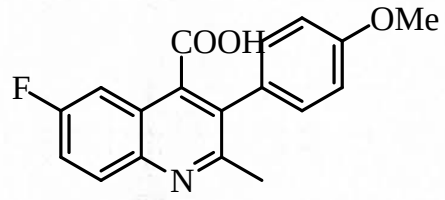

6-OMe-2-CH3-Cl
Pulse Sequence: s2pul
INOVA-400 "unityplus400"
Date: Sep 24 2010
Solvent: DMSO
Ambient temperature
Total 15984 repetitions
COOH
OMe
MeO
N
10b
39.712
39.500
39.295
39.917
39.083
168.380
158.950
157.532
155.061
142.296
139.385
130.607
130.221
129.212
122.800
121.988
113.817
102.712
55.517
55.191
40.129
38.878
24.165
0.166
180
160
140
120
100
80
60
40
20
ppm


6-F-2-CH3-CI
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
UNITYplus-400 "unity400"
Pulse 49.3 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
24 repetitions
OBSERVE H1, 400.2827946 MHz
DATA PROCESSING
FT size 65536
Total time 4 min, 0 sec
COOH
OMe
F
N
10c
8.134
8.120
8.111
8.097
7.461
7.454
7.437
7.314
7.309
7.298
7.292
7.068
7.063
7.052
7.046
3.828
2.515
2.511
2.506
2.445
9
8
7
6
5
4
3
2
1
ppm
9.63
10.14
9.54
20.00
20.09
30.64
29.18

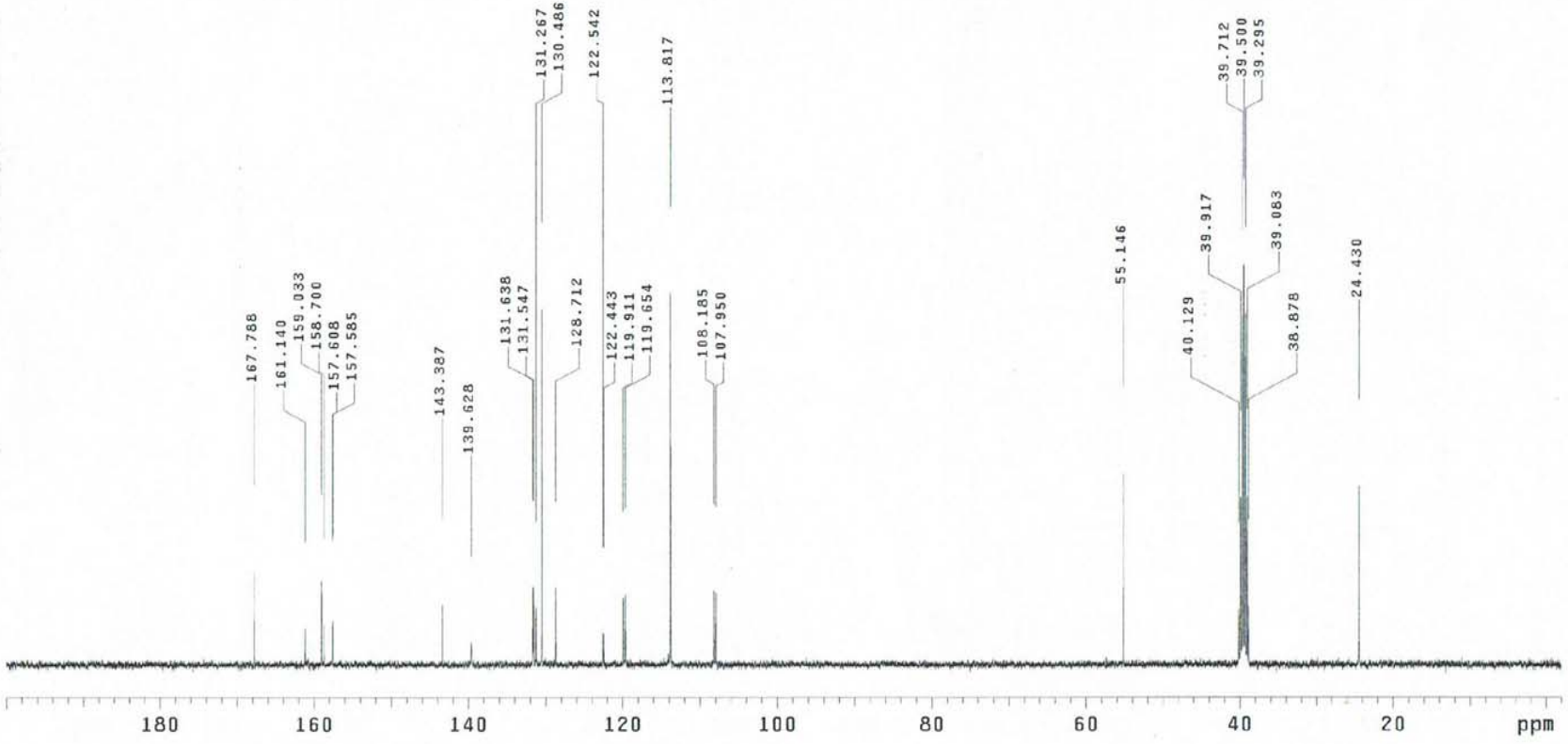
6-F-2-CH3-CI

Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
UNITYplus-400 "unity400"

Pulse 60.9 degrees
Acq. time 1.200 sec
Width 25000.0 Hz
2800 repetitions
OBSERVE C13, 100.6512351 MHz
DECOUPLE H1, 400.2848137 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 10 hr, 45 min, 47 sec



10c



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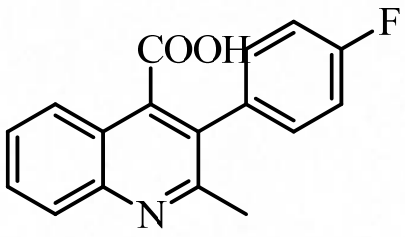
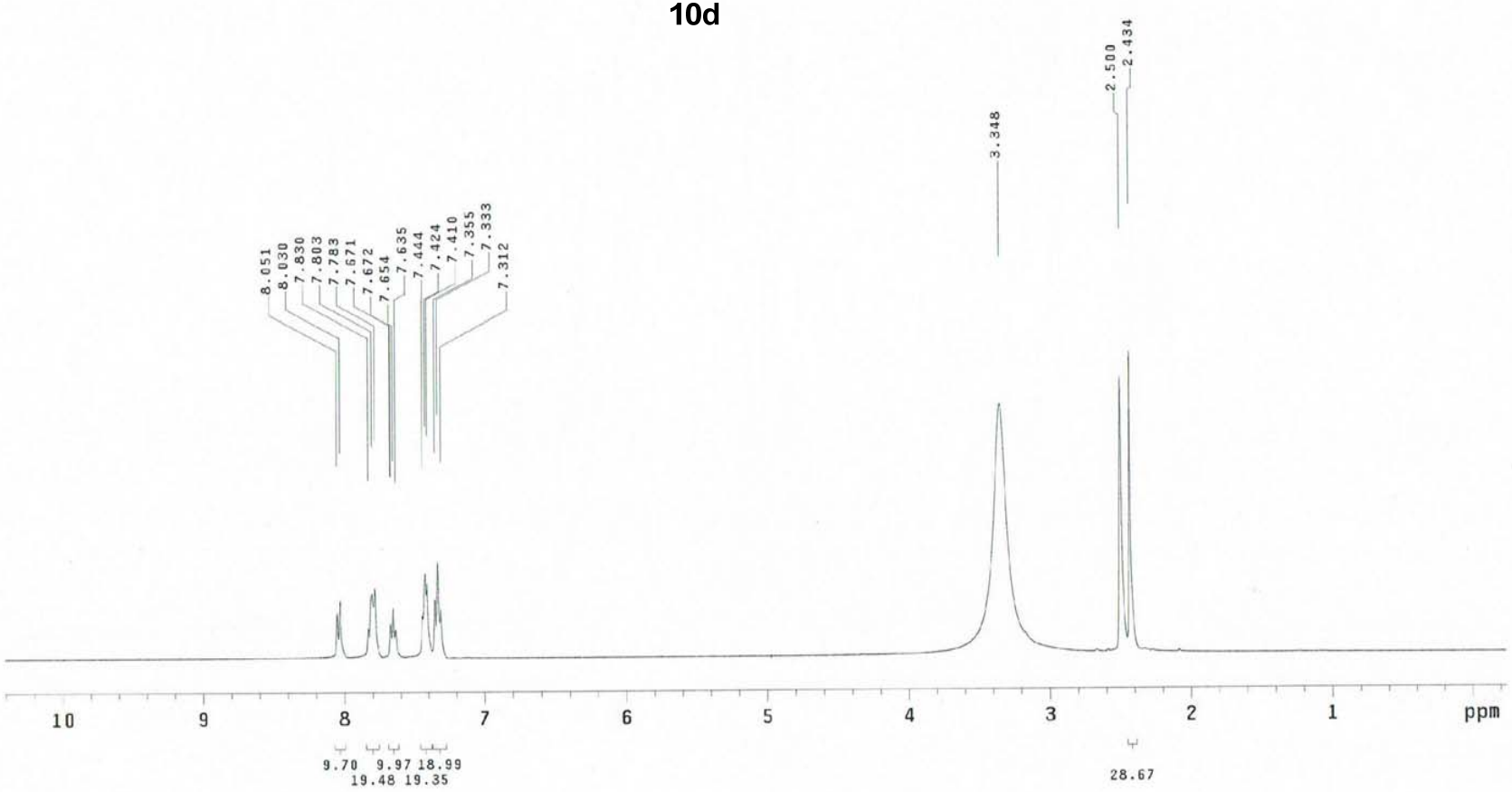
Ambient temperature
Total 100 repetitions



10d



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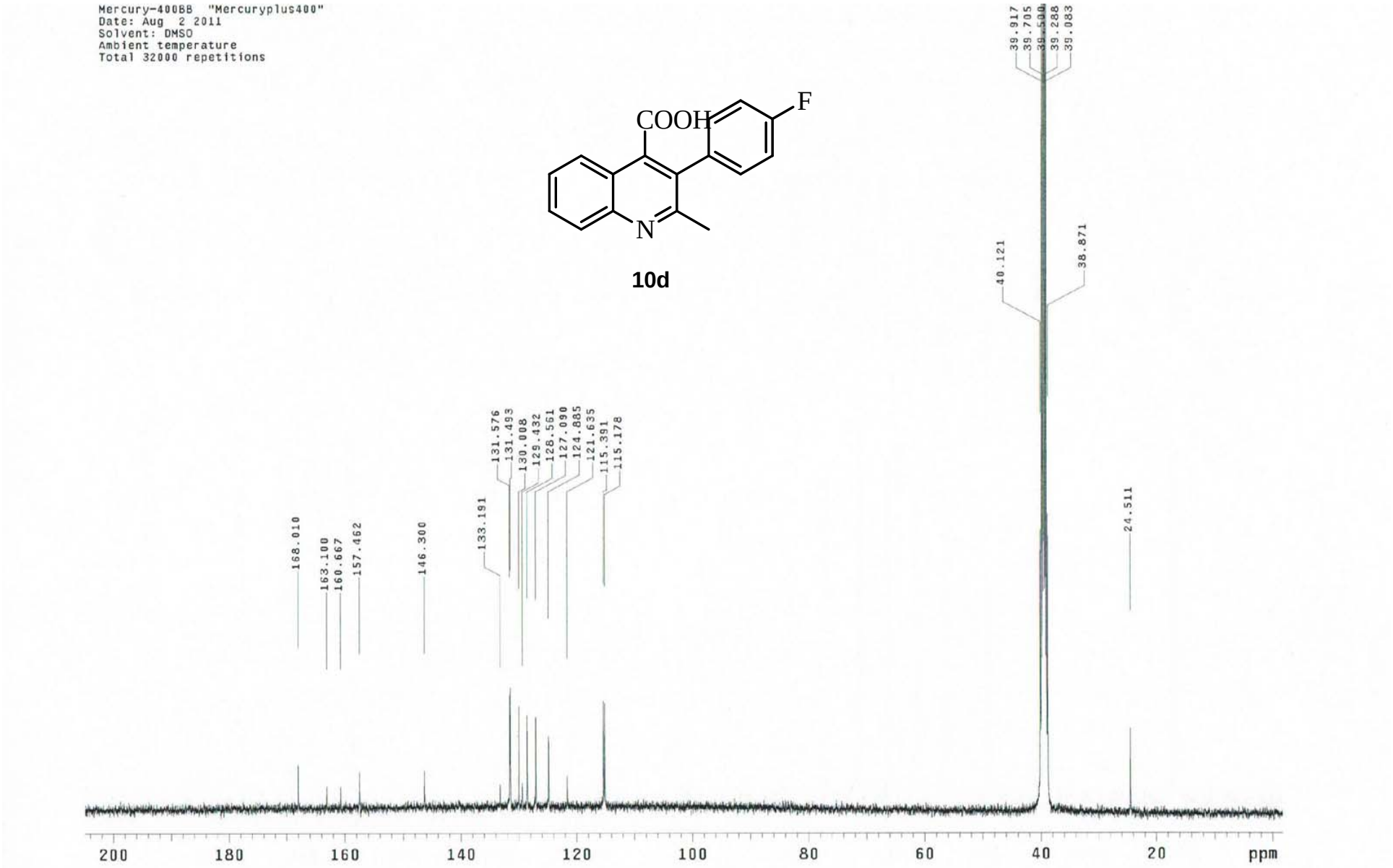

6F-para-F(COOH)

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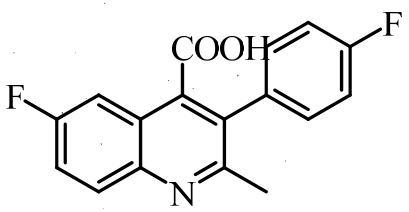
Solvent: DMSO
Ambient temperature
Total 152 repetitions



10e

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6F-para-F(COOH)

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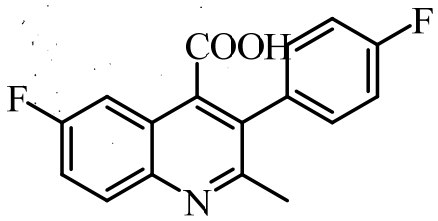
Date: Nov 21 2011
Solvent: DMSO
Ambient temperature
Total 816 repetitions



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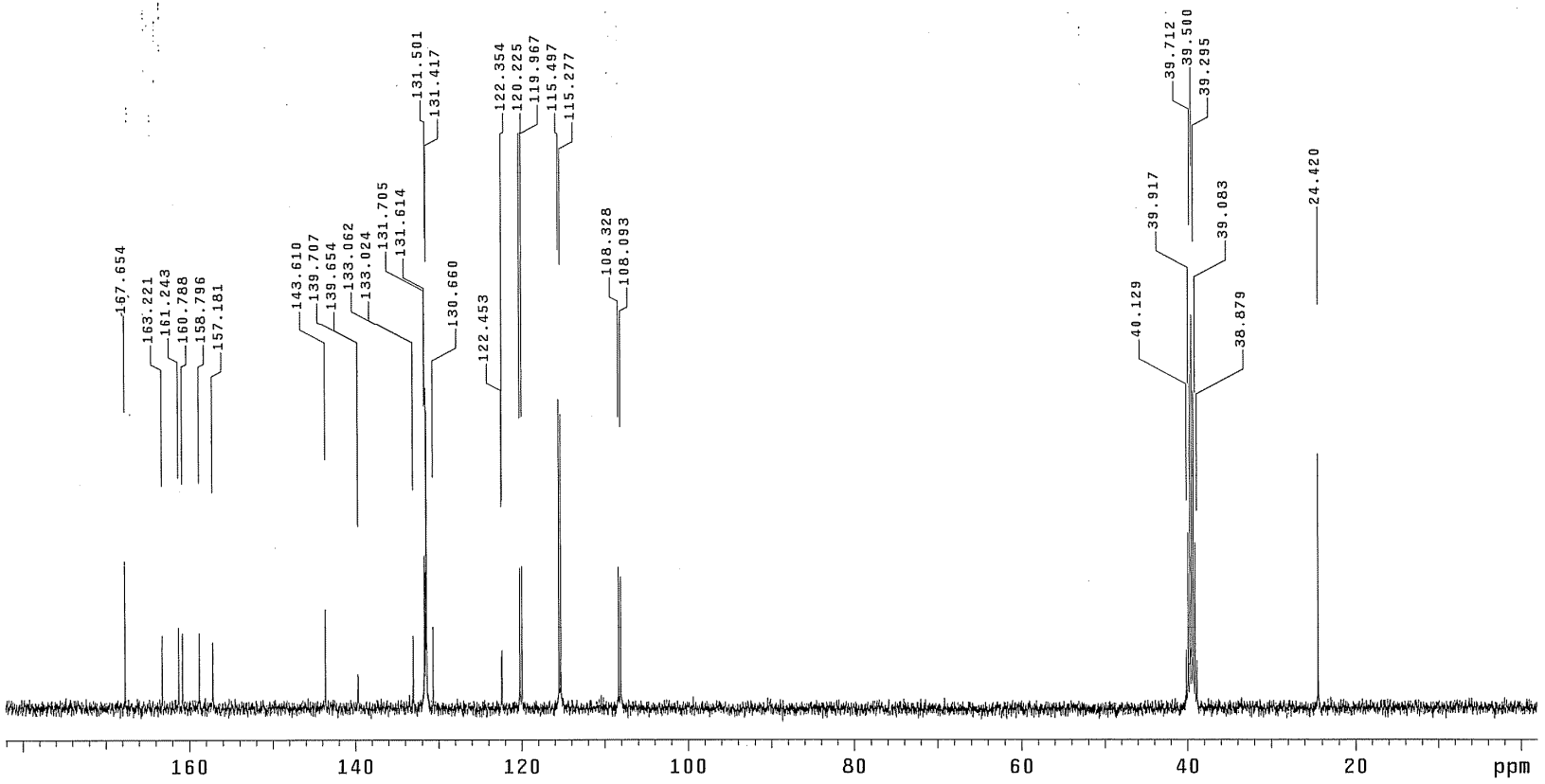

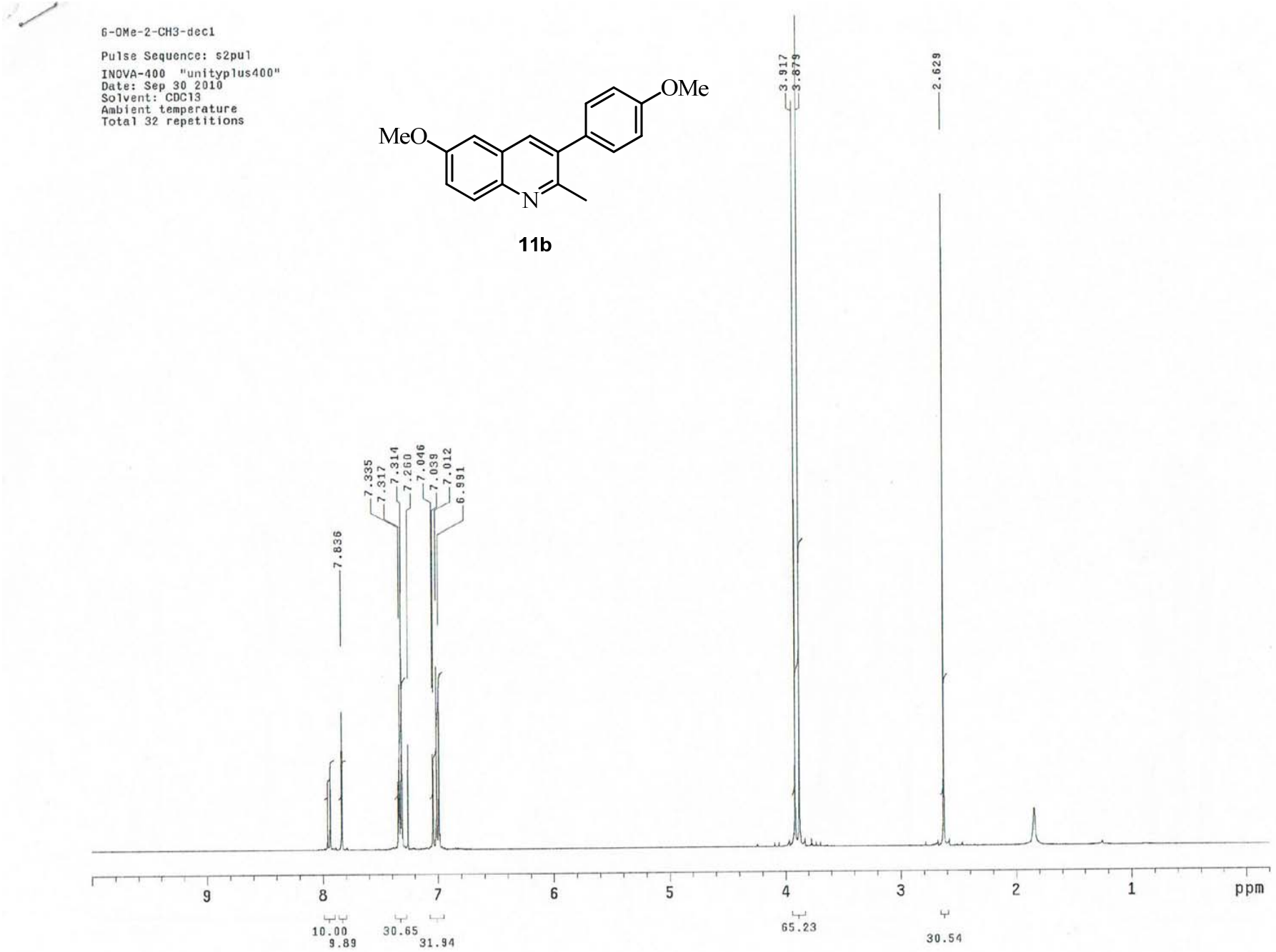
6-OMe-2-CH3-dec1
Pulse Sequence: s2pul
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Date: Sep 30 2010
Solvent: CDCl3
Ambient temperature
Total 32 repetitions
MeO
OMe
N
11b
3.917
3.879
2.629
7.836
7.335
7.317
7.314
7.260
7.046
7.039
7.012
6.991
9
8
7
6
5
4
3
2
1
ppm
10.00
9.89
30.65
31.94
65.23
30.54

INOVA-400 "unityplus400"
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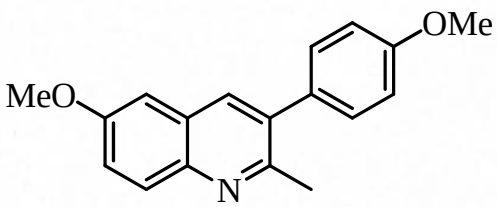
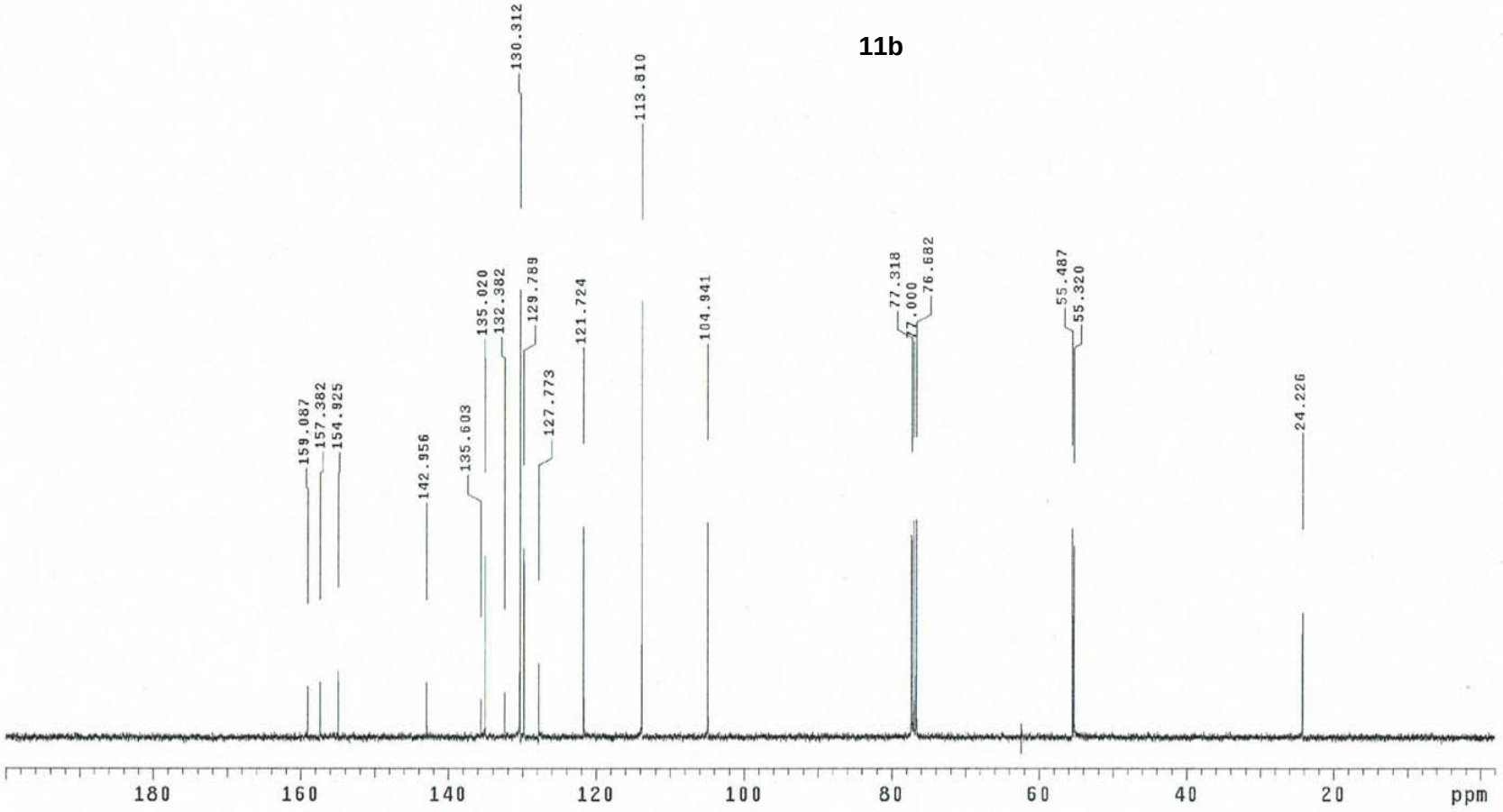
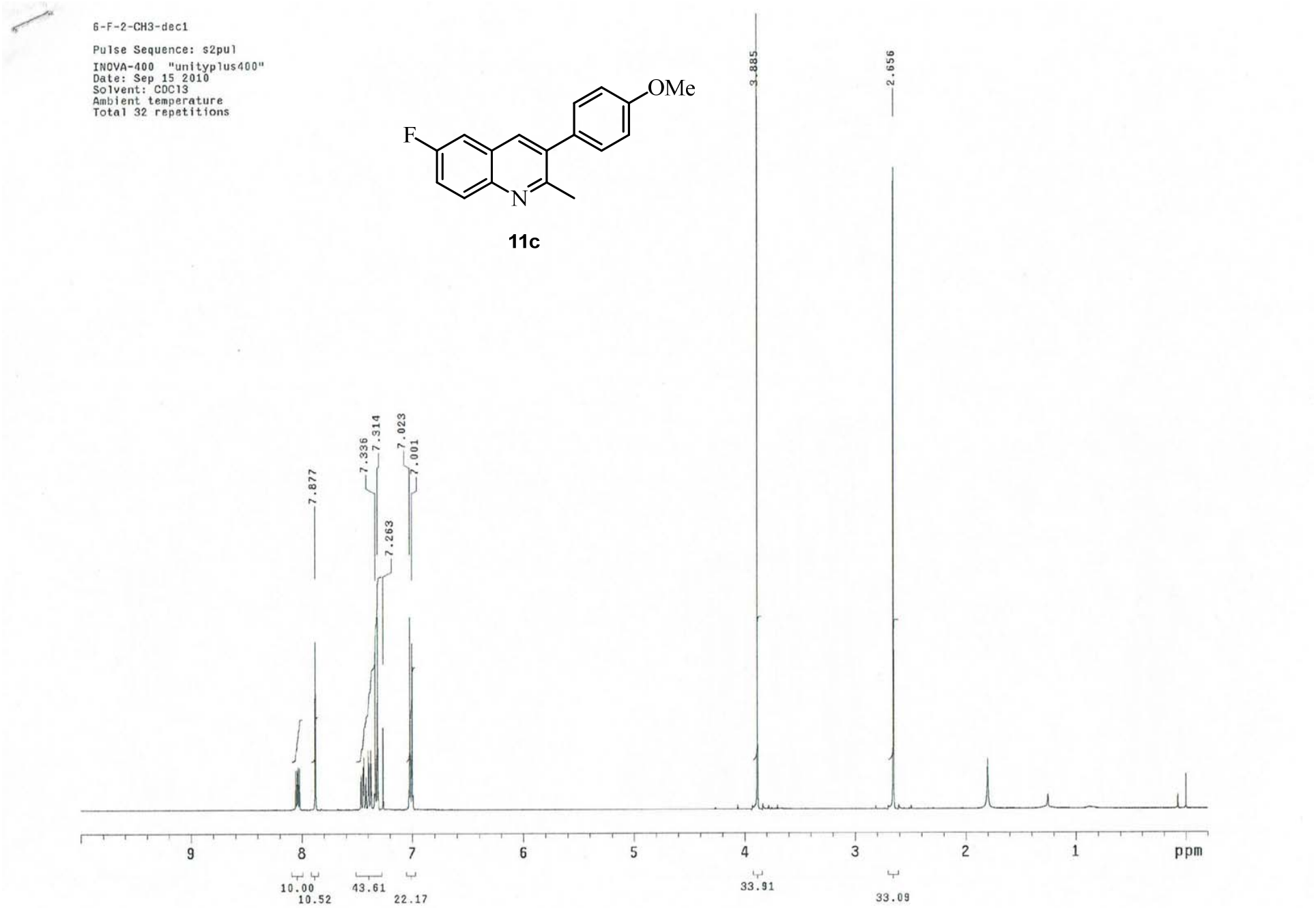
Solvent: CDCl3
Ambient temperature
Total 4864 repetitions



