*Supporting Information*

*For*

# Formation of 2-Imino benzo[*e*]-1,3-oxazin-4-ones from Reactions of Salicylic Acids and Anilines with HATU: Mechanistic and Synthetic Studies

Derek A. Leas,[†] Jianbo Wu,[†] Edward L. Ezell,[‡] Jered C. Garrison,[†] Jonathan L. Vennerstrom,[†] and Yuxiang Dong[*,†]

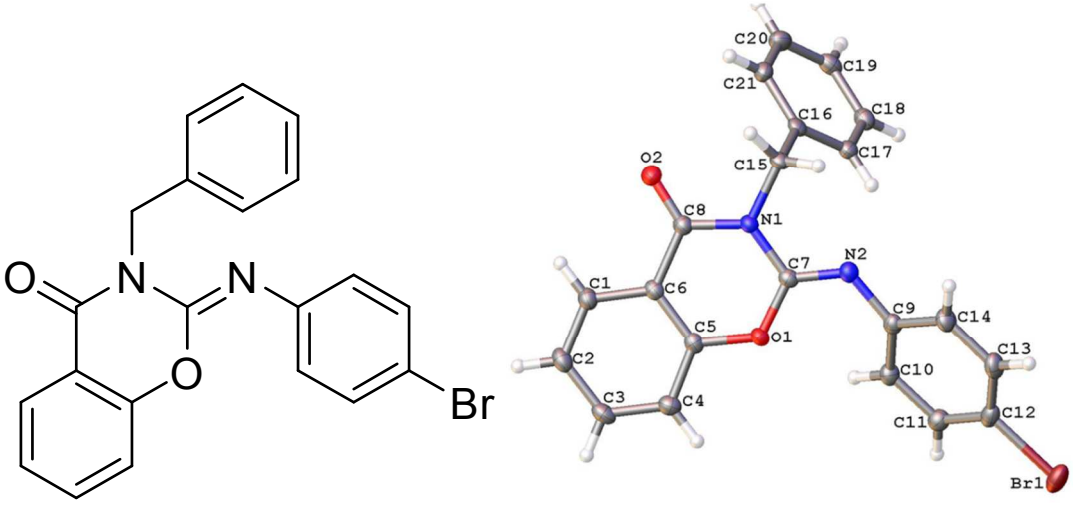
[†]College of Pharmacy and [‡]Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE 68198, United States

ydong@unmc.edu

## Table of Contents:

**Crystallographic Data**

Single crystals of $C_{21}H_{15}N_2O_2Br$ (**4f**) were grown via slow evaporation of EtOAc. A suitable crystal was selected and mounted on a CyroLoop™ using paratone oil on a Xcalibur, Onyx, Ultra diffractometer. The crystal was kept at 100 K during data collection. Using Olex2[1], the structure was solved with the ShelXS[2] structure solution program using Direct Methods and refined with the ShelXL[3] refinement package using Least Squares minimization.




Olex2 view – 50% probability level

**Figure S1**. Structural features of (Z)-3-benzyl-2-((4-bromophenyl)imino)-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (**4f**).

---

**Table S1**. Crystal data and structure refinement

| | |
|---|---|
| Empirical formula | $C_{21}H_{15}N_2O_2Br$ |
| Formula weight | 407.26 |
| Temperature/K | 100 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| a/Å | 10.92936(8) |
| b/Å | 12.80330(9) |
| c/Å | 13.37608(11) |

| | |
|---|---|
| α/° | 90 |
| β/° | 112.0814(9) |
| γ/° | 90 |
| Volume/Å$^3$ | 1734.45(2) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.560 |
| μ/mm$^{-1}$ | 3.379 |
| F(000) | 824.0 |
| Crystal size/mm$^3$ | 0.3 × 0.3 × 0.05 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection/° | 8.732 to 152.33 |
| Index ranges | $-13 \leq h \leq 13$, $-16 \leq k \leq 16$, $-16 \leq l \leq 16$ |
| Reflections collected | 59123 |
| Independent reflections | 3619 [$R_{int}$ = 0.0578, $R_{sigma}$ = 0.0164] |
| Data/restraints/parameters | 3619/0/235 |
| Goodness-of-fit on $F^2$ | 1.045 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0307, $wR_2$ = 0.0806 |
| Final R indexes [all data] | $R_1$ = 0.0324, $wR_2$ = 0.0822 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.27/-0.56 |

