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Graphical Abstract

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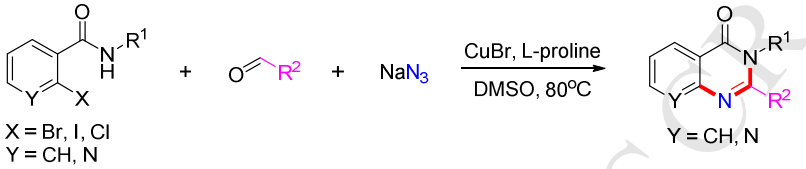

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ABSTRACT

An efficient and practical copper-catalyzed consecutive synthesis of quinazolin-4(3H)-ones and pyrido[2,3-d]pyrimidin-4(3H)-ones from easily available 2-halobenzamides (or 2-halonicotinamides), aldehydes, and sodium azide has been developed, which gave the corresponding target products in 50-95% yields for 29 examples. This remarkable consecutive process involved sequential copper-catalyzed S_NAr, reduction, cyclization, and oxidation. Notably, this work would provide a novel synthetic strategy for bioactive molecules containing quinazolinone class skeletons.

1. Introduction

Quinazolin-4(3H)-ones (**1**) are one of the most important fused nitrogen-containing heterocycles,[1] broadly occurring in many natural products and pharmaceutical drugs.[2] (Fig. 1) Various quinazolinone derivatives represent a wide range of biological activities,[3] such as anticancer[3a], anti-inflammatory[3b], antibacterial[3c], antitubercular[3d], antihypertensive[3e] and anticonvulsant[3f]. As one of these quinazolinone analogs, the pyrido[2,3-d]pyrimidin-4(3H)-ones (**2**) are also used as versatile building blocks for the direct synthesis of biologically active molecules.[4] For example, a series of compounds containing pyrido[2,3-d]pyrimidin-4(3H)-one scaffolds have been developed as microsomal prostaglandin E2 synthase-1 inhibitors.[4a]

In view of the great value of quinazolinones and their analogs, various methodologies for their synthesis have been developed.[5-9] The current synthetic methods of this skeleton are mainly summarized as the following five types: (i) the condensation of 2-aminobenzamide with suitable carbonyl compounds (ketones[5a], aldehydes[5b], acids[5c], or acid chlorides[5d]), aryl halides[5e], methylarenes[5f], and ketoalkynes[5g] under metal or metal-free conditions; (ii) the copper-catalyzed domino reactions of 2-halobenzamides with (aryl)methanamines[6a,6d], amides[6b], and enaminones[6c]; (iii) the palladium-catalyzed insertion of carbon monoxide (CO) with o-iodoanilines[7a], N-arylamidines[7b], N-(o-halophenyl)imidoyl chlorides[7c] or 2-aminobenzonitriles[7d] as starting materials; (iv) the copper-catalyzed expansion reaction of 2-arylindoles with amines using molecular oxygen as an oxidant;[8] (v) the copper-catalyzed N-arylation/condensation of 2-halobenzonitriles and amides[9]. Although these reactions provided efficient protocols to synthesize various substituted quinazolinones, their applications are limited due to certain disadvantages including tedious multi-step procedures, difficult-to-prepare starting materials, the use of large excess oxidants, long reaction time, and harsh reaction conditions. Therefore, the development of a simple, effective, mild and economic method for the preparation of quinazolinones is still highly desirable.

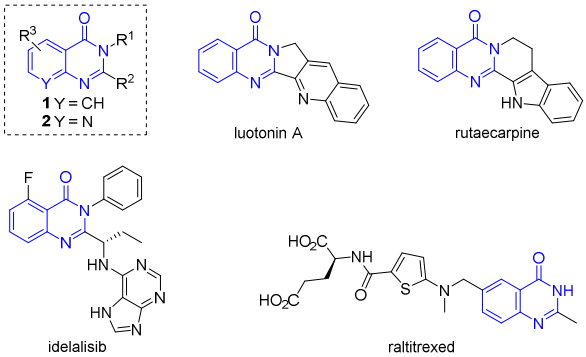

Fig. 1. Structures of some selected natural products and drugs containing quinazolinone moiety.

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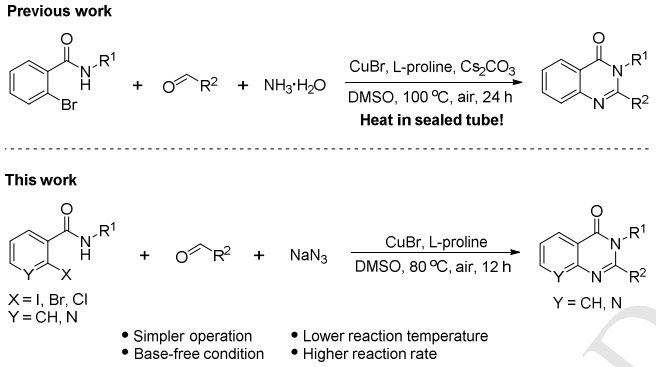
Recently, Guo and co-workers have developed a novel and efficient route toward quinazolinone derivatives through copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia (Scheme 1).[10] However, this strategy inevitably suffered from tedious operation, high reaction temperature, long reaction time, and the addition of base (Cs_2CO_3) due to the use of aqueous ammonia as nitrogen source in sealed tube. Sodium azide (NaN_3), as a convenient and inexpensive nitrogen source, has been widely applied in organic synthesis, mainly including 1,3-dipolar cycloaddition[11] and copper-catalyzed S_NAr reactions[12]. Based on the recent report on copper-catalyzed multicomponent synthesis of fused N-heterocycles utilizing sodium azide as nitrogen source,[13] herein we present a similar strategy to construct quinazolin-4(3H)-ones and pyrido[2,3-d]pyrimidin-4(3H)-ones from simple and readily available 2-halobenzamides (or 2-halonicotinamides) and aldehydes (Scheme 1). In this catalytic system, an integrated consecutive process involved copper-catalyzed S_NAr, reduction, cyclization, and oxidation sequences. Compared with the reported methods[5-10], this approach is more smoothly applied to synthesize multifarious 2-substituted, 3-substituted and 2,3-disubstituted quinazolinone derivertives from readily available substrates, featuring easy operation, high efficiency, and mild condition.



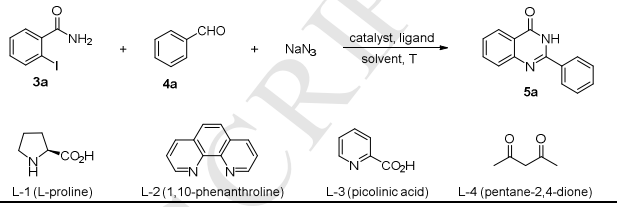
Scheme 1. Copper-catalyzed multicomponent synthesis of quinazolinone derivatives.

2. Results and discussion

To optimize the reaction conditions, an initial experiment was carried out using 2-iodobenzamide (**3a**), benzaldehyde (**4a**), and sodium azide as model substrates. Various reaction parameters were evaluated systematically, including catalysts, ligands, solvents, and temperatures; all cases are shown in Table 1. First, a series of copper catalysts were examined for this consecutive reaction with 0.2 equiv of L-proline (relative to amount of **3a**) as the ligand and DMSO as the solvent at 80 °C (Table 1, entries 1-7), and CuBr showed the highest efficiency (Table 1, entry 3). Then, other three ligands such as 1,10-phenanthroline, picolinic acid and pentane-2,4-dione, were tested using 0.1 equiv CuBr (relative to amount of **3a**) as the catalyst in DMSO, and they provided lower yields (Table 1, entries 8-10). In the absence of ligand, the product was obtained in 44% yield (Table 1, entry 11), and the result showed significant effect of a suitable ligand to the reaction system. Next, solvent effects on this consecutive transformation in the presence of CuBr and L-proline at 80 °C were investigated, and DMSO was found to be the optimal solvent (Table 1, compare entries 3 and 12-16). It should be noted that this transformation afforded desired product in a moderate yield when using H_2O as solvent (Table 1, entry 14), suggesting that it had the potential of green chemistry to be widely applied. Changed the reaction temperature did not lead to any further improvement in the yield, and 80 °C gave the best result (Table 1, compare entries 3 and 17-19). When increasing amount of CuBr and sodium azide, and adding a base such as K_2CO_3, the reactions did not give higher yields (Table 1, compare entries 3 and 20-22). Finally, the optimized reaction condition was determined that **3a** (2.0 mmol), **4a** (1.1 equiv) and sodium azide (2.0 equiv) were smoothly converted into 2-phenylquinazolin-4(3H)-one (**5a**) in 75% yield with CuBr (0.1 equiv) as the catalyst, L-proline (0.2 equiv) as the ligand, and DMSO as the solvent under an air atmosphere at 80 °C over 12 h (Table 1, entry 3).

Table 1

Investigation of conditions for copper-catalyzed synthesis of **5a** using **3a** and **4a** as the substrates[a]



Entry	Catalyst	Ligand	Solvent	*T* (°C)	Yield (%)[b]
1	CuI	L-1	DMSO	80	52
2	CuCl	L-1	DMSO	80	64
3	CuBr	L-1	DMSO	80	75
4	Cu_2O	L-1	DMSO	80	57
5	$CuBr_2$	L-1	DMSO	80	59
6	$Cu(OAc)_2$	L-1	DMSO	80	50
7	$CuCl_2$	L-1	DMSO	80	66
8	CuBr	L-2	DMSO	80	50
9	CuBr	L-3	DMSO	80	48
10	CuBr	L-4	DMSO	80	49
11	CuBr	-	DMSO	80	44
12	CuBr	L-1	DMF	80	52
13	CuBr	L-1	1,4-dioxane	80	66
14	CuBr	L-1	H_2O	80	60
15	CuBr	L-1	DCE	80	38
16	CuBr	L-1	toluene	80	trace
17	CuBr	L-1	DMSO	70	55
18	CuBr	L-1	DMSO	90	71
19	CuBr	L-1	DMSO	100	70
20[c]	CuBr	L-1	DMSO	80	73
21[d]	CuBr	L-1	DMSO	80	64
22[e]	CuBr	L-1	DMSO	80	68

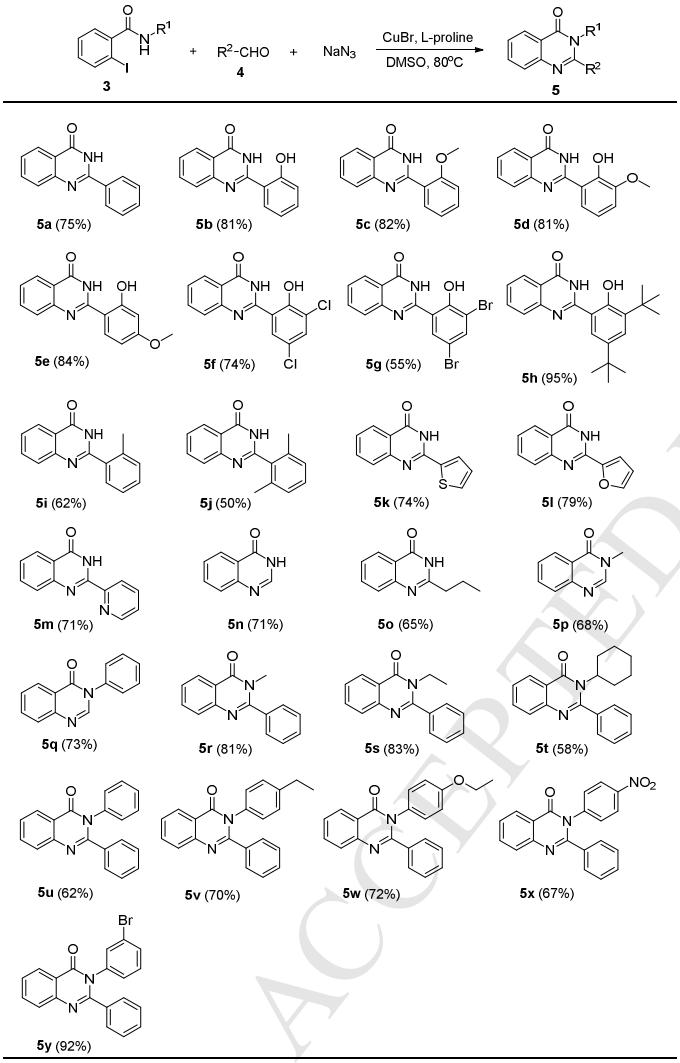
[a] Reactions conditions: **3a** (2.0 mmol), **4a** (2.2 mmol), NaN_3 (4.0 mmol), catalyst (0.2 mmol), ligand (0.4 mmol), solvent (3 mL), under air for 12 h.
[b] Isolated yield.
[c] Extra NaN_3 (2.0 mmol) was added.
[d] Extra NaN_3 (2.0 mmol) and K_2CO_3 (2.0 mmol) was added.
[e] Extra NaN_3 (2.0 mmol) and CuBr (0.2 mmol) were added.

Under the optimized conditions, we first investigated CuBr-catalyzed consecutive synthesis of quinazolinones **5** with 2-halobenzamides **3** and aldehydes **4** as substrates. As shown in Table 2, a variety of aromatic aldehydes bearing different substituents reacted with 2-iodobenzamide (**3a**) to give the corresponding products **5a**−**5j** in moderate to good yields (50%−95%). It was found that electron-neutral and electron-donating groups on the aromatic ring of aldehydes **4** did not impact the yields of the desired products. Much to our satisfaction, reactions with aromatic aldehydes containing 2-phenolic hydroxyl and 3,5-dihalo groups proceeded smoothly to afford the corresponding products, which provided the possibility for further functionalization. Notably, the optimized conditions were also suitable enough for the transformation of sterically hindered substrates such as 3,5-di-tert-butyl-2-hydroxybenzaldehyde, 2-methylbenzaldehyde and 2,6-

dimethylbenzaldehyde. Meanwhile, the CuBr-catalyzed consecutive reactions had been successfully applied to synthesis of 2-heteroaryl quinazolinones **5k**-**5m** in 71%−79% yields, when thiophene-2-carbaldehyde, furan-2-carbaldehyde, picolinaldehyde were employed as substrates respectively. Furthermore, 2-iodobenzamide **3a** showed higher reactivity to provide the desirable product **5a** in 75% yield, than the corresponding 2-bromobenzamide (give **5a** in 72% yield) and 2-chlorobenzamide (give **5a** in 33% yield). Beyond that, the reactions showed good tolerance of alkylaldehydes including formaldehyde and *n*-butylaldehyde, and provided quinazolin-4(3H)-one (**5n**) in 71% yield and 2-propylquinazolin-4(3H)-one (**5o**) in 65 % yield. Obviously, this is a quite general methodology for the preparation of 2-alkyl, 2-aryl, and 2-heteroaryl quinazolin-4(3H)-ones.

Table 2

Scope of 2-halobenzamides and aldehydes[a]



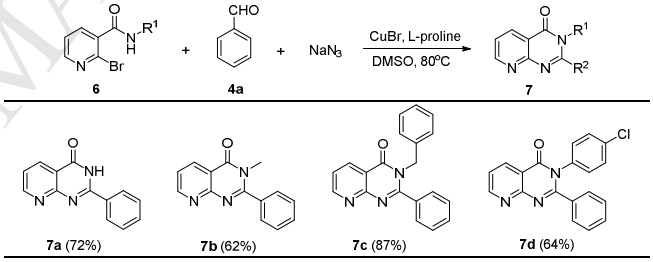
[a] Reaction conditions: 2-halobenzamide (2.0 mmol), aldehyde (2.2 mmol), NaN_3 (4.0 mmol), CuBr (0.2 mmol), and L-proline (0.4 mmol) in DMSO (3 mL) at 80 °C under air for 5−12 h.

Next, the effects of the N-substituents of 2-iodobenzamides **3** were explored. It is noteworthy to mention that N-alkyl groups (methyl, ethyl and cyclohexyl) and N-aryl groups (phenyl and substituted phenyl) were all well-tolerated in this reaction, affording a series of 3-substituented and 2,3-disubstituented quinazolinones **5p**−**5y** in moderate to good yields (58%−92%). Further, electron-neutral (4-H, 4-Et), electron-donating (4-OEt), and electron-withdrawing (4-NO_2) groups of N-phenyl groups showed no significant difference on the yields of corresponding products **5u**−**5x** (62%−72%). To our delight, the reaction for synthesis of **5y** containing N-(3-bromo)phenyl group proceeded smoothly in a good yield (92%), which allowed further modifications on the bromo group by coupling reactions. However, when using N-(2,6-dimethylphenyl)-2-iodobenzamide as substrate under the optimized condition, the 2-azidobenzamide intermediate was afforded as a main product (it's structure was confirmed by ^{1}H NMR and MS; see supporting information) and could not be converted into the desired product, possibly due to the large steric hindrance. Based on the above findings, except for the steric effects, this approach showed high functional group tolerance and proved to be a quite general methodology for the preparation of multifarious 2-substituted, 3-substituted and 2,3-disubstituted quinazolinone derivertives.

Besides that, we investigated the utility of this protocol for preparation of some pyrido[2,3-d]pyrimidin-4(3H)-one class compounds, which are structurally similar with quinazolin-4(3H)-ones. (Table 3) By this protocol, the pyrido[2,3-d]pyrimidin-4(3H)-ones **7a**-**7d** were prepared successfully in 62−87% yield with 2-bromonicotinamides **6** and benzaldehyde (**4a**) as starting materials. Therefore, the results gave us great confidence to apply this method for the construction of some novel quinazolinone analogues.

Table 3

Scope of 2-halonicotinamides[a]

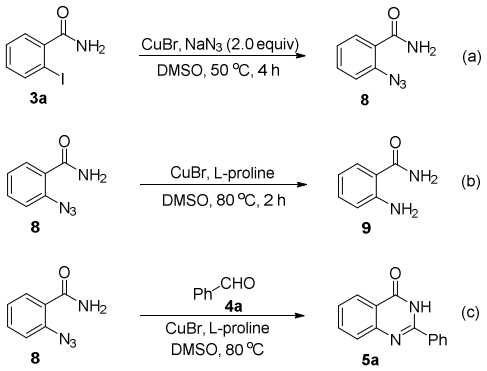


a Reaction conditions: 2-bromonicotinamide (2.0 mmol), benzaldehyde (2.2 mmol), NaN_3 (4.0 mmol), CuBr (0.2 mmol), and L-proline (0.4 mmol) in DMSO (3 mL) at 80 °C under air for 12 h.

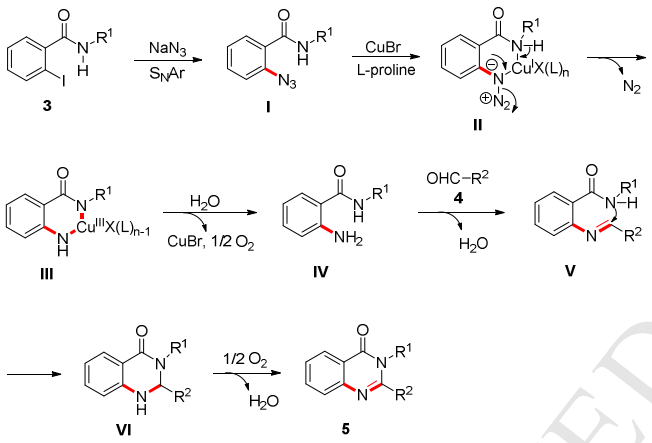
In order to explore the reaction mechanism, some control experiments were performed. Initially, 2-iodobenzamide (**3a**) reacted with sodium azide (2 equiv) in DMSO at 50 °C for 4 h, giving 2-azidobenzamide **8** in 83% yield (Scheme 2a). The structure of **8** was confirmed by ^{1}H NMR and MS. Next, **8** was heated at 80 °C for 2 h in DMSO in the presence of CuBr and L-proline (Scheme 2b), and we fortunately observed the mass for 2-aminobenzamide **9** (*m/z* = 159.1, $[M + Na]^+$). Another experiment of **8** and benzaldehyde (**4a**) proceeded smoothly under standard conditions, and the target product **5a** was obtained in 84% yield (Scheme 2c). Moreover, the MS spectrum after 1 h reaction time showed mass for Schiff's base **V** or possibly its cyclized intermediate **VI** (*m/z* = 247.1, $[M + Na]^+$).