11b




6-F-2-CH3-dec1
Pulse Sequence: s2pul
INOVA-400 "unityplus400"
Date: Sep 15 2010
Solvent: CDCl3
Ambient temperature
Total 32 repetitions
F
OMe
N
11c
3.885
2.656
7.877
7.336
7.314
7.263
7.023
7.001
9
8
7
6
5
4
3
2
1
ppm
10.00
10.52
43.61
22.17
33.91
33.09

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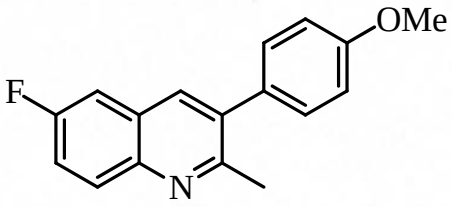
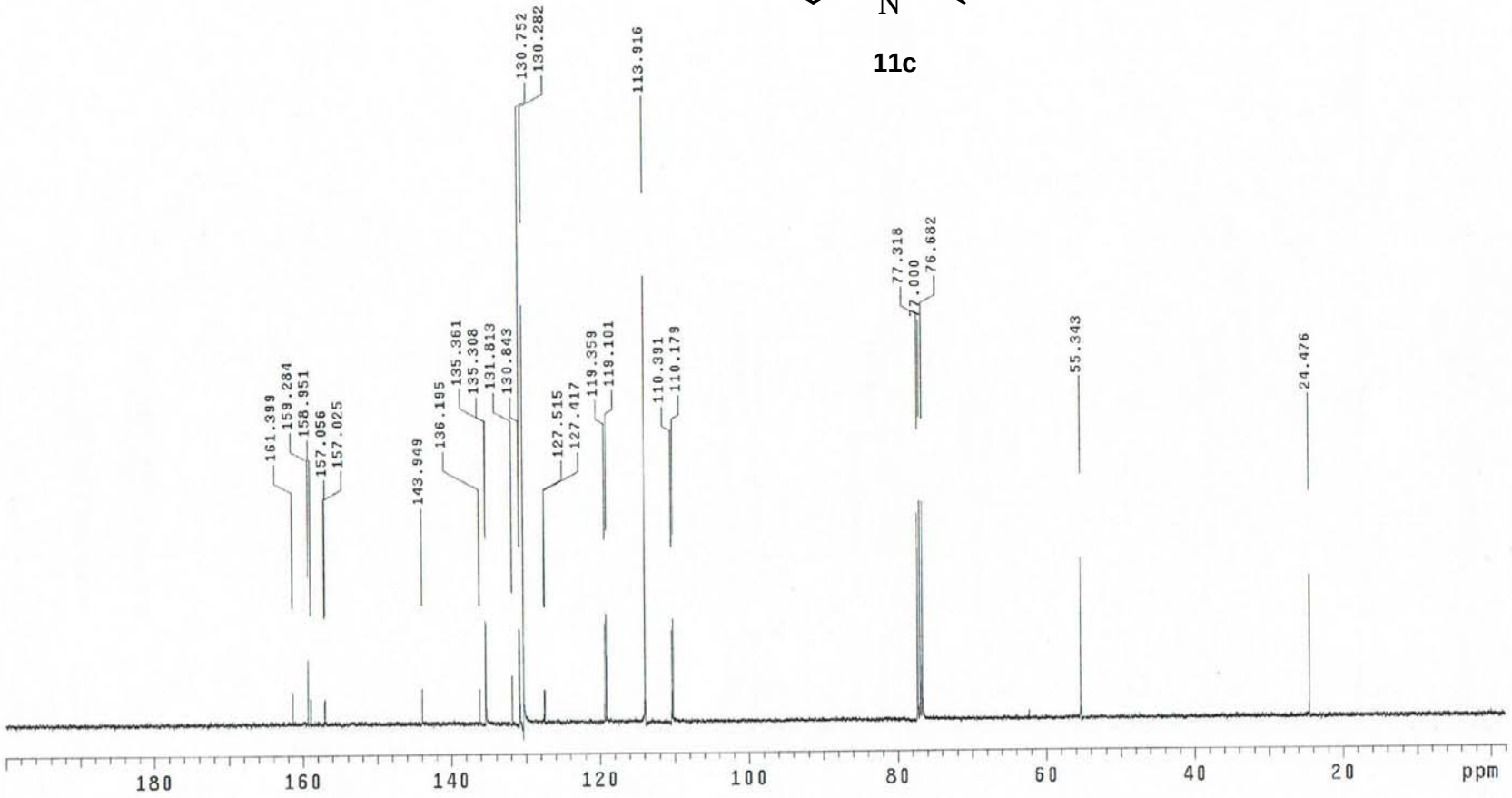
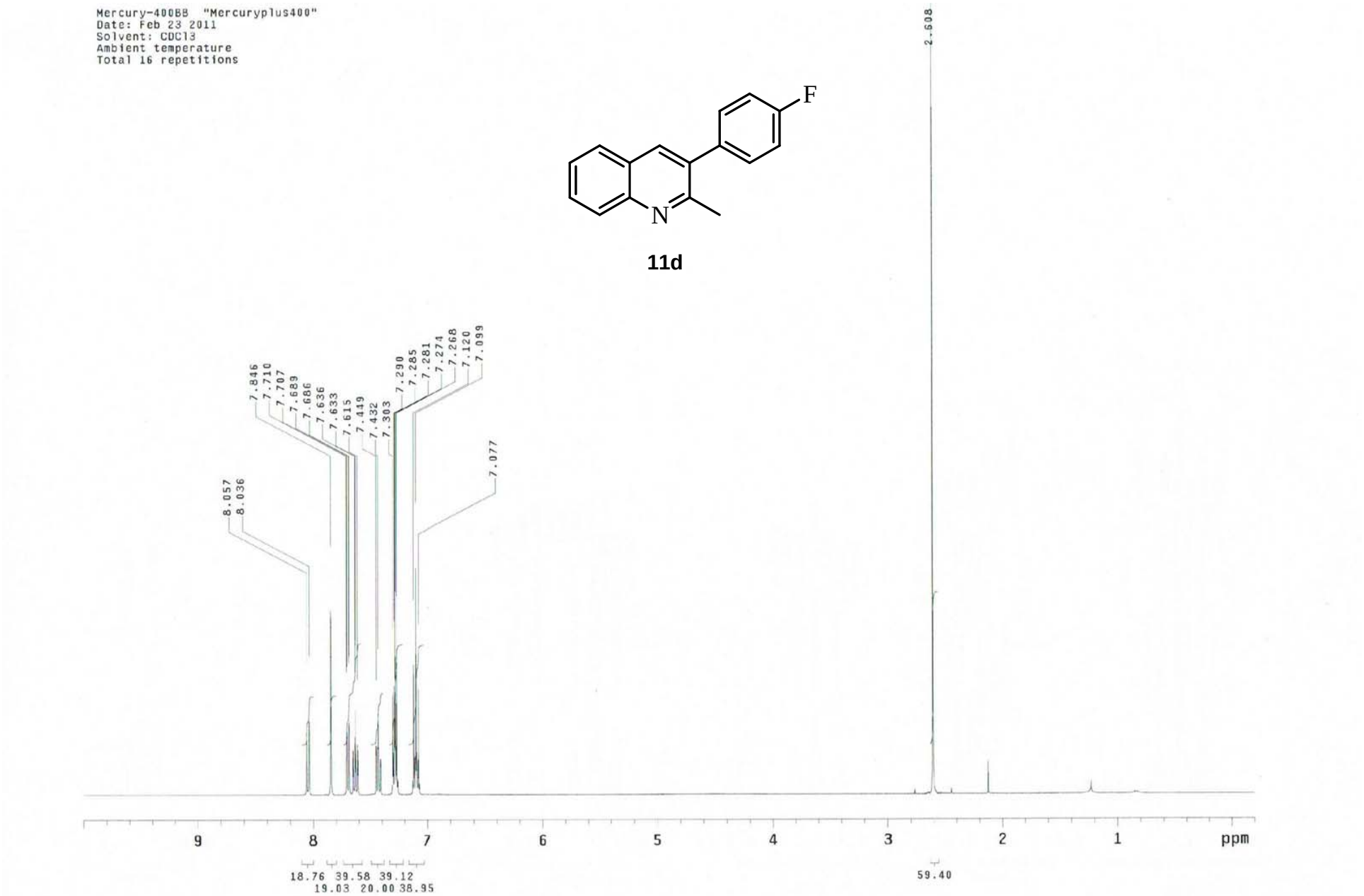
Date: Sep 15 2010
Solvent: CDCl3
Ambient temperature
Total 8112 repetitions



11c

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Solvent: CDCl3
Ambient temperature
Total 16 repetitions
F
N
11d
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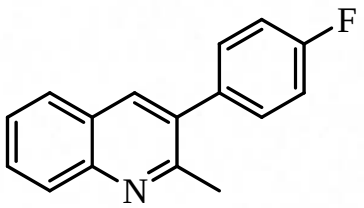
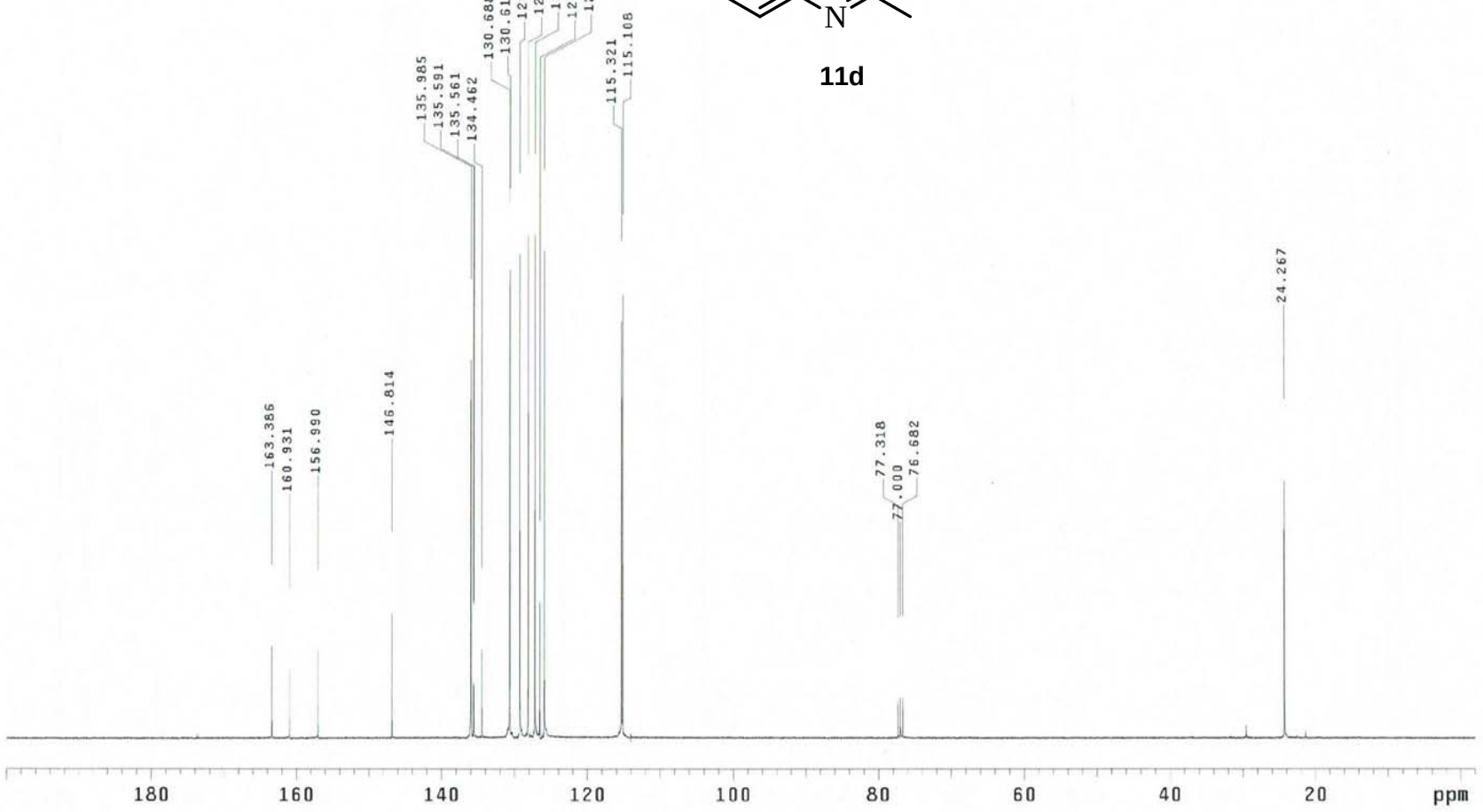
8.057
8.036
7.846
7.710
7.707
7.689
7.686
7.636
7.633
7.615
7.449
7.432
7.303
7.290
7.285
7.281
7.274
7.268
7.120
7.099
7.077
9
8
7
6
5
4
3
2
1
ppm
18.76
19.03
39.58
20.00
39.12
38.95
59.40

Mercury-400BB "Mercuryplus400"
Date: Feb 23 2011
Solvent: CDCl3
Ambient temperature
Total 32000 repetitions



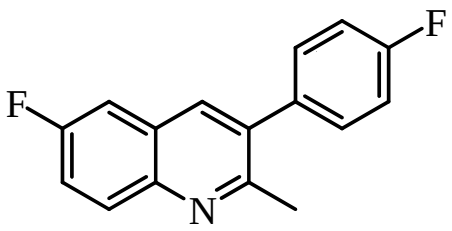
11d



ACCEPTED MANUSCRIPT

6F-para-F(de-COOH)

Mercury-400BB "Mercuryplus400"
Date: Jun 30 2011
Solvent: CDCl3
Ambient temperature
Total 28 repetitions

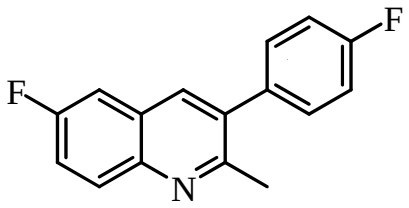


11e

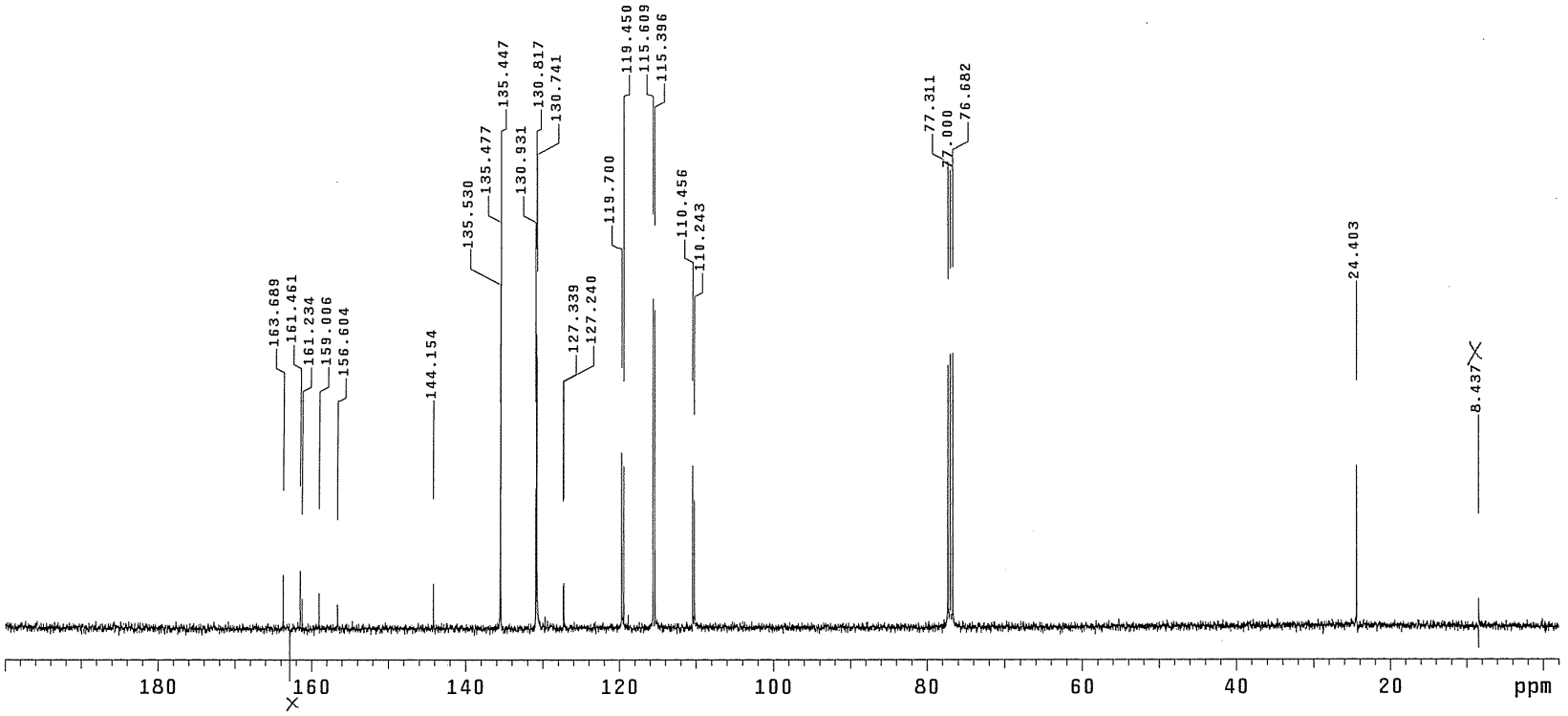
ACCEPTED MANUSCRIPT

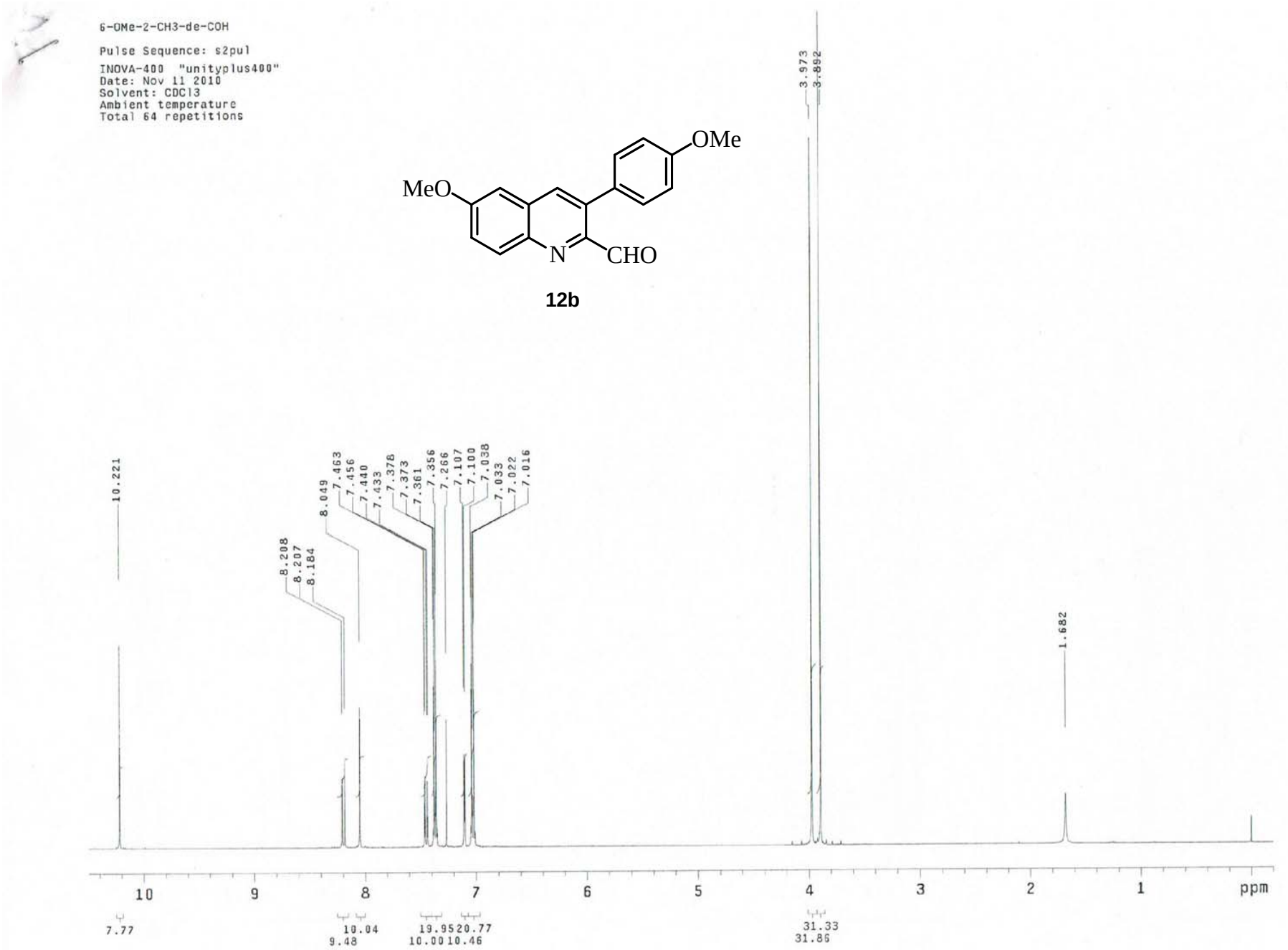
6F-para-F(de-COOH)

Mercury-400BB "Mercuryplus400"
Date: Jun 30 2011
Solvent: CDCl3
Ambient temperature
Total 2384 repetitions



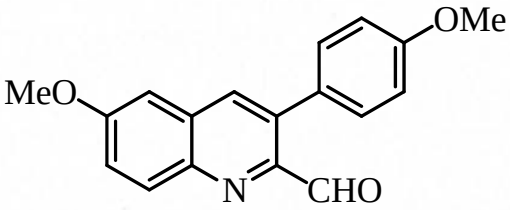
11e



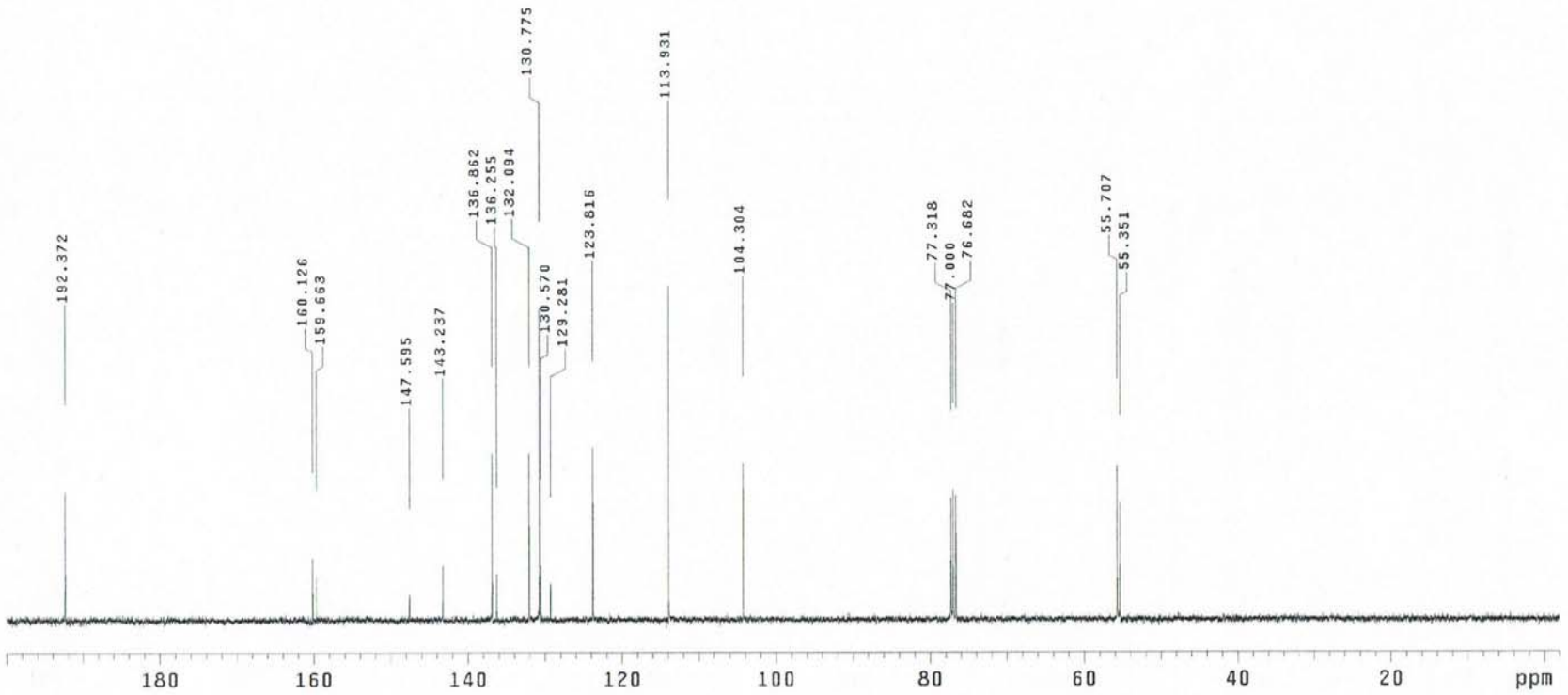

6-OMe-2-CH3-de-COH
Pulse Sequence: s2pul
INOVA-400 "unityplus400"
Date: Nov 11 2010
Solvent: CDCl3
Ambient temperature
Total 64 repetitions
MeO
OMe
N
CHO
12b
10.221
8.208
8.207
8.184
8.049
7.463
7.456
7.440
7.433
7.378
7.373
7.361
7.356
7.266
7.107
7.100
7.038
7.033
7.022
7.016
3.973
3.892
1.682
10
9
8
7
6
5
4
3
2
1
ppm
7.77
10.04
9.48
19.95
10.00
20.77
10.46
31.33
31.86