**Figure S2**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4a**.

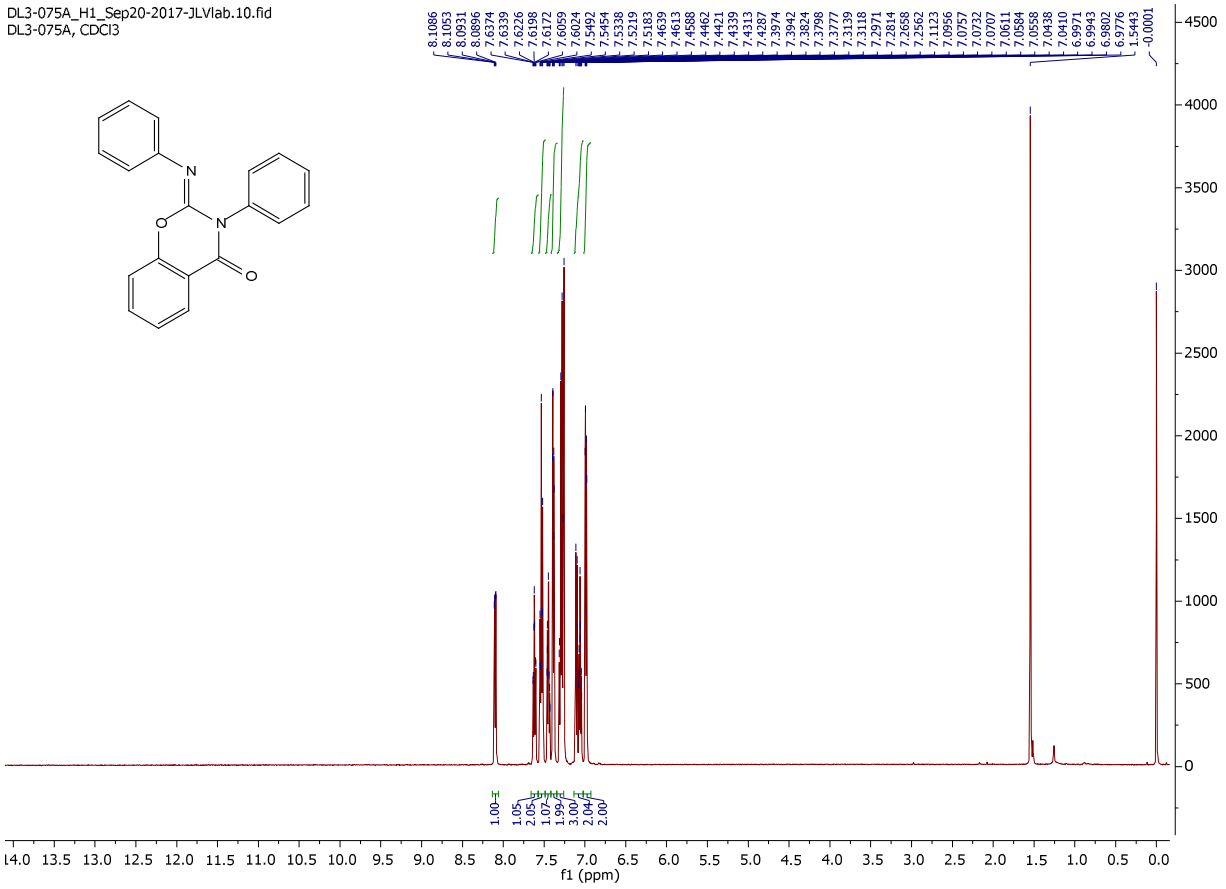


**Figure S3**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4a**.

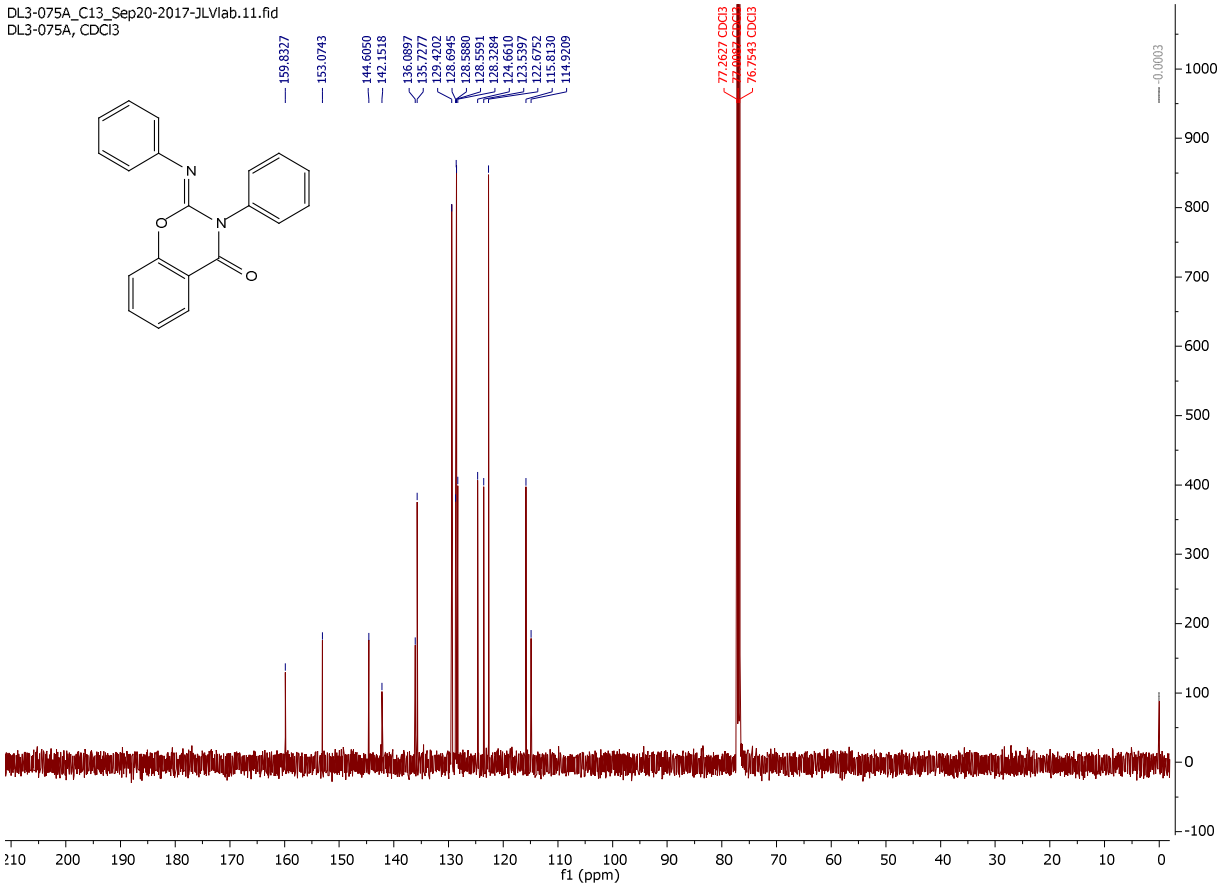


**Figure S4**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4b**.

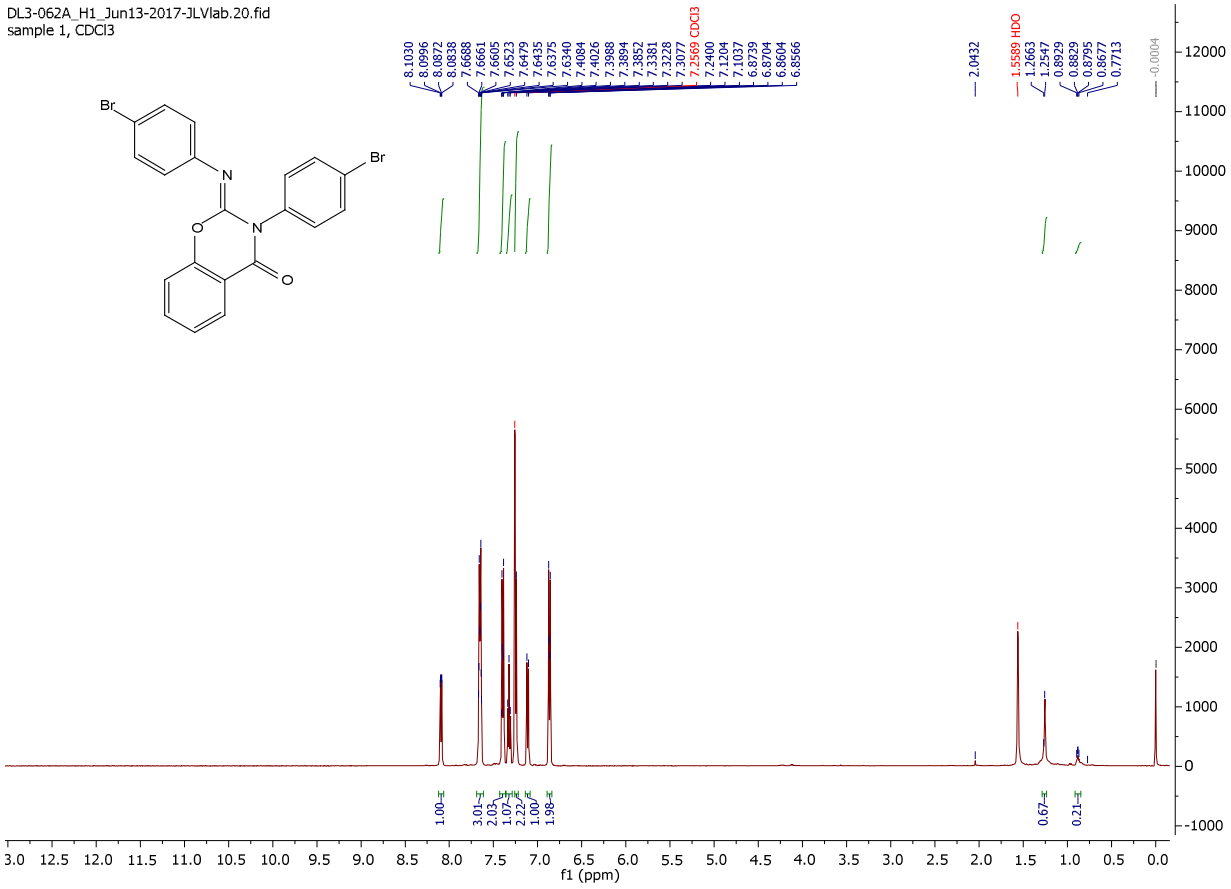


**Figure S5**. $^{1}H$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4b**.

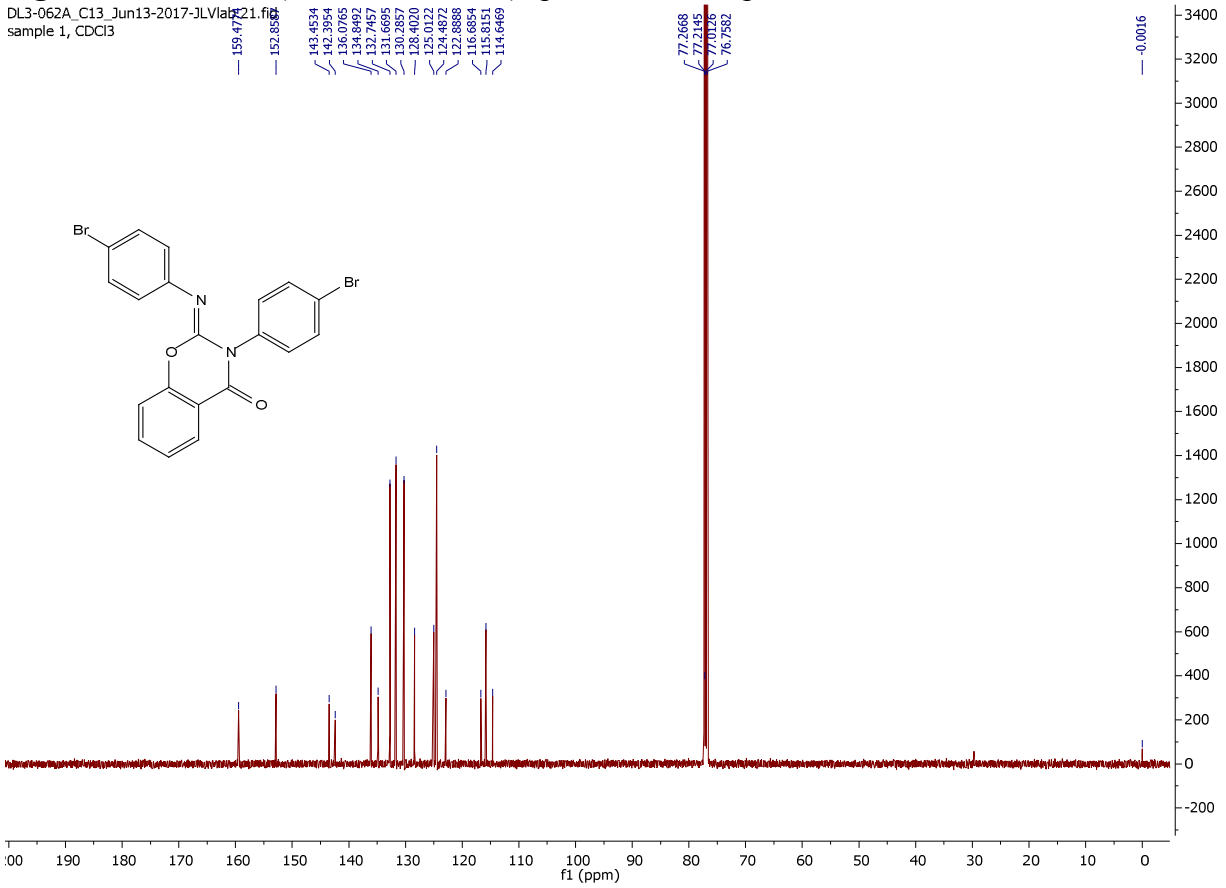


**Figure S6**. $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of compound **5**.

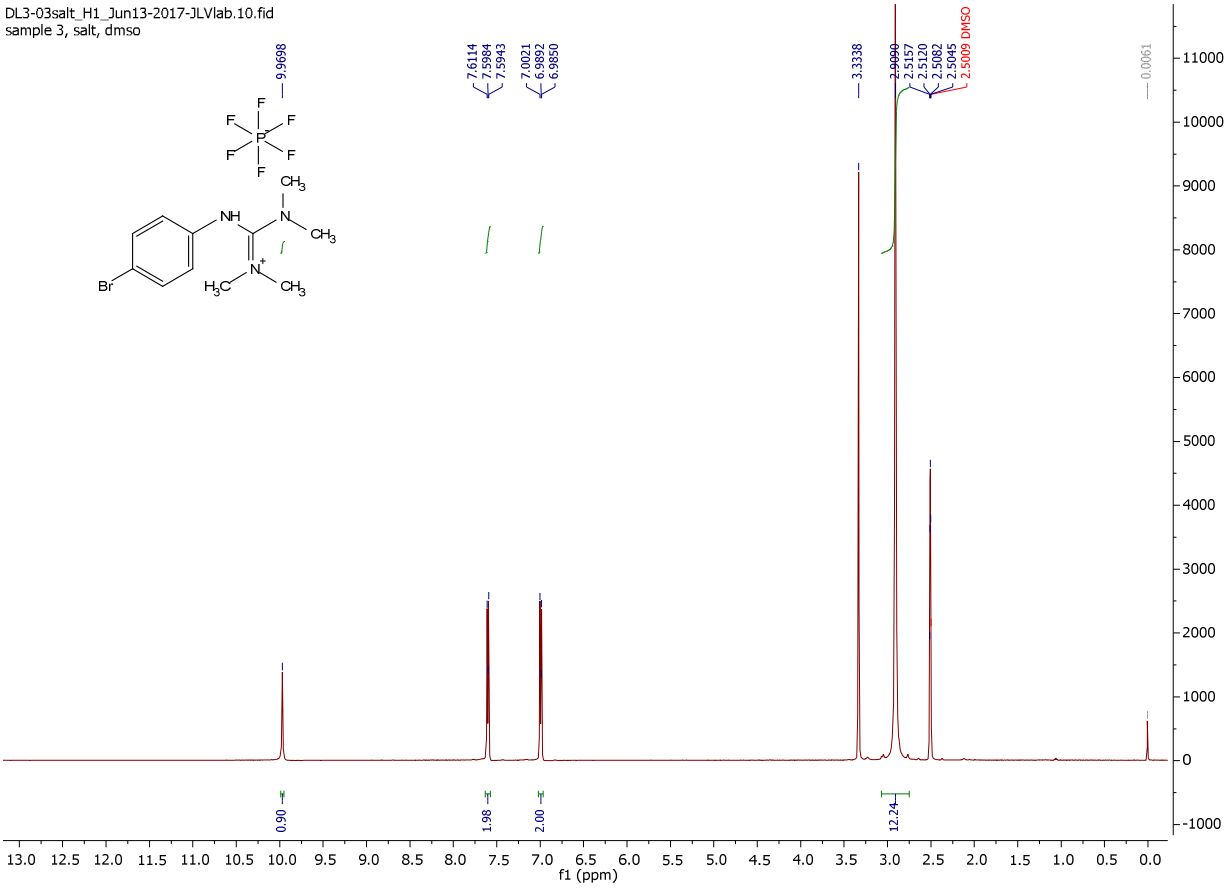


**Figure S7**. $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectrum of compound **5**.

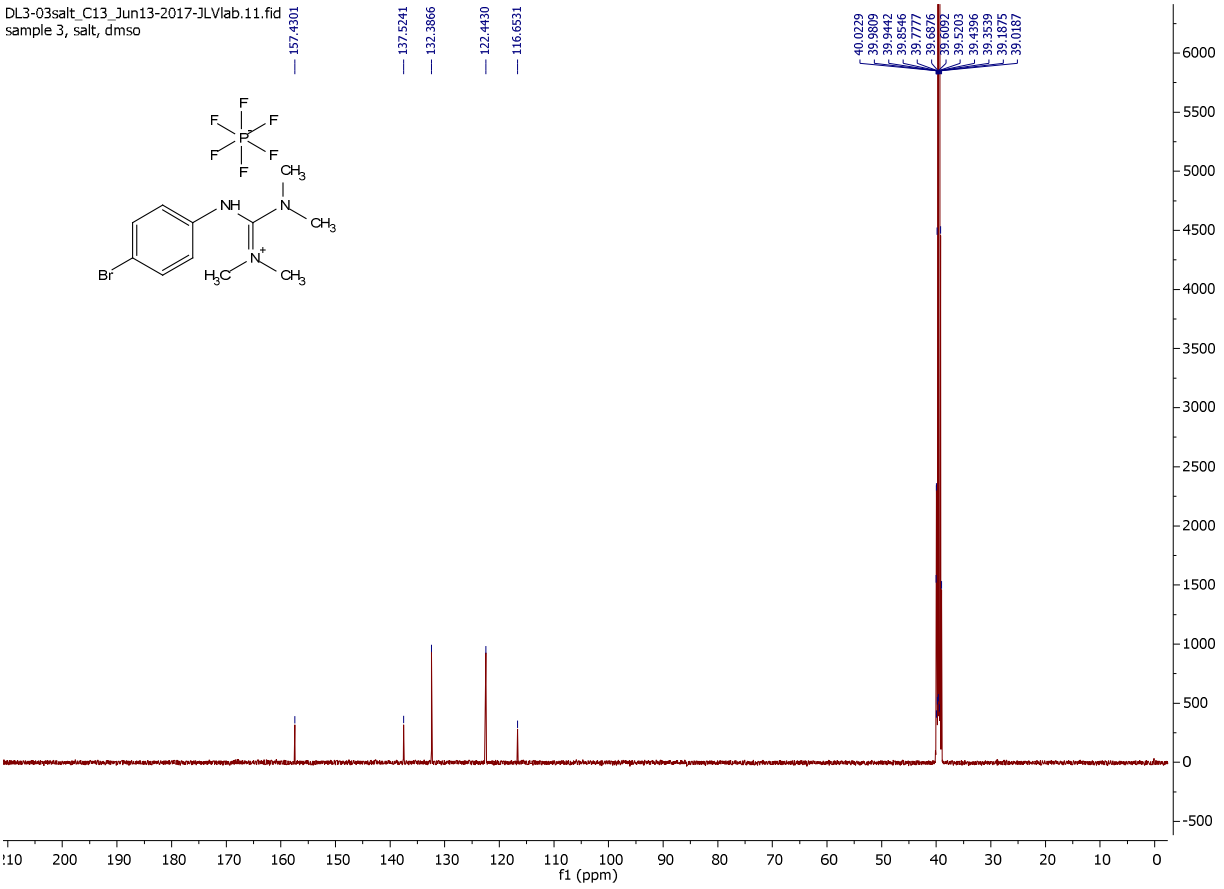


**Figure S8**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **6**.

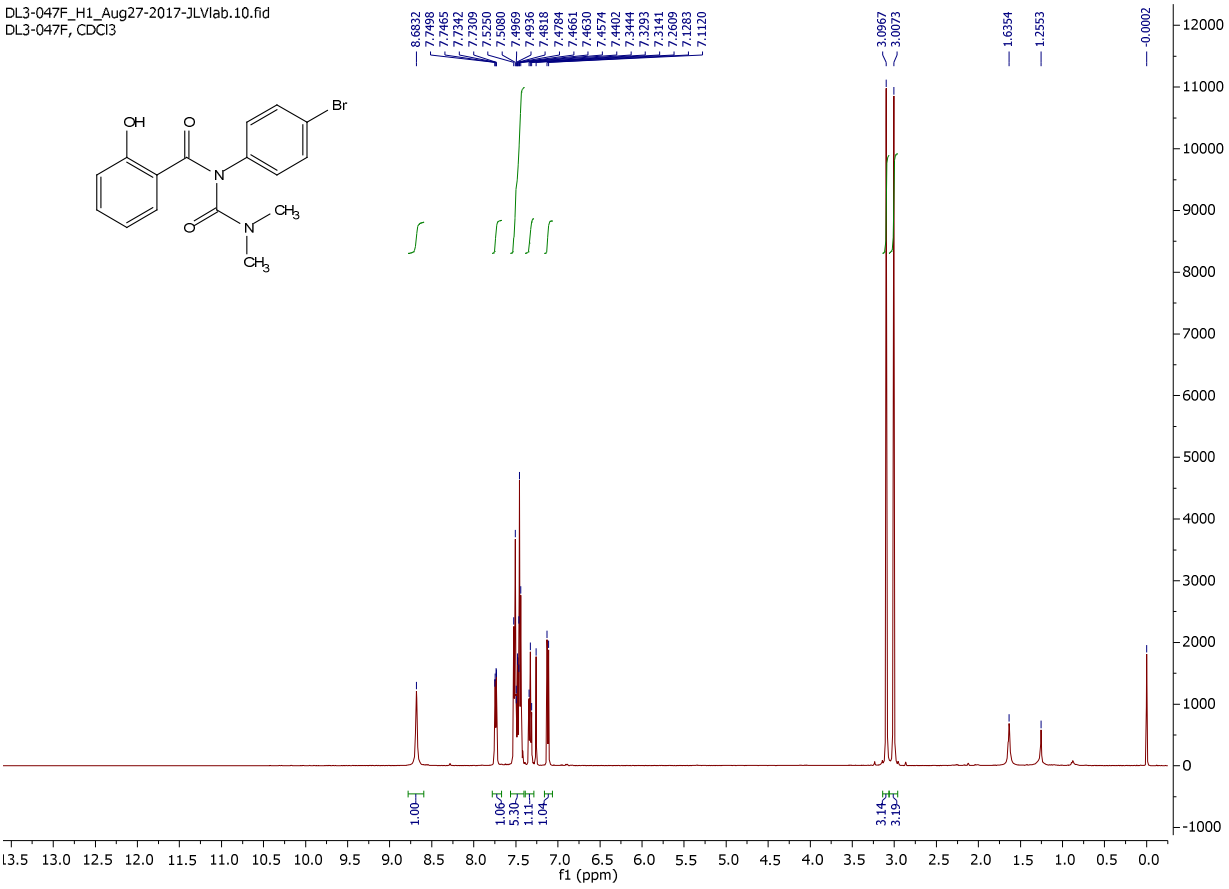


**Figure S9**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **6**.

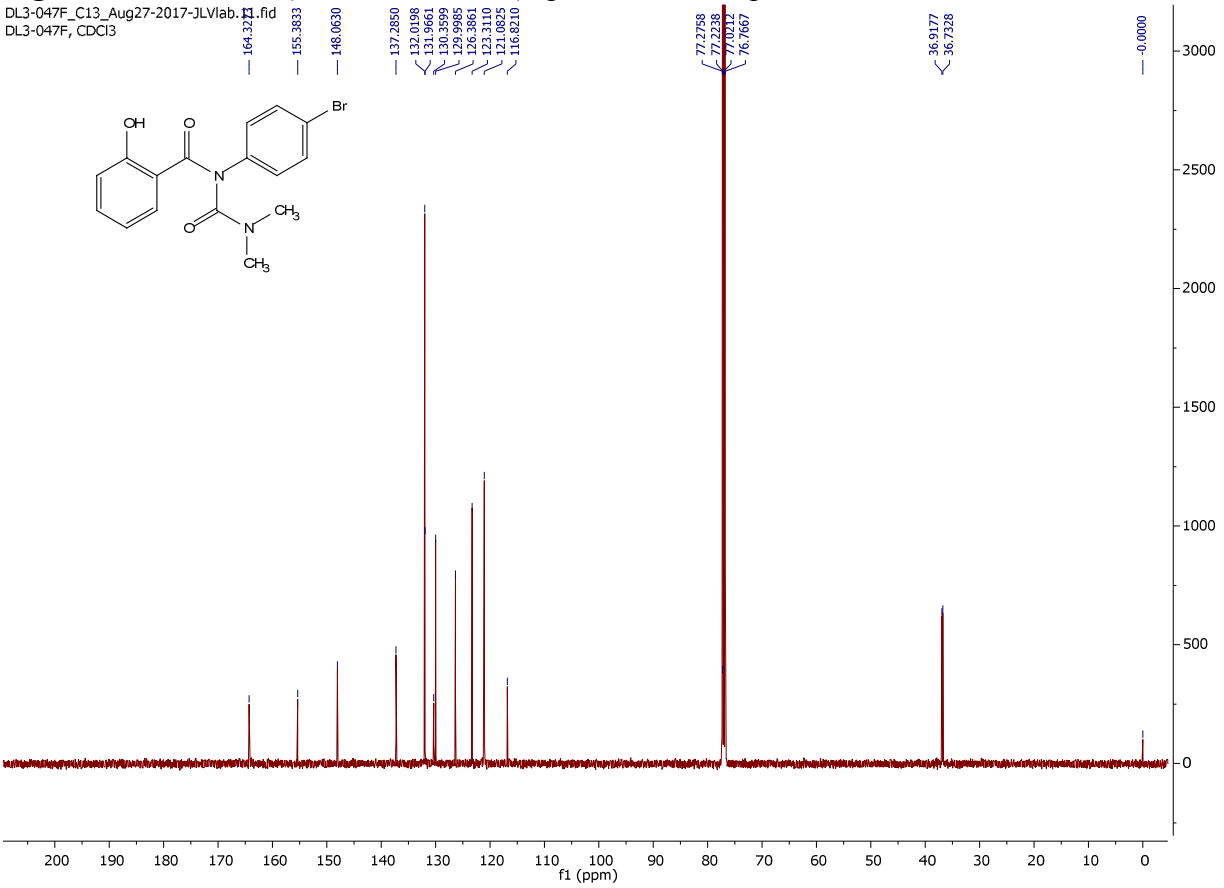


**Figure S10**. $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of compound **7**.

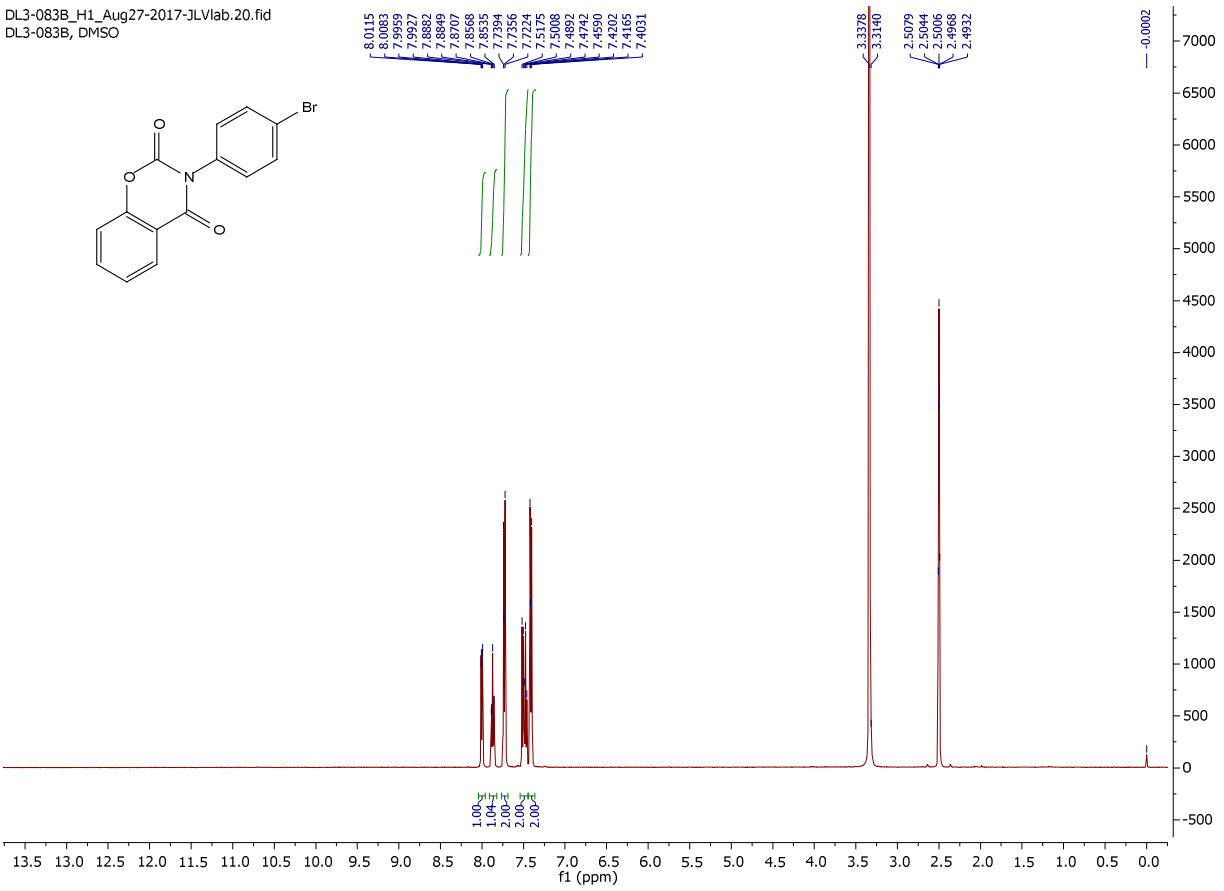


**Figure S11**. $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectrum of compound **7**.

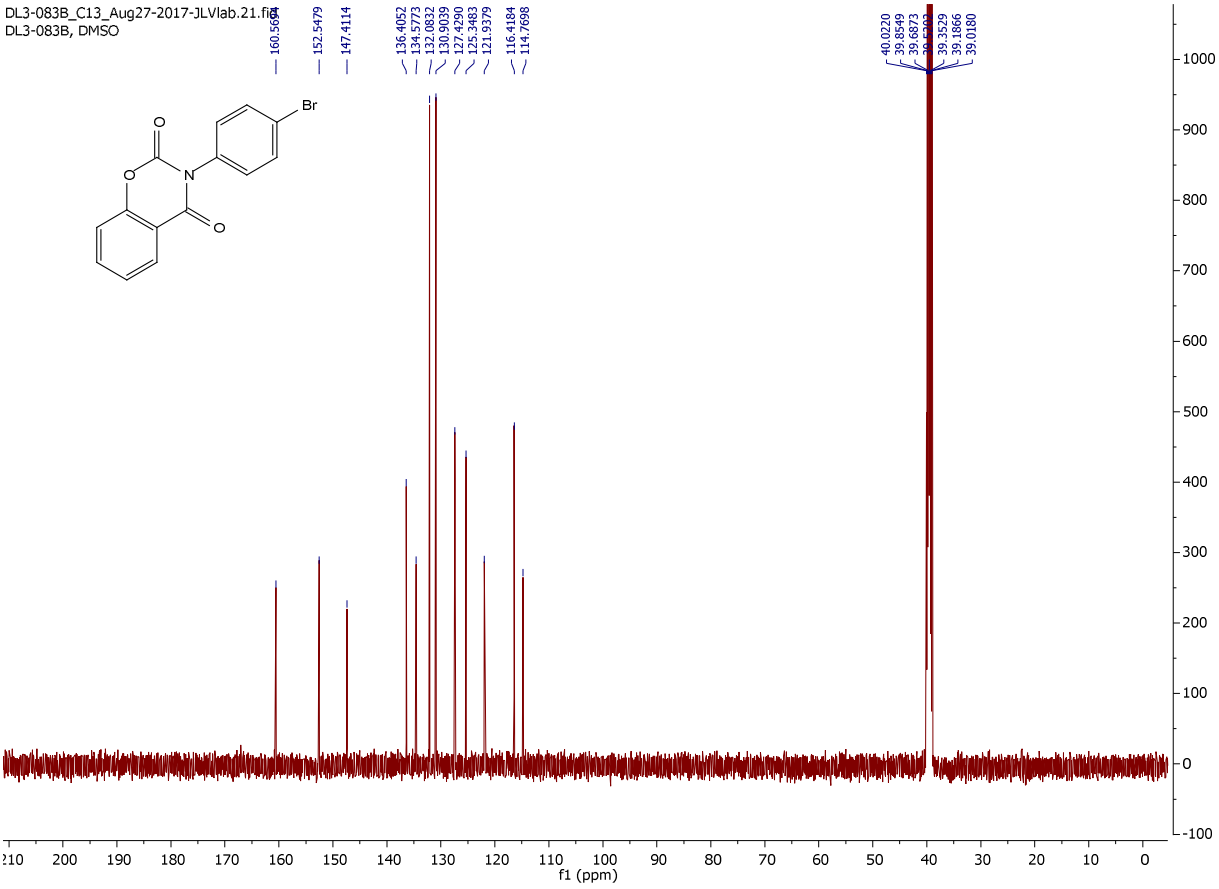


**Figure S12**. $^{1}H$ NMR (600 MHz, $CDCl_3$) spectrum of compound **4c**.

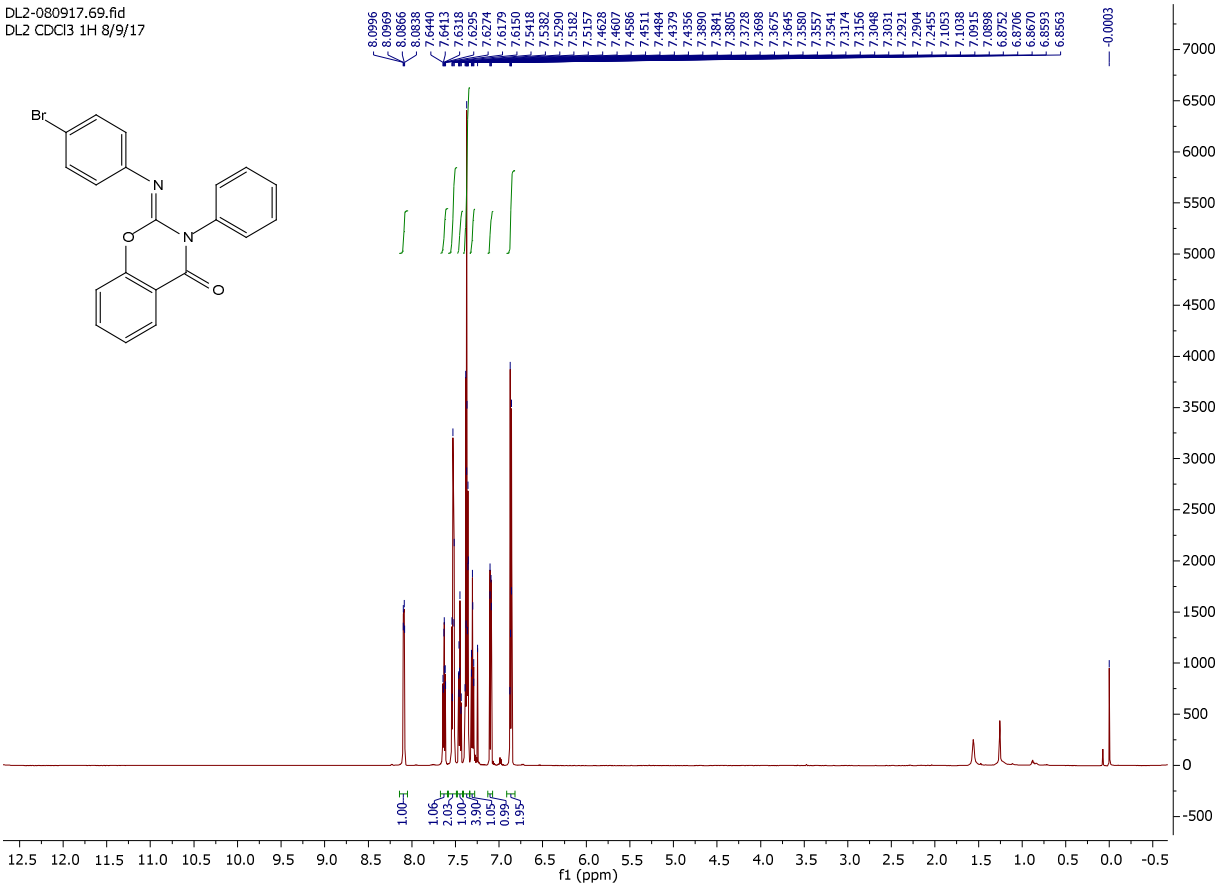


**Figure S13**. $^{13}C$ NMR (150 MHz, $CDCl_3$) spectrum of compound **4c**.

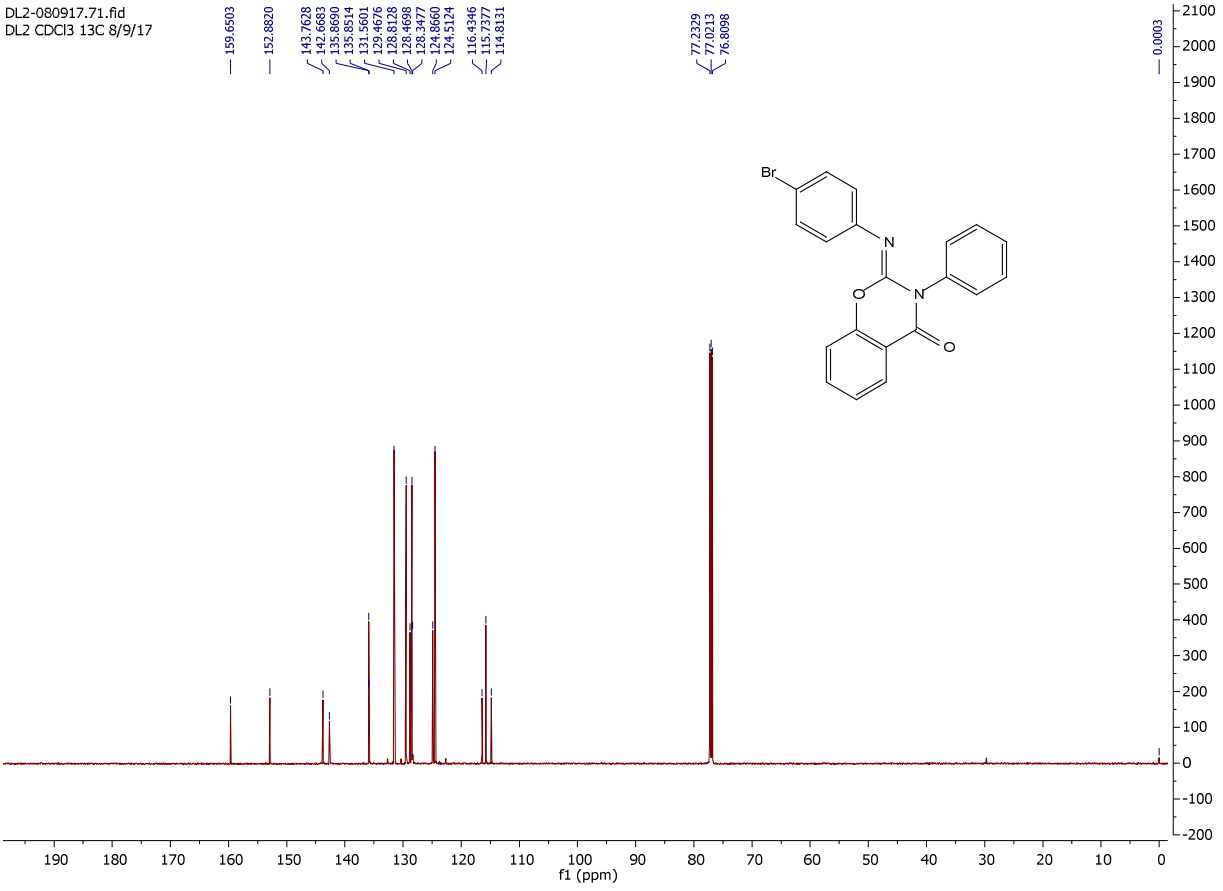


**Figure S14**. $^{1}H$ NMR (600 MHz, $CDCl_3$) spectrum of compound **4d**.

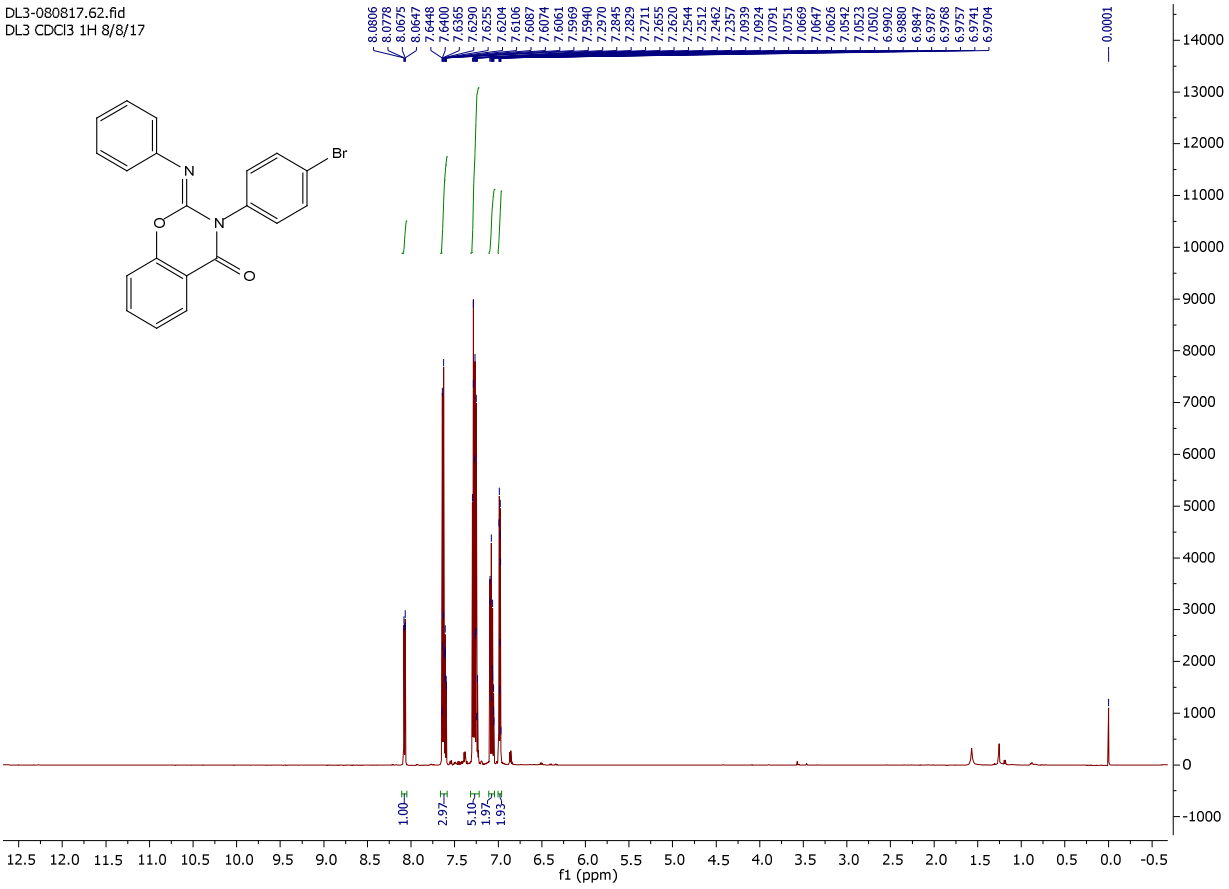


**Figure S15**. $^{13}C$ NMR (150 MHz, $CDCl_3$) spectrum of compound **4d**.

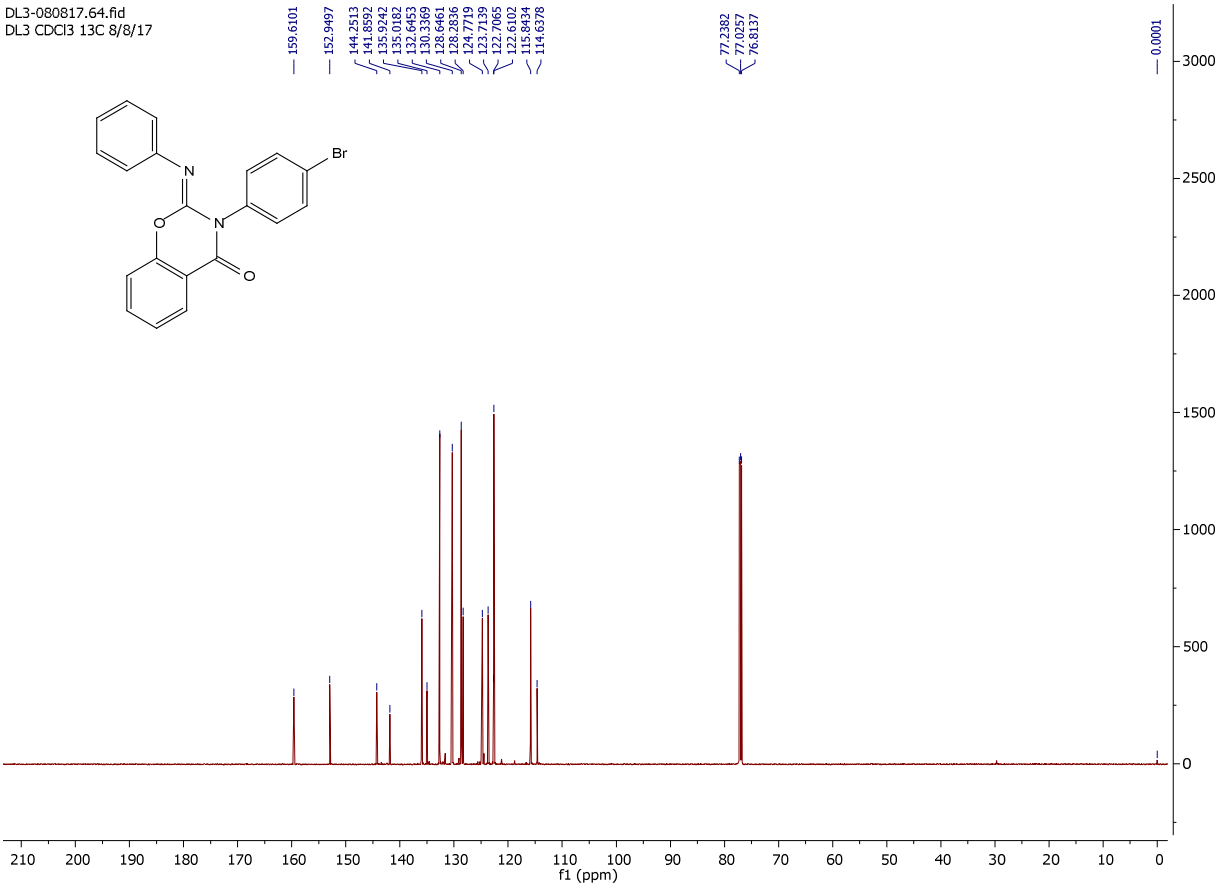


**Figure S16**. $^{1}H$ NMR (400 MHz, $CDCl_3$) spectrum of compound **3b**.

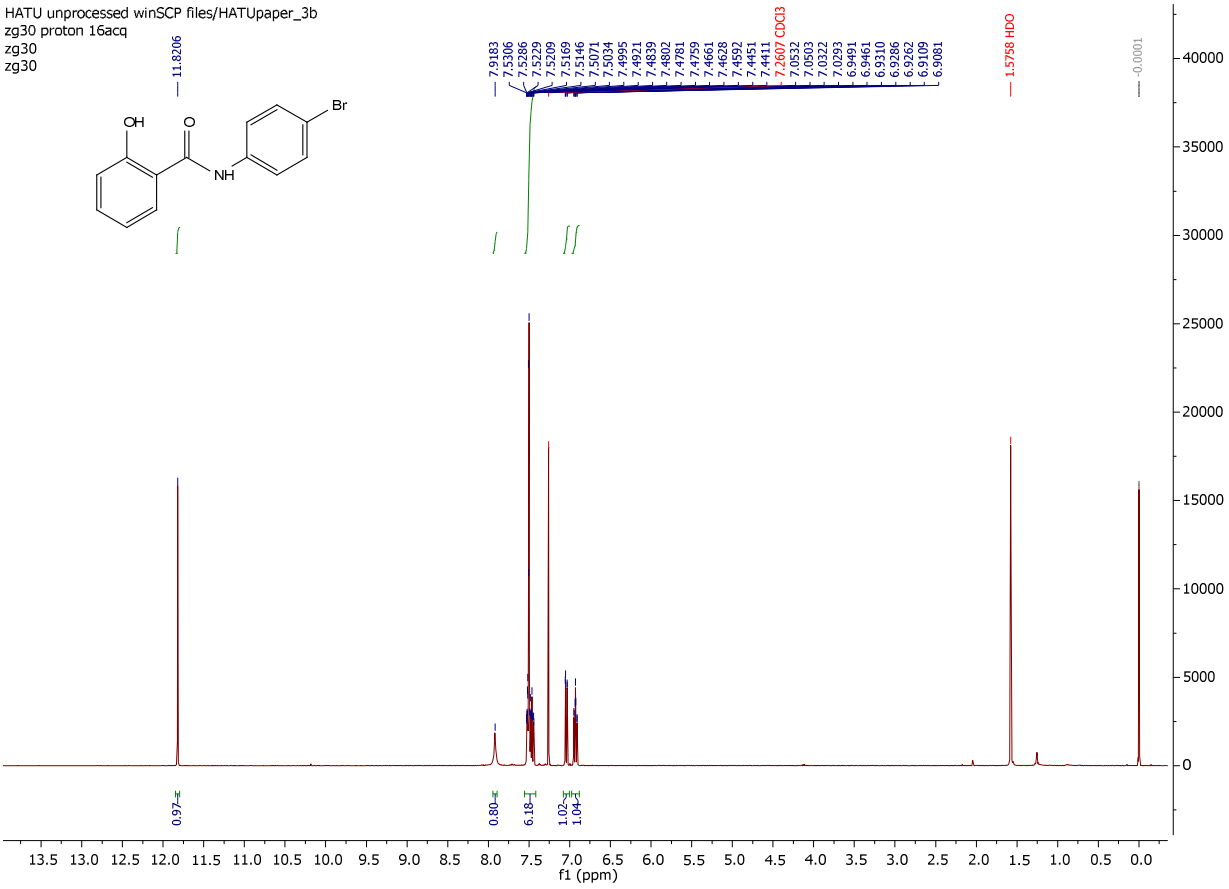


**Figure S17**. $^{1}H$ NMR (400 MHz, $CDCl_3$) spectrum of compound **4e**.

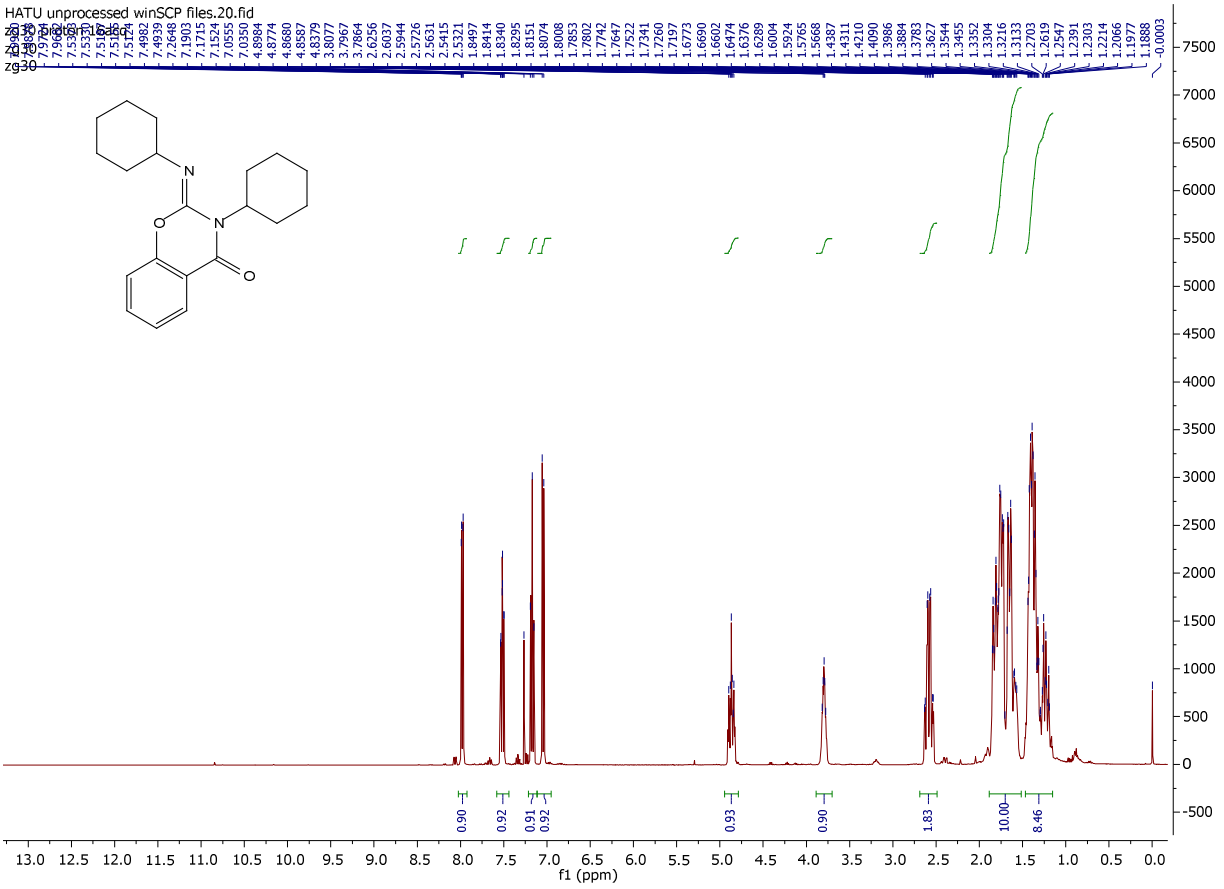