According to the above results and reported literature[13-15], we proposed a possible reaction mechanism for the copper-catalyzed consecutive process. As shown in Scheme 3, copper-catalyzed S_NAr product 2-azidobenzamide **I** is first prepared from sodium azide and 2-halobenzamide **3** despite the *ortho*-substituent effect.[14] Then, with the aid of L-proline and trace H_2O in DMSO, the copper-mediated denitrogenation of **I** affords 2-

aminobenzamide **IV** *via* Cu(I) complex **II** and Cu(III) complex **III** in turn,[15] meanwhile releasing nitrogen. Next, **IV** could easily condense with benzaldehyde **4**, leading to the formation of Schiff's base **V**. Subsequently, intramolecular nucleophilic attack of nitrogen in amide to carbon in imine in **V** gives intermediate **VI**. Finally, **VI** undergoes oxidative dehydrogenation to produce the target product **5**.



Scheme 2. Control experiments.



Scheme 3. A possible mechanism.

3. Conclusion

In summary, we have developed a highly efficient and practical copper-catalyzed reaction for the synthesis of quinazolin-4(3H)-ones and pyrido[2,3-d]pyrimidin-4(3H)-ones, starting from simple and readily available 2-halobenzamides (or 2-halonicotinamides), aldehydes, and sodium azide. The reactions underwent a consecutive process, involved copper-catalyzed S_NAr, reduction, cyclization, and oxidation sequences. It is worth mentioning that this protocol could provide diverse 2-substituted, 3-substituted and 2,3-disubstituted quinazolinone derivatives. Further utilizations of this protocol are underway to construct more complex molecules in our laboratory.

4. Experimental section

4.1. General information

All commercial materials and solvents were used directly without further purification. ^{1}H and ^{13}C NMR spectra were measured on a 300 MHz spectrometer using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) were recorded in electron impact mode. Melting points were determined on a melting point apparatus and were uncorrected. Reactions were monitored by TLC on silica gel 60 F254 plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200−300 mesh, Qingdao Ocean Chemical Company, China).

4.2. General procedure for preparation of quinazolin-4(3H)-ones (5) and pyrido[2,3-d]pyrimidin-4(3H)-ones (7)

To a solution of 2-iodobenzamide (**3**) or 2-bromonicotinamide (**6**) (2.0 mmol) in DMSO (3 mL), was added aldehyde (2.2 mmol), NaN_3 (260 mg, 4.0 mmol), CuBr (29 mg, 0.2 mmol), and L-proline (46 mg, 0.4 mmol). The reaction mixture was stirred at 80 °C under air. After disappearance of the reactant (monitored by TLC), water (30 mL) was added to the mixture, and then extracted with ethyl acetate (15 mL) for three times. The extraction was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1 to 3:1) as the eluent to give the desired products **5** or **7**.

*4.2.1. 2-Phenylquinazolin-4(3H)-one (**5a**).*[6a] White solid; 333 mg (75% yield); m.p. 228−229 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (br s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 8.17-8.19 (m, 2H), 7.79-7.89 (m, 2H), 7.59-7.61 (m, 3H), 7.49-7.58 (m, 1H). ESI-MS *m/z* 221.1 [M - H]$^-$.

*4.2.2. 2-(2-Hydroxyphenyl)quinazolin-4(3H)-one (**5b**).*[5a] Light yellow solid, 386 mg (81% yield); m.p. 250-252 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.35 (br s, 1H), 12.40 (br s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.83-7.88 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.42-7.48 (m, 1H), 6.93-7.02 (m, 2H). ESI-MS *m/z* 237.1 [M - H]$^-$.

*4.2.3. 2-(2-Methoxyphenyl)quinazolin-4(3H)-one (**5c**).*[16] Light brown solid, 414 mg (82% yield); m.p. 183-185 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.83 (t, J = 7.0 Hz, 1H), 7.68-7.71 (m, 2H), 7.50-7.55 (m, 2H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 3.86 (s, 3H). ESI-MS *m/z* 275.1 [M + Na]$^+$.

*4.2.4. 2-(2-Hydroxy-3-methoxyphenyl)quinazolin-4(3H)-one (**5d**).*[17] Light yellow solid, 434 mg (81% yield); m.p. 283-284 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.90 (br s, 1H), 12.44 (br s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.74-7.89 (m, 3H), 7.55 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 6.89 (t, J = 8.2 Hz, 1H), 3.83 (s, 3H). ESI-MS *m/z* 291.1 [M + Na]$^+$.

*4.2.5. 2-(2-Hydroxy-4-methoxyphenyl)quinazolin-4(3H)-one (**5e**).*[17] Light yellow solid, 451 mg (84% yield); m.p. 283-284 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.40 (br s, 1H), 12.59 (br s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.86 (t, J = 7.2 Hz, 1H), 7.74-7.77 (m, 2H), 7.52-7.57 (m, 1H), 6.96-7.09 (m, 1H), 6.94 (d, J = 8.9 Hz, 1H), 3.80 (s, 3H). ESI-MS *m/z* 269.1 [M + H]$^+$.

*4.2.6. 2-(3,5-Dichloro-2-hydroxyphenyl)quinazolin-4(3H)-one (**5f**).*[18] Light yellow solid, 454 mg (74% yield); m.p. > 290 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.49-7.59 (m, 3H), 7.33 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H). ESI-MS *m/z* 305.0 [M - H]$^-$.

*4.2.7. 2-(3,5-Dibromo-2-hydroxyphenyl)quinazolin-4(3H)-one (**5g**).*[19] Light yellow solid, 436 mg (55% yield); m.p. > 290 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 15.55 (br s, 1H), 12.87 (br s, 1H), 8.57 (s, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.99 (s, 1H), 7.84-7.92 (m, 2H), 7.59 (t, J = 7.3 Hz, 1H). ESI-MS *m/z* 394.9 [M - H]$^-$.

*4.2.8. 2-(3,5-Di-tert-butyl-2-hydroxyphenyl)quinazolin-4(3H)-one (**5h**).*[20] White solid, 666 mg (95% yield); m.p. >

290 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.88 (br s, 1H), 12.78 (br s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.04 (s, 1H), 7.76-7.87 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.43 (s, 1H), 1.43 (s, 9H), 1.33 (s, 9H). ESI-MS *m/z* 351.2 $[M + H]^+$.

4.2.9. 2-(o-Tolyl)quinazolin-4(3H)-one (***5i***).[8] Light yellow solid, 293 mg (62% yield); m.p. 223-224 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.48-7.55 (m, 2H), 7.40-7.45 (m, 1H), 7.29-7.35 (m, 2H), 2.37 (s, 3H). ESI-MS *m/z* 259.1 $[M + Na]^+$.

4.2.10. 2-(2,6-Dimethylphenyl)quinazolin-4(3H)-one (***5j***).[21] Light yellow solid, 250 mg (50% yield); m.p. 119-120 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.43 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.24-7.33 (m, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 2.15 (s, 6H). ESI-MS *m/z* 273.1 $[M + Na]^+$.

4.2.11. 2-(Thiophen-2-yl)quinazolin-4(3H)-one (***5k***).[6a] Yellow solid, 338 mg (74% yield); m.p. 137-139 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.23 (d, *J* = 3.7 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 4.9 Hz, 1H), 7.78-7.83 (m, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.46-7.51 (m, 1H), 7.22-7.25 (m, 1H). ESI-MS *m/z* 251.1 $[M + Na]^+$.

4.2.12. 2-(Furan-2-yl)quinazolin-4(3H)-one (***5l***).[6a] Brown solid, 335 mg (79% yield); m.p. 209-211 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 8.00 (s, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 3.3 Hz, 1H), 7.49 (t, *J* = 1.5 Hz, 1H), 6.75 (s, 1H). ESI-MS *m/z* 235.1 $[M + Na]^+$.

4.2.13. 2-(Pyridin-2-yl)quinazolin-4(3H)-one (***5m***).[22] Brown solid, 317 mg (71% yield); m.p. 144-146 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.77 (d, *J* = 4.3 Hz, 1H), 8.47 (d, *J* = 7.9 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.06-8.11 (m, 1H), 7.80-7.91 (m, 2H), 7.65-7.69 (m, 1H), 7.55-7.60 (m, 1H). ESI-MS *m/z* 246.1 $[M + Na]^+$.

4.2.14. Quinazolin-4(3H)-one (***5n***).[23] White solid, 208 mg (71% yield); m.p. 205-207 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.21 (br s, 1H), 8.09-8.14 (m, 2H), 7.79-7.84 (m, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.49-7.54 (m, 1H). ESI-MS *m/z* 147.0 $[M + H]^+$.

4.2.15. 2-Propylquinazolin-4(3H)-one (***5o***).[23] White solid, 245 mg (65% yield); m.p. 189-190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.14 (br s, 1H), 8.08 (d, *J* = 7.4 Hz, 1H), 7.74-7.79 (m, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 2.50-2.60 (m, 2H), 1.68-181 (m, 2H), 0.85-0.96 (m, 3H). ESI-MS *m/z* 189.1 $[M + H]^+$.

4.2.16. 3-Methylquinazolin-4(3H)-one (***5p***).[24] White solid, 218 mg (68% yield); m.p. 58-60 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.79-7.84 (m, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.51-7.56 (m, 1H), 3.50 (s, 3H). ESI-MS *m/z* 161.1 $[M + H]^+$.

4.2.17. 3-Phenylquinazolin-4(3H)-one (***5q***).[24] White solid, 324 mg (73% yield); m.p. 128-130 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.49-7.63 (m, 6H). ESI-MS *m/z* 223.1 $[M + H]^+$.

4.2.18. 3-Methyl-2-phenylquinazolin-4(3H)-one (***5r***).[5f] White solid, 383 mg (81% yield); m.p. 112-114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.82-7.87 (t, *J* = 7.3 Hz, 1H), 7.67-7.69 (m, 3H), 7.56-7.59 (m, 4H), 3.36 (s, 3H). ESI-MS *m/z* 237.1 $[M + H]^+$.

4.2.19. 3-Ethyl-2-phenylquinazolin-4(3H)-one (***5s***).[25] White solid, 415 mg (83% yield); m.p. 122-124 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, *J* = 7.9 Hz, 1H), 7.82-7.87 (m, 1H), 7.63-7.67 (m, 3H), 7.54-7.62 (m, 4H), 3.86-3.93 (m, 2H), 1.09 (t, *J* = 7.0 Hz, 3H). ESI-MS *m/z* 251.1 $[M + H]^+$.

4.2.20. 3-Cyclohexyl-2-phenylquinazolin-4(3H)-one (***5t***).[26] Light yellow solid, 353 mg (58% yield); m.p. 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.51-7.64 (m, 7H), 3.74 (t, *J* = 11.8 Hz, 1H), 2.50-2.60 (m, 2H), 1.72-1.74 (m, 4H), 1.47-1.52 (d, *J* = 12.8 Hz, 1H), 1.02-1.19 (m, 1H), 0.77-0.90 (m, 2H). ESI-MS *m/z* 305.2 $[M + H]^+$.

4.2.21. 2,3-Diphenylquinazolin-4(3H)-one (***5u***).[5f] Light yellow solid, 370 mg (62% yield); m.p. 143-144 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, *J* = 7.7 Hz, 1H), 7.88-7.93 (m, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.58-7.63 (m, 1H), 7.36-7.39 (m, 2H), 7.28-7.32 (m, 4H), 7.21-7.24 (m, 4H). ESI-MS *m/z* 299.1 $[M + H]^+$.

4.2.22. 3-(4-Ethylphenyl)-2-phenylquinazolin-4(3H)-one (***5v***). White solid, 457 mg (70% yield); m.p. 154-156 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17-8.21 (m, 1H), 7.87-7.92 (m, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.57-7.62 (m, 1H), 7.35-7.39 (m, *2*H), 7.19-7.26 (m, 5H), 7.13 (d, *J* = 8.3 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.12 (t, *J* = 7.6 Hz, 3H). ^{13}H NMR (75 MHz, DMSO-d_6) δ 161.4, 156.6, 155.3, 147.2, 143.6, 135.7, 135.4, 134.7, 129.2, 128.8, 127.8, 127.4, 127.3, 127.1, 126.4, 27.6, 15.3. ESI-MS *m/z* 327.1 $[M + H]^+$. HRMS calcd for $C_{22}H_{18}N_2ONa$ $[M + Na]^+$ 349.1317, found 349.1323.

4.2.23. 3-(4-Ethoxyphenyl)-2-phenylquinazolin-4(3H)-one (***5w***).[27] White solid, 493 mg (72% yield); m.p. 147-149 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (d, *J* = 7.9 Hz, 1H), 7.86-7.92 (m, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.36-7.39 (m, 2H), 7.18-7.26 (m, 5H), 7.54 (d, *J* = 8.9 Hz, 2H), 3.92-3.99 (m, 2H), 1.26-1.29 (m, 3H). ESI-MS *m/z* 365.1 $[M + Na]^+$.

4.2.24. 3-(4-Nitrophenyl)-2-phenylquinazolin-4(3H)-one (***5x***).[27] Yellow solid, 460 mg (67% yield); m.p. 163-165 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, *J* = 7.7 Hz, 1H), 7.89-7.94 (m, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.34-7.41 (m, 2H), 7.23-7.28 (m, 5H). ESI-MS *m/z* 366.1 $[M + Na]^+$.

4.2.25. 3-(3-Bromophenyl)-2-phenylquinazolin-4(3H)-one (***5y***). Yellow solid, 694 mg (92% yield); m.p. 189-191 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16-8.23 (m, 3H), 7.91-7.95 (m, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.66-7.70 (m, 2H), 7.61-7.63 (m, 1H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.25-7.28 (m, 3H). ^{13}H NMR (75 MHz, DMSO-d_6) δ 161.1, 154.1, 147.1, 146.7, 143.8, 135.1, 135.0, 131.2, 129.2, 128.9, 127.7, 127.5, 127.3, 126.4, 123.7, 120.6. ESI-MS *m/z* 400.1 $[M + Na]^+$. HRMS calcd for $C_{20}H_{13}BrN_2ONa$ $[M + Na]^+$ 399.1317, found 399.1321.

4.2.26. 2-Phenylpyrido[2,3-d]pyrimidin-4(3H)-one (***7a***).[28] White solid, 321 mg (72% yield); m.p. 178-180 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.77 (d, *J* = 4.3 Hz, 1H), 8.47 (d, *J* = 3.9 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.09 (t, *J* = 8.0 Hz, 1H), 7.80-7.91 (m, 2H), 7.65-7.69 (m, 1H), 7.56-7.61 (m, 1H). ESI-MS *m/z* 246.1 $[M + Na]^+$.

4.2.27. 3-Methyl-2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one (***7b***).[29] Light yellow solid, 294 mg (62% yield); m.p. 193-195 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97-8.99 (m, 1H), 8.55-8.59 (m, 1H), 7.69-7.72 (m, 2H), 7.56-7.60 (m, 4H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 159.1, 156.9, 156.0, 135.8, 135.0, 130.0, 128.4, 128.2, 122.5, 115.2, 34.1. ESI-MS *m/z* 260.1 $[M + Na]^+$.

4.2.28. 3-Benzyl-2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one (***7c***).[30] White solid, 545 mg (87% yield); m.p. 110-111 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.01-9.03 (m, 1H), 8.60 (d, *J* = 7.9 Hz, 1H), 7.60-7.64 (m, 1H), 7.42-7.52 (m, 5H), 7.21-7.23 (m, 3H), 6.96 (d, *J* = 7.1 Hz, 2H), 5.19 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.1, 159.3, 156.8, 156.3, 156.1, 136.4, 136.2, 134.8, 130.0, 128.7, 128.4, 128.3, 128.1, 127.9, 127.2, 126.3, 122.9, 48.6. ESI-MS *m/z* 336.1 $[M + Na]^+$.

4.2.29. 3-(4-Chlorophenyl)-2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one (***7d***). White solid, 427 mg (64% yield); m.p. 217-218 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.58 (d, *J* = 7.8 Hz, 1H), 7.60-7.65 (m, 1H), 7.38-7.42 (m, 6H), 7.28-7.30 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.9, 157.9, 157.1, 156.2, 136.5, 136.1, 135.1, 132.9, 131.3, 129.3,

128.8, 128.6, 127.6, 122.8, 116.0. ESI-MS *m/z* 356.0 $[M + Na]^+$. HRMS calcd for $C_{19}H_{12}ClN_3ONa$ $[M + Na]^+$ 356.1319, found 349.1323.

4.3. Experimental procedure for control experiments

To a solution of 2-iodobenzamide (**3a**) (2.0 mmol) in DMSO (3 mL), was added NaN_3 (260 mg, 4.0 mmol) and CuBr (29 mg, 0.2 mmol). The reaction mixture was stirred at 50 °C under air for 4 h. Water (30 mL) was added to the mixture, and then extracted with ethyl acetate (15 mL) for three times. The extraction was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (8:1) as the eluent to give **8** as a light brown solid (269 mg, 83% yield).

To a solution of **8** (162 mg, 1.0 mmol) in DMSO (3 mL), was added L-proline (23 mg, 0.2 mmol) and CuBr (15 mg, 0.1 mmol). The reaction mixture was stirred at 80 °C under air for 2 h to give 2-aminobenzamide **9** (*m/z* = 159.1, $[M + Na]^+$).

To a solution of **8** (162 mg, 1.0 mmol) in DMSO (3 mL), was added benzaldehyde (**4a**) (117 mg, 1.1 mmol), L-proline (23 mg, 0.2 mmol) and CuBr (15 mg, 0.1 mmol). The reaction mixture was stirred at 80 °C under air. After disappearance of the reactant (monitored by TLC), water (30 mL) was added to the mixture, and then extracted with ethyl acetate (15 mL) for three times. The extraction was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give **5a** as a white solid (186 mg, 84% yield).

*4.3.1. 2-Azidobenzamide (**8**).*[31] ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.54-7.59 (m, 2H), 7.49-7.52 (m, 1H), 7.32-7.35 (m, 1H), 7.21-7.26 (m, 1H). ESI-MS *m/z* 163.1 $[M + H]^+$.

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Supplementary Material

^{1}H NMR and ^{13}C NMR copies of all synthesized compounds.

