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## Graphical Abstract

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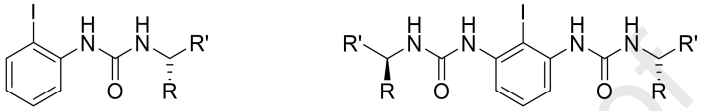

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# Design and synthesis of chiral urea-derived iodoarenes and their assessment in the enantioselective dearomatizing cyclization of a naphthyl amide

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ABSTRACT

A novel family of urea-derived chiral iodoarenes was designed and synthesized for use in enantioselective iodine(I/III) catalysis. Their preparation required the development of a bidirectional synthetic strategy. These new chiral iodoarenes were assessed as catalysts in the dearomatizing cyclization of a naphthyl amide and provided moderate yields of product in some cases with low enantioselectivities.



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## 1. Introduction

Enantioselective reactions mediated or catalyzed by chiral hypervalent iodine reagents or chiral iodoarene precatalysts have attracted significant attention over the past decade.[1] In this regard, a variety of chiral iodoarene backbones have been reported; however, the most successful, and most reported, framework is the bislactate ethers **1** and **2** reported independently by Fujita and Ishihara (Fig. 1).[2,3] A number of modifications of this skeleton have been investigated,[4] as each new application often requires a new derivative for optimal results. Other reported chiral iodoarenes include Zhang's spirobiindane derivative **3**,[5] Quideau's helicene **4**,[6] Maruoka's indane **5**,[7] Ibrahim's dimethanoanthracene **6**,[8] and Moran's pseudoephedrine derivative **7**.[9] More recently, Nachtsheim reported his second generation triazole catalyst **8** which appears to yield superior selectivities in a range of enantioselective oxidation reactions.[10] It is clear that, as in other areas of enantioselective catalysis, there is no panacea and the investigation of new chiral iodoarenes and hypervalent iodine reagents is still of interest and importance.

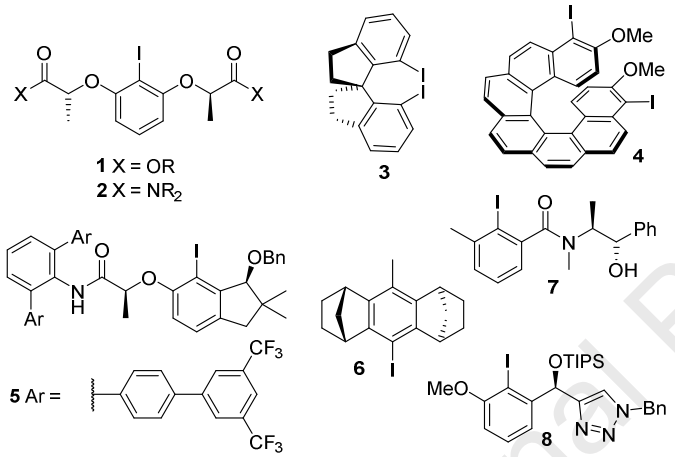
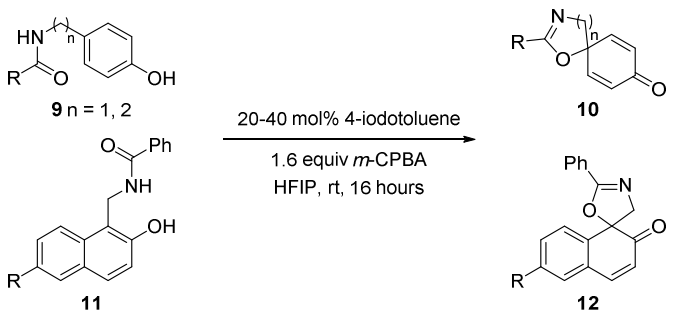



**Fig. 1.** Examples of chiral iodoarenes

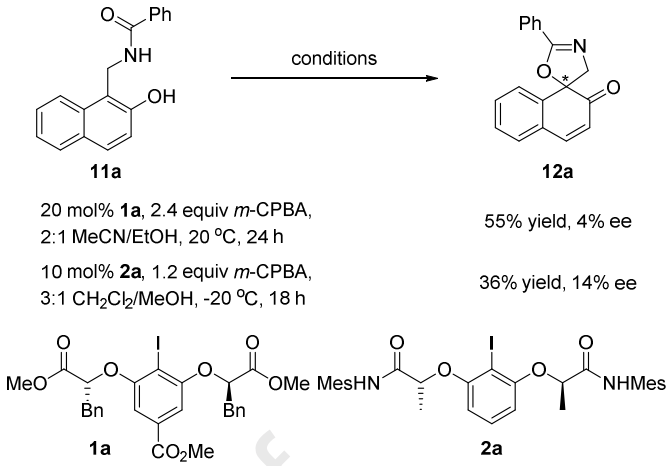
We recently reported the dearomatizing cyclization of phenols and naphthols with pendent amides catalyzed by iodoarenes (Scheme 1).[11] We envisaged that the use of chiral iodoarene precatalysts would enable the enantioselective cyclization of the naphthols.




**Scheme 1.** Dearomatizing cyclization of phenols and naphthols bearing pendent amides

## 2. Results and Discussion

At the outset of the project we tested the efficacy of the known iodoarenes **1a** and **2a** on their ability to catalyze the dearomatizing cyclization of naphthol **11a**.[12] After some experimentation with differentwe did weeyes solvents and temperature, the best selectivity observed with **1a** was 4% ee and with **2a** was 14% ee (Scheme 2). These preliminary observations but that an alternative catalyst structure would probably be required for high levels of enantioinduction.




**Scheme 2.** Initial attempts at the dearomatizing cyclization of naphthyl amide **11a**

At this juncture we wished to design a new family of chiral iodoarenes for use in iodine(I/III) catalysis and investigate their efficacy in the enantioselective dearomatizing cyclization of naphthols. Specifically, we aimed to prepare novel iodoarenes that could potentially form helical structures in solution in a similar manner to lactates **1** and **2**, as shown by Muñiz.[13] It is known that oligomeric ureas can adopt helical conformations,[14,15] therefore we designed a small family of iodoarenes containing urea appendages (Fig. 2).[16] It was anticipated that ureas **13** would be readily prepared from the isocyanate **14**, itself derived from 2-iodoaniline **15**. In a similar manner, the $C_2$ symmetric bisureas **16** would be obtained from isocyanates **18**, which could be prepared from bisanilines **18** or dicarboxylic acids **19**. We knew that these ureas would not display helicity, as a chain of at least four ureas would be required, but this was our starting point.

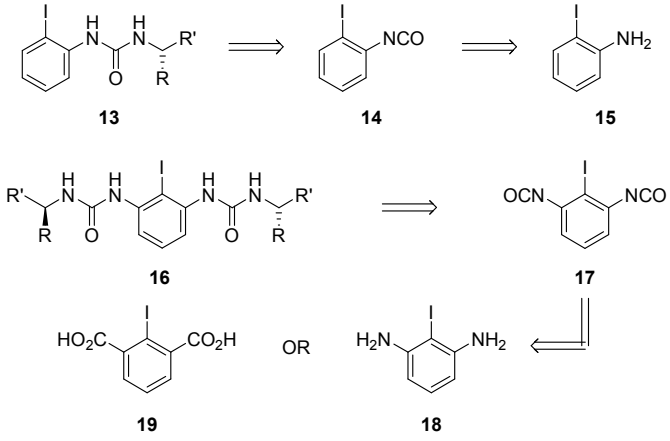
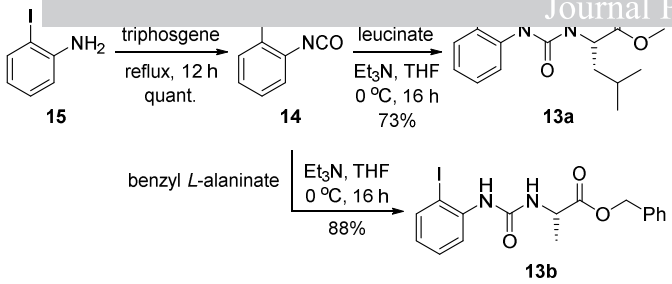


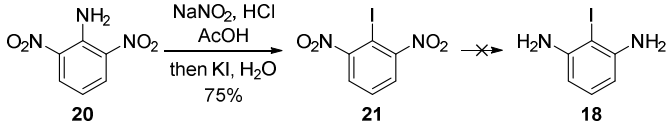

**Fig. 2.** Retrosynthesis of novel chiral iodoarenes **13** and **16** containing urea appendages

In the event, 2-iodoaniline **15** was readily converted into isocyanate **14**, by the literature procedure,[17] and this was efficiently transformed into ureas **13a** and **13b** in very good yields under typical reaction conditions (Scheme 3).



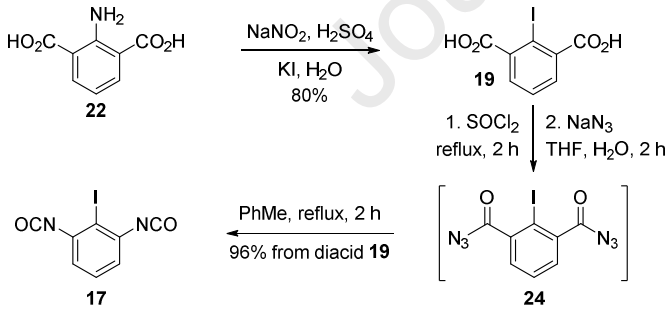

**Scheme 3.** Preparation of ureas **13a** and **13b**

Delighted by this success, we endeavored to prepare bisaniline **18** by an identical, but two-directional, two-step protocol starting from commercially available 2,6-dinitroaniline **20** (Scheme 4). Initial conversion of the amino group to an iodide through diazotization proceeded to give **21** in good yield,[18] however subsequent attempts to reduce the two nitro groups were unsuccessful. Treatment with Fe powder (under a variety of conditions), $H_2$ gas or hydrazine over Pd on charcoal, and trichlorosilane were all ineffective. In all cases studied, partial reductions and/or side reactions including deiodination were observed.



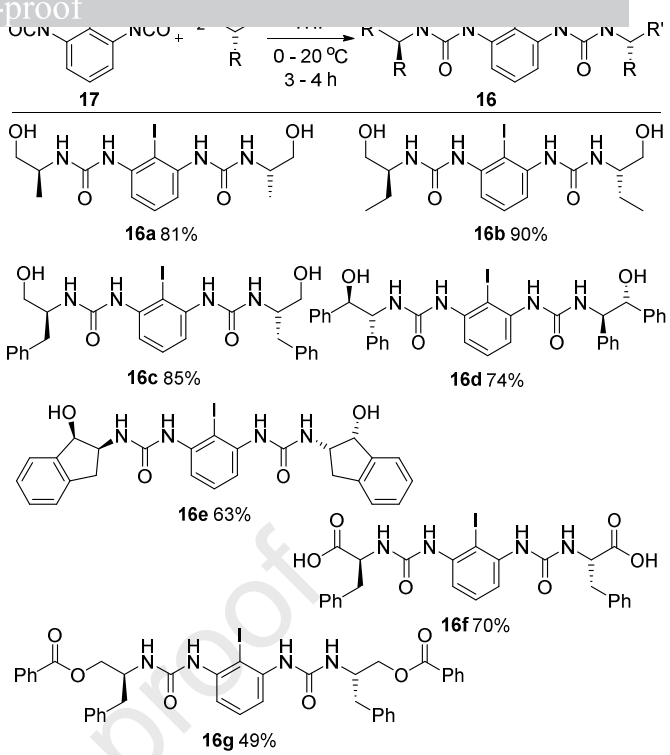

**Scheme 4.** Initial attempts to prepare bisaniline **18**

Accordingly, we turned our attention to the second route starting from 2-aminoisophthalic acid **22**; this was converted readily into iodide **19** in 80% yield (Scheme 5).[19] Conversion of the carboxylic acid directly to the isocyanate **17** using diphenylphosphoroyl azide was unsuccessful; however, successive conversion to the acid chloride and the azide **24** led to the isocyanate **17** in quantitative yield by a Curtius rearrangement.



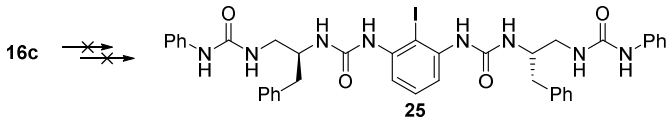

**Scheme 5.** Successful route to bisisocyanate **17**

With the isocyanate **17** in hand, a variety of bisureas were prepared by addition of amines in THF (Scheme 6). A range of amino alcohols were used to generate ureas **16a**-**16e**, which carry primary or secondary alcohols apparently ready for further derivatization. **16f** has terminal carboxylic acid groups prone for further functionalization. Finally, **16g** is the benzoyl ester of **16c**, although it was prepared by the coupling reaction shown rather than esterification.



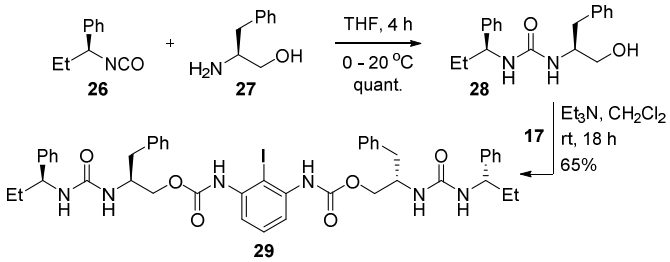

**Scheme 6.** Preparation of bisureas **16**

Attempts to convert bisurea **16c** into tetraurea **25** via conversion of the primary alcohols into tosylates or primary amines were unsuccessful (Scheme 7). In both cases, mixtures of unknown compounds were formed. Similarly, attempts to convert the carboxylic acids in **16f** into amides via acid chloride formation were unproductive. These ureas **16a-f** exhibit low solubility in organic solvents, which could explain the difficulties faced in their synthetic manipulation.




**Scheme 7.** Unsuccessful attempts to prepare tetraurea **25**

Next, we prepared alcohol **28**, which contained a urea functionality, and coupled this with bisisocyanate **17** (Scheme 8). The desired product **29**, which contained two urethanes and two ureas, was isolated in good yield.

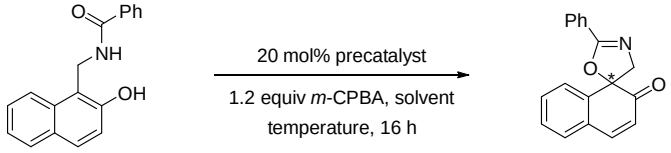



**Scheme 8.** Preparation of mixed urethane-urea **29**

The ability of these 10 novel urea-containing chiral iodoarenes to effect the enantioselective dearomatizing cyclization of naphthyl amide **11a** was investigated (Table 1). A subset of the experiments undertaken are presented but it can be seen that products were typically obtained in low yields, and that they

iodoarene **16c** did lead to pure samples of **12a** being isolated, however selectivity was very low (entries 7-9). Using polar solvents like EtOH, MeOH and HFIP often leads to higher yields of product but poorer levels of selectivity in hypervalent iodine mediated reactions.[9,20] The highest yield of product was obtained with precatalyst **29**, but the selectivity was just 2% ee. It is likely that the active catalytic species, i.e. the iodine(III) compounds, are even more sparingly soluble than the parent iodoarenes, which could explain their low reactivities.

**Table 1.** Efficacy of novel urea-based iodoarenes in the dearomatizing cyclization of naphthyl amide **11a**




**11a** **12a**

| Entry | ArI | Solvent | T/°C | Yield %[a] | % ee[c] |
|---|---|---|---|---|---|
| 1 | **13a** | MeCN | 20 | <5 | - |
| 2 | **13b** | MeCN | 20 | <20 | - |
| 3 | **16a** | MeCN | -20 (4 h), then 20 | <30 | - |
| 4 | **16b** | MeCN | -20 (4 h), then 20 | <10 | - |
| 5 | **16b** | 3:1 $CH_2Cl_2$/MeOH | -78 (6 h), then 20 | <10 | - |
| 6 | **16c** | MeCN | 20 | <5 | |
| 7 | **16c** | 2:1 MeCN/EtOH | 20 | 68 (41)[b] | 1 |
| 8 | **16c** | HFIP | 40 | 25 (14)[b] | 4 |
| 9 | **16c** | 3:1 $CH_2Cl_2$/MeOH | -78 (6 h), then 20 | (30)[b] | 3 |
| 10 | **16d** | MeCN | -20 (4 h), then 20 | <10 | - |
| 11 | **16e** | MeOH | 20 | <5 | - |
| 12 | **16e** | 3:1 $CH_2Cl_2$/MeOH | -78 (6 h), then 20 | <5 | - |
| 13 | **16f** | MeCN | 20 | <5 | - |
| 14 | **16g** | $CH_2Cl_2$ | -78 (6 h), then 20 | <10 | - |
| 15 | **16g** | HFIP | 40 | <36 | - |
| 16 | **29** | MeCN | 20 | 56 (46)[b] | 2 |

[a] Yield determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Yield of pure isolated compound. [c] Determined by chiral HPLC analysis.