**Figure S18**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4e**.

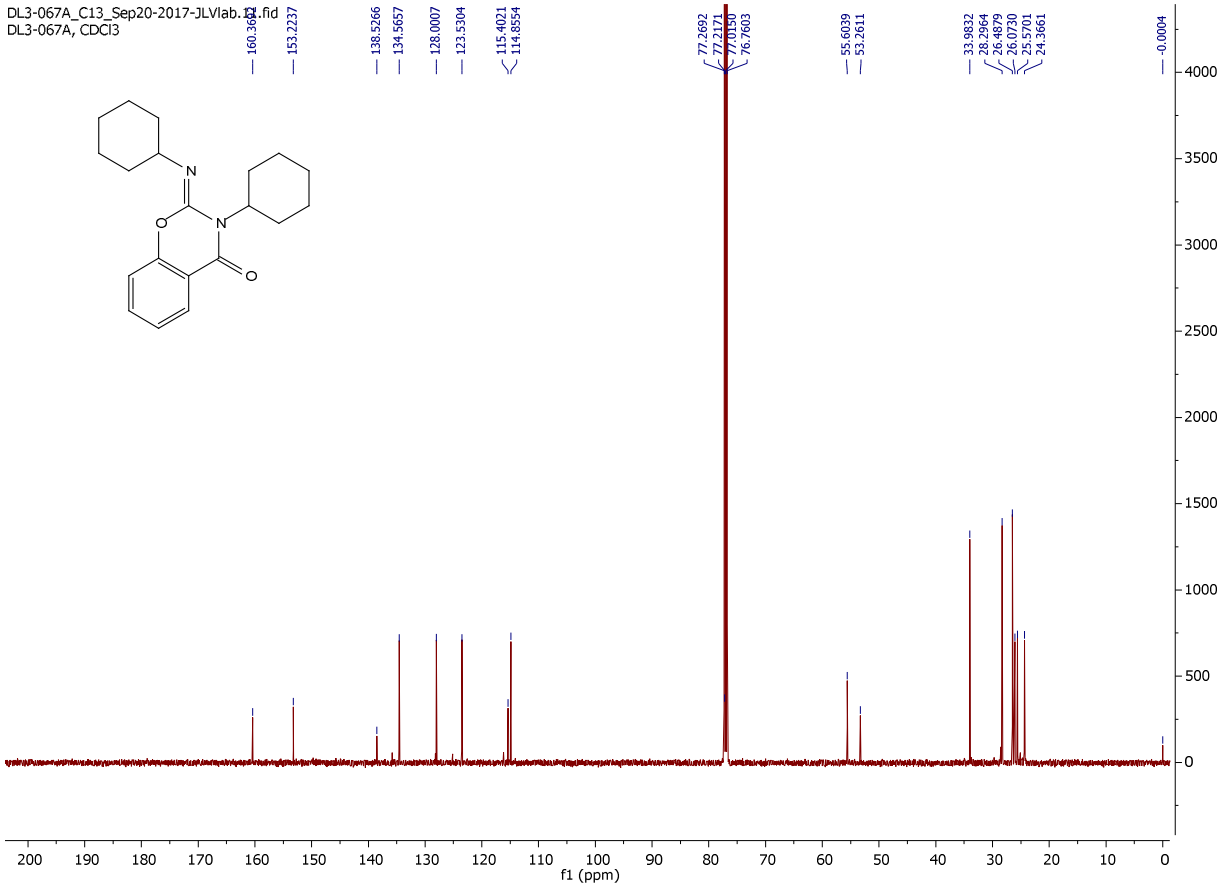


**Figure S19**. $^{1}H$ NMR (400 MHz, $CDCl_3$) spectrum of compound **3c**.

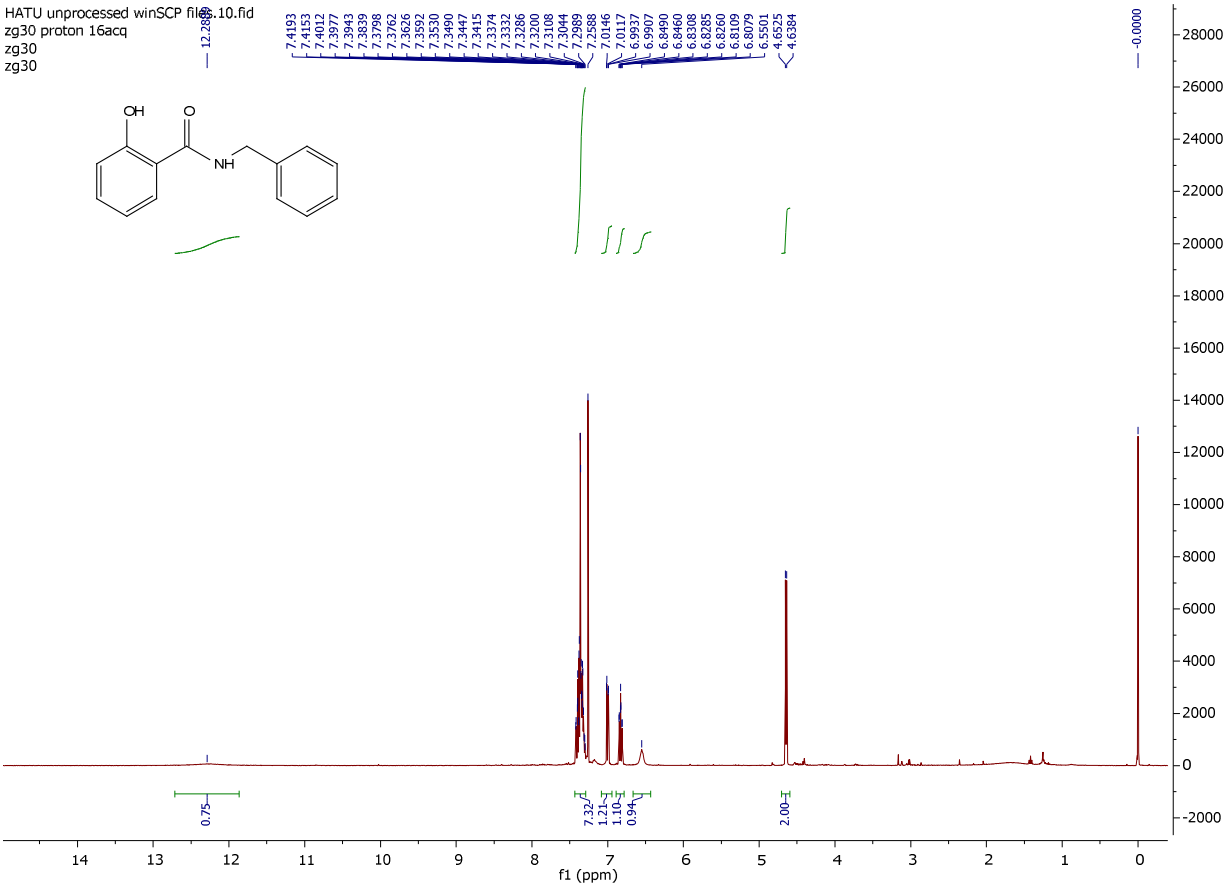


**Figure S20**. $^{1}$H NMR (600 MHz, $CDCl_3$) spectrum of compound **4f**.

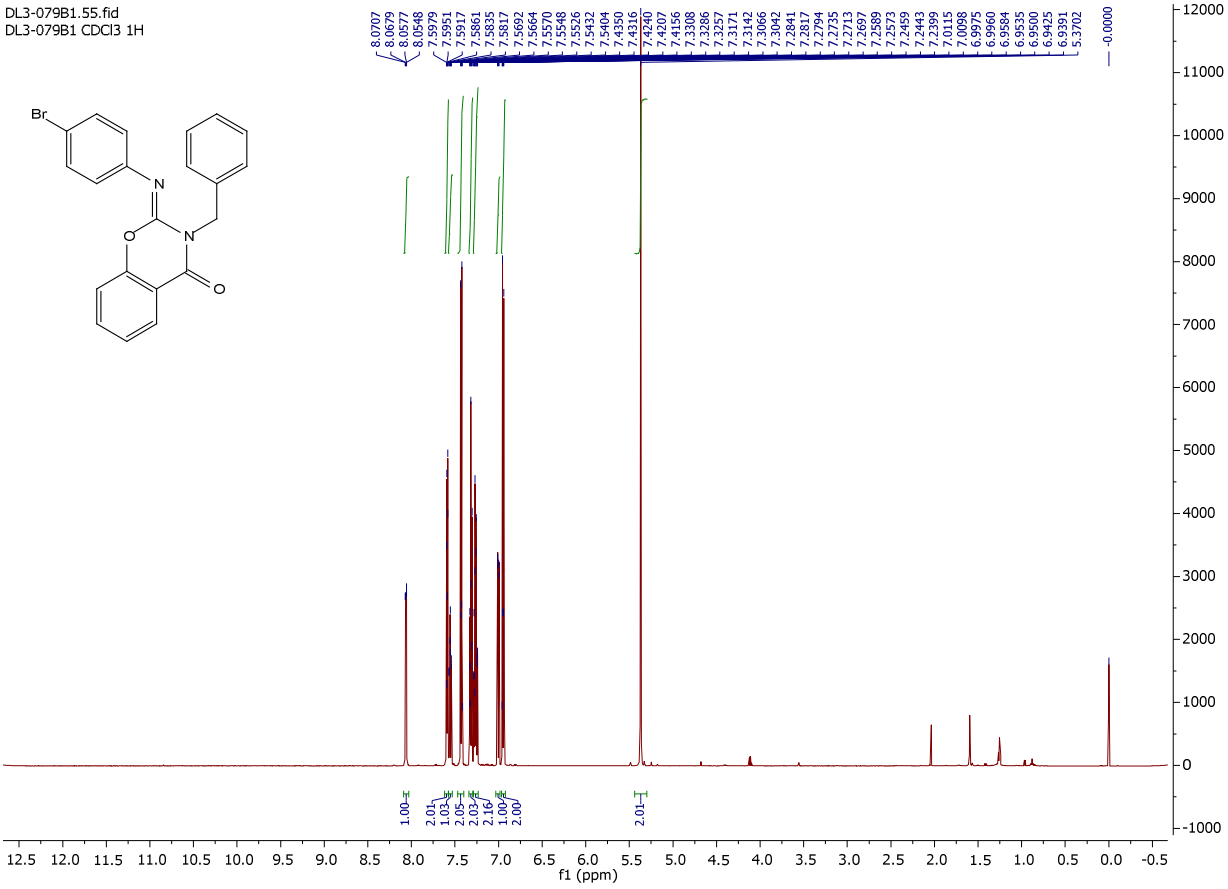


**Figure S21**. $^{13}C$ NMR (150 MHz, $CDCl_3$) spectrum of compound **4f**.

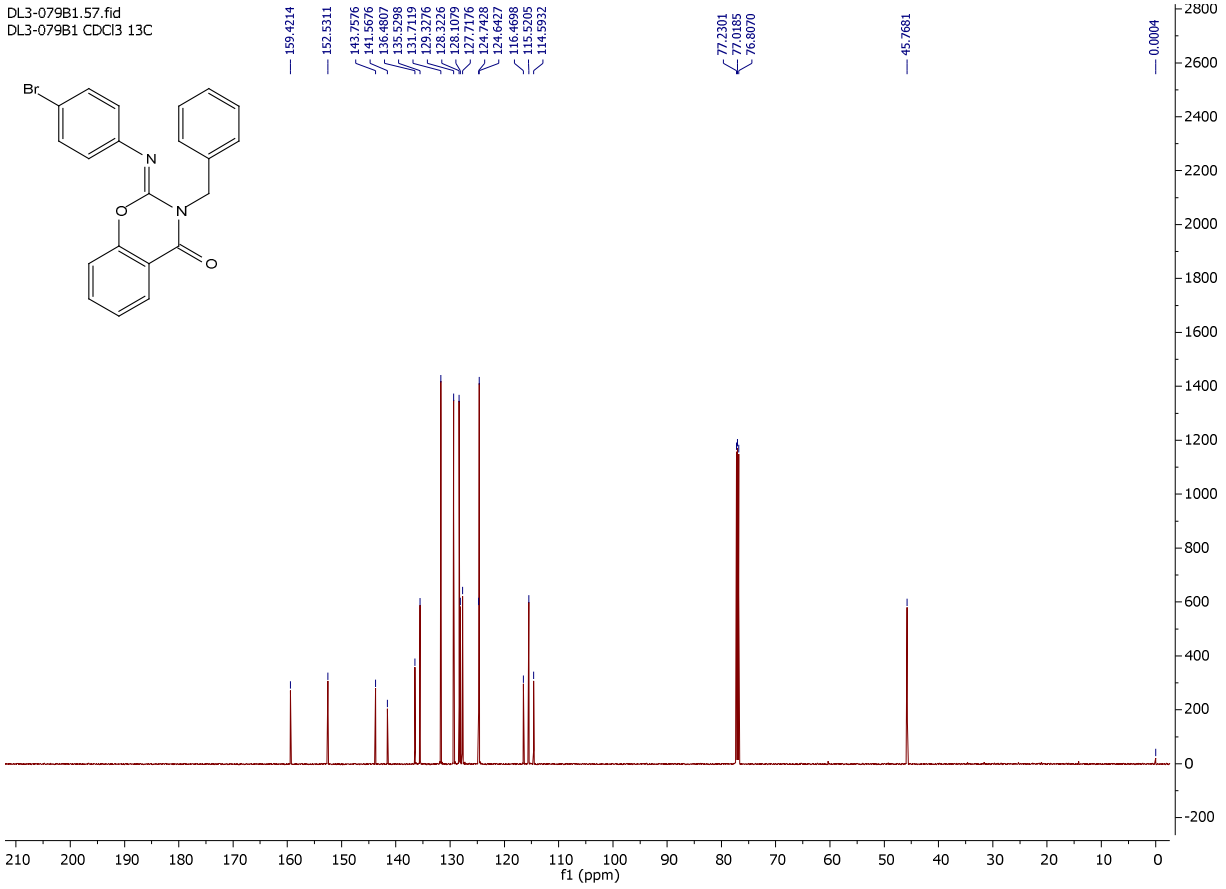


**Figure S22**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4h**.

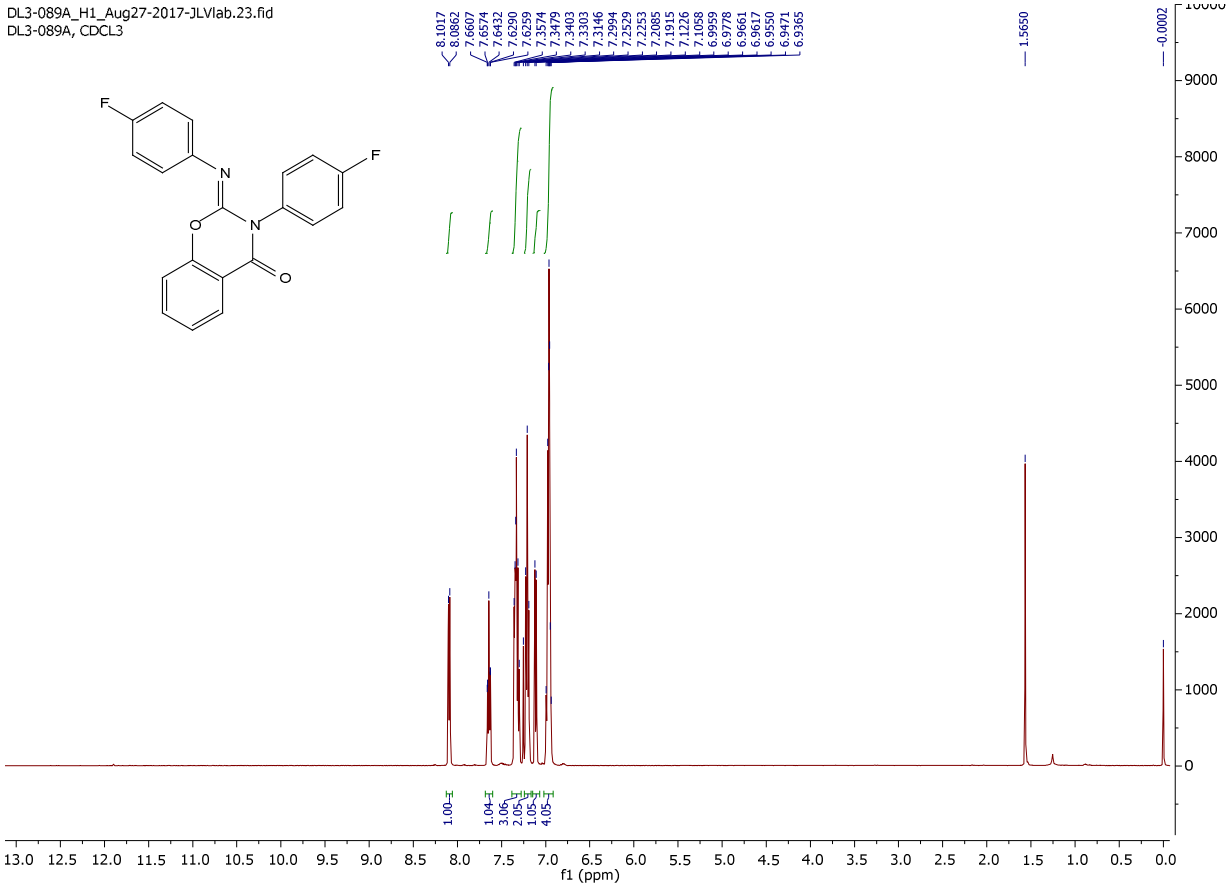


**Figure S23**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4h**.

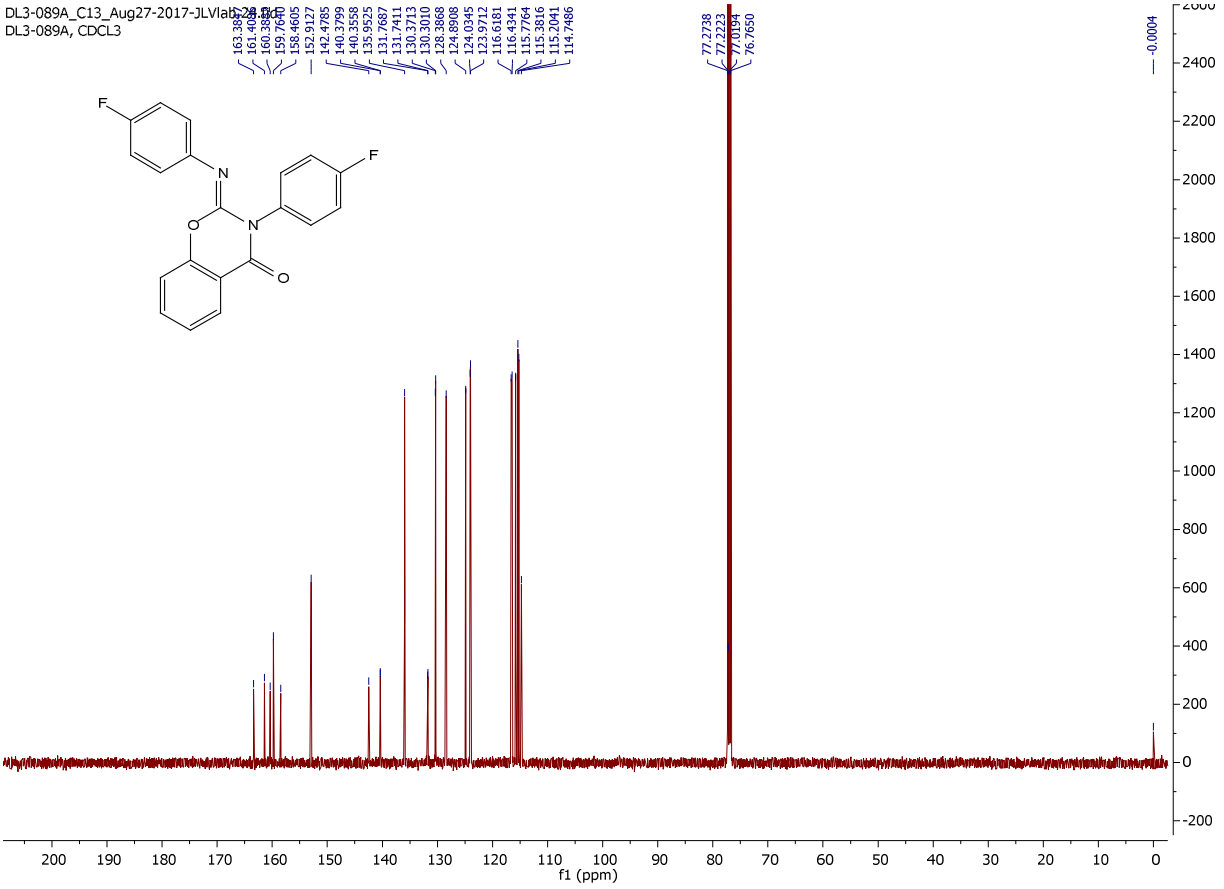


**Figure S24**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4i**.

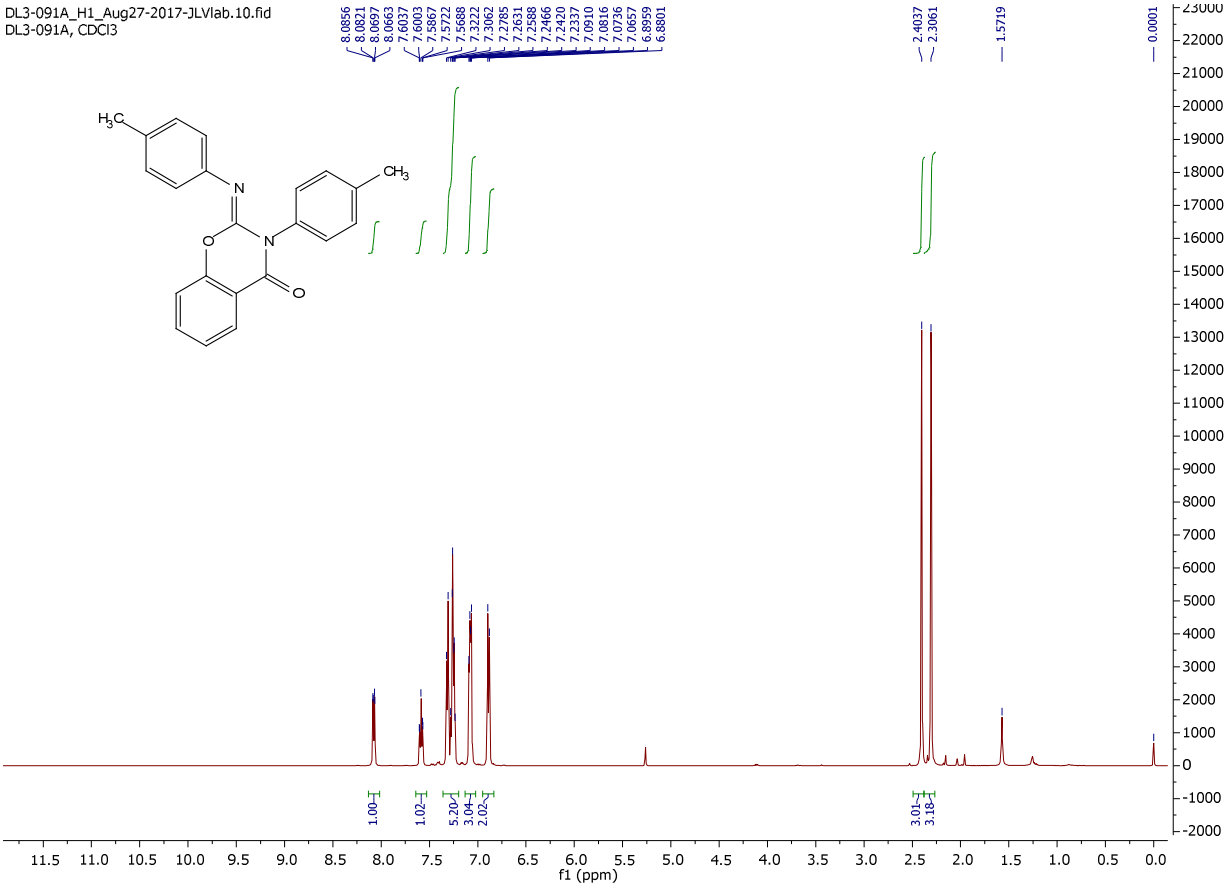


**Figure S25**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4i**.

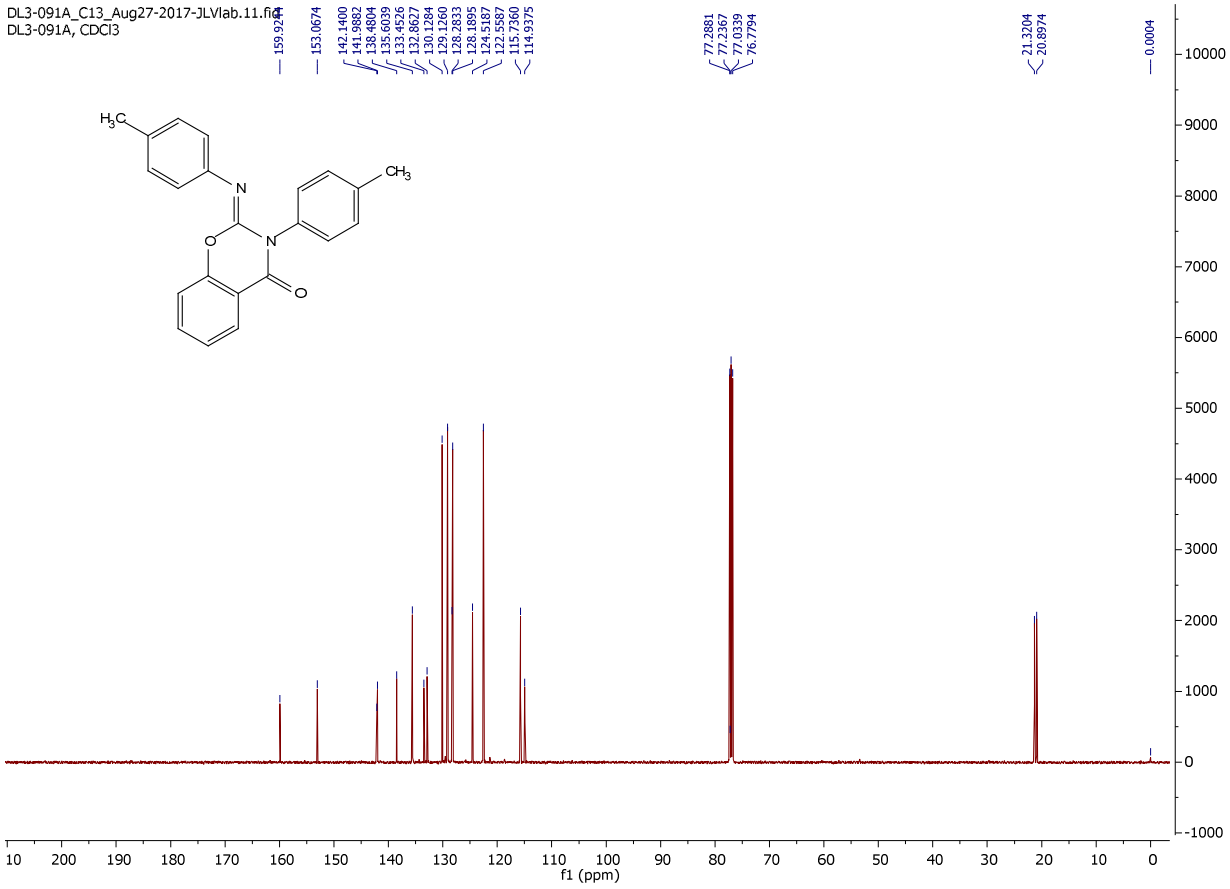


**Figure S26**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4l**.

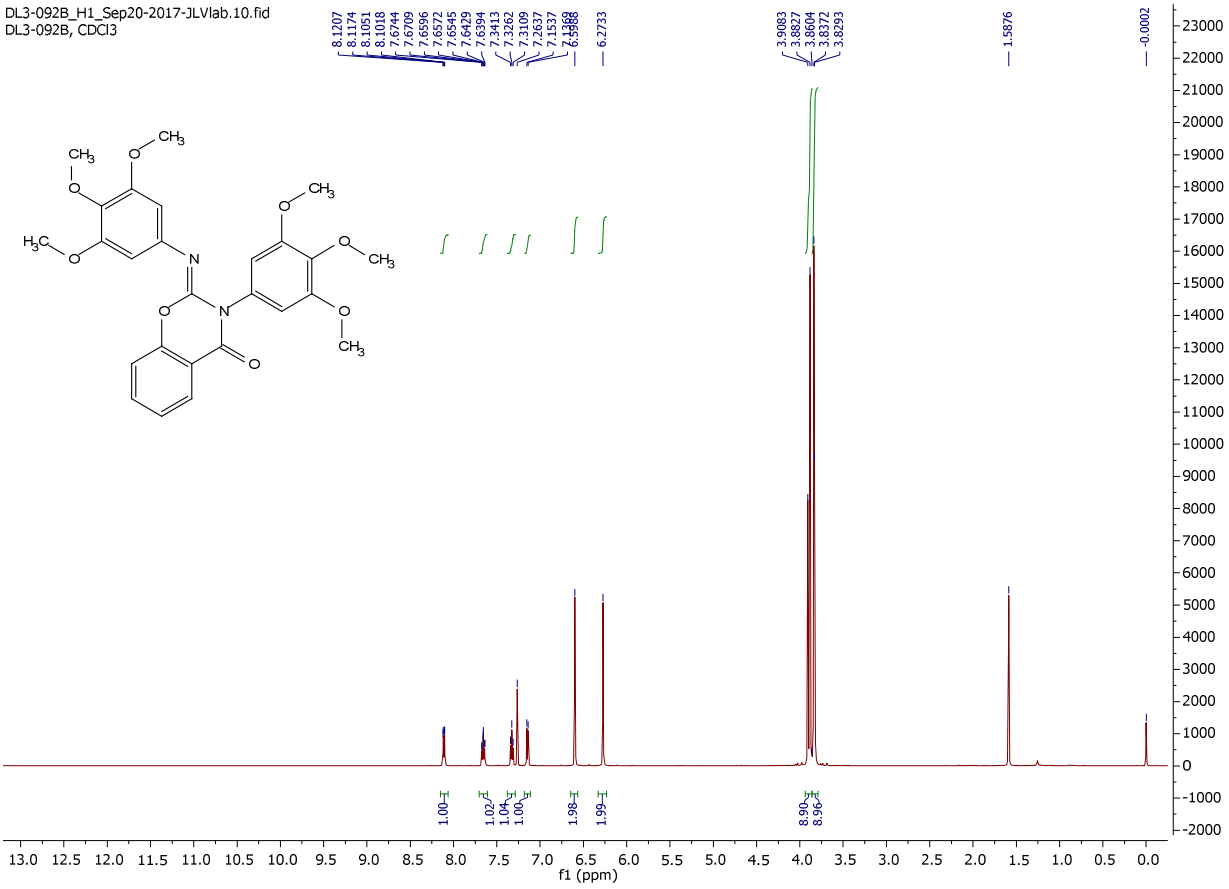


**Figure S27**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4l**.

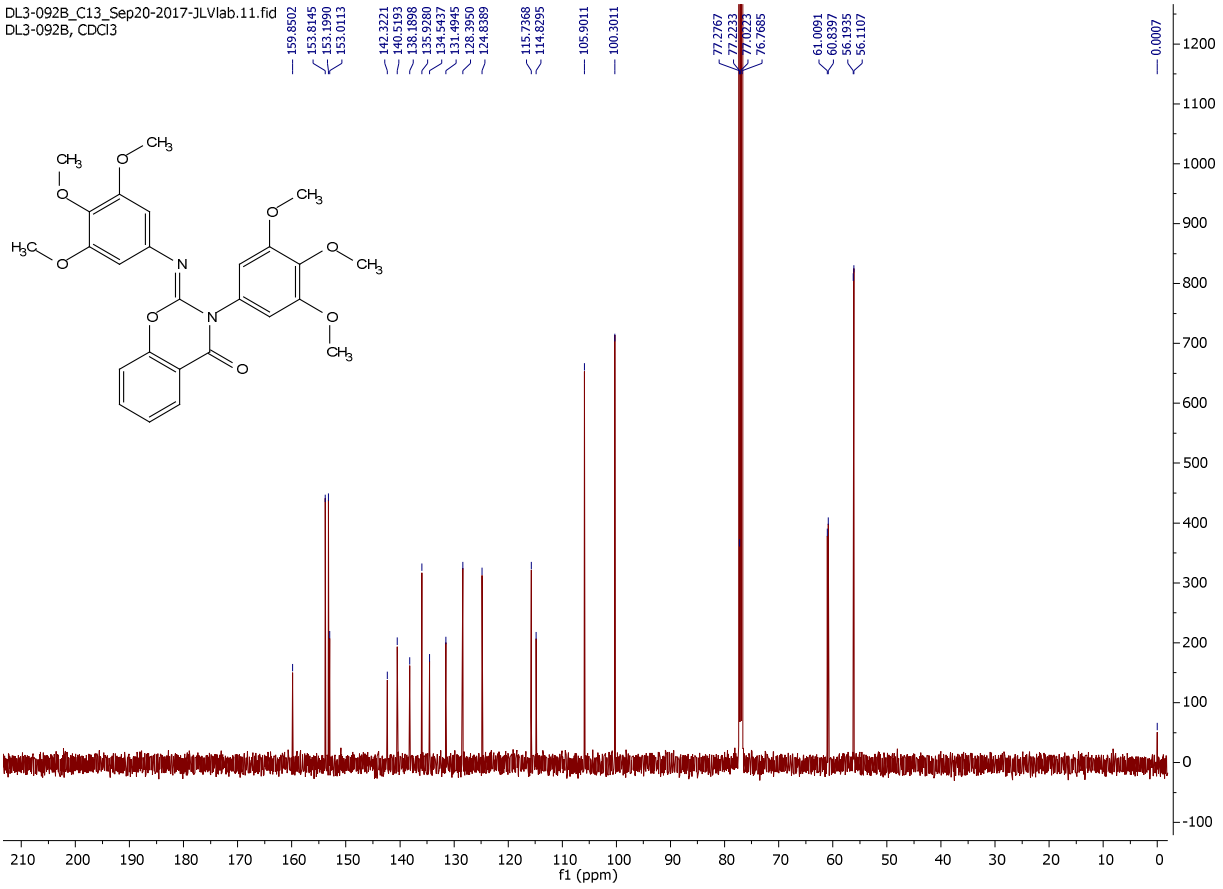


**Figure S28**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4m**.

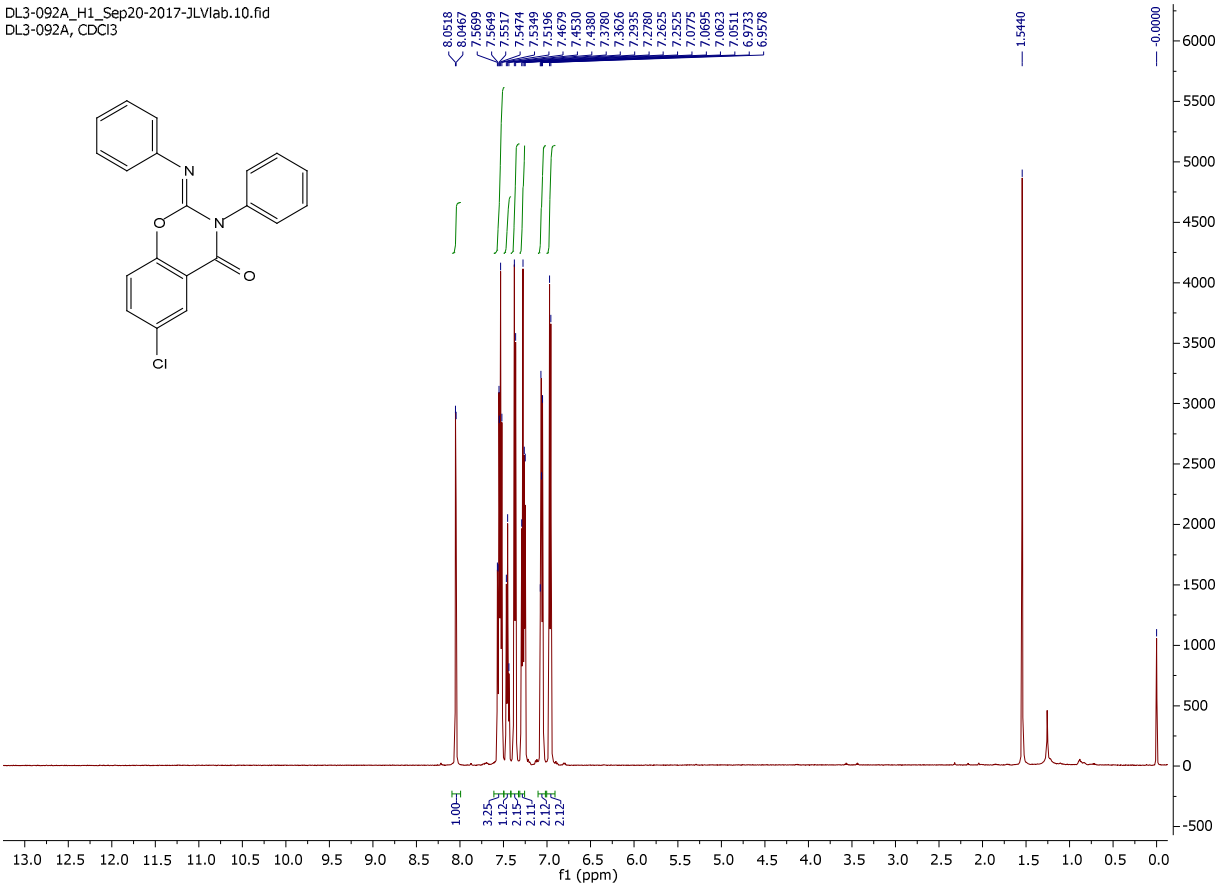


**Figure S29**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4m**.

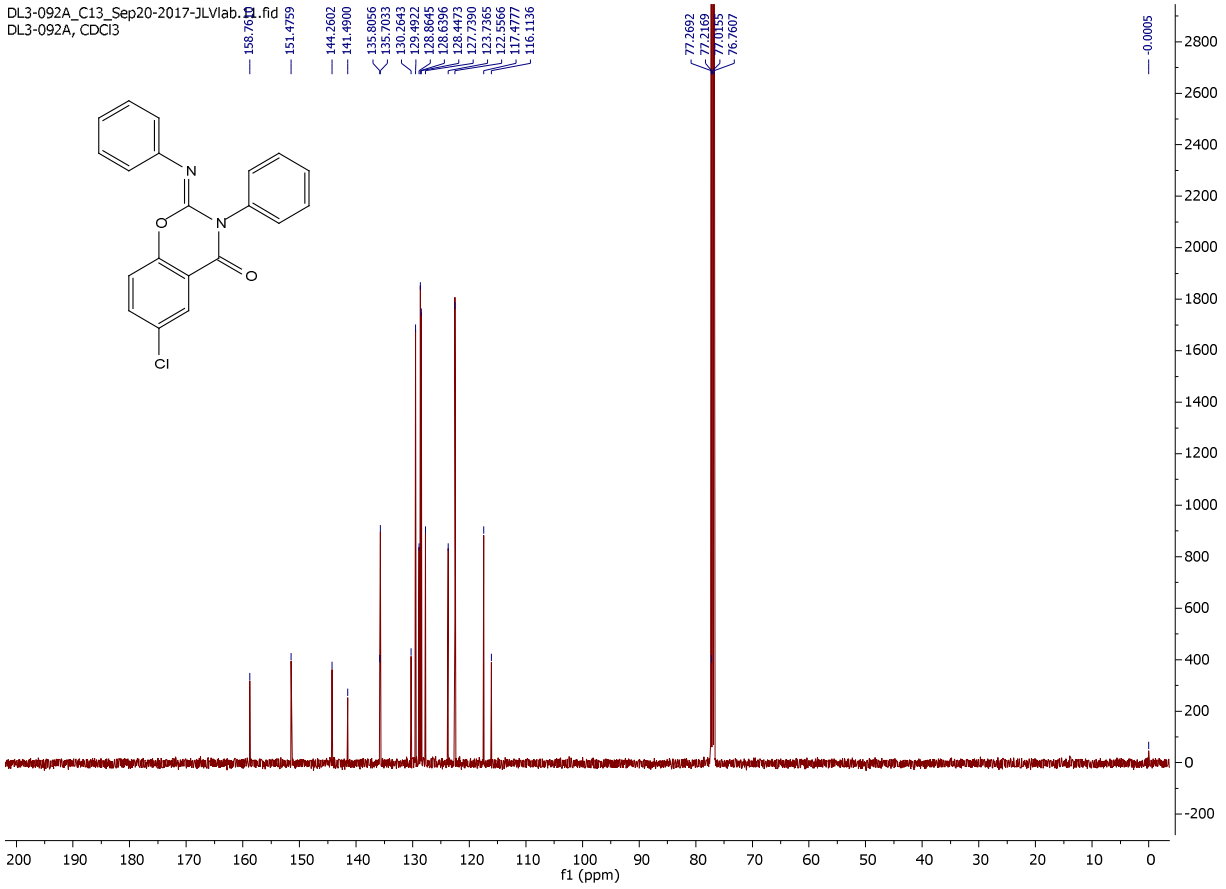


**Figure S30**. $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of compound **4n**.

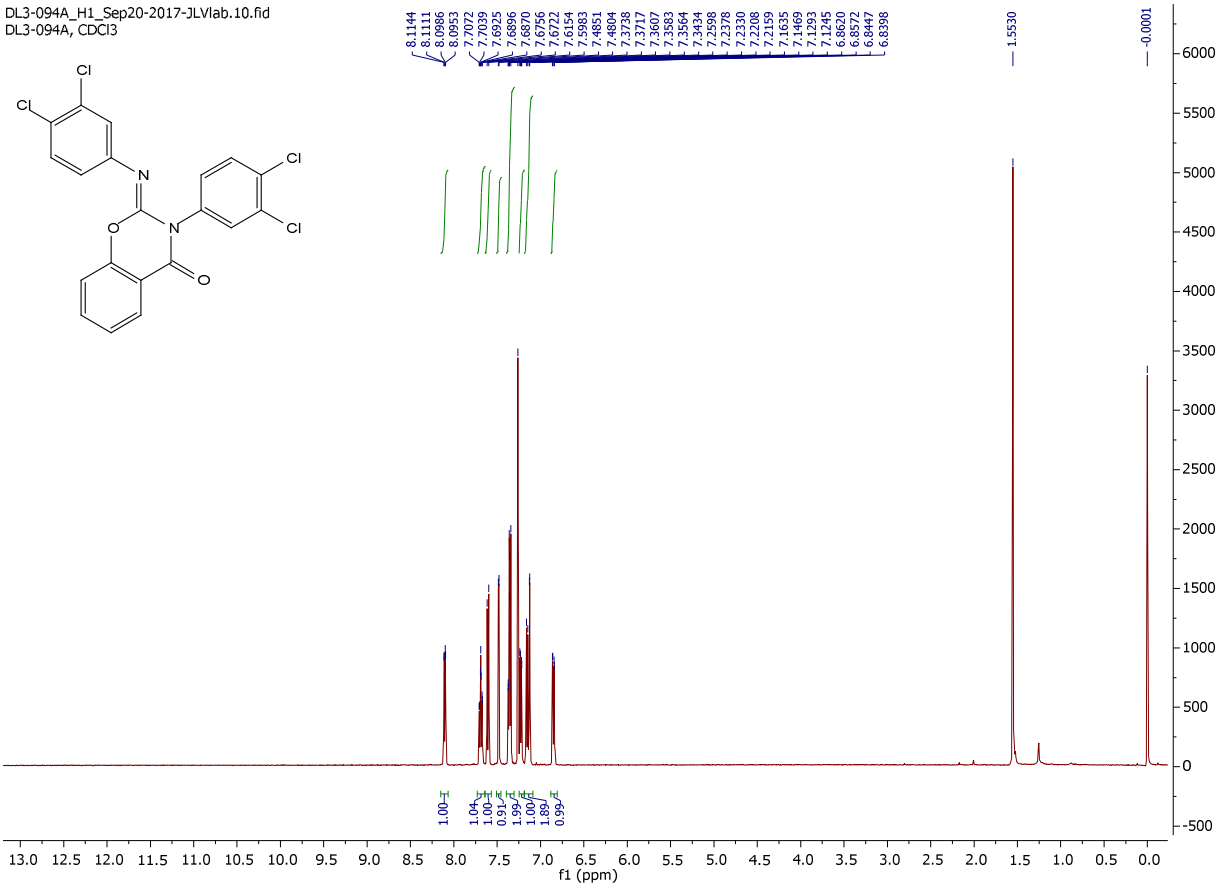


**Figure S31**. $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4n**.

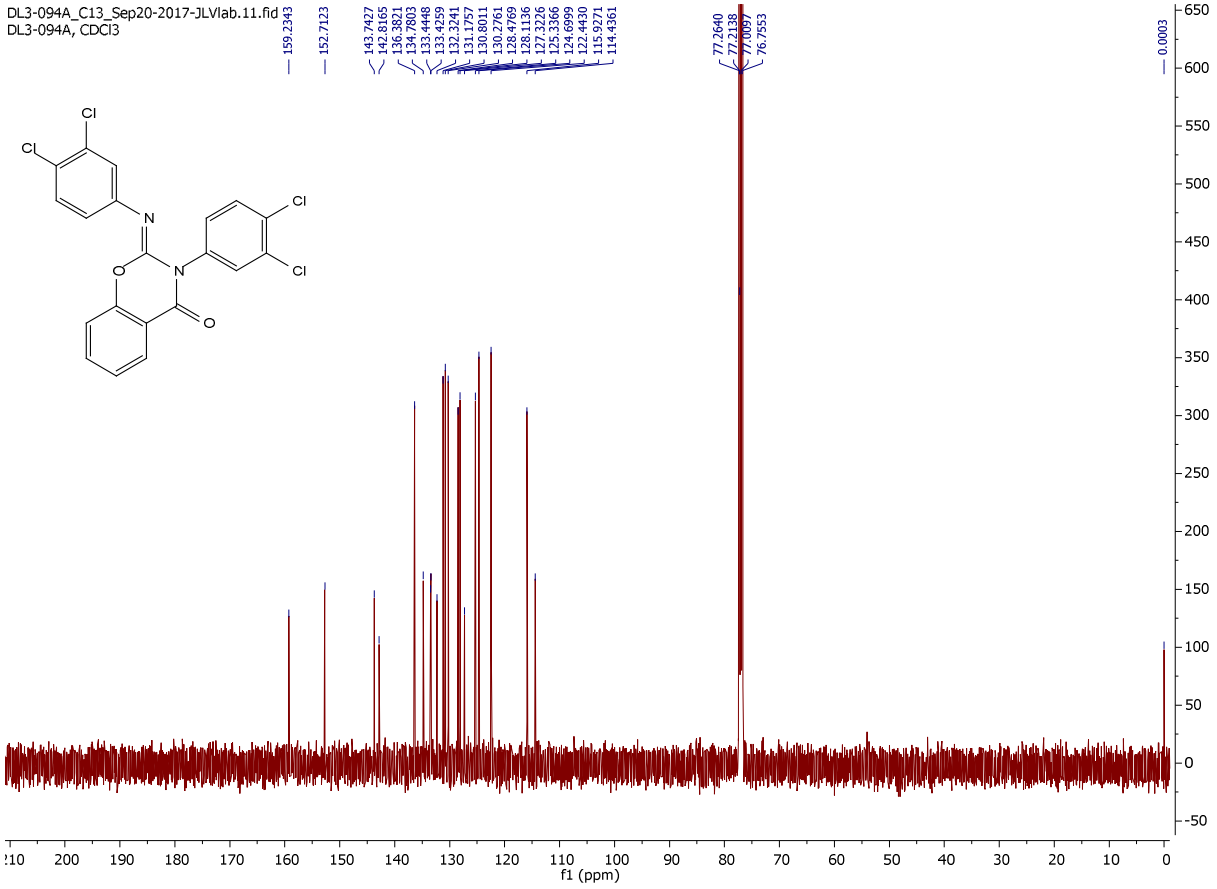


**Figure S32**. 1H NMR (600 MHz, DMSO-$d_6$) spectrum of compound **4o**.

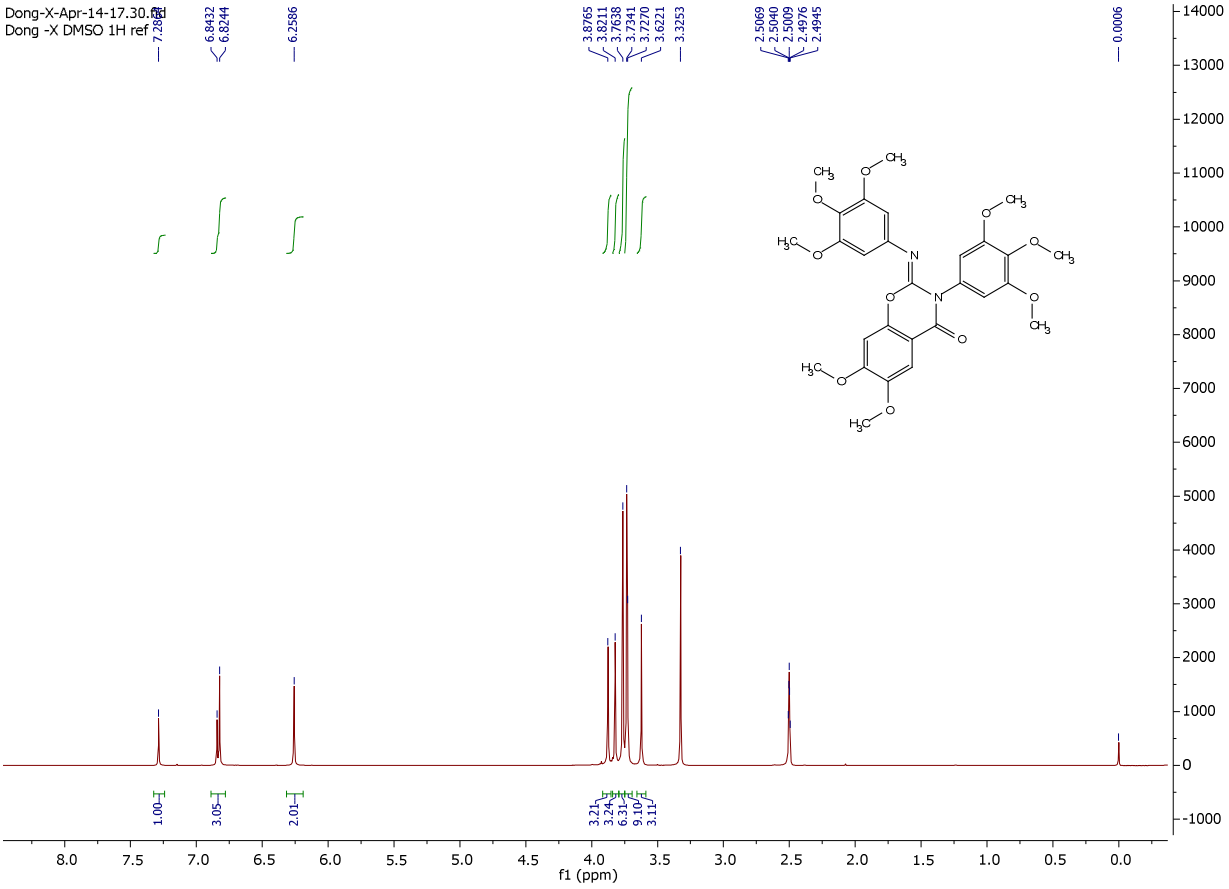


**Figure S33**. 13C NMR (150 MHz, DMSO-$d_6$) spectrum of compound **4o**.

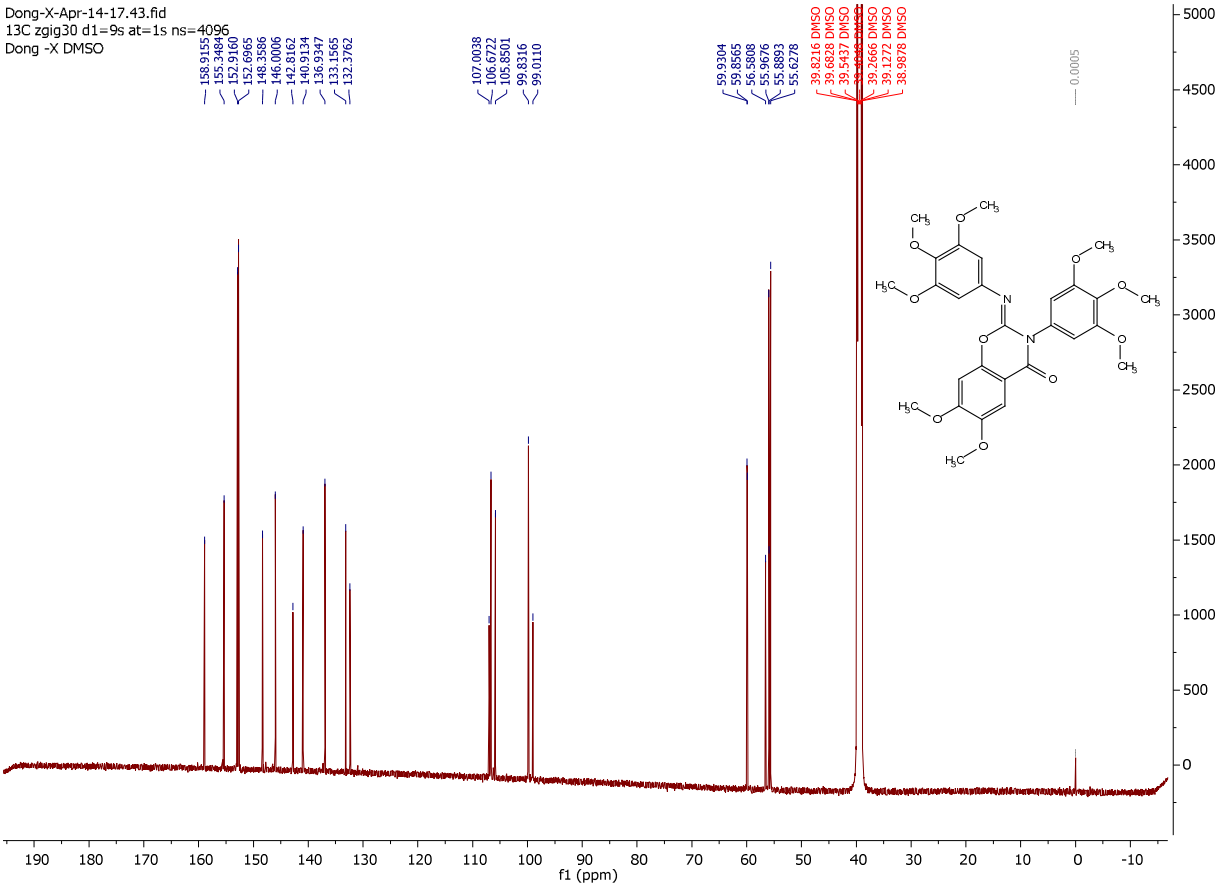
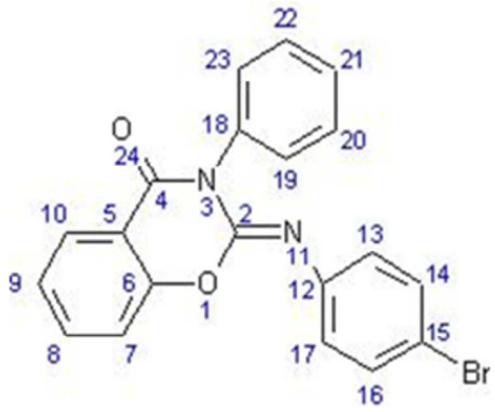