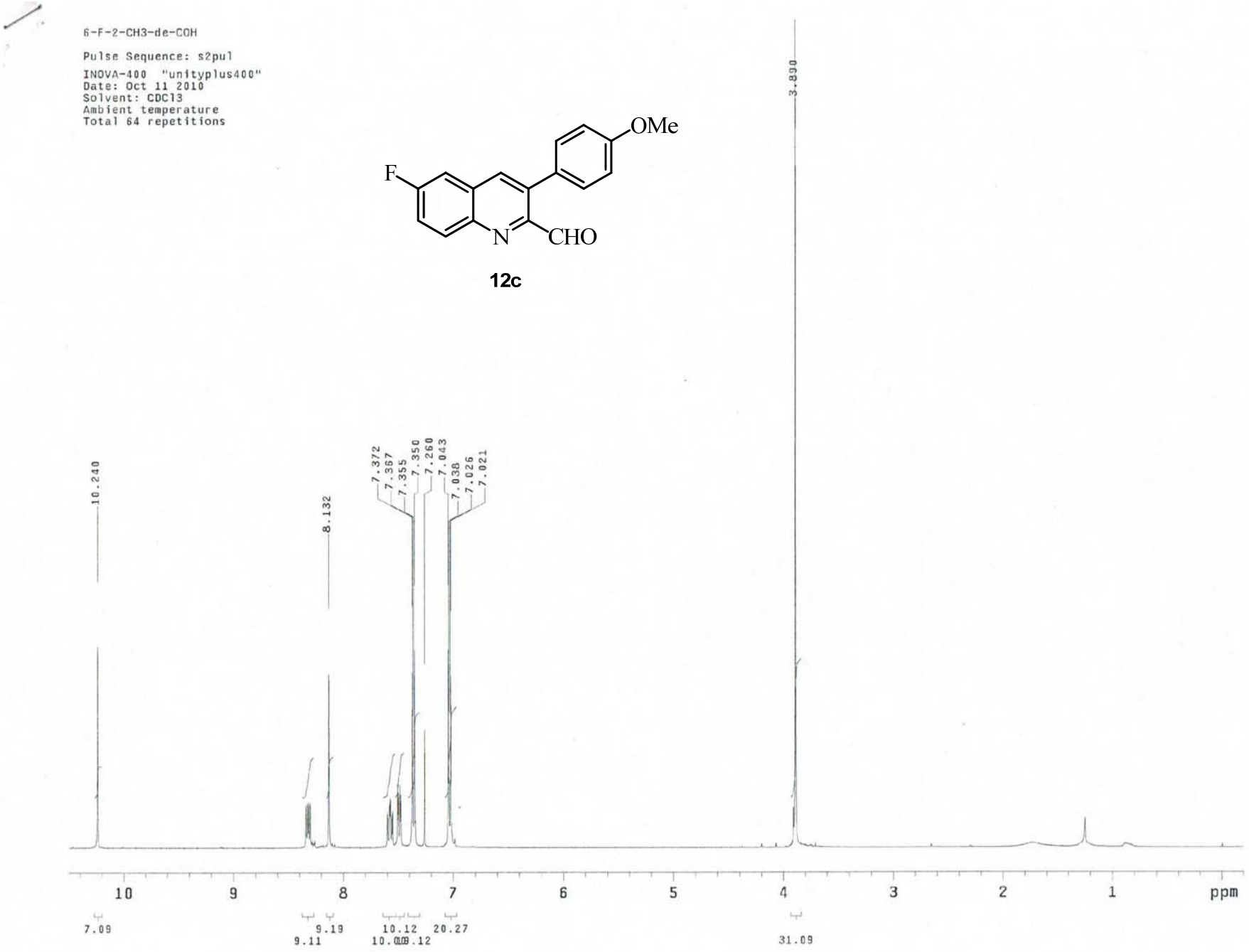
6-OMe-2-CH3-de-COH

Pulse Sequence: s2pul
INOVA-400 "unityplus400"
Date: Nov 11 2010
Solvent: CDCl3
Ambient temperature
Total 2304 repetitions



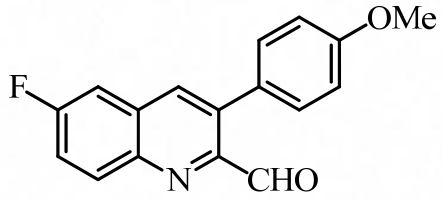
12b



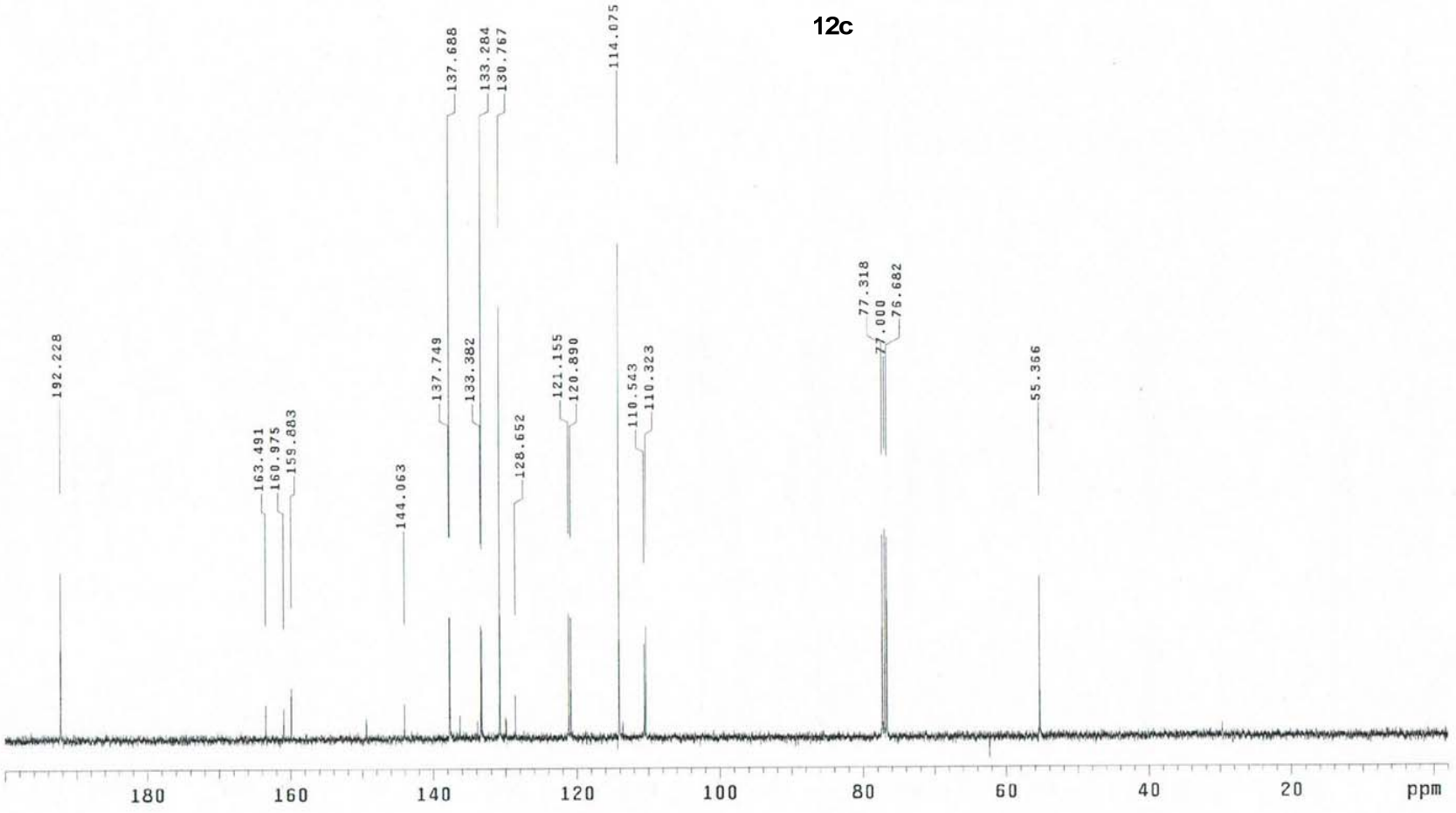

6-F-2-CH3-de-COH
Pulse Sequence: s2pul
INOVA-400 "unityplus400"
Date: Oct 11 2010
Solvent: CDCl3
Ambient temperature
Total 64 repetitions
OMe
F
N
CHO
12c
3.890
10.240
8.132
7.372
7.367
7.355
7.350
7.260
7.043
7.038
7.026
7.021
10
9
8
7
6
5
4
3
2
1
ppm
7.09
9.19
9.11
10.12
20.27
31.09

6-F-2-CH3-de-COH

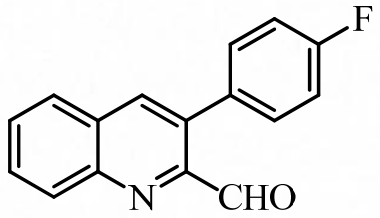
Pulse Sequence: s2pul
INOVA-400 "unityplus400"
Date: Oct 11 2010
Solvent: CDCl3
Ambient temperature
Total 4544 repetitions



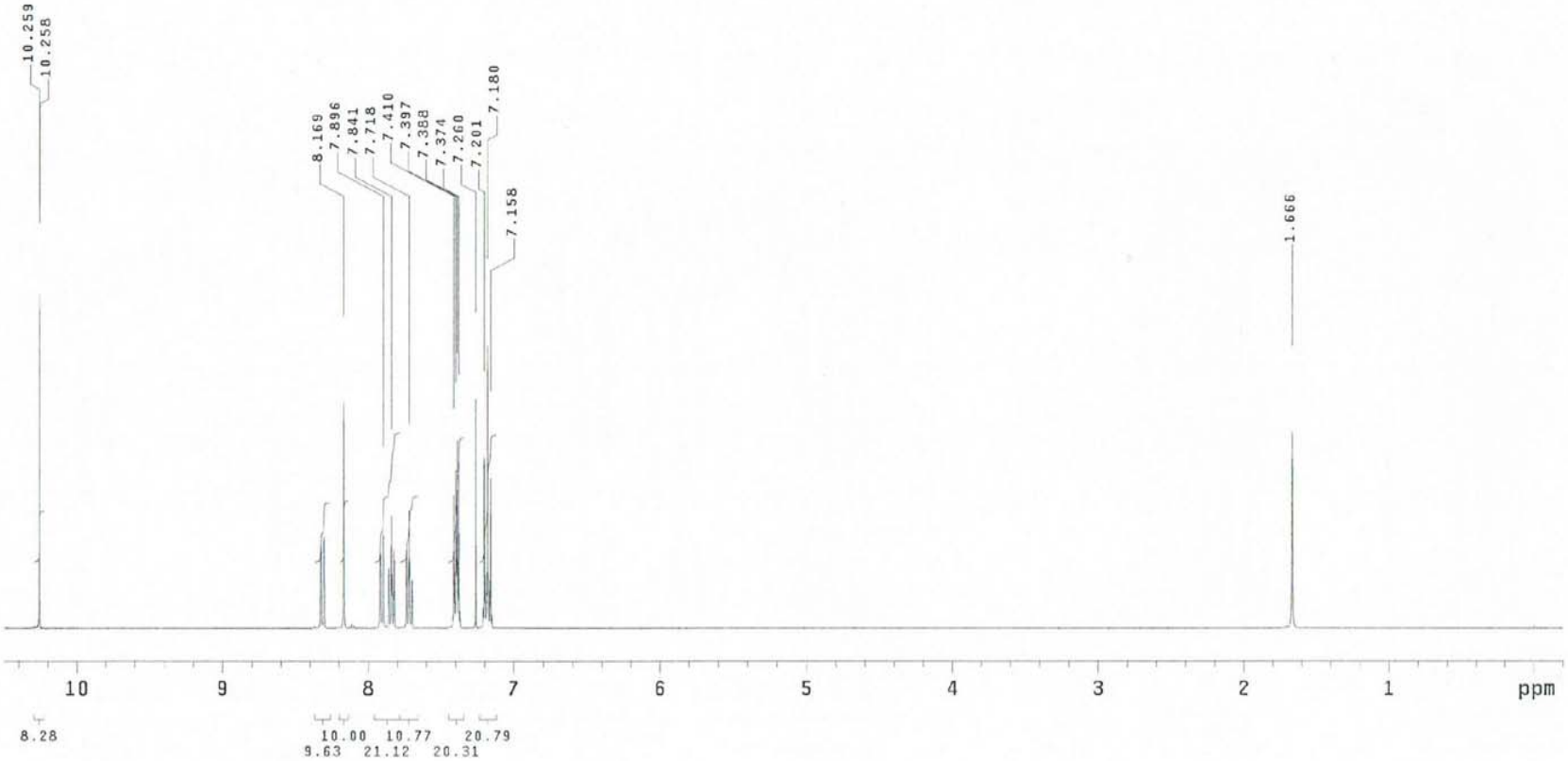
12c



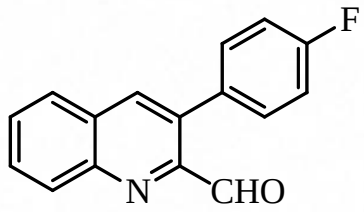
INOVA-400 "unityplus400"
Date: Feb 23 2011
Solvent: CDCl3
Ambient temperature
Total 32 repetitions



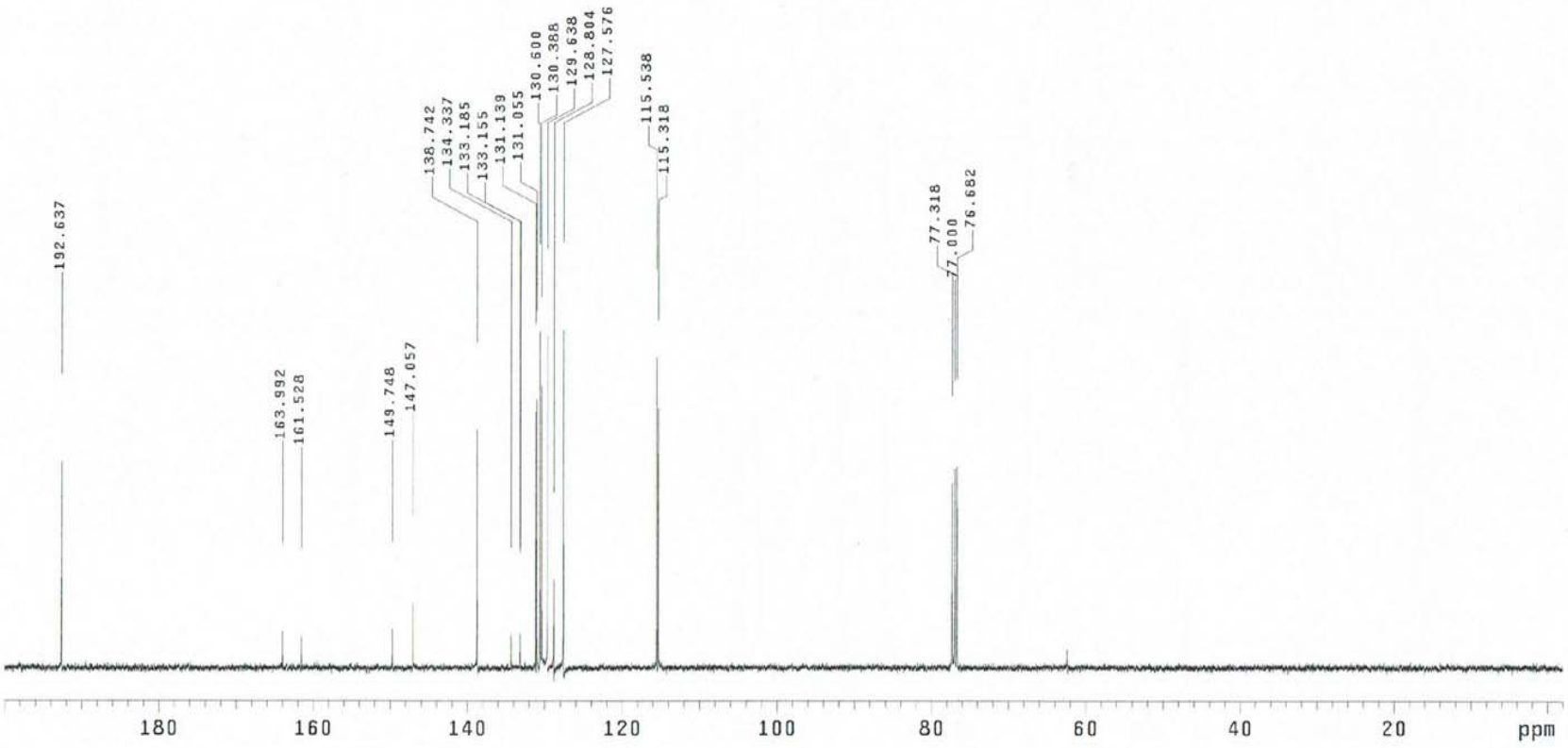
12d



INOVA-400 "unityplus400"
Date: Feb 23 2011
Solvent: CDCl3
Ambient temperature
Total 5280 repetitions



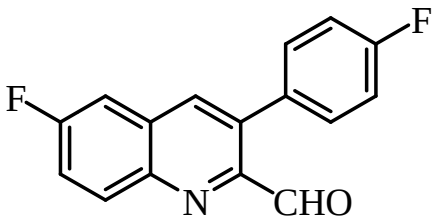
12d



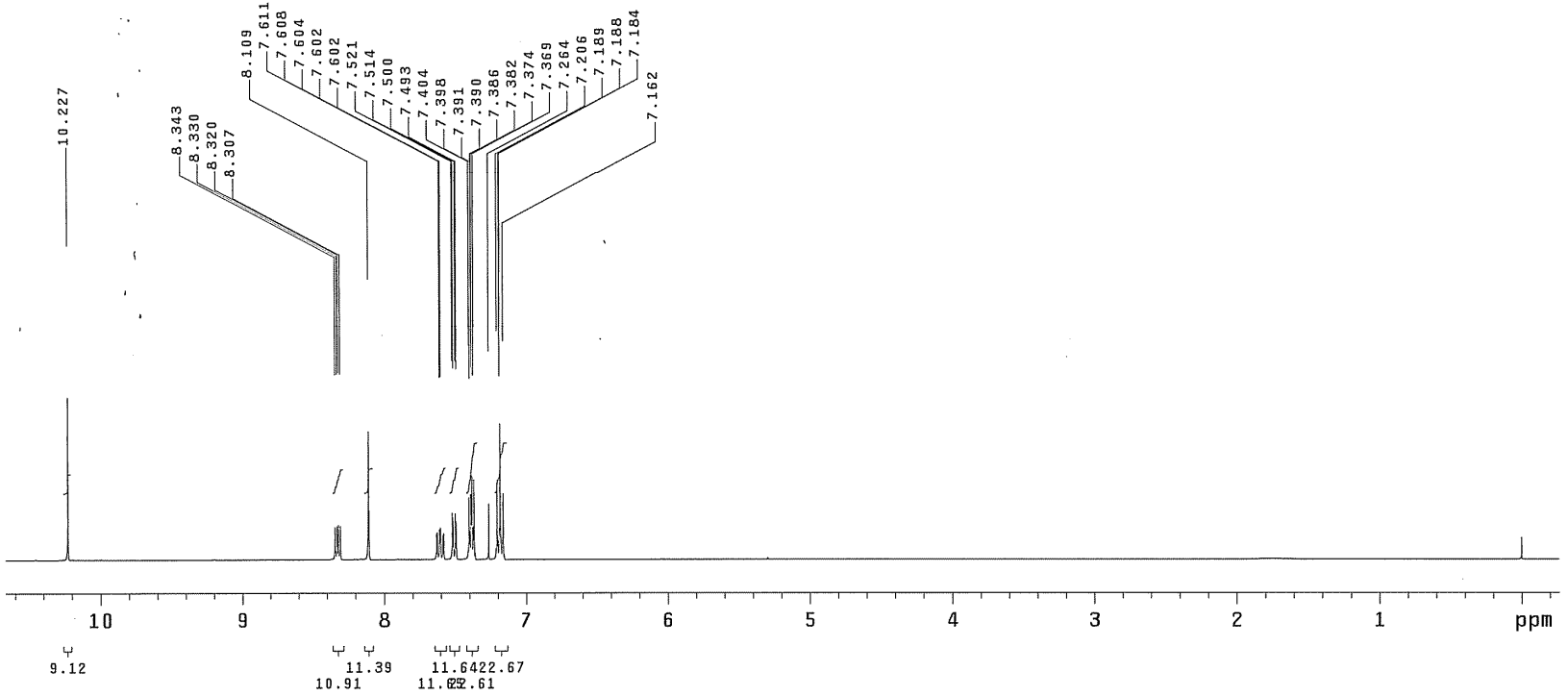
ACCEPTED MANUSCRIPT

6-F-para-F(CHO)

Mercury-400BB "Mercuryplus400"
Date: Nov 21 2011
Solvent: CDCl3
Ambient temperature
Total 68 repetitions



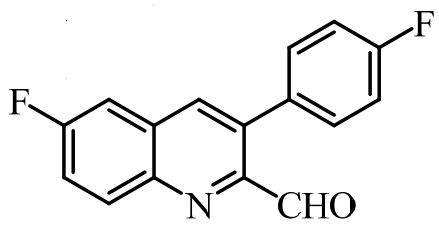
12e



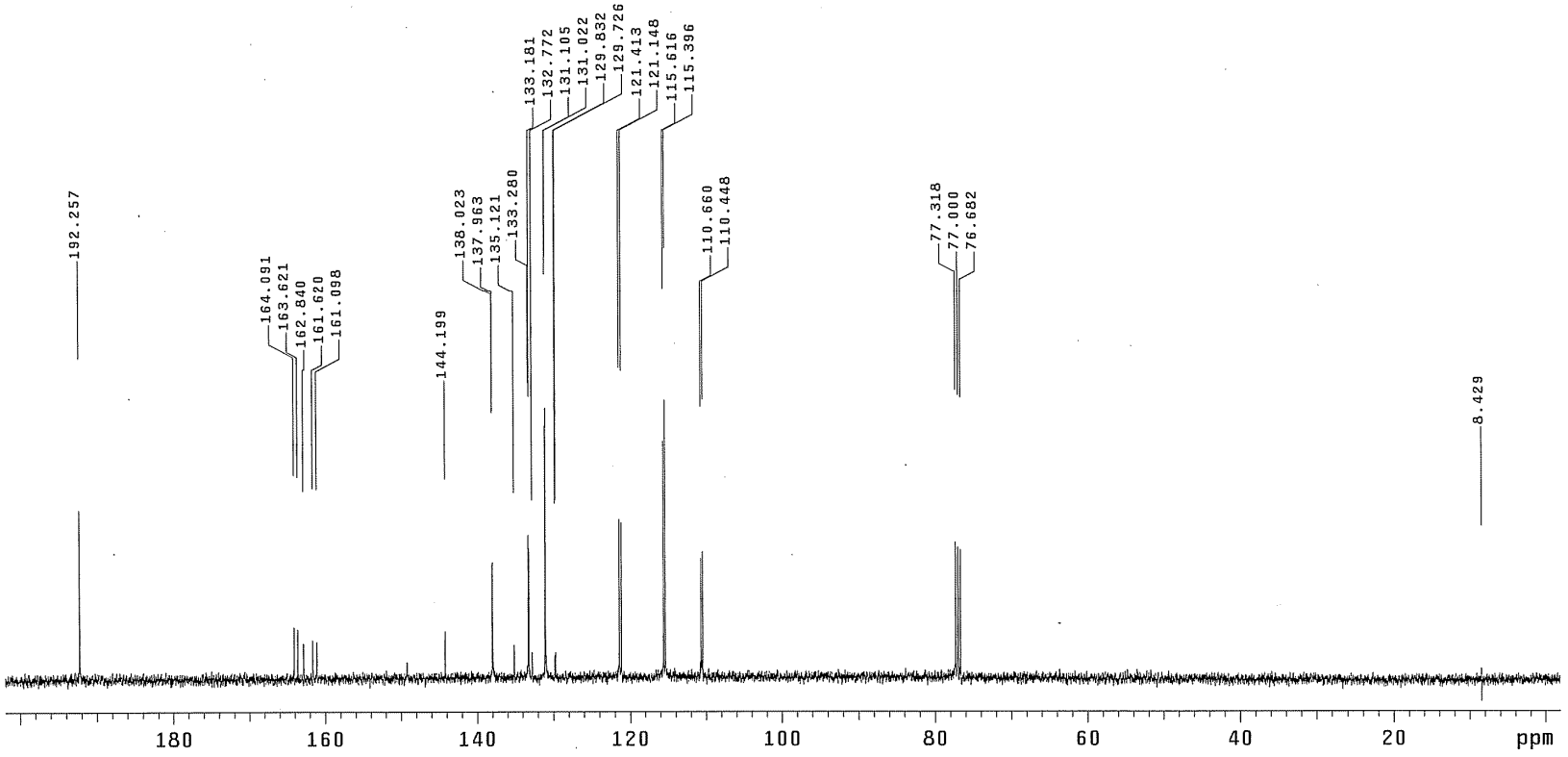
ACCEPTED MANUSCRIPT

6-F-para-F(CHO)

Mercury-400BB "Mercuryplus400"
Date: Nov 21 2011
Solvent: CDCl3
Ambient temperature
Total 800 repetitions



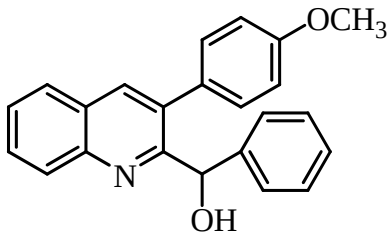
12e



WKY-H-OMe-1d

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Sep 5 2012
Solvent: CDCl3
Ambient temperature
Total 64 repetitions



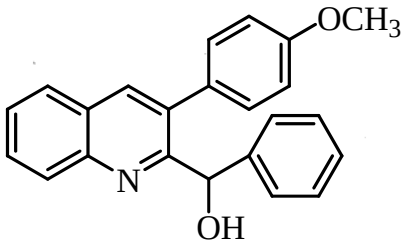
13a

ACCEPTED MANUSCRIPT

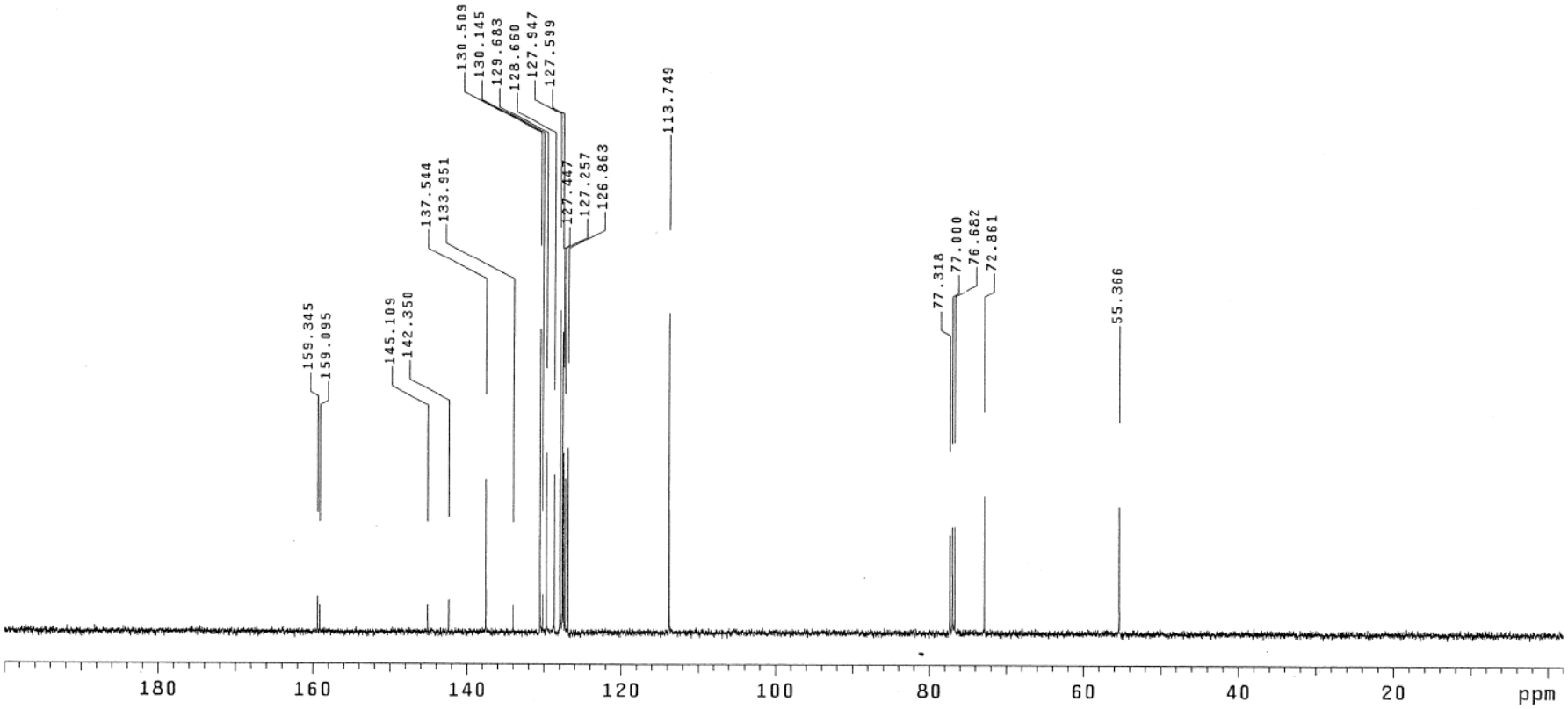
WKY-H-OMe-1d

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Sep 5 2012
Solvent: CDCl3
Ambient temperature
Total 1904 repetitions