In summary, we have developed a synthetic route into urea-based chiral iodoarenes. In particular, a two-directional strategy to symmetrical bisureas has been revealed. Some of these compounds can effectively catalyze the dearomatizing cyclization of a naphthyl amide. Unfortunately, these precatalysts were not effective in delivering the dearomatizing cyclization products in high enantioselectivities, but they may be useful in other iodine(I/III)-catalyzed processes.

### 3.1. *General*

Infrared (IR) spectra were recorded on a Nicolet 380, equipped with a diamond probe ATR attachment. Low and high resolution mass spectra (m/z) were obtained in the electrospray (ESI) mode. Melting points (uncorrected) were measured on a Stuart SMP10 apparatus. All reagents and solvents were used without further purification except THF (dried over 3 Å MS and then distilled over Na/benzophenone under $N_2$). The reactions were monitored by thin layer chromatography (TLC) using F254 pre-coated silica gel plates. Spots were visualized with UV, $KMnO_4$ stain or vanillin stain. Flash chromatography was performed with 35-70 μm, 60 Å silica gel.

### 3.2. *Synthesis of 2'-phenyl-2H,4'H-spiro[naphthalene-1,5'-oxazol]-2-one (**12a**)*

To a solution of amide **11a** (1 equiv) in anhydrous solvent (0.030 M) at room temperature (or below) was added *m*-CPBA (2.2 equiv) and iodoarene catalyst (0.1 or 0.2 equiv). The reaction mixture was stirred for 16 h and then quenched with a saturated solution of $NaHCO_3$. The organic layer was extracted with ethyl acetate (three times), dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to afford **12a** as a pale yellow oil. IR (thin film) 3160, 3053, 2869, 1715, 1673, 1652, 1603, 1569, 1547, 1367, 1338, 1283, 770 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) 8.08-8.06 (m, 2H), 7.56-7.35 (m, 8H), 6.21 (d, *J* = 10.0 Hz, 1H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 15.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$ 100 MHz) 197.8, 164.3, 145.8, 142.3, 132.0, 131.0, 129.7, 129.0, 128.9, 128.8, 128.6, 127.0, 125.7, 123.7, 86.6, 69.8; HRMS $[M+H]^+$ *m/z* calc'd for $C_{18}H_{14}NO_2$ requires 276.1019, found 276.1019. HPLC: Chiralpak IB, 254 nm, hexane/IPA gradient (100:0 to 90:10 over 35 min), 1 mL/min, retention times 12.9 & 15.1 minutes.

### 3.3. *Preparation of ureas **13***

To the solution of 1-iodo-2-isocyanatobenzene **14** (0.50 g, 2.0 mmol, 1 equiv) in THF (30 mL) at 0 °C was added a solution of amino ester (2.2 mmol, 1.1 equiv) and triethylamine (0.57 mL, 4.1 mmol, 2.0 equiv) in THF (10 mL) dropwise. Then, the ice bath was removed and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure was washed with hexanes multiple times. Recrystallization either with dichloromethane/ethyl acetate or ethanol provided the urea **13**.

#### *3.3.1. Methyl ((2-iodophenyl)carbamoyl)-L-leucinate (**13a**)*

Yellow solid (0.58 g, 73%). M.p. 158-160 °C; IR 3301, 2951, 2868, 1737, 1641, 1573, 1557, 1519, 1463, 1433, 1367, 1273, 1255, 1205, 1155, 1016 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 7.84-7.78 (m, 2H), 7.72 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 4.26-4.21 (m, 1H), 3.65 (s, 3H), 1.73-1.66 (m, 1H), 1.58 (t, *J* = 7.3 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 173.7, 154.7, 140.3, 138.9, 128.5, 124.3, 122.0, 90.0, 51.8, 51.0, 40.6, 24.3, 22.7, 21.5; HRMS $[M+H]^+$ *m/z* calc'd for $C_{14}H_{20}IN_2O_3$ 391.0513, found 391.0510.

#### *3.3.2. Benzyl ((2-iodophenyl)carbamoyl)-L-alaninate (**13b**)*

Pale yellow solid (0.37 g, 88%). M.p. 161-163 °C; IR 3299, 3060, 2979, 2605, 2498, 1720, 1633, 1556, 1512, 1463, 1452,

143 ... H), 400 MHz) 7.84-7.79 (m, 2H), 7.74 (s, 1H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.39-7.27 (m, 6H), 6.77 (t, *J* = 7.4 Hz, 1H), 5.20-5.11 (m, 2H), 4.33-4.24 (m, 1H), 1.35 (d, *J* = 7.4 Hz, 3H); $^{13}$C NMR (DMSO-*d6*, 100 MHz) 173.2, 154.5, 140.3, 138.9, 136.1, 128.5, 128.5, 128.0, 127.7, 124.4, 122.1, 90.1, 65.9, 48.5, 17.6; HRMS $[M+H]^+$ *m/z* calc'd for $C_{17}H_{18}IN_2O_3$ 425.0357, found 425.0359.

3.4. *Preparation of 2-iodo-1,3-diisocyanatobenzene **17***

A solution of 2-iodoisophthalic acid **19** (1.5 g, 5.1 mmol) in thionyl chloride (40 mL) was heated to reflux for 2 h then concentrated under reduced pressure to afford 2-iodoisophthaloyl chloride. This crude mixture was dissolved in THF (15 mL), cooled to 0 $^{o}$C and $NaN_3$ (2.2 g, 34 mmol) dissolved in water (8 mL) was added. After 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) solution and extracted with toluene (30 mL). This was dried over $MgSO_4$ and evaporated to half under reduced pressure to give a toluene solution of 2-iodoisophthaloyl diazide **24**. Without further purification, the crude mixture was heated at reflux for 2 hours and then concentrated to ~3 mL to afford **17** as a light brown solution (1.42 g, 96% – determined by NMR). The progress of the reaction was monitored by IR. IR 3370, 3024, 2251, 2141, 1723, 1573, 1494, 1396, 1214, 781, 728 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) 7.20-7.30 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) 138.2, 130.0, 129.8, 122.2, 97.2; HRMS $[M-CO+3H]^+$ *m/z* calc'd for $C_7H_6IN_2O$ 260.9519, found 260.9516.

3.5. *Preparation of bisureas **16***

To a solution of 2-iodo-1,3-diisocyanatobenzene **17** (0.70 mL, 4.3 mmol, 1 equiv) in THF (60 mL) at 0 $^{o}$C was added dropwise a solution of amine (1.5 g, 9.5 mmol, 2.2 equiv) in THF (10 mL). The ice bath was removed and the reaction mixture was stirred for 3-4 hours or until TLC analysis showed completion of the reaction. Then, the reaction mixture was concentrated under reduced pressure and the residue washed with hexanes multiple times. Recrystallization from ethyl acetate and ethanol provided the bisurea **16**. Typically, solvents could not be completely removed from these compounds.

*3.5.1. 1,1'-(2-iodo-1,3-phenylene)bis(3-((S)-1-hydroxypropan-2-yl)urea)(**16a**)*

White solid. (0.50 g, 81%). M.p. 249-250 °C; IR 3284, 2980, 2851, 1632, 1162, 1035 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 7.60 (s, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 4.77 (br s, 2H), 3.70-3.65 (m, 2H), 3.42-3.28 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 6H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 154.7, 141.2, 127.8, 117.1, 89.3, 64.8, 47.0, 17.8; HRMS $[M+H]^+$ *m/z* calc'd for $C_{14}H_{22}IN_4O_4$ 437.0680, found 437.0698.

*3.5.2. 1,1'-(2-iodo-1,3-phenylene)bis(3-((S)-1-hydroxybutan-2-yl)urea) (**16b**)*

Pale yellow solid (0.60 g, 90%). M.p. 252-254 °C; IR 3290, 2962, 2930, 2873, 2355, 1633, 1556, 1463, 1410, 1274, 1223, 1074, 1018 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 7.62 (s, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.72 (br s, 2H), 3.56-3.42 (m, 4H), 3.35-3.32 (m, 2H), 1.64-1.54 (m, 2H), 1.43-1.31 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 6H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 155.0, 141.3, 127.8, 117.1, 89.3, 63.0, 52.5, 24.2, 10.5; HRMS $[M+H]^+$ *m/z* calc'd for $C_{16}H_{26}IN_4O_4$ 465.0993, found 465.0990.

*3.5.3. 1,1'-(2-iodo-1,3-phenylene)bis(3-((S)-1-hydroxy-3-phenylpropan-2-yl)urea) (**16c**)*

Yellow solid (1.7 g, 85%). M.p. 265-266 °C; IR 3297, 3024, 2919, 1634, 1548, 1465, 1271 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 7.64 (s, 2H), 7.32-7.20 (m, 12H), 7.10 (t, *J* = 8.1 Hz, 1H), 3.43-3.32 (m, 4H), 2.91-2.81 (m, 2H), 2.73-2.65 (m, 2H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 154.7, 141.2, 139.2, 129.3, 128.2, 127.7, 125.9, 117.2, 89.5, 62.4, 52.8, 37.3; HRMS $[M+H]^+$ *m/z* calc'd for $C_{26}H_{30}IN_4O_4$ 589.1306, found 589.1321.

*3.5.4. 1,1'-(2-iodo-1,3-phenylene)bis(3-((1S,2R)-2-hydroxy-1,2-diphenylethyl)urea) (**16d**)*

White solid (370 mg, 74%). M.p. 221-223 °C; IR 3343, 3213, 2981, 1647, 1587, 1556, 1503, 1465, 1396, 1276, 1231, 1068, 1047 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 7.98 (s, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 4H), 7.42 (d, *J* = 7.4 Hz, 4H), 7.36-7.32 (m, 8H), 7.26-7.20 (m, 4H), 7.07-7.06 (m, 2H), 6.99-6.93 (m, 1H), 5.67 (d, *J* = 4.1 Hz, 2H), 4.90-4.83 (m, 4H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 154.7, 143.7, 142.8, 141.1, 127.8, 127.6, 127.4, 127.1, 126.8, 126.6, 126.4, 117.6, 90.0, 75.6, 59.1; HRMS $[M+Na]^+$ *m/z* calc'd for $C_{36}H_{33}IN_4O_4Na$ 735.1439, found 735.1441.

*3.5.5. 1,1'-(2-iodo-1,3-phenylene)bis(3-((1R,2S)-1-hydroxy-2,3-dihydro-1H-inden-2-yl)urea) (**16e**)*

Off-white solid (0.52 g, 63%). M.p. 247-248 °C; IR 3318, 3240, 2912, 1682, 1632, 1550, 1465, 1400, 1359, 1231, 1142, 1047 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 8.09 (s, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.29-7.18 (m, 11H), 5.23 (d, *J* = 4.1 Hz, 2H), 5.11 (dd, *J* = 8.7, 4.9 Hz, 2H), 4.47 (q, *J* = 4.5 Hz, 2H), 3.07 (dd, *J* = 16.2, 4.6 Hz, 2H), 2.81 (d, *J* = 16.1 Hz, 2H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 155.5, 143.2, 141.4, 140.5, 127.8, 127.1, 126.3, 124.9, 124.1, 118.3, 90.9, 72.3, 57.6; HRMS $[M+H]^+$ *m/z* calc'd for $C_{26}H_{26}IN_4O_4$ 585.0993, found 585.0989.

*3.5.6. (2S,2'S)-2,2'-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(azanediyl))bis(3-phenylpropanoic acid) (**16f**)*

Pale-yellow solid (0.76 g, 70%). M.p. 227-229 °C; IR 3217, 3025, 2890, 1714, 1638, 1547, 1494, 1464, 1407, 1275, 1214, 1075 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 7.88 (s, 2H), 7.33-7.21 (m, 16H), 7.15-7.11 (m, 1H), 4.48-4.40 (m, 2H), 3.14-3.07 (m, 2H), 2.98-2.90 (m, 2H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 173.5, 154.6, 141.0, 137.3, 136.6, 129.5, 128.5, 126.5, 117.8, 90.1, 54.0, 37.6; HRMS: $[M+H]^+$ *m/z* calc'd for $C_{26}H_{26}IN_4O_6$ 617.0892, found 617.0898.

*3.5.7. (2S,2'S)-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(azanediyl))bis(3-phenylpropane-2,1-diyl) dibenzoate (**16g**)*

Yellow solid (120 mg, 49%). M.p. 230-232 °C; IR 3288, 3064, 2923, 2852, 1716, 1641, 1538 cm$^{-1}$; $^1$H NMR (DMSO-*d*$^6$, 400 MHz) 8.05-8.02 (m, 4H), 7.70-7.66 (m, 2H), 7.57-7.52 (m, 4H), 7.41-7.37 (m, 2H), 7.33-7.30 (m, 10H), 7.26-7.21 (m, 4H), 7.14-7.08 (m, 1H), 4.36-4.17 (m, 6H), 2.99-2.84 (m, 4H); $^{13}$C NMR (DMSO-*d*$^6$, 100 MHz) 165.7, 154.7, 149.2, 138.2, 133.5, 129.7, 129.4, 129.2, 128.8, 128.4, 128.0, 126.3, 119.3, 87.9, 66.1, 49.8, 37.4; HRMS $[M+H]^+$ *m/z* calc'd for $C_{40}H_{38}IN_4O_6$ 797.1831, found 797.1835.

3.6. *Preparation of 1-((S)-1-hydroxy-3-phenylpropan-2-yl)-3-((S)-1-phenylpropyl)urea **28***

To a solution of (*S*)-(1-isocyanatopropyl)benzene **26** (0.50 g, 3.1 mmol, 1 equiv) in THF (40 mL) at 0 $^{o}$C was added dropwise a solution of amine **27** (0.52 g, 3.4 mmol, 1.1 equiv) in THF (10 mL). The ice bath was removed and the reaction mixture was stirred for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was washed with hexanes multiple times and then purified by flash chromatography (silica gel; 1:1 petroleum ether/EtOAc) to provide **28** as a white solid (1.0 g, 99%). M.p. 130-131 °C; IR 3336, 3026, 2927, 2356, 2341,

NMR (DMSO-$d^6$, 400 MHz) 7.32-7.14 (m, 10H), 6.40 (d, $J$ = 8.6 Hz, 1H), 5.79 (d, $J$ = 8.6 Hz, 1H), 4.83 (br s, 1H), 4.50 (q, $J$ = 7.3 Hz, 1H), 3.71-3.67 (m, 1H), 3.35-3.25 (m, 2H), 2.80-2.75 (m, 1H), 2.62-2.57 (m, 1H), 1.67-1.53 (m, 2H), 0.80 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (DMSO-$d^6$, 100 MHz) 157.2, 144.6, 139.2, 129.2, 128.1, 128.1, 126.2, 62.5, 54.3, 52.4, 37.2, 30.0, 10.6; HRMS $[M+H]^+$ $m/z$ calc'd for $C_{19}H_{25}N_2O_2$ 313.1911, found 313.1909.

### 3.7. *Preparation of bis((S)-3-phenyl-2-(3-((S)-1-phenylpropyl)ureido)propyl)(2-iodo-1,3-phenylene)dicarbamate **29***

2-Iodo-1,3-diisocyanatobenzene **17** (350 mg, 1.2 mmol, 1 equiv – as a solution in toluene) and triethylamine (0.37 mL, 2.7 mmol, 2.2 equiv) were dissolved in dichloromethane (30 mL) and cooled to 0 $^o$C under $N_2$. Urea **28** (0.75 g, 2.4 mmol, 2.2 equiv) was dissolved in dichloromethane (20 mL) in a separate flask and added to the first solution dropwise over 10 minutes. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was quenched with 1 N HCl (20 mL) and extracted with EtOAc (20 mL x 3), dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from $CH_2Cl_2$/EtOAc afforded **29** as a dark brown solid (0.73 g, 65%). M.p. 249-251 °C; IR 3270, 3026, 2961, 1702, 1633, 1584, 1519, 1461, 1398, 1202, 1109, 1109, 1018 cm$^{-1}$; $^1$H NMR (DMSO-$d^6$, 400 MHz) 9.01 (s, 2H), 7.32-7.17 (m, 23H), 6.43 (d, $J$ = 8.0 Hz, 2H), 5.86 (d, $J$ = 8.0 Hz, 2H), 4.56-4.49 (m, 2H), 4.02-3.95 (m, 6H), 2.83-2.70 (m, 4H), 1.67-1.59 (m, 4H), 0.79 (t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (DMSO-$d^6$, 100 MHz) 157.0, 154.2, 144.5, 140.6, 138.2, 129.3, 128.5, 128.5, 128.1, 126.4, 126.2, 83.2, 65.8, 54.4, 49.8, 37.3, 29.9, 10.7; HRMS $[M+Na]^+$ $m/z$ calc'd for $C_{46}H_{51}IN_6NaO_6$ 933.2807, found 933.2813.