**Figure S34.** 2D NMR spectra atom numbering for **4c**.




4c

**Figure S35**. $^{1}$H NMR spectra expansion of **4c**.

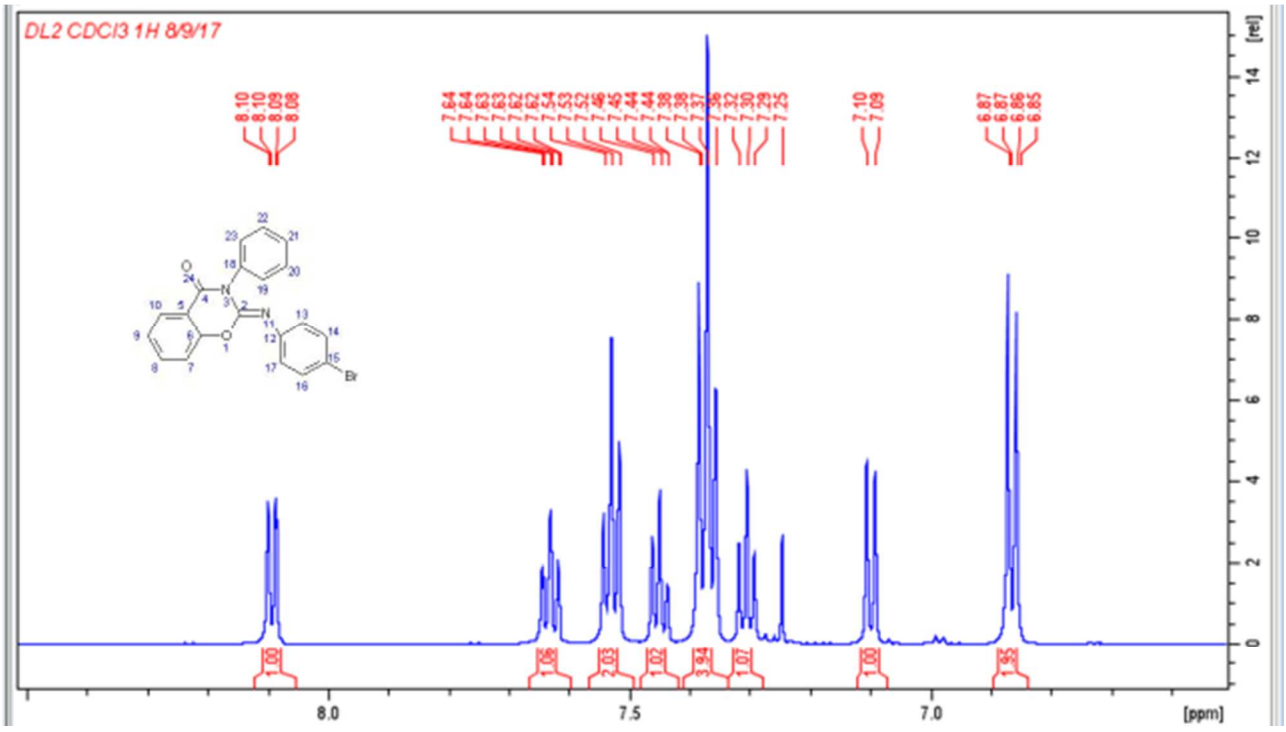


**Figure S36**. TOCSY expansion spectra 1 of compound **4c**.

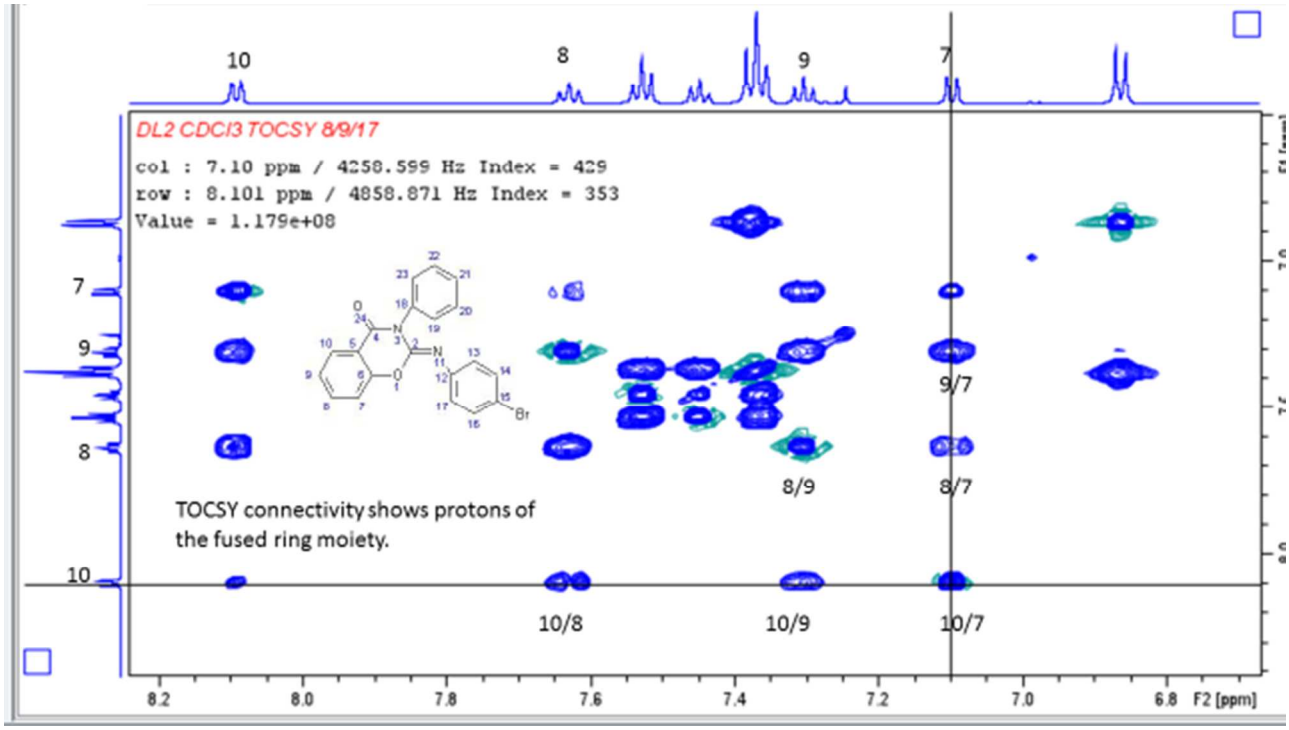



**Figure S37**. $^{13}$C-HSQC expansion spectra 1 of **4c**.

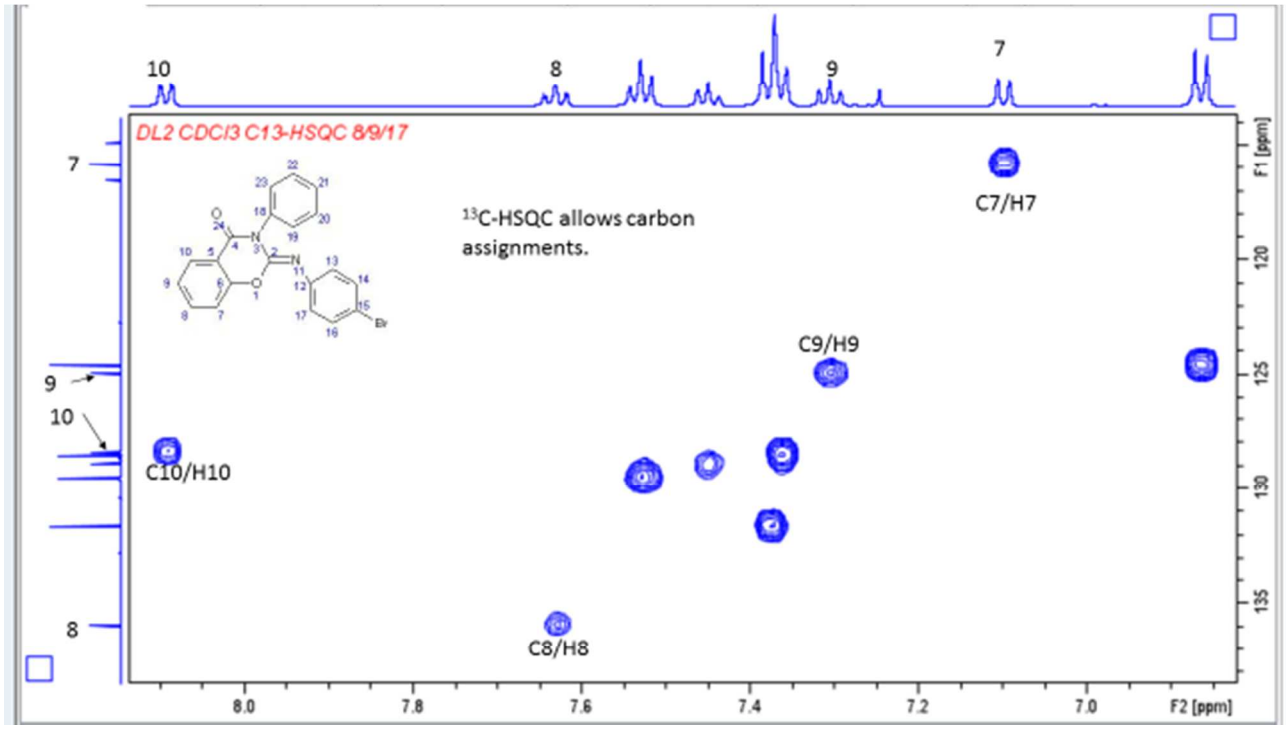


**Figure S38**. $^{13}$C NMR spectra expansion of compound **4c**.

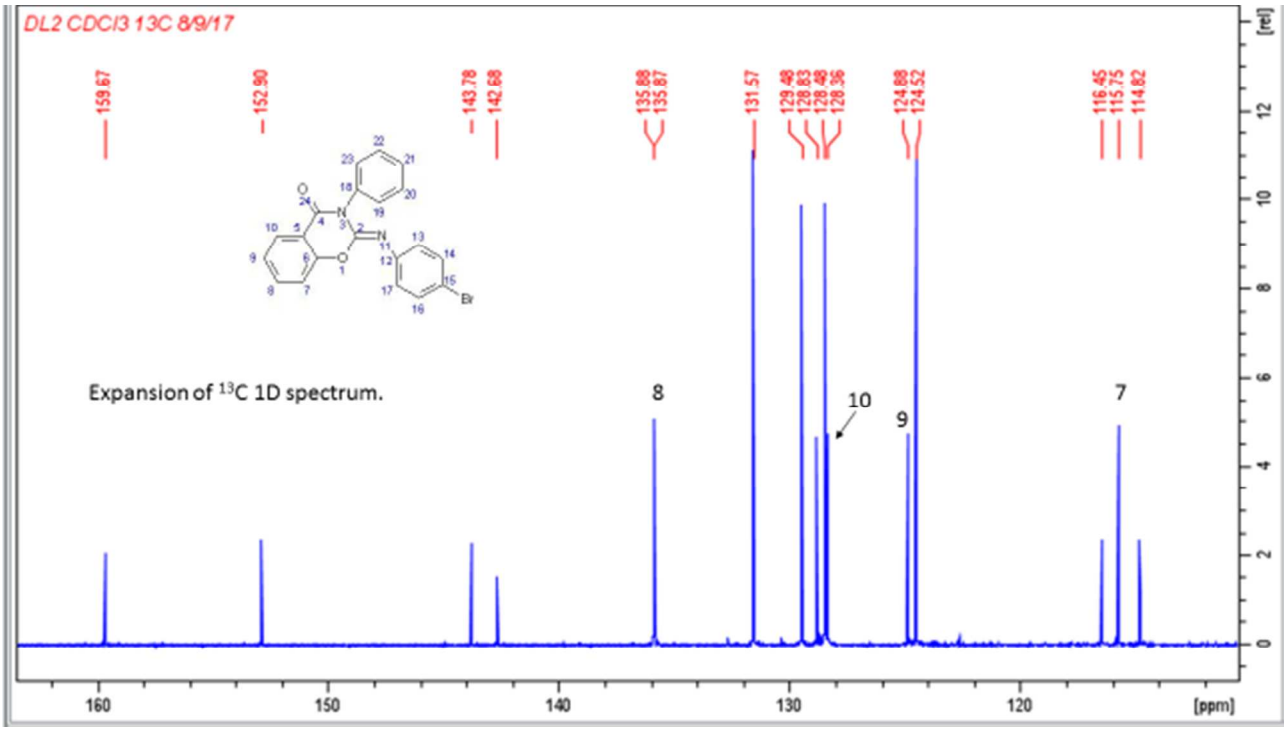



**Figure S39**. TOCSY expansion spectra 2 of compound **4c**.

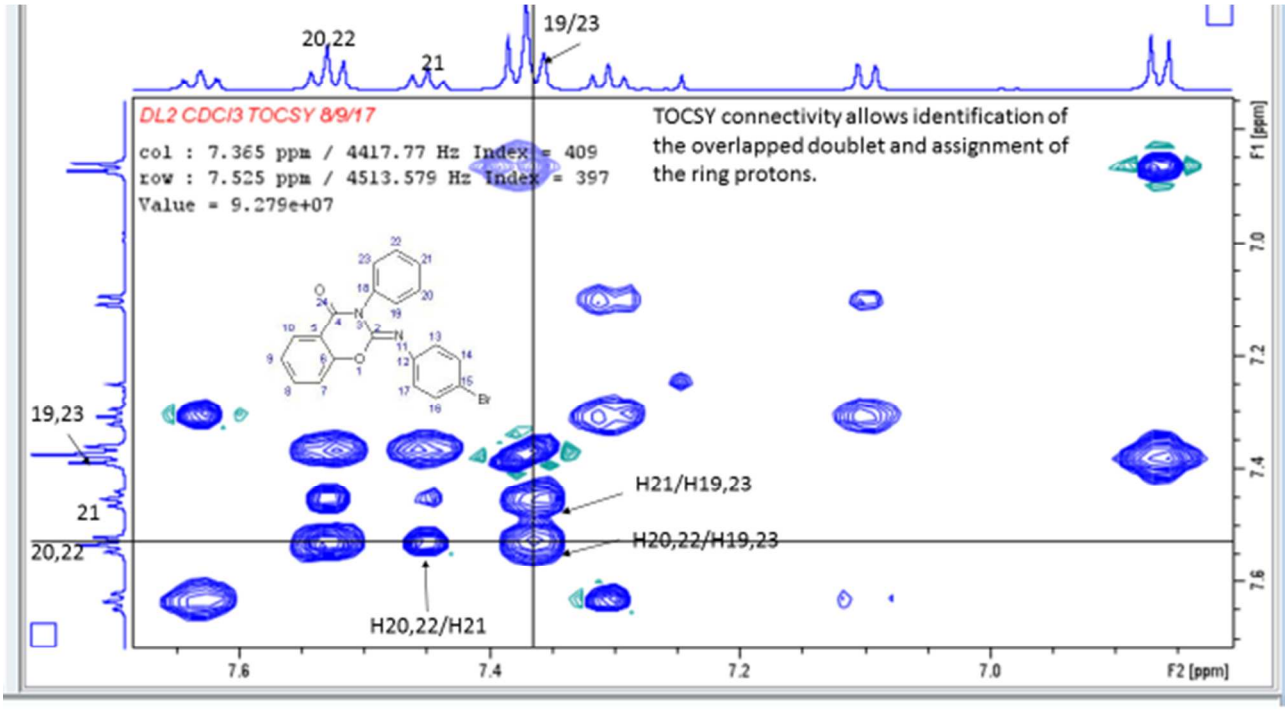


**Figure S40**. $^{13}$C-HSQC expansion spectra 2 of **4c**.

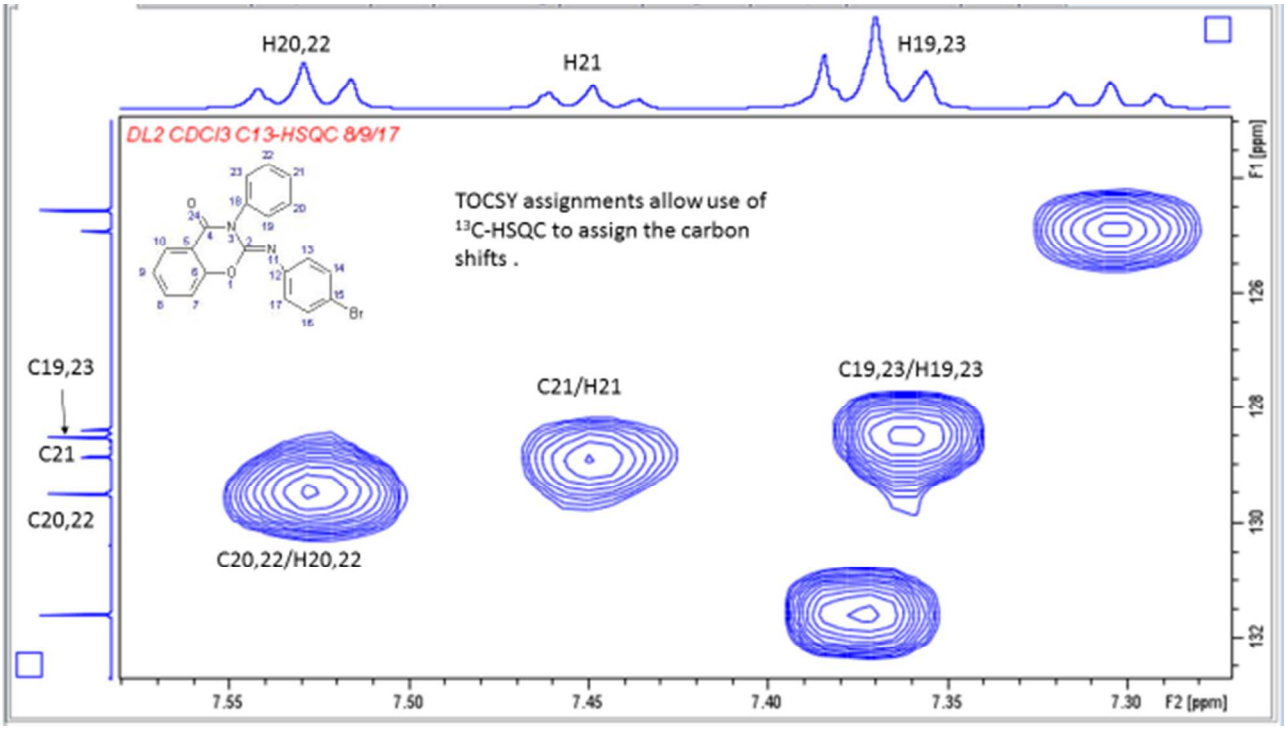



**Figure S41**. TOCSY expansion spectra 3 of compound **4c**.

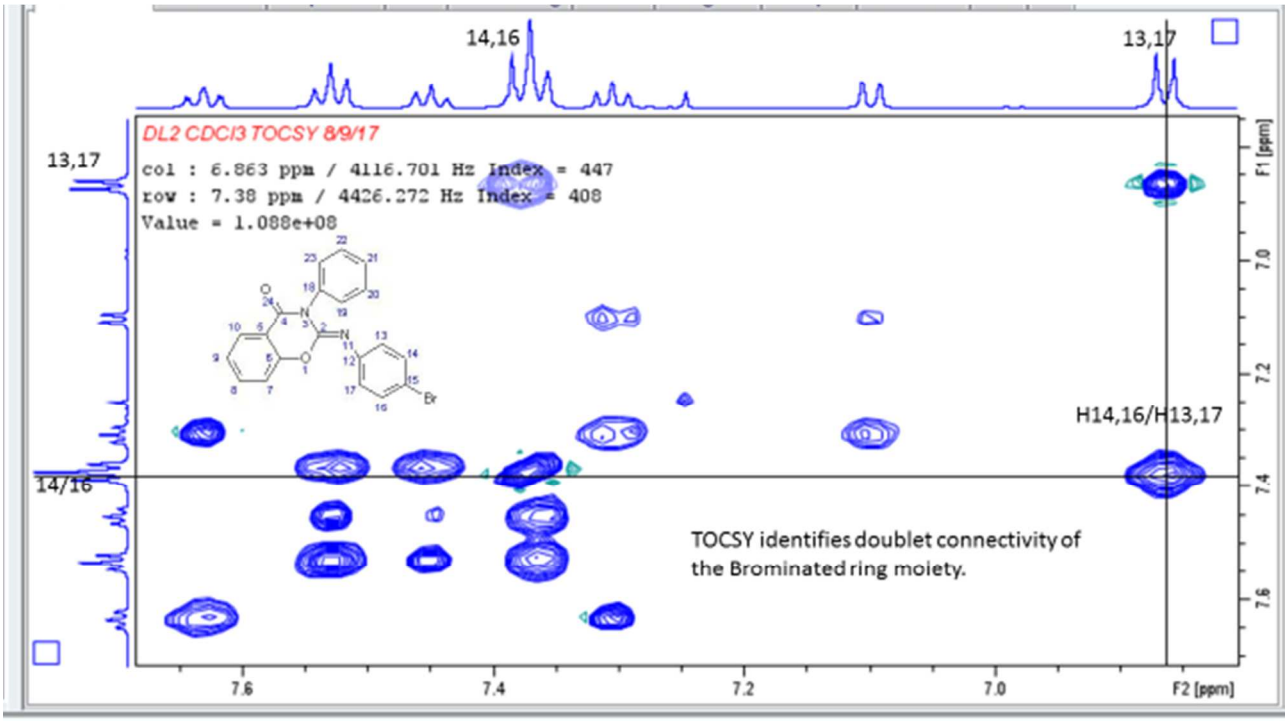


**Figure S42**. $^{15}$N-HMBC expansion spectra of **4c**.

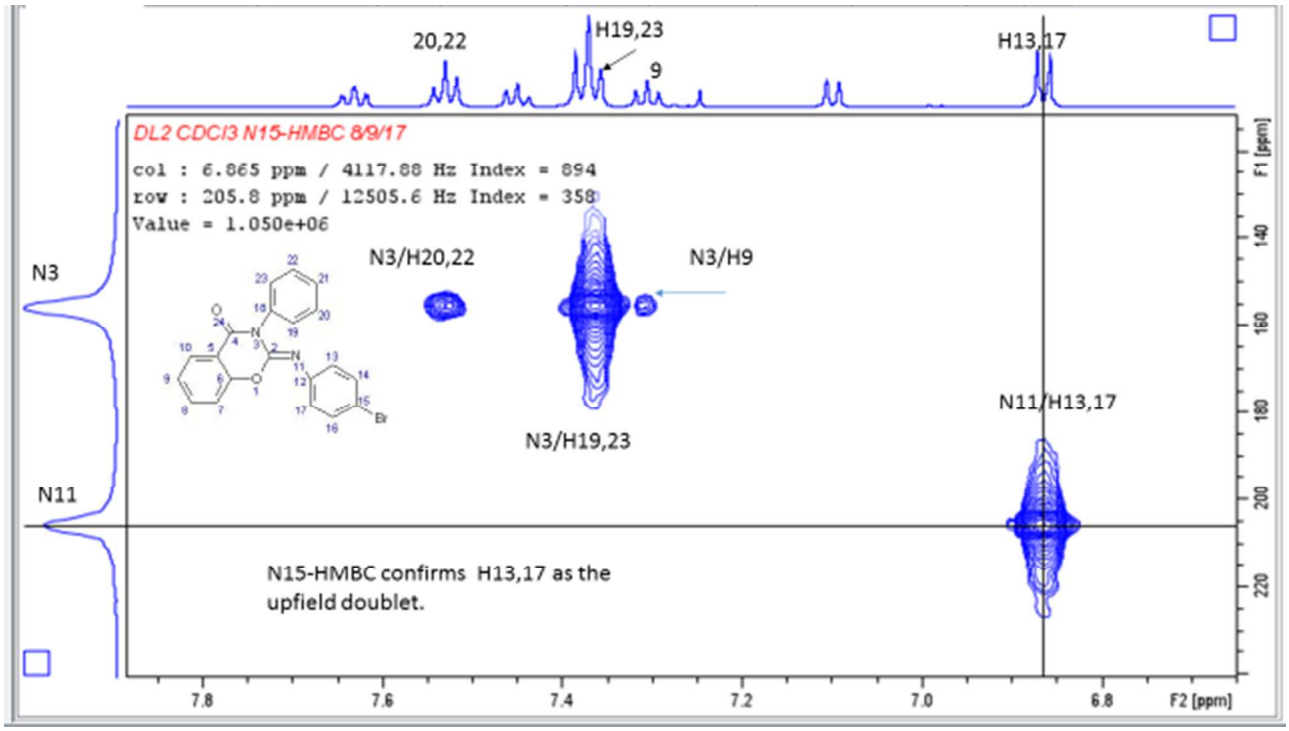



**Figure S43**. $^{13}$C-HSQC spectra of compound **4c**.

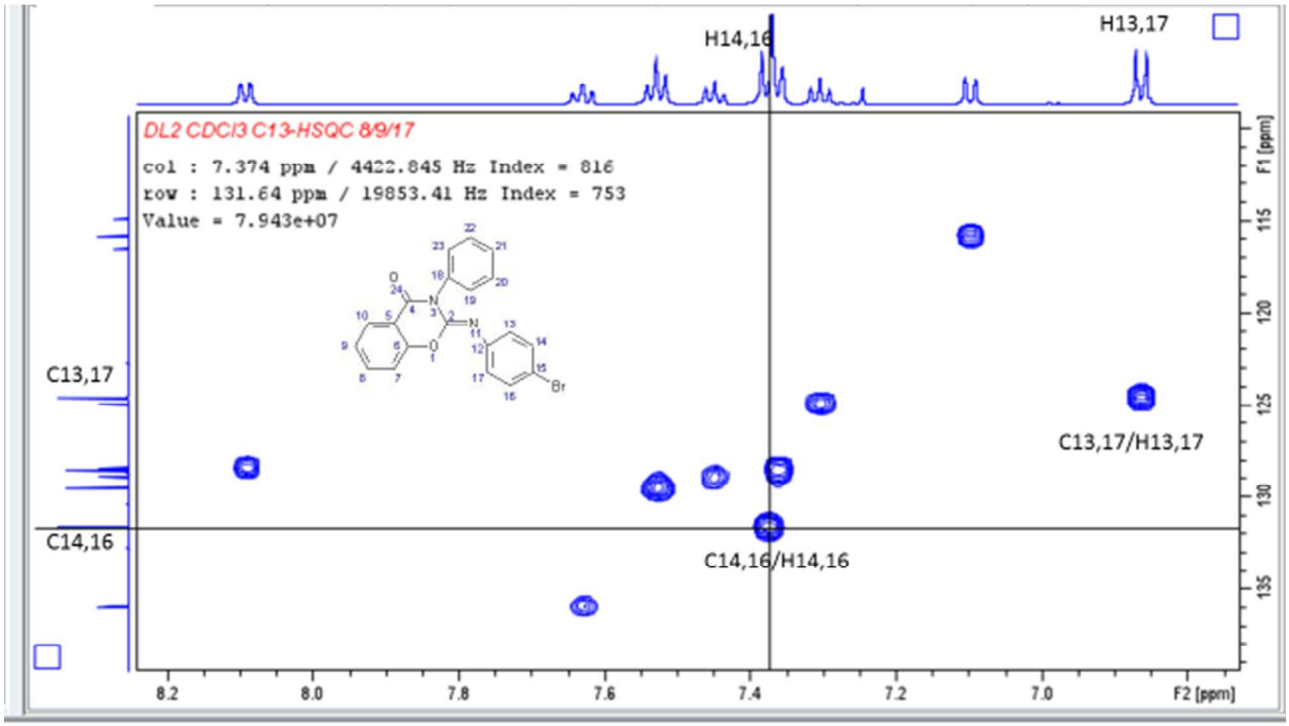


**Figure S44**. $^{13}$C-HMBC spectra of compound **4c**.

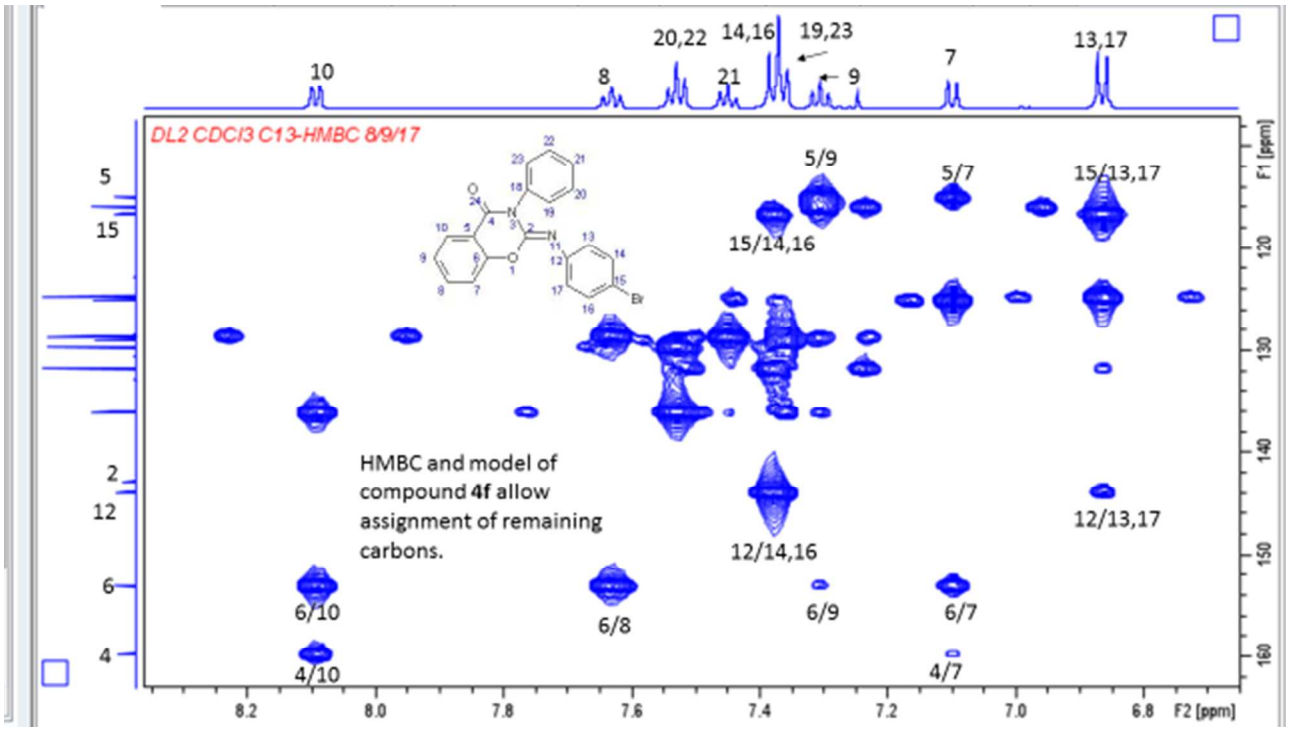
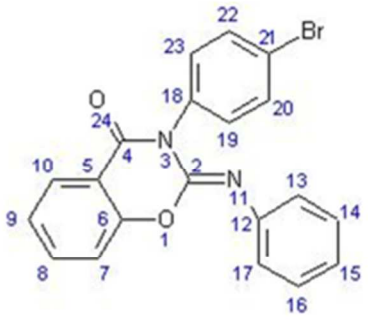