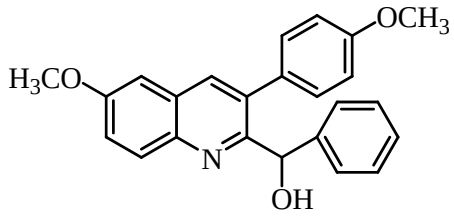
13a



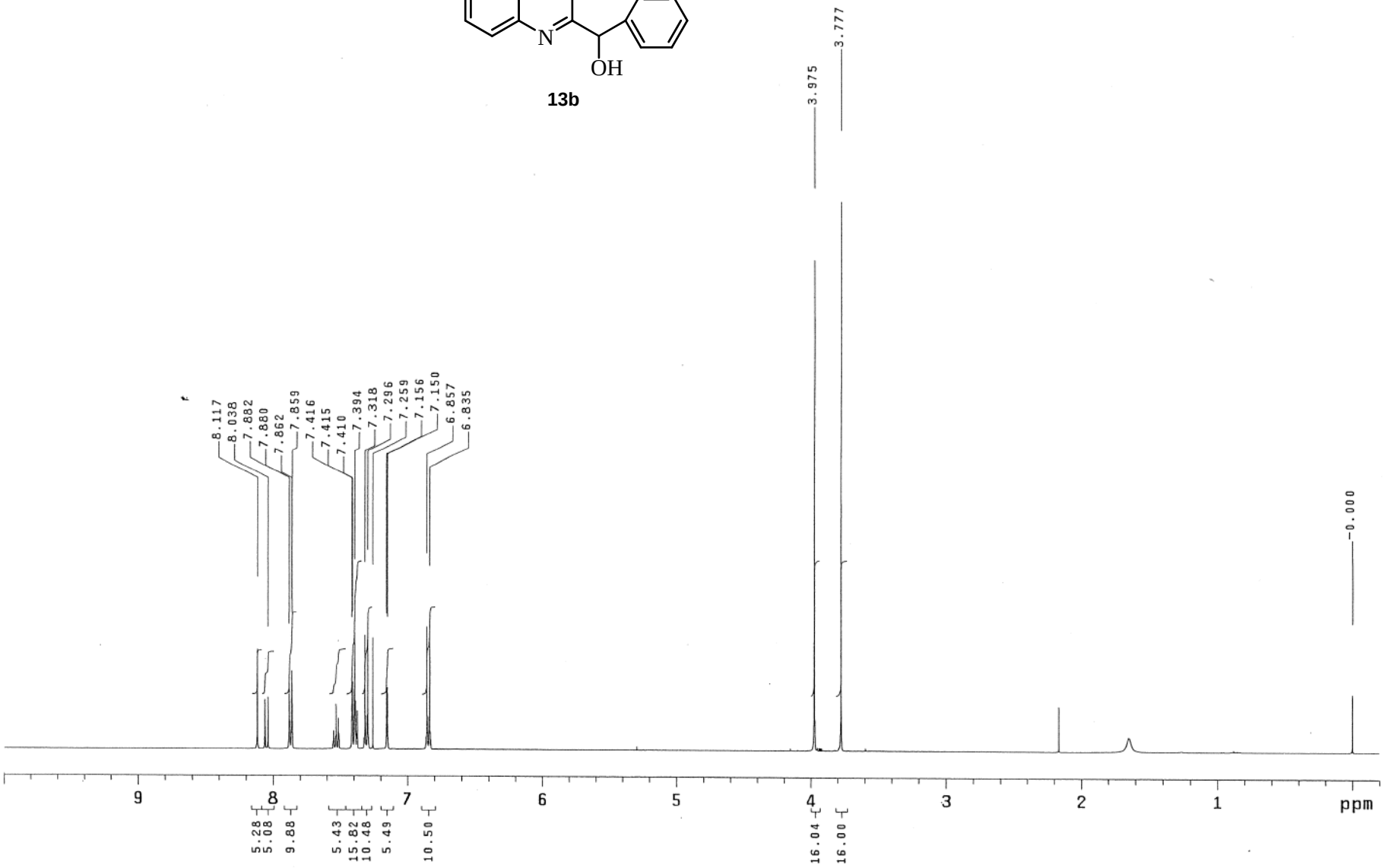
WKY-OMe-OMe-17b

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 24 2012
Solvent: CDCl3
Ambient temperature
Total 64 repetitions



13b

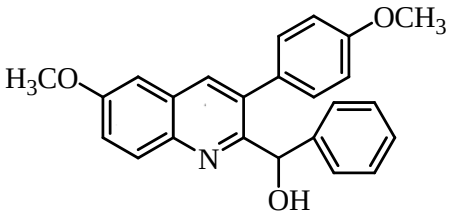


ACCEPTED MANUSCRIPT

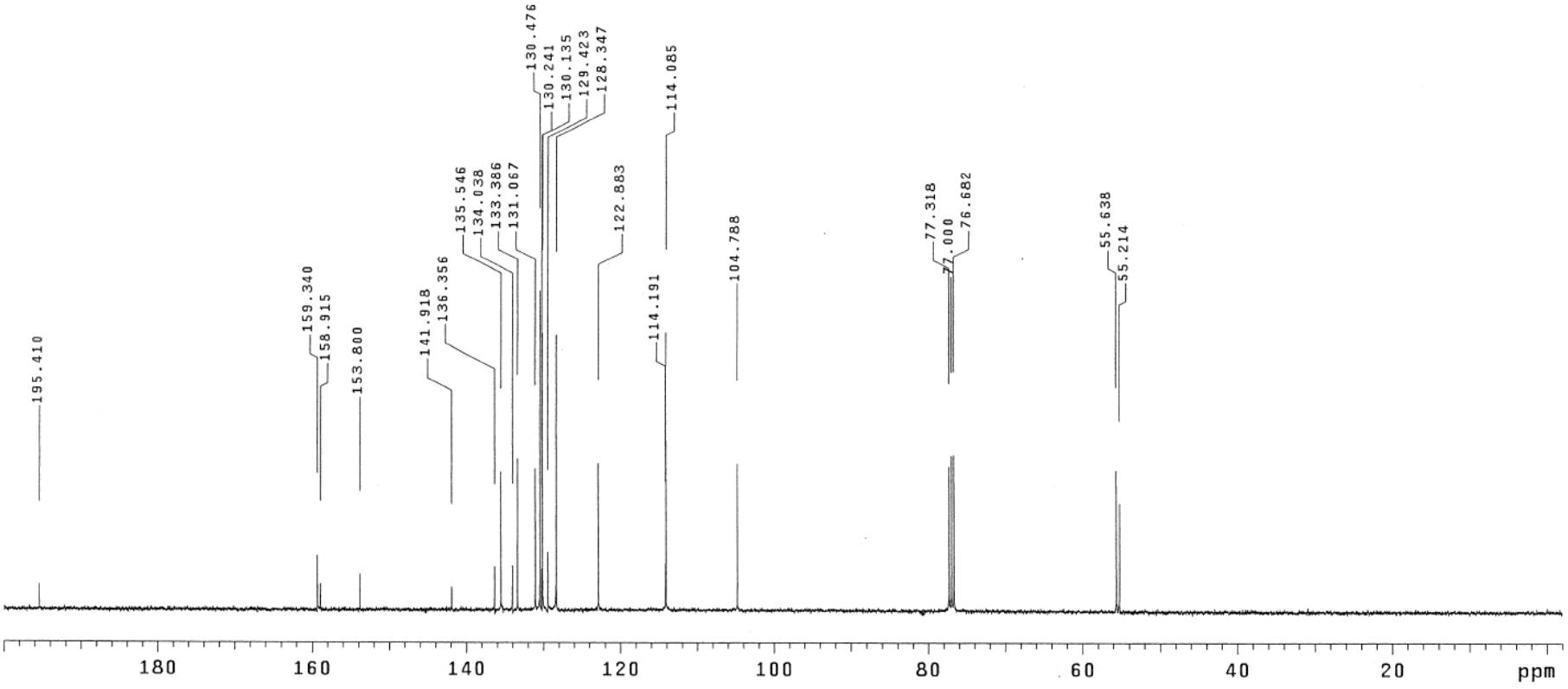
WKY-OMe-OMe-17b

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 24 2012
Solvent: CDCl3
Ambient temperature
Total 3024 repetitions



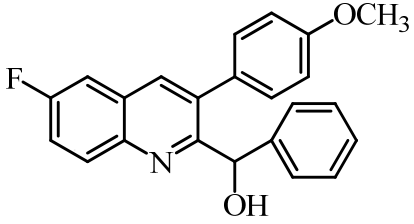
13b



WKY-F-OMe-17c

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Oct 1 2012
Solvent: CDCl3
Ambient temperature
Total 80 repetitions



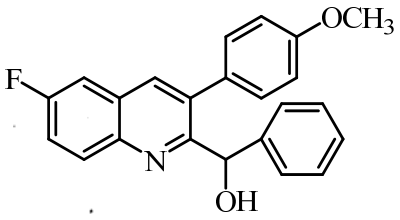
13c

ACCEPTED MANUSCRIPT

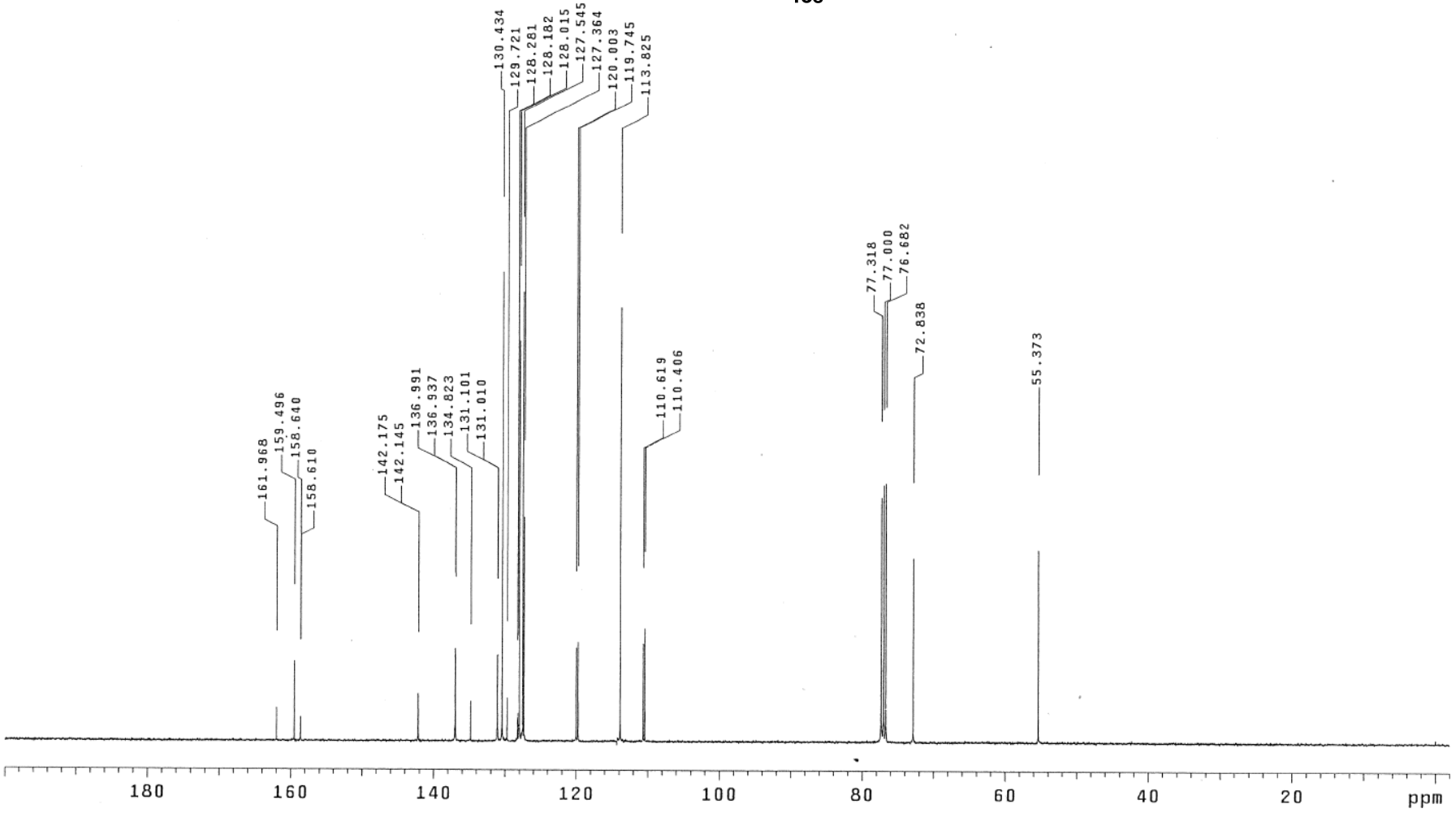
WKY-F-OMe-17c

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Oct 1 2012
Solvent: CDCl3
Ambient temperature
Total 33712 repetitions

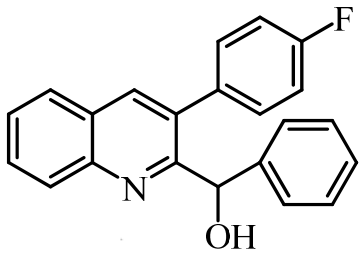


13c

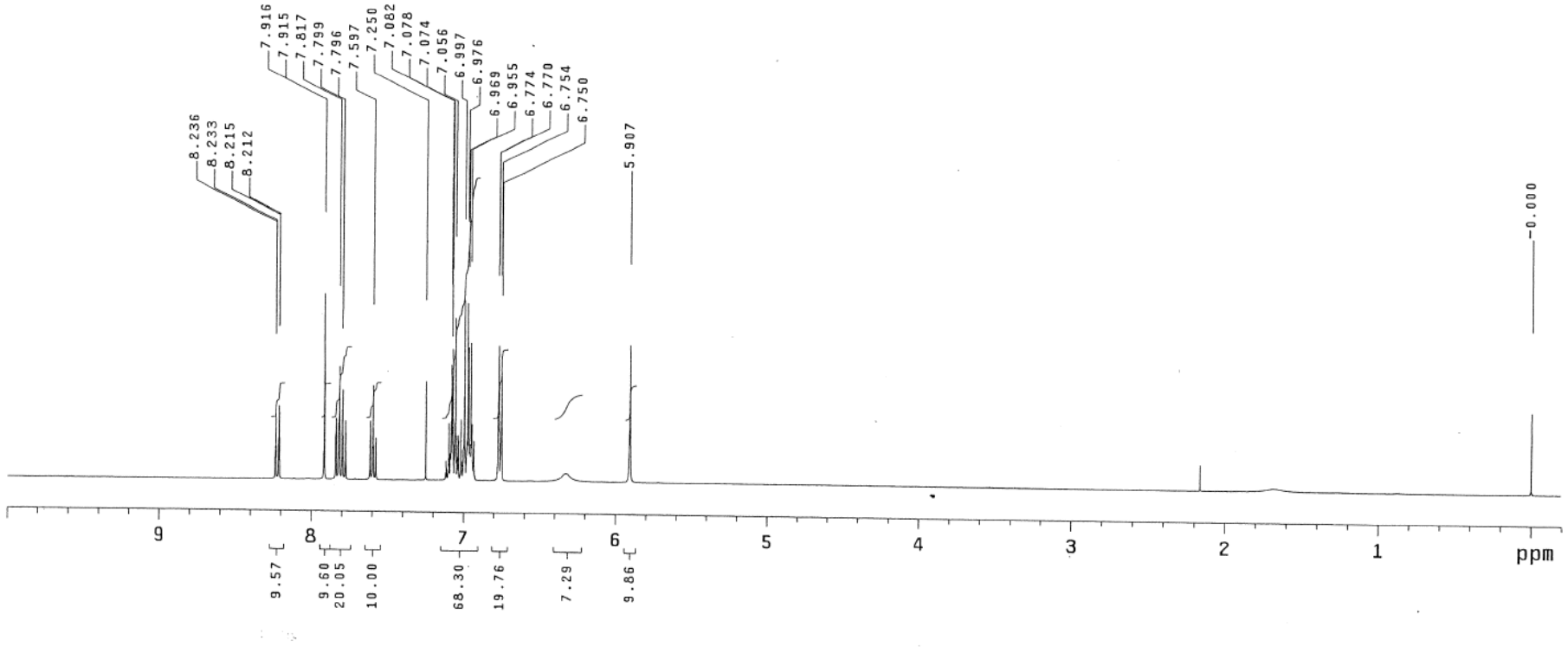


WKY-H-F-17d

Pulse Sequence: s2pul
Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 32 repetitions



13d

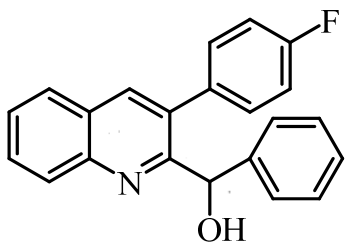


ACCEPTED MANUSCRIPT

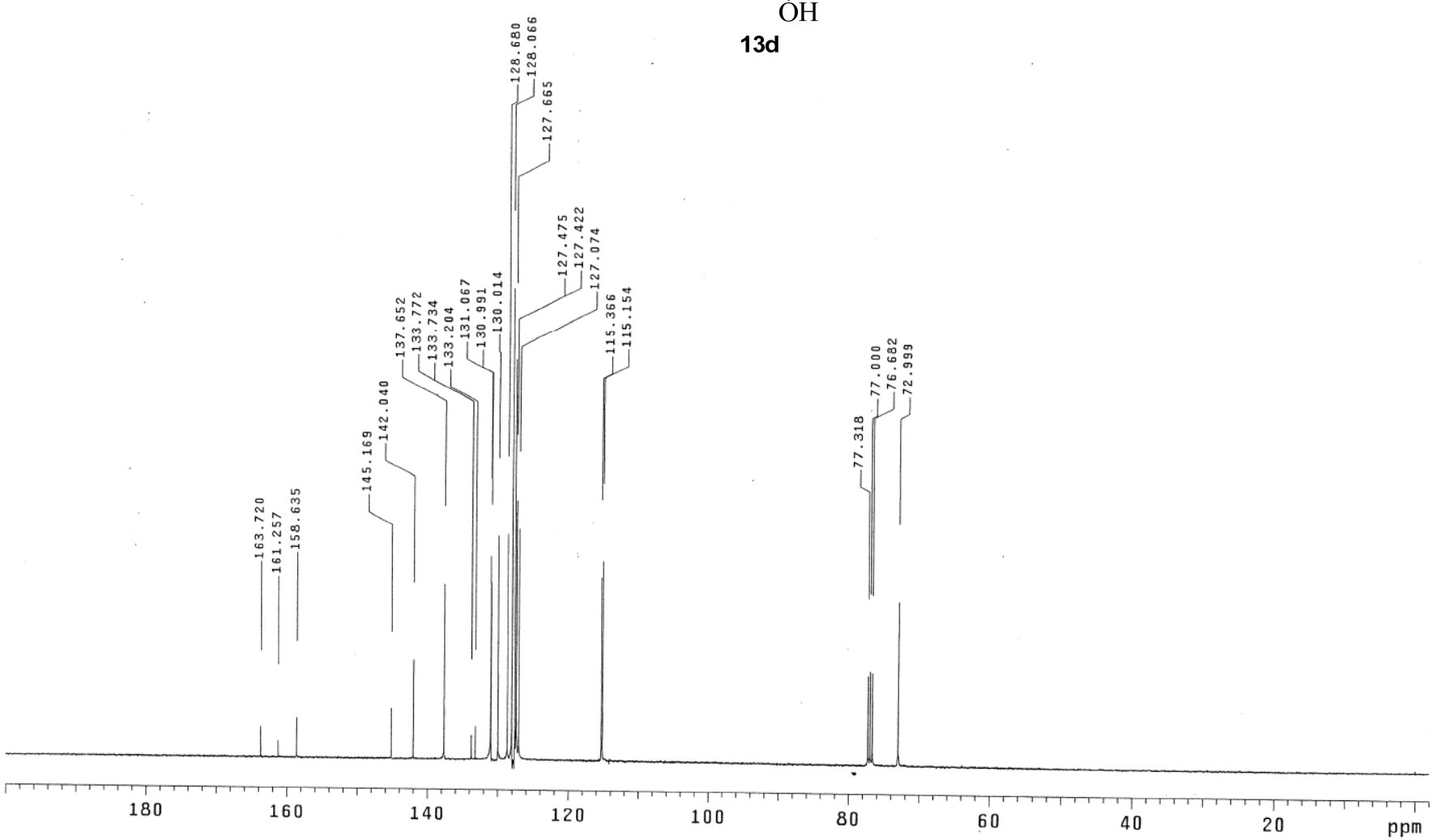
WKY-H-F-17d

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 6176 repetitions



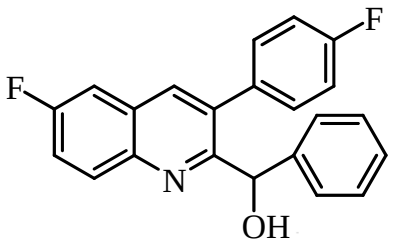
13d



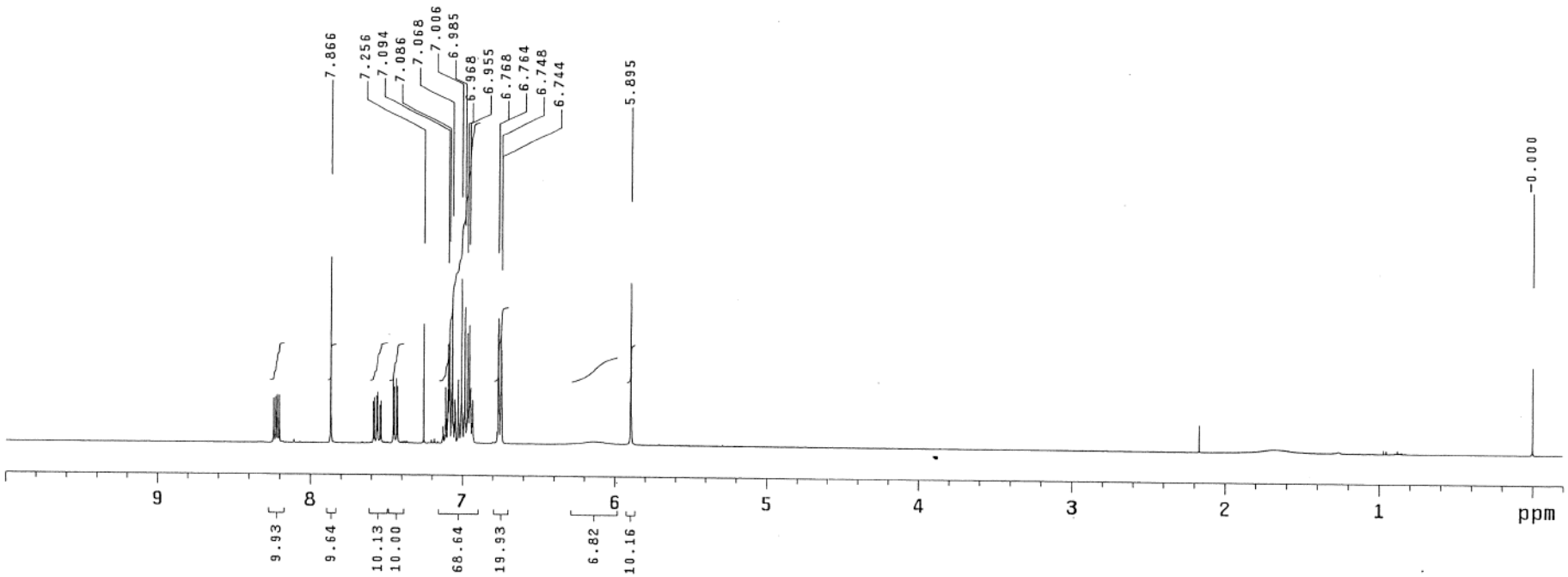
WKY-F-F-17e

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 64 repetitions



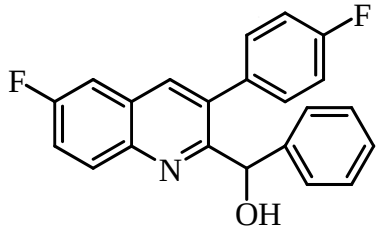
13e



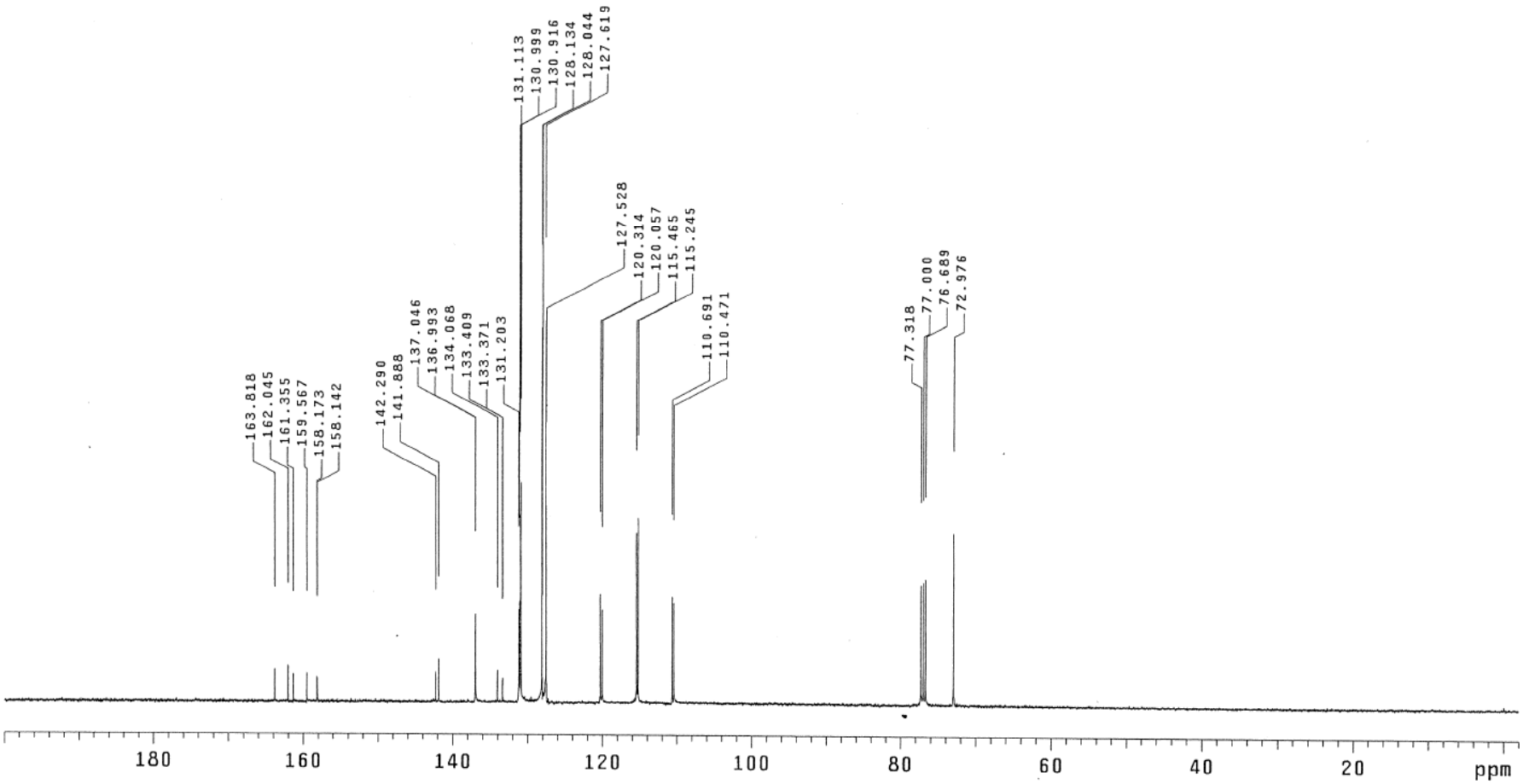
WKY-F-F-17e

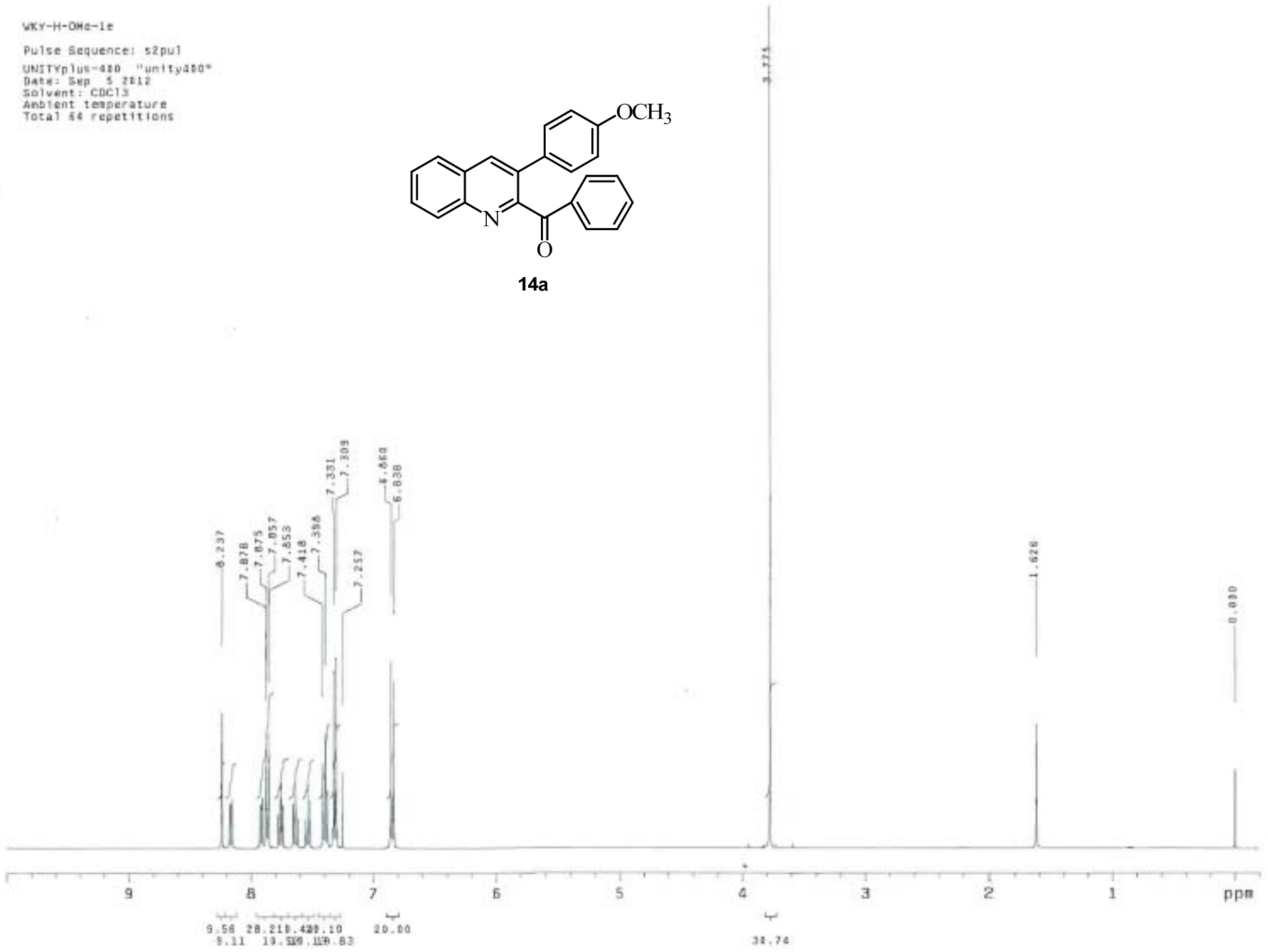
Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 5056 repetitions