## Acknowledgments

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## Appendix A. Supplementary Material

Supplementary data to this article can be found online at

## Highlights

- Preparation of novel chiral $C_1$ and $C_2$ symmetric iodoarenes
- Robust bidirectional synthetic strategy
- Evaluation as catalysts in iodine(I/III) mediated cyclization

# Supporting Information

## Design and synthesis of chiral urea-derived iodoarenes and their assessment in the enantioselective dearomatizing cyclization of a naphthyl amide

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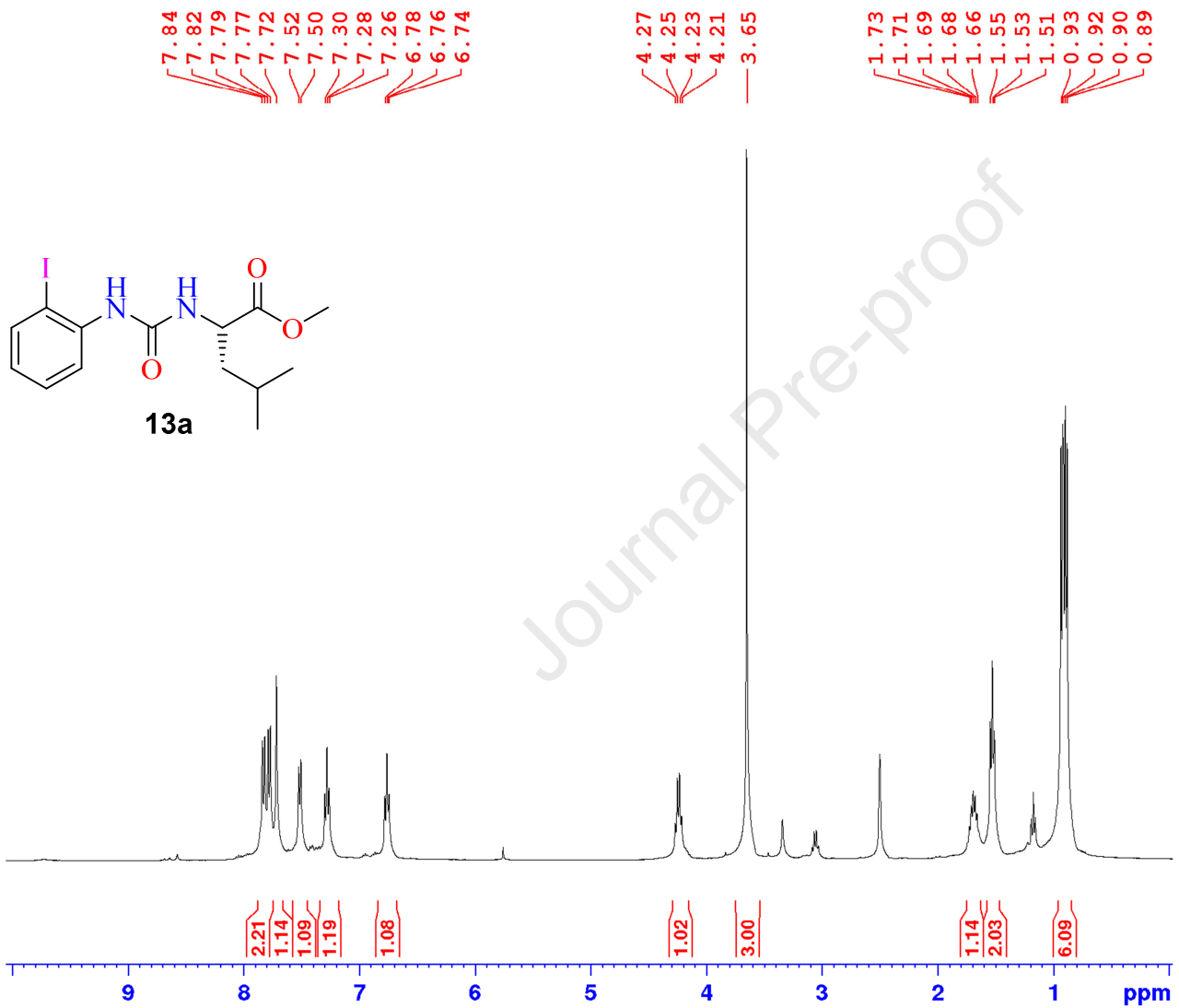




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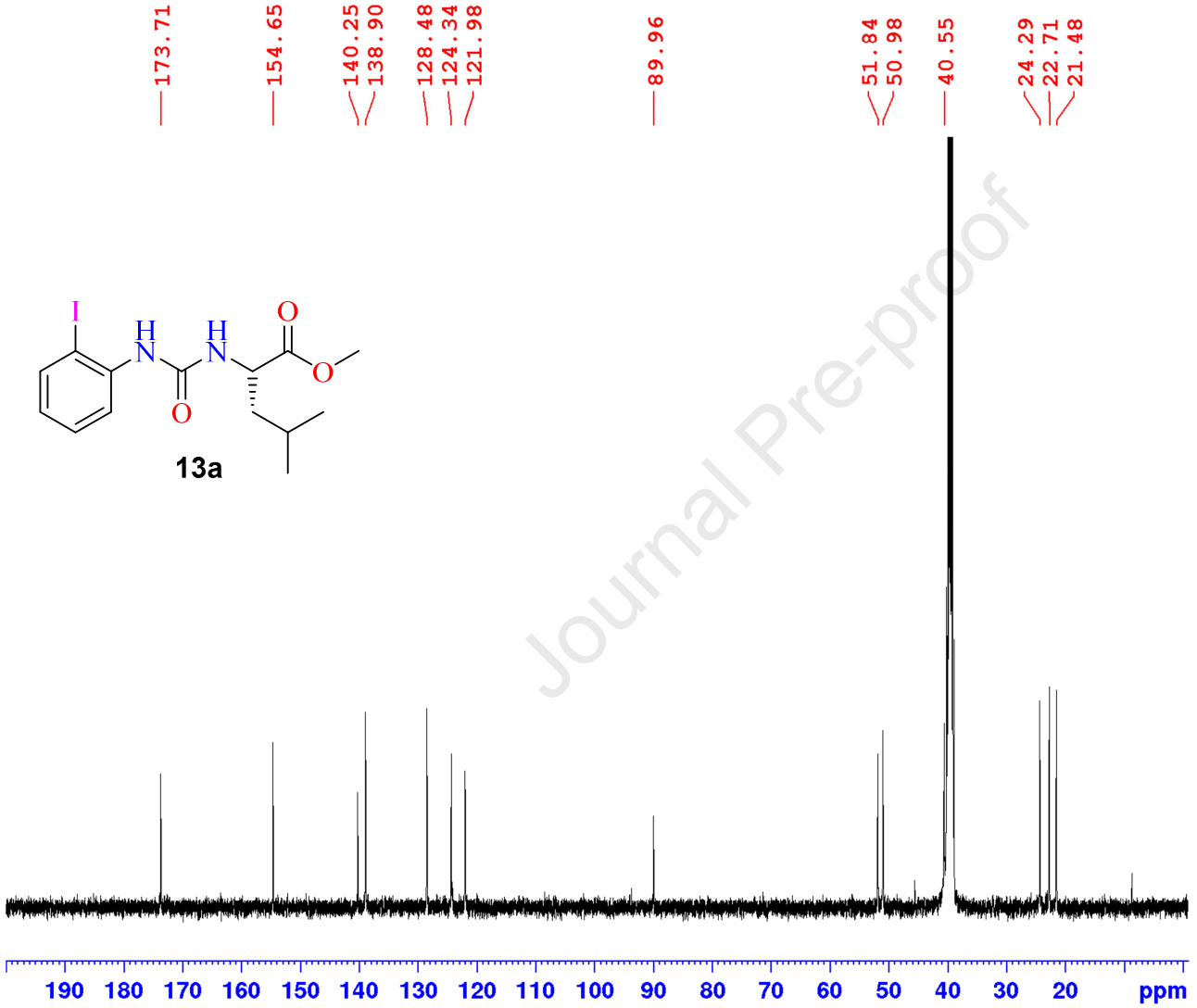




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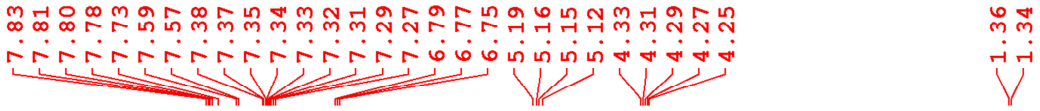


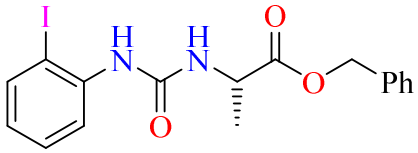


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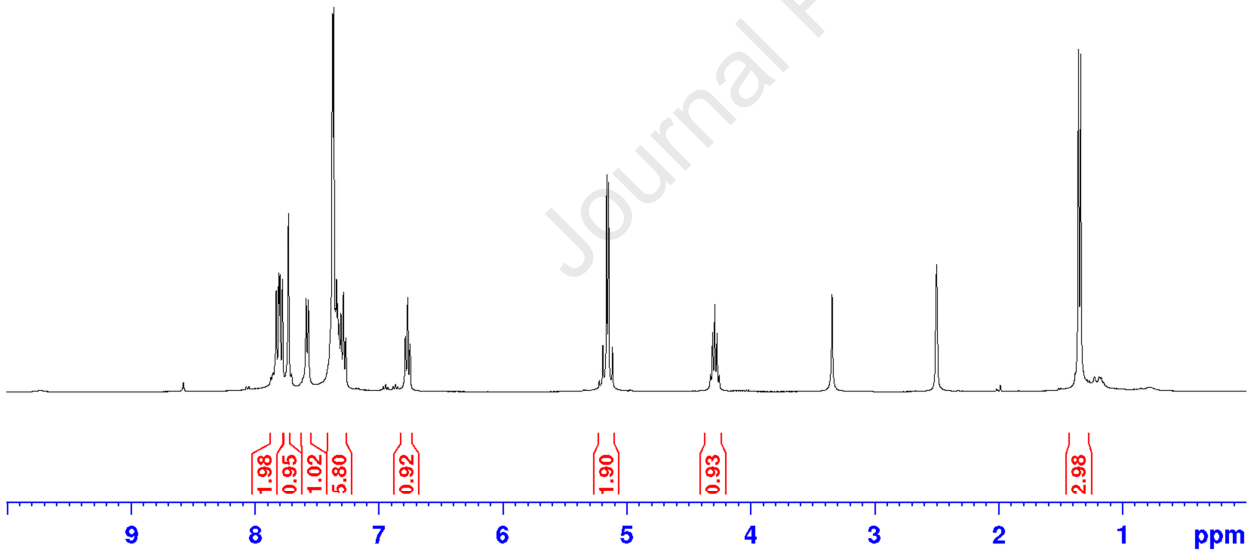




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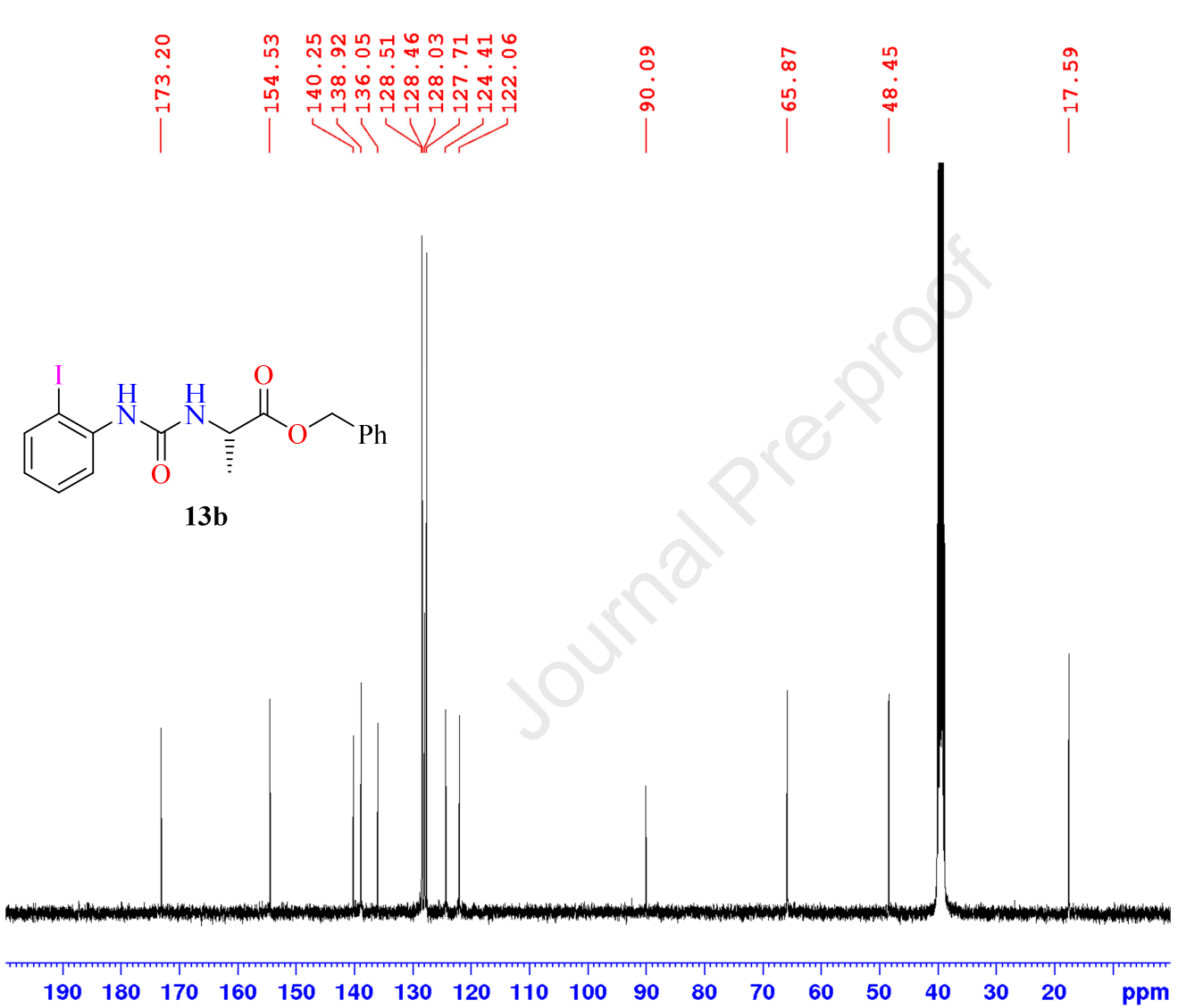