**Figure S45**. 2D NMR spectra atom numbering for **4d**.




4d

**Figure S46**. $^{1}$H NMR expansion spectra of compound **4d**.

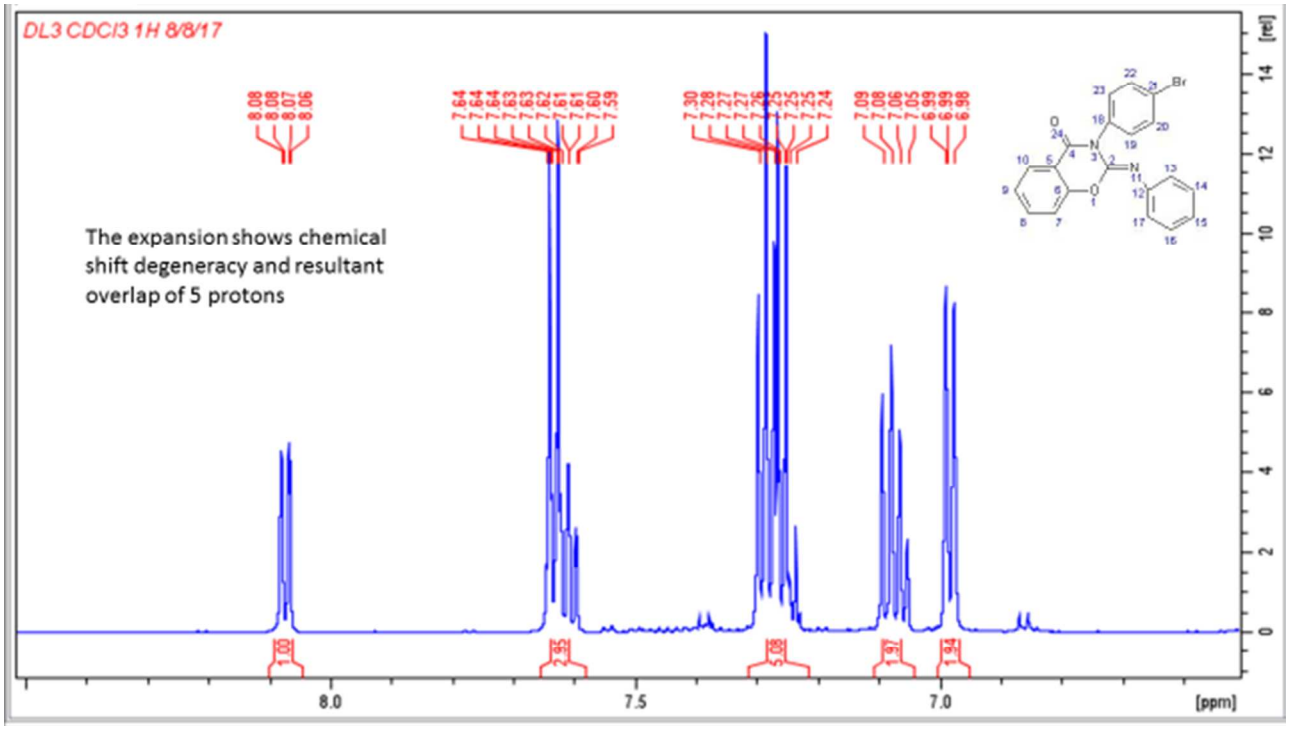



**Figure S47**. TOCSY expansion spectra 1 of compound **4d**.

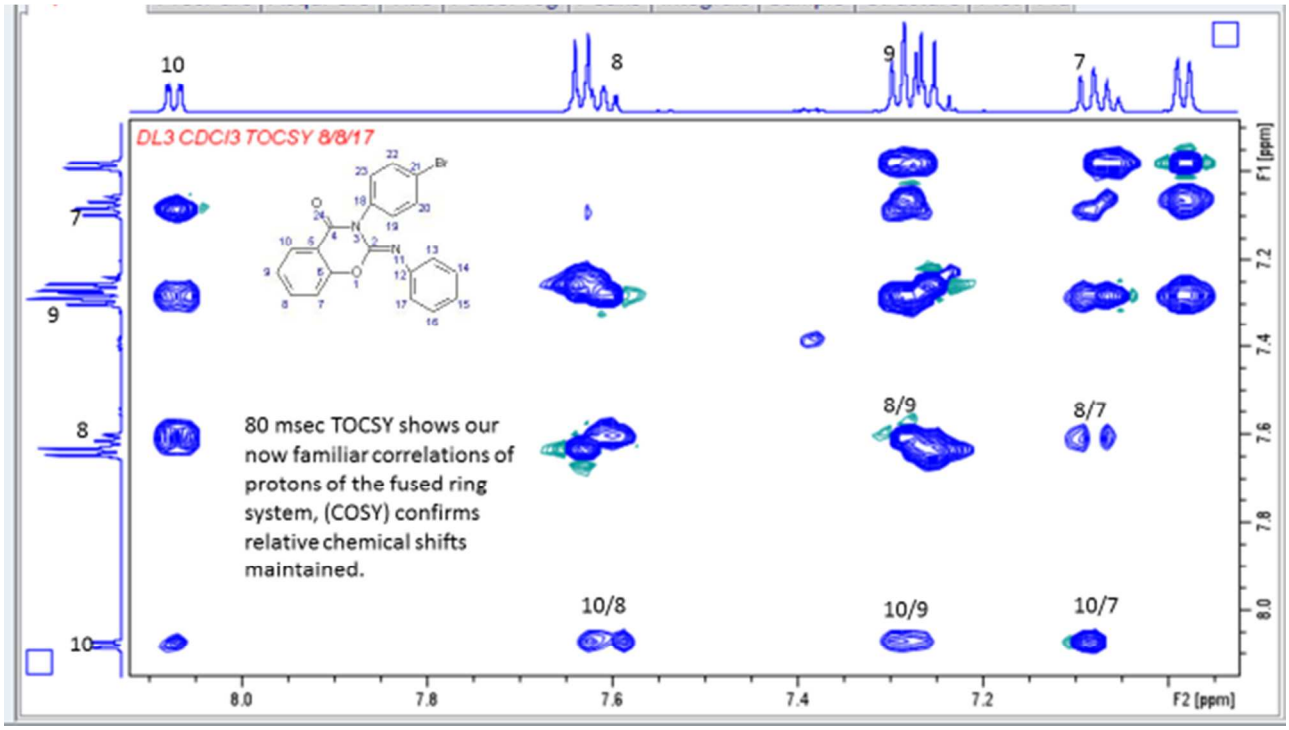


**Figure S48**. $^{13}$C-HSQC expansion spectra 1 of compound **4d**.

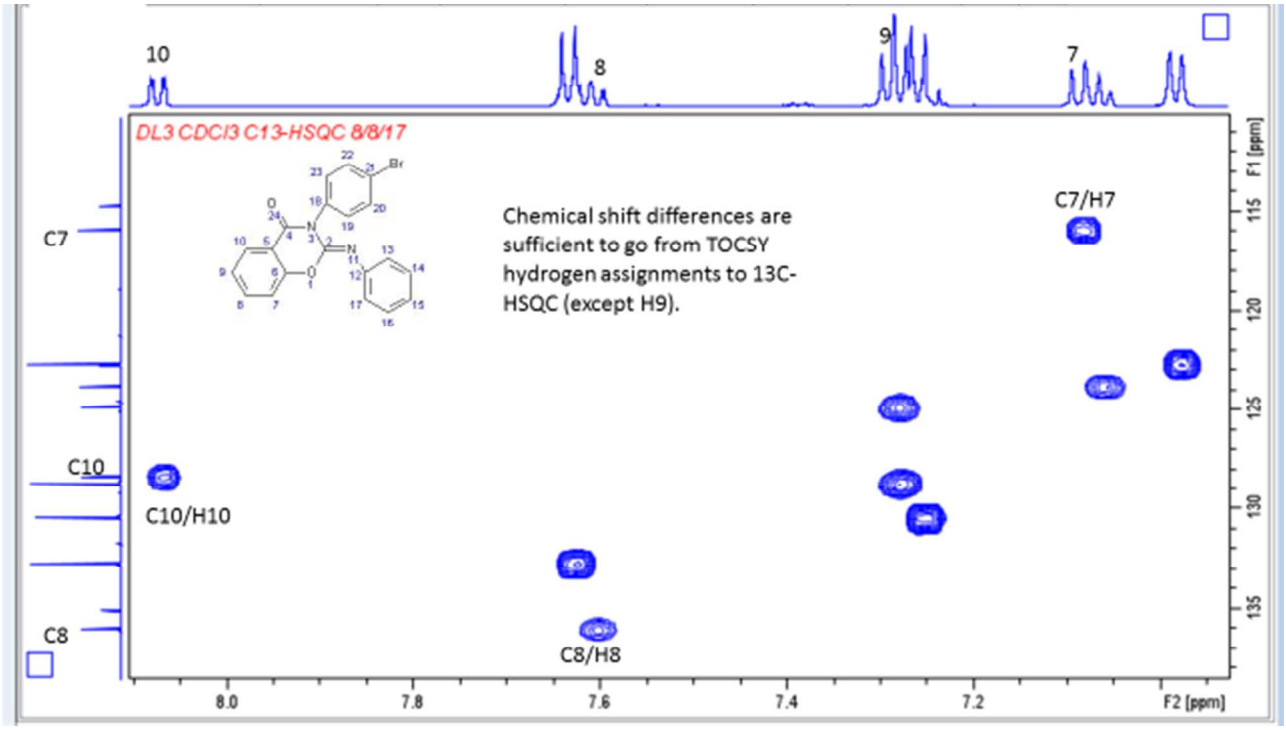



**Figure S49**. $^{13}$C-HSQC with $^{13}$C-HMBC overlay spectra of compound **4d**.

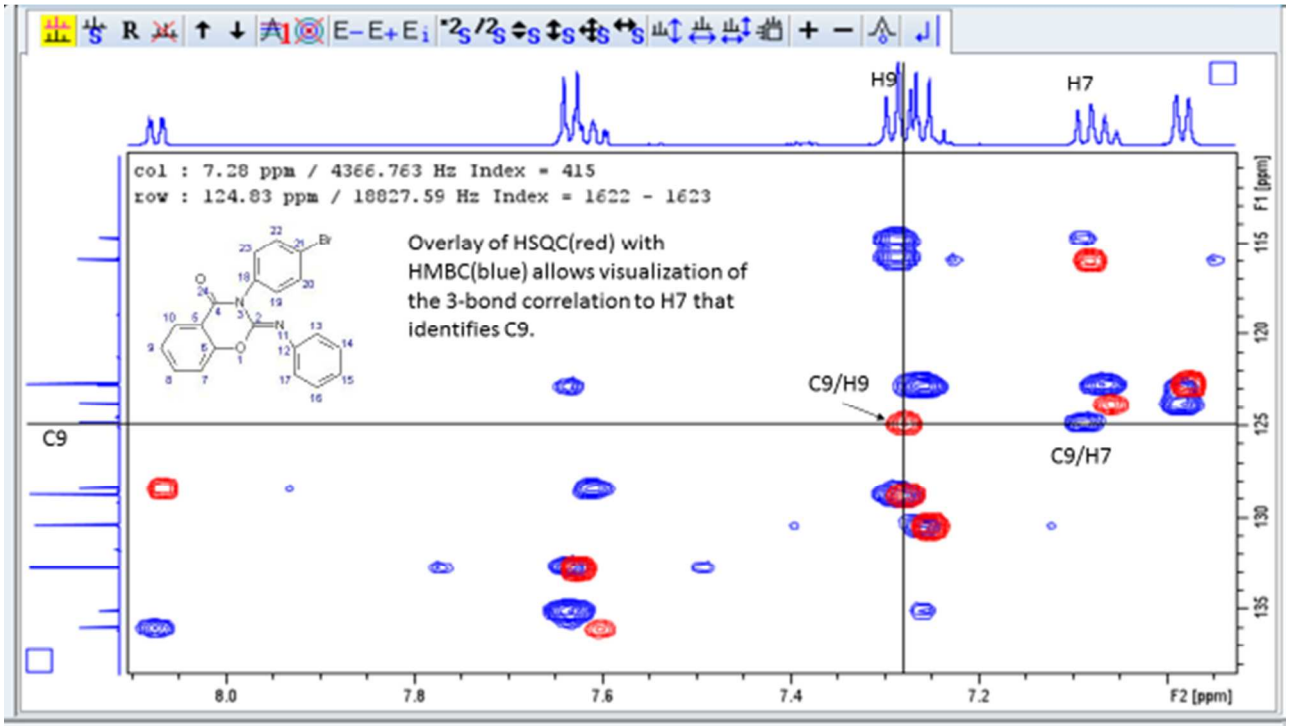


**Figure S50**. TOCSY expansion spectra 2 of compound **4d**.

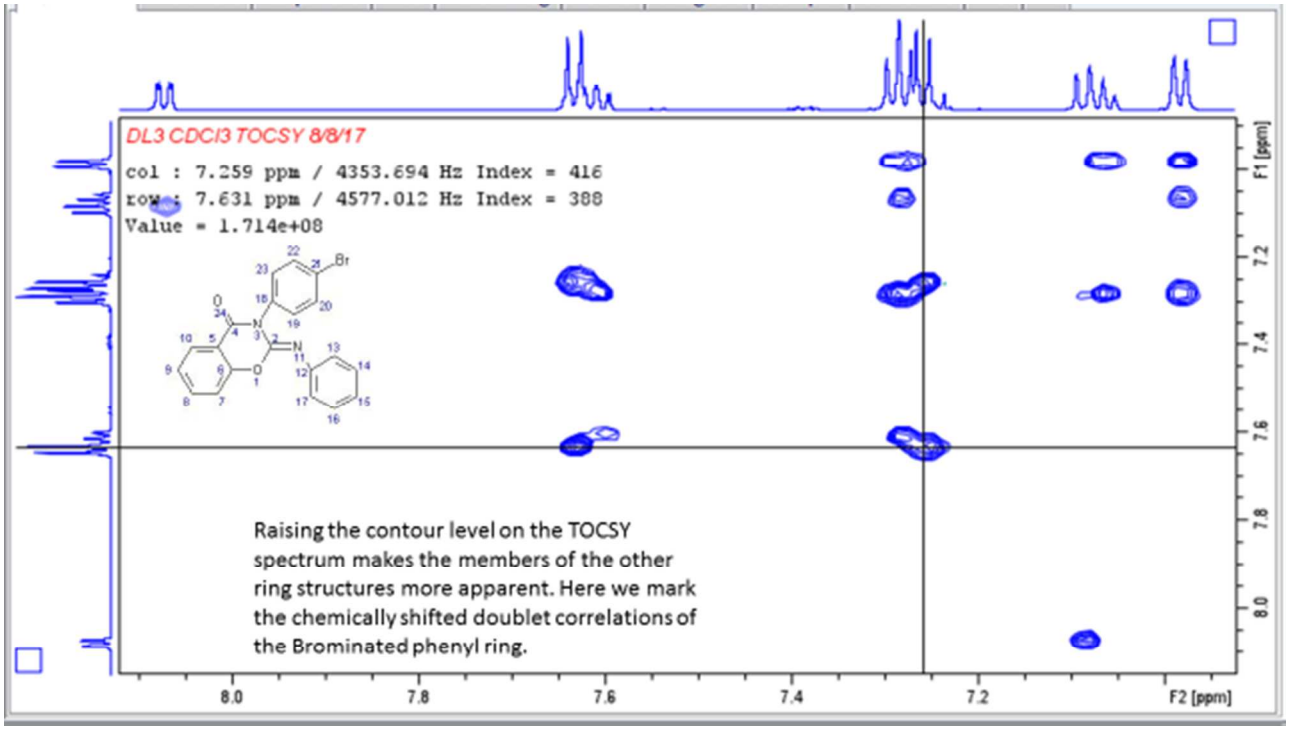



**Figure S51**. $^{15}$N-HMBC spectra of compound **4d**.

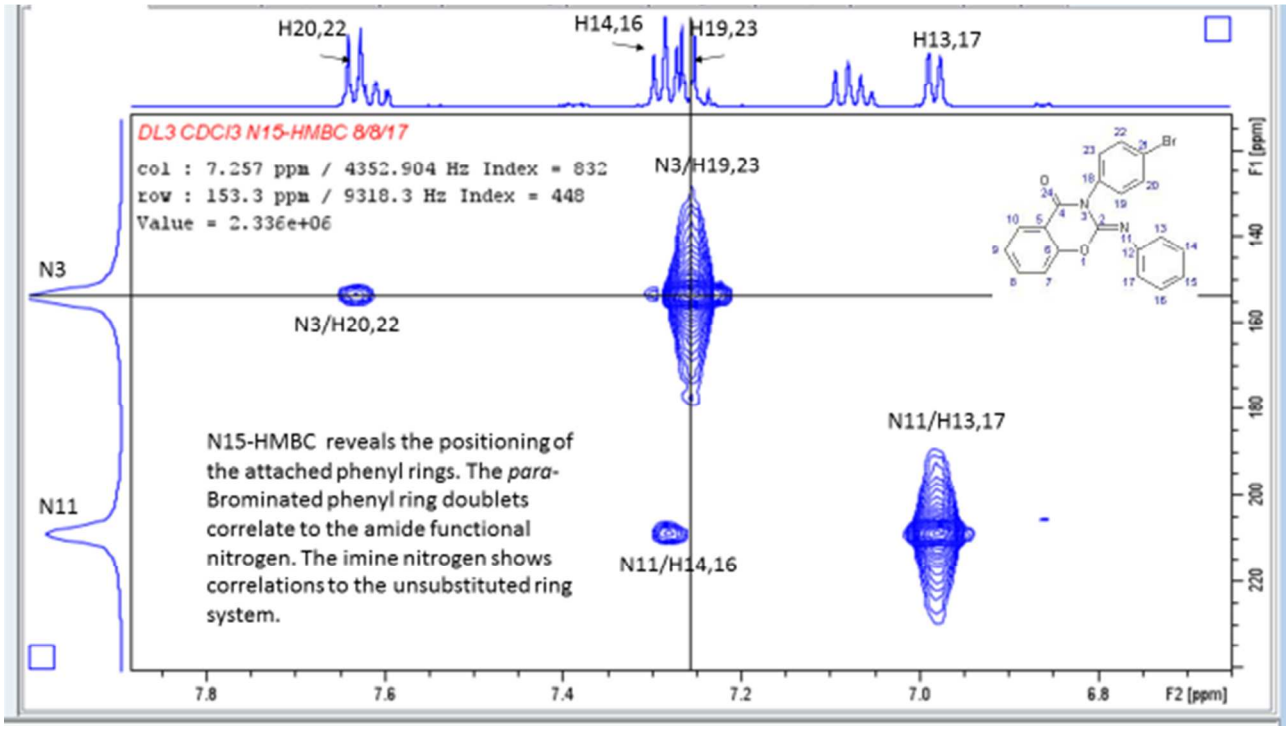


**Figure S52**. $^{13}$C-HSQC expansion spectra 2 of compound **4d**.

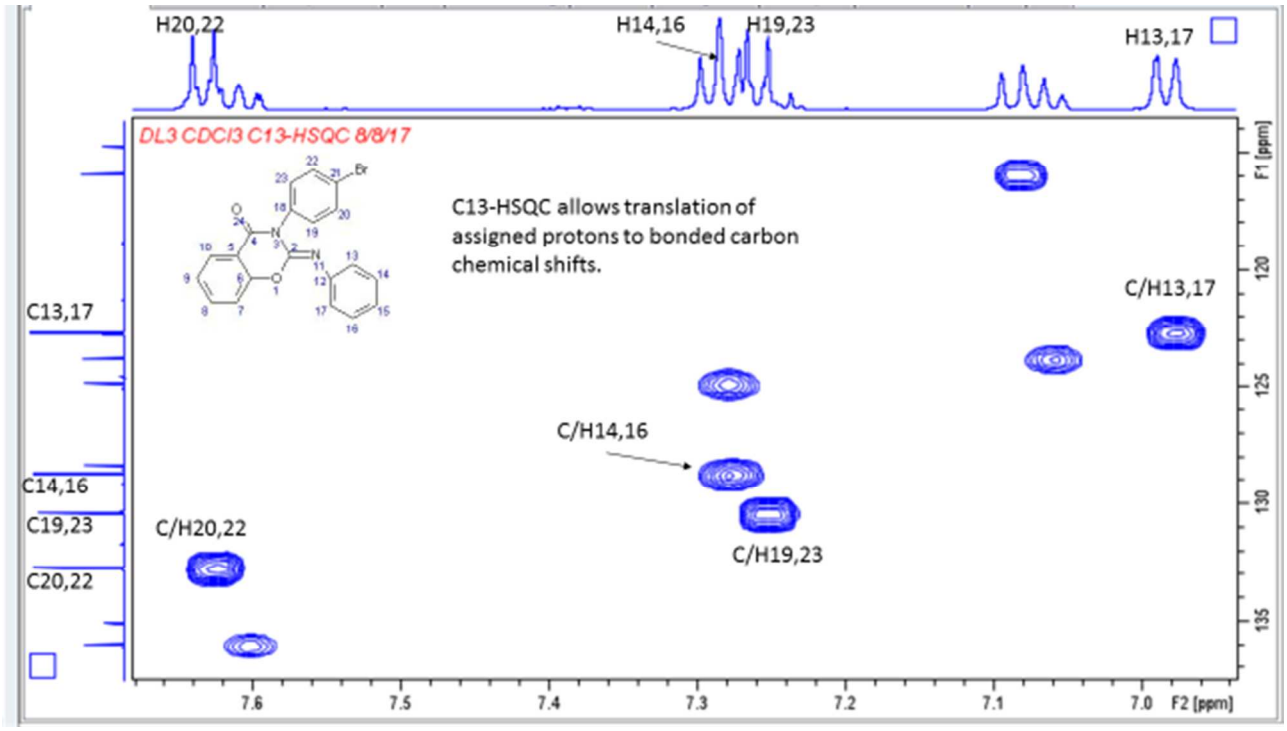



**Figure S53**. TOCSY expansion spectra 3 of compound **4d**.

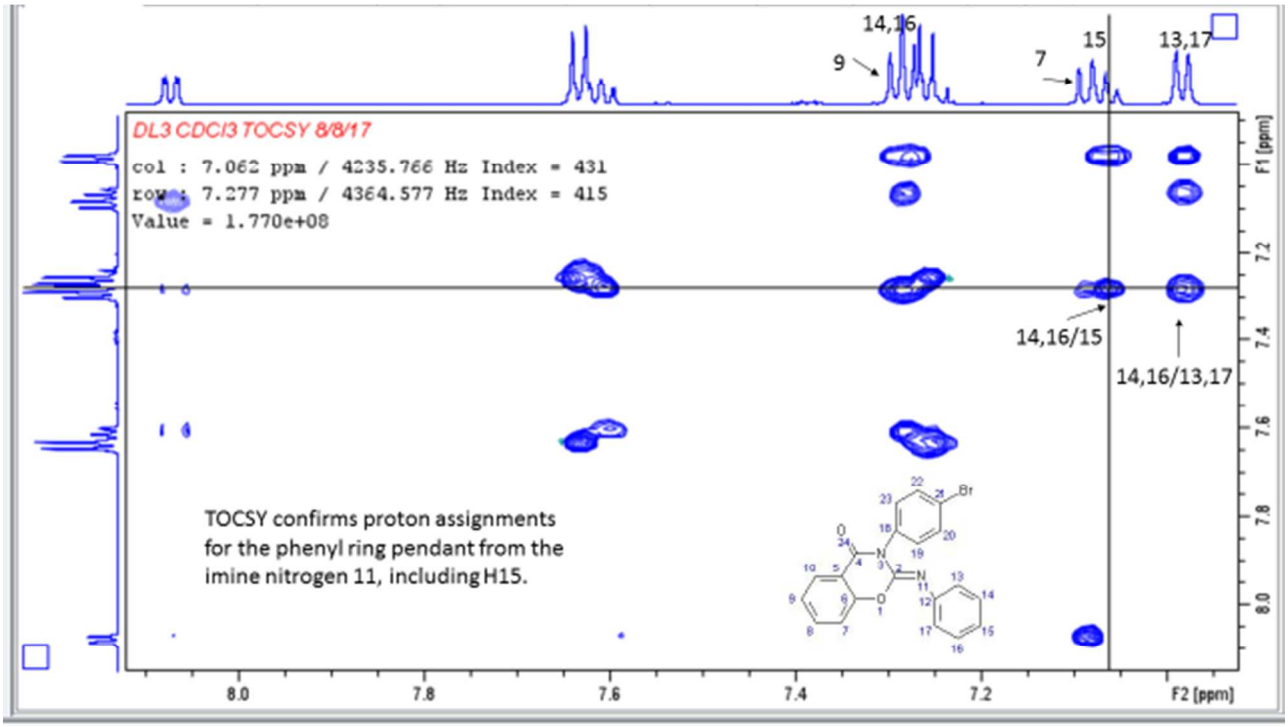


**Figure S54**. $^{13}$C-HSQC expansion spectra 3 of compound **4d**.

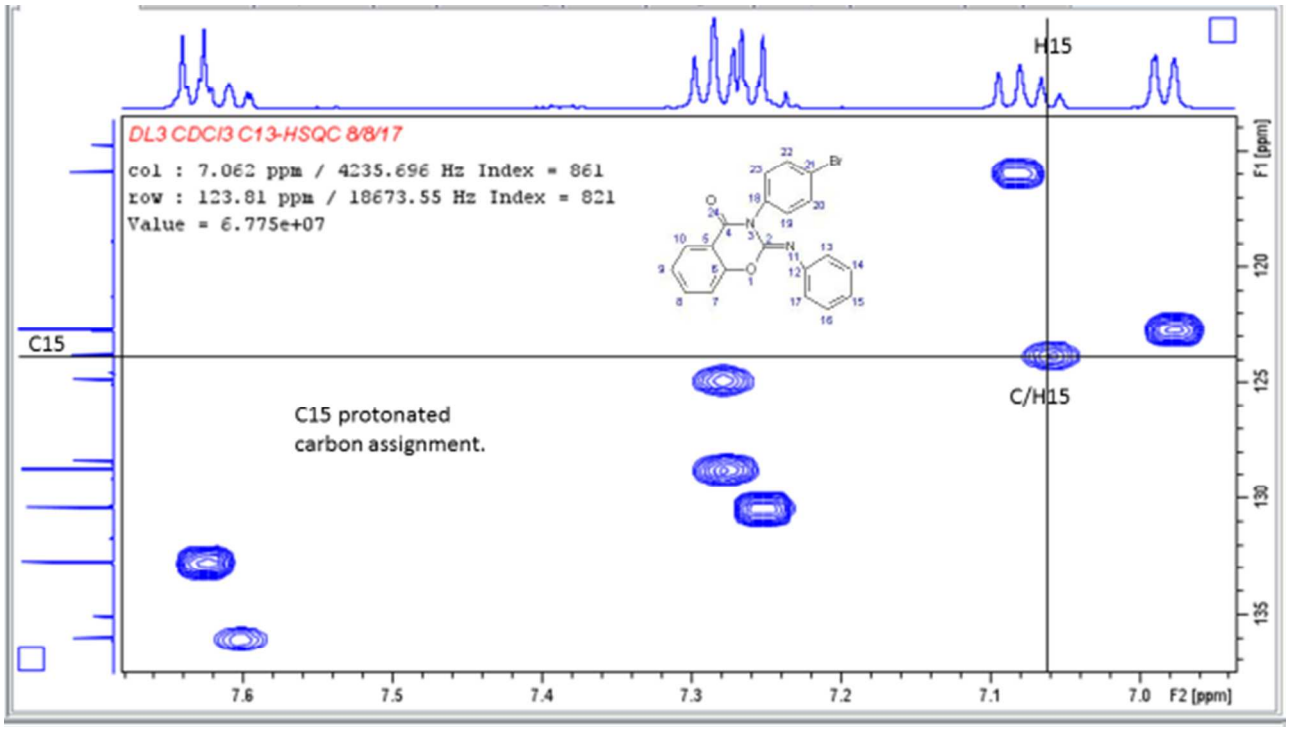



**Figure S55**. $^{13}$C-HMBC expansion spectra 1 of compound **4d**.

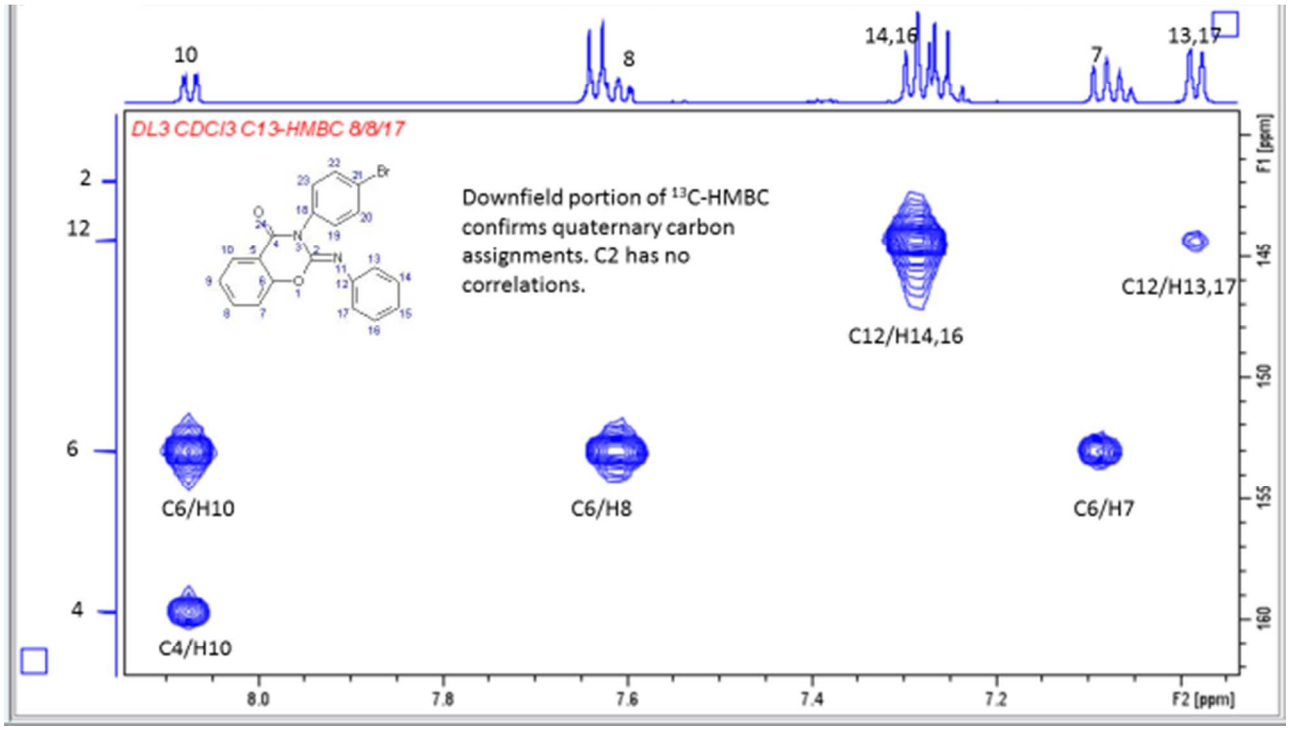


**Figure S56**. $^{13}$C-HMBC expansion spectra 2 of compound **4d**.

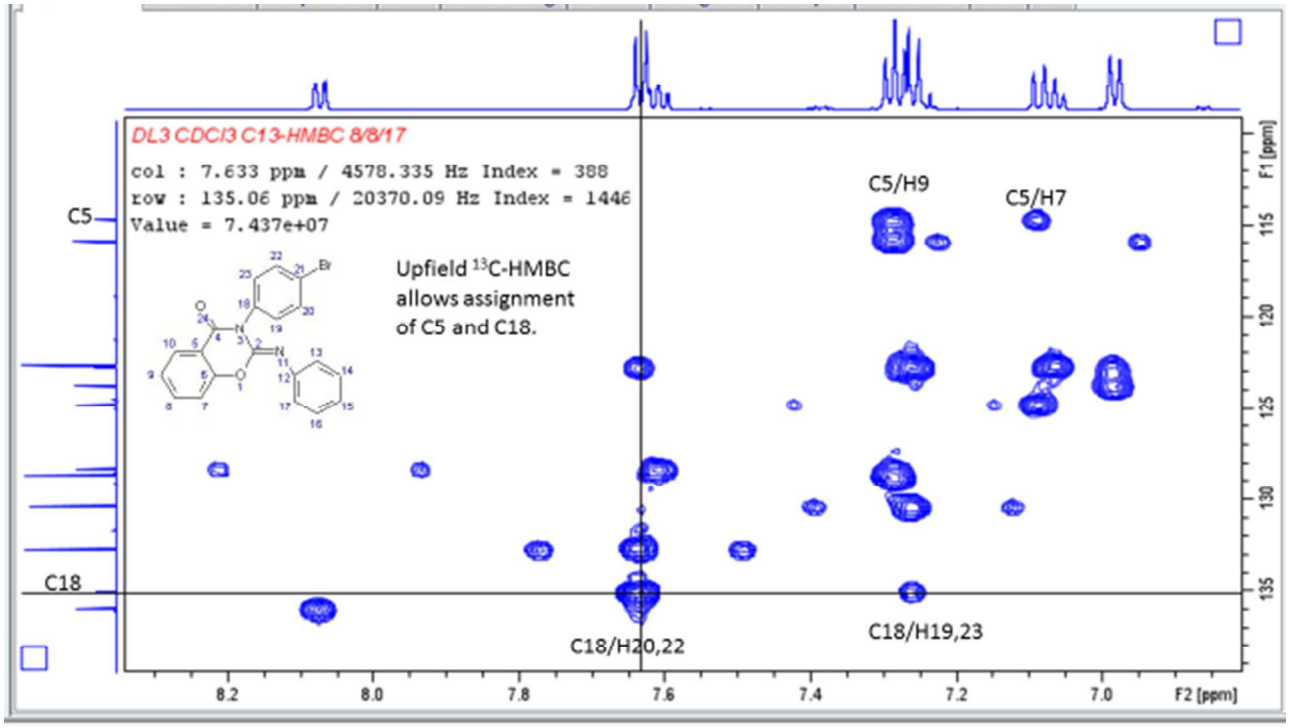



**Figure S57**. $^{13}$C-HMBC expansion spectra 3 of compound **4d**.

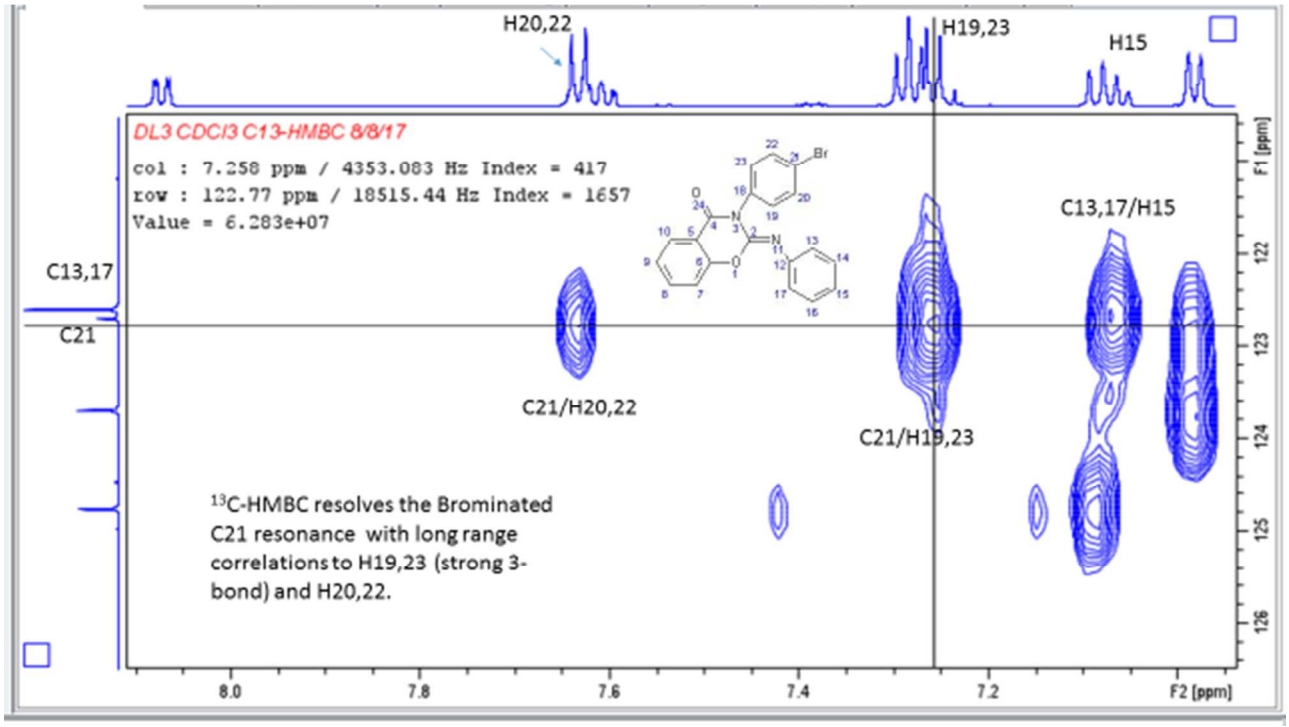
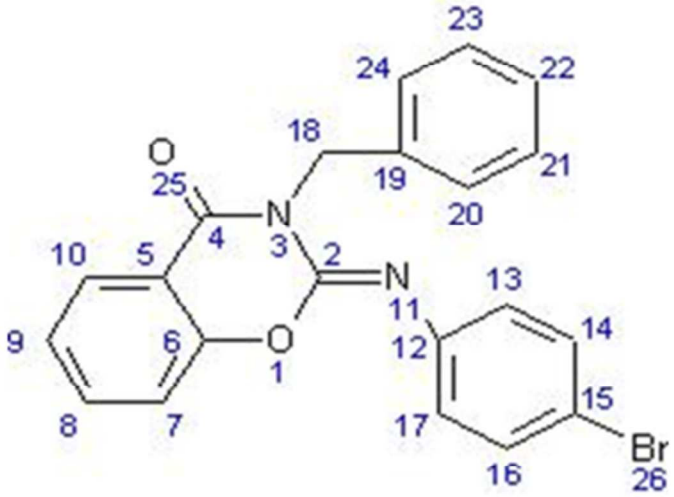