Supporting Information

Copper-Catalyzed Consecutive Reaction To Construct Quinazolin-4(3H)-ones and Pyrido[2,3-d]pyrimidin-4(3H)-ones

Ting Li, Minglu Chen, Lei Yang, Zhengxin Xiong, Yongwei Wang, Fei Li* and Dongyin Chen*

Department of Medicinal Chemistry, School of Pharmacy, Nanjing Medical University, Nanjing 211166, China

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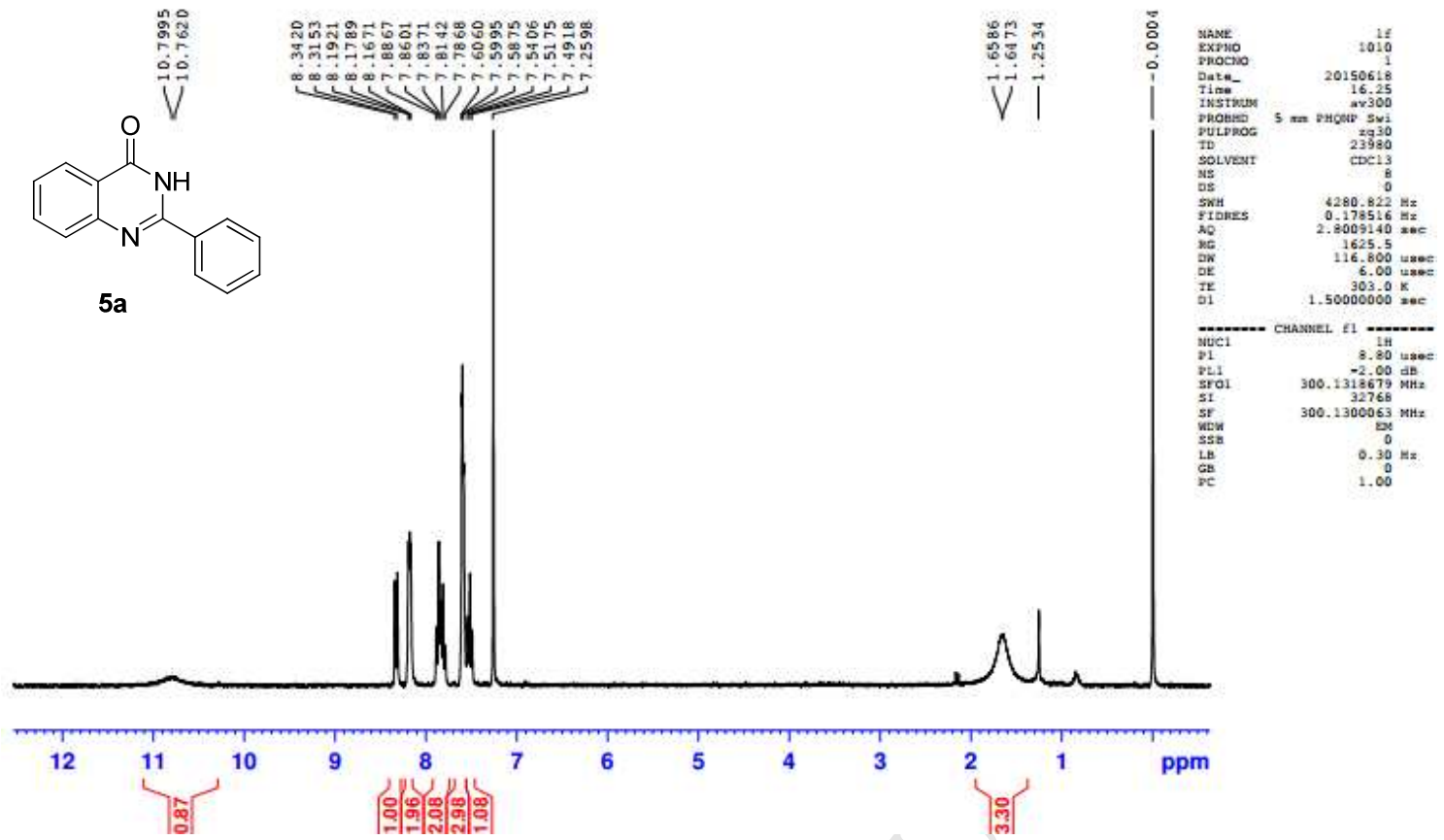
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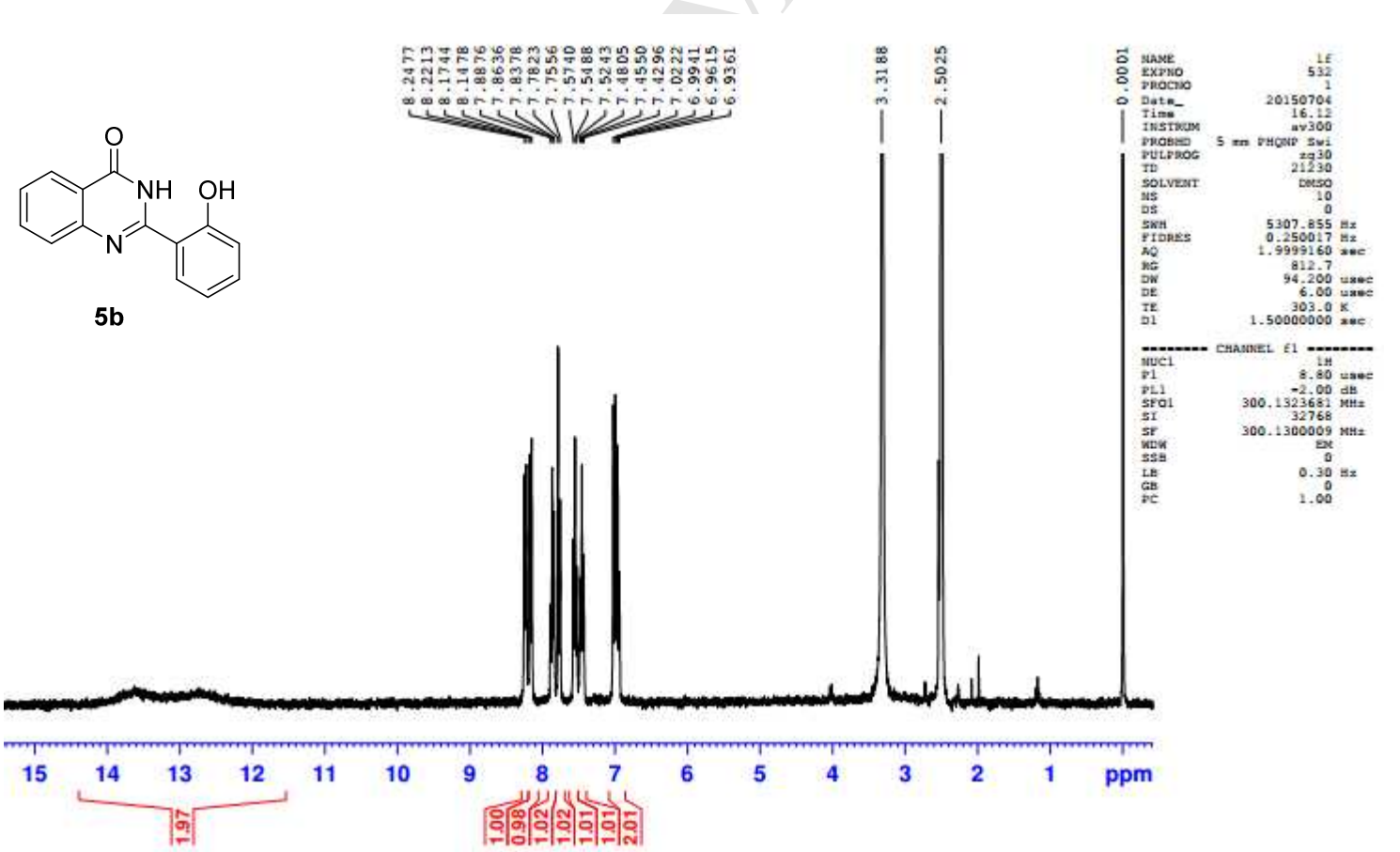
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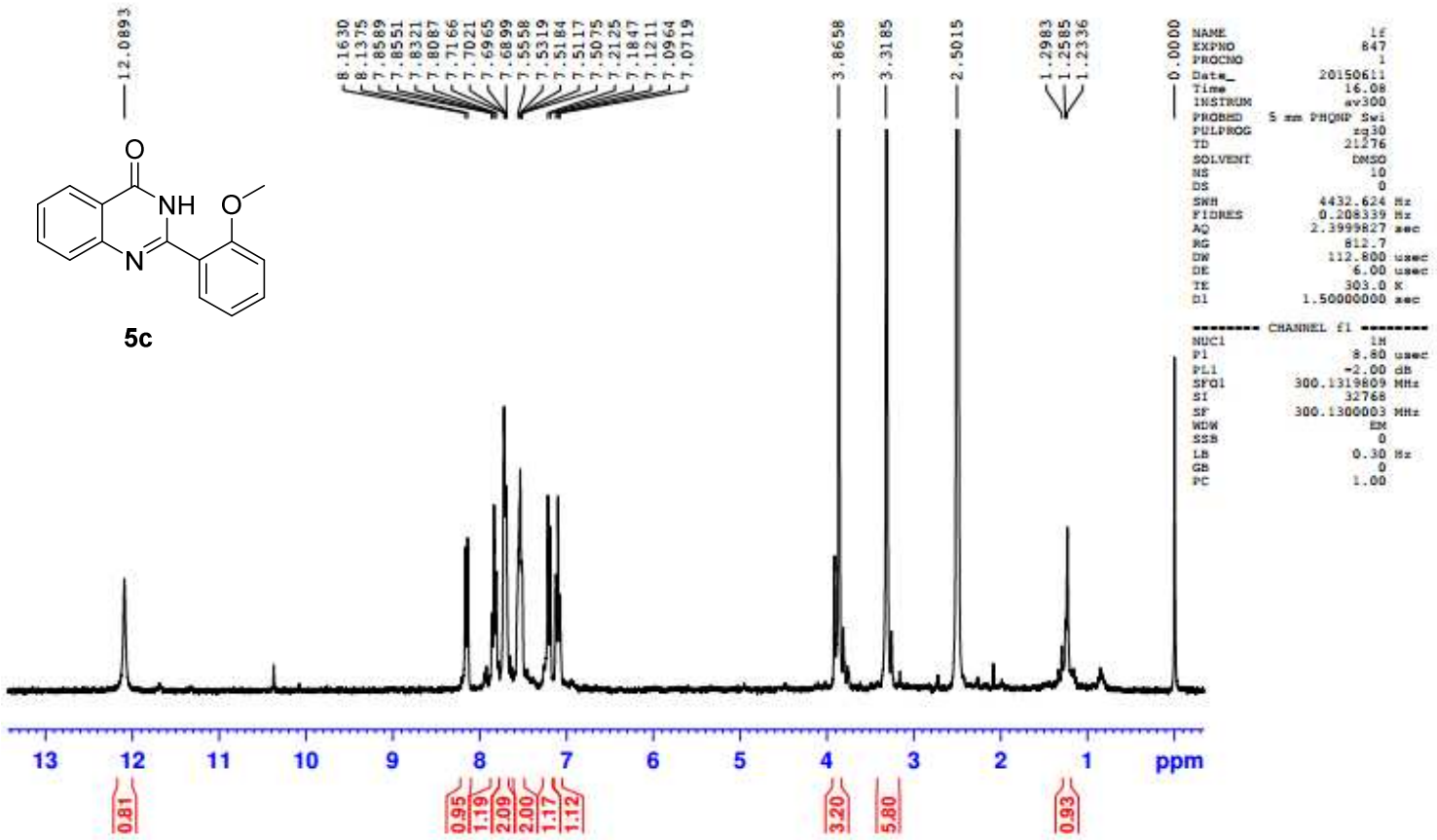