BRUKER

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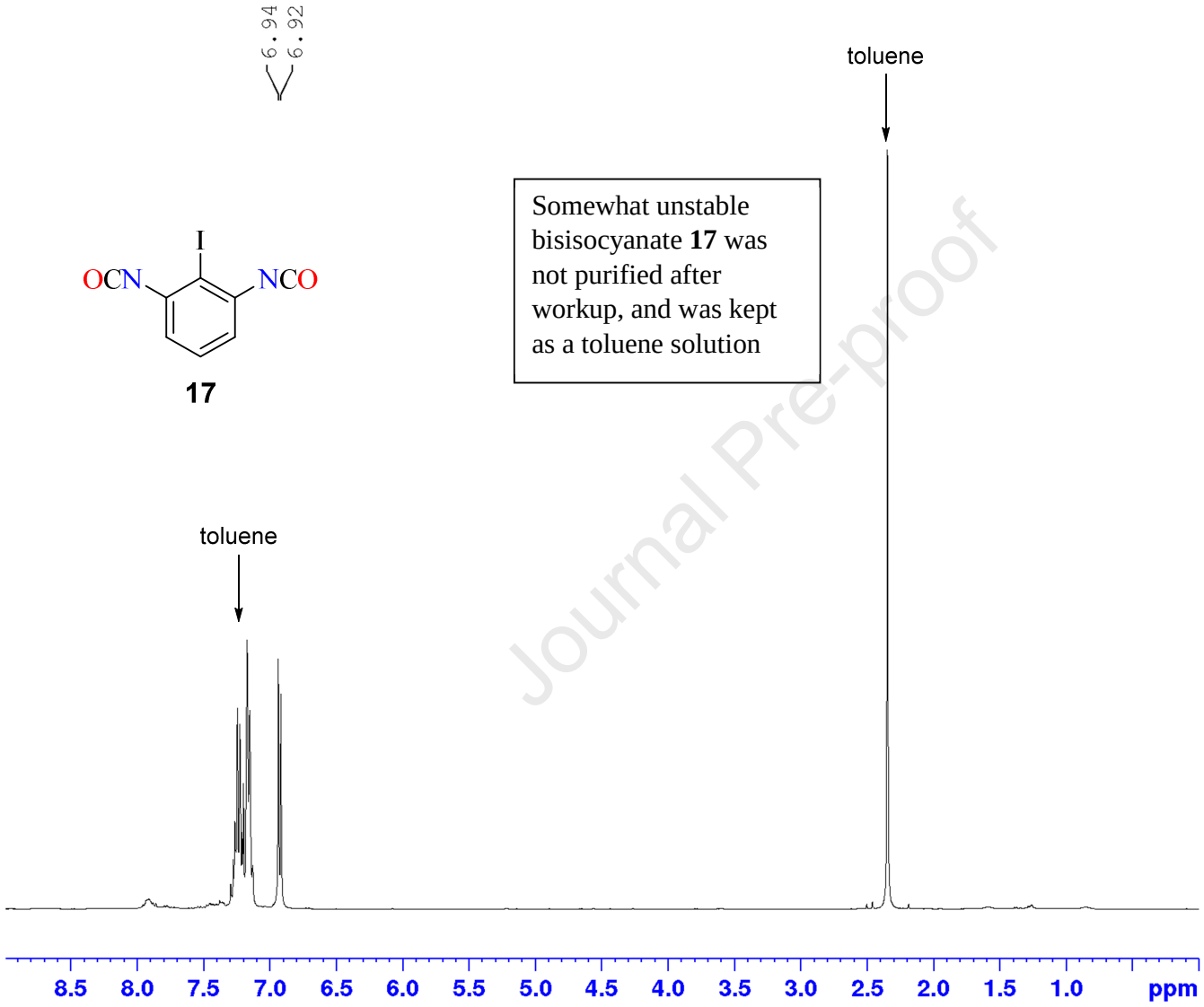





**17**

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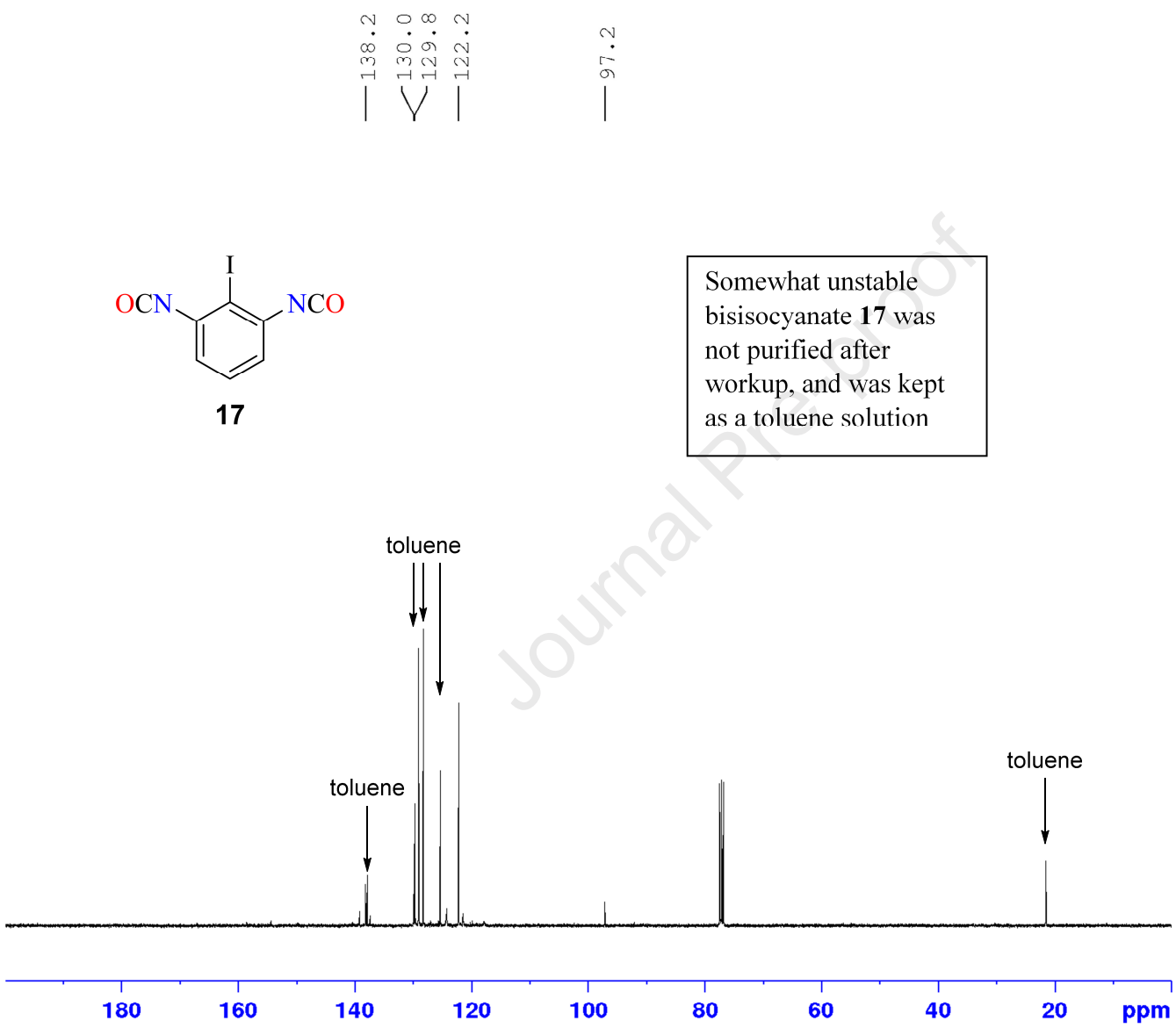


Somewhat unstable bisisocyanate **17** was not purified after workup, and was kept as a toluene solution

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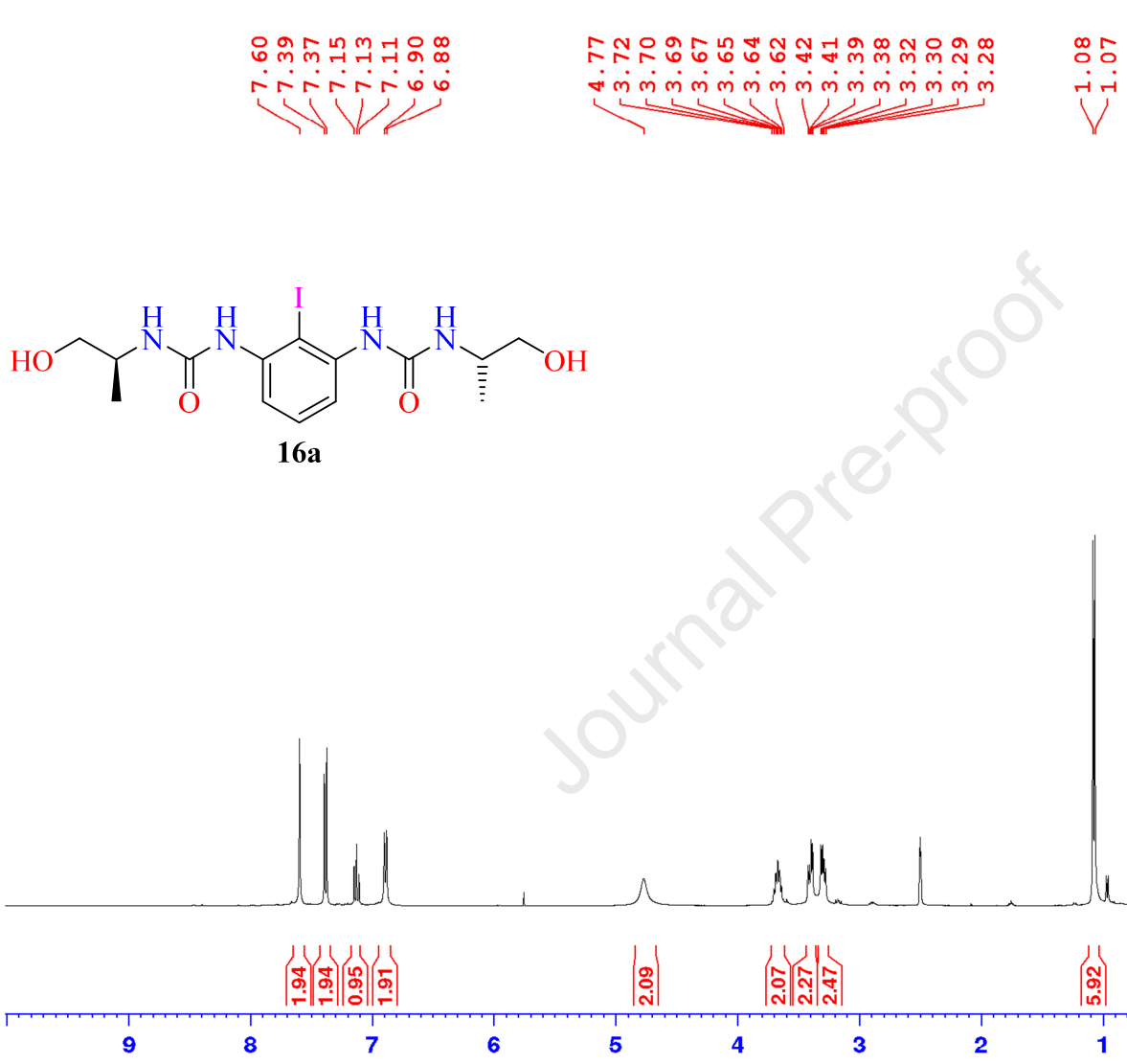




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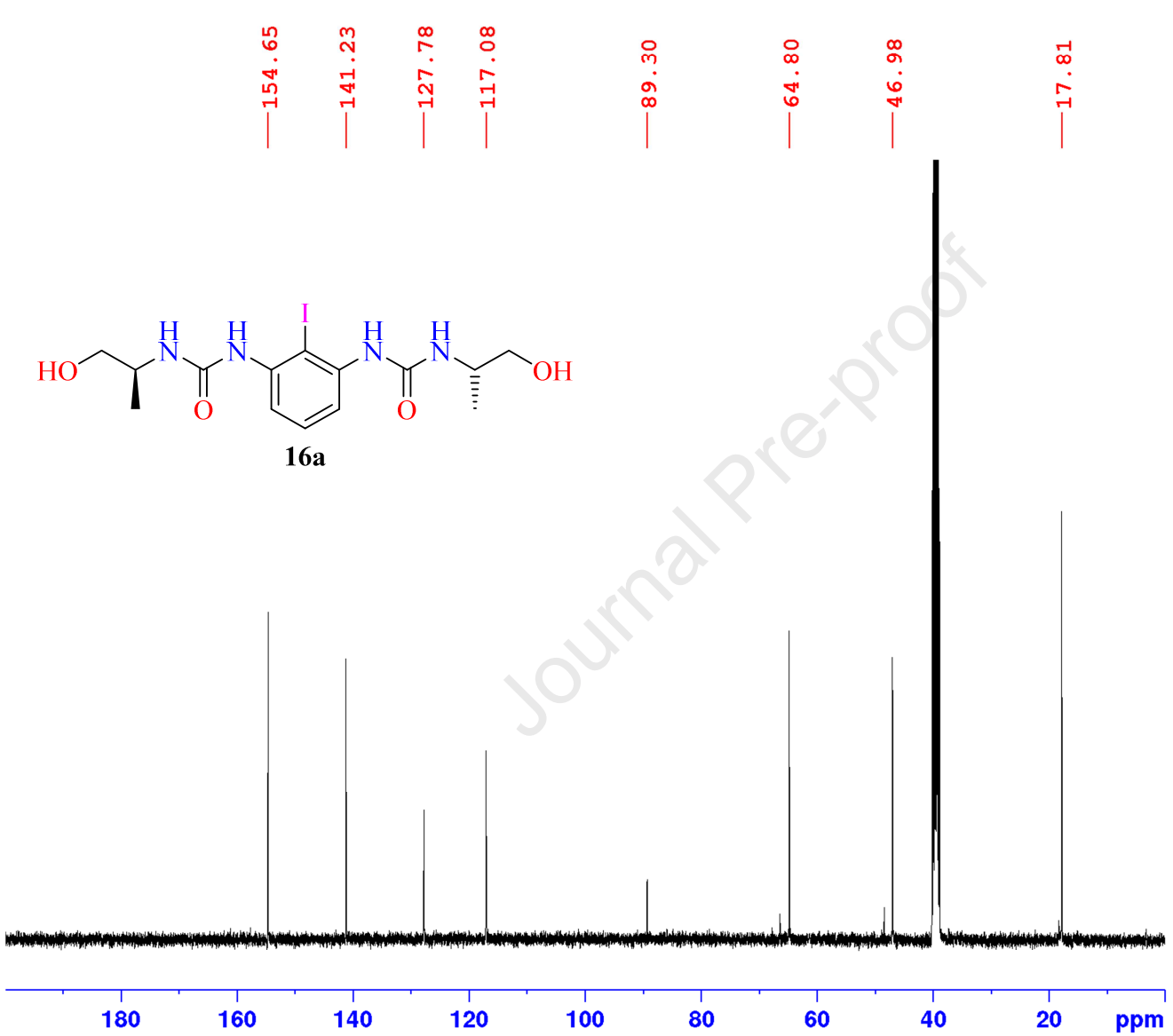


16a



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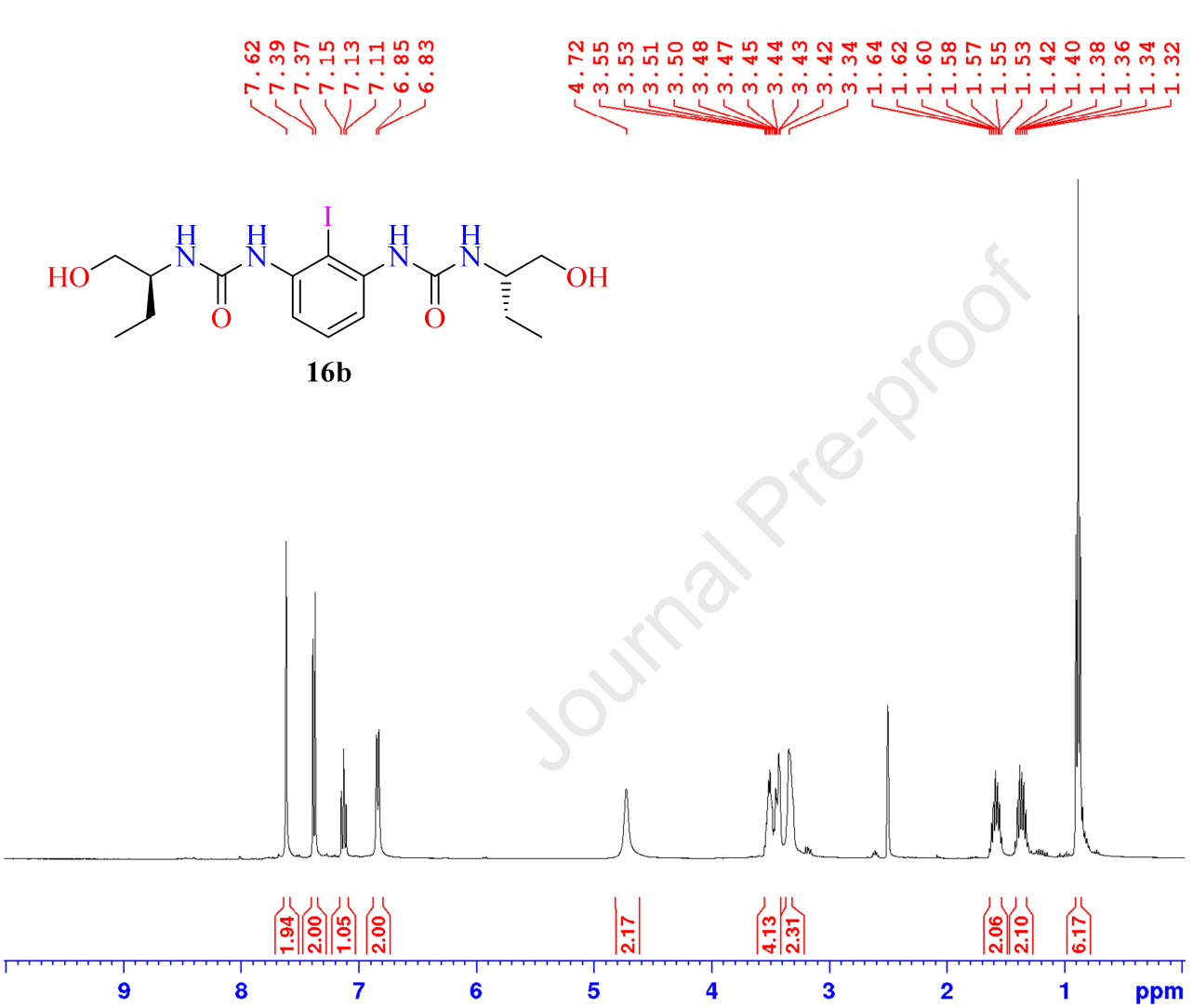
TD                 65536
SOLVENT             DMSO
NS                  1024
DS                     4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                181.72
DW                20.800 usec
DE                 8.18 usec
TE                294.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   32
SFO1         100.6228303 MHz
NUC1                 13C
P1                 9.00 usec
PLW1          77.00000000 W
SFO2         400.1316005 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2          24.00000000 W
PLW12          0.17567000 W
PLW13          0.08836300 W