13e

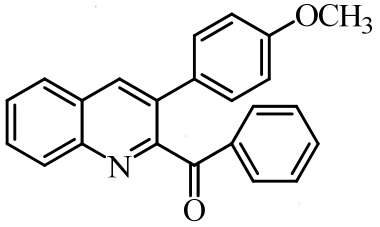



WKY-H-OMe-1e
Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Sep 5 2012
Solvent: CDCl3
Ambient temperature
Total 64 repetitions
OCH3
N
O
14a
8.237
7.878
7.875
7.857
7.853
7.418
7.398
7.331
7.309
7.257
6.858
6.838
3.775
1.626
0.000
9
8
7
6
5
4
3
2
1
ppm
9.56
28.21
9.42
9.10
20.00
38.74

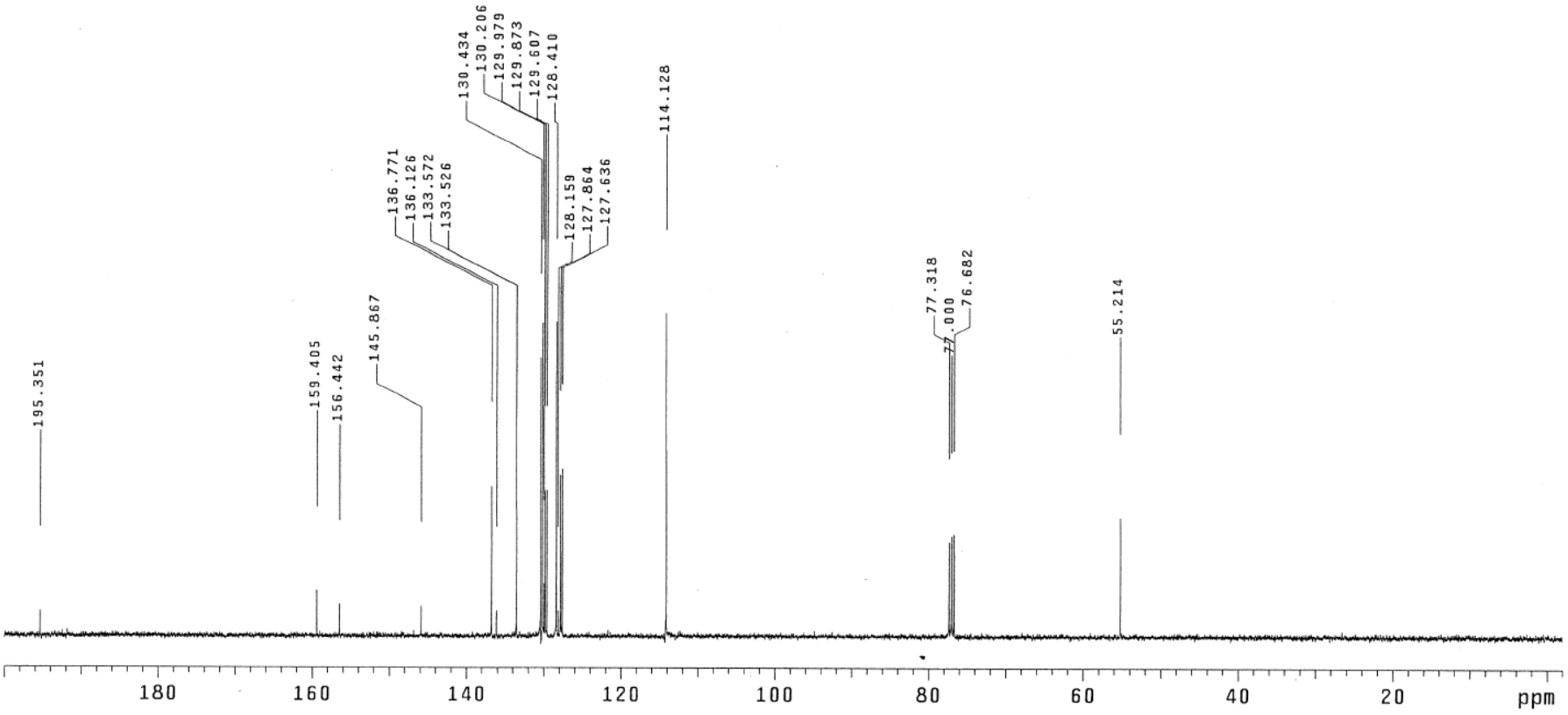
WKY-H-OMe-1e

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Sep 5 2012
Solvent: CDCl3
Ambient temperature
Total 3120 repetitions



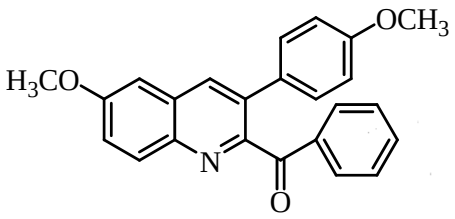
14a



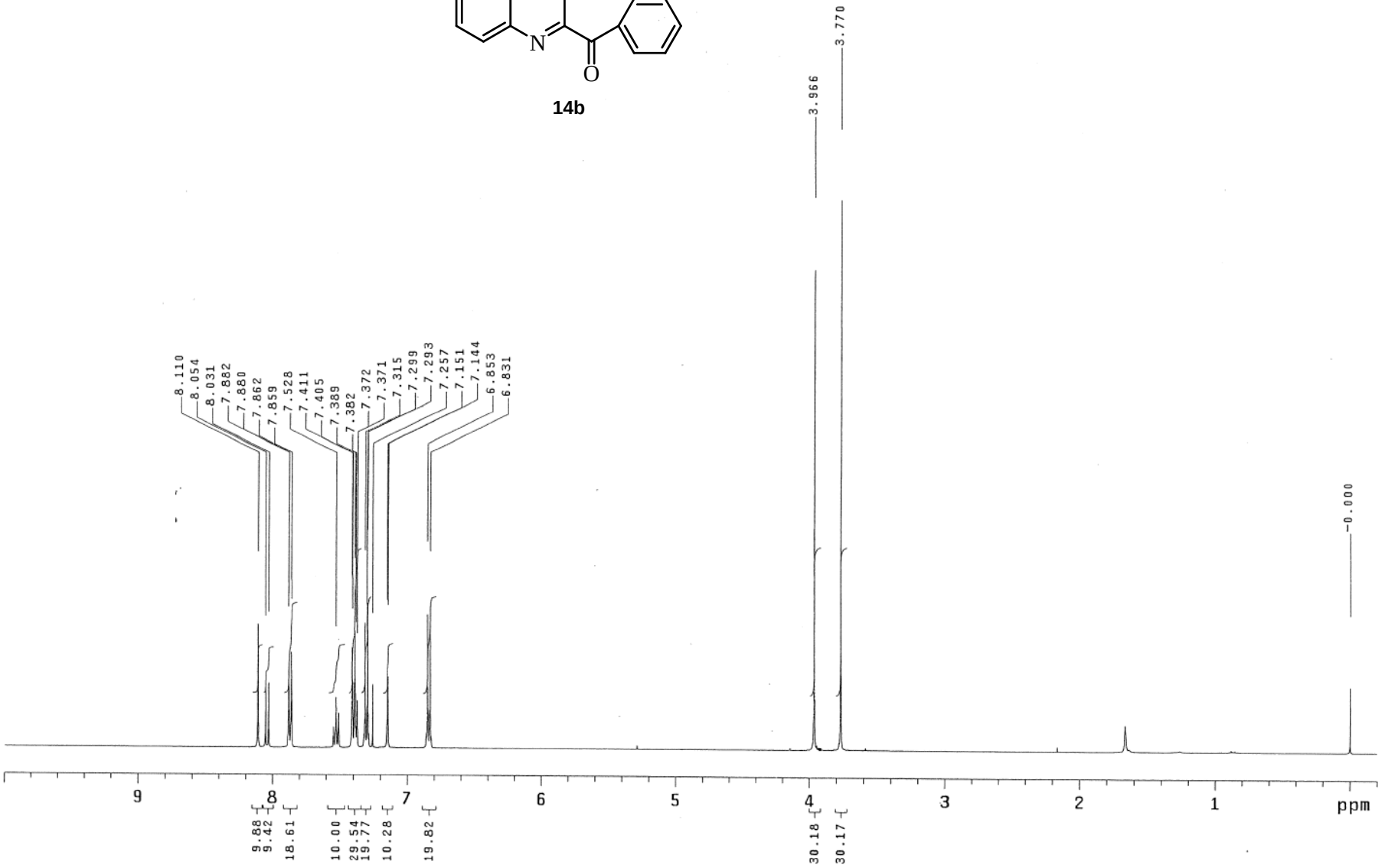
WKY-OMe-OMe-18b

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 24 2012
Solvent: CDCl3
Ambient temperature
Total 32 repetitions



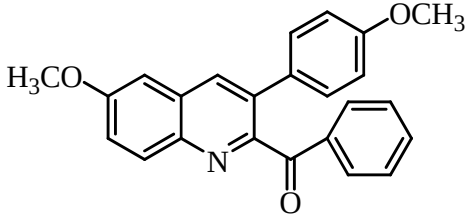
14b



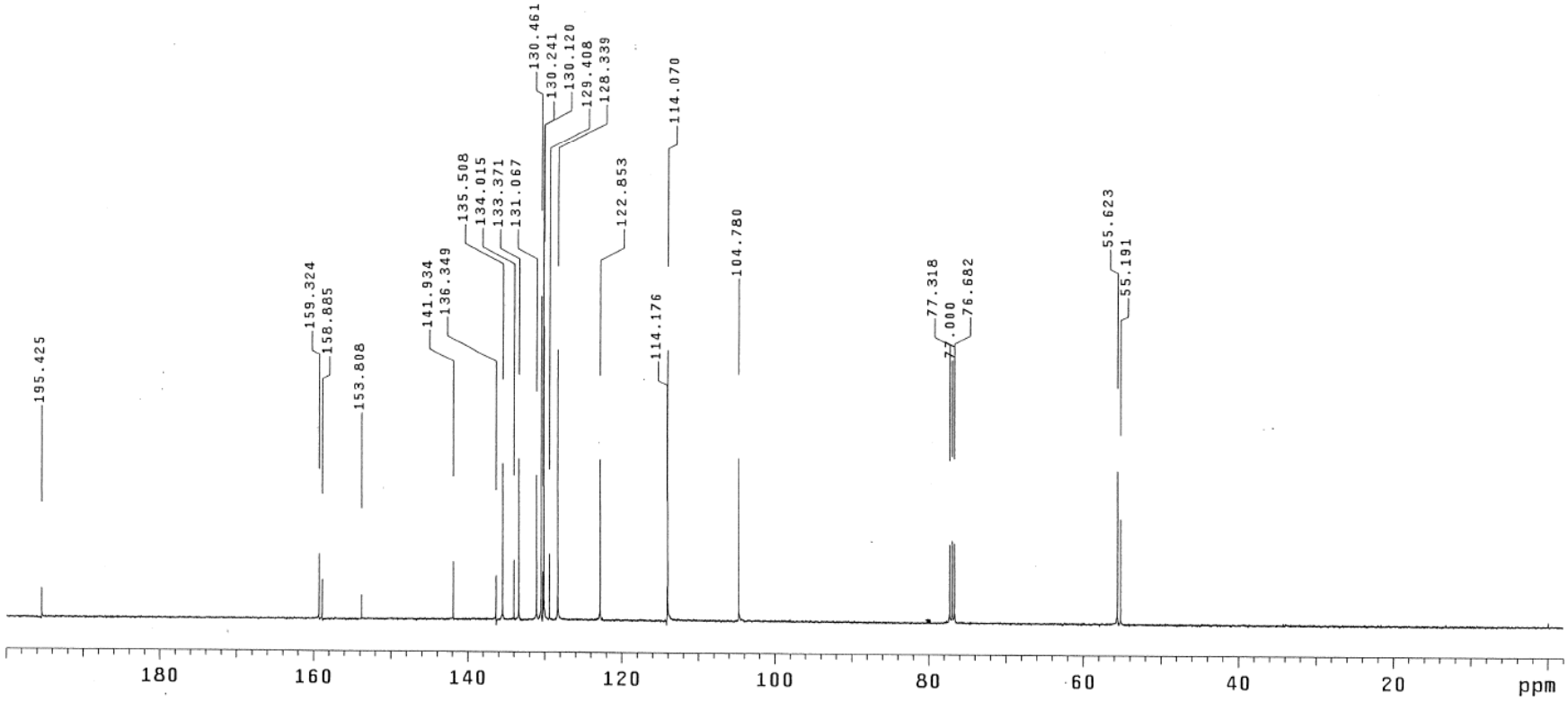
WKT-OMe-OMe-18b

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 24 2012
Solvent: CDCl3
Ambient temperature
Total 288 repetitions



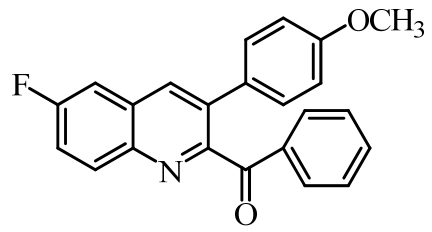
14b



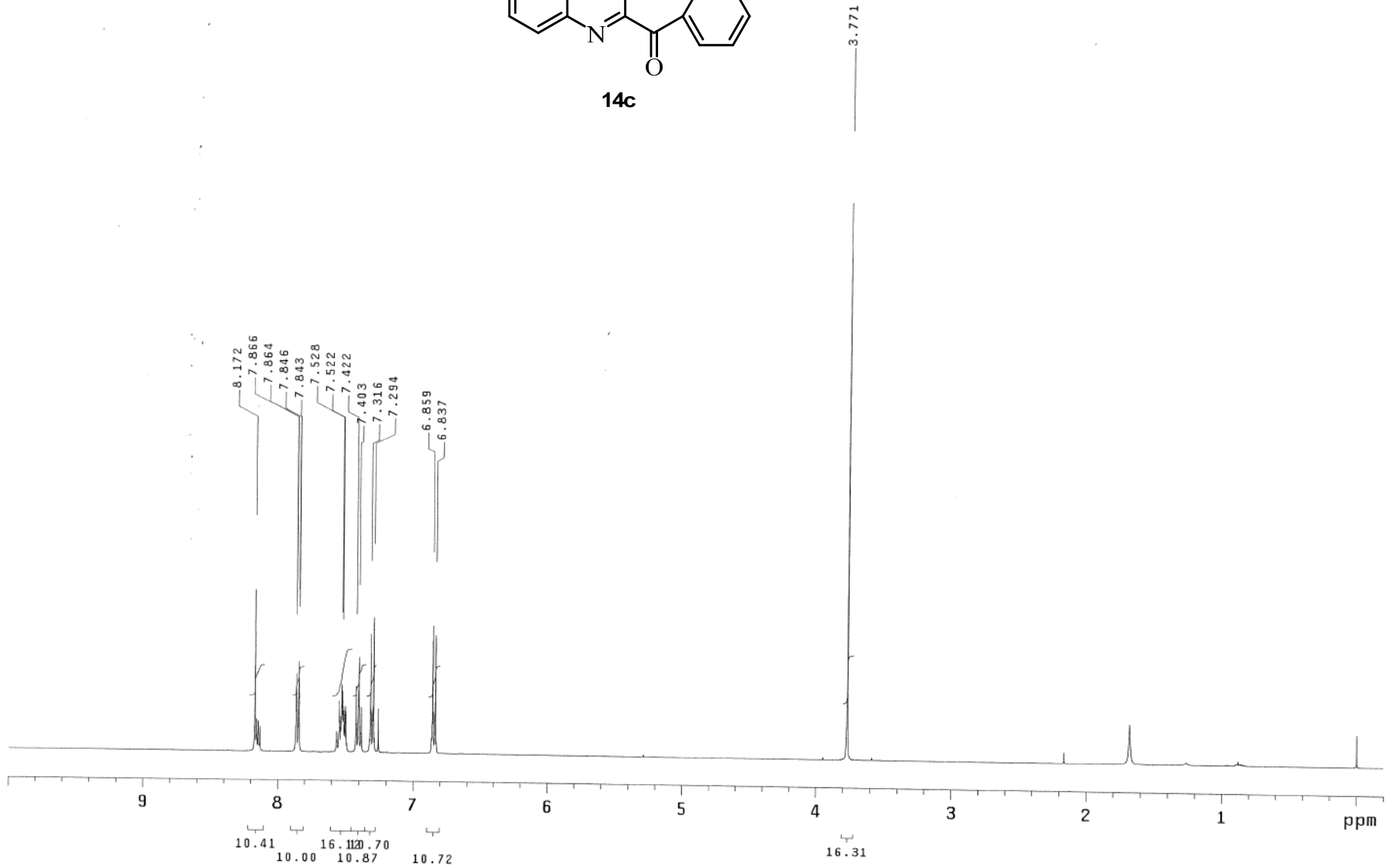
WKY-F-OMe-18c

Pulse Sequence: s2pul

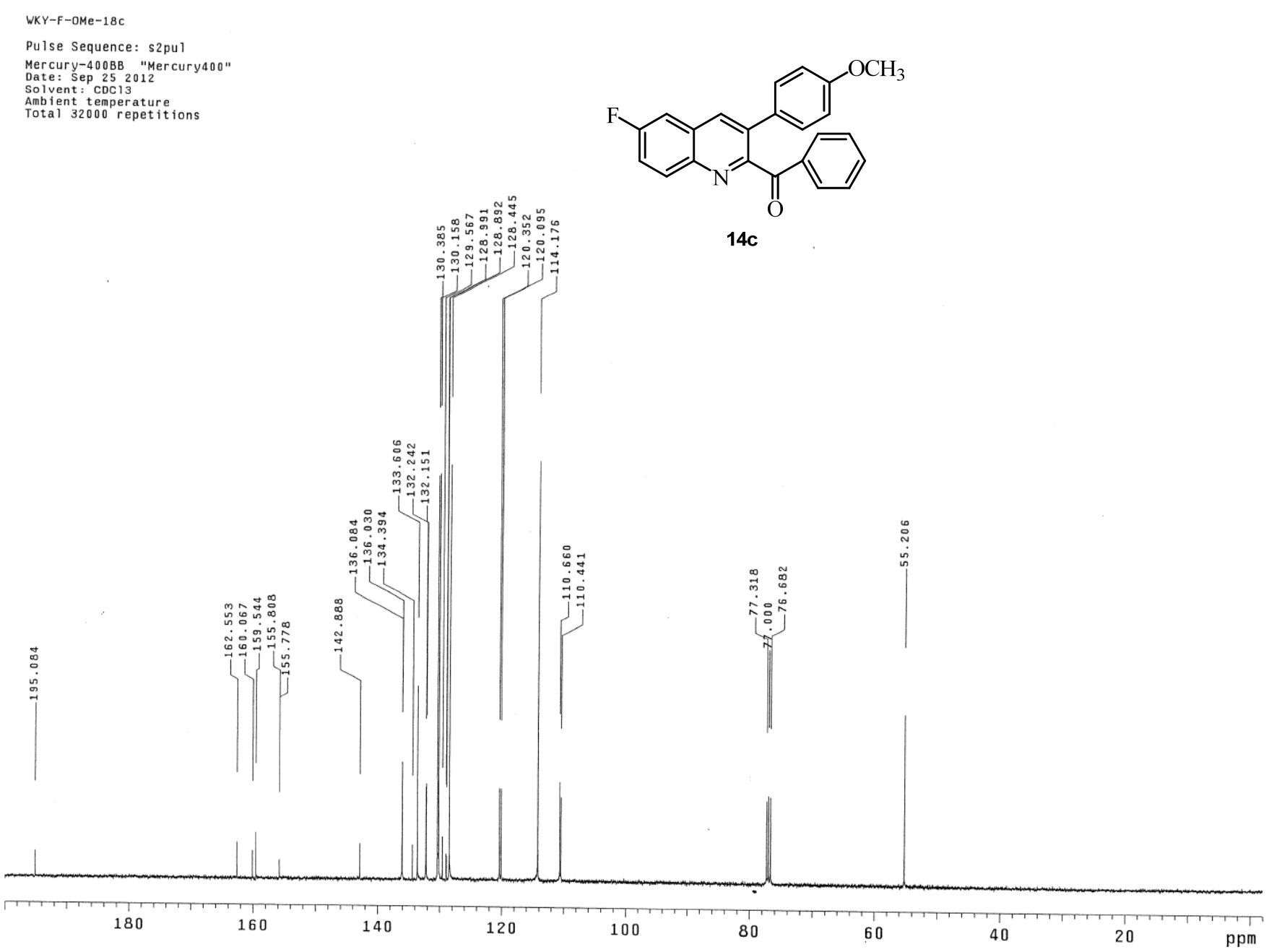
Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 32 repetitions