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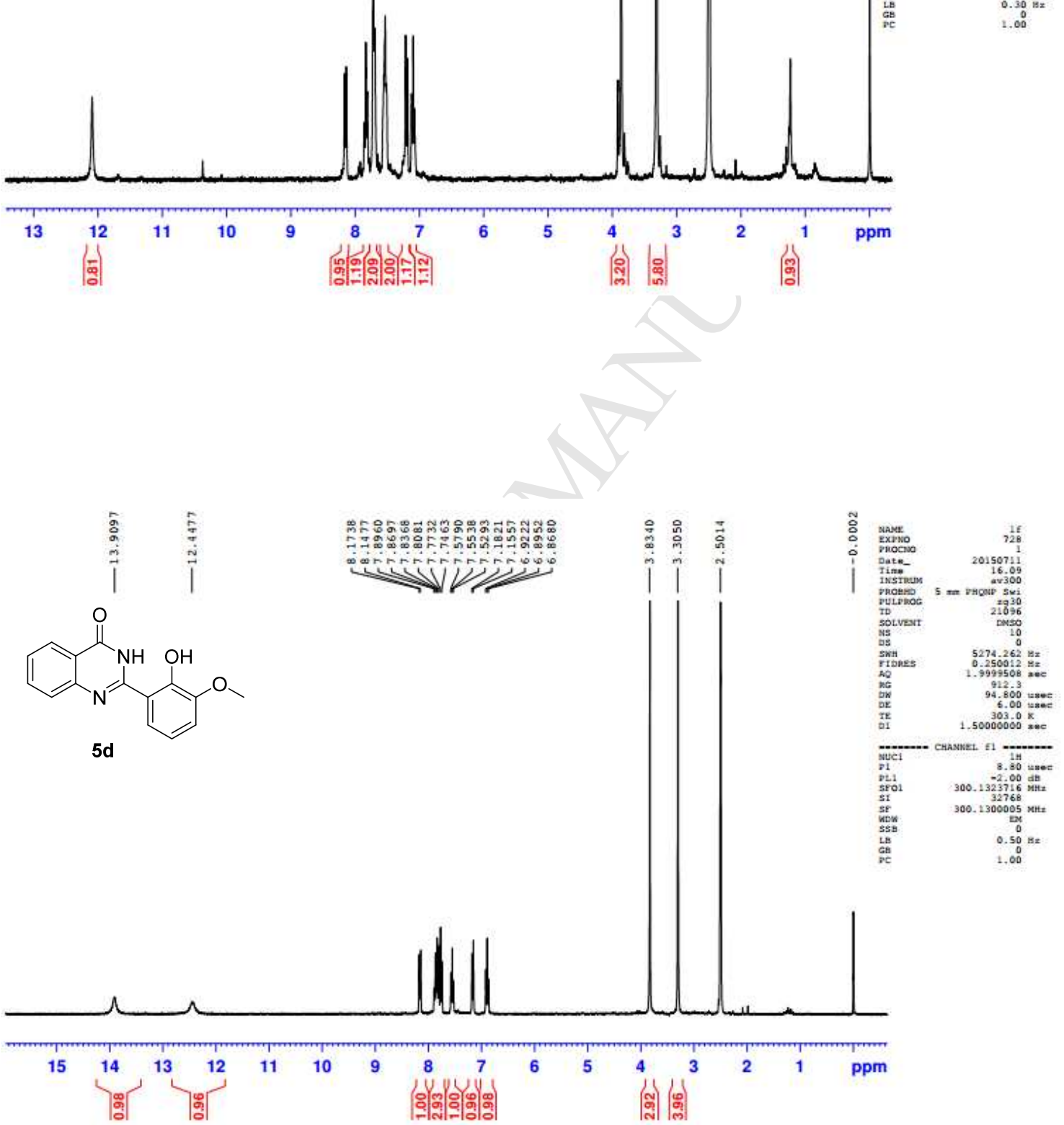
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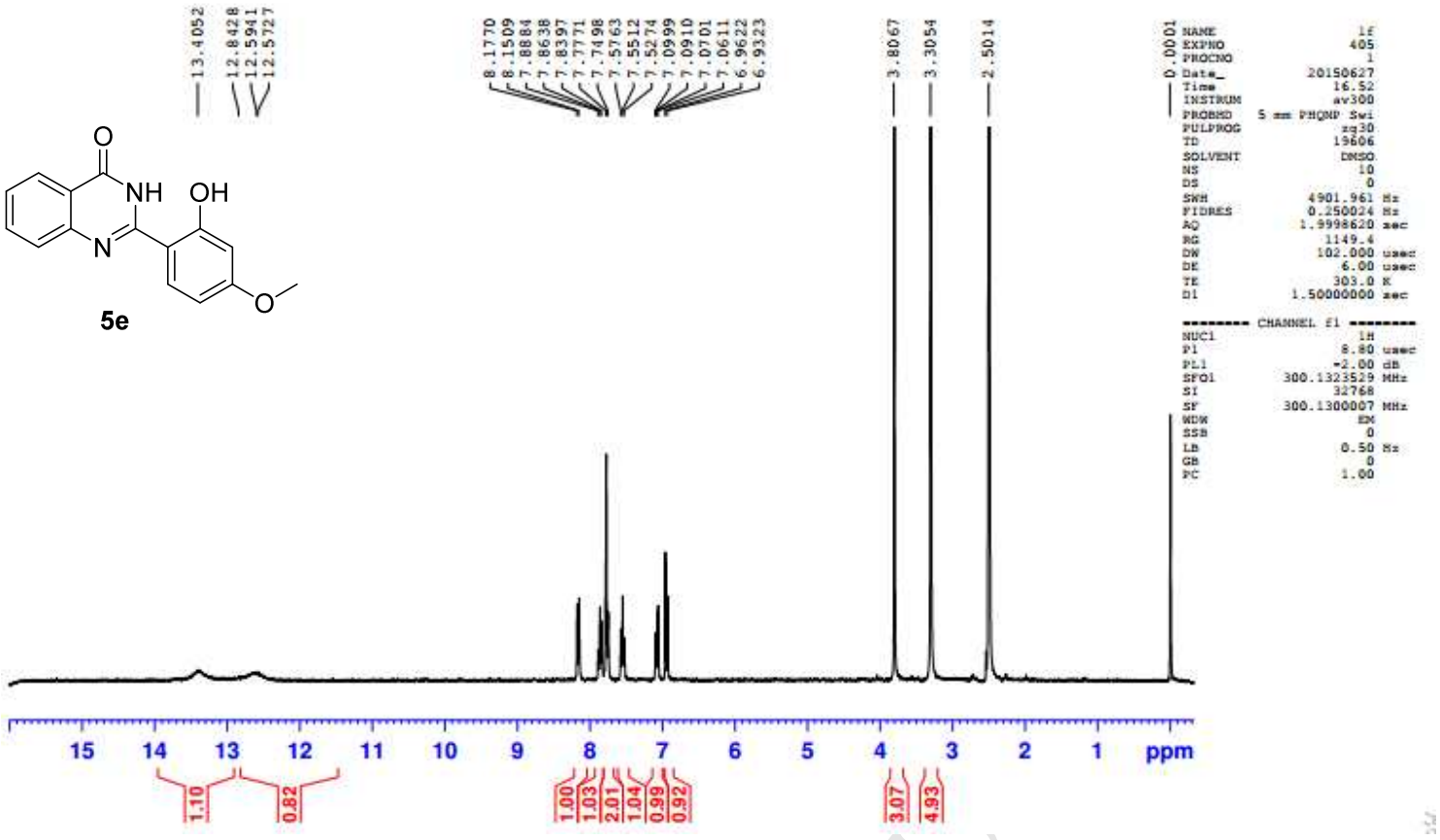
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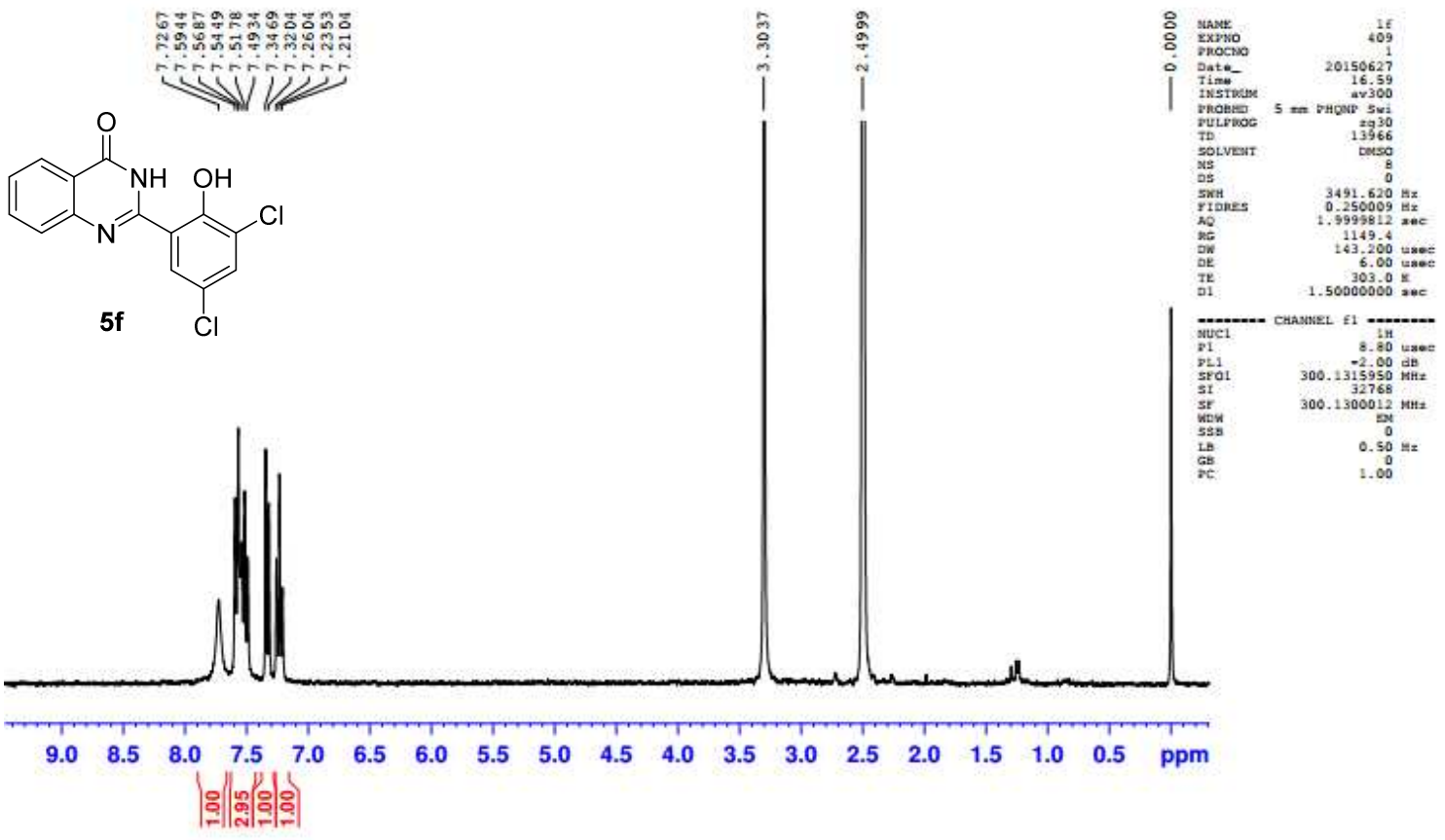
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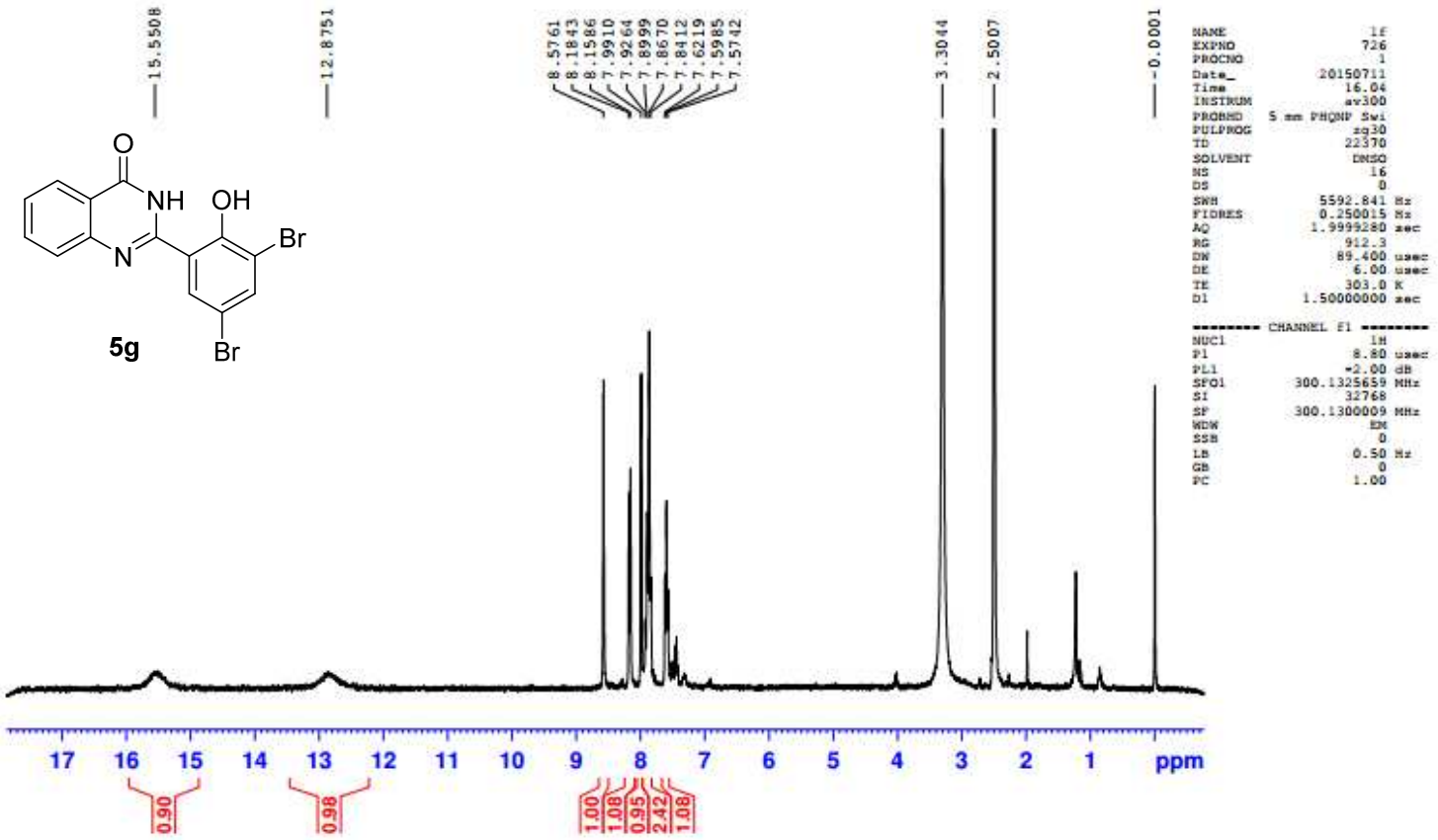
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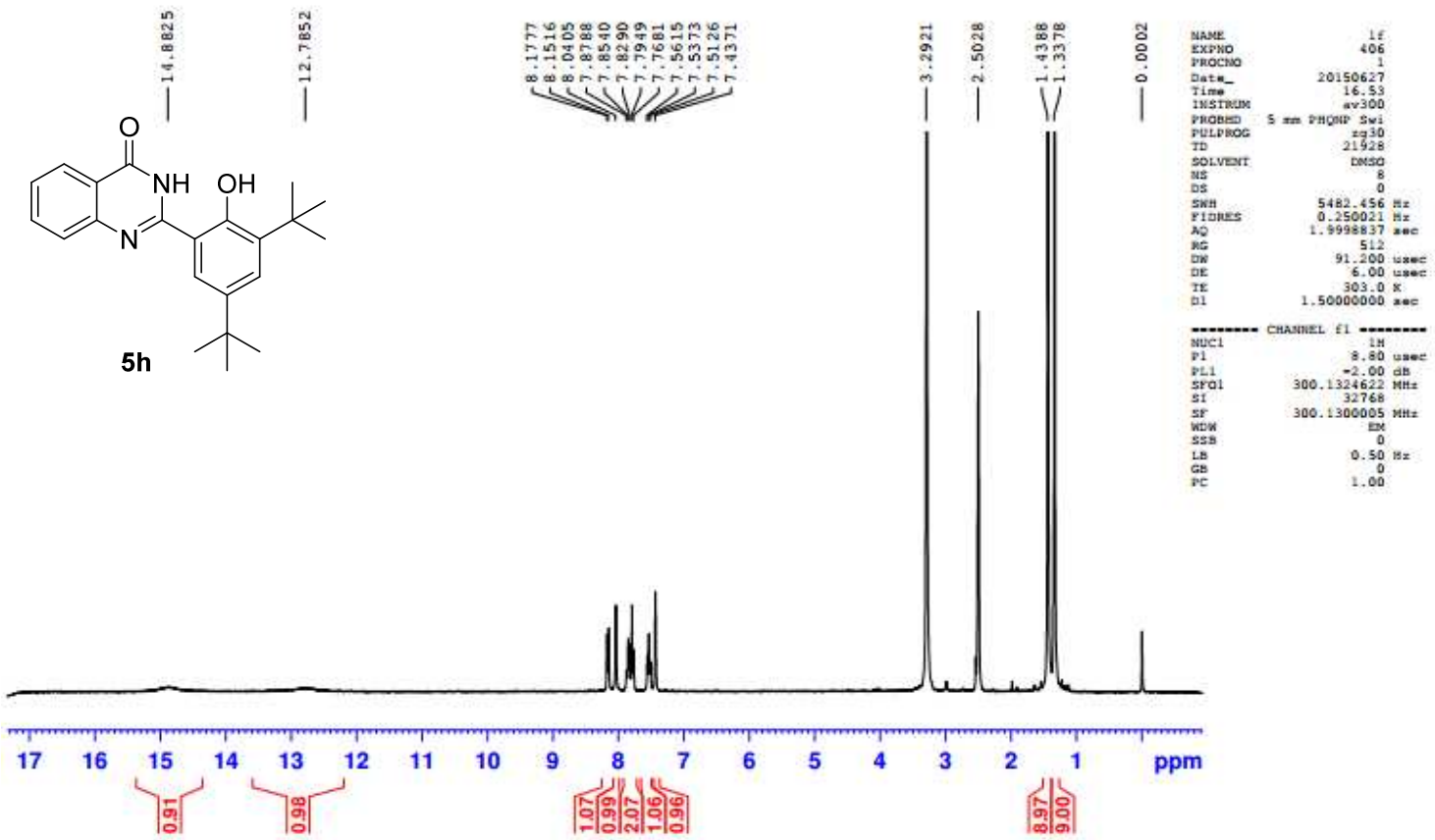
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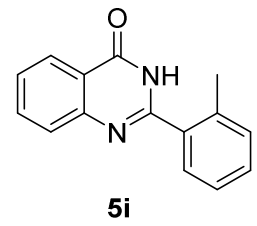