F2 - Processing parameters
SI                 65536
SF           100.6128132 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

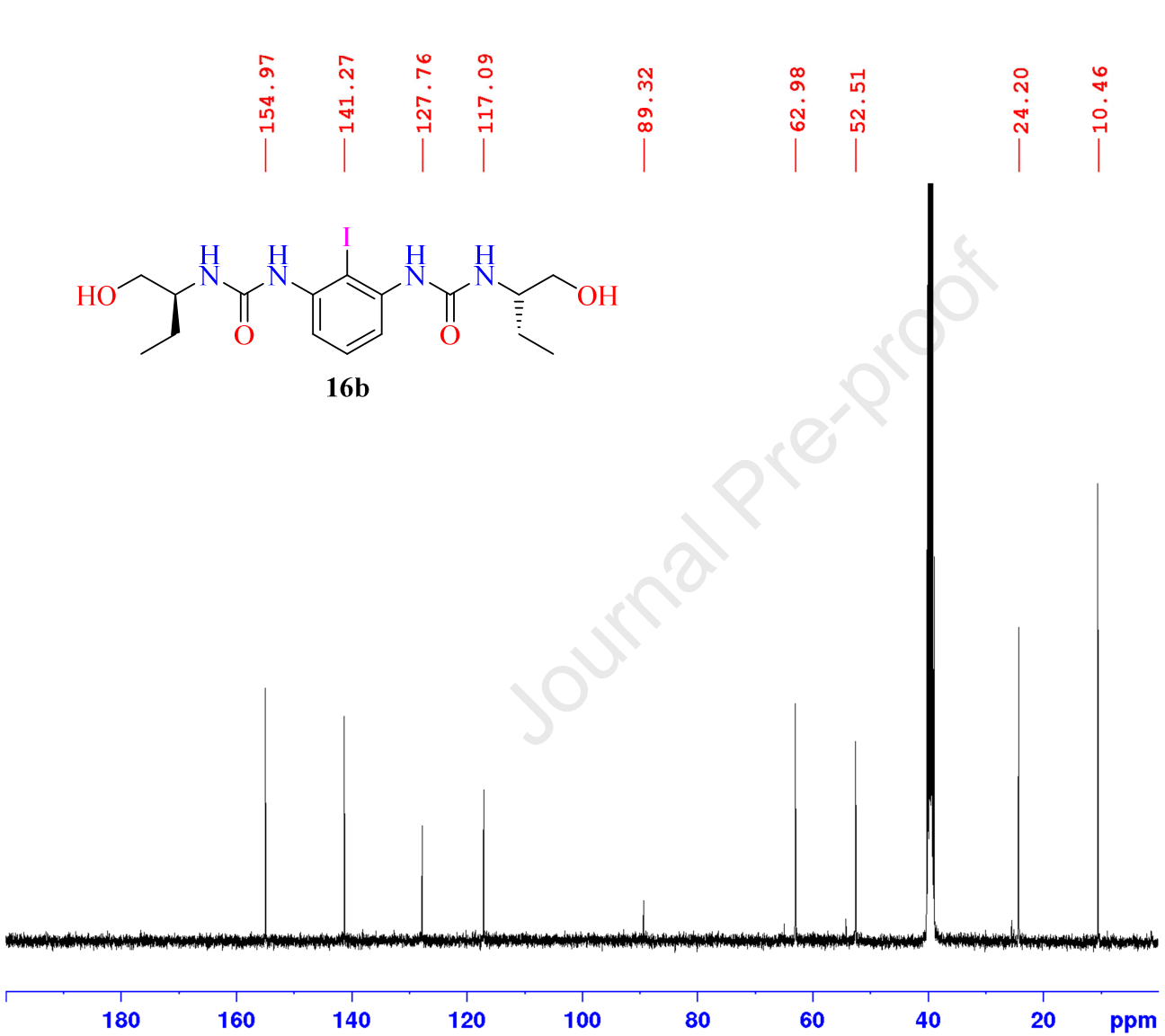





```
Current Data Parameters
NAME          UT-289 DMSO
EXPNO                  20
PROCNO                  1

F2 - Acquisition Parameters
Date_            20180424
Time               23.58 h
INSTRUM             spect
PROBHD    Z116098_0048 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    64
DS                     2
SWH             8223.685 Hz
FIDRES          0.250967 Hz
AQ              3.9845889 sec
RG                 81.67
DW                 60.800 usec
DE                 10.69 usec
TE                 294.9 K
D1             1.00000000 sec
TD0                    4
SFO1          400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          24.00000000 W

F2 - Processing parameters
SI                 32768
SF            400.1300036 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.50
```



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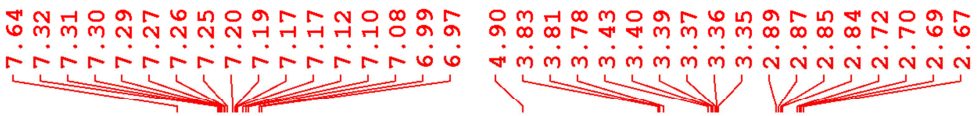
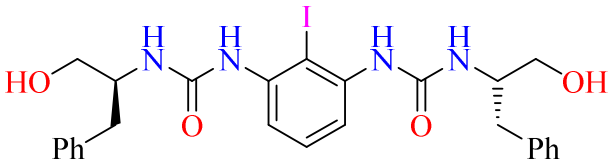
```
Current Data Parameters
NAME         UT-289 DMSO
EXPNO                 21
PROCNO                 1

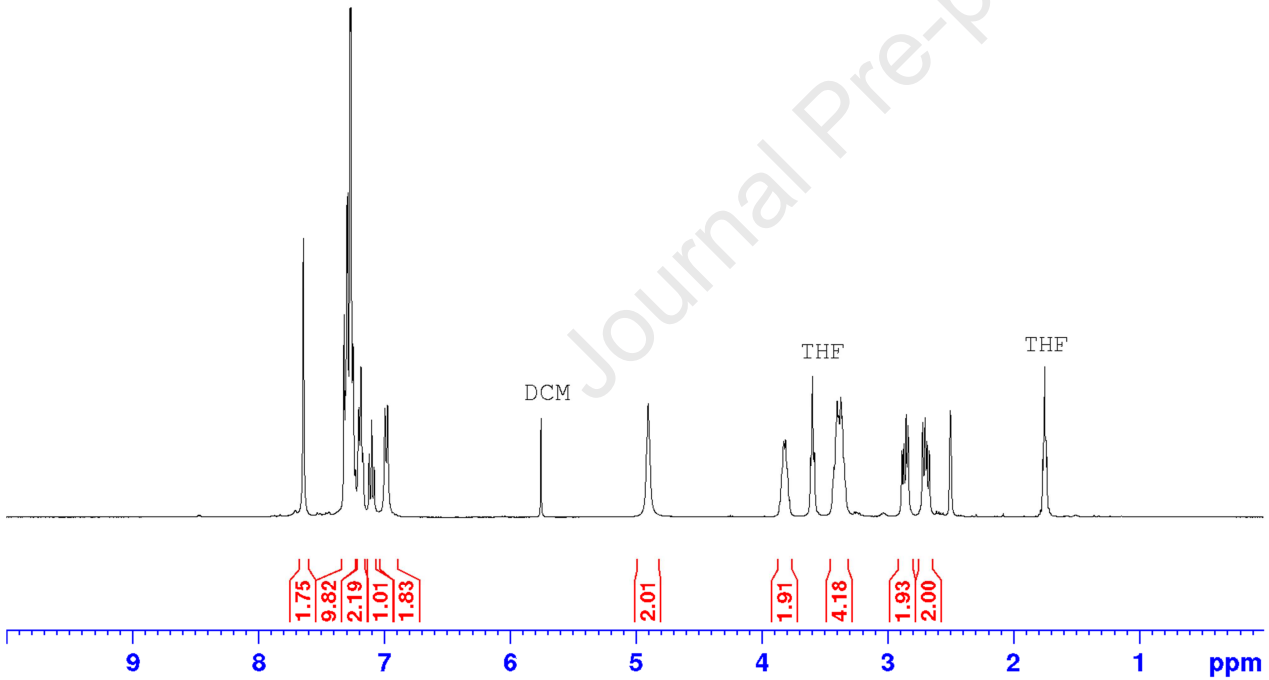
F2 - Acquisition Parameters
Date_           20180425
Time                0.58 h
INSTRUM            spect
PROBHD   Z116098_0048 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                  1024
DS                     4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                181.72
DW                20.800 usec
DE                 8.18 usec
TE                294.9 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   32
SFO1         100.6228303 MHz
NUC1                 13C
P1                  9.00 usec
PLW1         77.00000000 W
SFO2         400.1316005 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2         24.00000000 W
PLW12         0.17567000 W
PLW13         0.08836300 W

F2 - Processing parameters
SI                 65536
SF           100.6128133 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```




**16c**



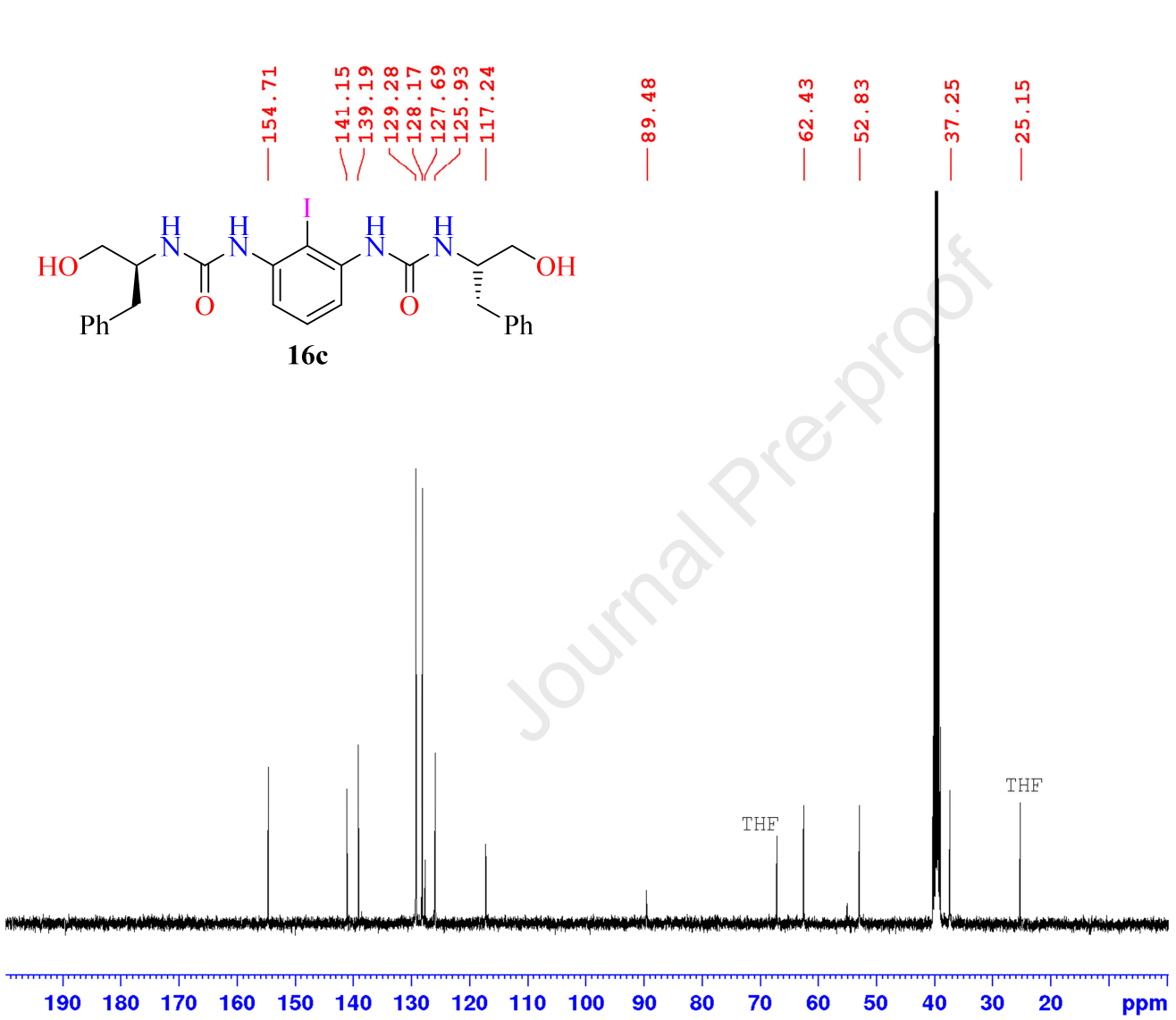



```
Current Data Parameters
NAME         UT-196 DMSO
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20170928
Time              10.53 h
INSTRUM            spect
PROBHD   Z116098_0048 (
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    64
DS                     2
SWH            8223.685 Hz
FIDRES        0.250967 Hz
AQ            3.9845889 sec
RG                 59.2
DW               60.800 usec
DE               10.69 usec
TE               294.5 K
D1           1.00000000 sec
TD0                    4
SFO1        400.1324710 MHz
NUC1                1H
P1                8.00 usec
PLW1        24.00000000 W

F2 - Processing parameters
SI                 32768
SF          400.1300034 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC
```

Solvents, especially THF, could not always be completely removed from these ureas

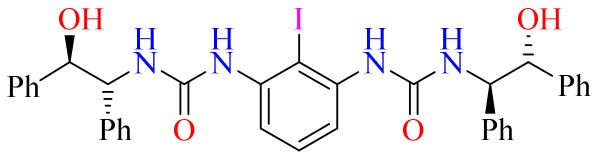




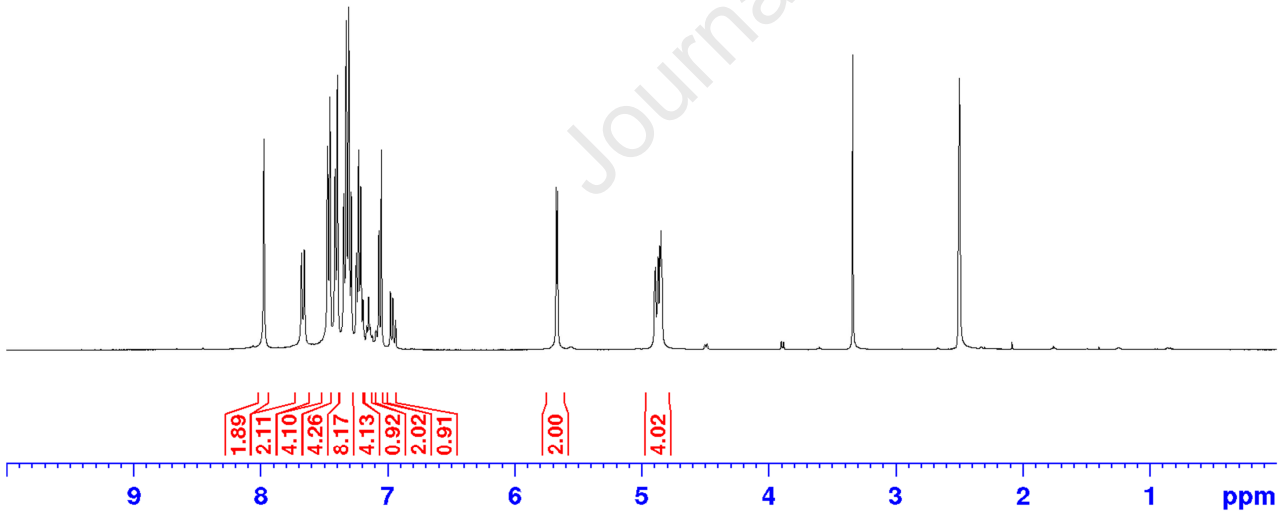