14c

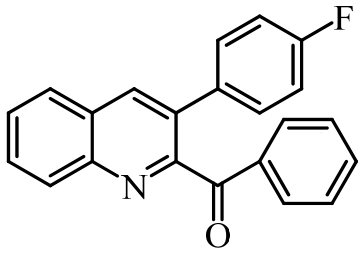


ACCEPTED MANUSCRIPT

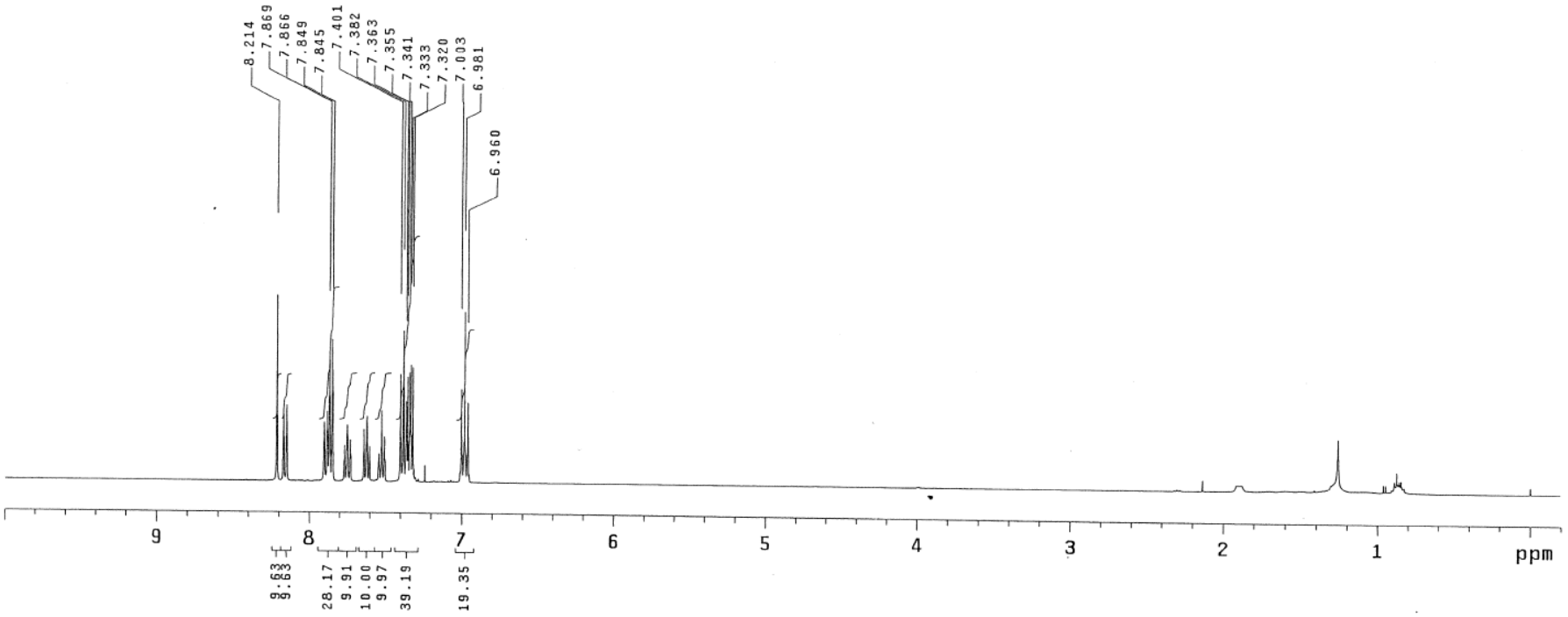


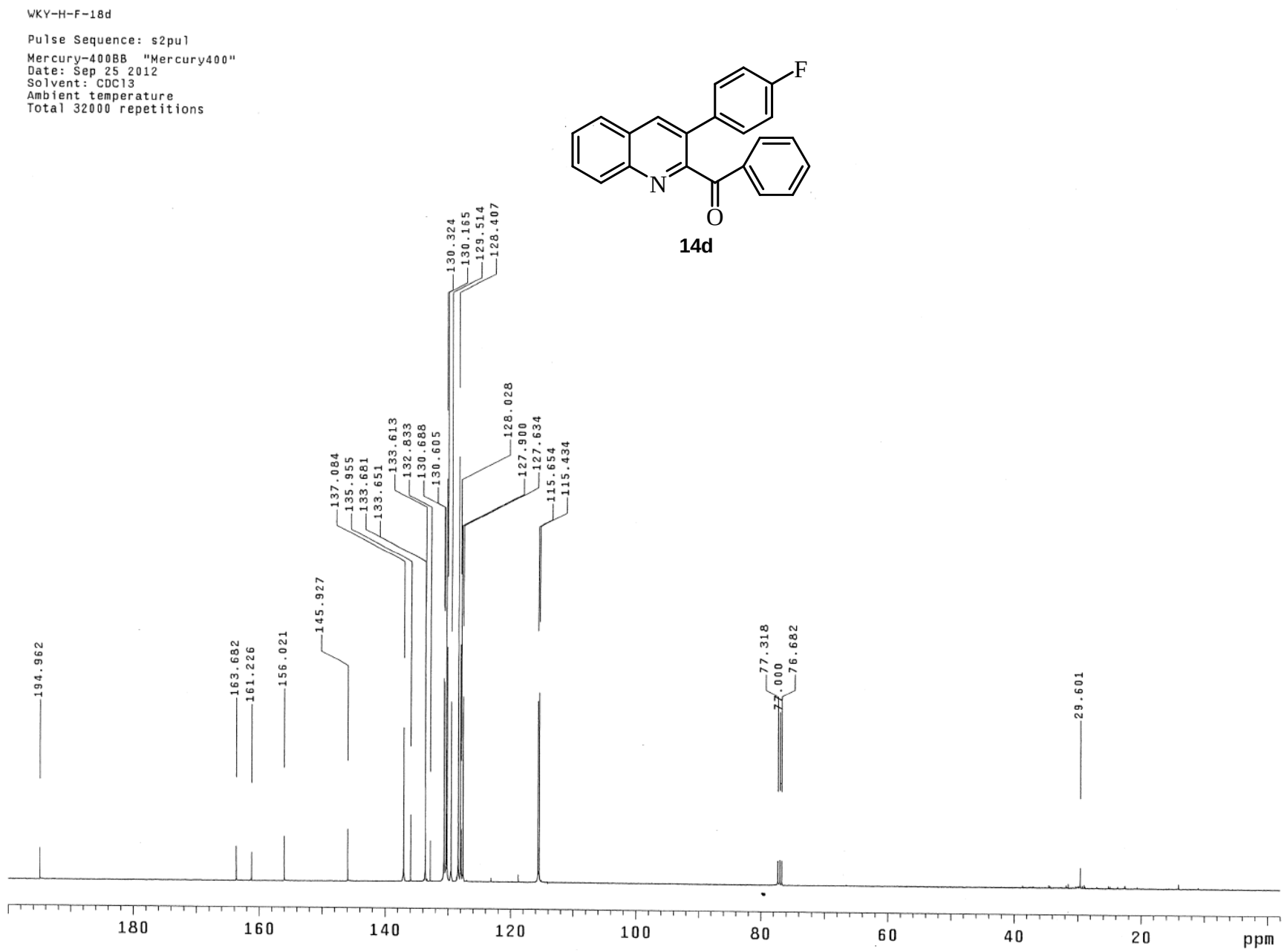
WKY-H-F-18d

Pulse Sequence: s2pul
Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 32 repetitions



14d

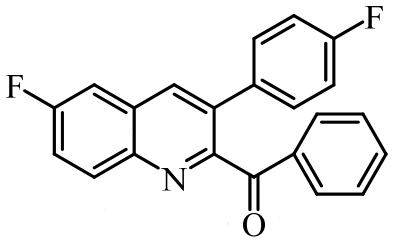



WKY-H-F-18d
Pulse Sequence: s2pul
Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 32000 repetitions
F
N
O
14d
194.962
163.682
161.226
156.021
145.927
137.084
135.955
133.681
133.651
133.613
132.833
130.688
130.605
130.324
130.165
129.514
128.407
128.028
127.900
127.634
115.654
115.434
77.318
77.000
76.682
29.601
180
160
140
120
100
80
60
40
20
ppm

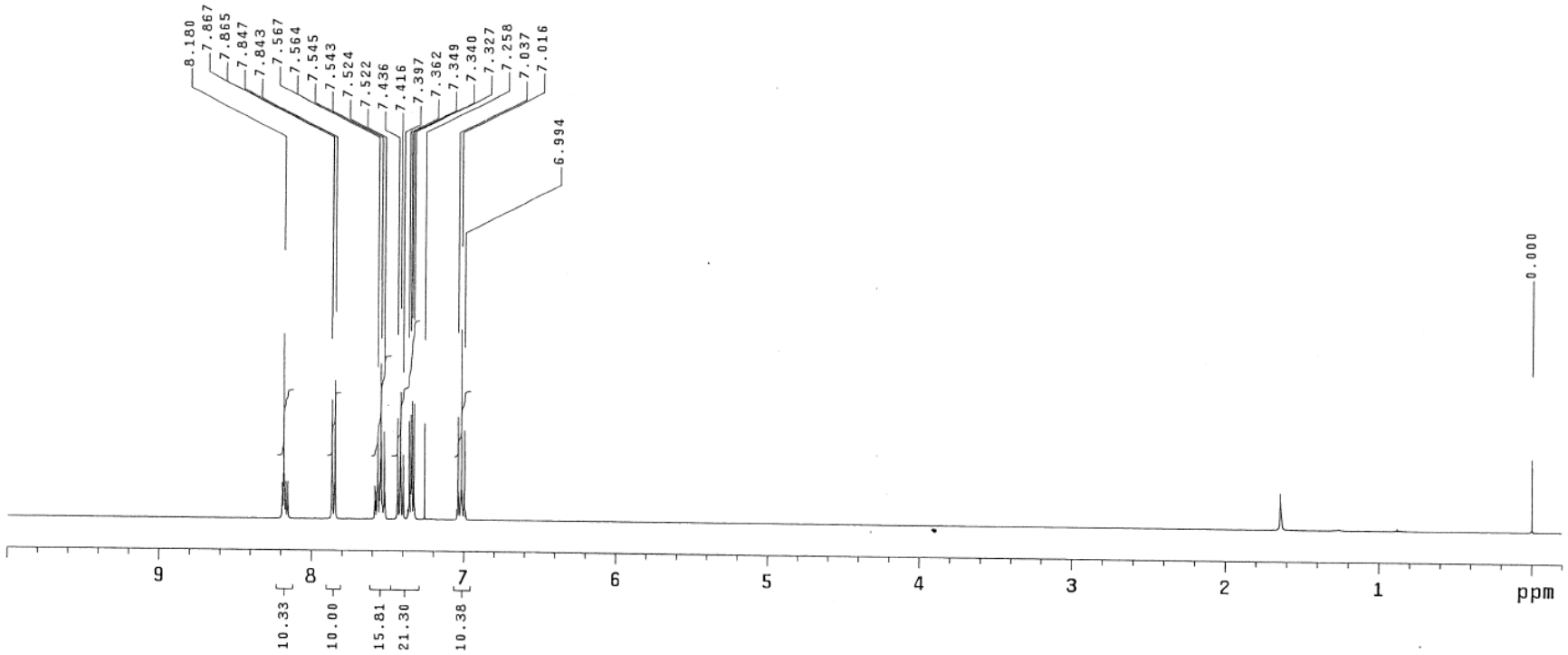
WKY-F-F-18e

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 64 repetitions



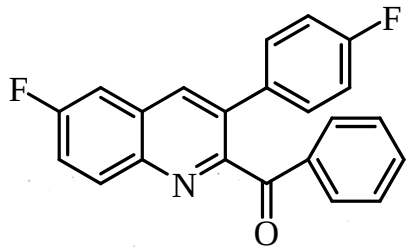
14e



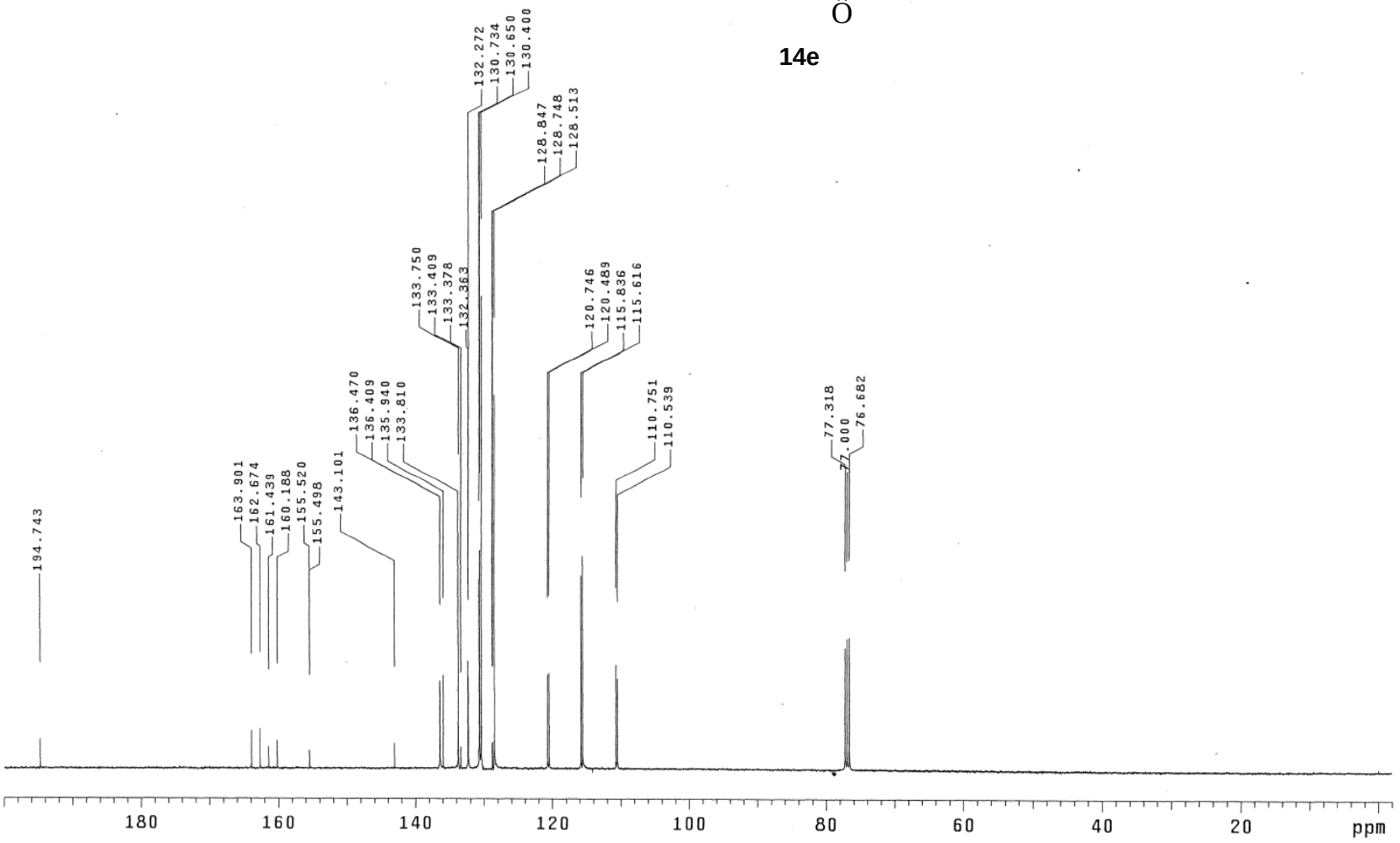
WKY-F-F-18e

Pulse Sequence: s2pul

Mercury-400BB "Mercury400"
Date: Sep 25 2012
Solvent: CDCl3
Ambient temperature
Total 32000 repetitions

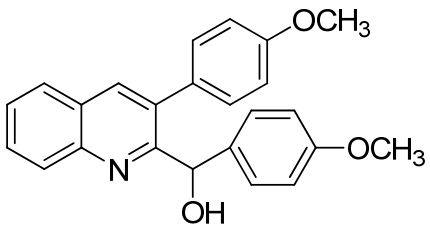


14e



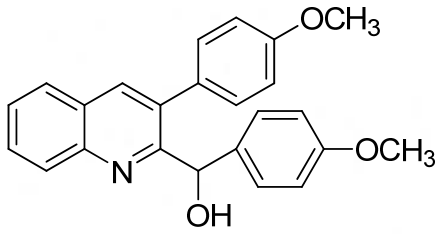
CTC-4334

Mercury-400BB "Mercuryplus400"
Date: Feb 22 2012
Solvent: CDCl3
Ambient temperature
Total 32 repetitions

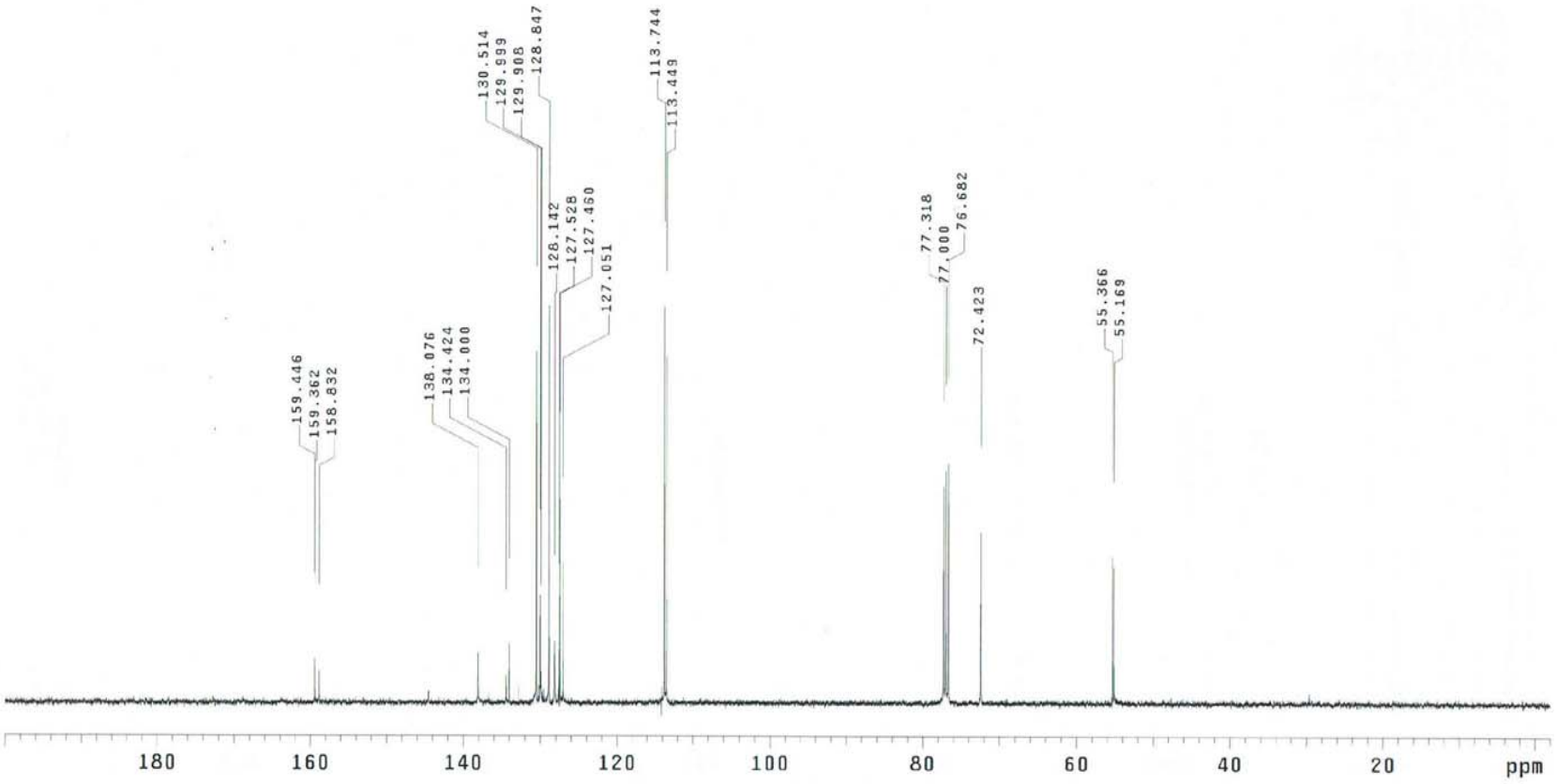


15a

Mercury-400BB Mercuryplus400
Date: Feb 22 2012
Solvent: CDCl3
Ambient temperature
Total 3744 repetitions

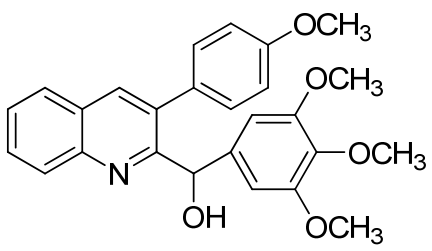


15a



CTC-4337

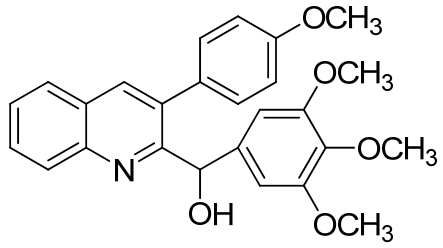
Mercury-400BB "Mercuryplus400"
Date: Feb 22 2012
Solvent: CDCl3
Ambient temperature
Total 64 repetitions



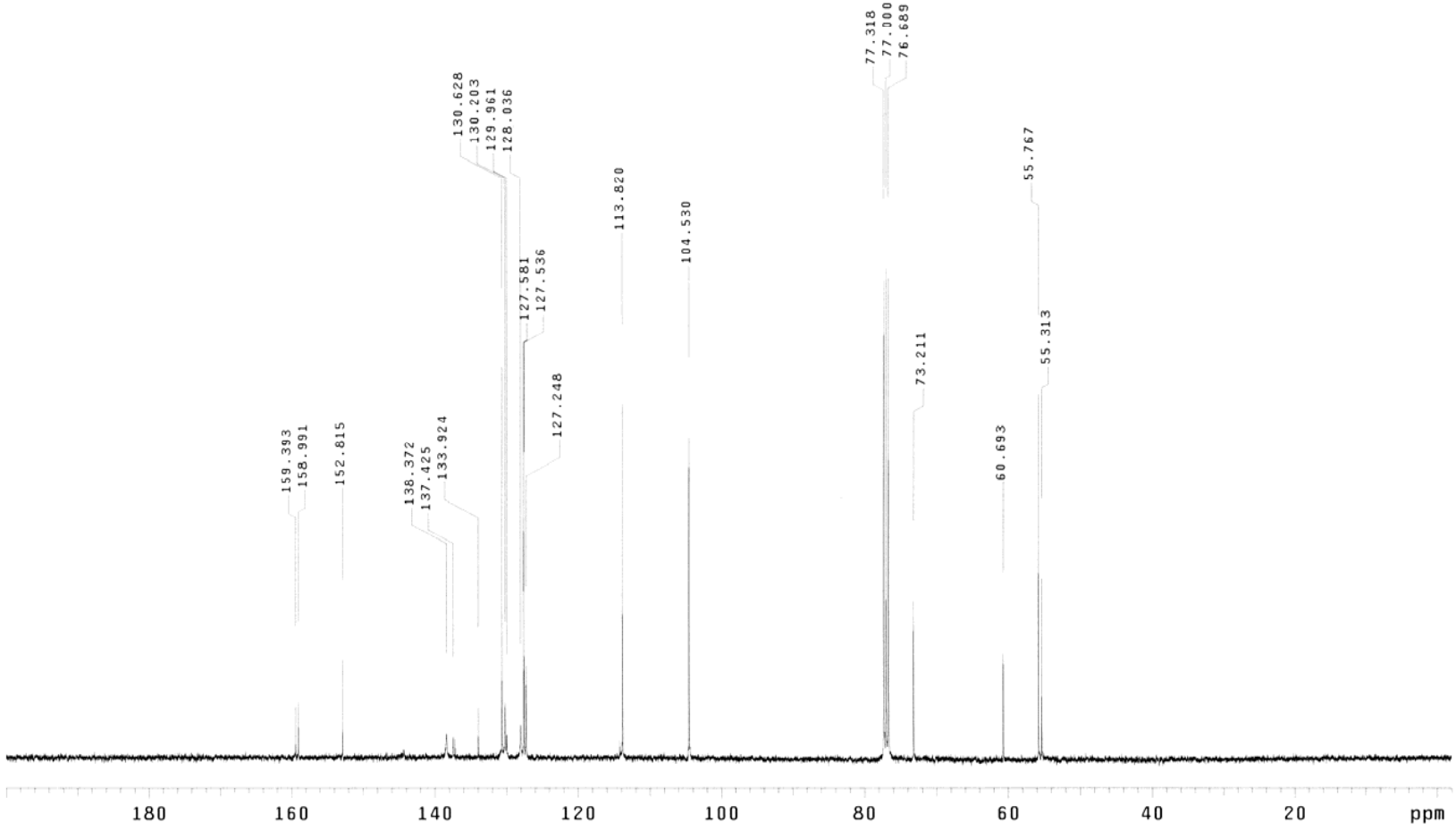
15b

CTC-4337

Mercury-400BB "Mercuryplus400"
Date: Feb 22 2012
Solvent: CDCl3
Ambient temperature
Total 6352 repetitions

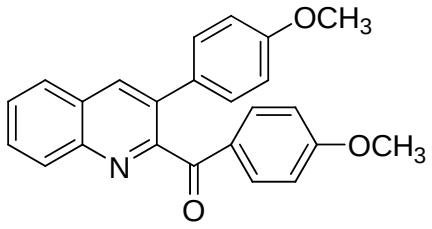


15b



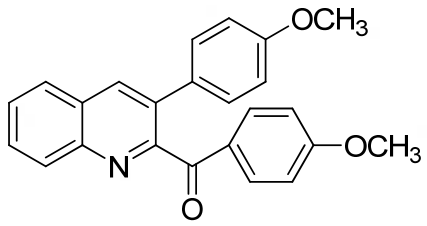
2pyl2OMe 4335

Mercury-400BB "Mercuryplus400"
Date: Apr 20 2011
Solvent: CDCl3
Ambient temperature
Total 64 repetitions

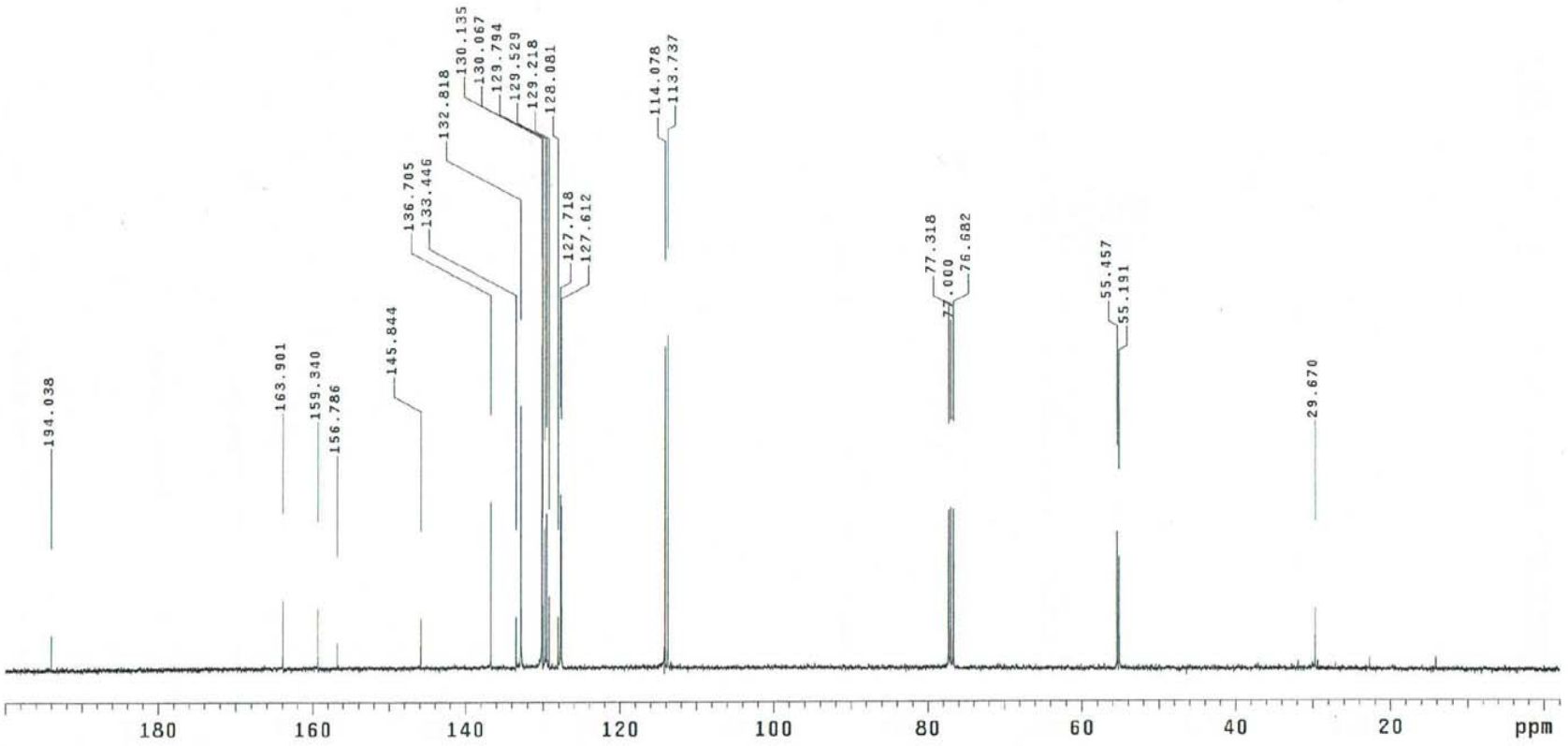


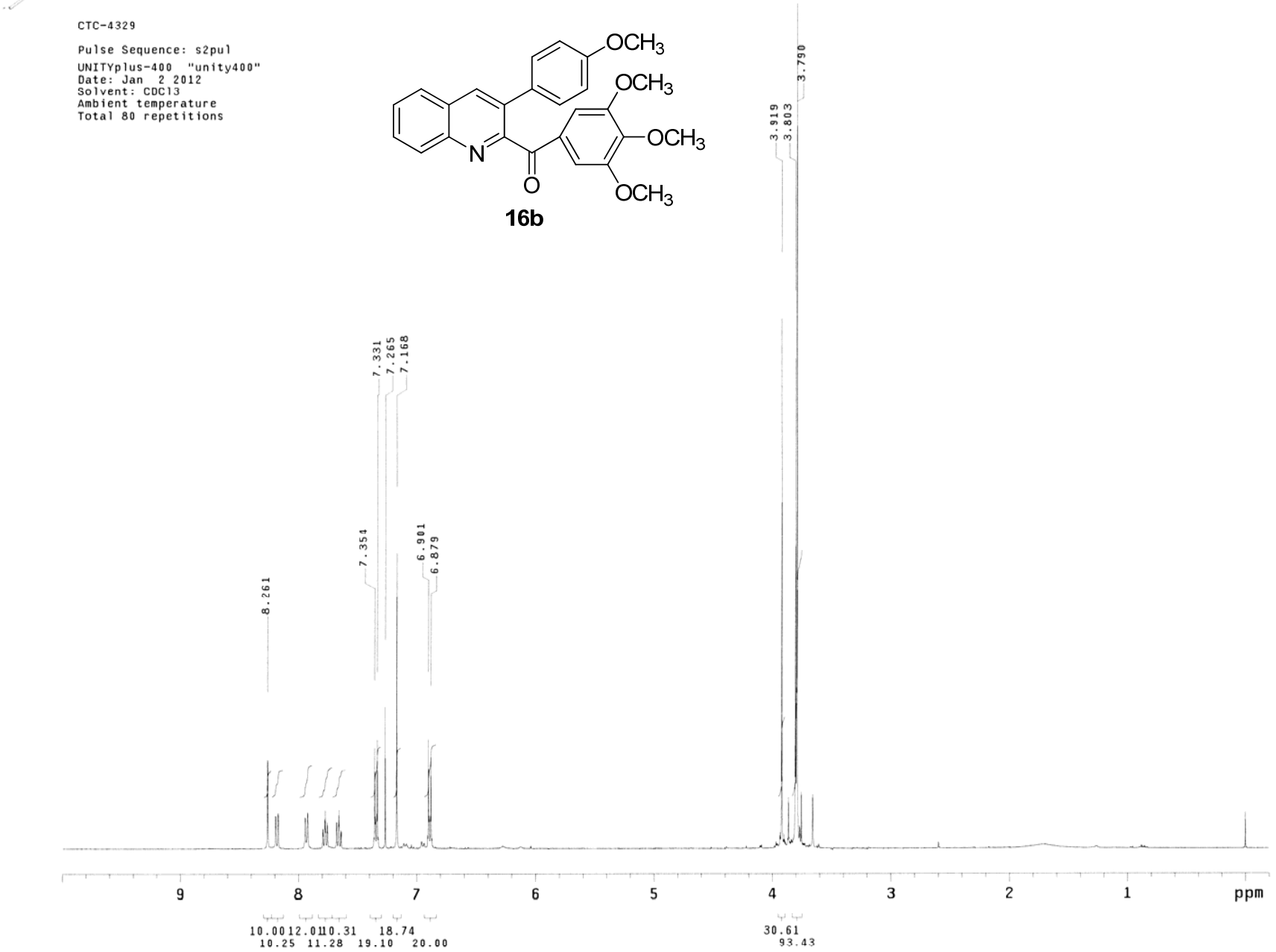
16a

Mercury-400BB "Mercuryplus400"
Date: Apr 20 2011
Solvent: CDCl3
Ambient temperature
Total 1424 repetitions