**Figure S58**. 2D NMR spectra atom numbering for **4f**.




4f

**Figure S59**. $^{1}$H NMR expansion spectra 1 of compound **4f**.

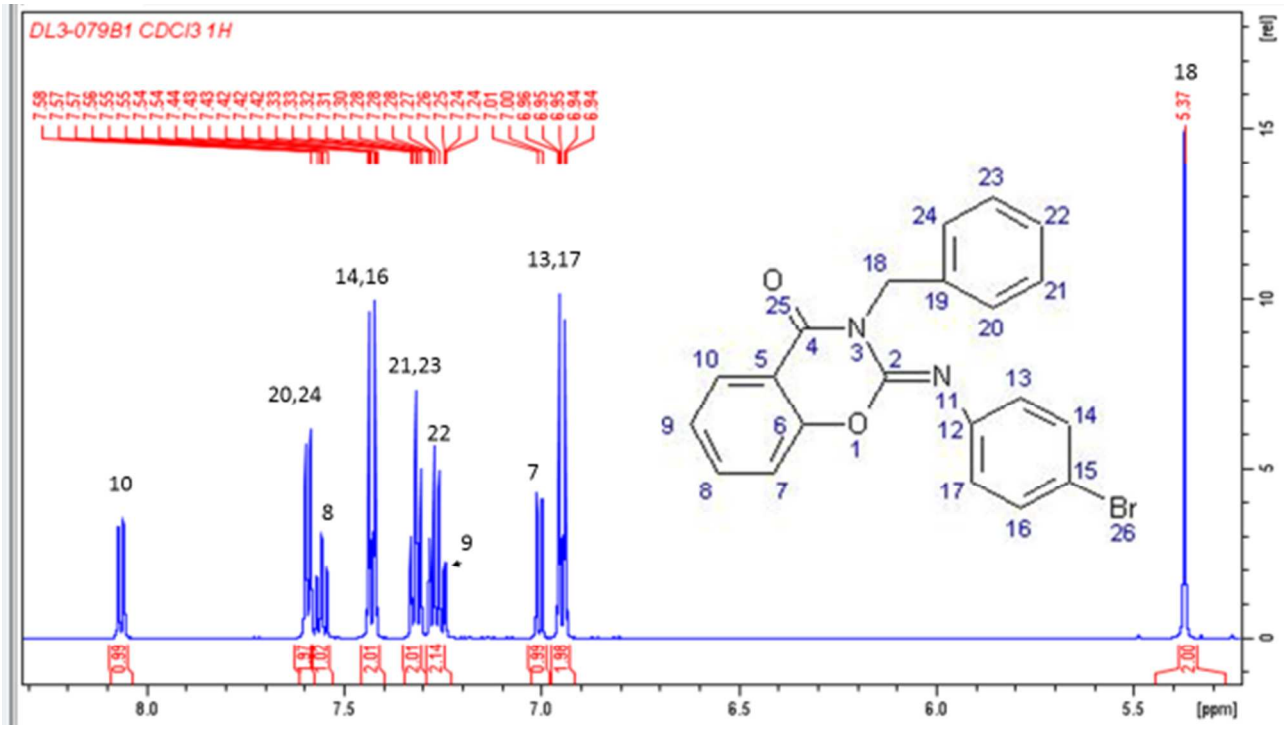


**Figure S60**. $^{1}$H NMR expansion spectra 2 of compound **4f**.

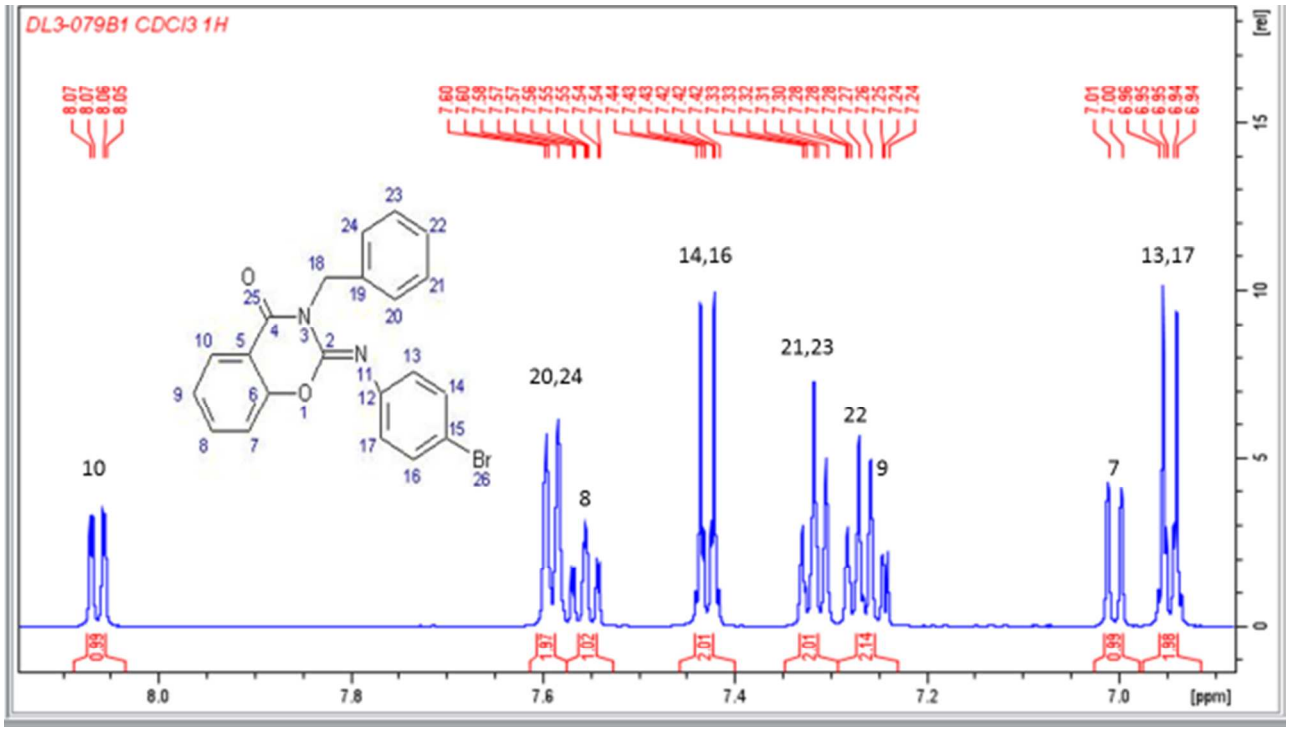



**Figure S61**. $^{13}$C NMR expansion spectra 1 of compound **4f**.

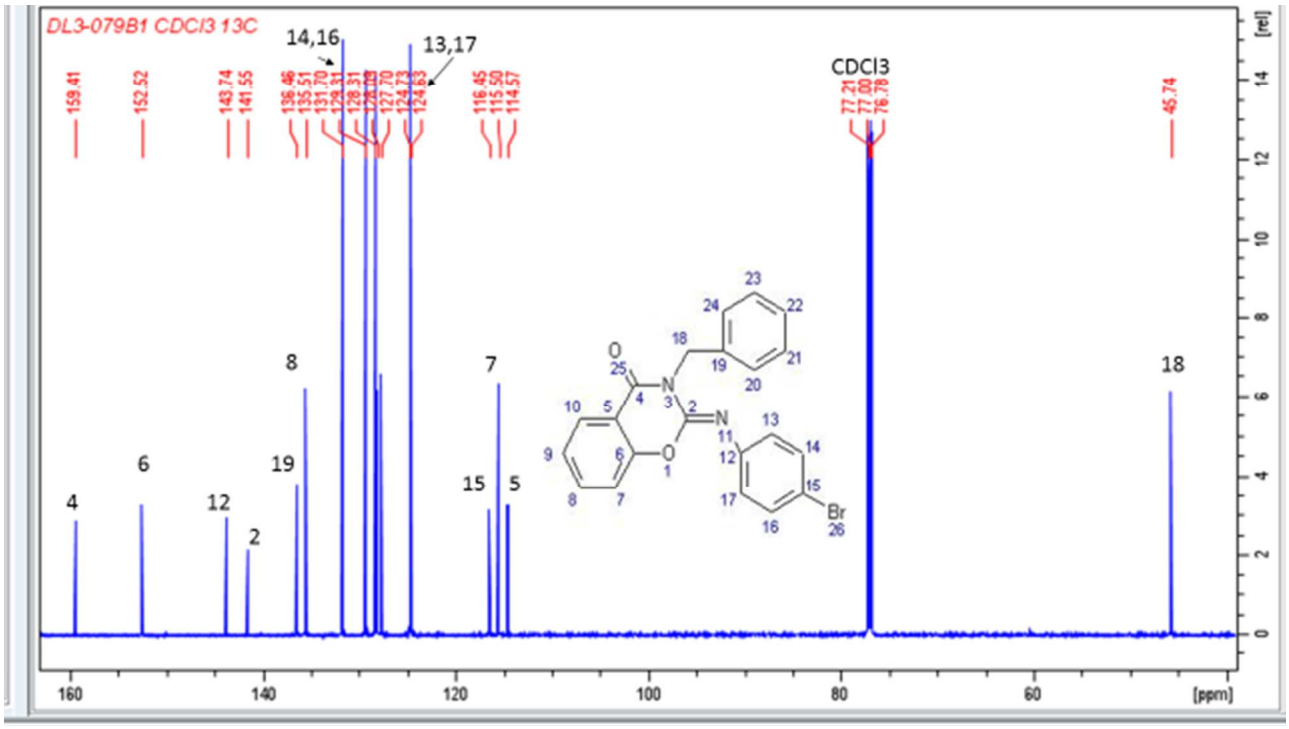


**Figure S62**. $^{13}$C NMR expansion spectra 2 of compound **4f**.

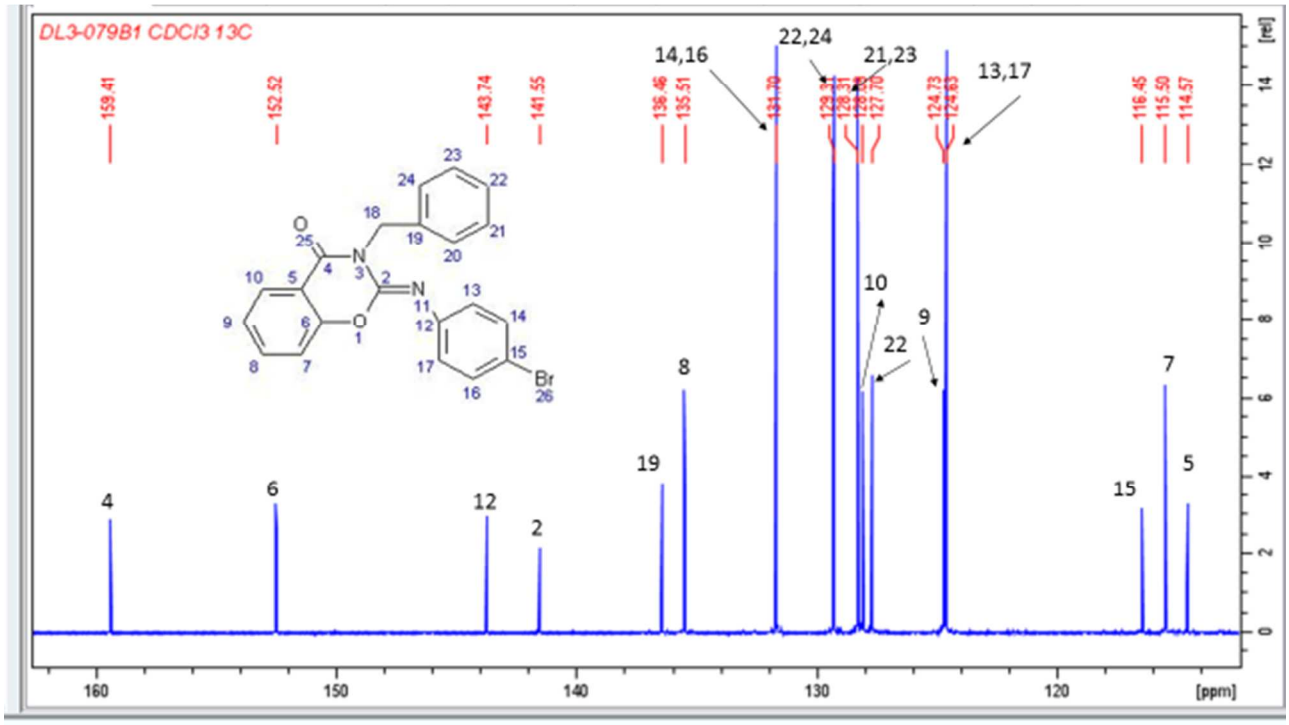



**Figure S63**. $^{13}$C-HMBC expansion spectra 1 of compound **4f**.

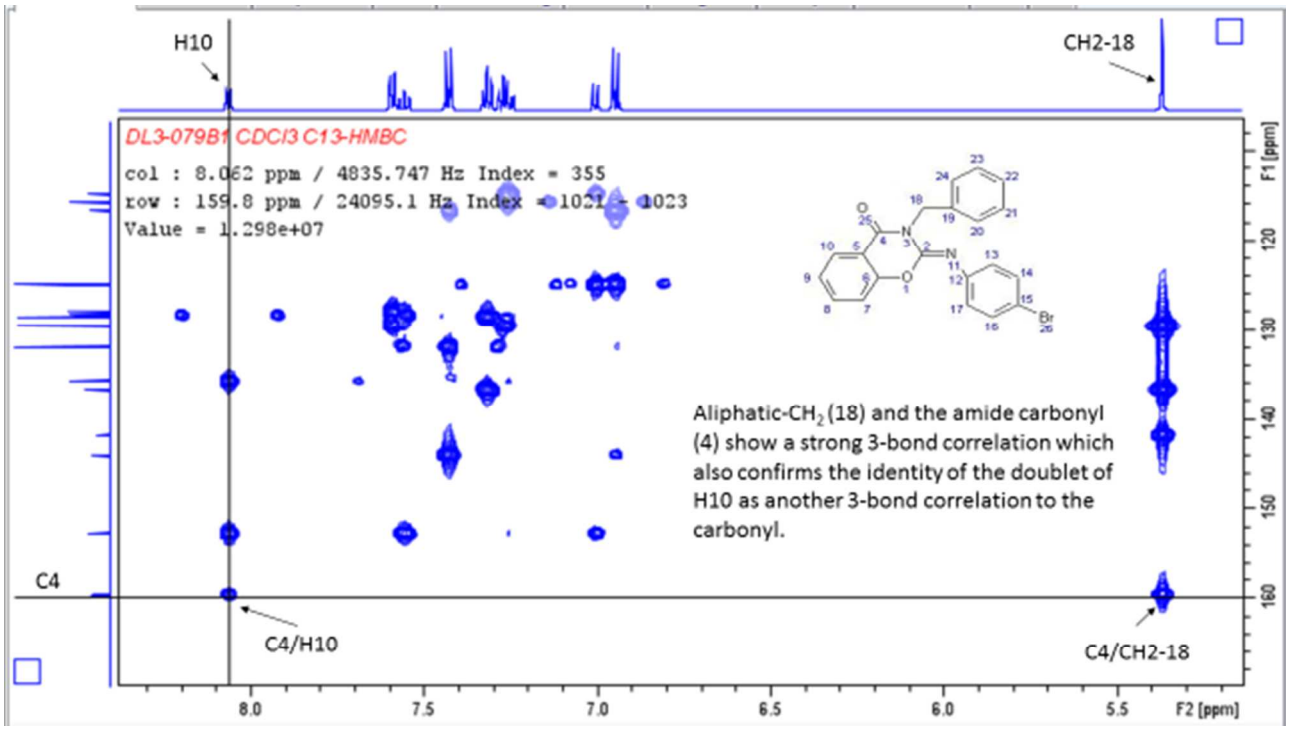


**Figure S64**. COSY expansion spectra 1 of compound **4f**.

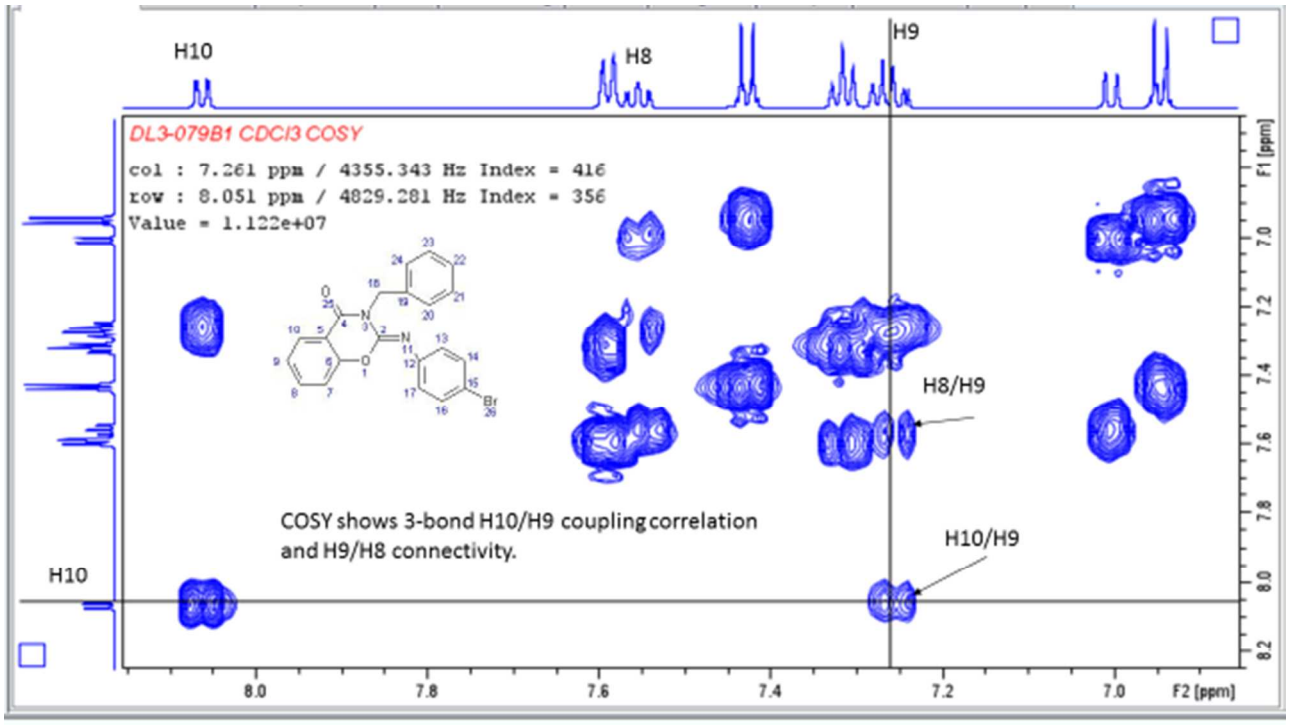



**Figure S65**. COSY expansion spectra 2 of compound **4f**.

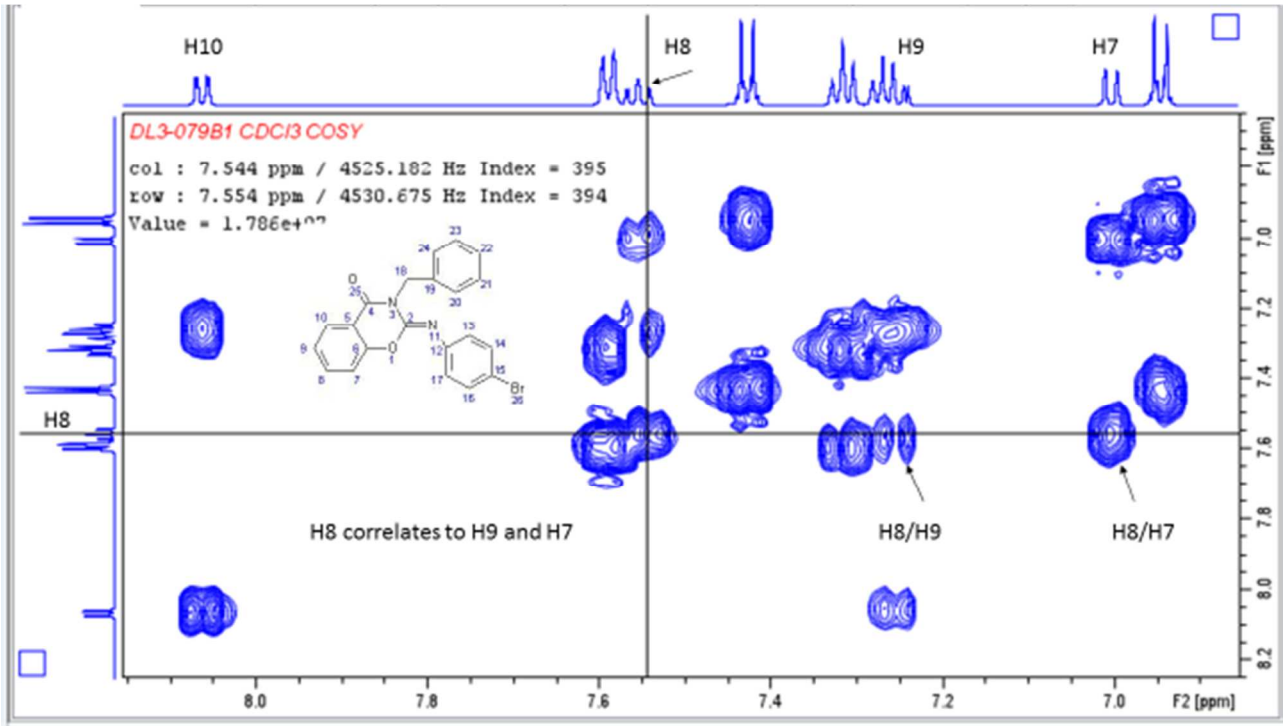


**Figure S66**. $^{13}$C-HSQC expansion spectra 1 of compound **4f**.

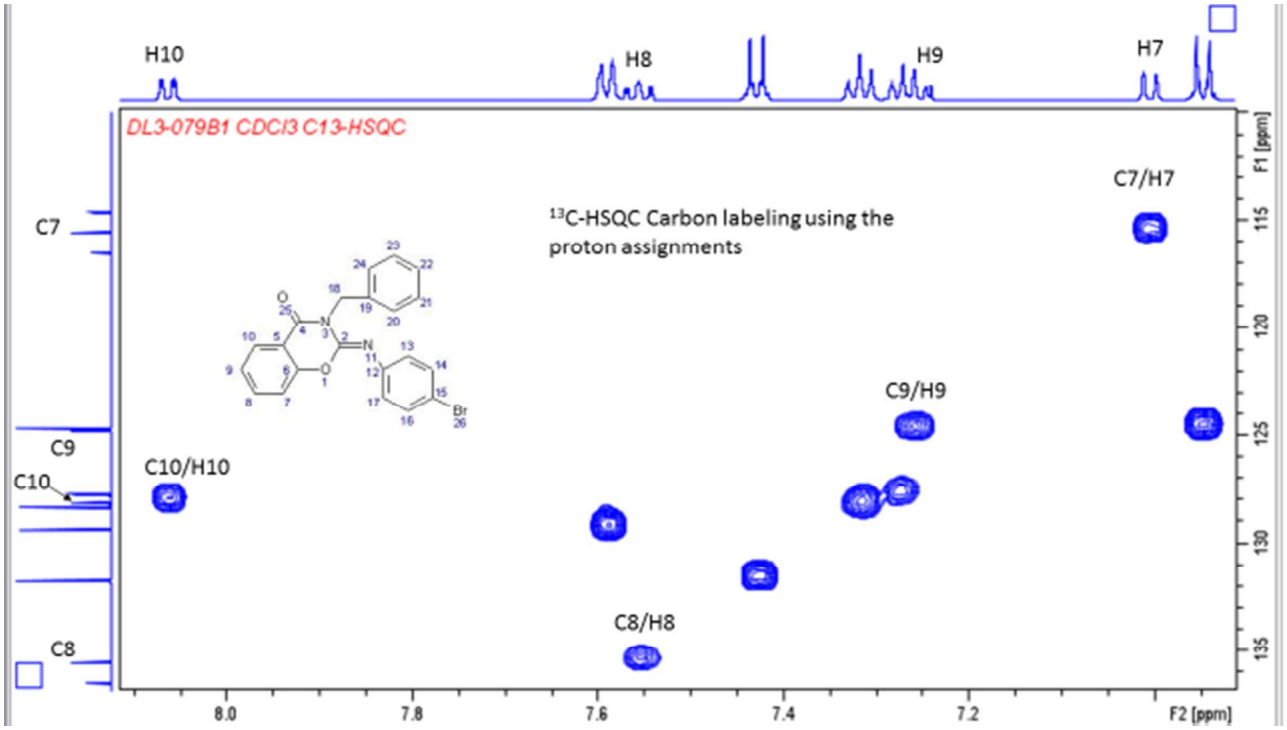



**Figure S67**. $^{13}$C-HMBC expansion spectra 2 of compound **4f**.

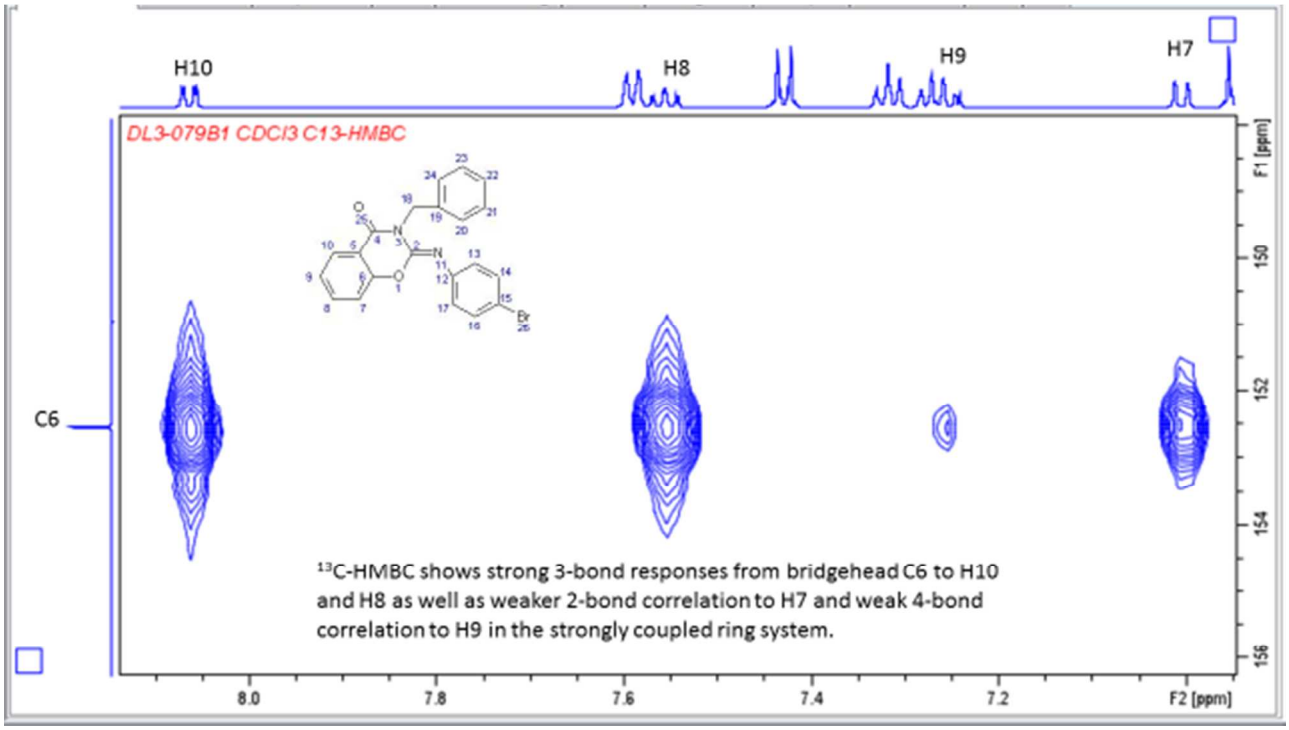


**Figure S68**. $^{13}$C-HMBC expansion spectra 3 of compound **4f**.

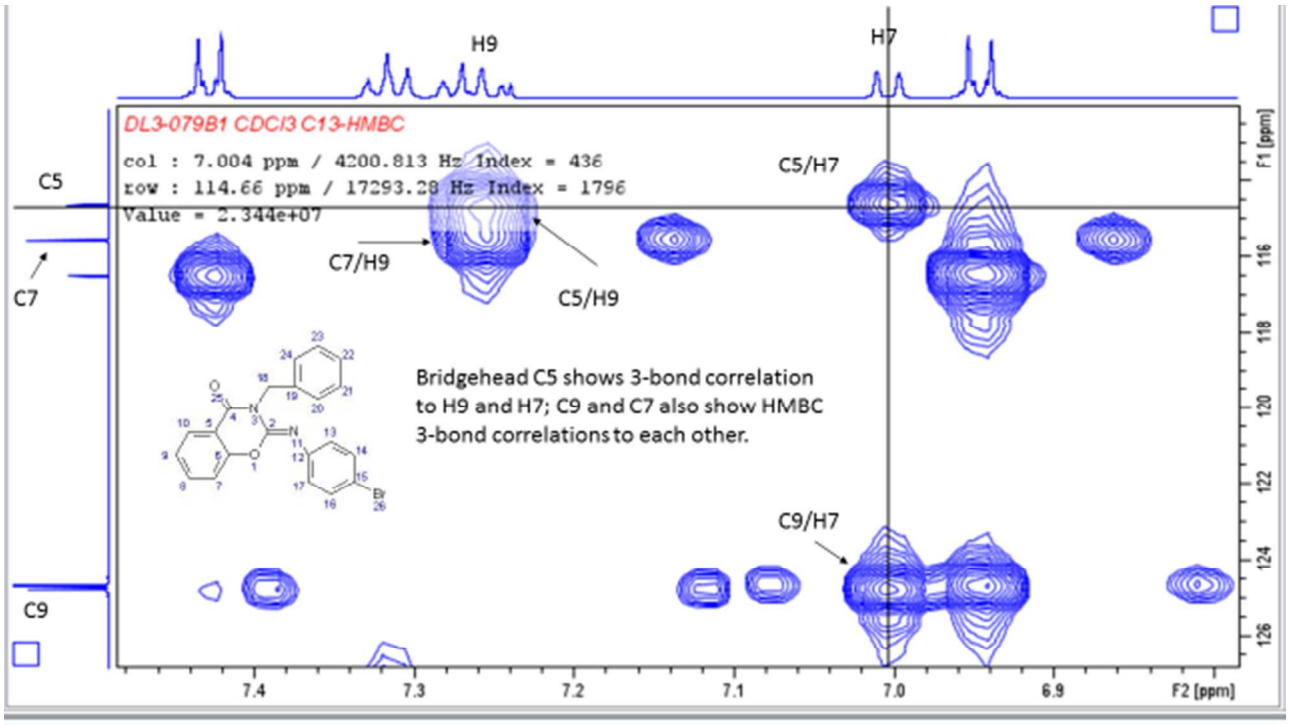



**Figure S69**. $^{13}$C-HMBC expansion spectra 4 of compound **4f**.

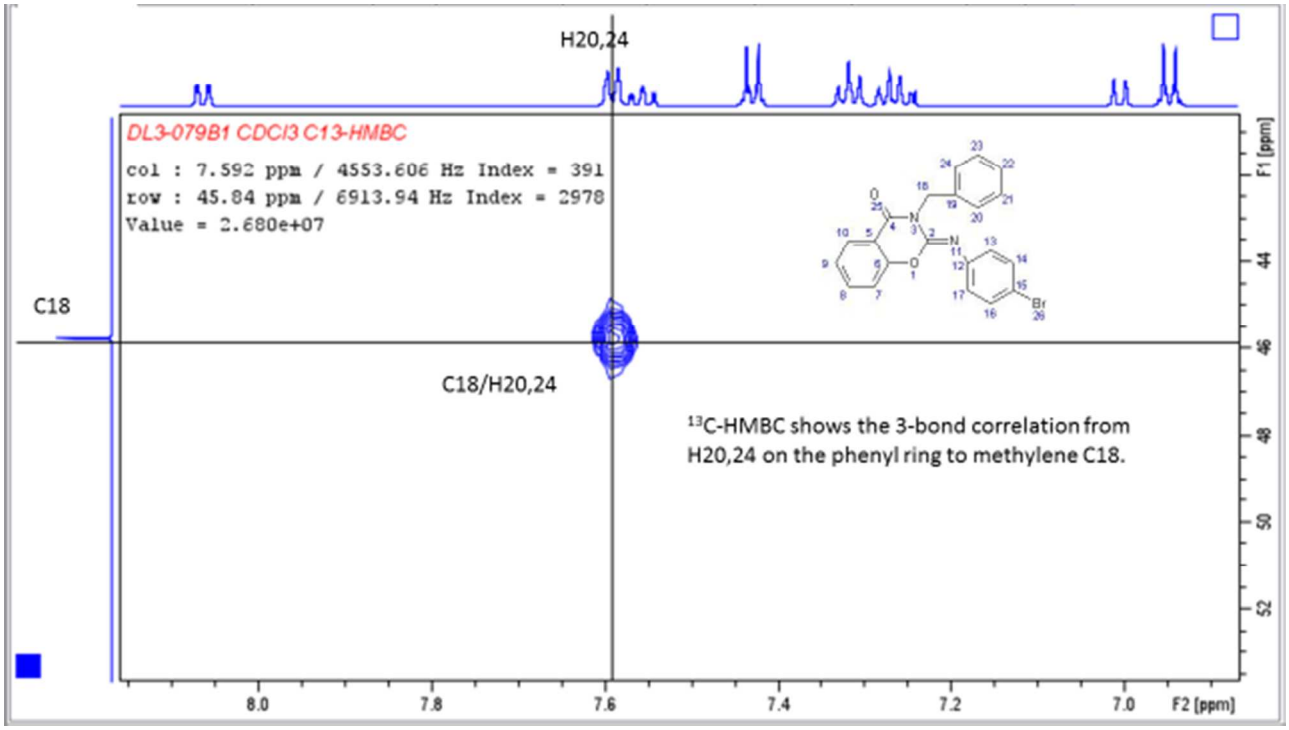



**Figure S70**. COSY expansion spectra 3 of compound **4f**.

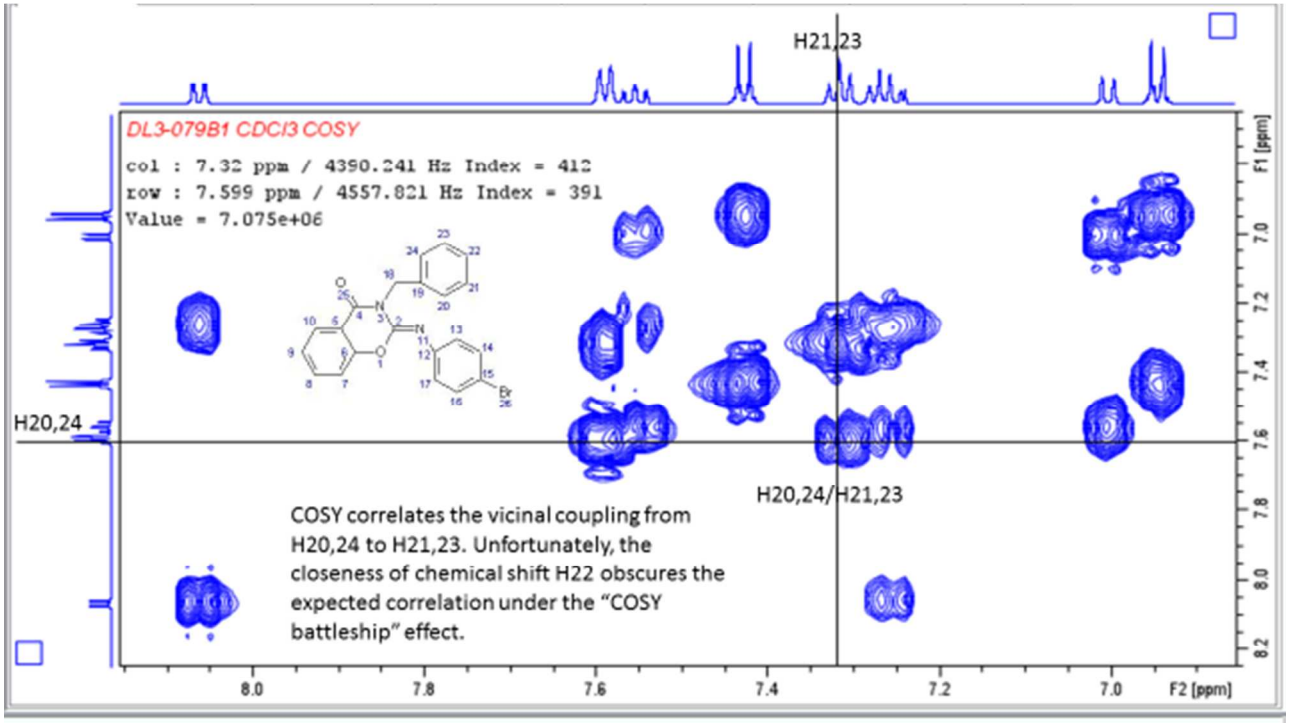


**Figure S71**. TOCSY expansion spectra of compound **4f**.

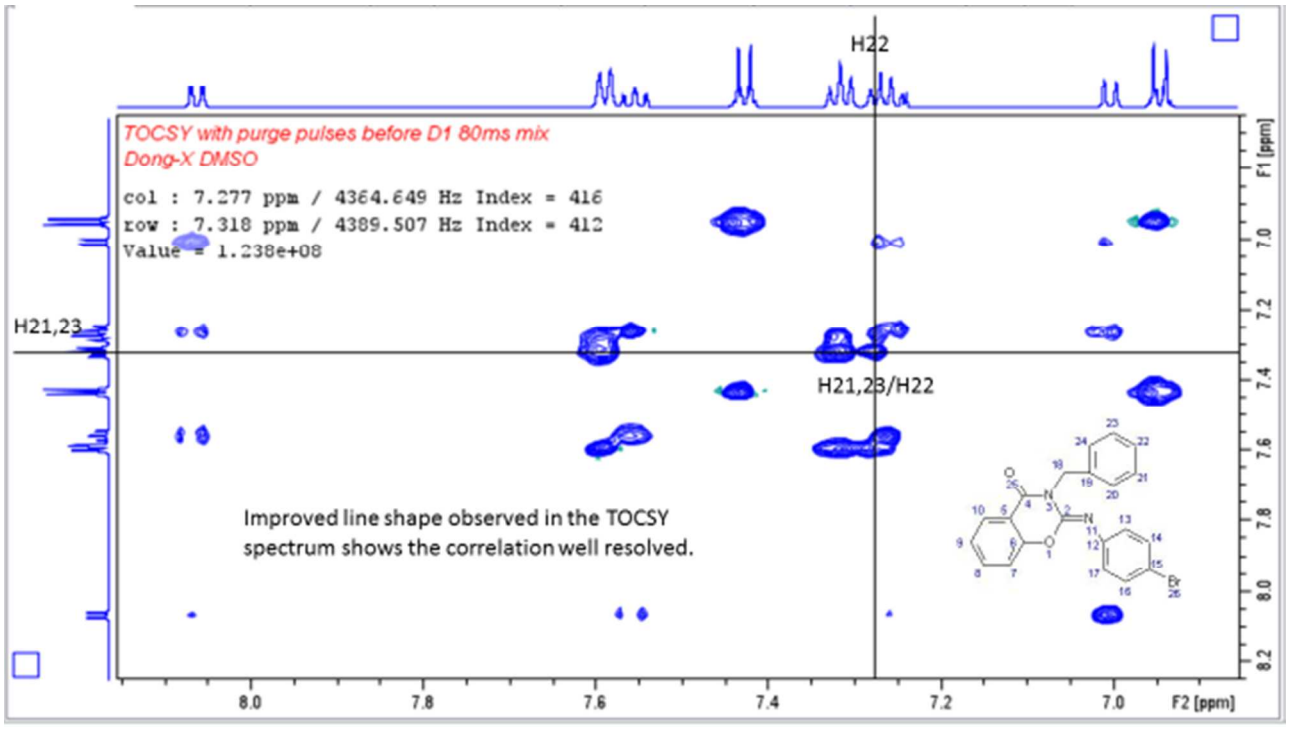



**Figure S72**. $^{13}$C-HSQC expansion spectra 2 of compound **4f**.

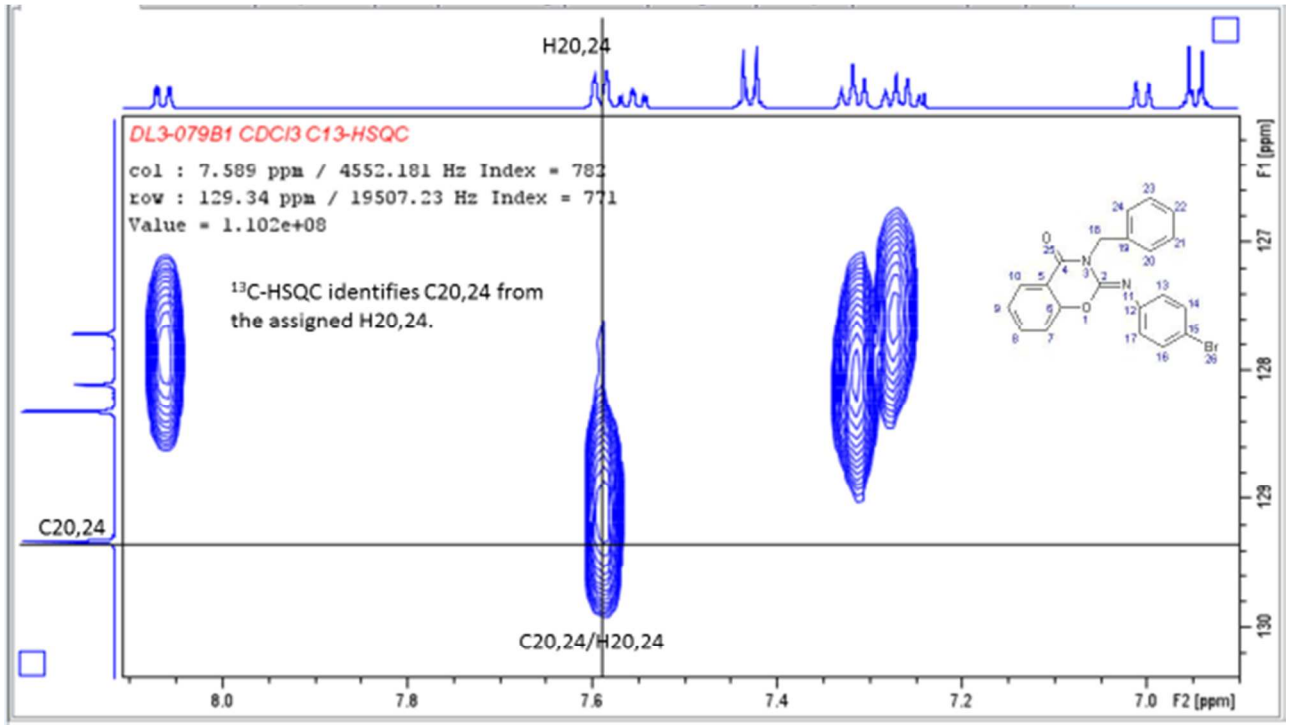


**Figure S73**. $^{13}$C-HSQC expansion spectra 3 of compound **4f**.

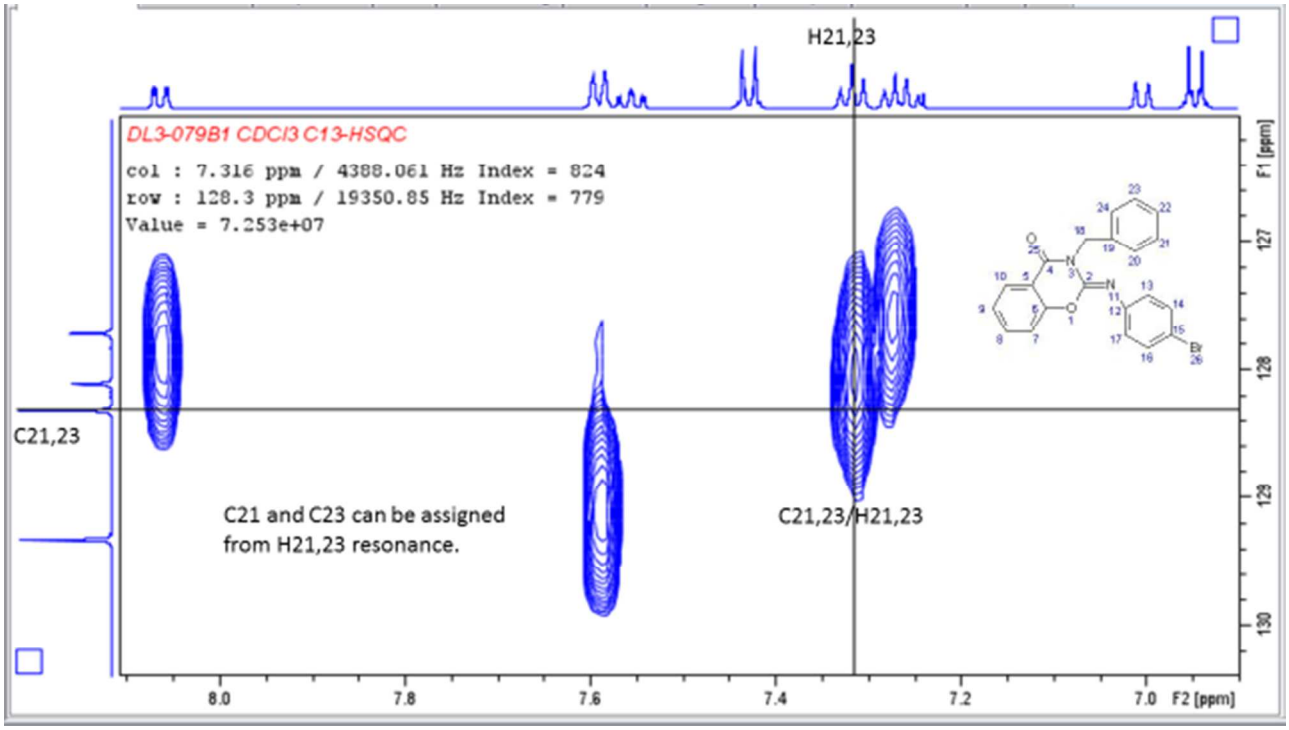



**Figure S74**. $^{13}$C-HSQC expansion spectra 4 of compound **4f**.

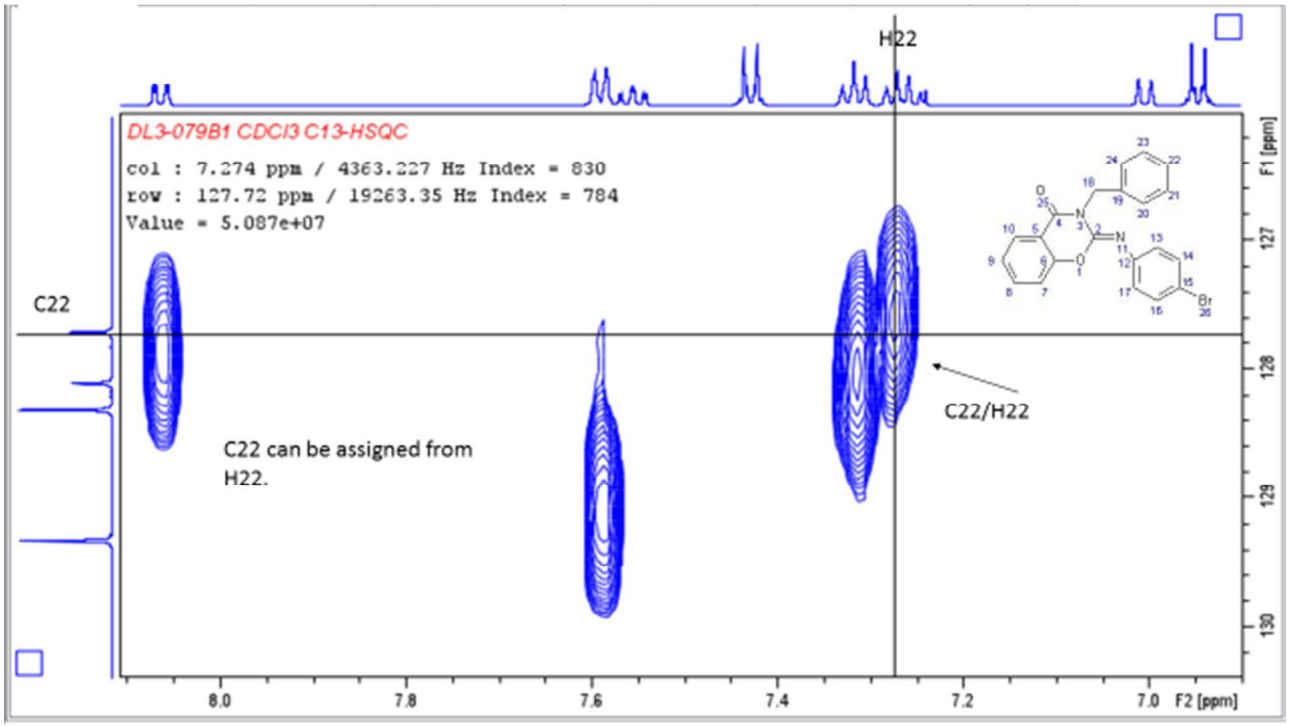


**Figure S75**. $^{13}$C-HMBC expansion spectra 5 of compound **4f**.

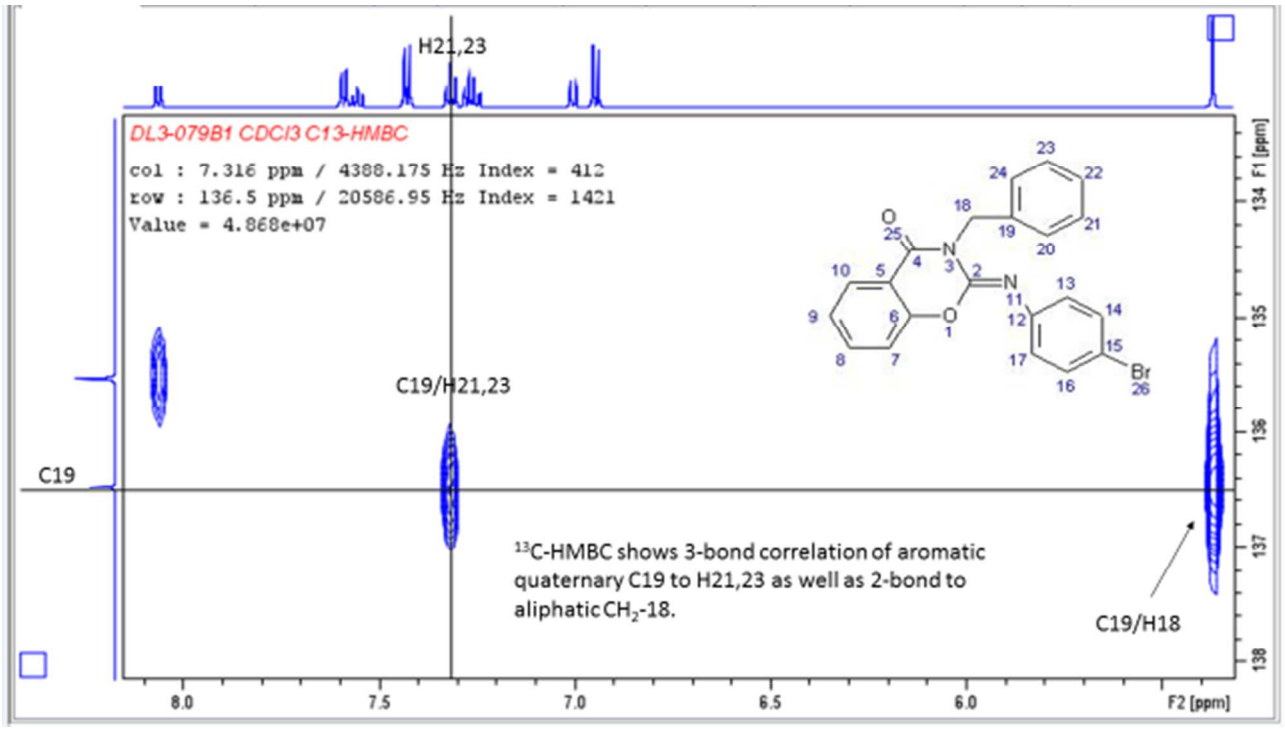



**Figure S76**. $^{13}$C-HMBC expansion spectra 6 of compound **4f**.

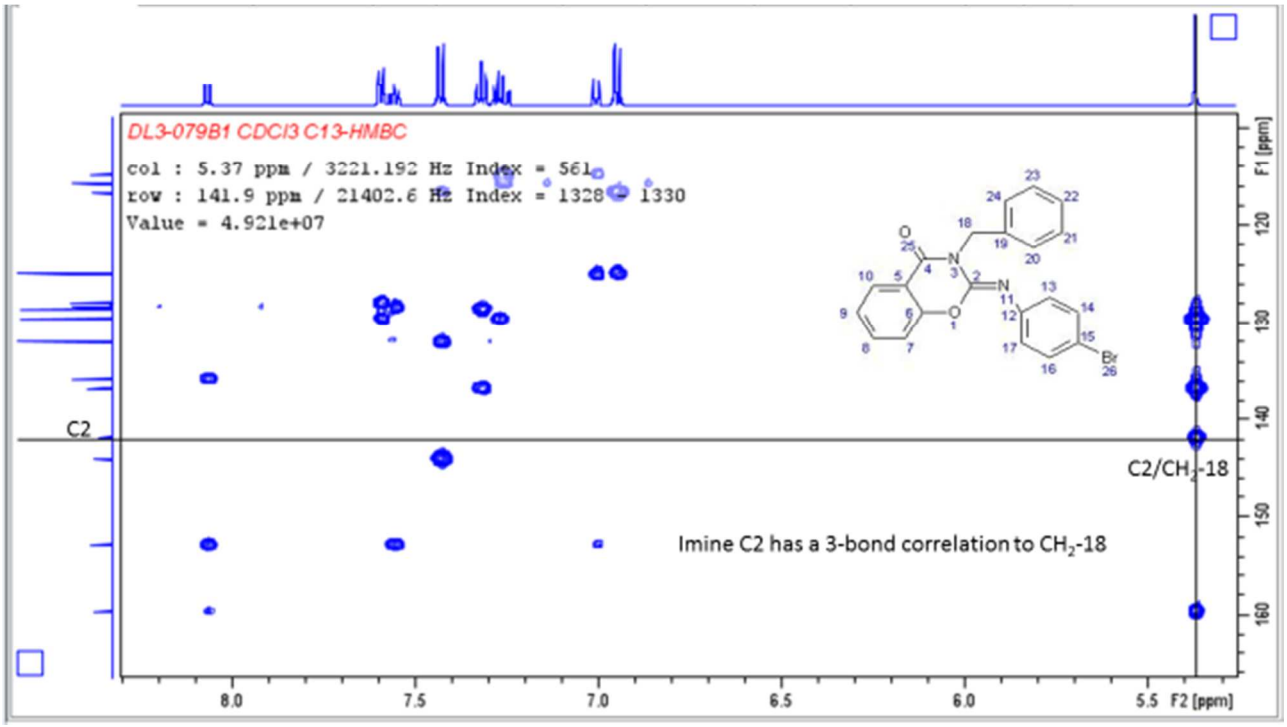


**Figure S77**. COSY expansion spectra 4 of compound **4f**.

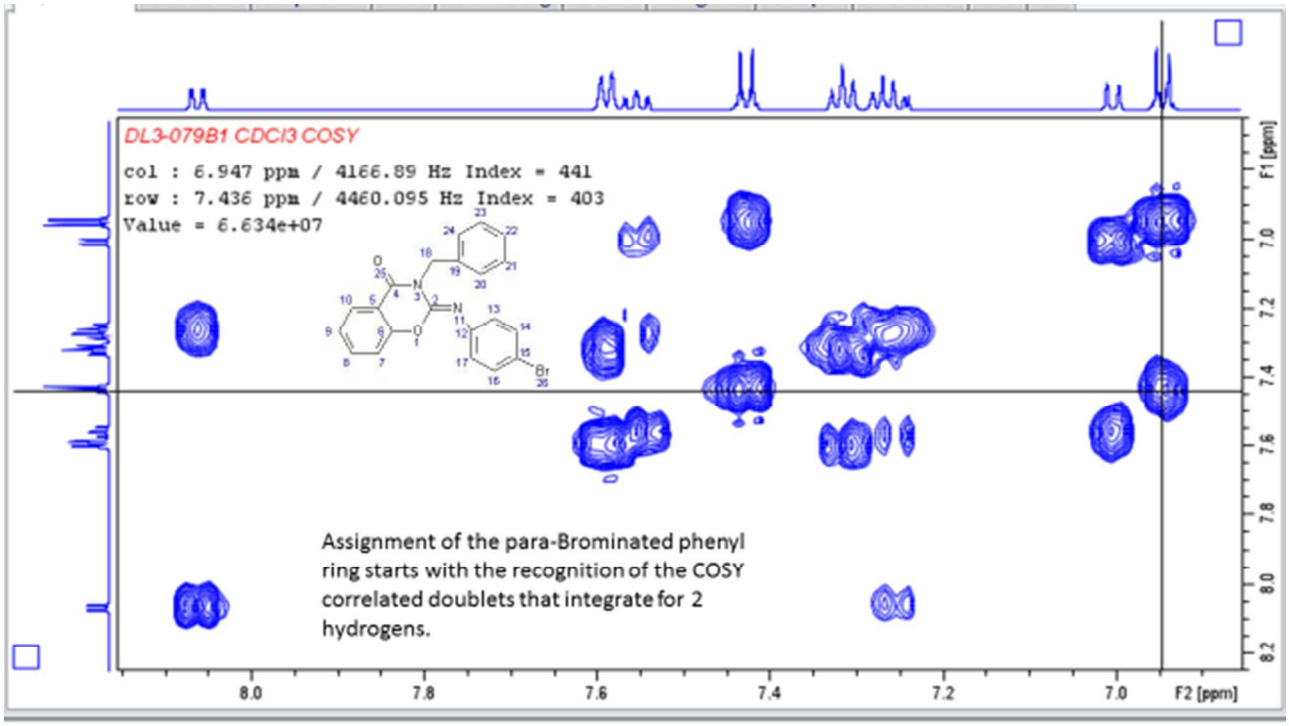



**Figure S78**. $^{15}$N-HMBC expansion spectra 1 of compound **4f**.

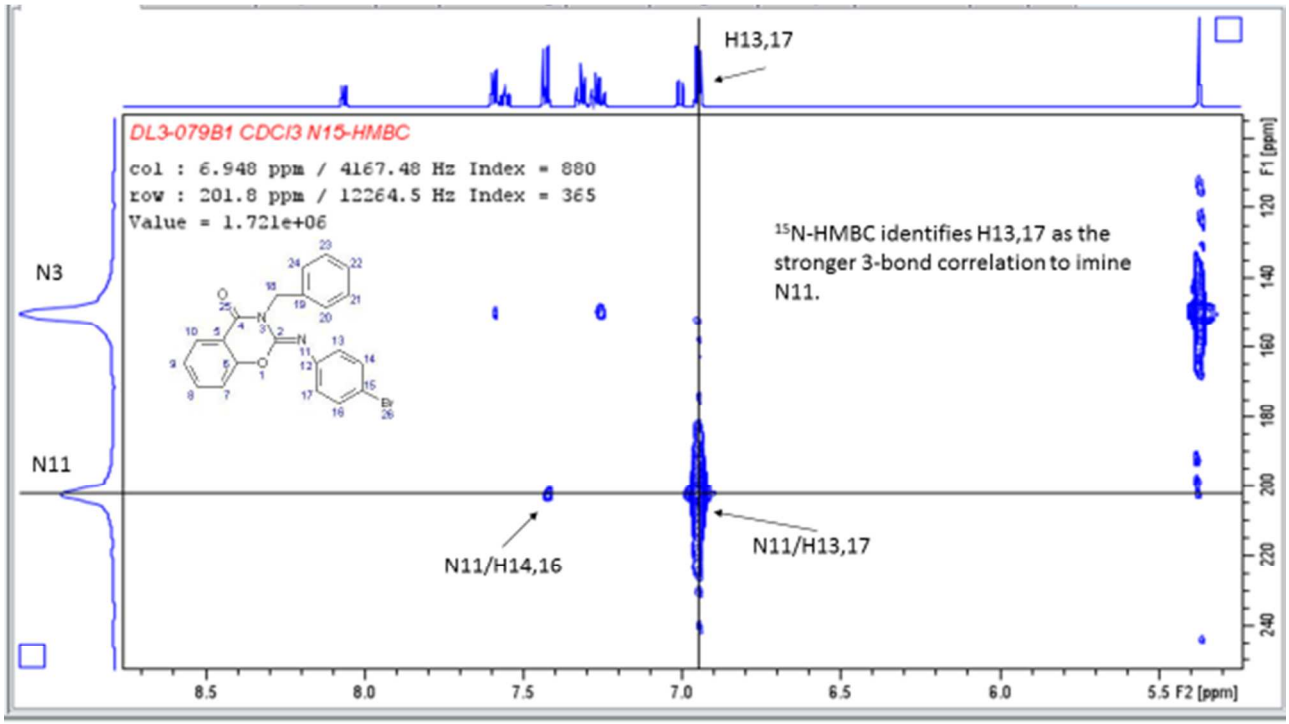


**Figure S79**. $^{15}$N-HMBC expansion spectra 2 of compound **4f**.

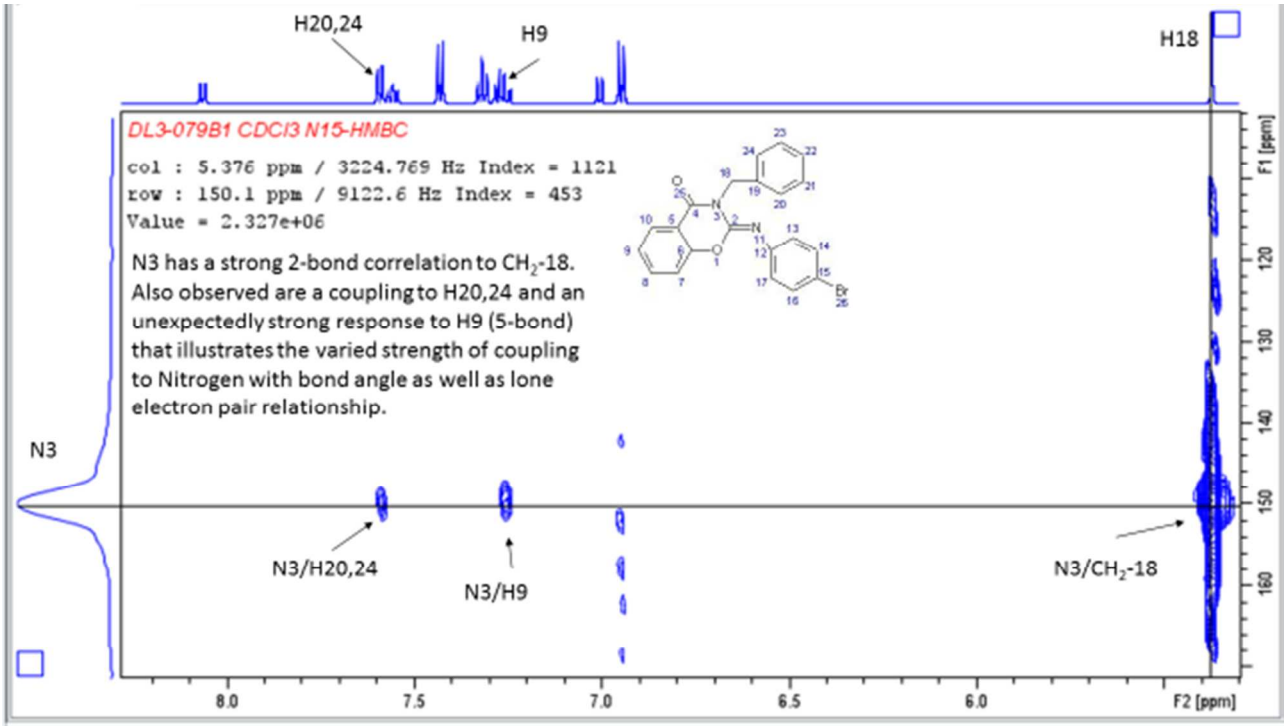



**Figure S80**. $^{13}$C-HSQC expansion spectra 5 of compound **4f**.

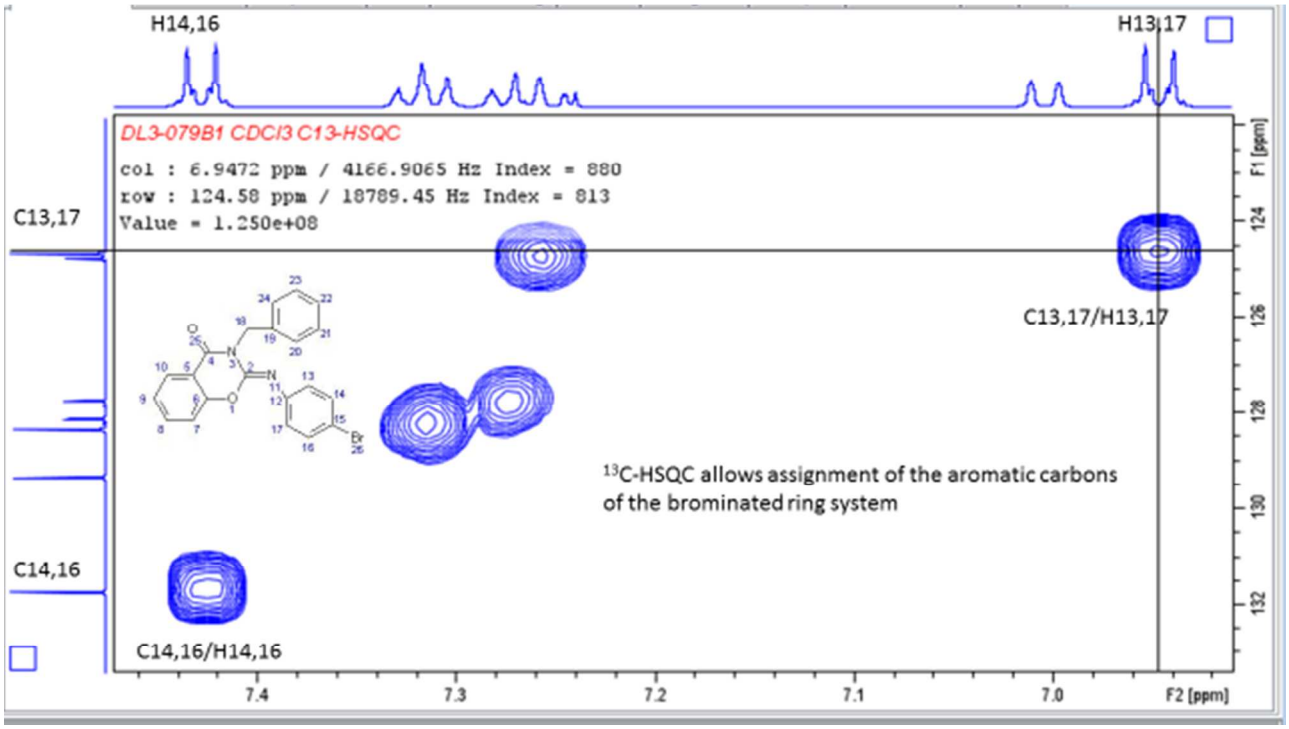


**Figure S81**. $^{13}$C-HMBC expansion spectra 7 of compound **4f**.

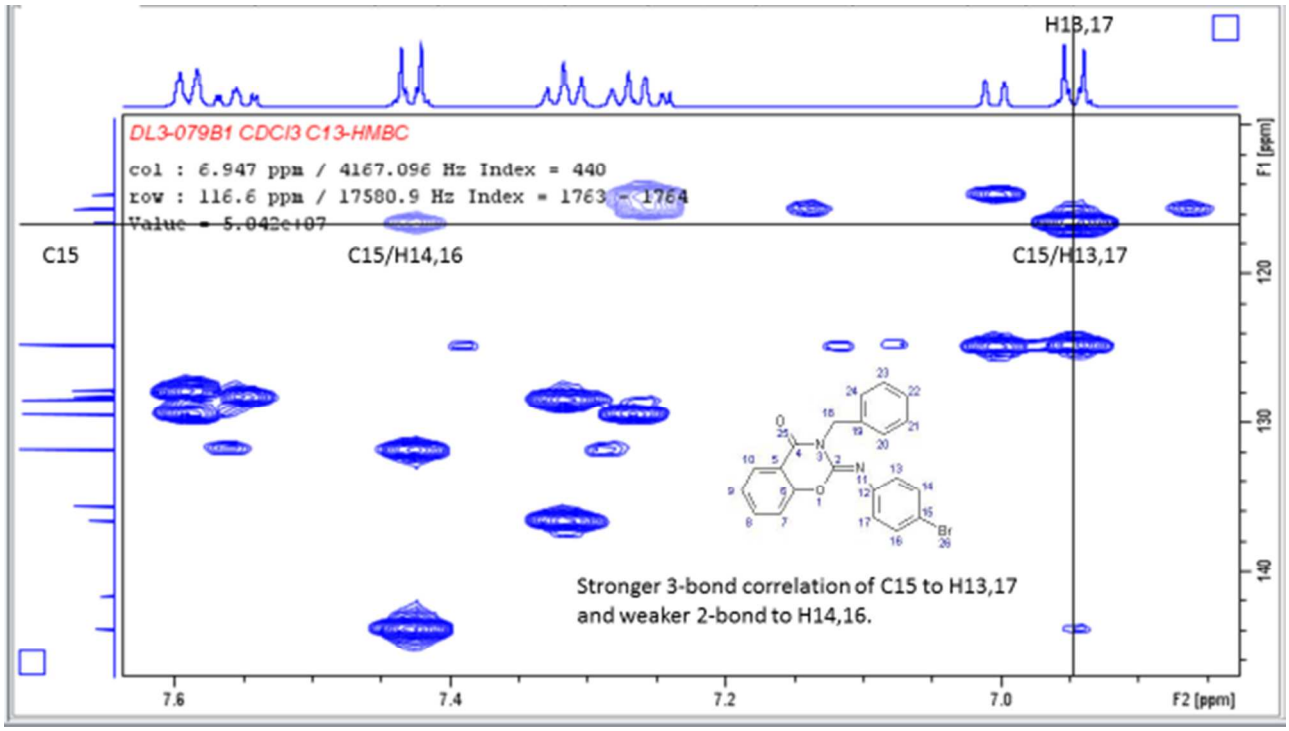



**Figure S82**. $^{13}$C-HMBC expansion spectra 8 of compound **4f**.

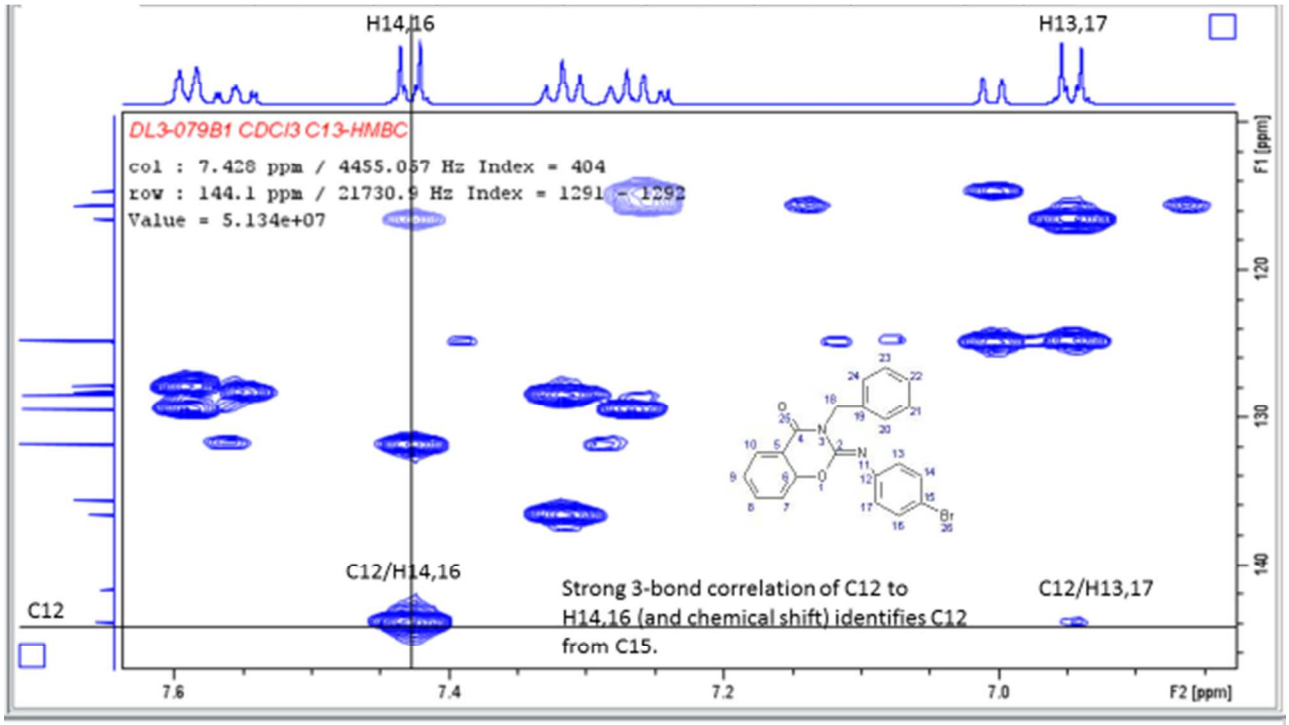
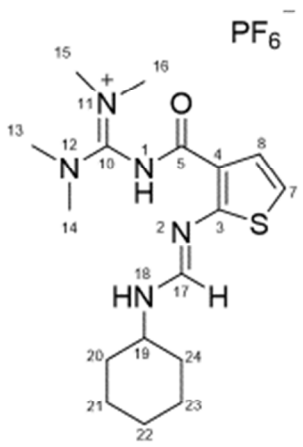


**Figure S83**. 2D NMR spectra atom numbering for **10**.




**10**

**Figure S84**. $^{1}$H NMR spectra of compound **10**.

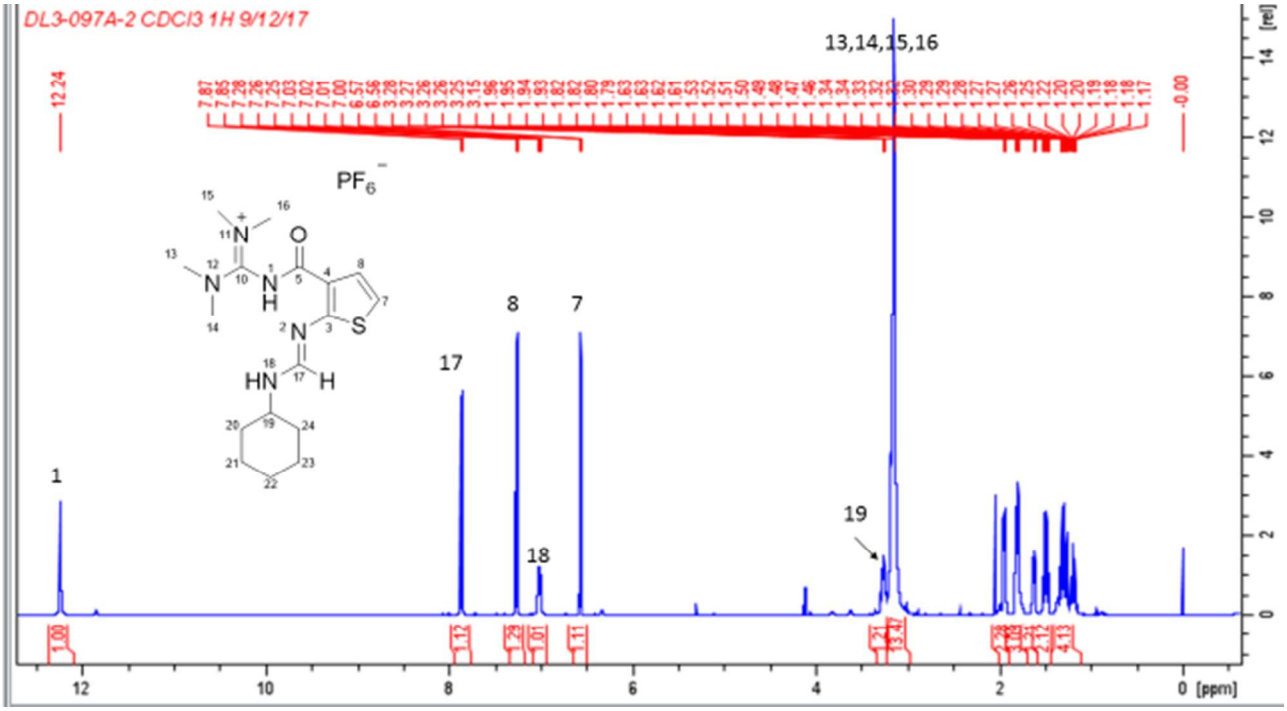


**Figure S85**. $^{1}$H NMR expansion spectra 1 of compound **10**.

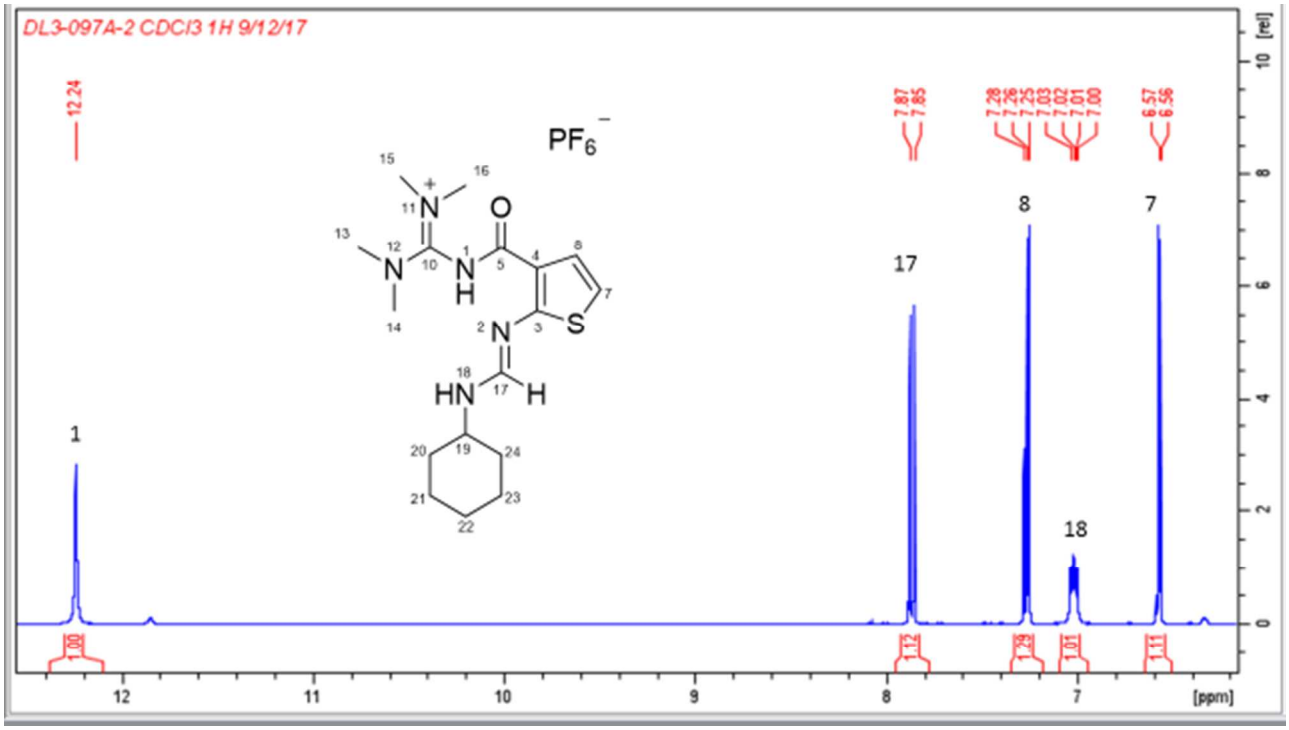



**Figure S86**. $^{1}$H NMR expansion spectra 2 of compound **10**.

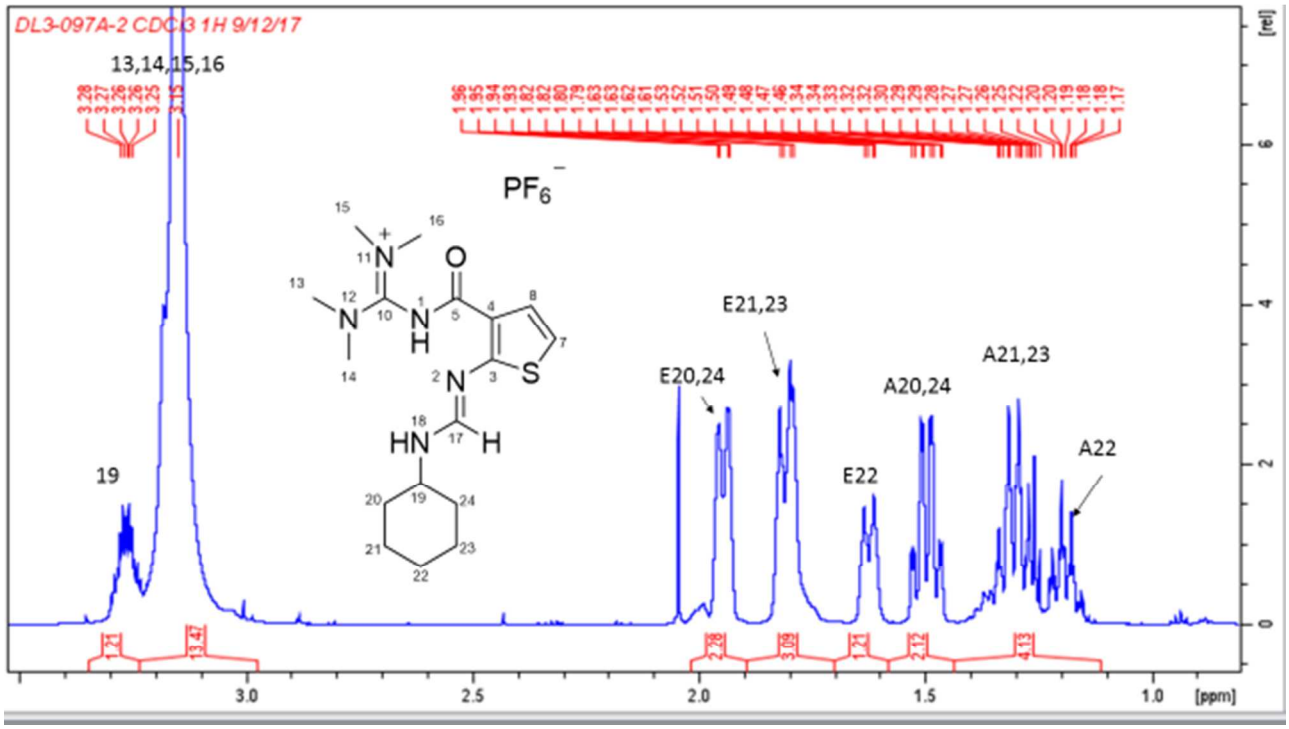


**Figure S87**. COSY spectra of compound **10**.

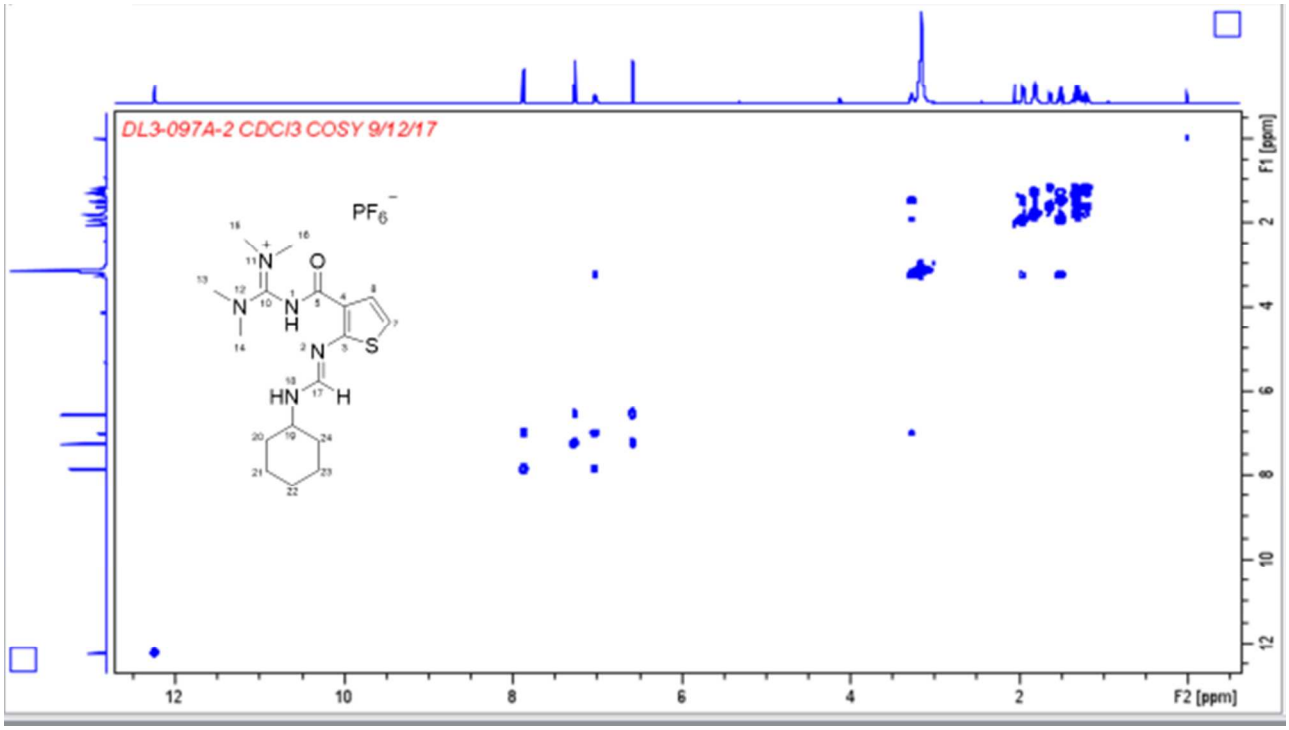



**Figure S88**. COSY expanded spectra 1 for compound **10**.

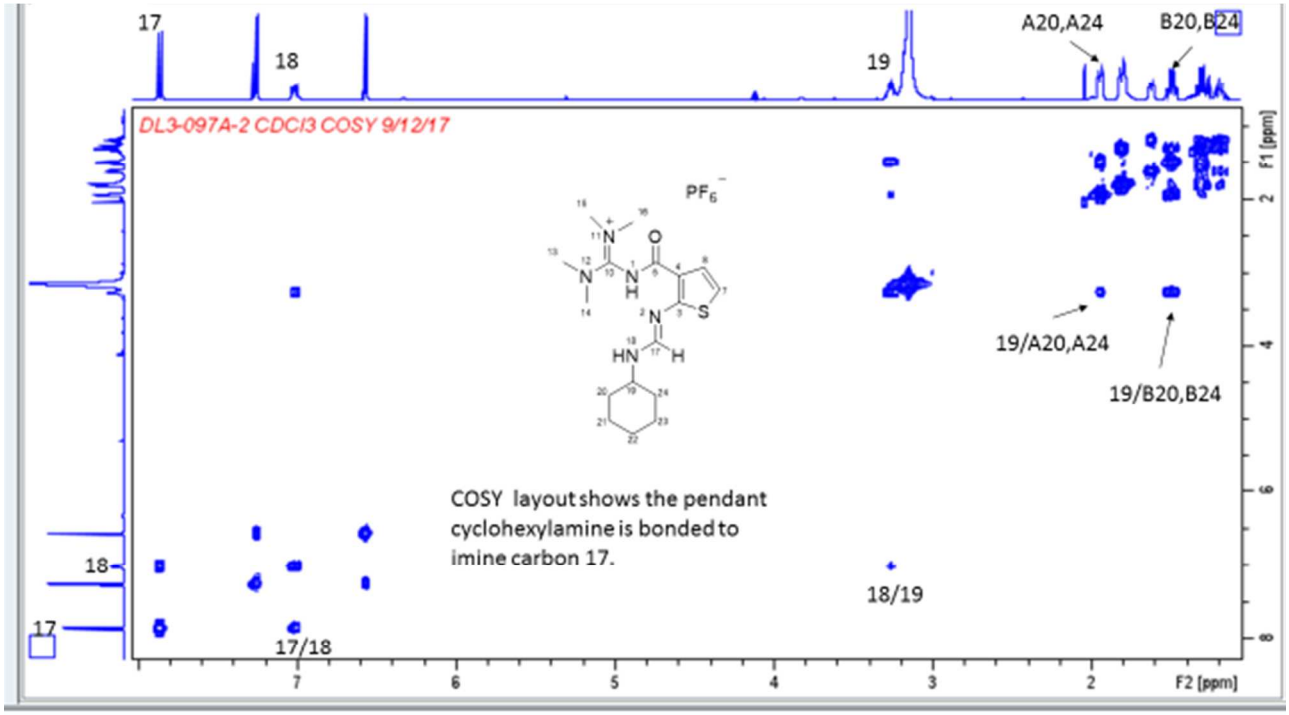


**Figure S89**. $^{13}$C-HMBC NMR expanded spectra 1 for compound **10**.

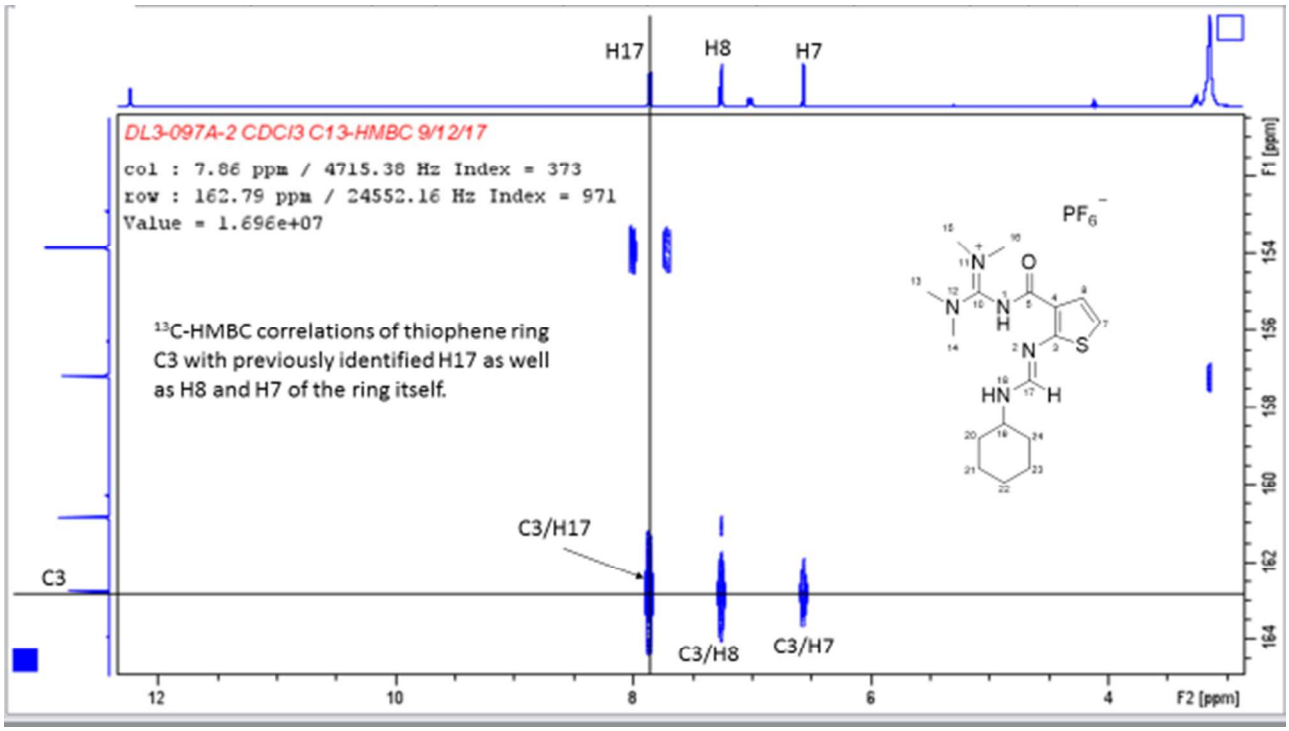



**Figure S90**. $^{13}$C-HMBC NMR expanded spectra 2 for compound **10**.

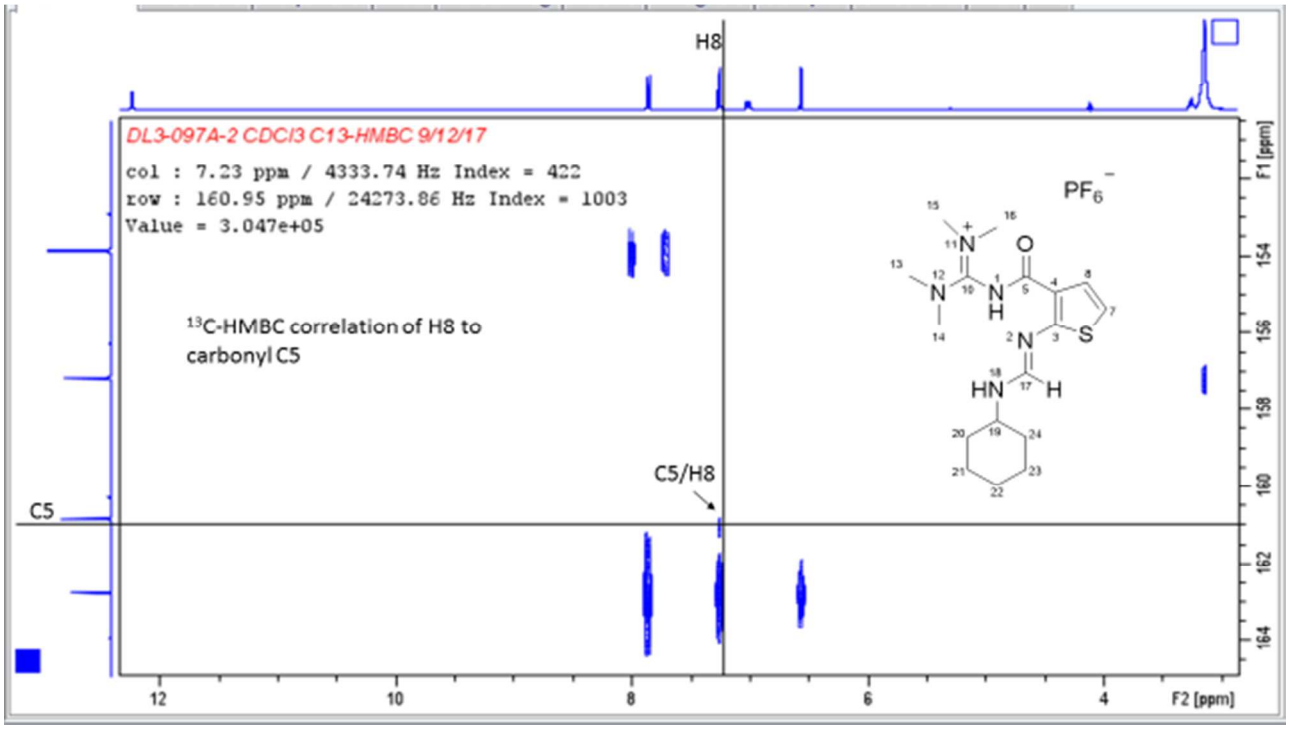


**Figure S91**. $^{13}$C-HMBC NMR expanded spectra 3 for compound **10**.

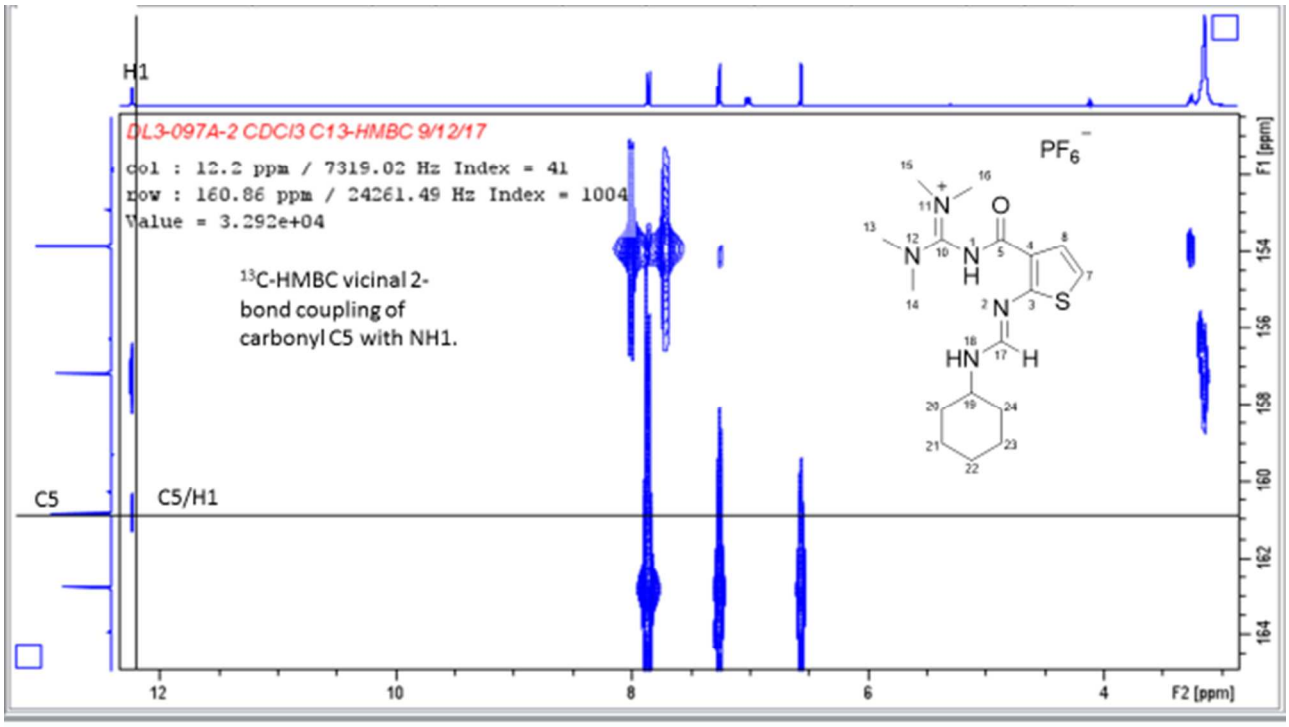



**Figure S92**. $^{13}$C-HMBC NMR expanded spectra 4 for compound **10**.

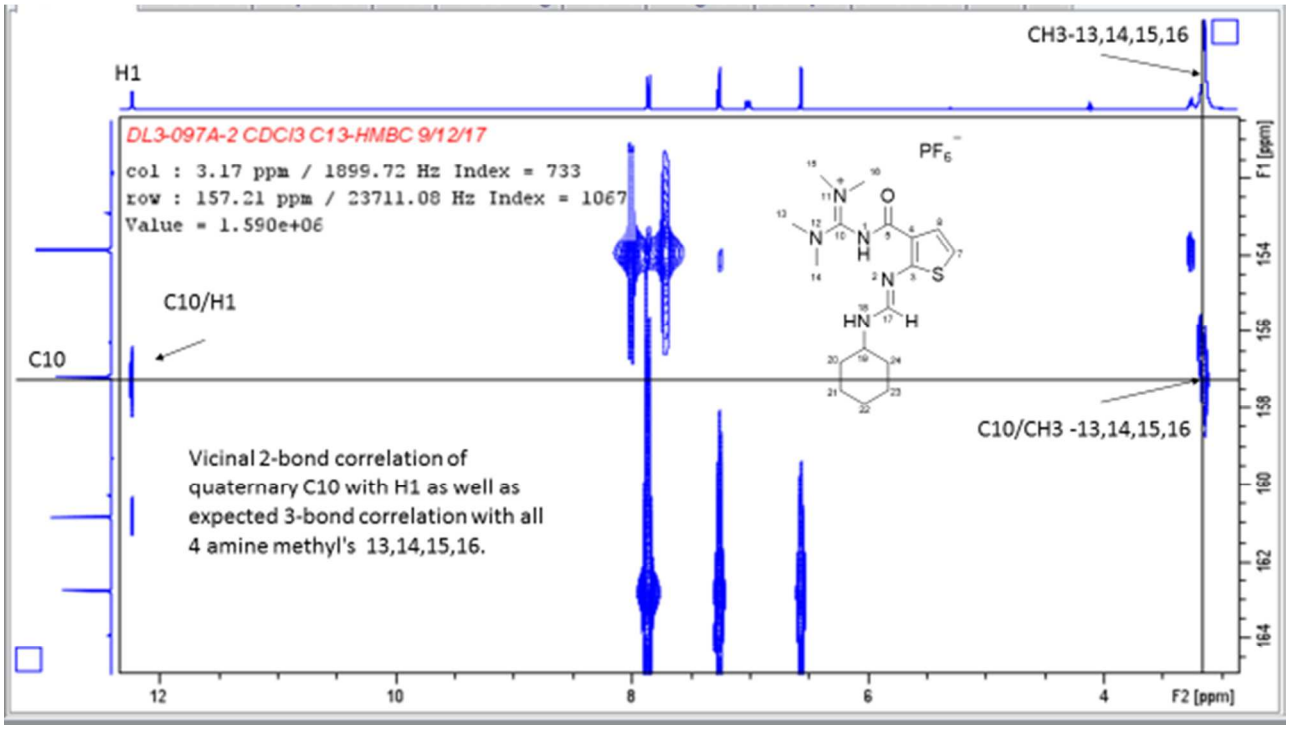


**Figure S93**. $^{13}$C-HMBC NMR expanded spectra 5 for compound **10**.

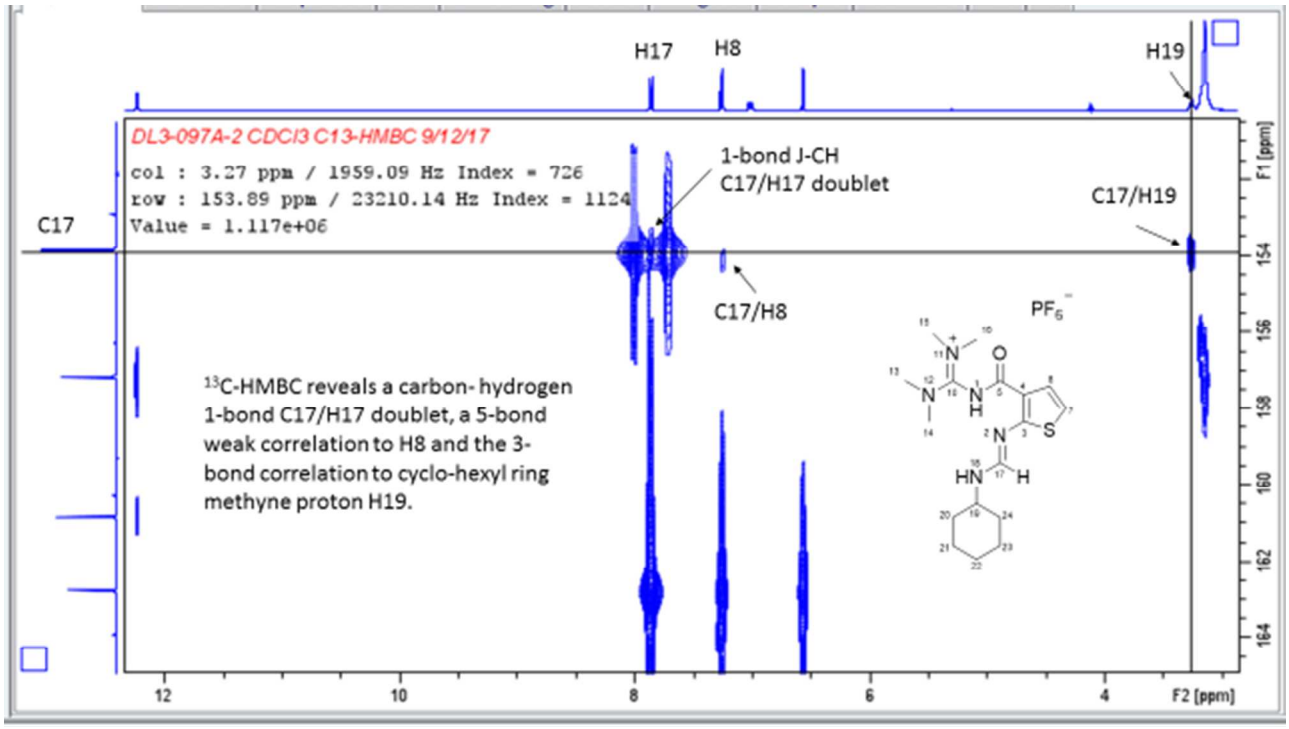



**Figure S94**. $^{13}$C-HMBC NMR expanded spectra 6 for compound **10**.

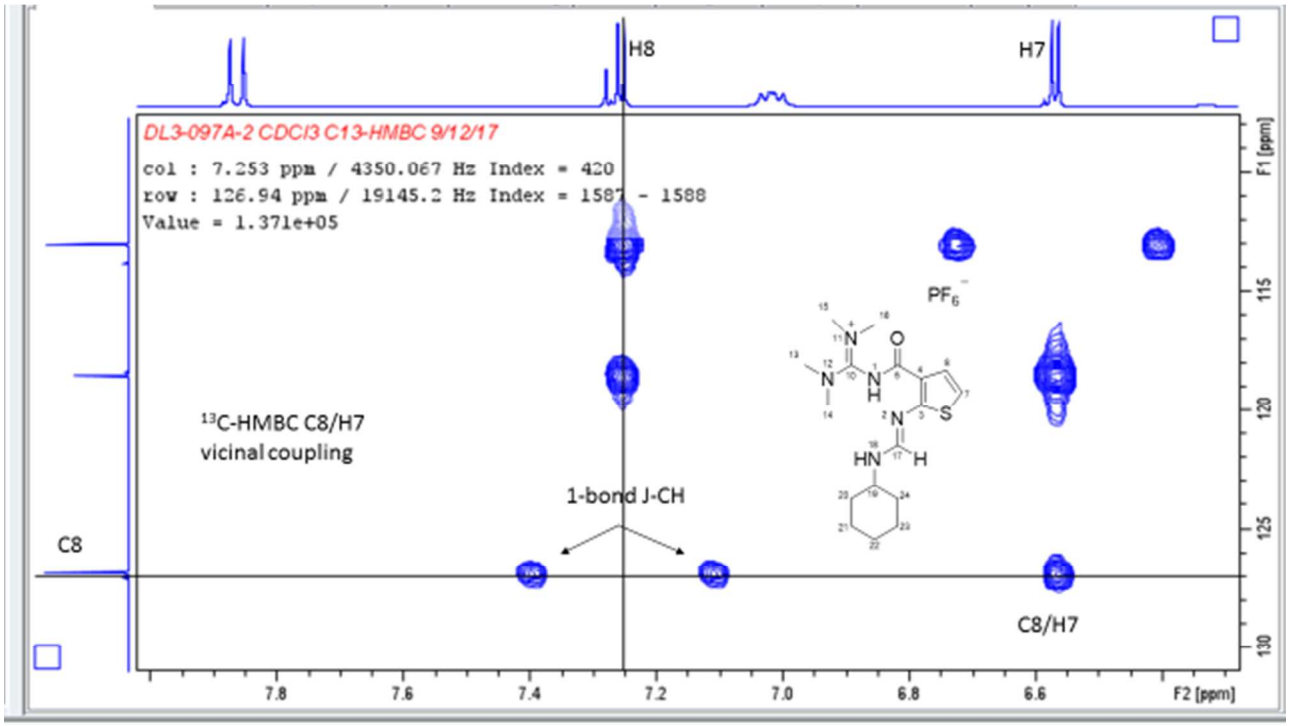


**Figure S95**. $^{13}$C-HMBC NMR expanded spectra 7 for compound **10**.

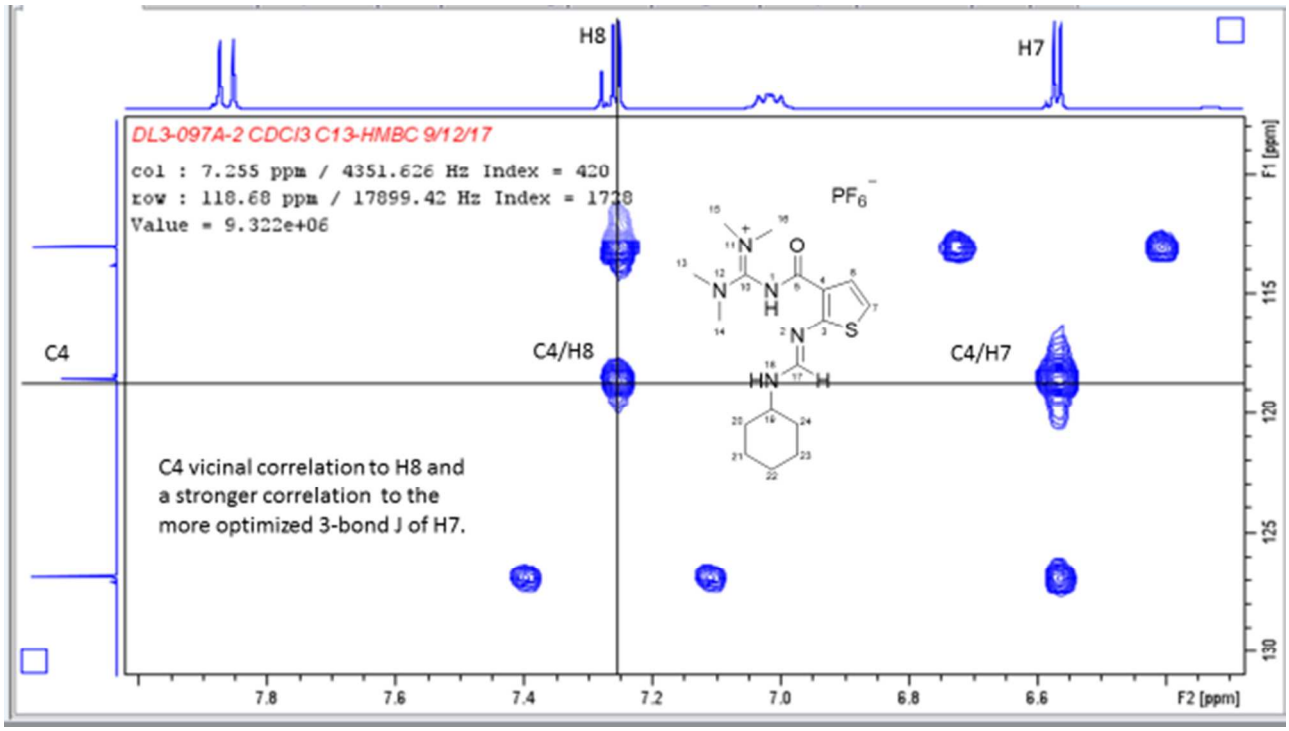



**Figure S96**. $^{13}$C-HMBC NMR expanded spectra 8 for compound **10**.

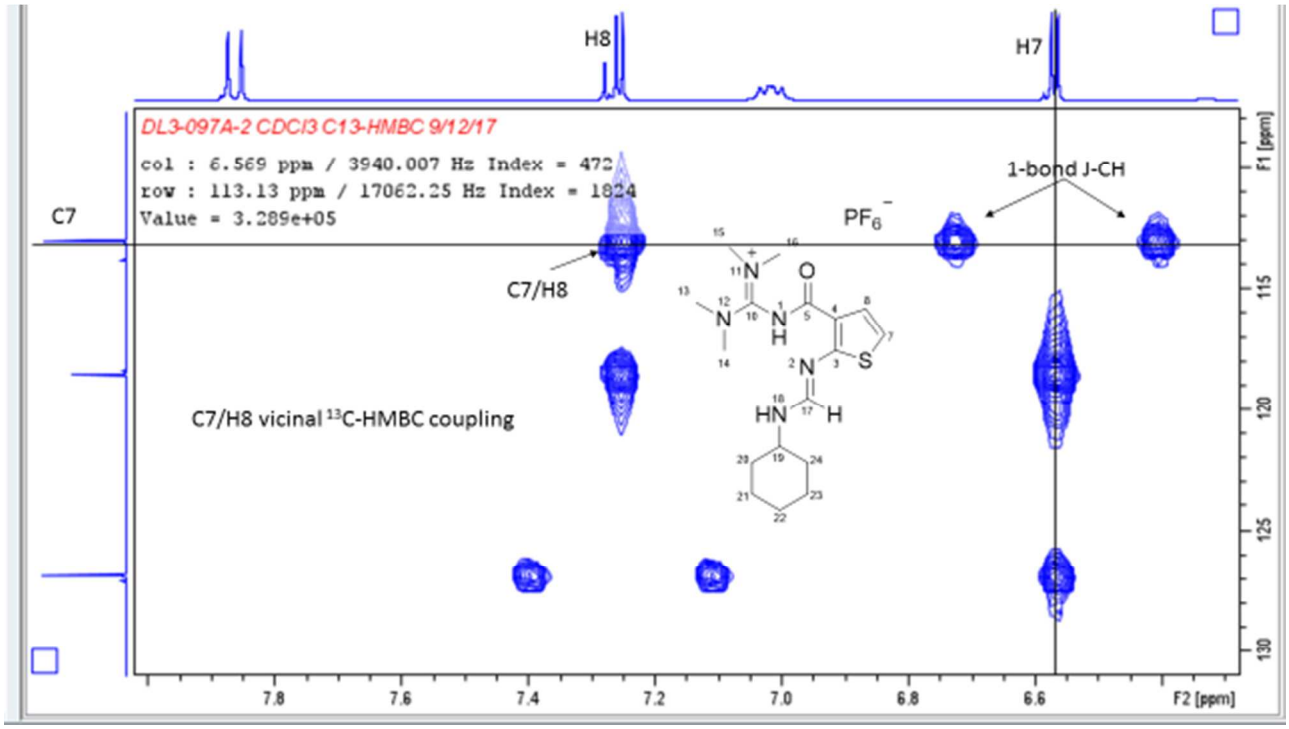


**Figure S97.** COSY expanded spectra 2 for compound **10**.

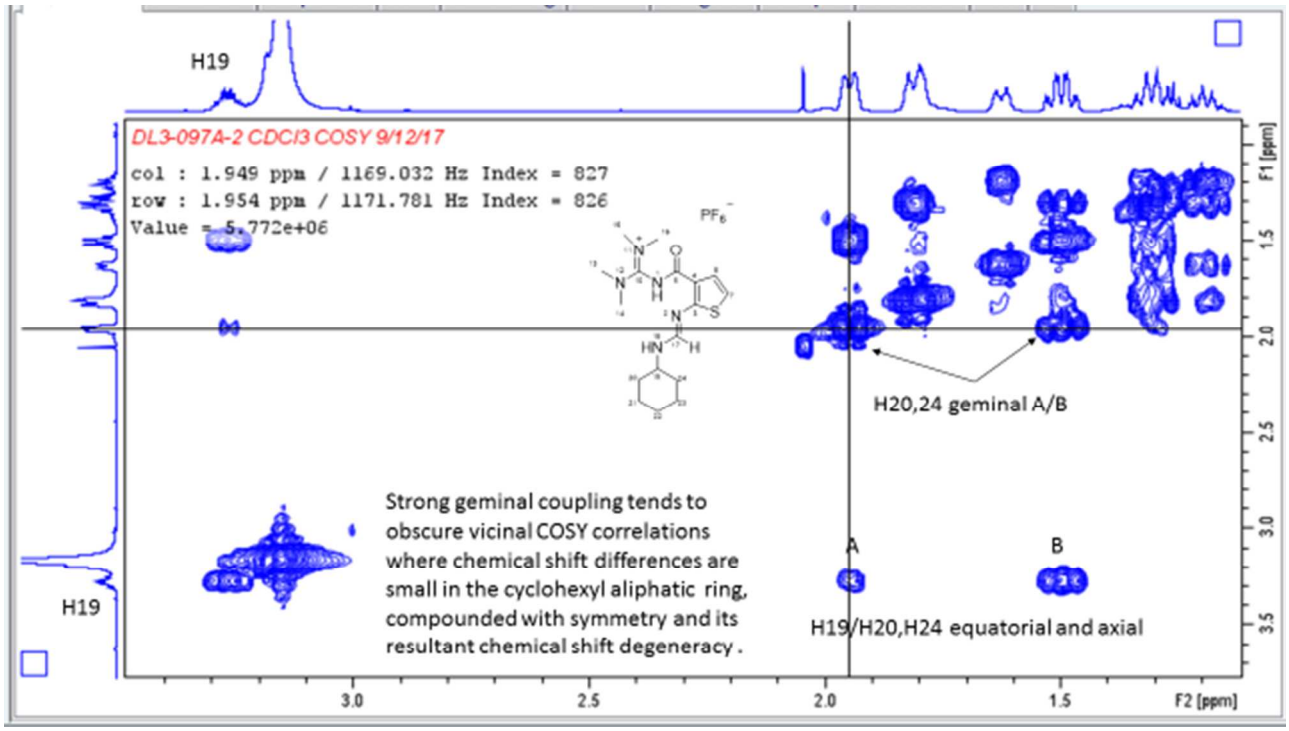



**Figure S98.** Inverse gated quantitatvie $^{13}$C NMR spectra for compound **10**.

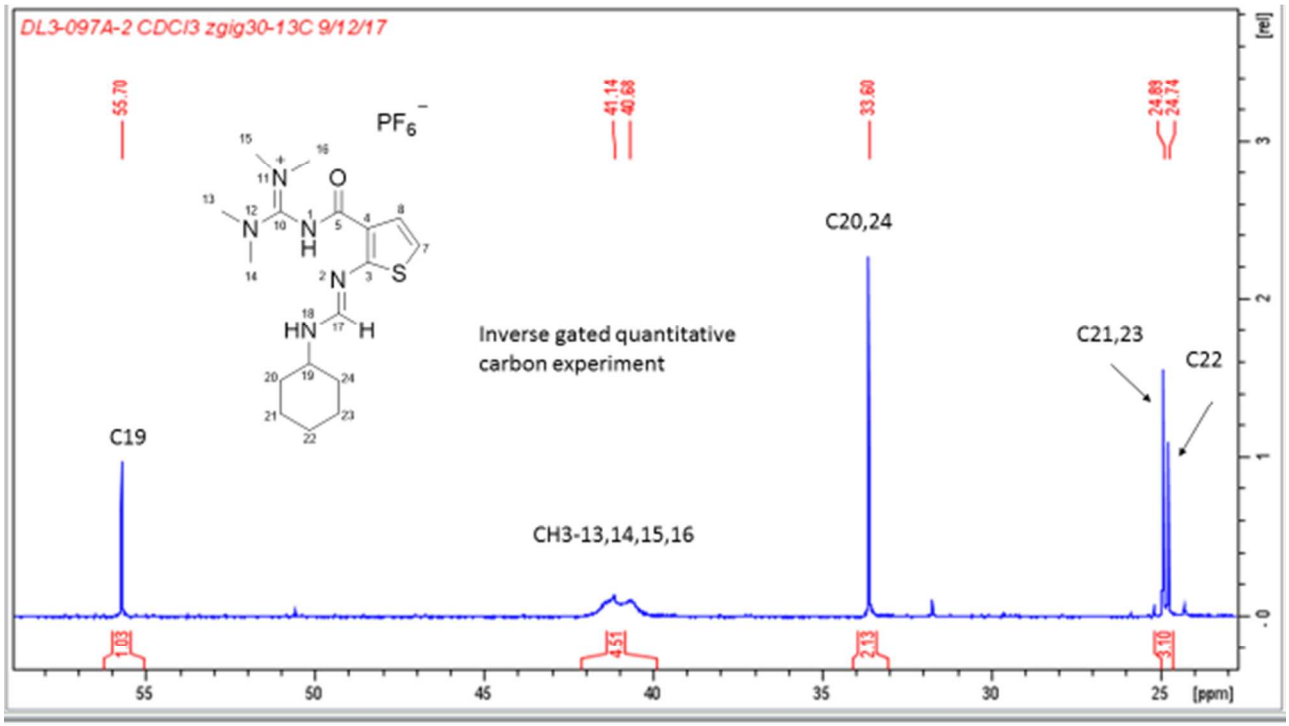


**Figure S99.** HSQC spectra of compound **10.**

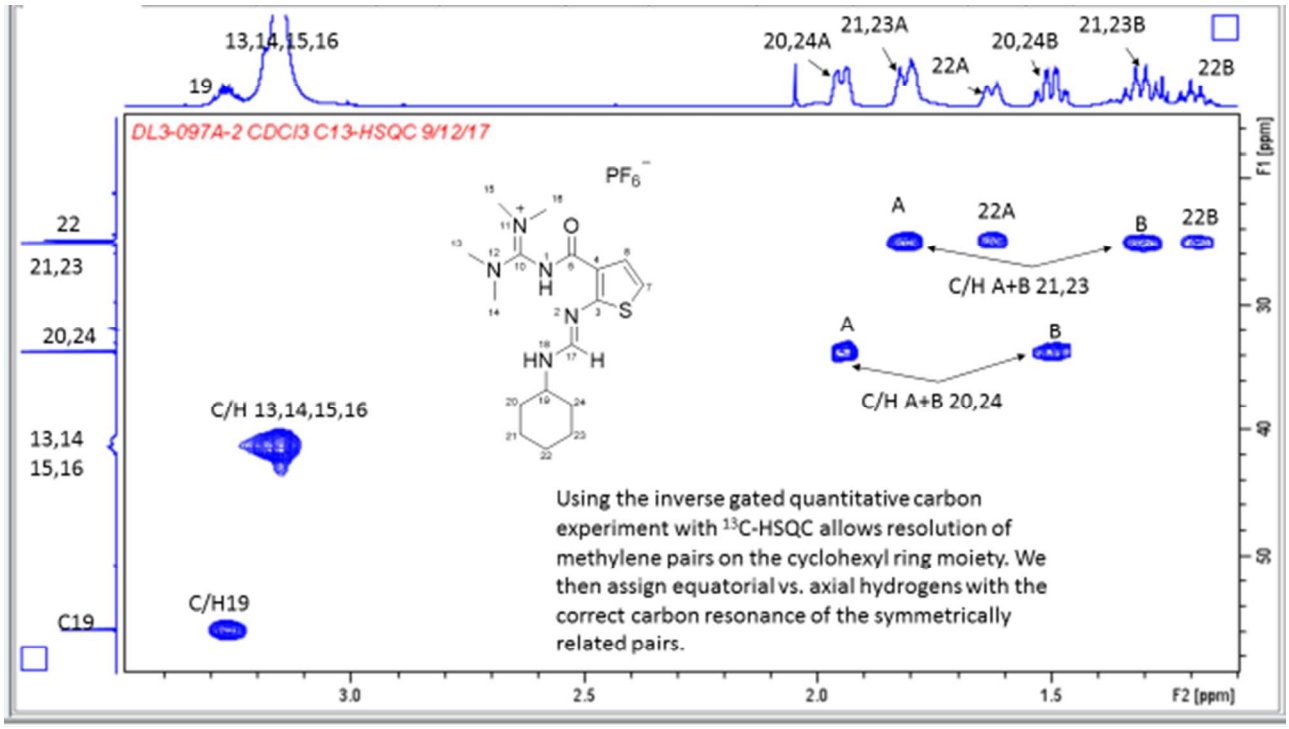



**Figure S100.** 10 Hz long range $^{15}$N-HMBC spectra of compound **10**.

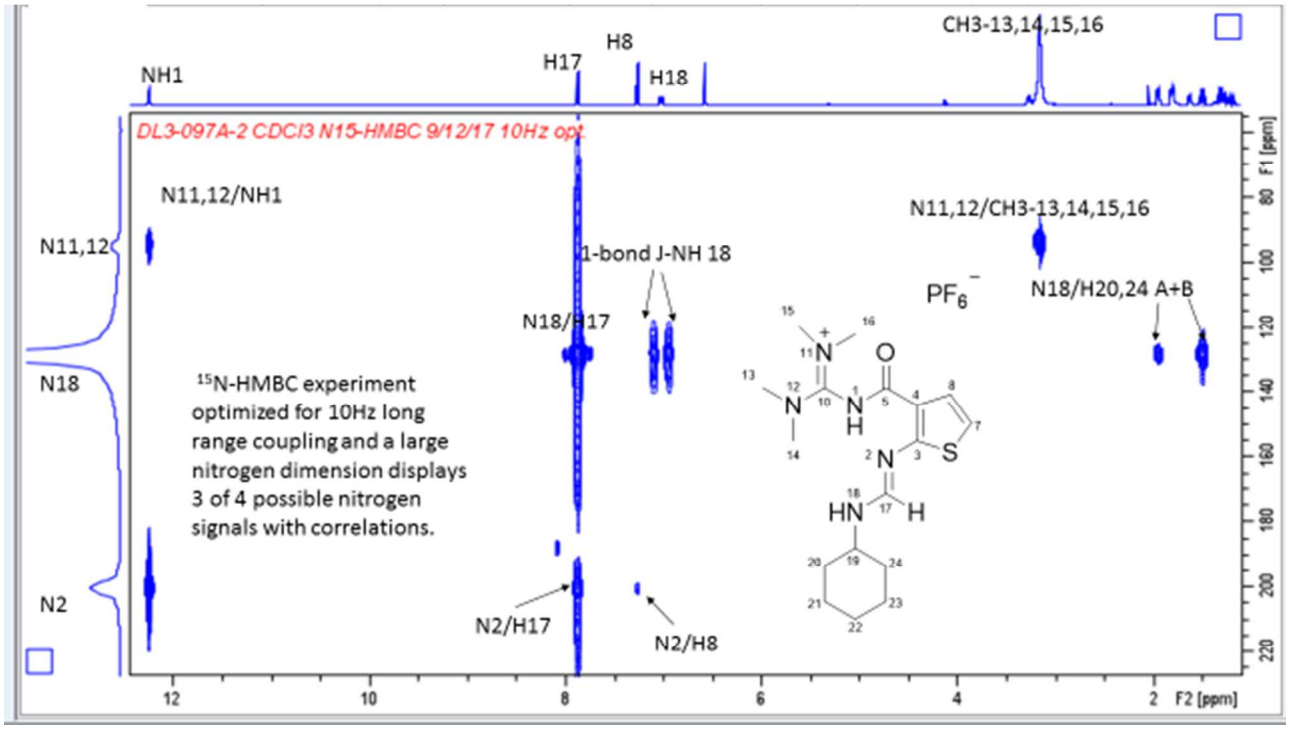


**Figure S101.** 3 Hz long range $^{15}$N-HMBC spectra of compound **10**.

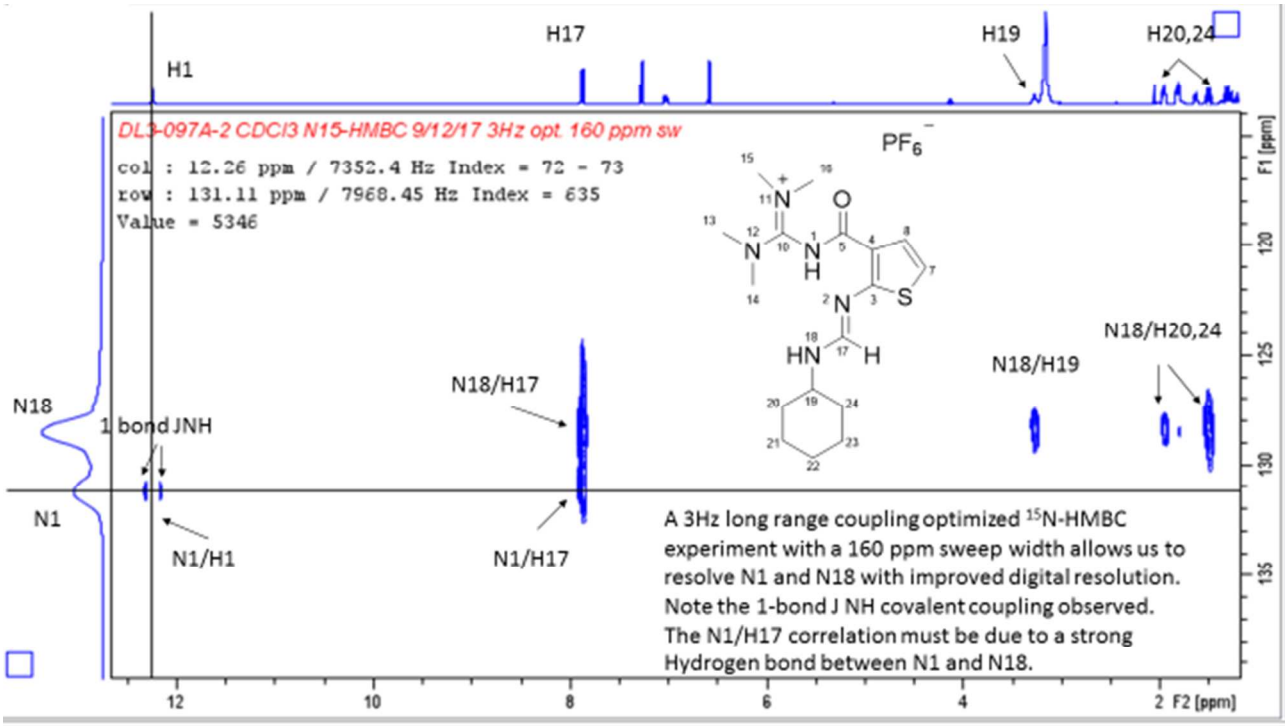
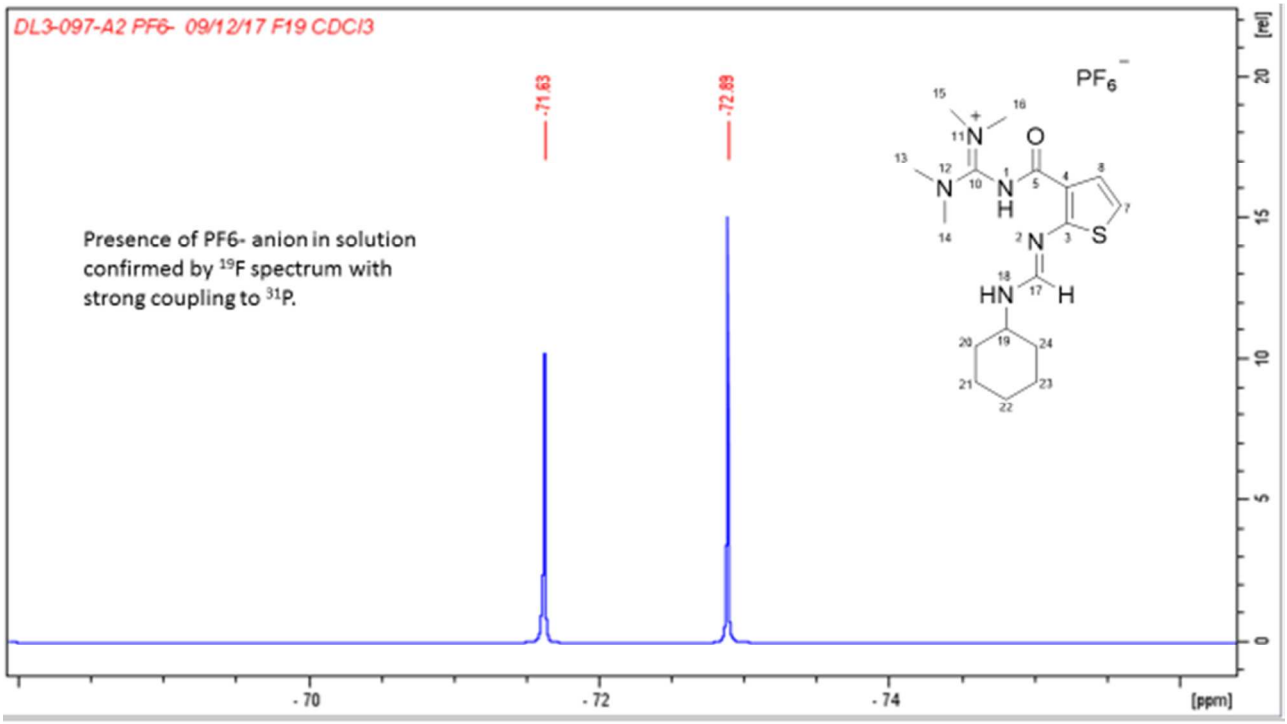



**Figure S102.** $^{19}$F NMR spectra of compound **10**.



## References


1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. *J. Appl. Cryst*. **2009**, *42*, 339–341.
2. Sheldrick, G.M. *Acta Cryst*. **2008**, *A64*, 112–122.
3. Sheldrick, G.M. *Acta Cryst*. **2015**, *C71*, 3–8.