```
Current Data Parameters
NAME          UT-196 DMSO
EXPNO                  11
PROCNO                  1

F2 - Acquisition Parameters
Date_            20170928
Time                11.09 h
INSTRUM             spect
PROBHD    Z116098_0048 (
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                    256
DS                      4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                181.72
DW                20.800 usec
DE                 8.18 usec
TE                294.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                     8
SFO1        100.6228303 MHz
NUC1                13C
P1                 9.00 usec
PLW1        77.00000000 W
SFO2        400.1316005 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2        24.00000000 W
PLW12        0.17567000 W
PLW13        0.08836300 W

F2 - Processing parameters
SI                 65536
SF          100.6128144 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```


**16d**

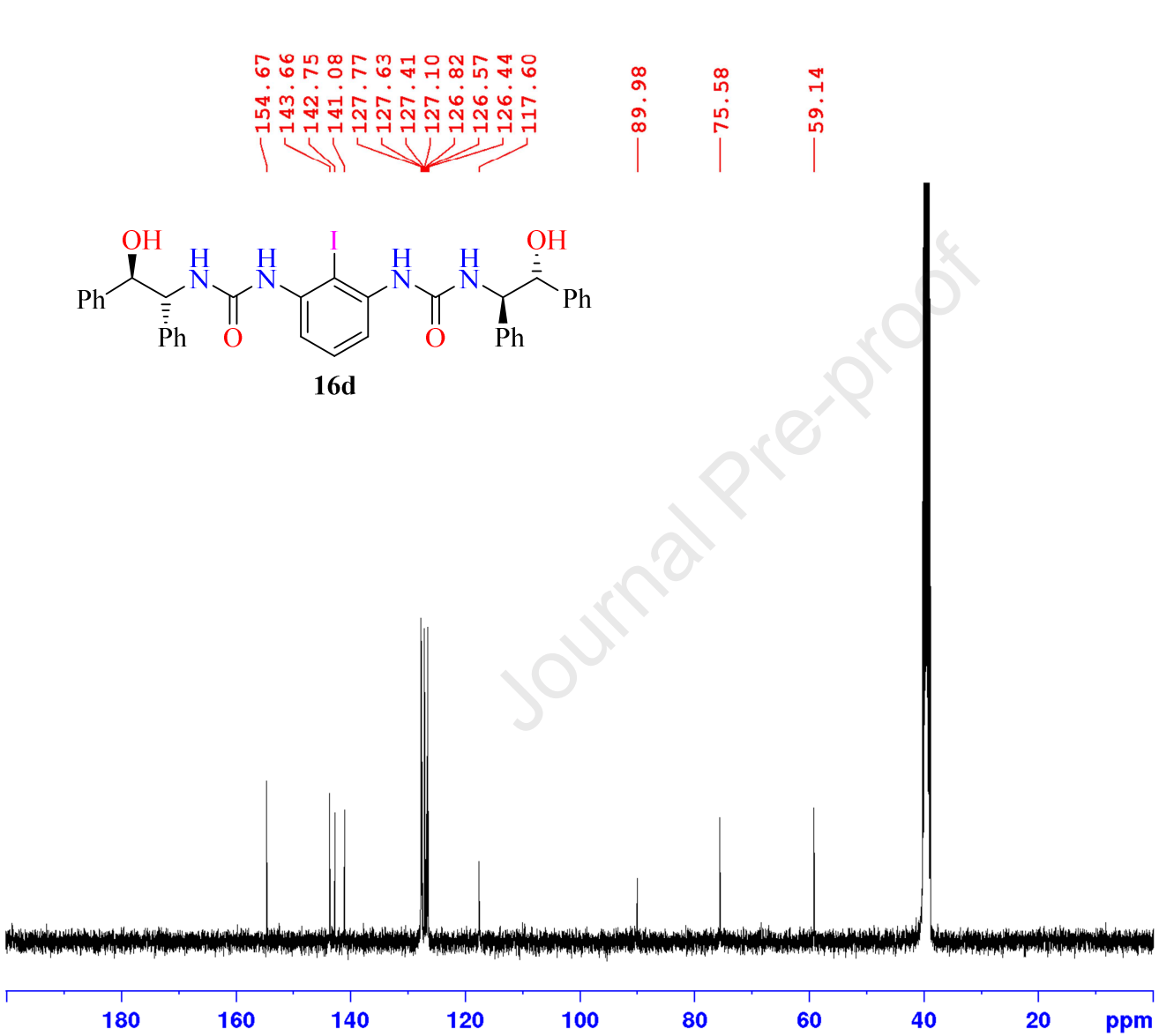




```
Current Data Parameters
NAME          UT-290 DMSO
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_            20180212
Time                5.30 h
INSTRUM             spect
PROBHD   Z116098_0048 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    64
DS                     2
SWH              8223.685 Hz
FIDRES           0.250967 Hz
AQ               3.9845889 sec
RG                 120.59
DW                 60.800 usec
DE                 10.69 usec
TE                 294.9 K
D1            1.00000000 sec
TD0                    4
SFO1         400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1         24.00000000 W

F2 - Processing parameters
SI                 32768
SF           400.1300035 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.50
```

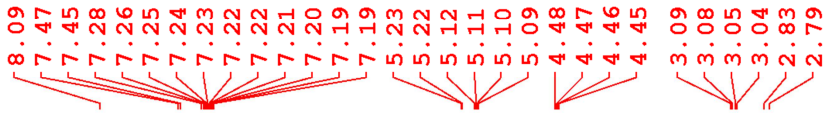


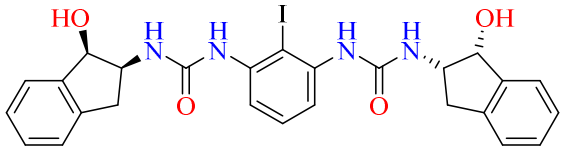



```
Current Data Parameters
NAME         UT-290 DMSO
EXPNO                11
PROCNO                1

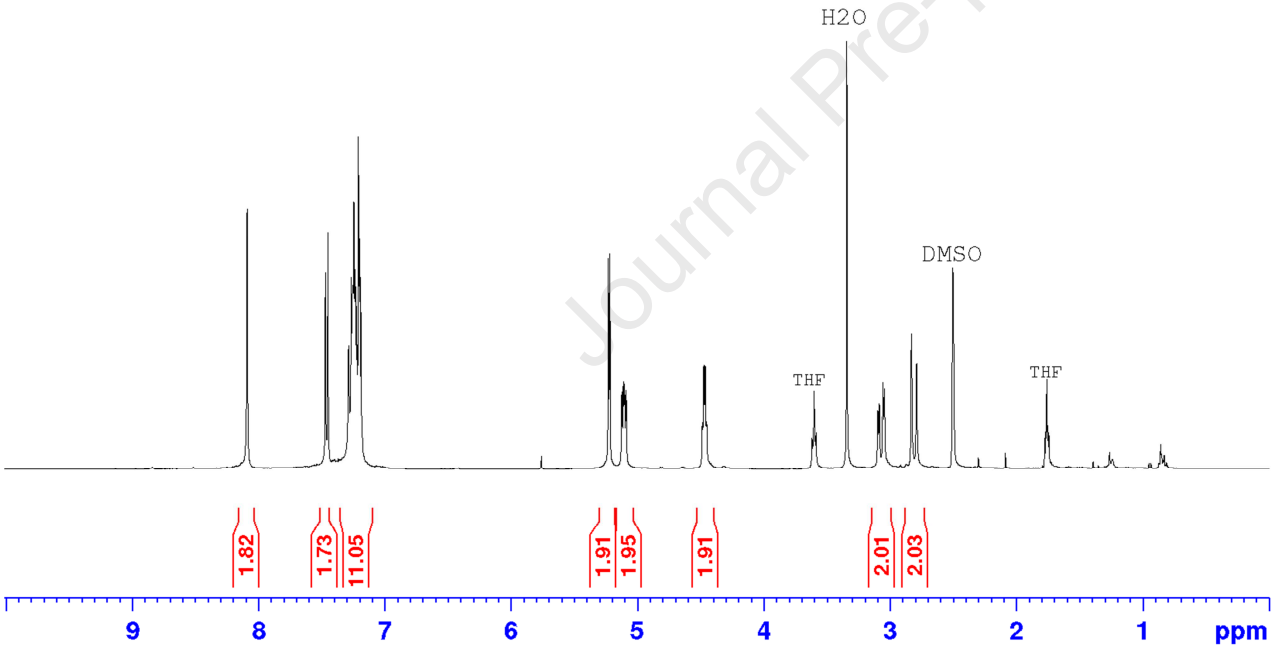
F2 - Acquisition Parameters
Date_          20180212
Time               6.29 h
INSTRUM           spect
PROBHD   Z116098_0048 (
PULPROG         zgpg30
TD               65536
SOLVENT           DMSO
NS                1024
DS                   4
SWH          24038.461 Hz
FIDRES        0.733596 Hz
AQ            1.3631488 sec
RG               181.72
DW               20.800 usec
DE                8.18 usec
TE               295.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                 32
SFO1        100.6228303 MHz
NUC1               13C
P1                9.00 usec
PLW1        77.00000000 W
SFO2        400.1316005 MHz
NUC2               1H
CPDPRG[2       waltz16
PCPD2            90.00 usec
PLW2        24.00000000 W
PLW12        0.17567000 W
PLW13        0.08836300 W

F2 - Processing parameters
SI               65536
SF          100.6128158 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40
```




16e



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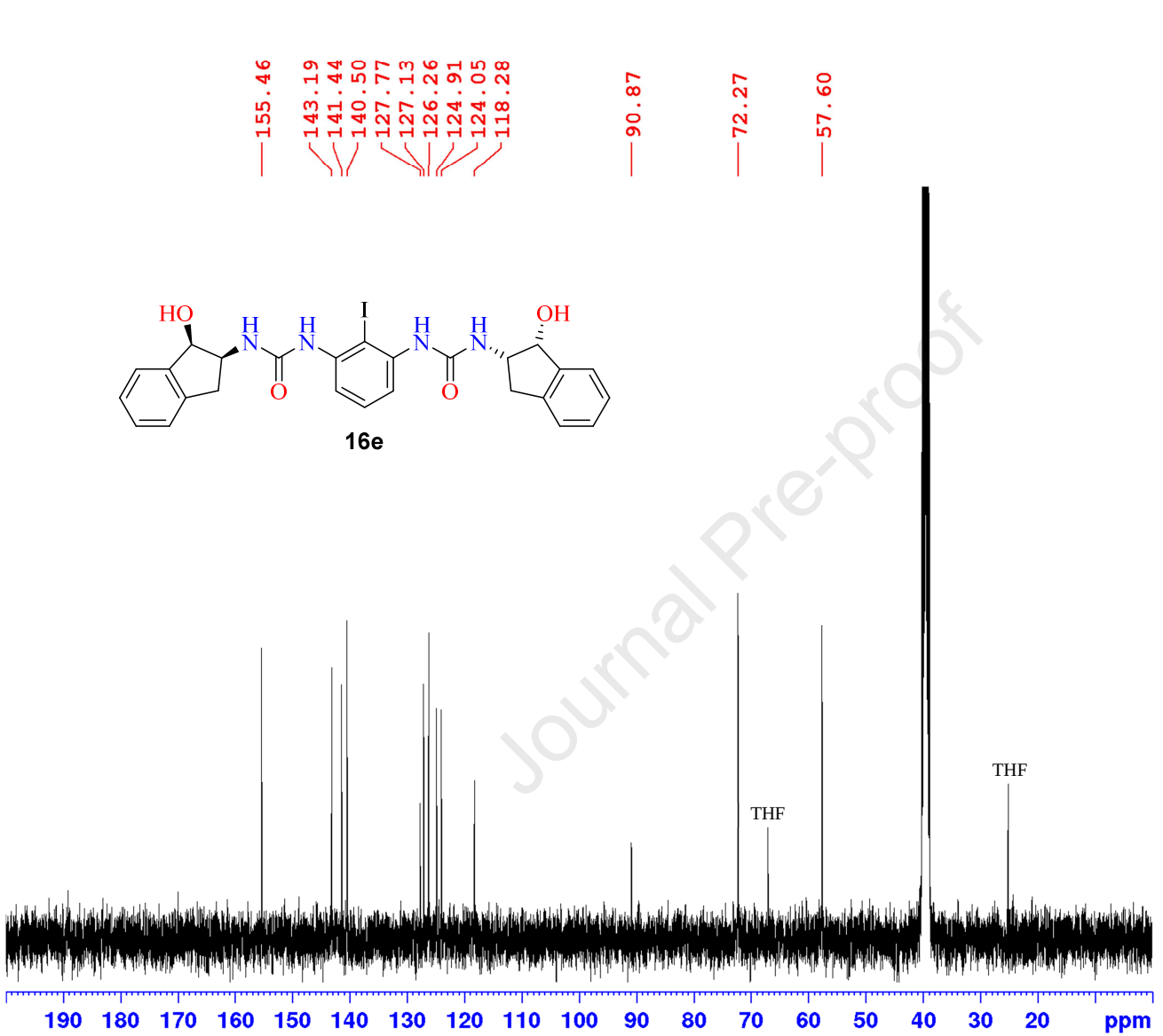
```
Current Data Parameters
NAME         UT-291 DMSO
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20180212
Time                6.48 h
INSTRUM            spect
PROBHD    Z116098_0048 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    64
DS                     2
SWH             8223.685 Hz
FIDRES          0.250967 Hz
AQ              3.9845889 sec
RG                104.33
DW                60.800 usec
DE                10.69 usec
TE                295.1 K
D1             1.00000000 sec
TD0                    4
SFO1          400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          24.00000000 W

F2 - Processing parameters
SI                 32768
SF            400.1300038 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.50
```