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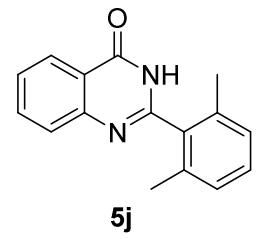

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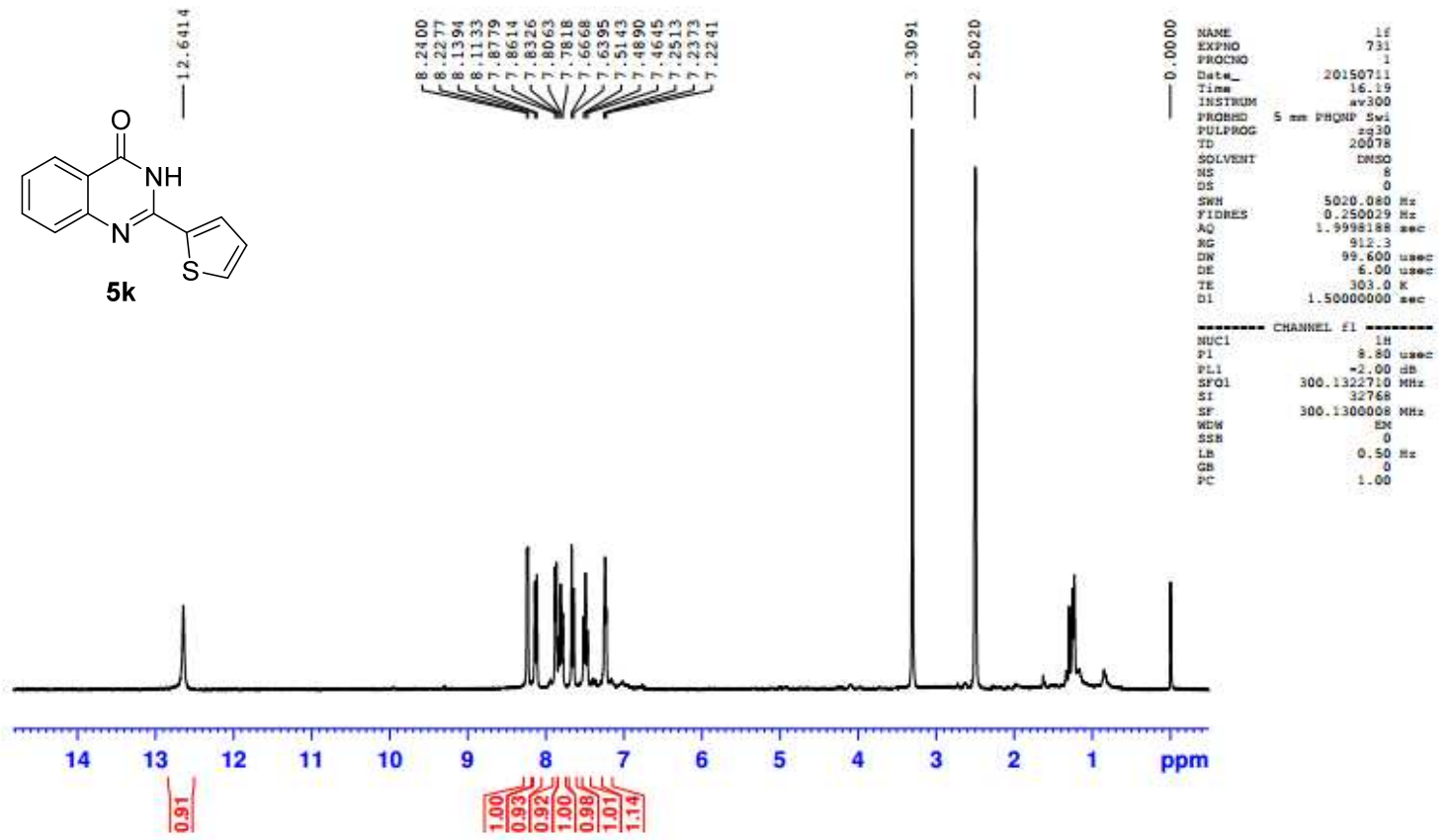
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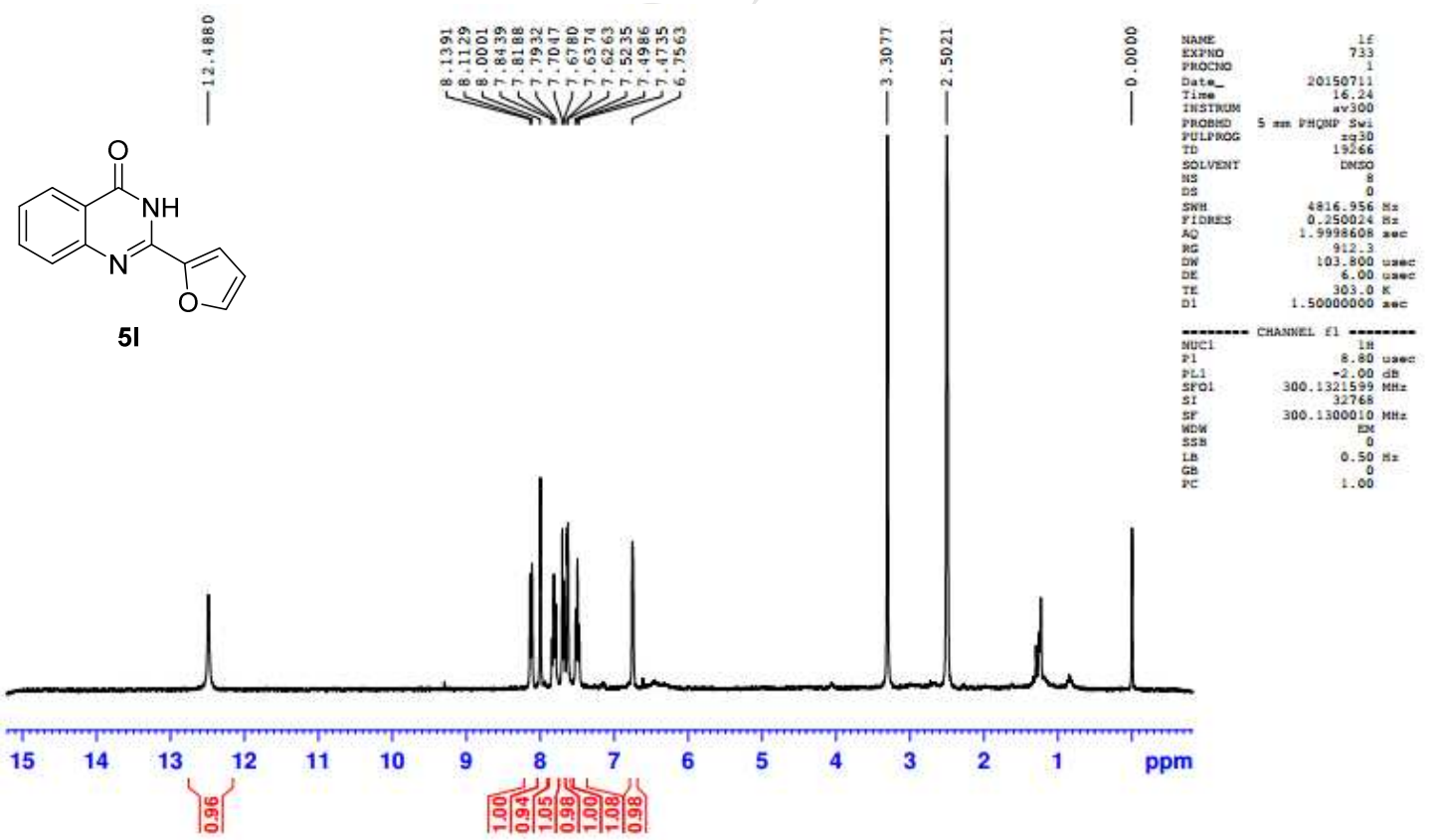
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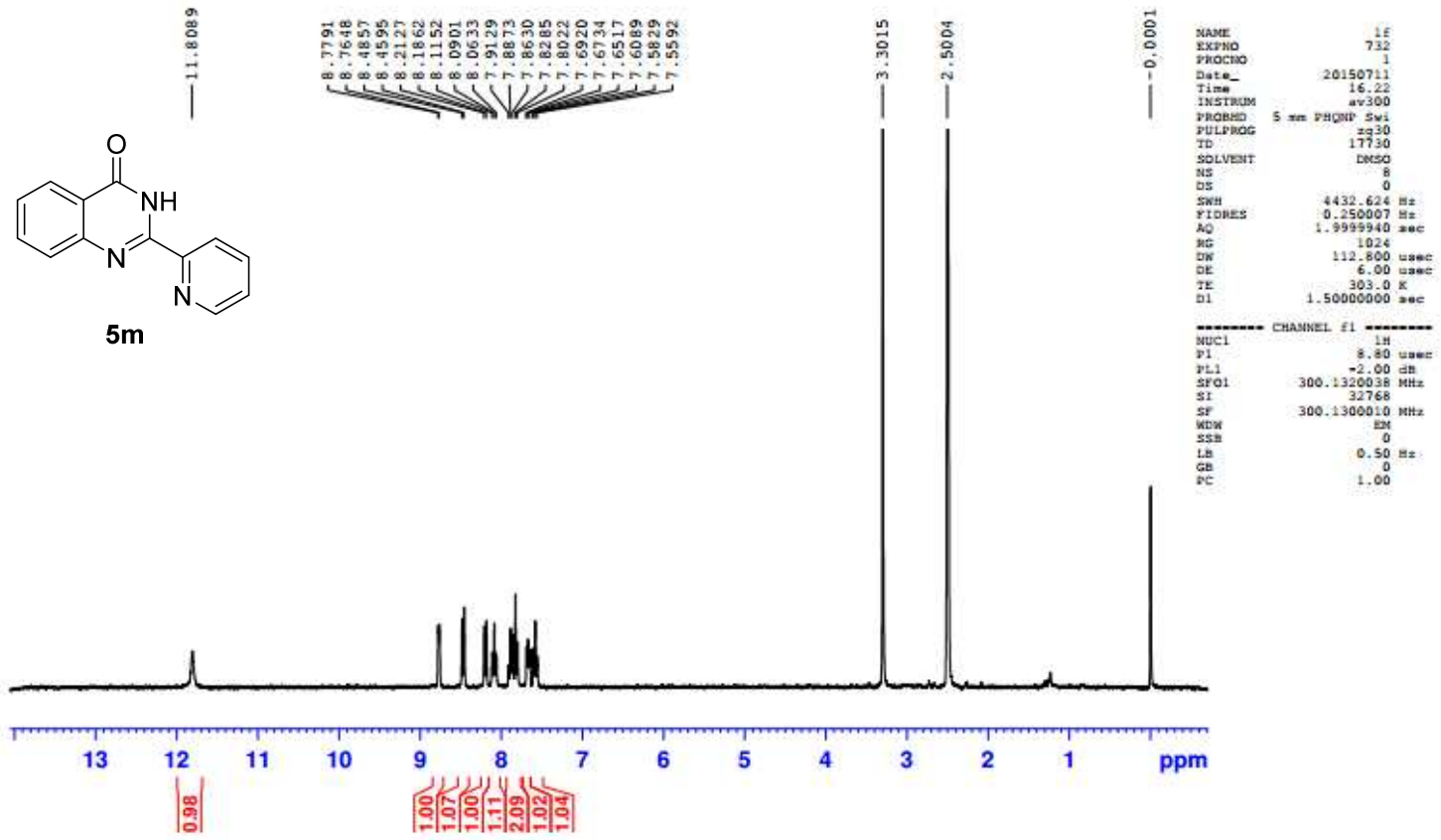
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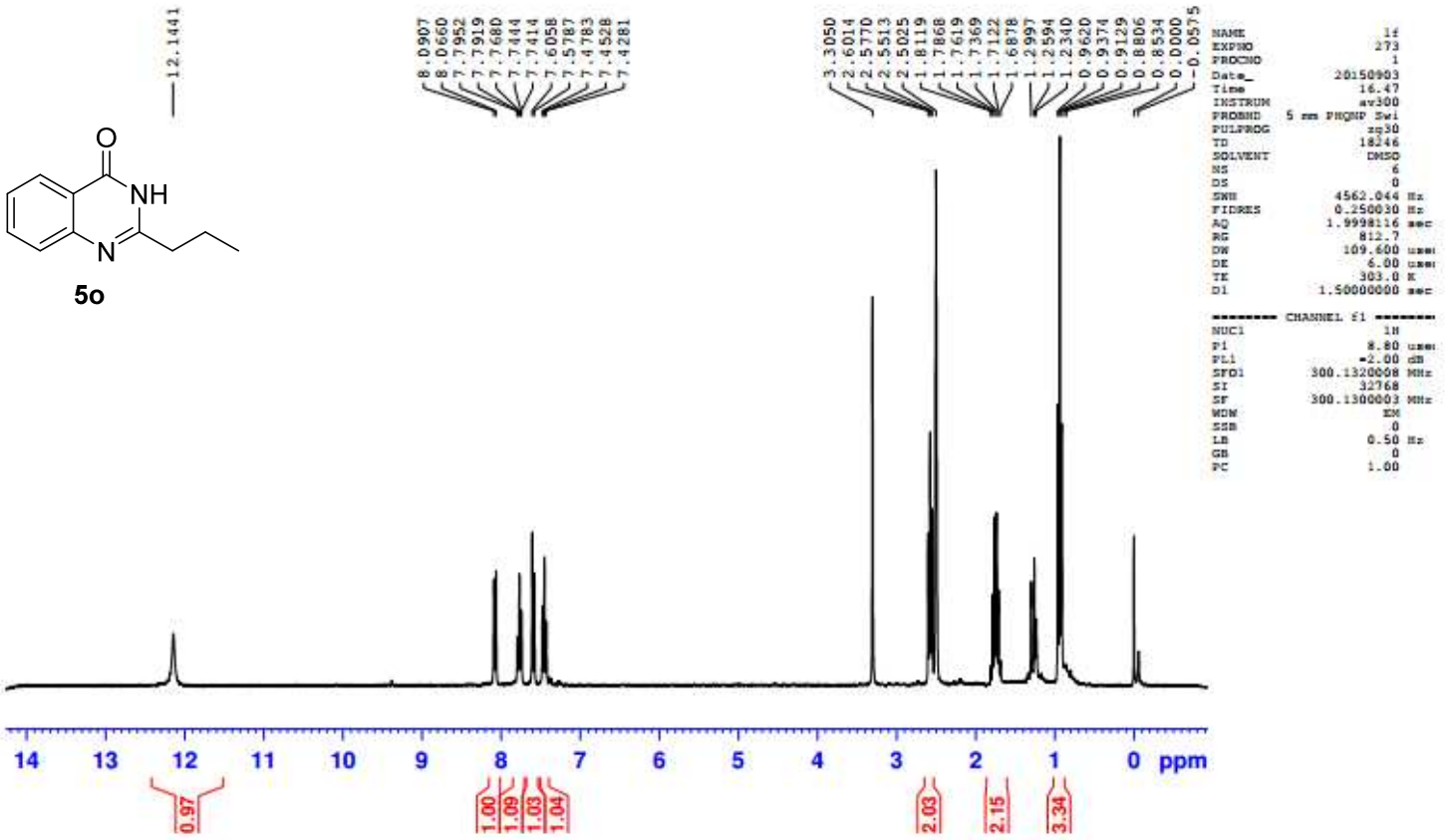
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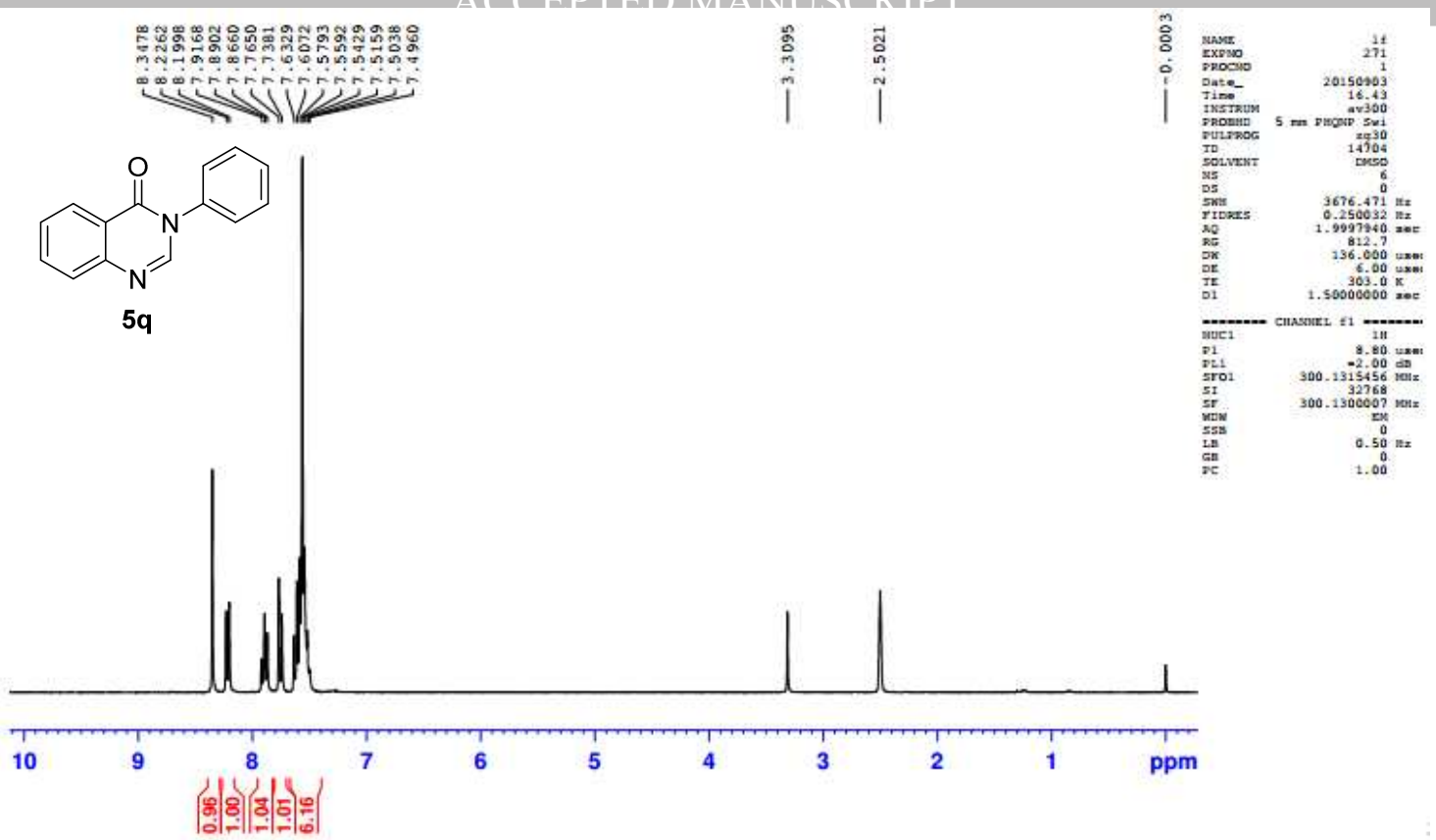
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1320008 MHz
SI 32768
SF 300.1300003 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.97
1.00
1.09
1.03
1.04
2.03
2.15
3.34

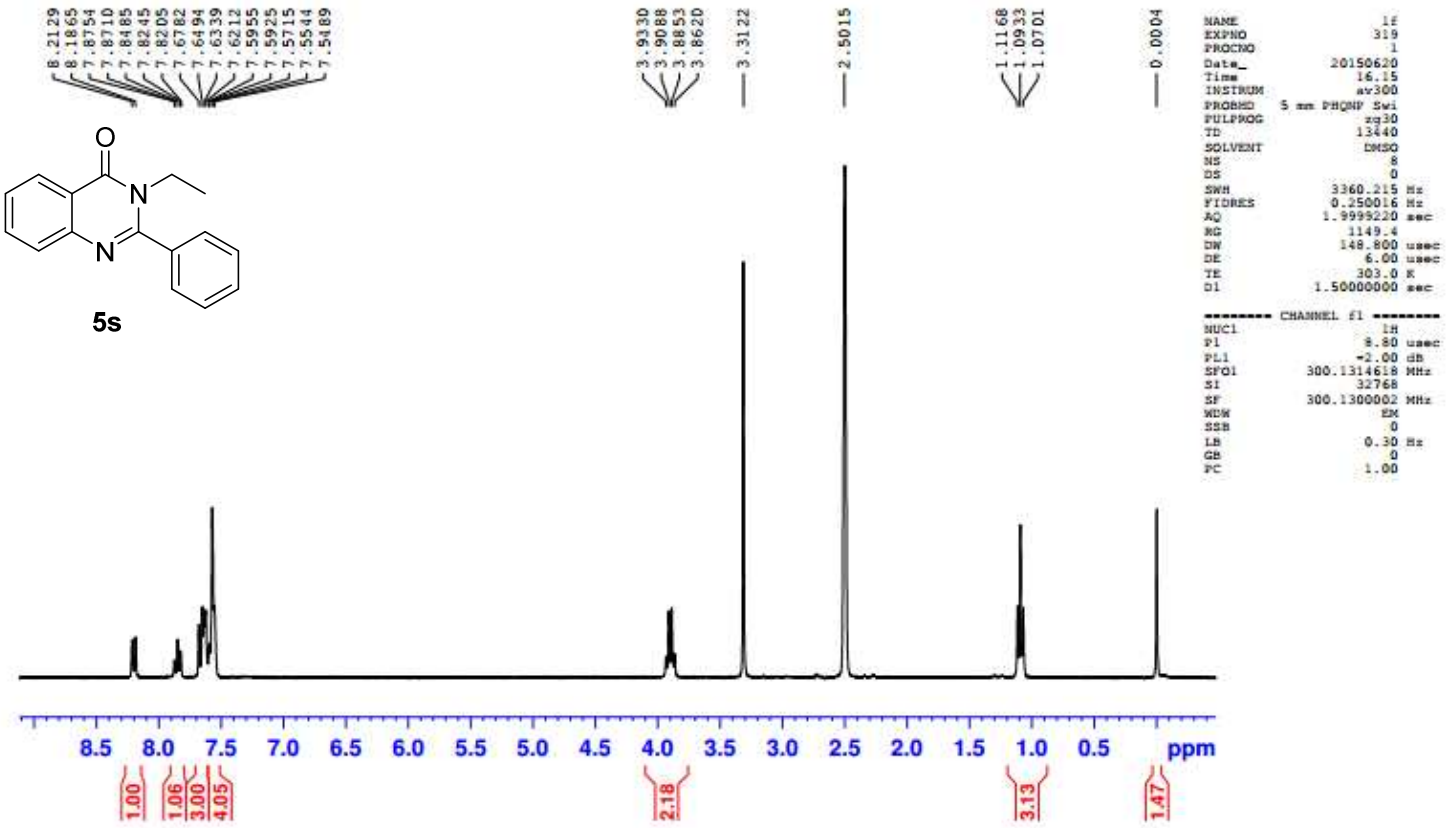
5o

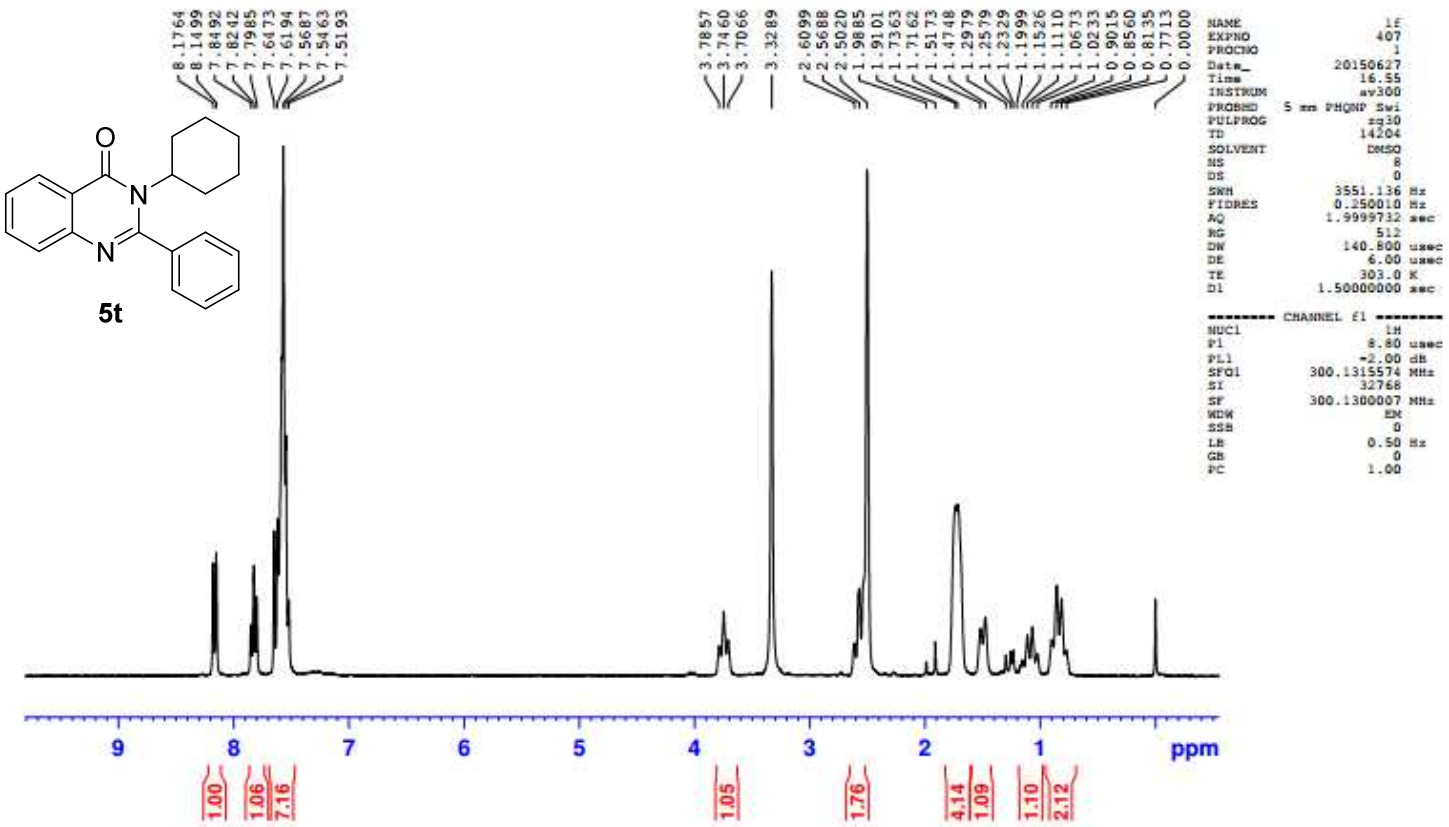
8.3710
8.1750
8.1486
7.8466
7.8208
7.7962
7.6870
7.6604
7.5685
7.5423
7.5187
3.5040
3.3163
2.5050
0.0000
NAME 1f
EXPNO 270
PROCNO 1
Date_ 20150903
Time 16.41
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 14534
SOLVENT DMSO
NS 6
DS 0
SWH 3633.721 Hz
FIDRES 0.250015 Hz
AQ 1.9999284 sec
RG 812.7
DW 137.600 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1315350 MHz
SI 32768
SF 300.1299992 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 ppm
1.01
1.00
1.06
1.00
1.08
3.16
2.04