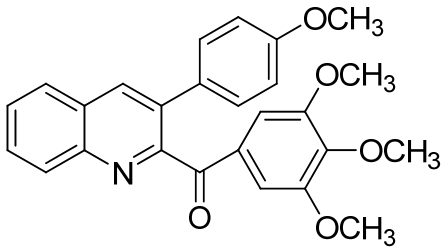
16a



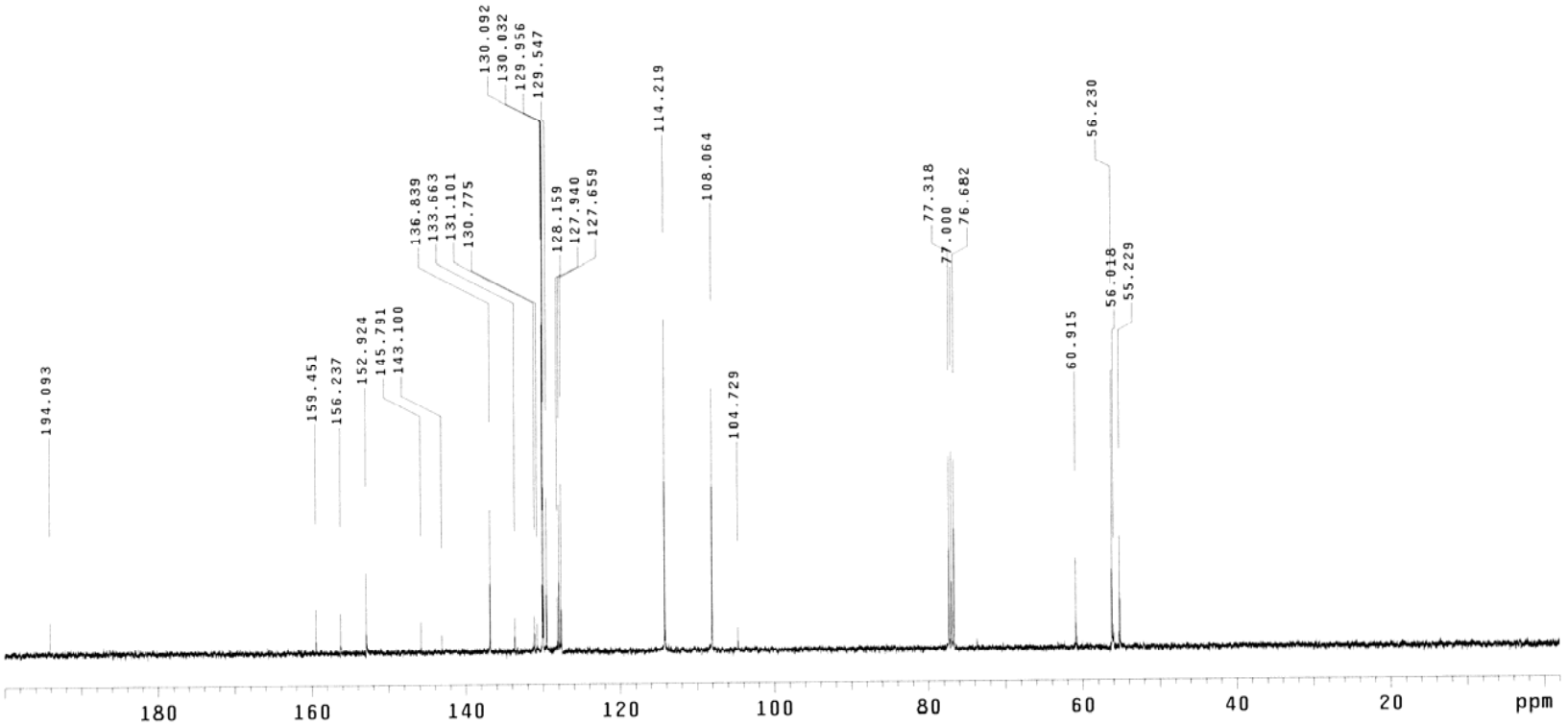

CTC-4329
Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Jan 2 2012
Solvent: CDCl3
Ambient temperature
Total 80 repetitions
OCH3
OCH3
OCH3
OCH3
N
O
16b
8.261
7.354
7.331
7.265
7.168
6.901
6.879
3.919
3.803
3.790
9
8
7
6
5
4
3
2
1
ppm
10.00 12.01 10.31 18.74
10.25 11.28 19.10 20.00
30.61
93.43

CTC-4329

Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Jan 2 2012
Solvent: CDCl3
Ambient temperature
Total 4160 repetitions

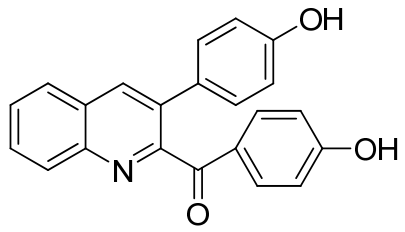


16b

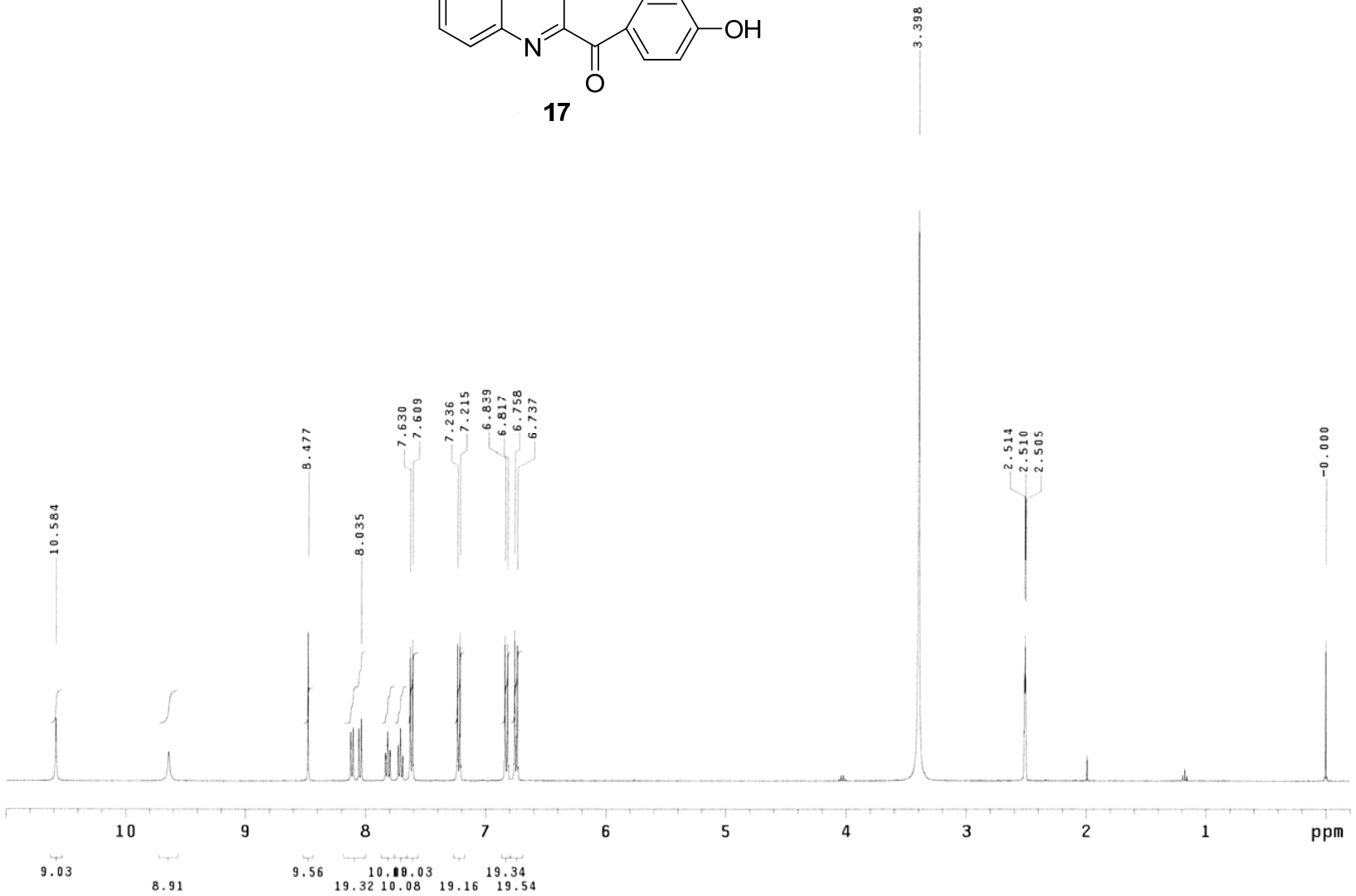


CTC-4336

Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Feb 22 2012
Solvent: DMSO
Ambient temperature
Total 68 repetitions

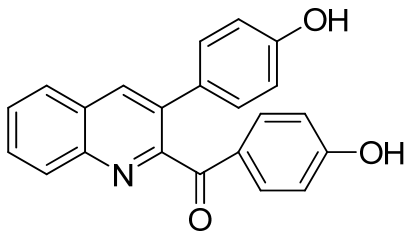


17

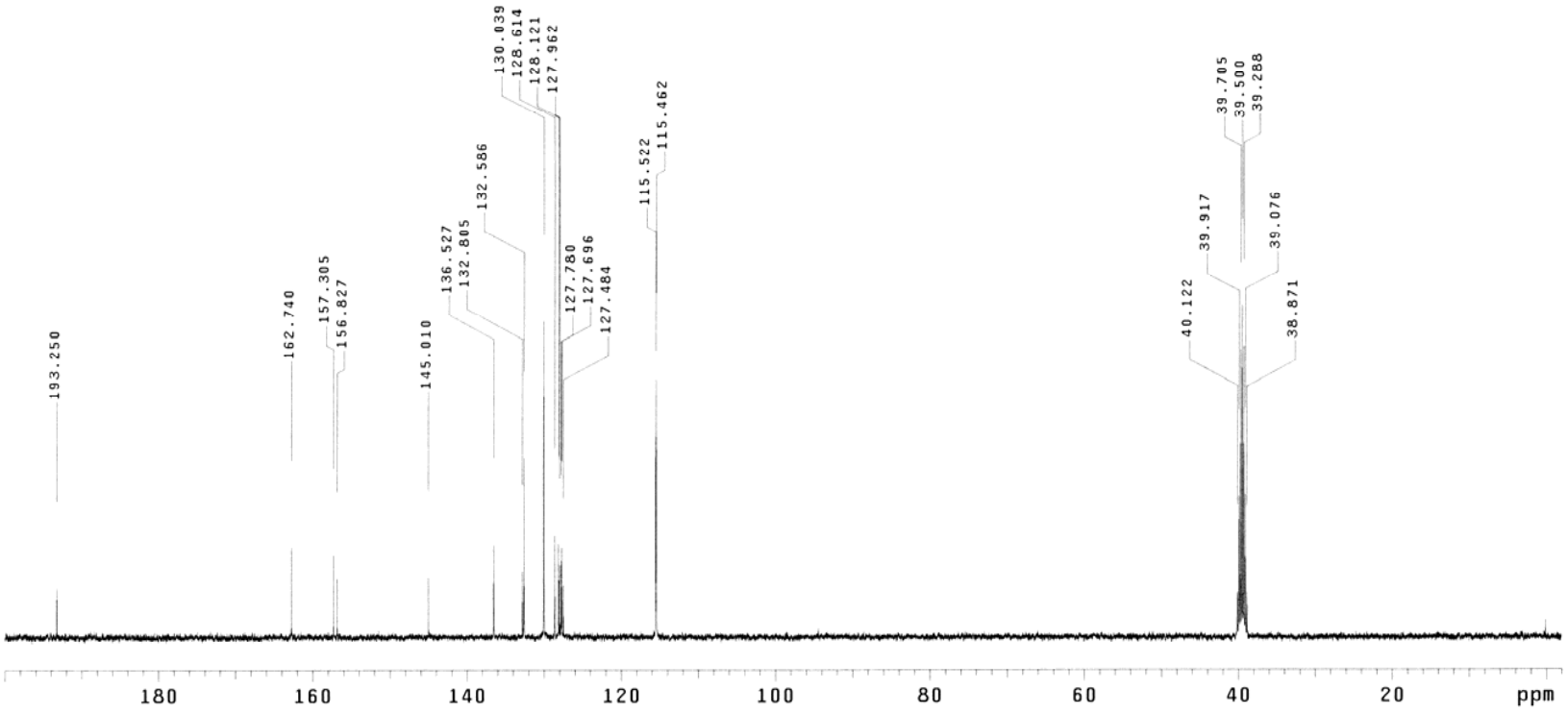


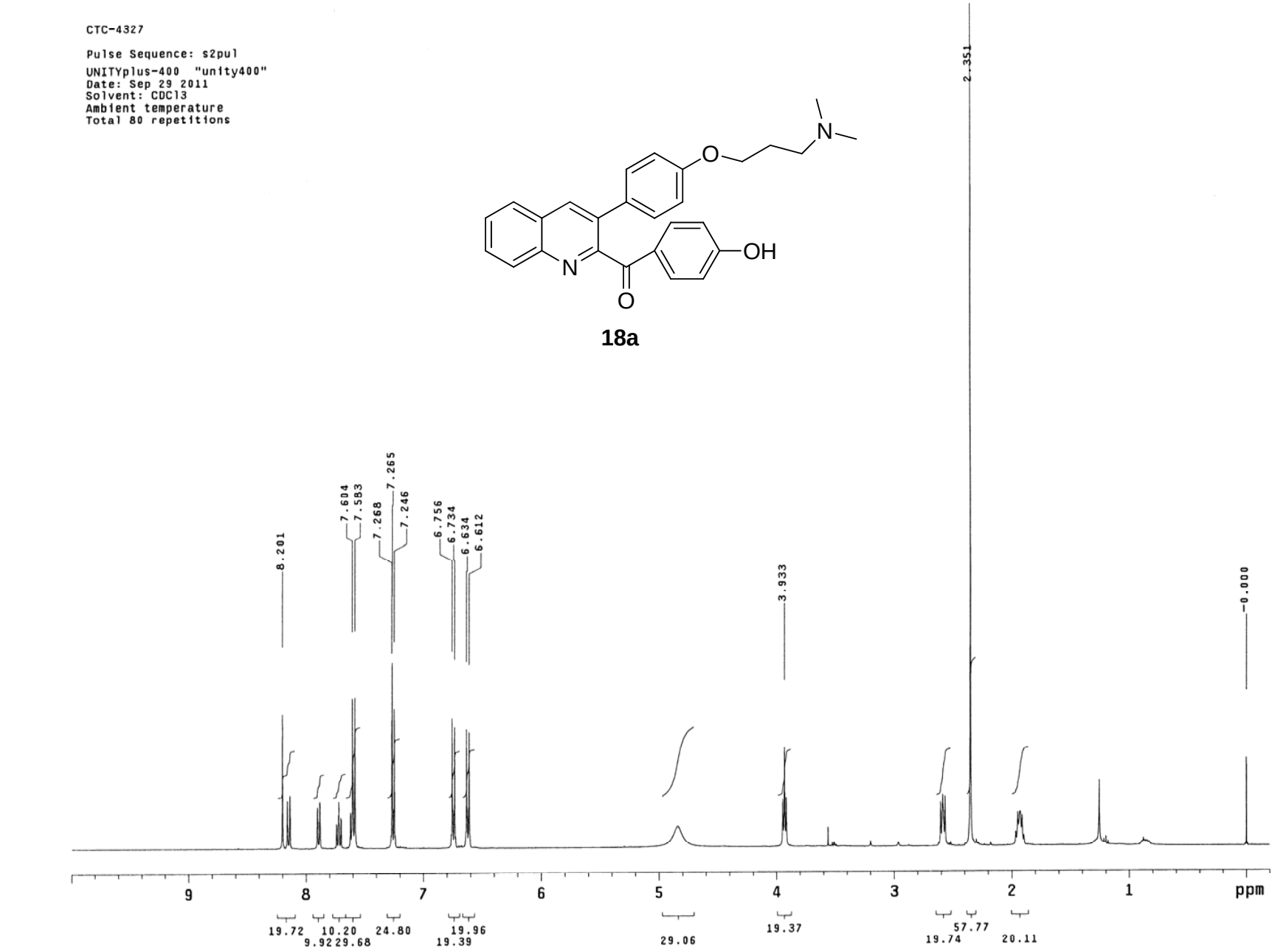
CTC-4336

Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Feb 22 2012
Solvent: DMSO
Ambient temperature
Total 2400 repetitions



17



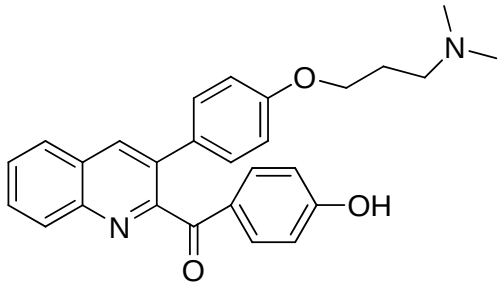

CTC-4327
Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Sep 29 2011
Solvent: CDCl3
Ambient temperature
Total 80 repetitions
N
O
OH
N
O
18a
2.351
8.201
7.604
7.583
7.268
7.265
7.246
6.756
6.734
6.634
6.612
3.933
-0.000
9
8
7
6
5
4
3
2
1
ppm
19.72
10.20
9.92
29.68
24.80
19.96
19.39
29.06
19.37
19.74
57.77
20.11

ACCEPTED MANUSCRIPT

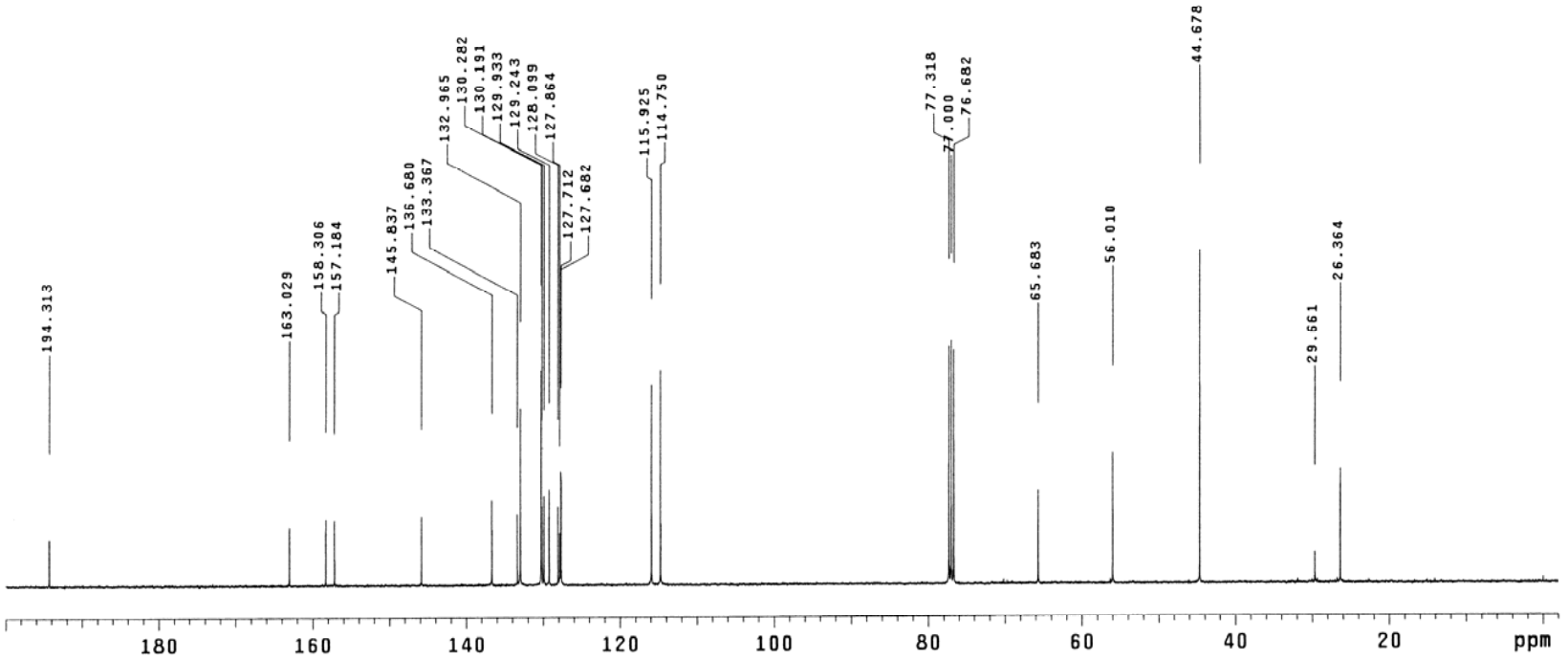
CTC-4327

Pulse Sequence: s2pul

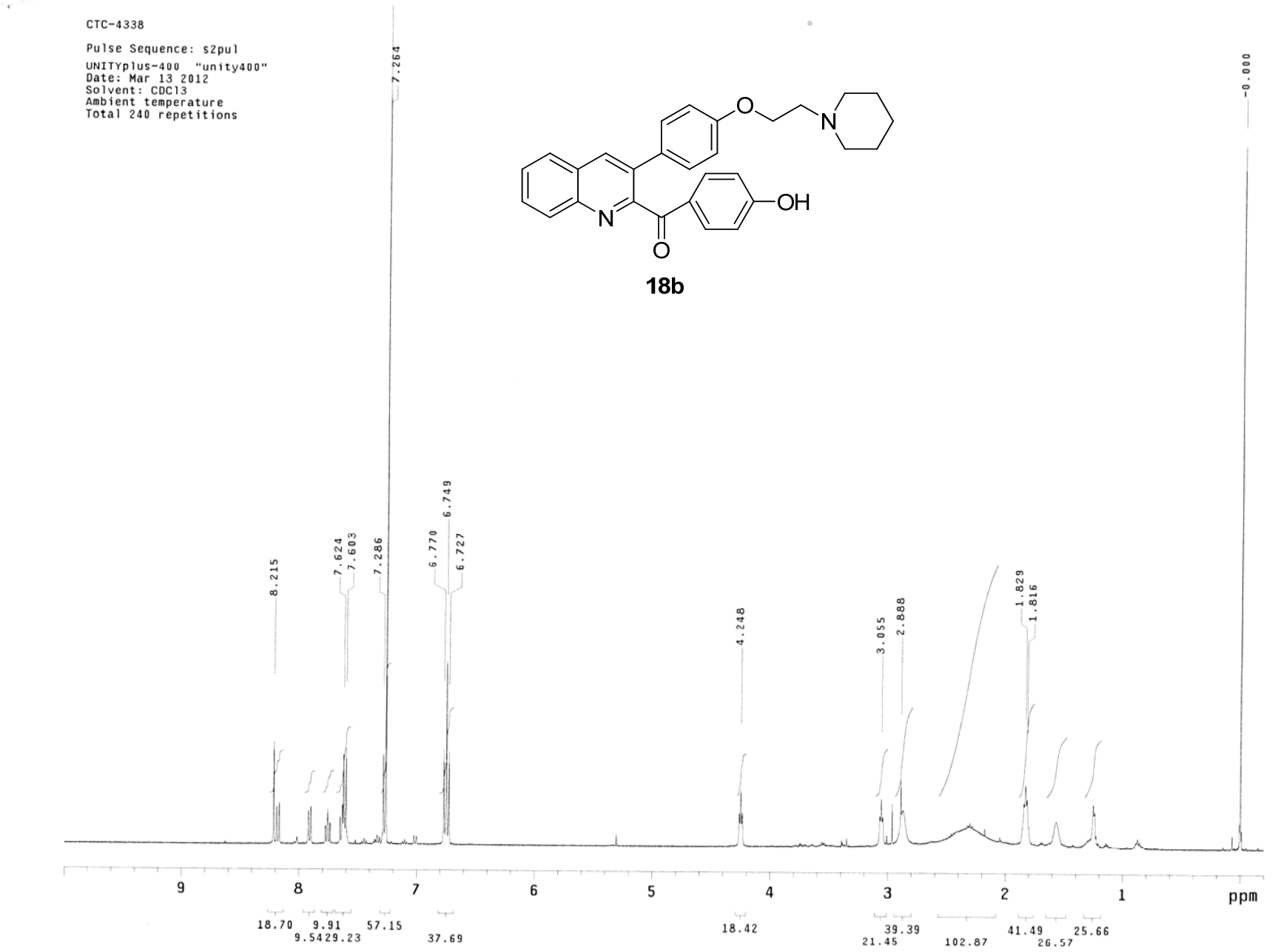
UNITYplus-400 "unity400"
Date: Sep 29 2011
Solvent: CDCl3
Ambient temperature
Total 16000 repetitions



18a



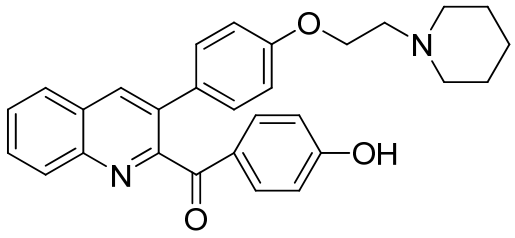
ACCEPTED MANUSCRIPT



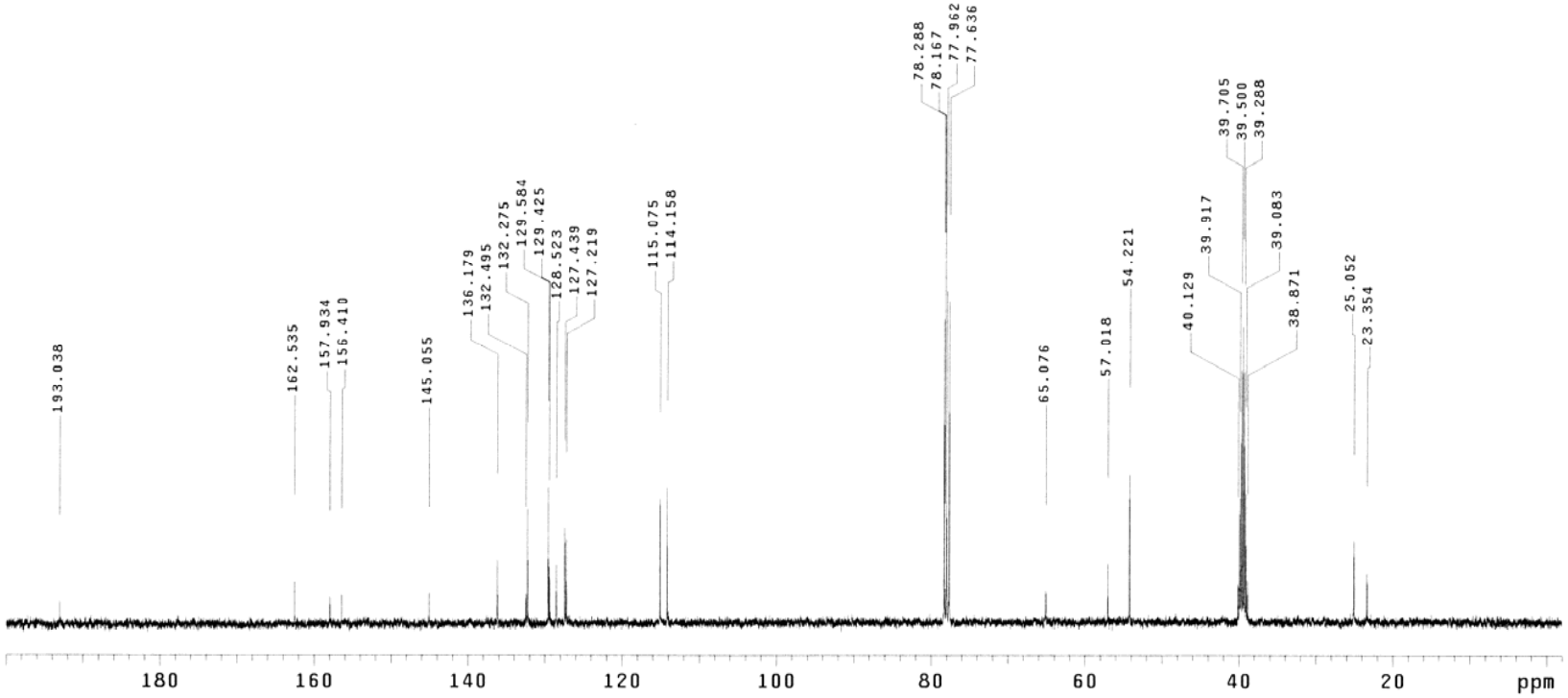
18b

CTC-4338

Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Mar 13 2012
Solvent: DMSO
Ambient temperature
Total 7168 repetitions



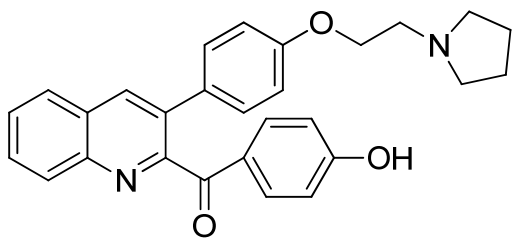
18b



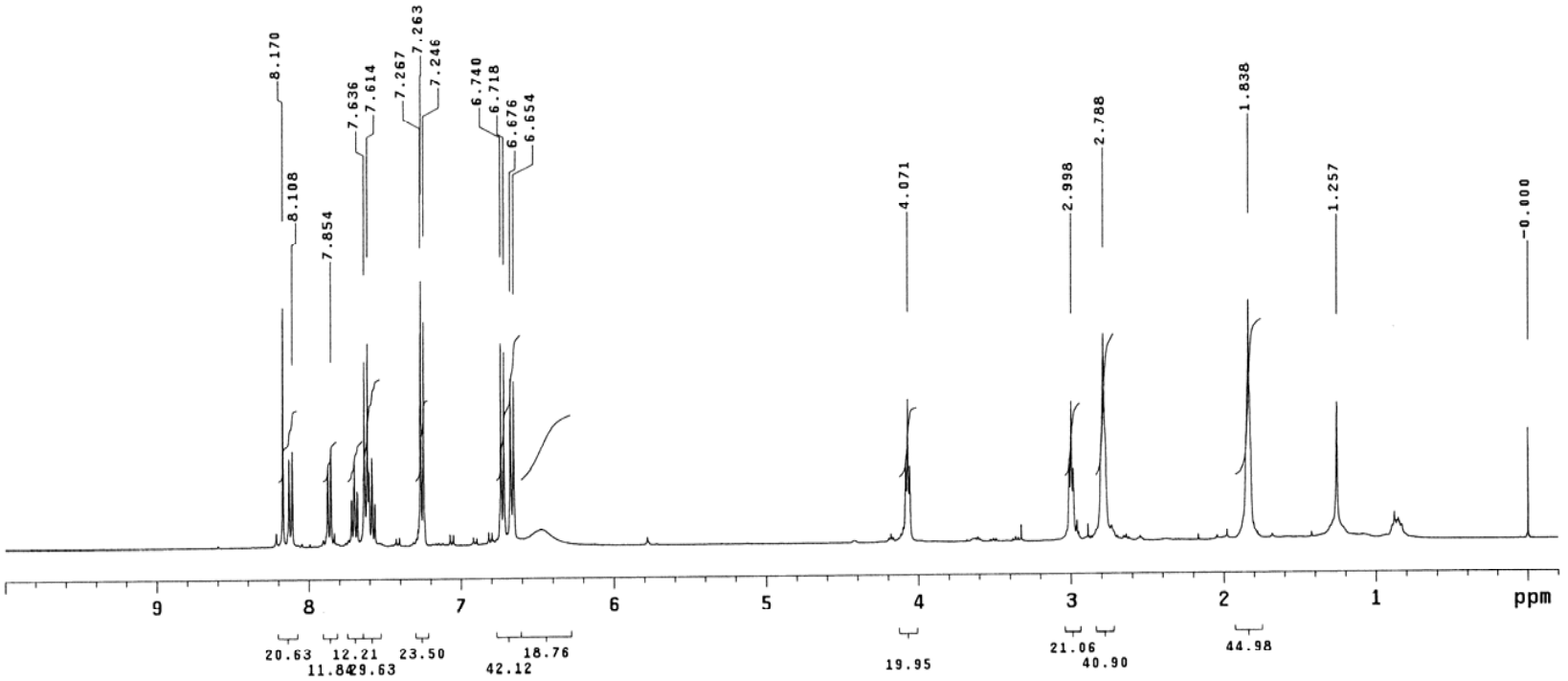
CTC-4328

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Oct 13 2011
Solvent: CDCl3
Ambient temperature
Total 48 repetitions



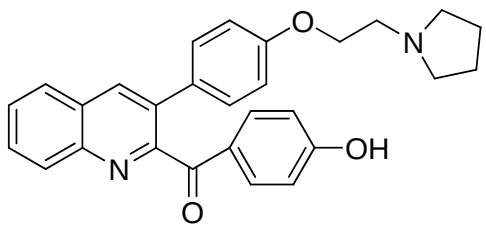
18c



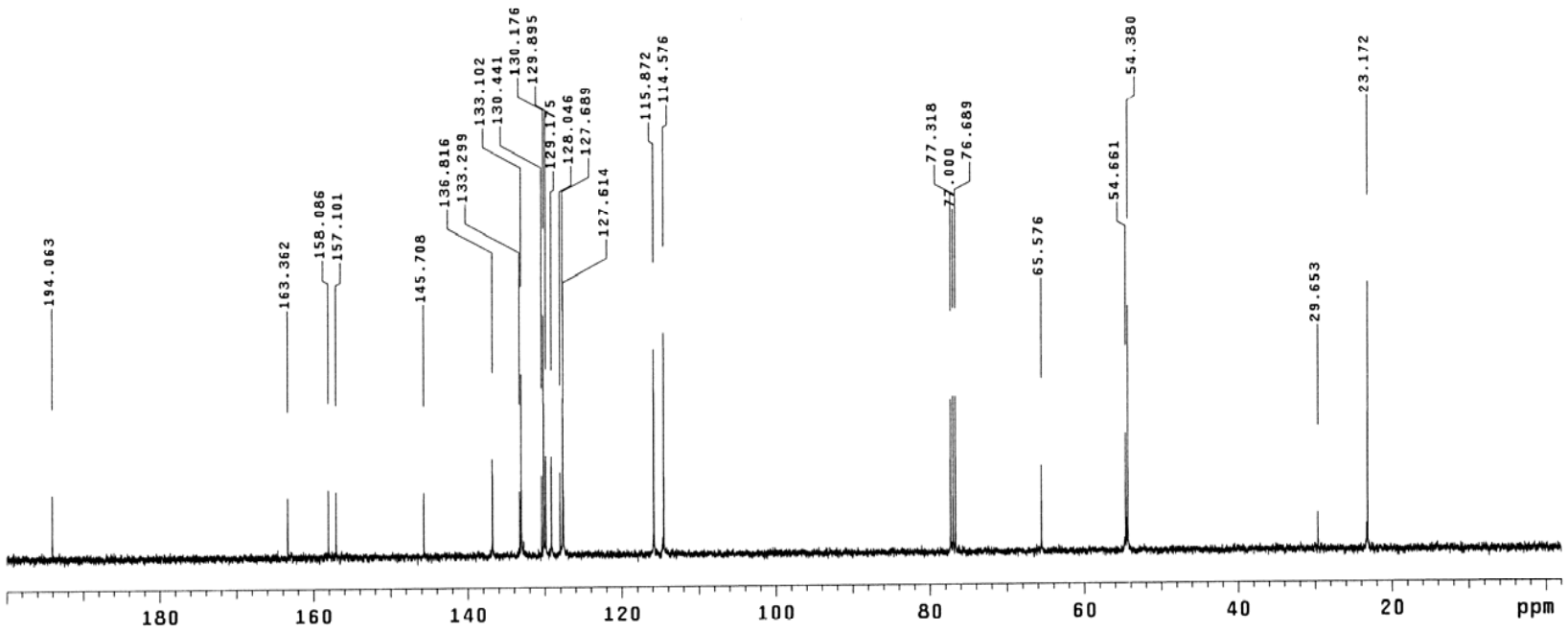
CTC-4328

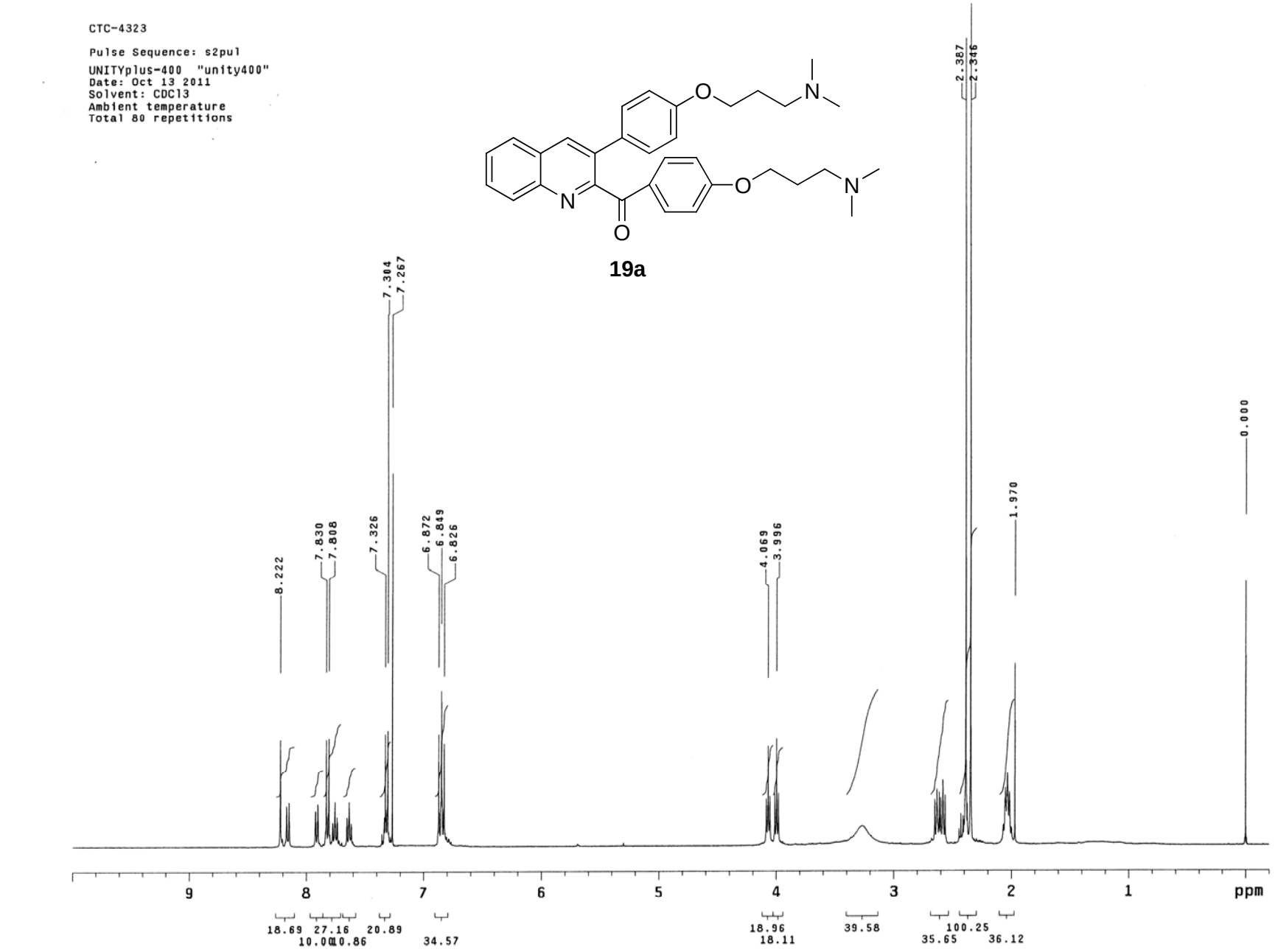
Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Oct 13 2011
Solvent: CDCl3
Ambient temperature
Total 1872 repetitions



18c

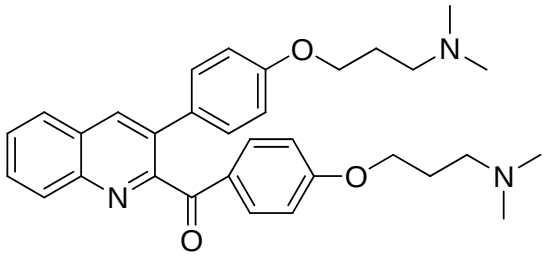



CTC-4323
Pulse Sequence: s2pul
UNITYplus-400 "unity400"
Date: Oct 13 2011
Solvent: CDCl3
Ambient temperature
Total 80 repetitions
O
N
O
N
O
19a
2.387
2.346
7.304
7.267
8.222
7.830
7.808
7.326
6.872
6.849
6.826
4.069
3.996
1.970
0.000
9
8
7
6
5
4
3
2
1
ppm
18.69
27.16
20.89
10.00
10.86
34.57
18.96
18.11
39.58
100.25
35.65
36.12

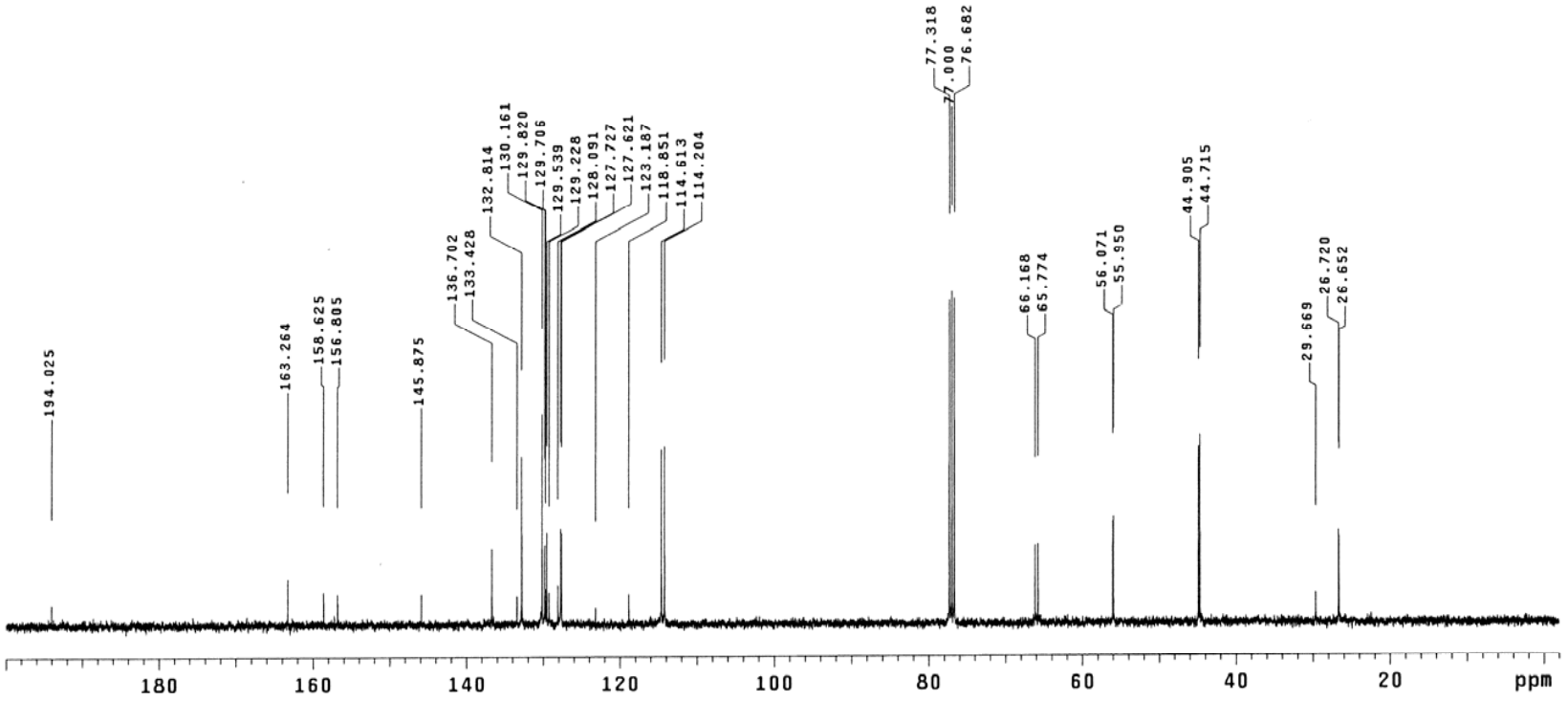
CTC-4323

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Oct 13 2011
Solvent: CDCl3
Ambient temperature
Total 5888 repetitions

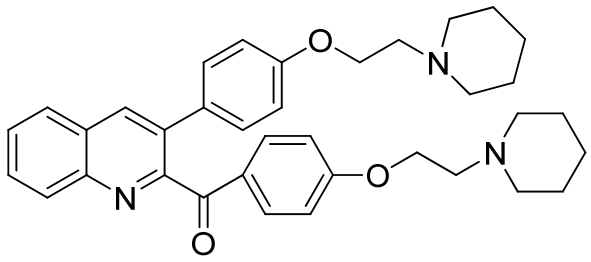


19a



STANDARD 1H OBSERVE
CTC-4321

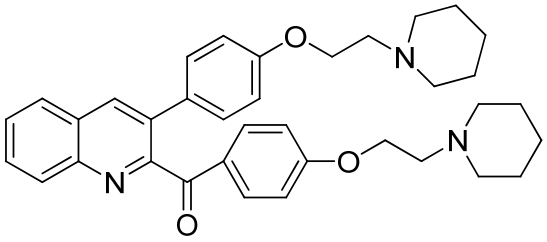
Mercury-400BB "Mercuryplus400"
Date: Aug 4 2011
Solvent: CDCl3
Ambient temperature
Total 80 repetitions



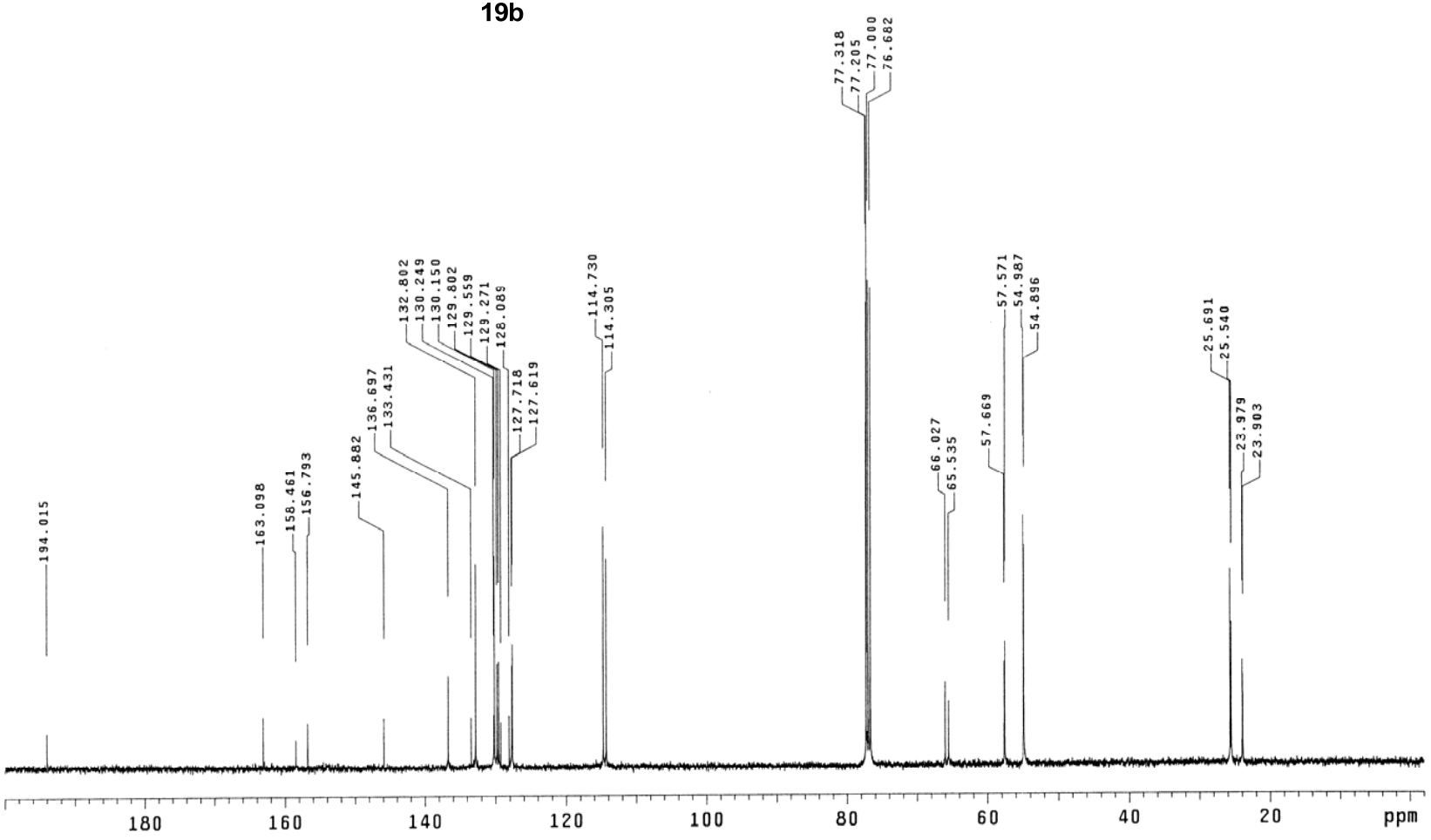
19b

CTC-4321

Mercury-400BB "Mercuryplus400"
Date: Aug 4 2011
Solvent: CDCl3
Ambient temperature
Total 1728 repetitions



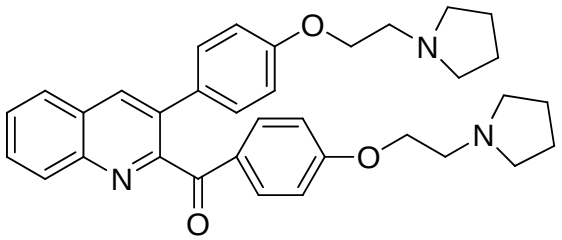
19b



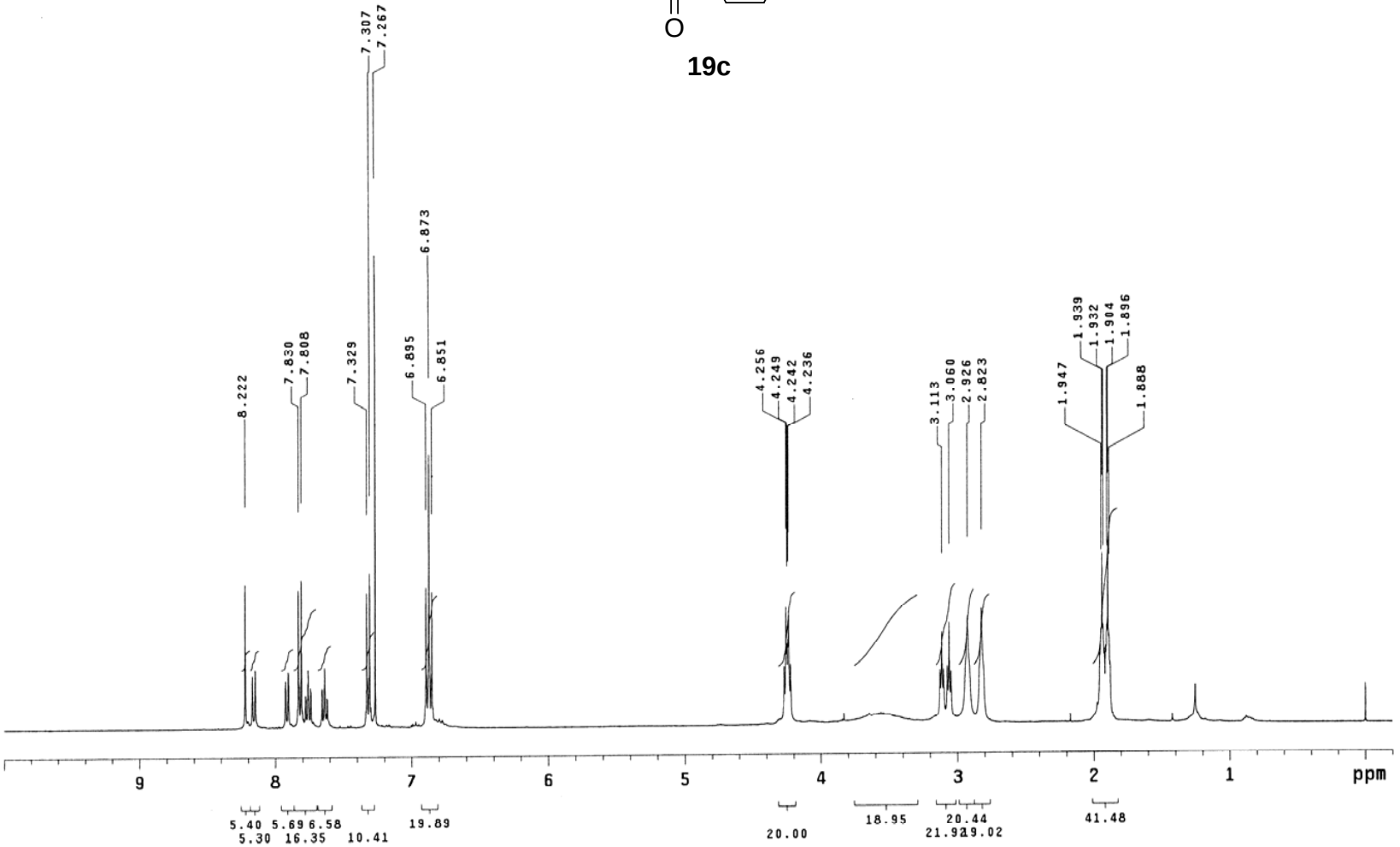
CTC-4319

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Jul 11 2011
Solvent: CDCl3
Ambient temperature
Total 160 repetitions



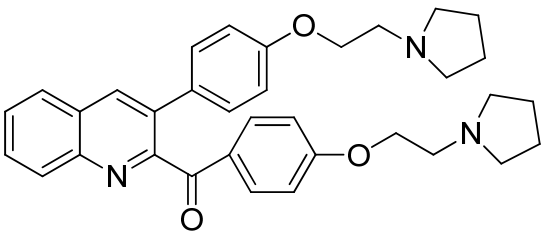
19c



CTC-4319

Pulse Sequence: s2pul

UNITYplus-400 "unity400"
Date: Jul 8 2011
Solvent: CDCl3
Ambient temperature
Total 32000 repetitions



19c