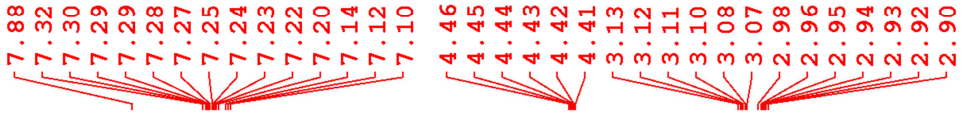


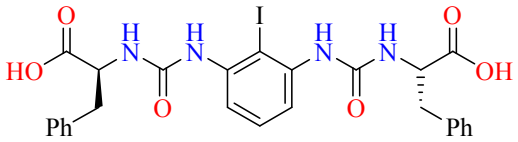



```
Current Data Parameters
NAME          UT-291 DMSO
EXPNO                  11
PROCNO                  1

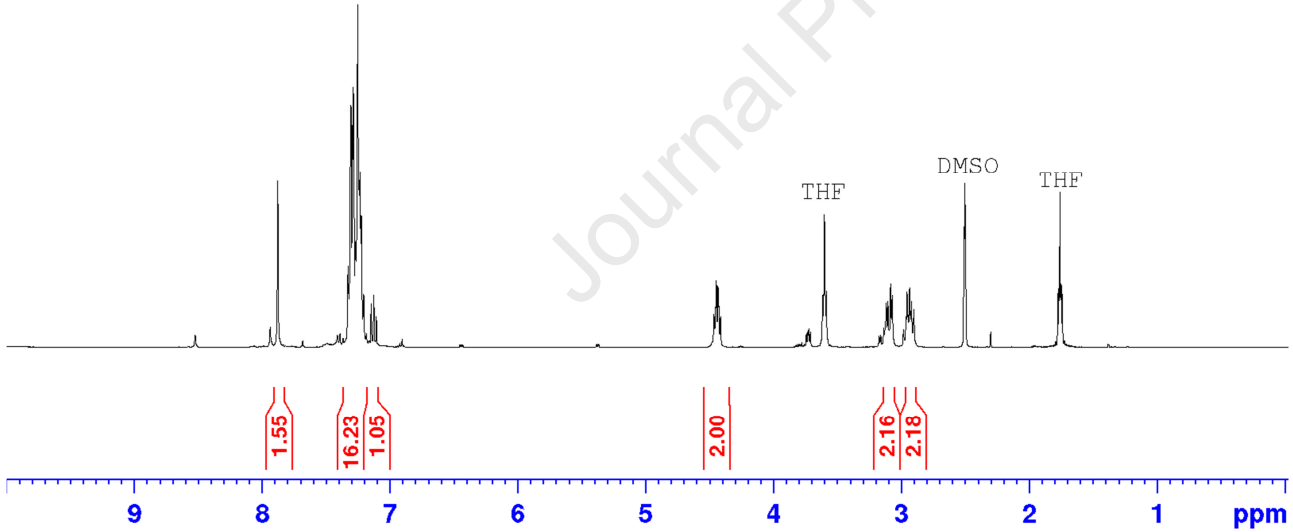
F2 - Acquisition Parameters
Date_            20180212
Time                7.04 h
INSTRUM             spect
PROBHD    Z116098_0048 (
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                    256
DS                      4
SWH             24038.461 Hz
FIDRES           0.733596 Hz
AQ               1.3631488 sec
RG                 181.72
DW                20.800 usec
DE                 8.18 usec
TE                 295.1 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                     8
SFO1          100.6228303 MHz
NUC1                  13C
P1                 9.00 usec
PLW1          77.00000000 W
SFO2          400.1316005 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          24.00000000 W
PLW12          0.17567000 W
PLW13          0.08836300 W

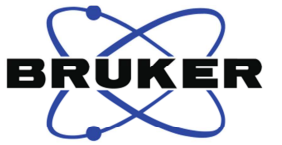
F2 - Processing parameters
SI                 65536
SF            100.6128145 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```




**16f**

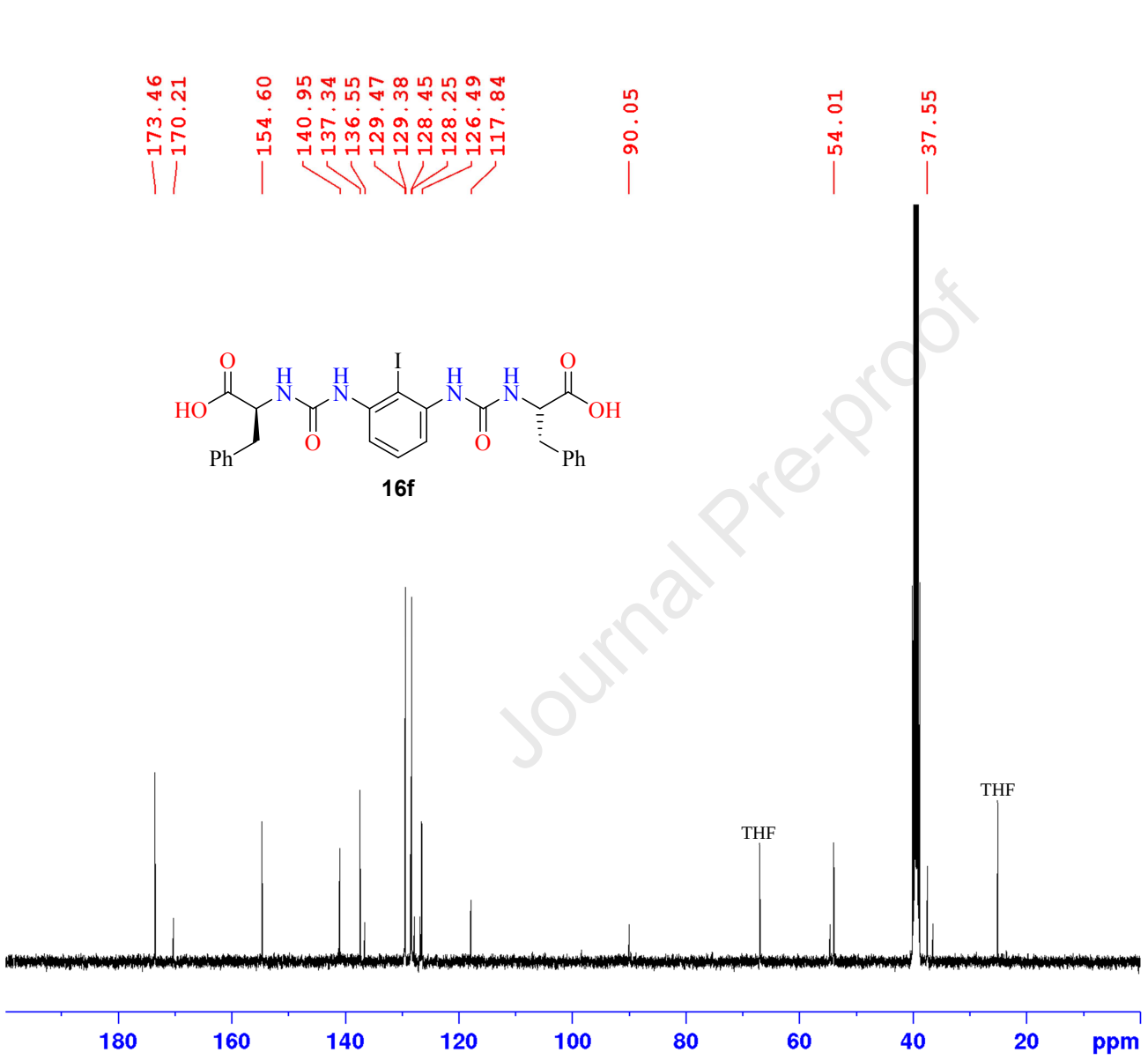



```
Current Data Parameters
NAME         UT-181 DMSO
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170829
Time              16.44 h
INSTRUM             spect
PROBHD    Z116098_0048 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    64
DS                     2
SWH            8223.685 Hz
FIDRES         0.250967 Hz
AQ             3.9845889 sec
RG                 92.46
DW                60.800 usec
DE                10.69 usec
TE                294.6 K
D1            1.00000000 sec
TD0                    4
SFO1         400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1         24.00000000 W

F2 - Processing parameters
SI                 32768
SF           400.1300035 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.50
```







16f



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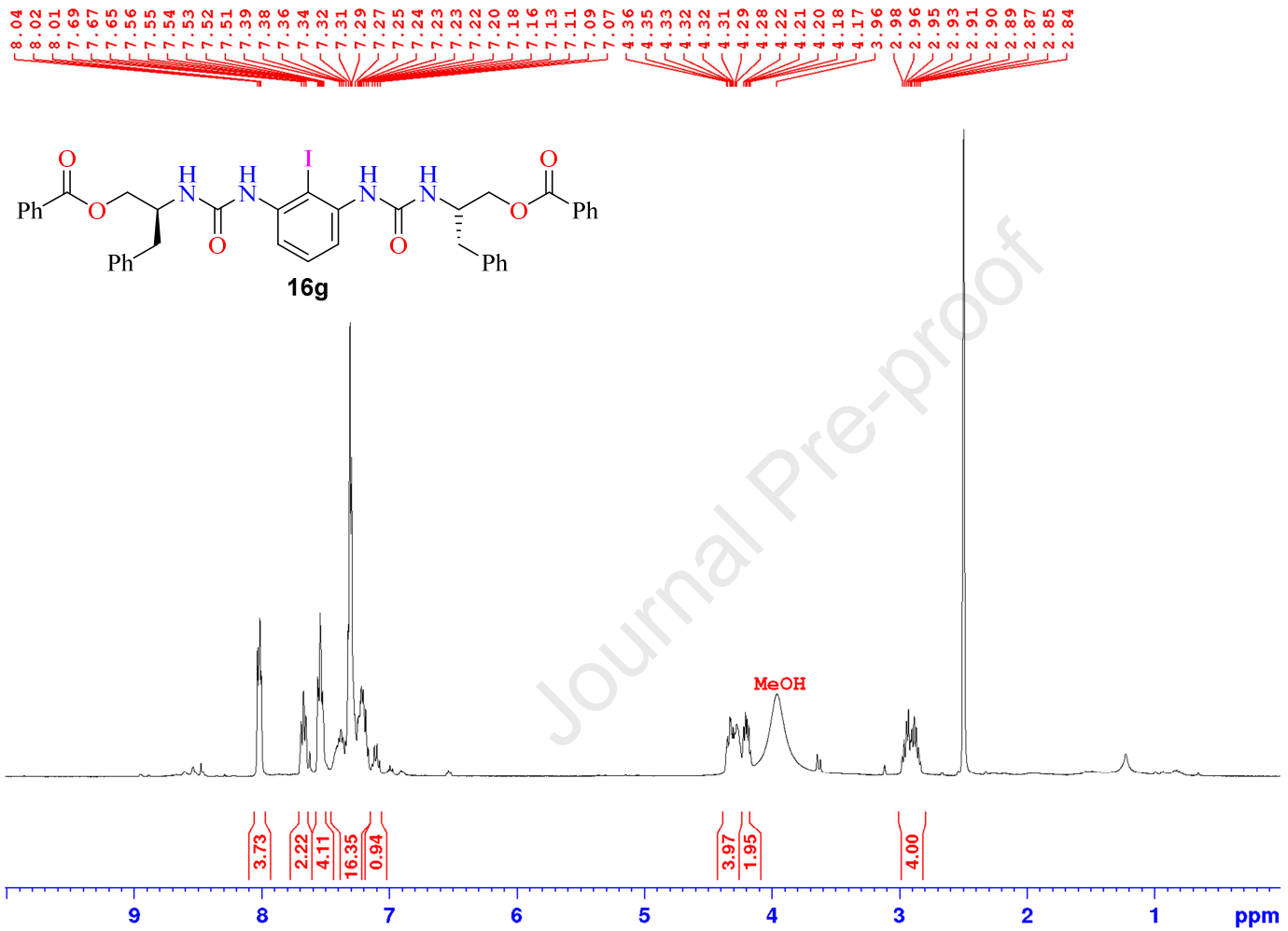
```
Current Data Parameters
NAME         UT-181 DMSO
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170829
Time              20.55 h
INSTRUM             spect
PROBHD    Z116098_0048 (
PULPROG           zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                181.72
DW                20.800 usec
DE                 8.18 usec
TE                294.7 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   32
SFO1         100.6228303 MHz
NUC1                 13C
P1                 9.00 usec
PLW1         77.00000000 W
SFO2         400.1316005 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         24.00000000 W
PLW12         0.17567000 W
PLW13         0.08836300 W

F2 - Processing parameters
SI                 65536
SF           100.6128134 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

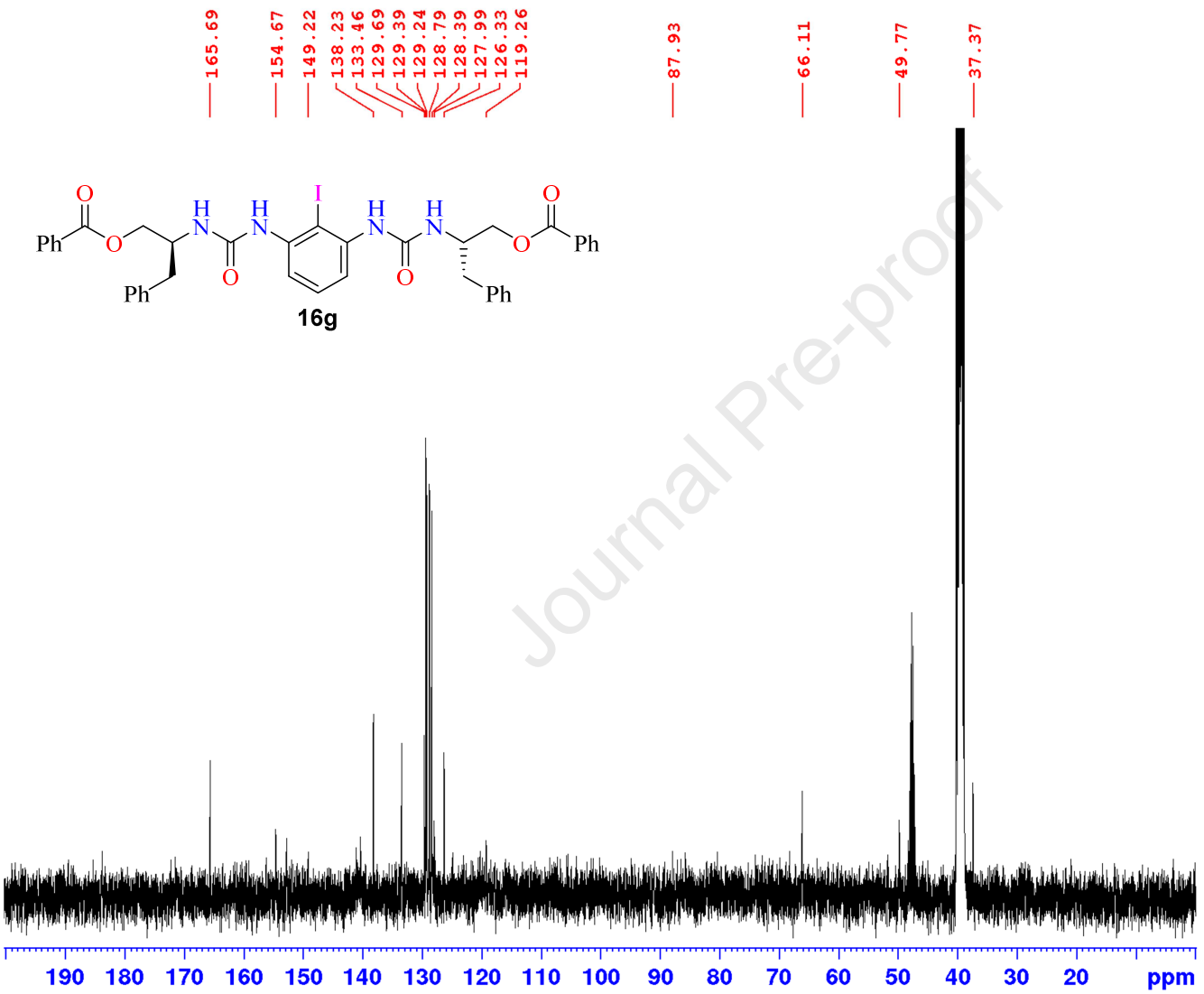


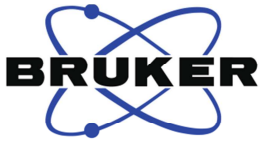



```
Current Data Parameters
NAME      UT-100 RECRYS DMSO
EXPNO                   20
PROCNO                   1

F2 - Acquisition Parameters
Date_             20170820
Time                17.41 h
INSTRUM              spect
PROBHD    Z116098_0048 (
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     64
DS                      2
SWH              8223.685 Hz
FIDRES           0.250967 Hz
AQ               3.9845889 sec
RG                  134.04
DW                  60.800 usec
DE                  10.69 usec
TE                  294.3 K
D1              1.00000000 sec
TD0                     4
SFO1           400.1324710 MHz
NUC1                   1H
P1                   8.00 usec
PLW1           24.00000000 W

F2 - Processing parameters
SI                  32768
SF             400.1300039 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.50
```