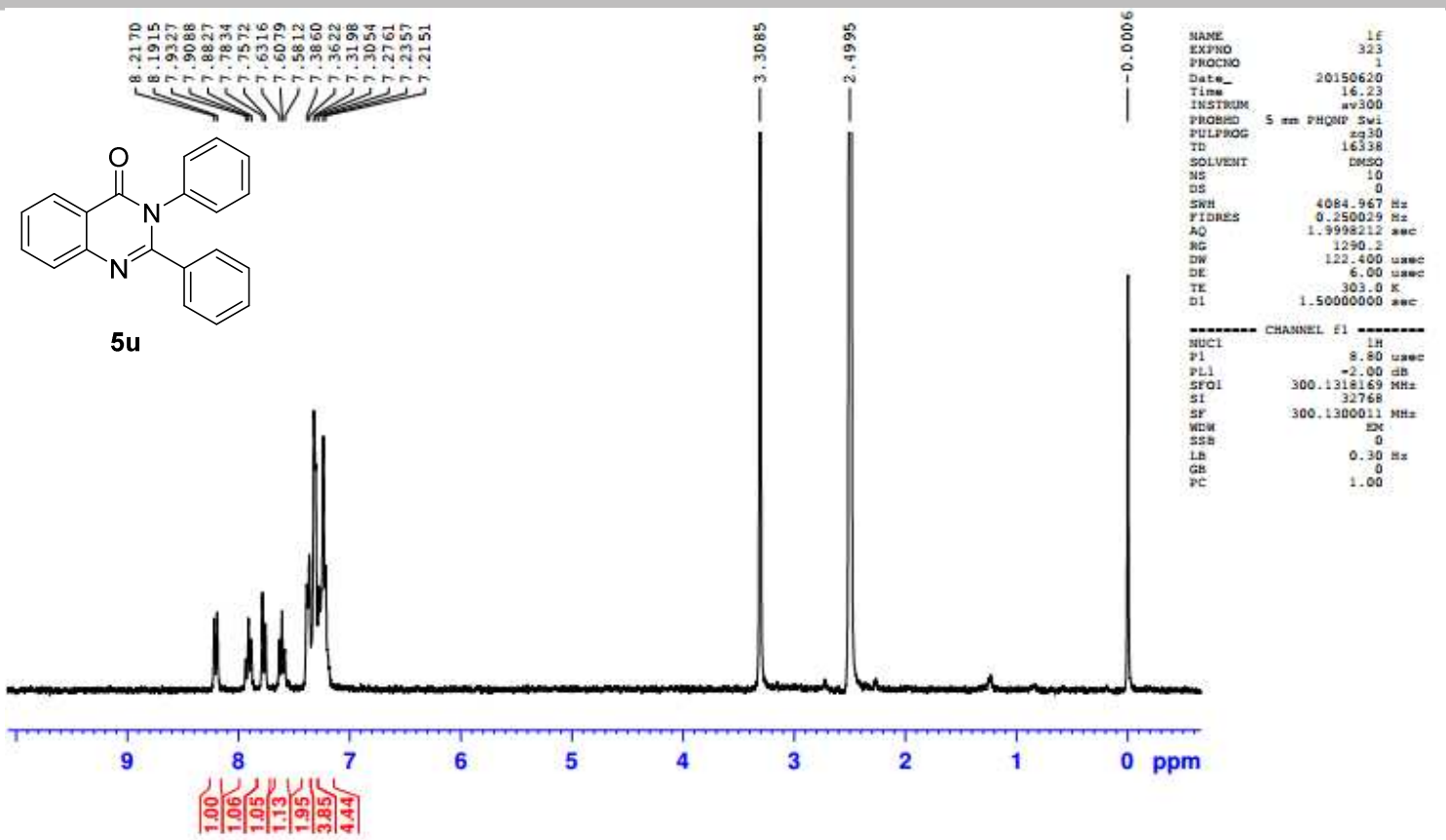
5p

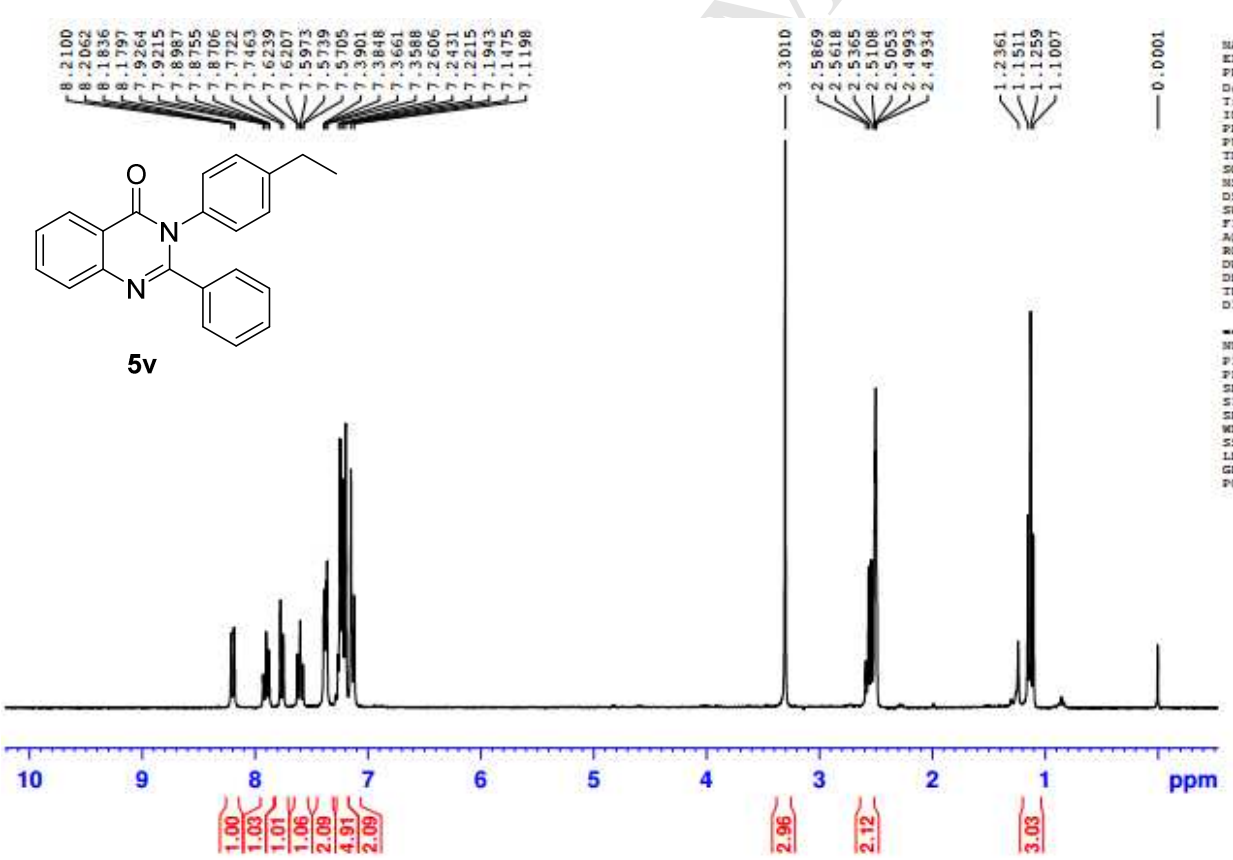

8.3478
8.2262
8.1998
7.9168
7.8902
7.8660
7.7650
7.7381
7.6329
7.6072
7.5793
7.5592
7.5429
7.5159
7.5038
7.4960
3.3095
2.5021
0.0003
5q
10
9
8
7
6
5
4
3
2
1
ppm
0.96
1.00
1.04
1.01
6.16
NAME 1f
EXPNO 271
PROCNO 1
Date_ 20150903
Time 16.43
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 14704
SOLVENT DMSO
NS 6
DS 0
SWH 3676.471 Hz
FIDRES 0.250032 Hz
AQ 1.9997940 sec
RG 812.7
DW 136.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1315456 MHz
SI 32768
SF 300.1300007 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00

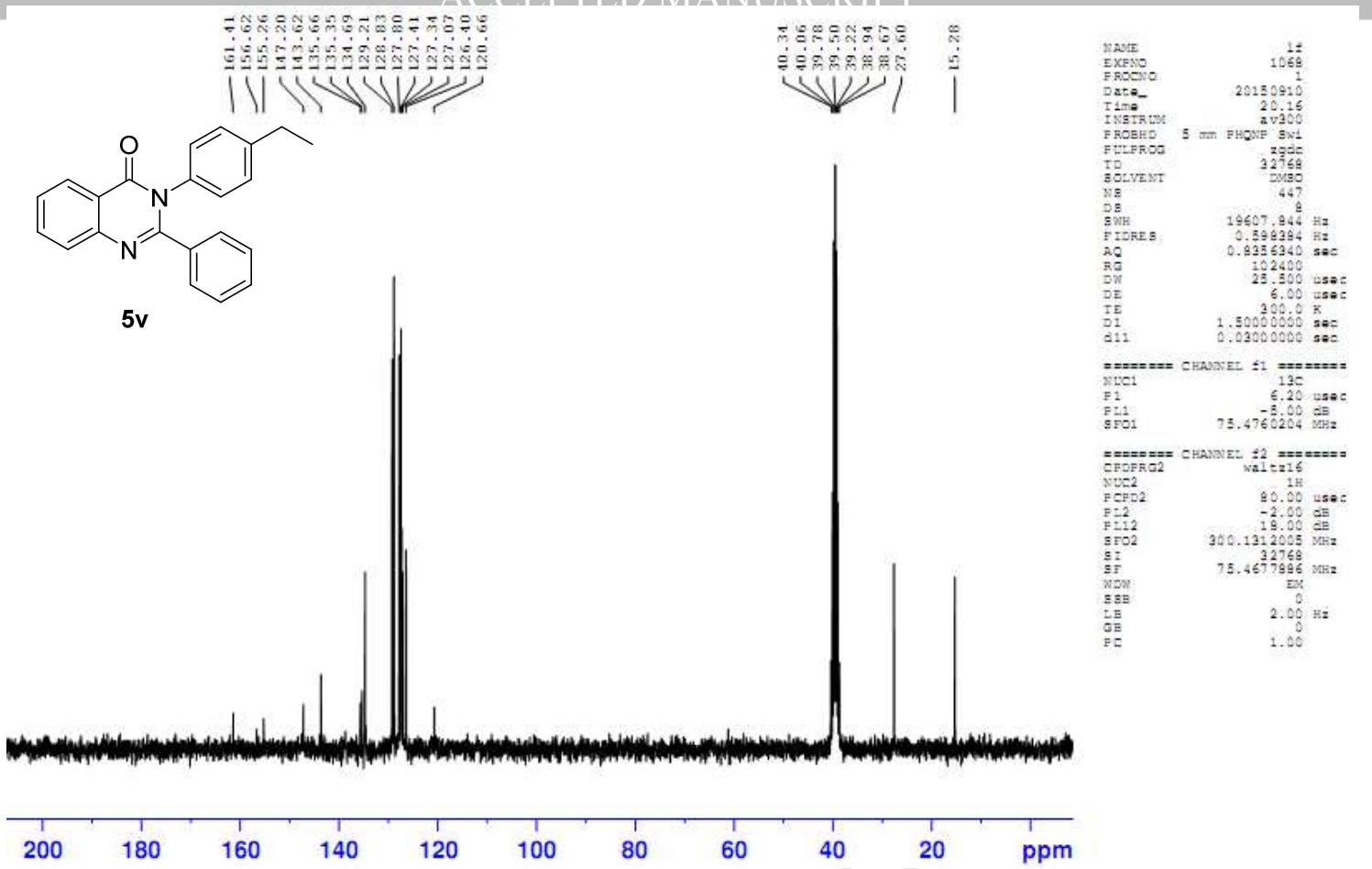
8.2053
8.1786
7.8694
7.8424
7.8180
7.6923
7.6645
7.5875
7.5616
3.3667
3.3144
2.5005
0.0005
5r
9
8
7
6
5
4
3
2
1
ppm
1.04
1.08
3.00
3.82
3.08
NAME 1f
EXPNO 530
PROCNO 1
Date_ 20150704
Time 16.08
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 14122
SOLVENT DMSO
NS 10
DS 0
SWH 3531.073 Hz
FIDRES 0.250041 Hz
AQ 1.9997252 sec
RG 1024
DW 141.600 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1315424 MHz
SI 32768
SF 300.1300014 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

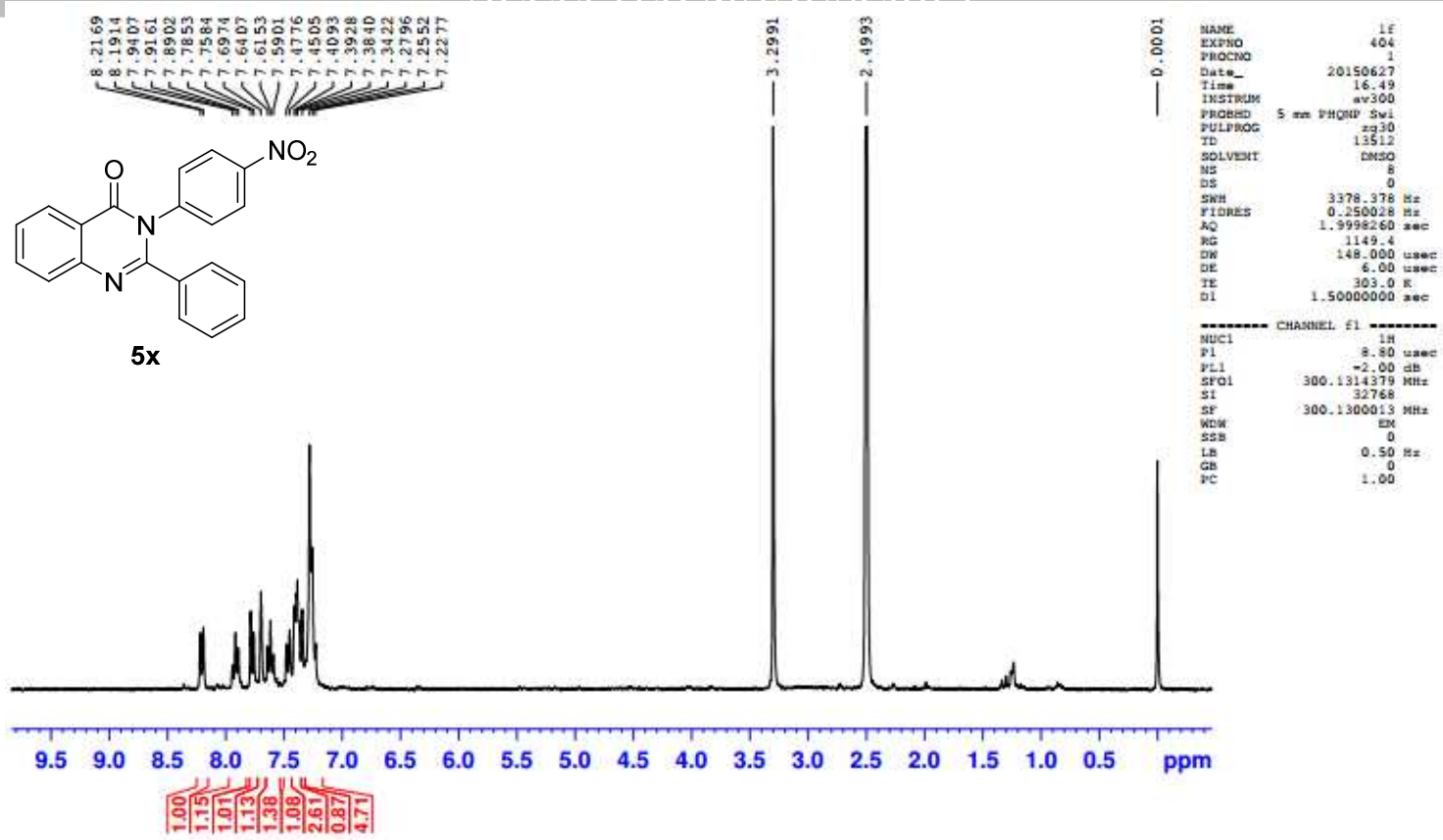

8.2129
8.1865
7.8754
7.8710
7.8485
7.8245
7.8205
7.6782
7.6494
7.6339
7.6212
7.5955
7.5925
7.5715
7.5544
7.5489
3.9330
3.9088
3.8853
3.8620
3.3122
2.5015
1.1168
1.0933
1.0701
0.0004
O
N
N
5s
NAME 1f
EXPNO 319
PROCNO 1
Date_ 20150620
Time 16.15
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 13440
SOLVENT DMSO
NS 8
DS 0
SWH 3360.215 Hz
FIDRES 0.250016 Hz
AQ 1.9999220 sec
RG 1149.4
DW 148.800 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1314618 MHz
SI 32768
SF 300.1300002 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.06
3.00
4.05
2.18
3.13
1.47

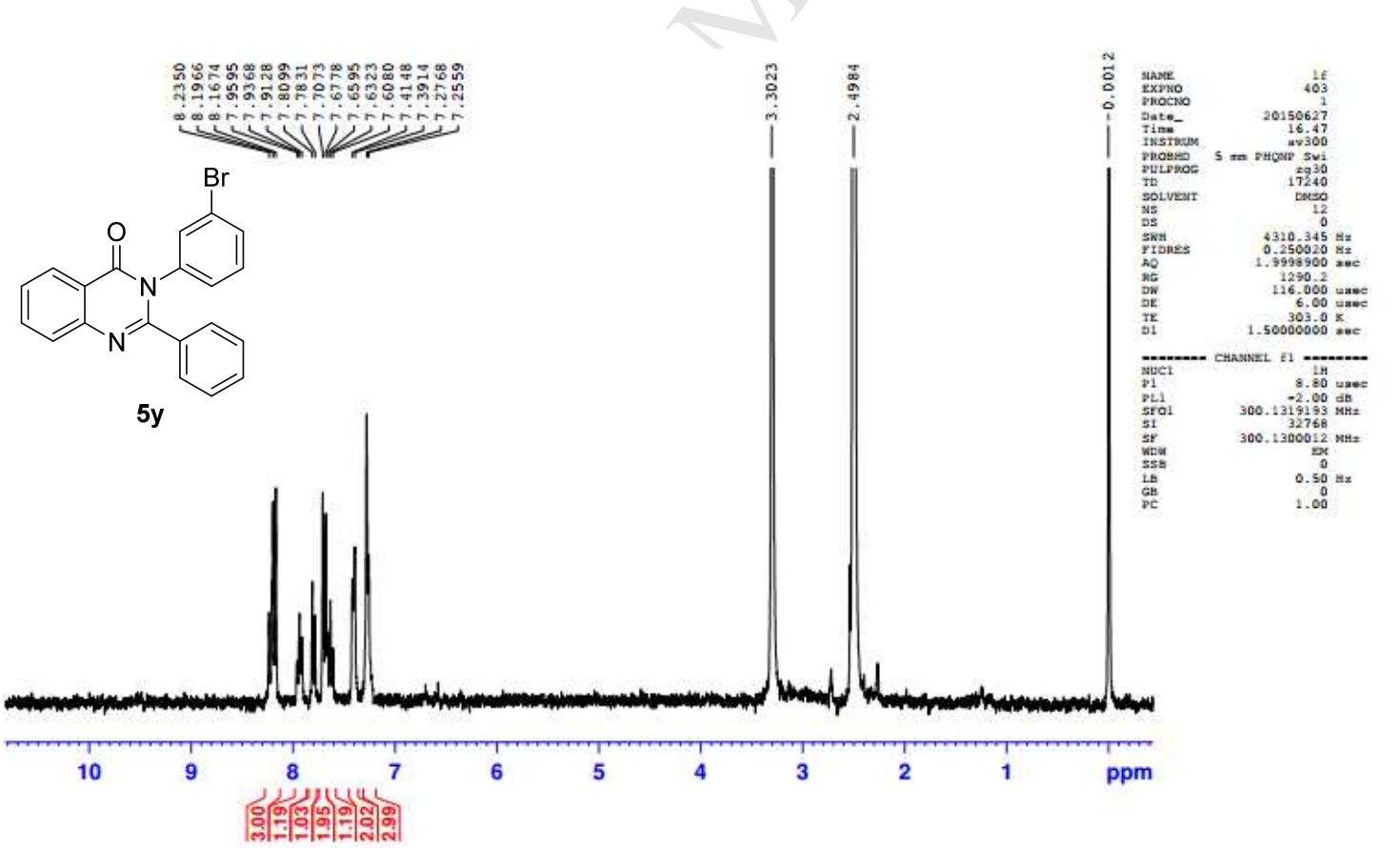

8.1764
8.1499
7.8492
7.8242
7.7985
7.6473
7.6194
7.5687
7.5463
7.5193
3.7857
3.7460
3.7066
3.3289
2.6099
2.5688
2.5020
1.9885
1.9101
1.7363
1.7162
1.5173
1.4748
1.2979
1.2579
1.2329
1.1999
1.1526
1.1110
1.0673
1.0233
0.9015
0.8560
0.8135
0.7713
0.0000
O
N
N
5t
NAME 1f
EXPNO 407
PROCNO 1
Date_ 20150627
Time 16.55
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 14204
SOLVENT DMSO
NS 8
DS 0
SWH 3551.136 Hz
FIDRES 0.250010 Hz
AQ 1.9999732 sec
RG 512
DW 140.800 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1315574 MHz
SI 32768
SF 300.1300007 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 ppm
1.00
1.06
7.16
1.05
1.76
4.14
1.09
1.10
2.12

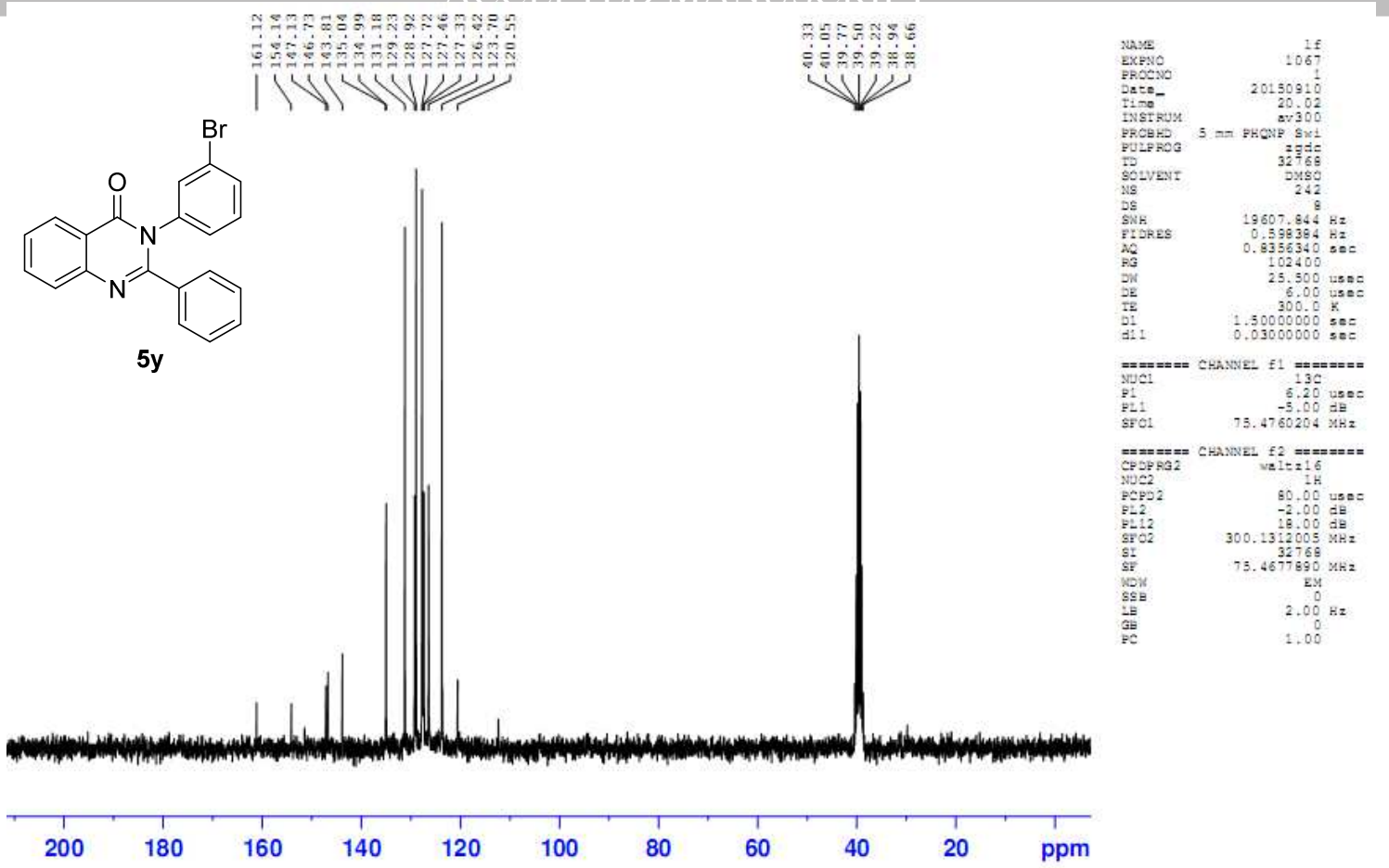

8.2170
8.1915
7.9327
7.9088
7.8827
7.7834
7.7572
7.6316
7.6079
7.5812
7.3860
7.3622
7.3198
7.3054
7.2761
7.2357
7.2151
3.3085
2.4995
0.0006
O
N
N
5u
NAME 1f
EXPNO 323
PROCNO 1
Date_ 20150620
Time 16.23
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 16338
SOLVENT DMSO
NS 10
DS 0
SWH 4084.967 Hz
FIDRES 0.250029 Hz
AQ 1.9998212 sec
RG 1290.2
DW 122.400 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1318169 MHz
SI 32768
SF 300.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.06 1.05 1.13 1.95 3.85 4.44

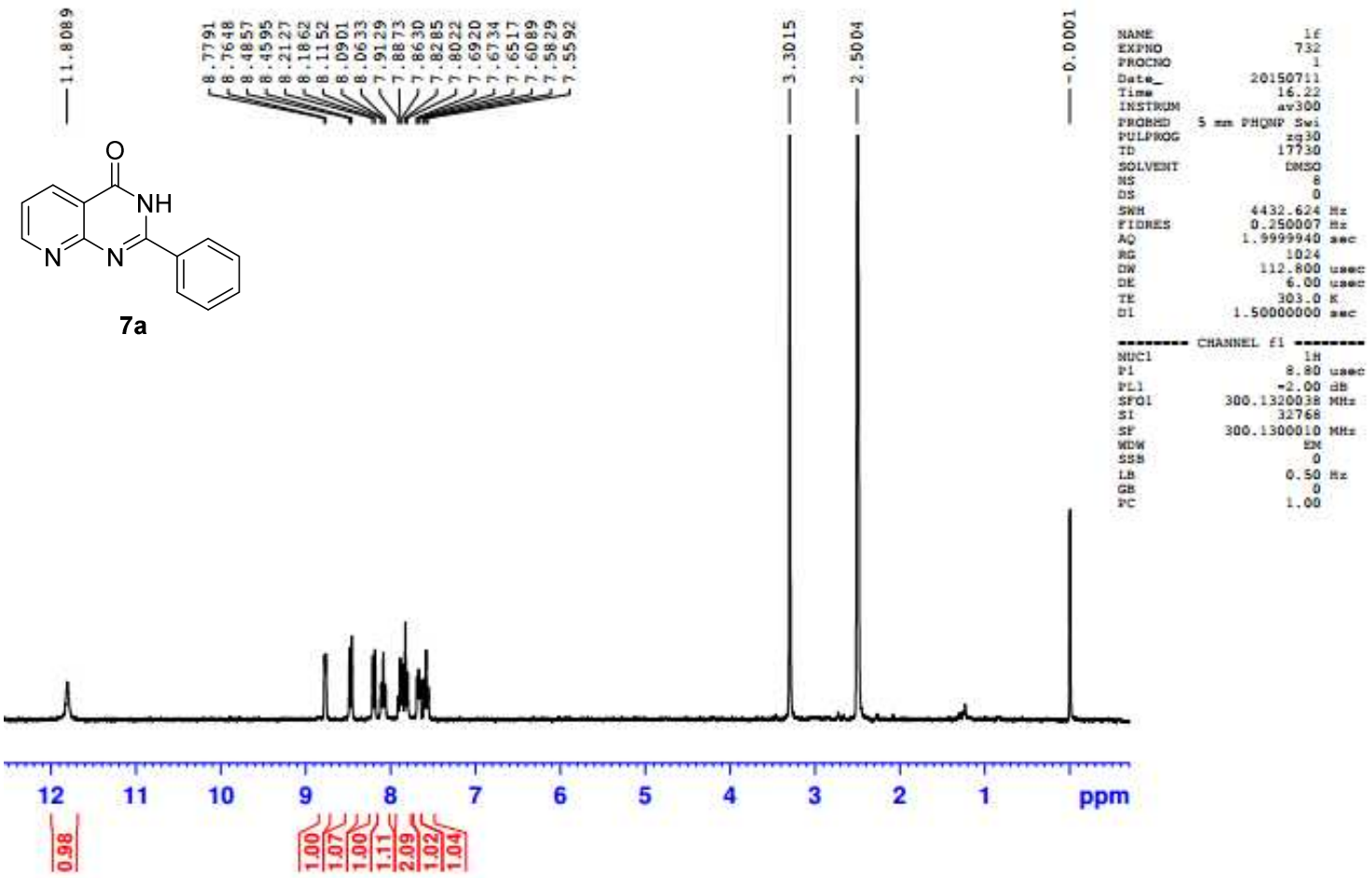

8.2100
8.2062
8.1836
8.1797
7.9264
7.9215
7.8987
7.8755
7.8706
7.7722
7.7463
7.6239
7.6207
7.5973
7.5739
7.5705
7.3901
7.3848
7.3661
7.3588
7.2606
7.2431
7.2215
7.1943
7.1475
7.1198
3.3010
2.5869
2.5618
2.5365
2.5108
2.5053
2.4993
2.4934
1.2361
1.1511
1.1259
1.1007
0.0001
O
N
N
5v
NAME 1f
EXPNO 268
PROCNO 1
Date_ 20150903
Time 16.37
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 14044
SOLVENT DMSO
NS 6
DS 0
SWH 3511.236 Hz
FIDRES 0.250017 Hz
AQ 1.9999156 sec
RG 812.7
DW 142.400 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1314895 MHz
SI 32768
SF 300.1300014 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 ppm
1.00 1.03 1.01 1.06 2.09 4.91 2.09
2.96 2.12 3.03

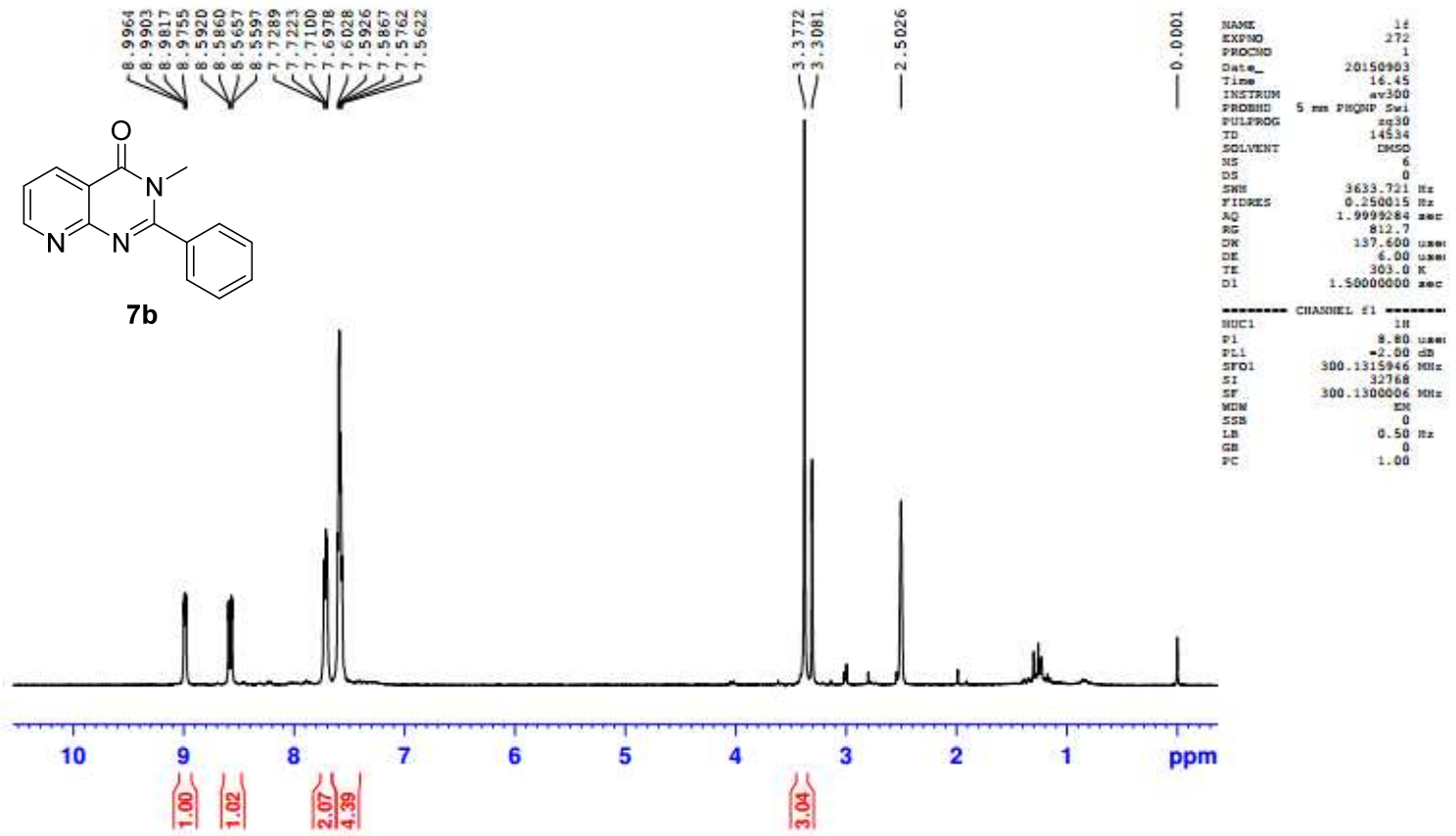


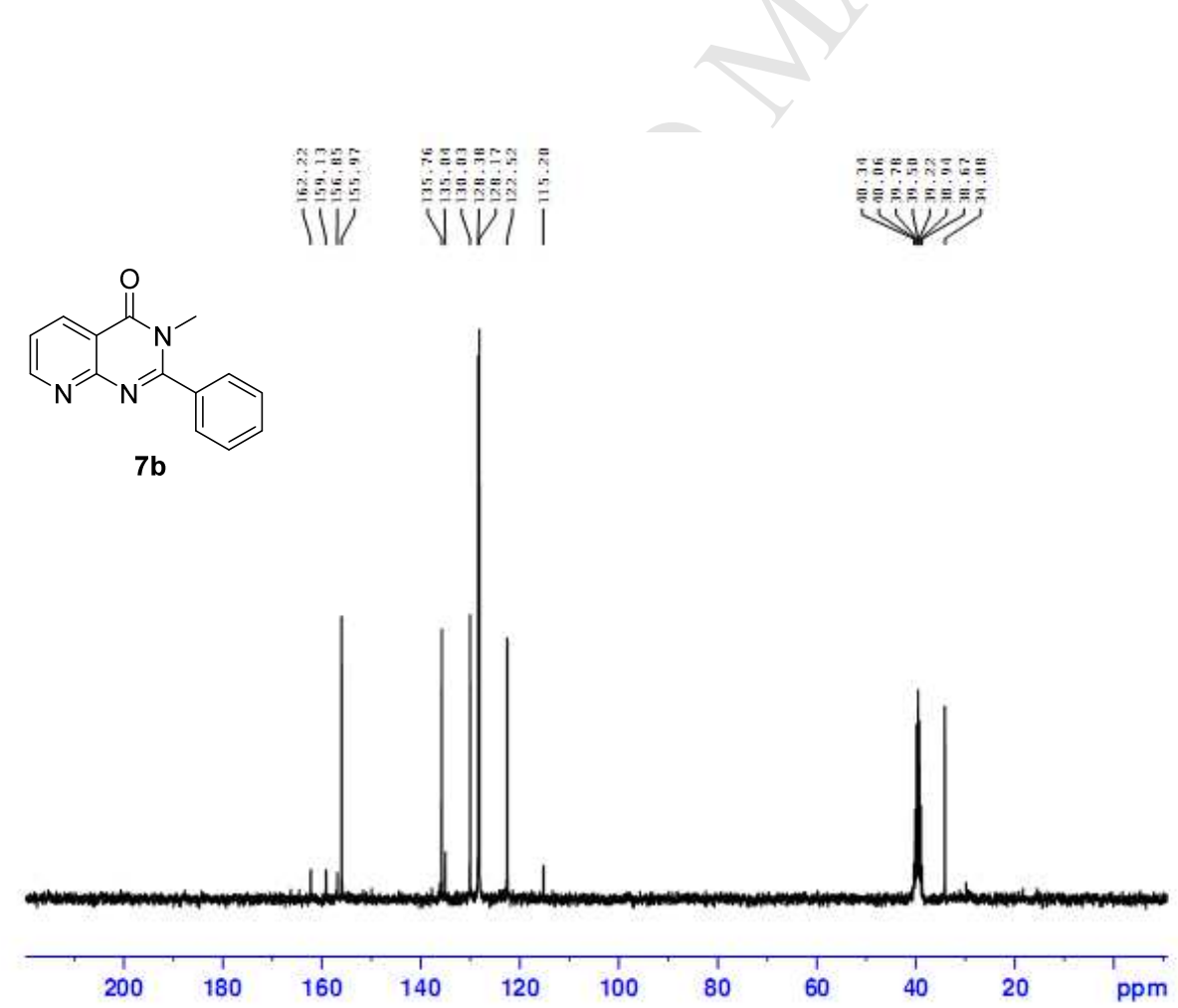

8.2169
8.1914
7.9407
7.9161
7.8902
7.7853
7.7584
7.6974
7.6407
7.6153
7.5901
7.4776
7.4505
7.4093
7.3928
7.3840
7.3422
7.2796
7.2552
7.2277
3.2991
2.4993
0.0001
O
N
N
NO2
5x
NAME 1f
EXPNO 404
PROCNO 1
Date_ 20150627
Time 16.49
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 13512
SOLVENT DMSO
NS 8
DS 0
SWH 3378.378 Hz
FIDRES 0.250028 Hz
AQ 1.9998260 sec
RG 1149.4
DW 148.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1314379 MHz
SI 32768
SF 300.1300013 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 1.15 1.01 1.13 1.38 1.08 2.61 0.87 4.71

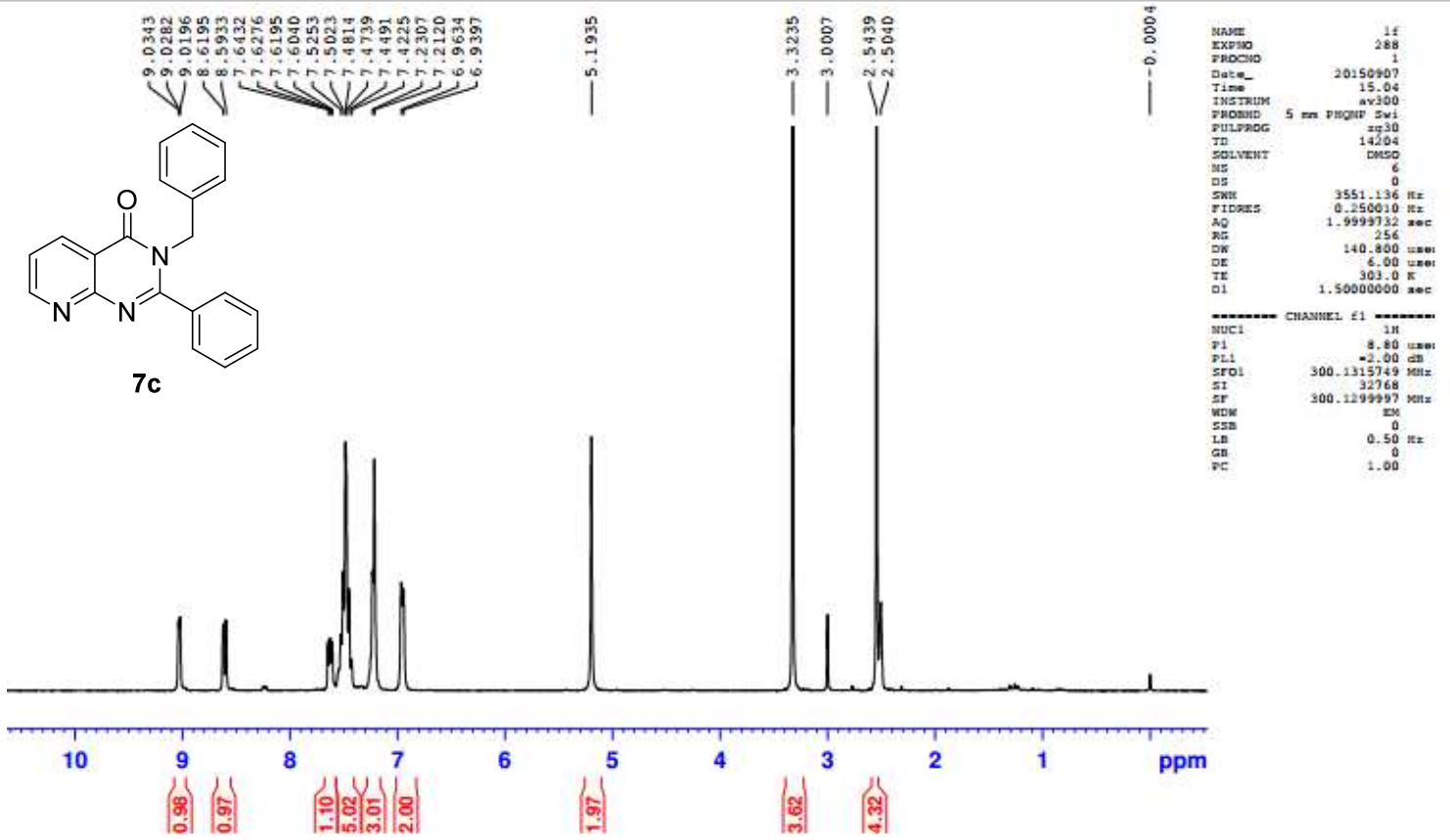

8.2350
8.1966
8.1674
7.9595
7.9368
7.9128
7.8099
7.7831
7.7073
7.6778
7.6595
7.6323
7.6080
7.4148
7.3914
7.2768
7.2559
3.3023
2.4984
0.0012
O
N
N
Br
5y
NAME 1g
EXPNO 403
PROCNO 1
Date_ 20150627
Time 16.47
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 17240
SOLVENT DMSO
NS 12
DS 0
SWH 4310.345 Hz
FIDRES 0.250020 Hz
AQ 1.9998900 sec
RG 1290.2
DW 116.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1319193 MHz
SI 32768
SF 300.1300012 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 ppm
3.00 1.19 1.03 1.95 1.19 2.02 2.99


161.12
154.14
147.13
146.73
143.81
135.04
134.99
131.18
129.23
128.92
127.72
127.46
127.33
126.42
123.70
120.55
60.33
60.05
39.77
39.50
39.22
38.94
38.66
Br
O
N
N
5y
NAME 1f
EXPNO 1067
PROCNO 1
Date_ 20150910
Time 20.02
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zgdc
TD 32768
SOLVENT DMSO
NS 242
DS 8
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 102400
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
d11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 6.20 usec
PL1 -5.00 dB
SFO1 75.4760204 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 18.00 dB
SFO2 300.1312005 MHz
SI 32768
SF 75.4677890 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
200
180
160
140
120
100
80
60
40
20
ppm


11.8089
8.7791
8.7648
8.4857
8.4595
8.2127
8.1862
8.1152
8.0901
8.0633
7.9129
7.8873
7.8630
7.8285
7.8022
7.6920
7.6734
7.6517
7.6089
7.5829
7.5592
3.3015
2.5004
0.0001
O
NH
N
N
7a
NAME 1f
EXPNO 732
PROCNO 1
Date_ 20150711
Time 16.22
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 17730
SOLVENT DMSO
NS 8
DS 0
SWH 4432.624 Hz
FIDRES 0.250007 Hz
AQ 1.9999940 sec
RG 1024
DW 112.800 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1320038 MHz
SI 32768
SF 300.1300010 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.00
1.07
1.00
1.11
2.09
1.02
1.04

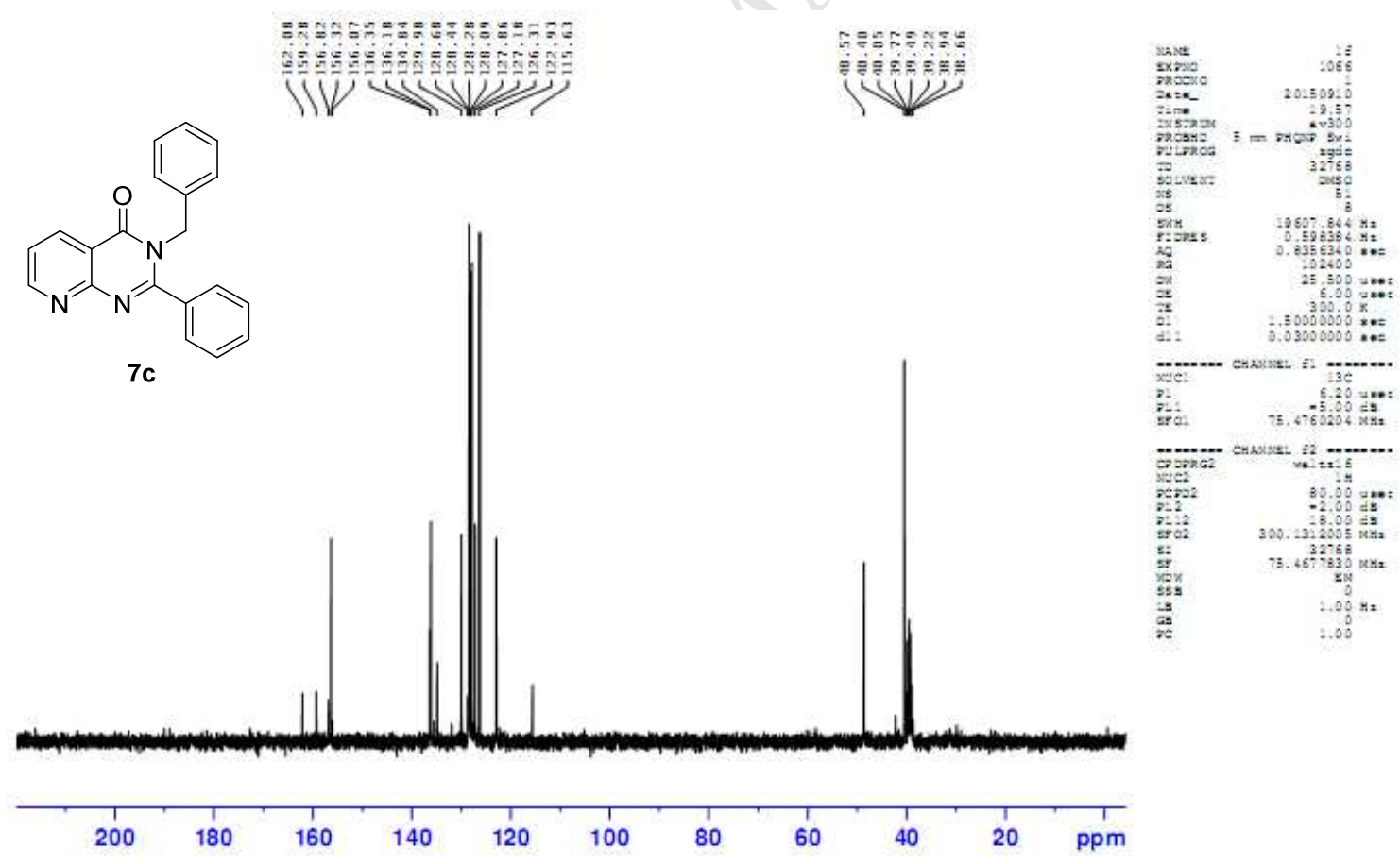

8.9964
8.9903
8.9817
8.9755
8.5920
8.5860
8.5657
8.5597
7.7289
7.7223
7.7100
7.6978
7.6028
7.5926
7.5867
7.5762
7.5622
3.3772
3.3081
2.5026
0.0001
O
N
N
N
7b
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
2.07
4.39
3.04
NAME 1f
EXPNO 272
PROCNO 1
Date_ 20150903
Time 16.45
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 14534
SOLVENT DMSO
NS 6
DS 0
SWH 3633.721 Hz
FIDRES 0.250015 Hz
AQ 1.9999284 sec
RG 812.7
DW 137.600 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1315946 MHz
SI 32768
SF 300.1300006 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00


162.22
159.13
156.85
155.97
135.76
135.04
130.83
128.38
128.17
122.52
115.28
40.34
40.06
39.78
39.50
39.22
38.94
38.67
38.38
O
N
N
N
7b
200
180
160
140
120
100
80
60
40
20
ppm
NAME 1f
EXPNO 1064
PROCNO 1
Date_ 20150910
Time 19.26
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zgpg
TD 18114
SOLVENT DMSO
NS 269
DS 8
SWH 19607.844 Hz
FIDRES 1.082469 Hz
AQ 0.4613870 sec
RG 10240
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
d11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 6.20 usec
PL1 -5.00 dB
SFO1 75.4760204 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 18.00 dB
SFO2 300.1312005 MHz
SI 32768
SF 75.4677881 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00




```
NAME                 1f
EXPNO                288
PROCNO               1
Date_          20150907
Time               15.04
INSTRUM            av300
PROBHD   5 mm PHQNP Swi
PULPROG            zg30
TD                14204
SOLVENT            DMSO
NS                    6
DS                    0
SWH          3551.136 Hz
FIDRES       0.250010 Hz
AQ           1.9999732 sec
RG                  256
DW           140.800 usec
DE             6.00 usec
TE             303.0 K
D1          1.50000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1              8.80 usec
PL1            -2.00 dB
SFO1    300.1315749 MHz
SI                32768
SF      300.1299997 MHz
WDW                  EM
SSB                   0
LB             0.50 Hz
GB                    0
PC                 1.00
```




```
NAME                 1f
EXPNO                1066
PROCNO               1
Date_          20150910
Time               19.57
INSTRUM            av300
PROBHD   5 mm PHQNP Swi
PULPROG            zgpg
TD                32768
SOLVENT            DMSO
NS                   51
DS                    8
SWH         19607.844 Hz
FIDRES       0.598384 Hz
AQ           0.8356340 sec
RG                 10240
DW             25.500 usec
DE              6.00 usec
TE             300.0 K
D1          1.50000000 sec
d11         0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1              6.20 usec
PL1            -5.00 dB
SFO1    75.4760204 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2           80.00 usec
PL2             -2.00 dB
PL12            18.00 dB
SFO2    300.1312005 MHz
SI                32768
SF      75.4677830 MHz
WDW                  EM
SSB                   0
LB             1.00 Hz
GB                    0
PC                 1.00
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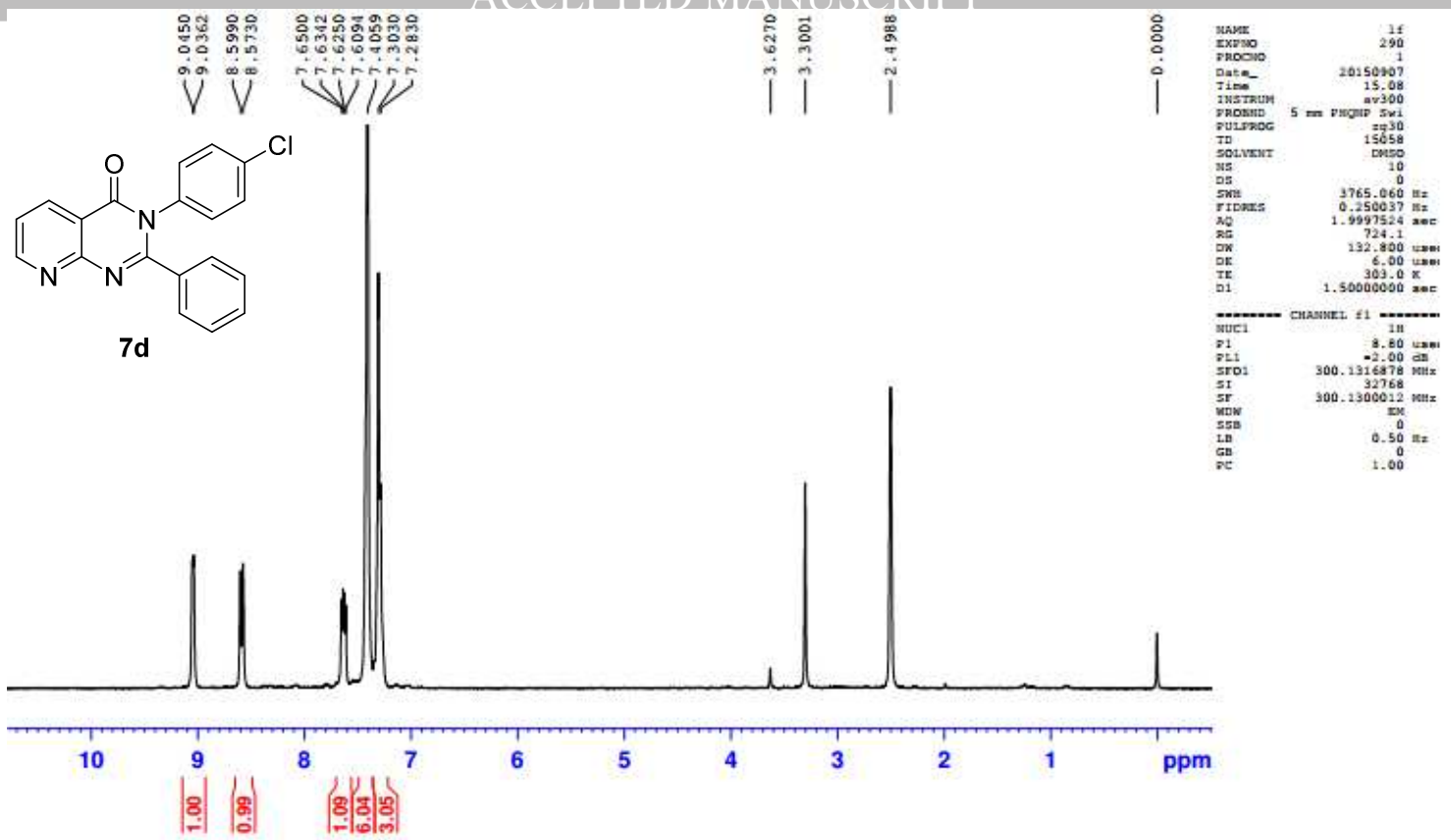
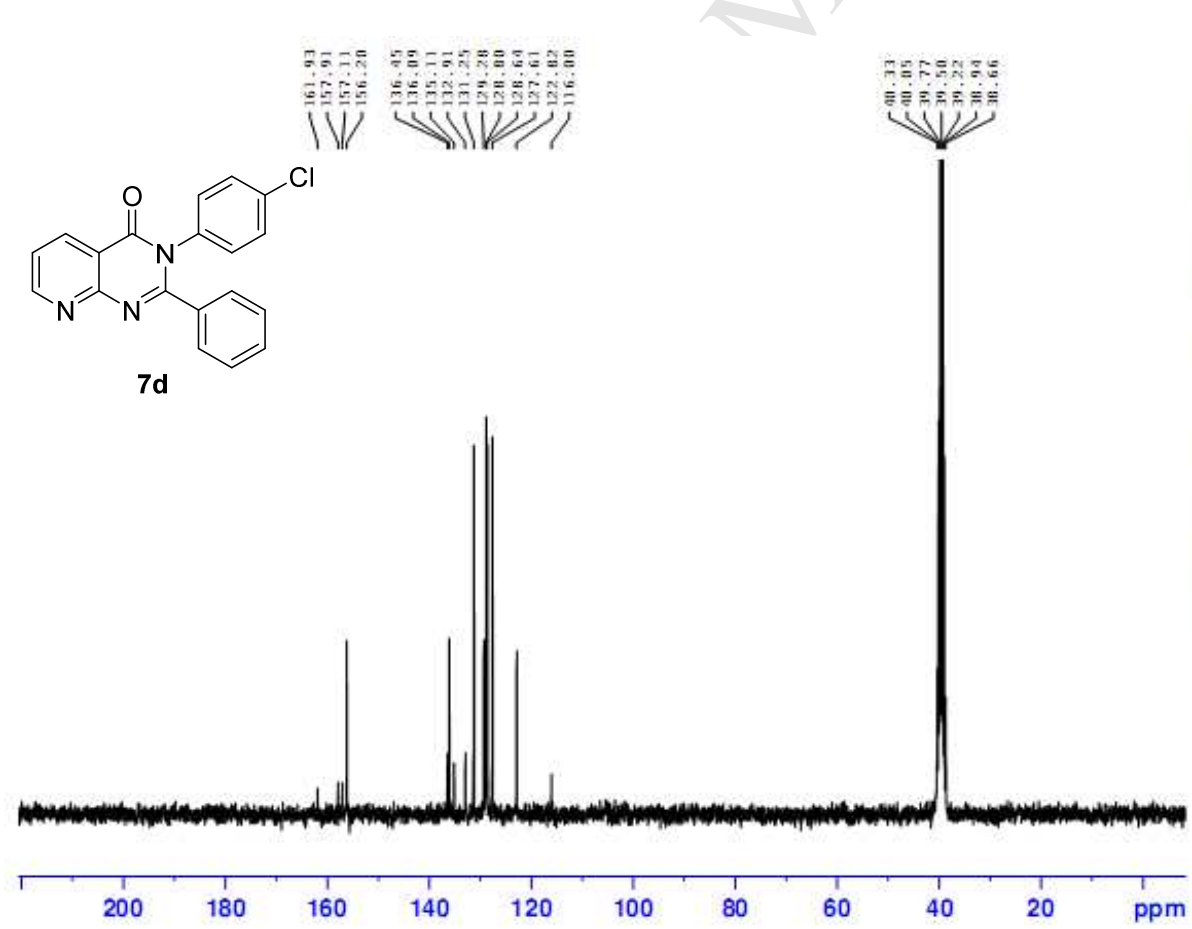

9.0450
9.0362
8.5990
8.5730
7.6500
7.6342
7.6250
7.6094
7.4059
7.3030
7.2830
3.6270
3.3001
2.4988
0.0000
O
N
N
N
Cl
7d
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.99
1.09
6.04
3.05
NAME 1f
EXPNO 290
PROCNO 1
Date_ 20150907
Time 15.08
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zg30
TD 15058
SOLVENT DMSO
NS 10
DS 0
SWH 3765.060 Hz
FIDRES 0.250037 Hz
AQ 1.9997524 sec
RG 724.1
DW 132.800 usec
DE 6.00 usec
TE 303.0 K
D1 1.50000000 sec
CHANNEL f1
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 300.1316878 MHz
SI 32768
SF 300.1300012 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.00


161.93
157.91
157.11
156.20
136.45
136.09
135.11
132.91
131.25
129.28
128.80
128.64
127.61
122.82
116.80
40.33
40.05
39.77
39.50
39.22
38.94
38.66
O
N
N
N
Cl
7d
200
180
160
140
120
100
80
60
40
20
ppm
NAME 1f
EXPNO 1065
PROCNO 1
Date_ 20150910
Time 19.37
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zgpg
TD 32768
SOLVENT DMSO
NS 447
DS 8
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 102400
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
D11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 6.20 usec
PL1 -5.00 dB
SFO1 75.4760204 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 18.00 dB
SFO2 300.1312005 MHz
SI 32768
SF 75.4677893 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00