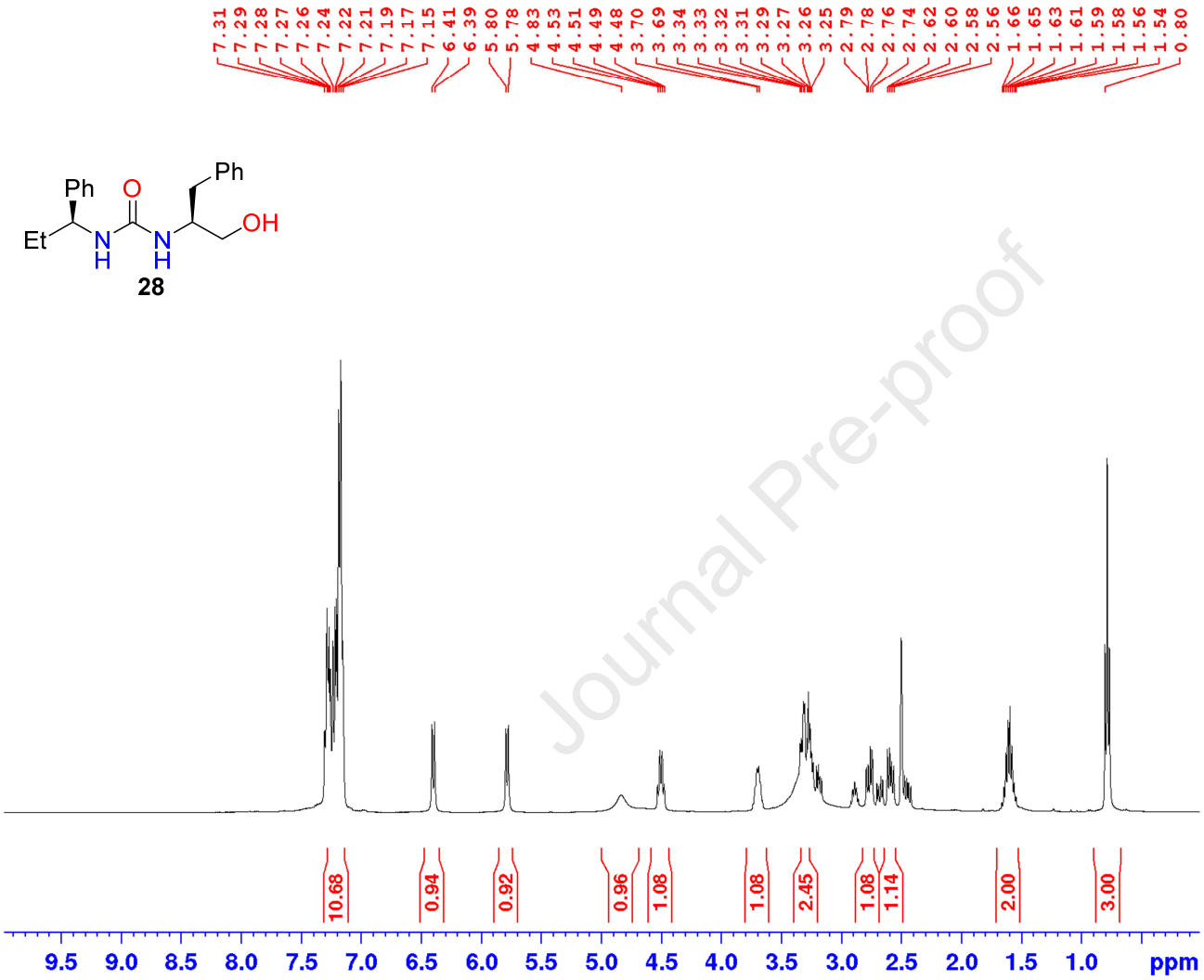


```
Current Data Parameters
NAME      UT-100 RECRYS DMSO
EXPNO                 21
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170820
Time              18.41 h
INSTRUM            spect
PROBHD    Z116098_0048 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                181.72
DW                20.800 usec
DE                 8.18 usec
TE                294.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   32
SFO1         100.6228303 MHz
NUC1                 13C
P1                 9.00 usec
PLW1         77.00000000 W
SFO2         400.1316005 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         24.00000000 W
PLW12         0.17567000 W
PLW13         0.08836300 W

F2 - Processing parameters
SI                65536
SF           100.6128112 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

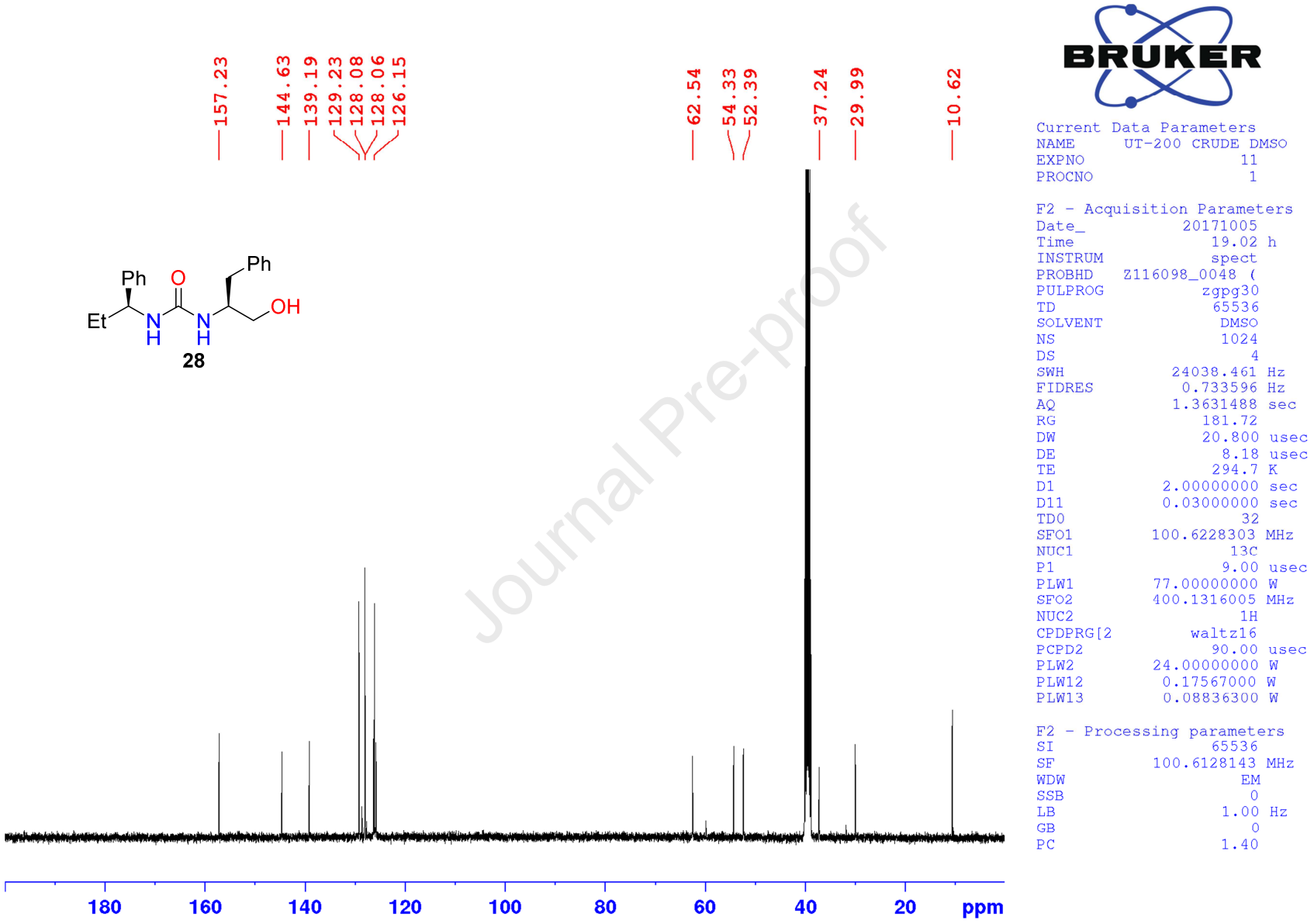





```
Current Data Parameters
NAME      UT-201 CW DMSO
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20171009
Time              10.45 h
INSTRUM             spect
PROBHD    Z116098_0048 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    64
DS                     2
SWH             8223.685 Hz
FIDRES          0.250967 Hz
AQ              3.9845889 sec
RG                 72.76
DW                60.800 usec
DE                10.69 usec
TE                294.3 K
D1             1.00000000 sec
TD0                    4
SFO1          400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          24.00000000 W

F2 - Processing parameters
SI                 32768
SF            400.1300037 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.50
```

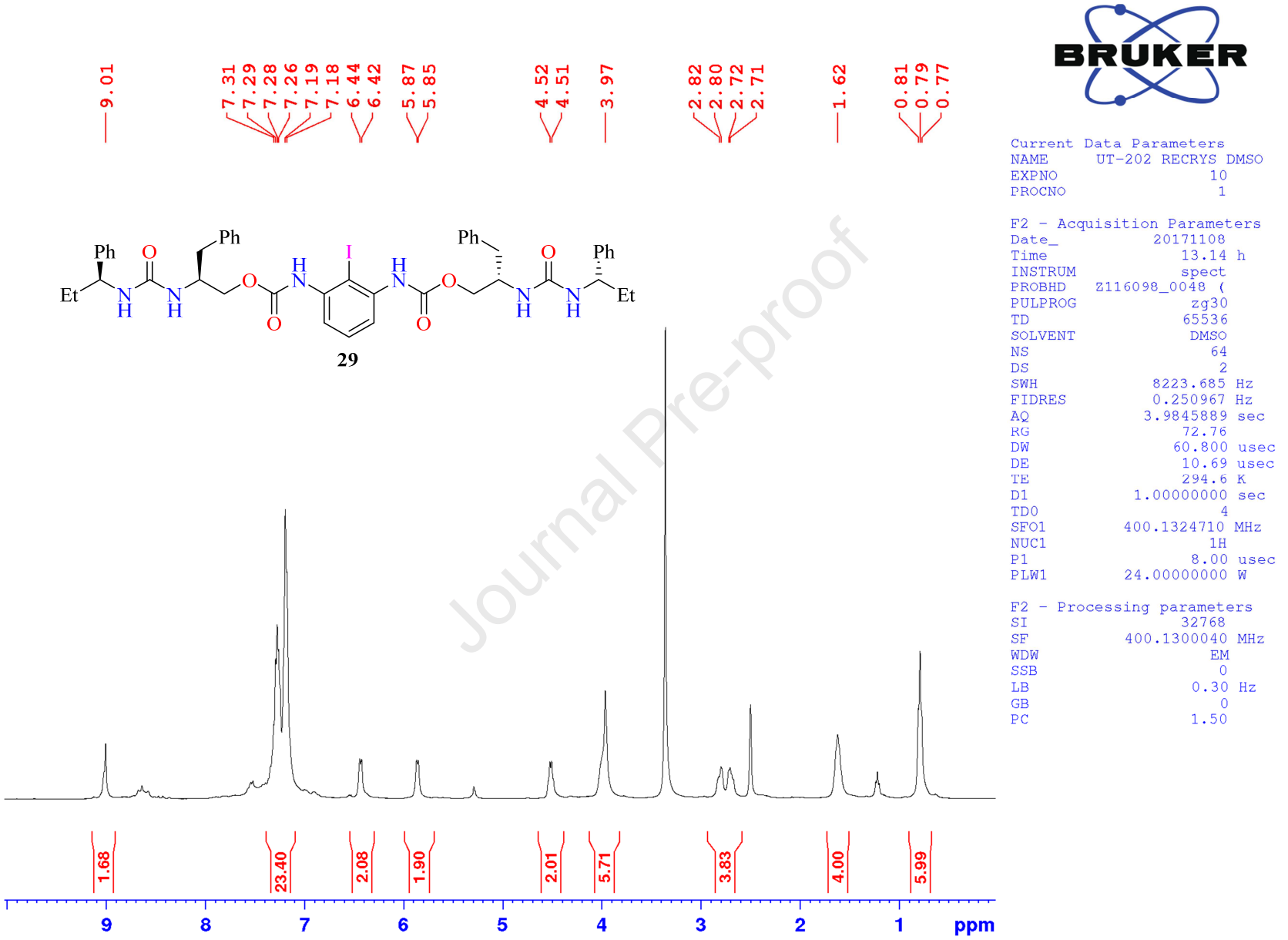





```
Current Data Parameters
NAME      UT-200 CRUDE DMSO
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_             20171005
Time                19.02 h
INSTRUM               spect
PROBHD    Z116098_0048 (
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                    1024
DS                       4
SWH             24038.461 Hz
FIDRES           0.733596 Hz
AQ              1.3631488 sec
RG                 181.72
DW                 20.800 usec
DE                  8.18 usec
TE                 294.7 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                     32
SFO1          100.6228303 MHz
NUC1                  13C
P1                  9.00 usec
PLW1          77.00000000 W
SFO2          400.1316005 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          24.00000000 W
PLW12          0.17567000 W
PLW13          0.08836300 W

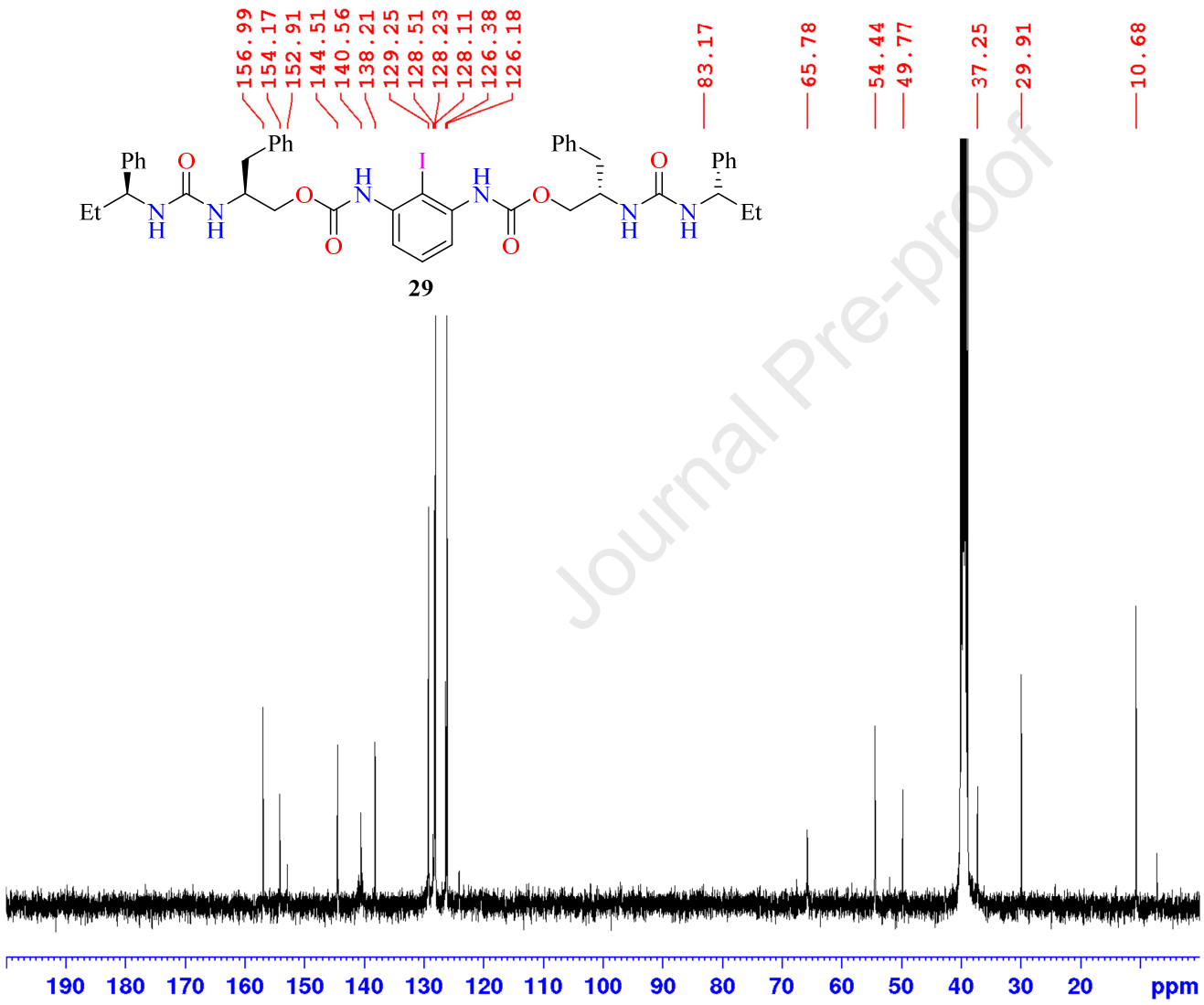
F2 - Processing parameters
SI                   65536
SF            100.6128143 MHz
WDW                     EM
SSB                      0
LB                  1.00 Hz
GB                       0
PC                  1.40
```




```
Current Data Parameters
NAME      UT-202 RECRYS DMSO
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_             20171108
Time                13.14 h
INSTRUM              spect
PROBHD    Z116098_0048 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       64
DS                        2
SWH                8223.685 Hz
FIDRES             0.250967 Hz
AQ                 3.9845889 sec
RG                     72.76
DW                    60.800 usec
DE                    10.69 usec
TE                    294.6 K
D1              1.00000000 sec
TD0                       4
SFO1           400.1324710 MHz
NUC1                     1H
P1                    8.00 usec
PLW1           24.00000000 W

F2 - Processing parameters
SI                    32768
SF             400.1300040 MHz
WDW                      EM
SSB                       0
LB                    0.30 Hz
GB                        0
PC                    1.50
```




**29**

```
Current Data Parameters
NAME      UT-202 RECRYS DMSO
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20171108
Time              21.21 h
INSTRUM            spect
PROBHD   Z116098_0048 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ            1.3631488 sec
RG               181.72
DW               20.800 usec
DE                8.18 usec
TE               294.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  32
SFO1        100.6228303 MHz
NUC1                13C
P1                9.00 usec
PLW1        77.00000000 W
SFO2        400.1316005 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2            90.00 usec
PLW2        24.00000000 W
PLW12        0.17567000 W
PLW13        0.08836300 W

F2 - Processing parameters
SI                65536
SF          100.6128143 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40
```

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: