

ANEXOS

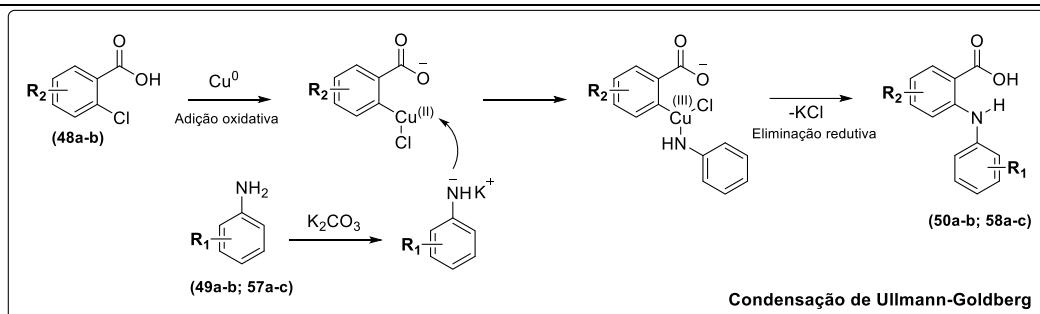


Figura S1. Esquema de intermediários proposto para formação dos ácidos *N*-fenilantranílicos.

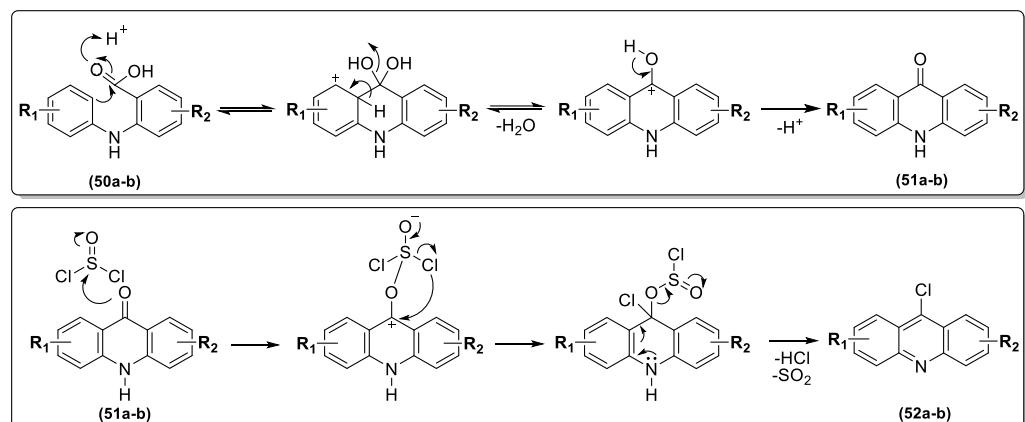


Figura S2. Esquema de intermediários proposto para formação do núcleo acridínico (Rota A).

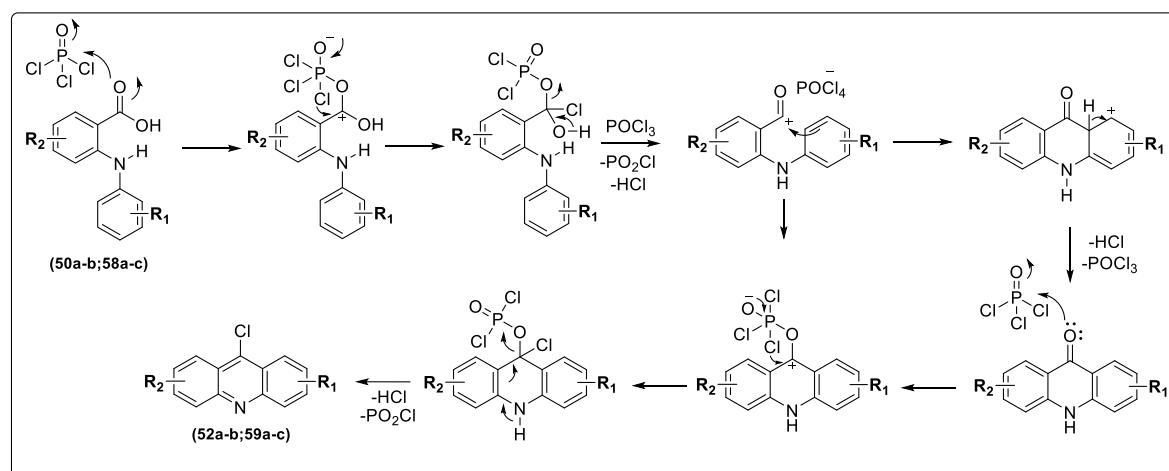


Figura S3. Esquema de intermediários proposto para formação do núcleo acridínico (Rota B).

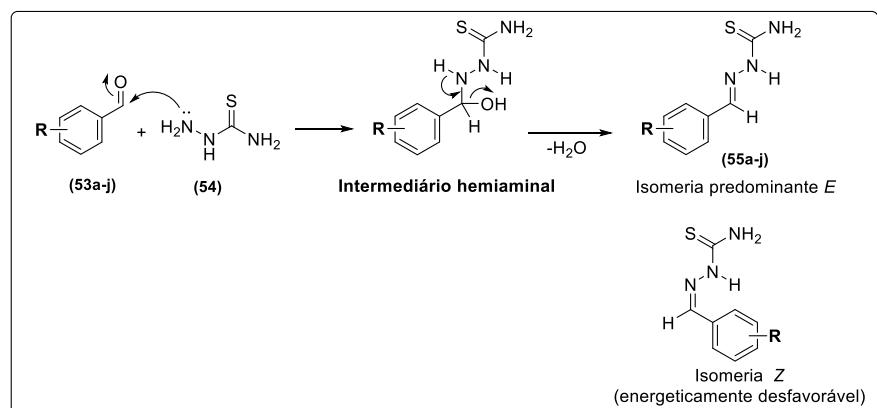


Figura S4. Esquema de intermediários proposto para formação dos intermediários tiossemicarbazônicos.

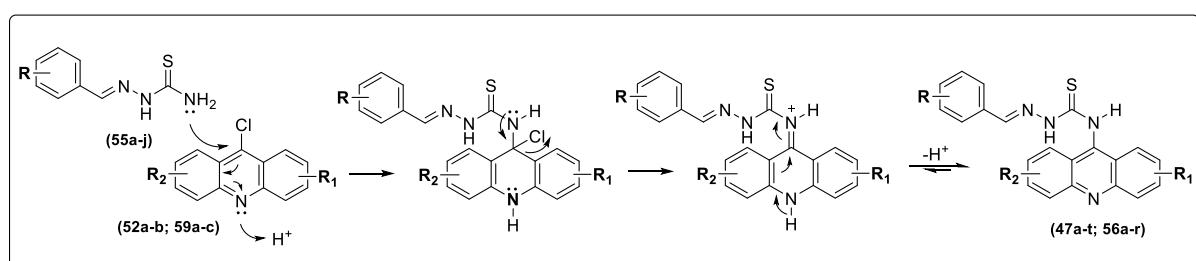


Figura S5. Esquema de intermediários proposto para formação dos novos derivados tiossemicarbazono-acridínicos.

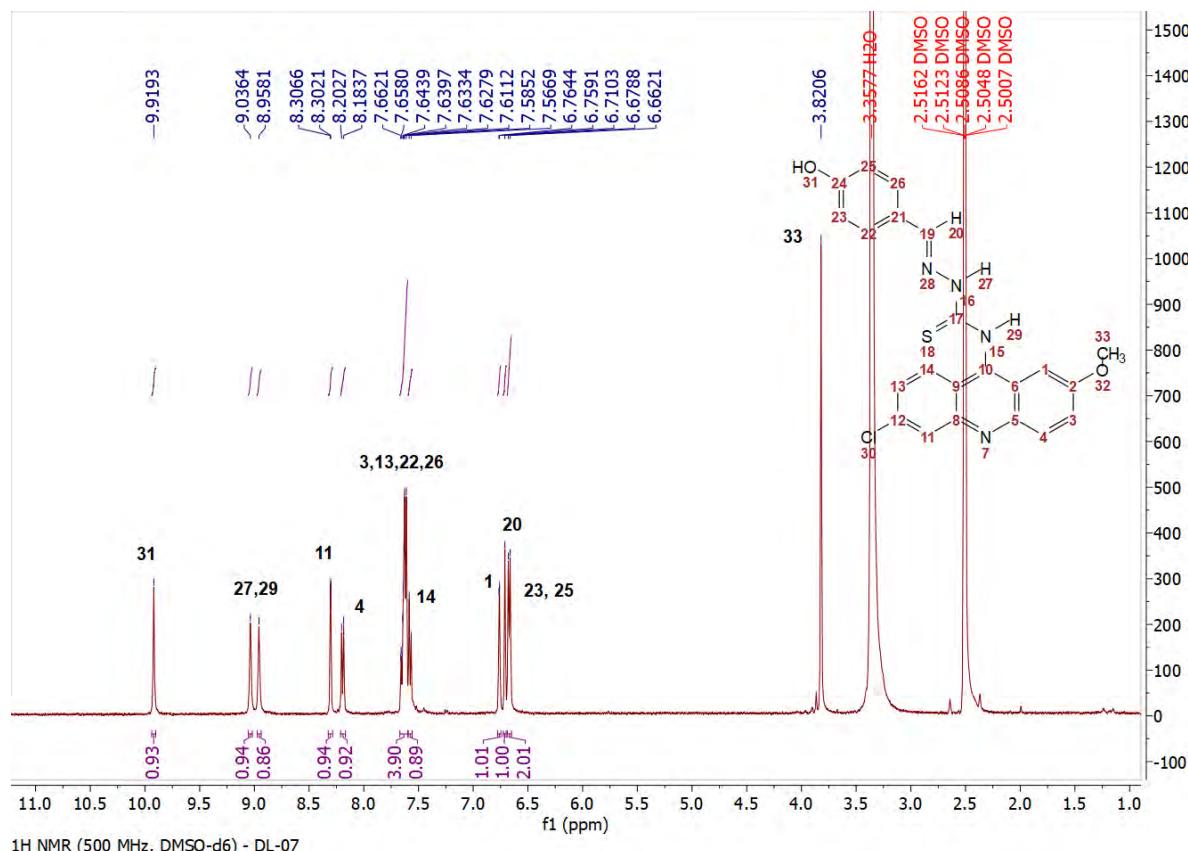


Figura S6. Espectro de RMN ^1H do DL-07.

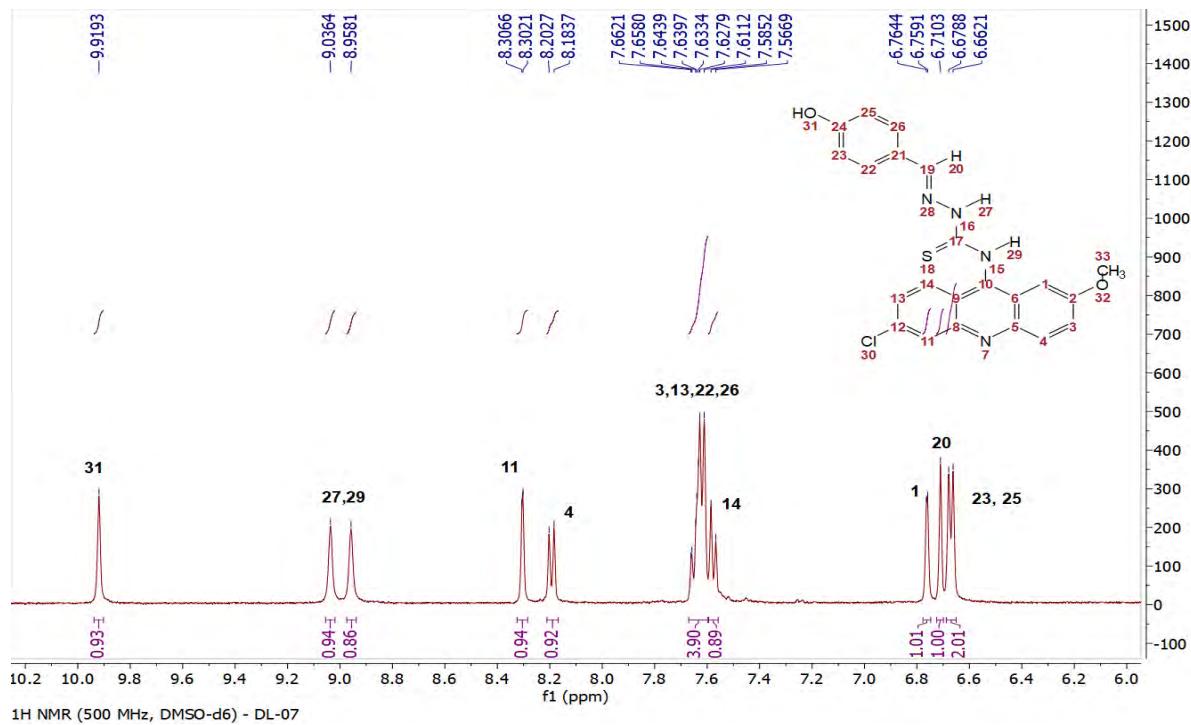


Figure S7. Expansão do espectro de RMN ¹H do DL-07.

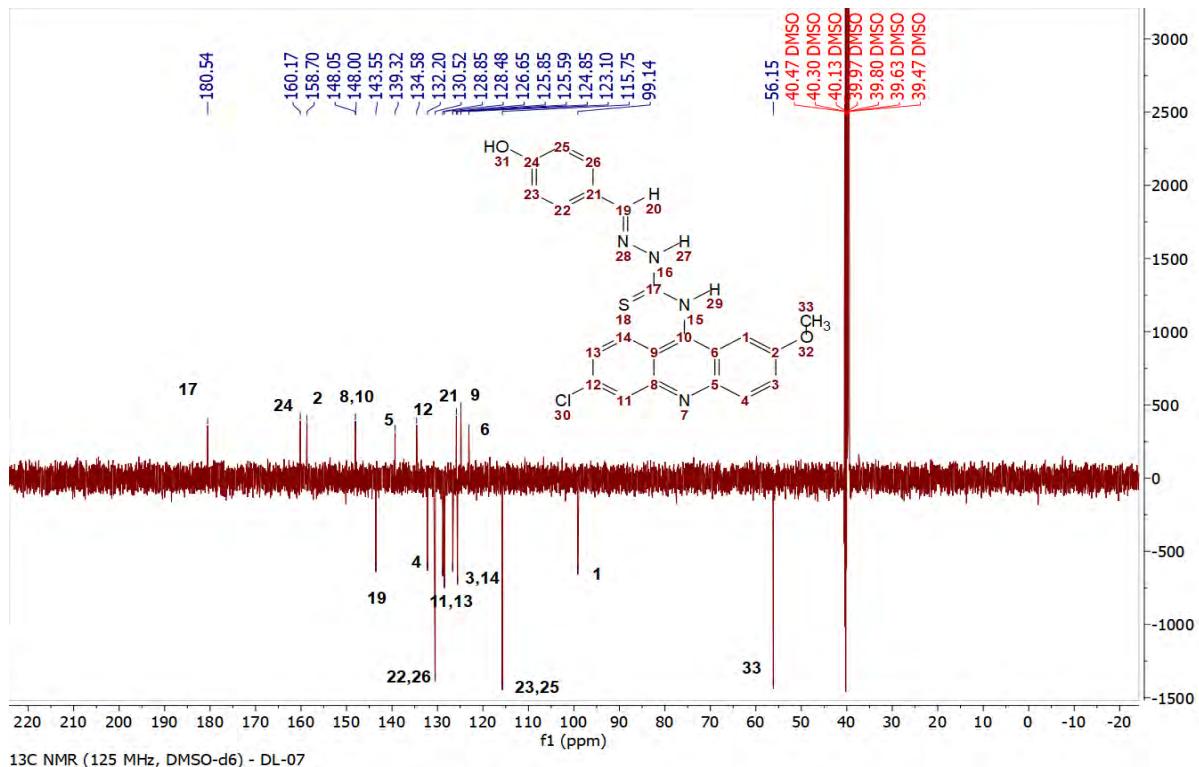


Figure S8. Espectro de RMN ¹³C do DL-07.

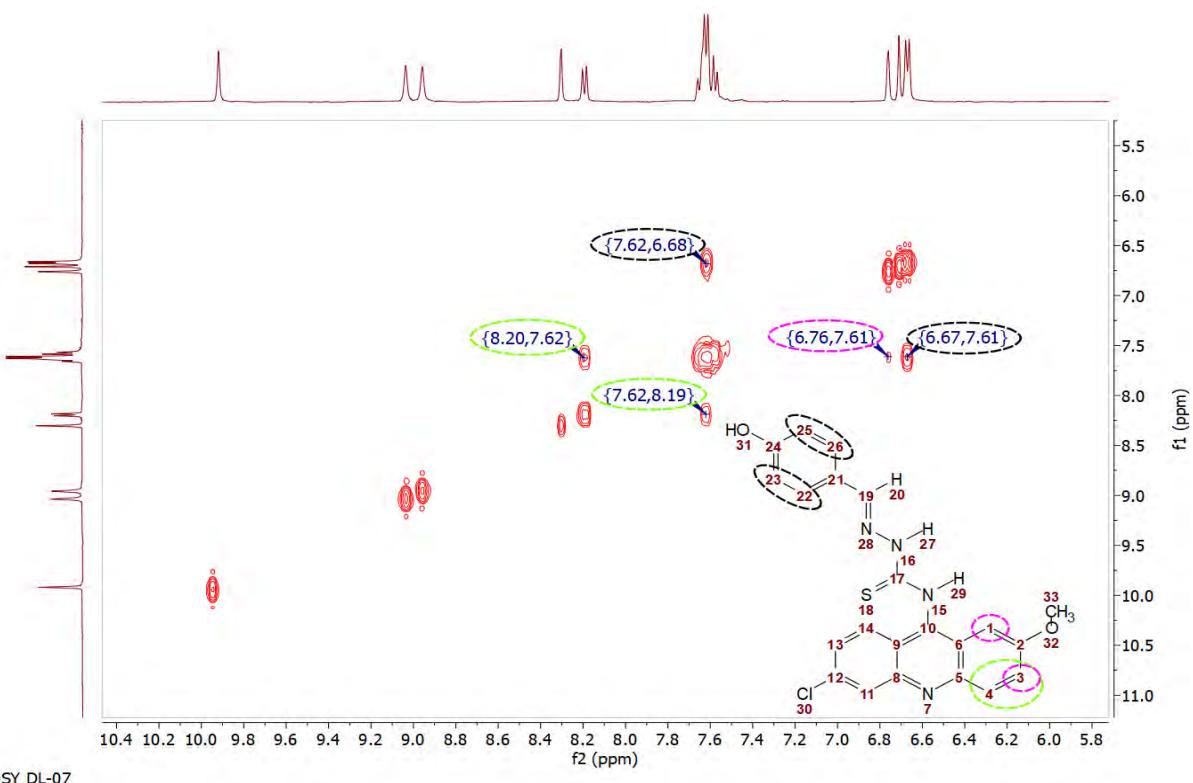


Figure S9. Espectro de correlação COSY do **DL-07**.

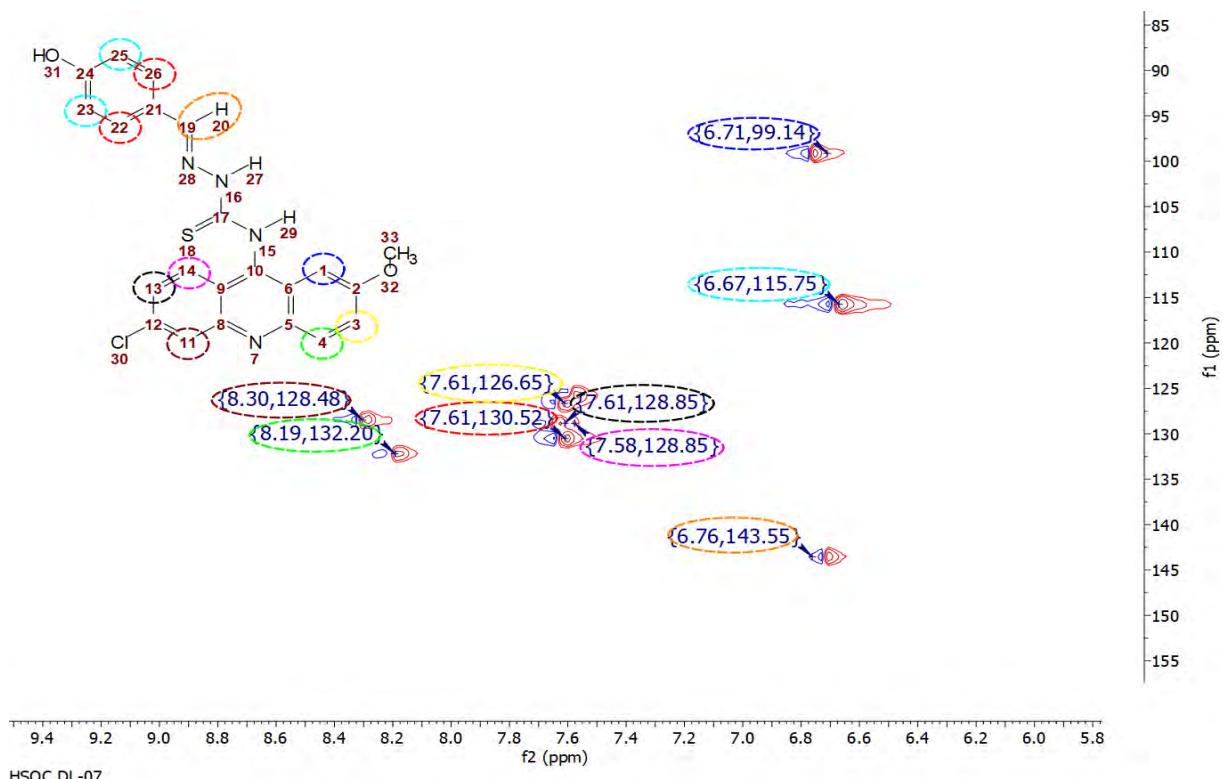


Figure S10. Espectro de correlação HSQC do **DL-07**.

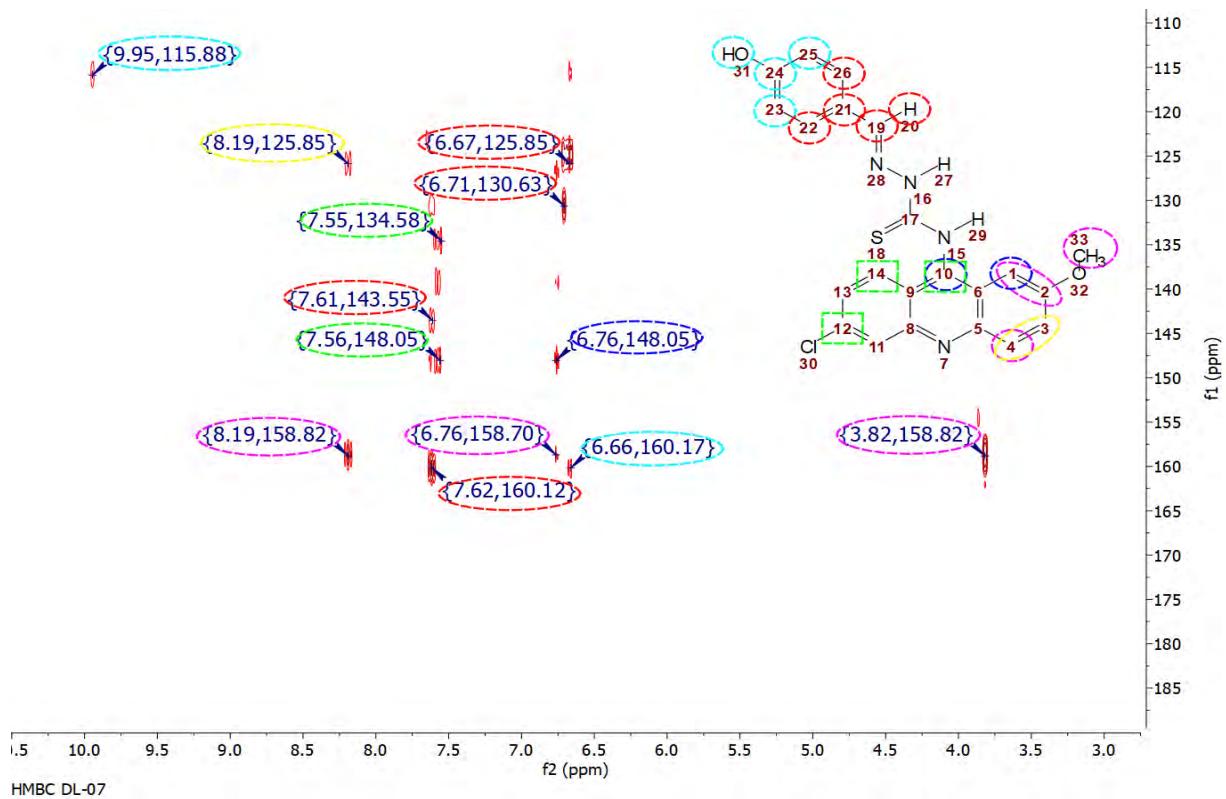


Figure S11. Espectro de correlação HMBC do **DL-07**.

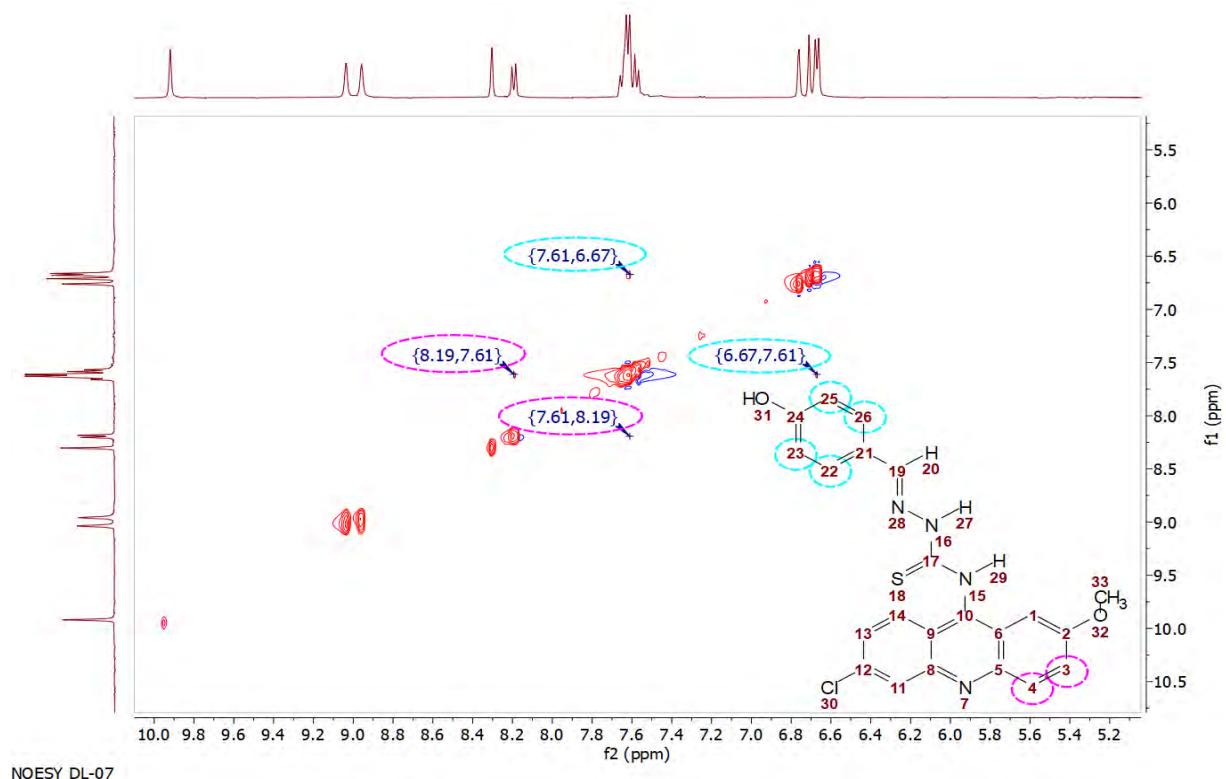


Figura S12. Espectro de correlação NOESY do **DL-07**.

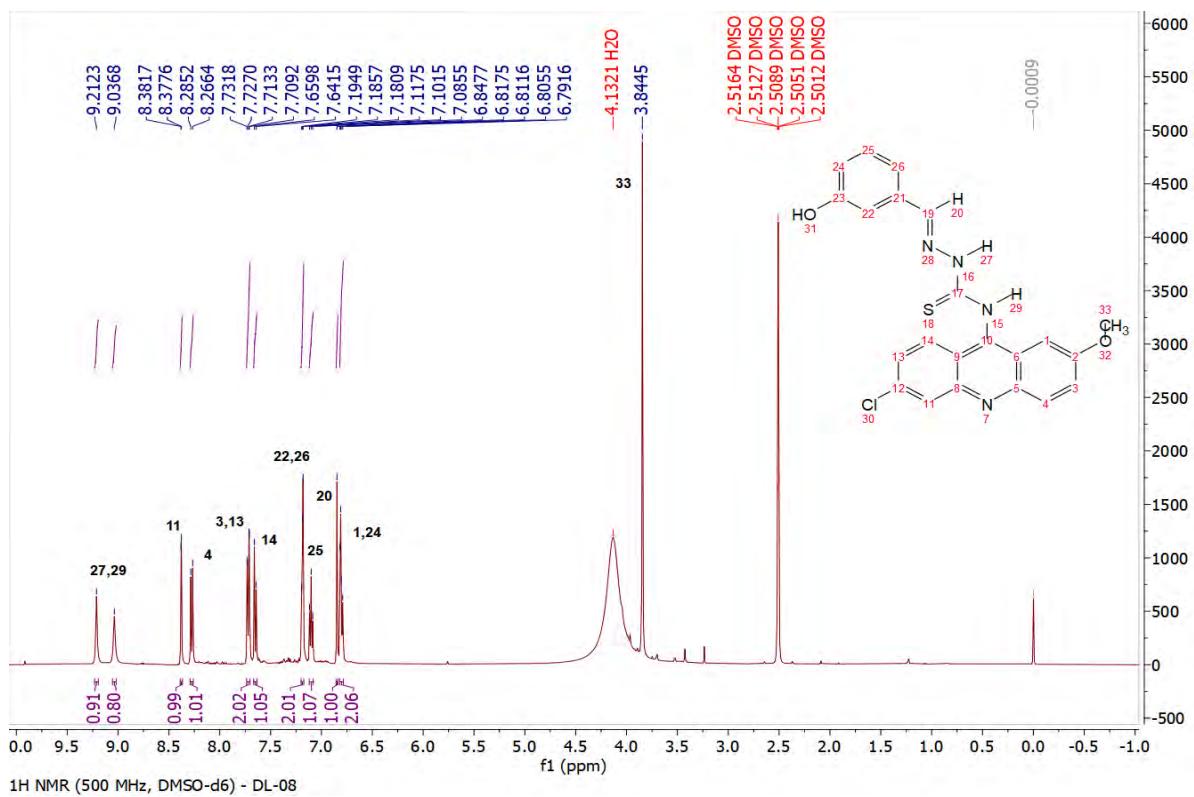


Figura S13. Espectro de RMN ¹H do DL-08.

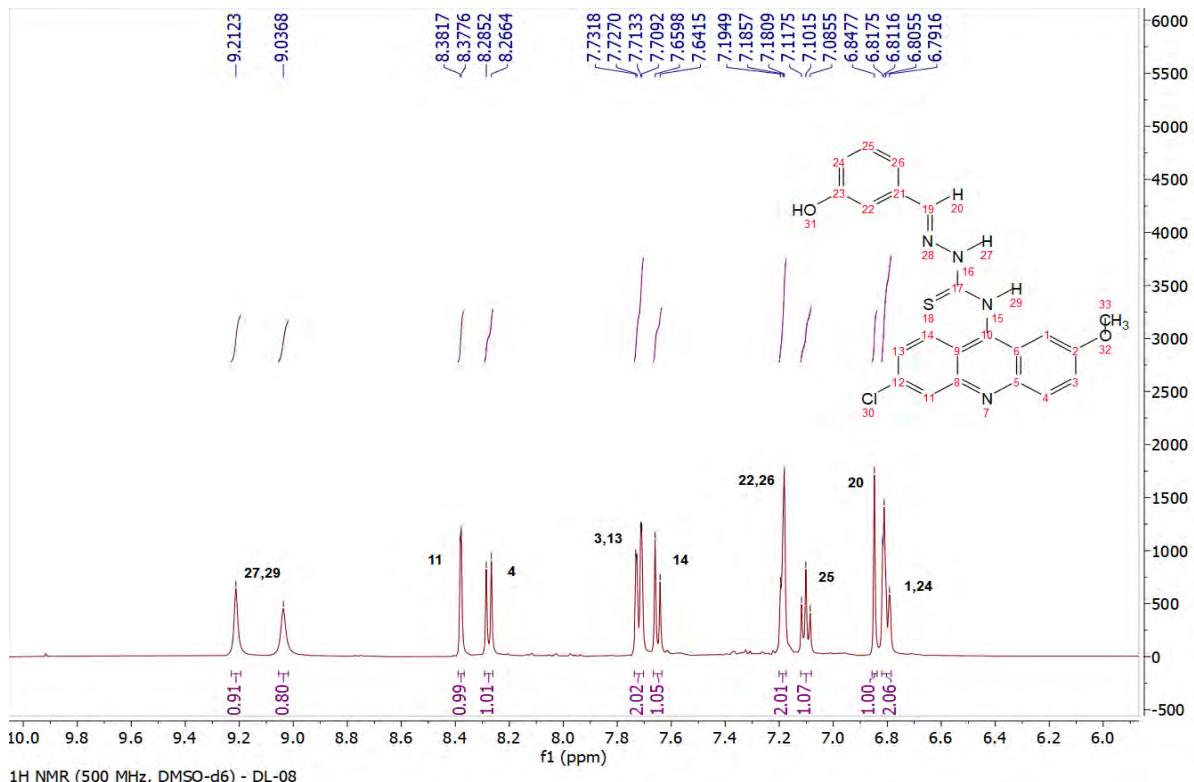


Figura S14. Expansão do espectro de RMN ¹H do DL-08.

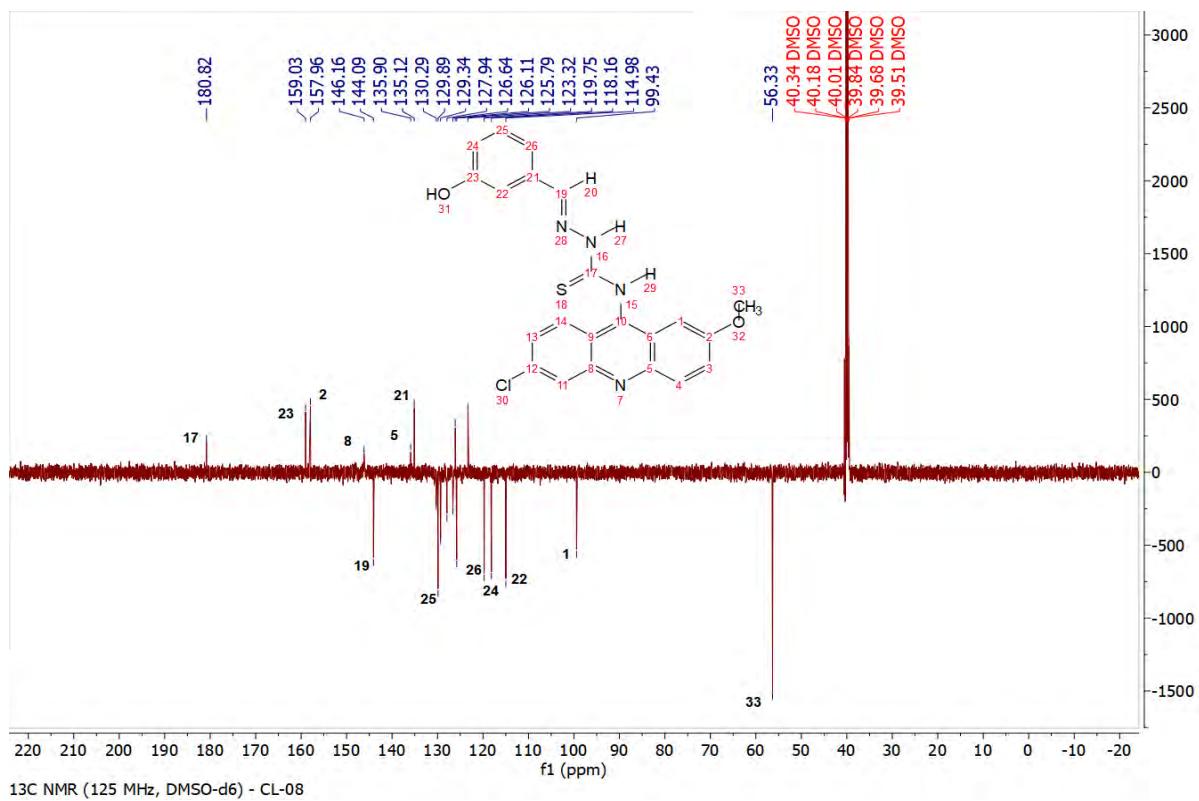


Figura S15. Espectro de RMN ¹³C do DL-08.

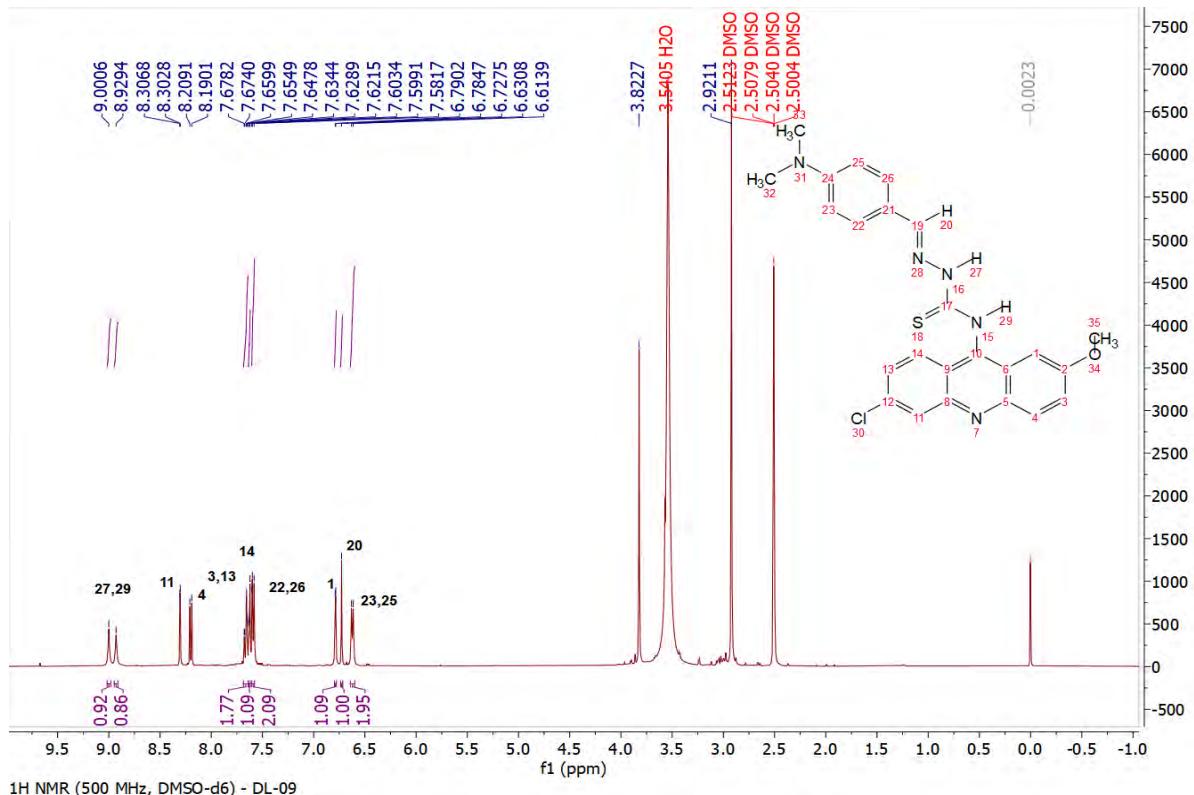


Figura S16. Espectro de RMN ¹H do DL-09.

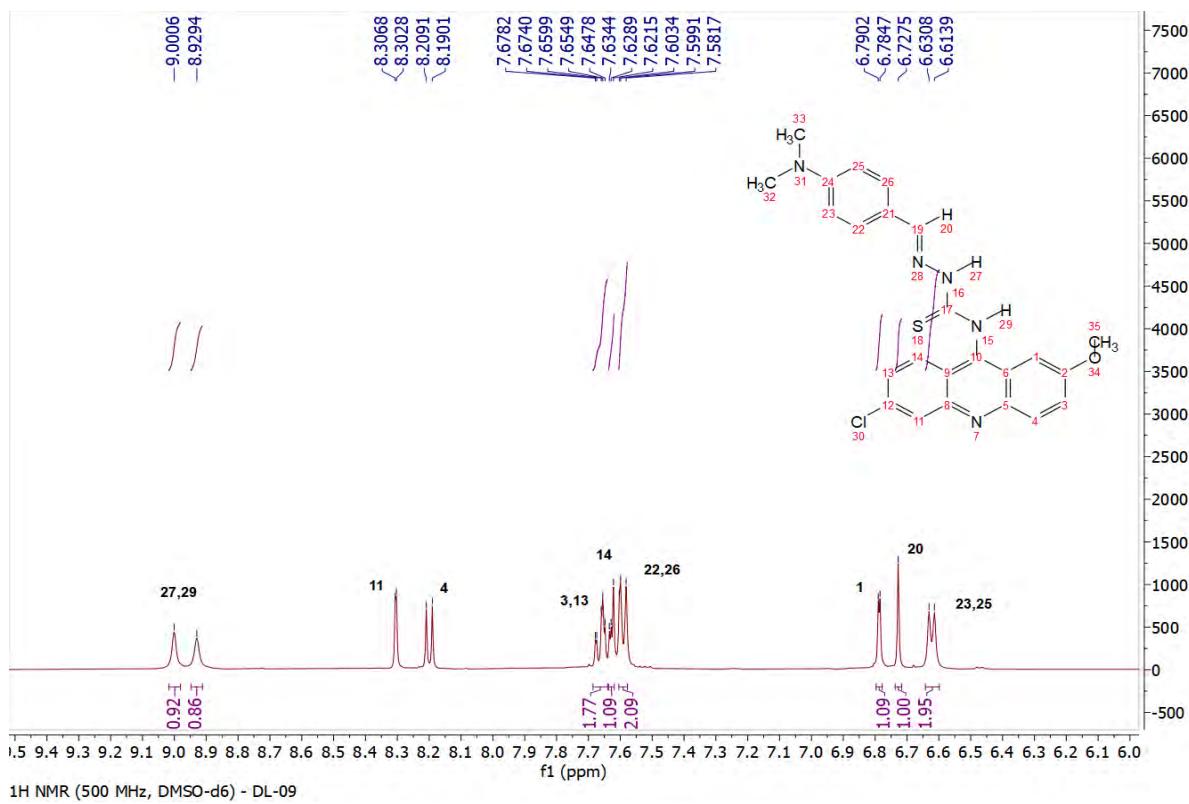


Figura S17. Expansão do espectro de RMN ¹H do **DL-09**.

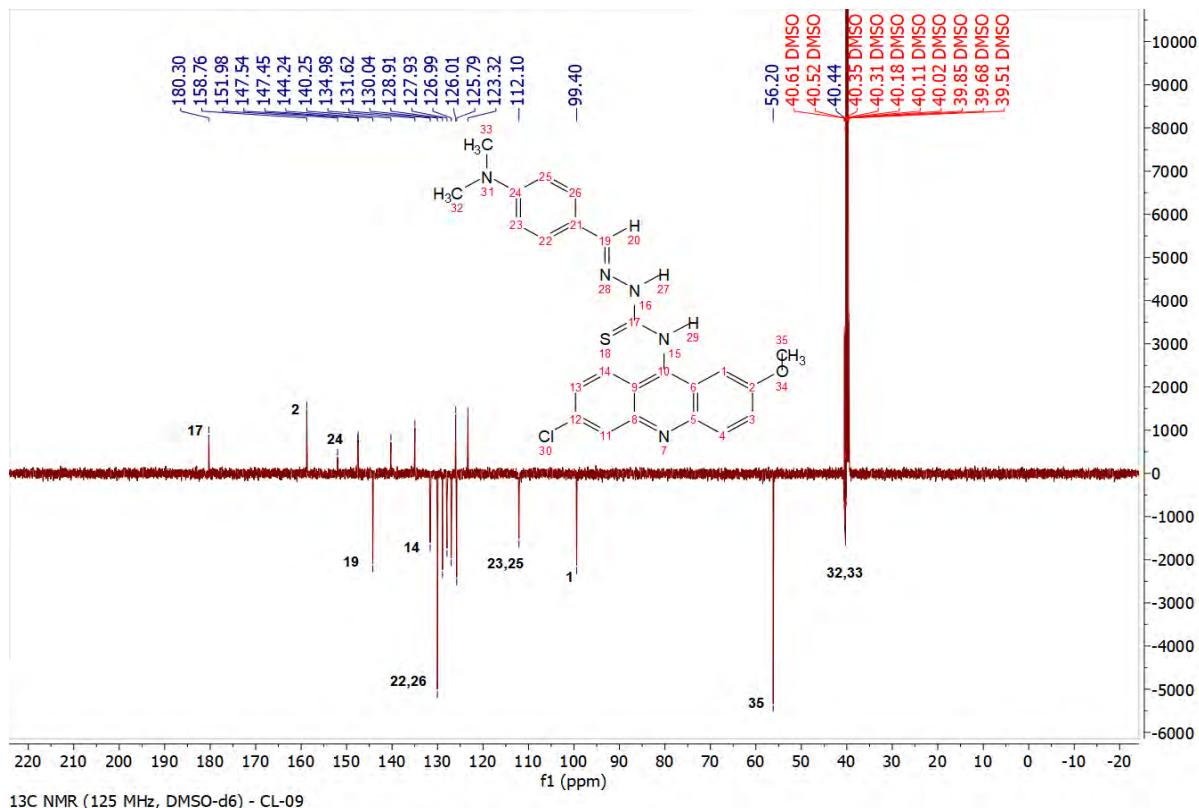


Figure S18. Espectro de RMN ¹³C do **DL-09**.

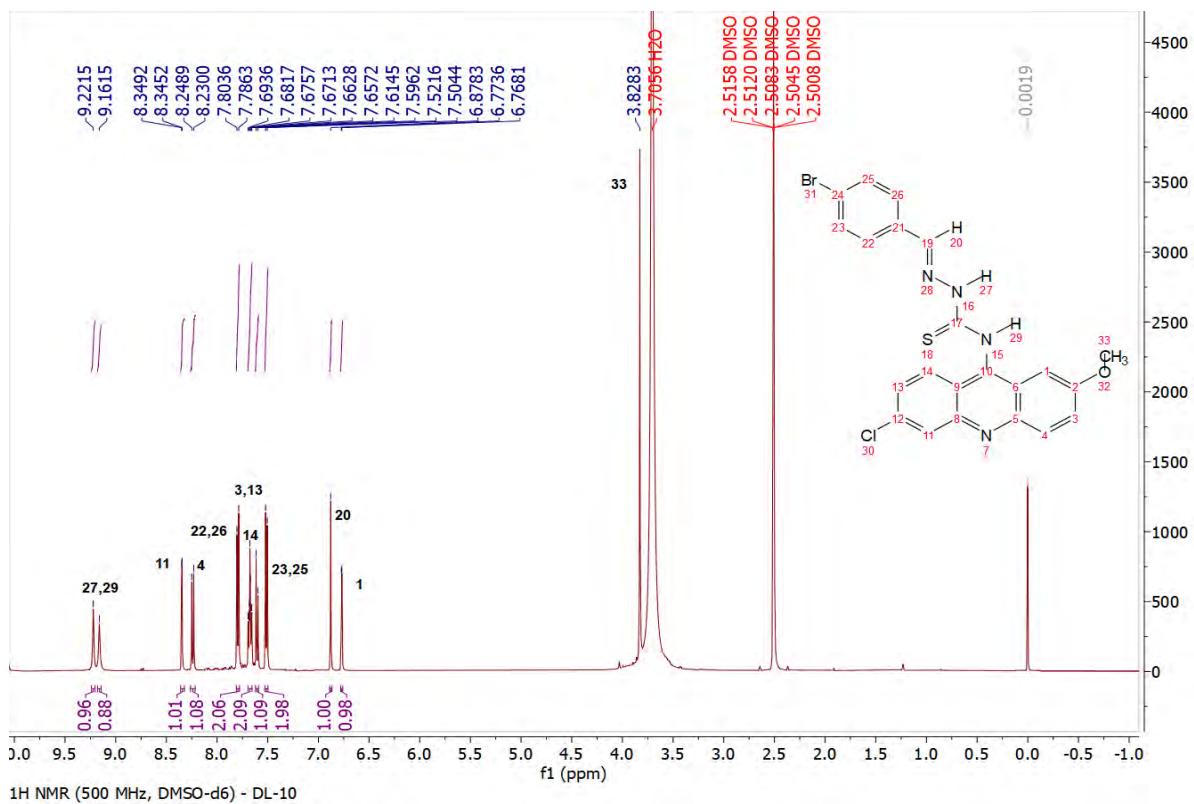


Figura S19. Espectro de RMN ^1H do DL-10.

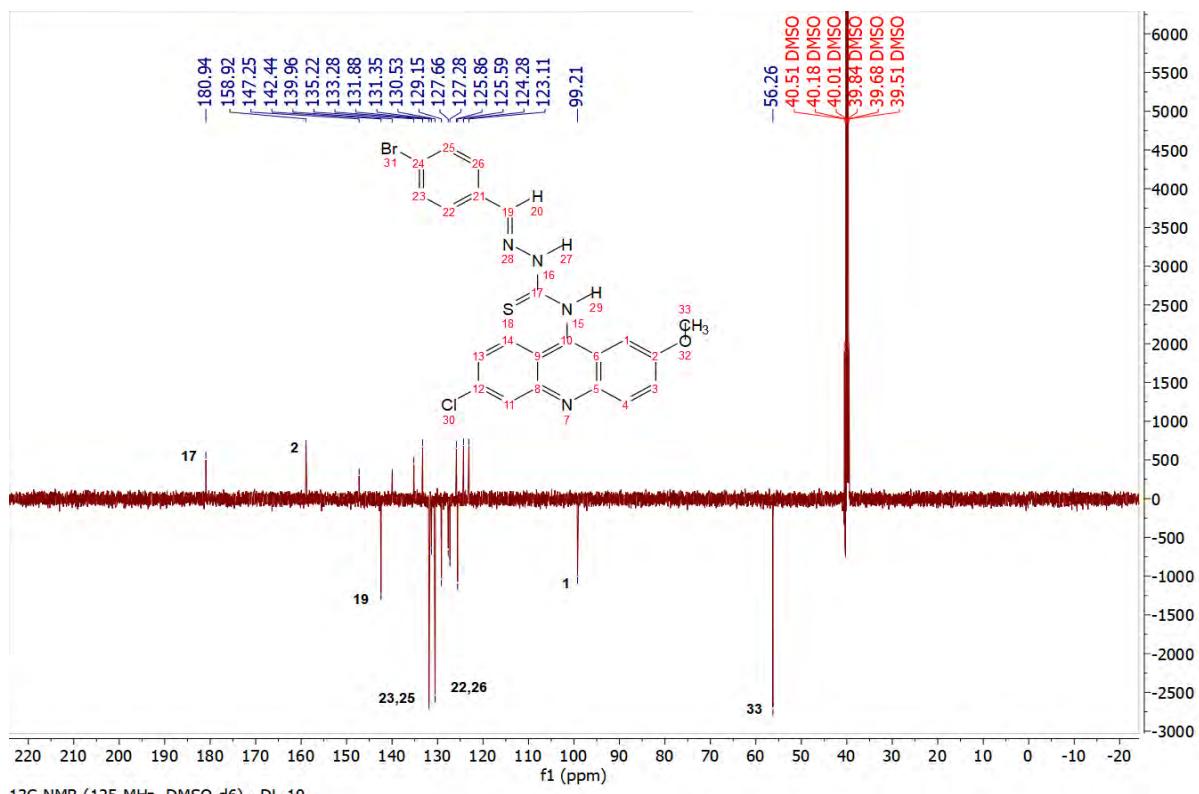


Figure S20. Espectro de RMN ^{13}C do DL-10.

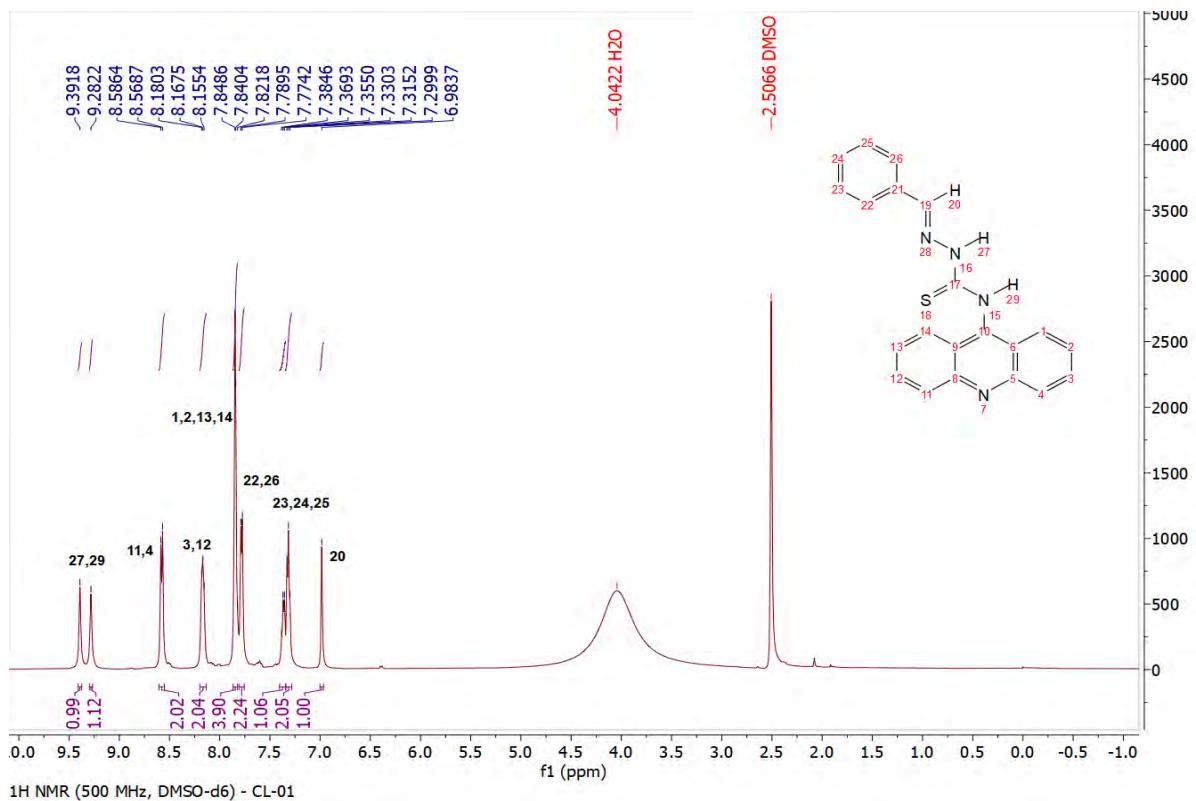


Figura S21. Espectro de RMN ¹H do CL-01.

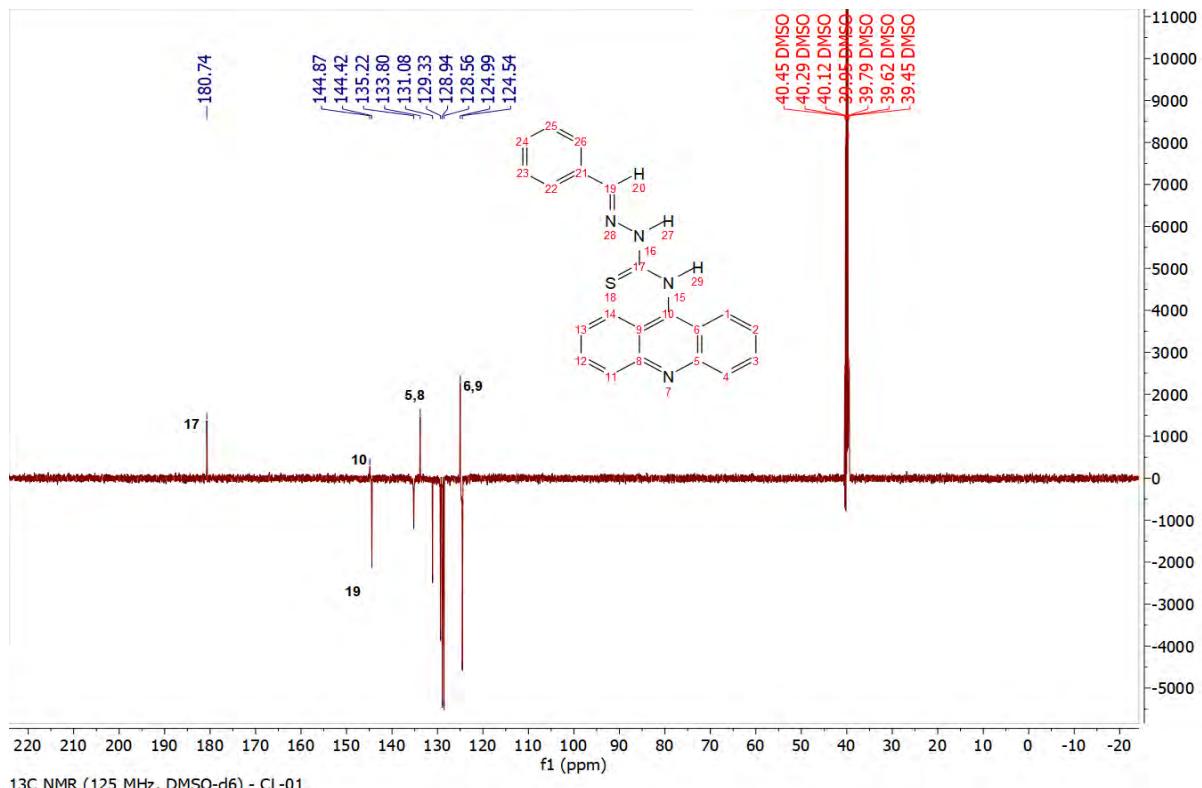


Figura S22. Espectro de RMN ¹³C do CL-01.

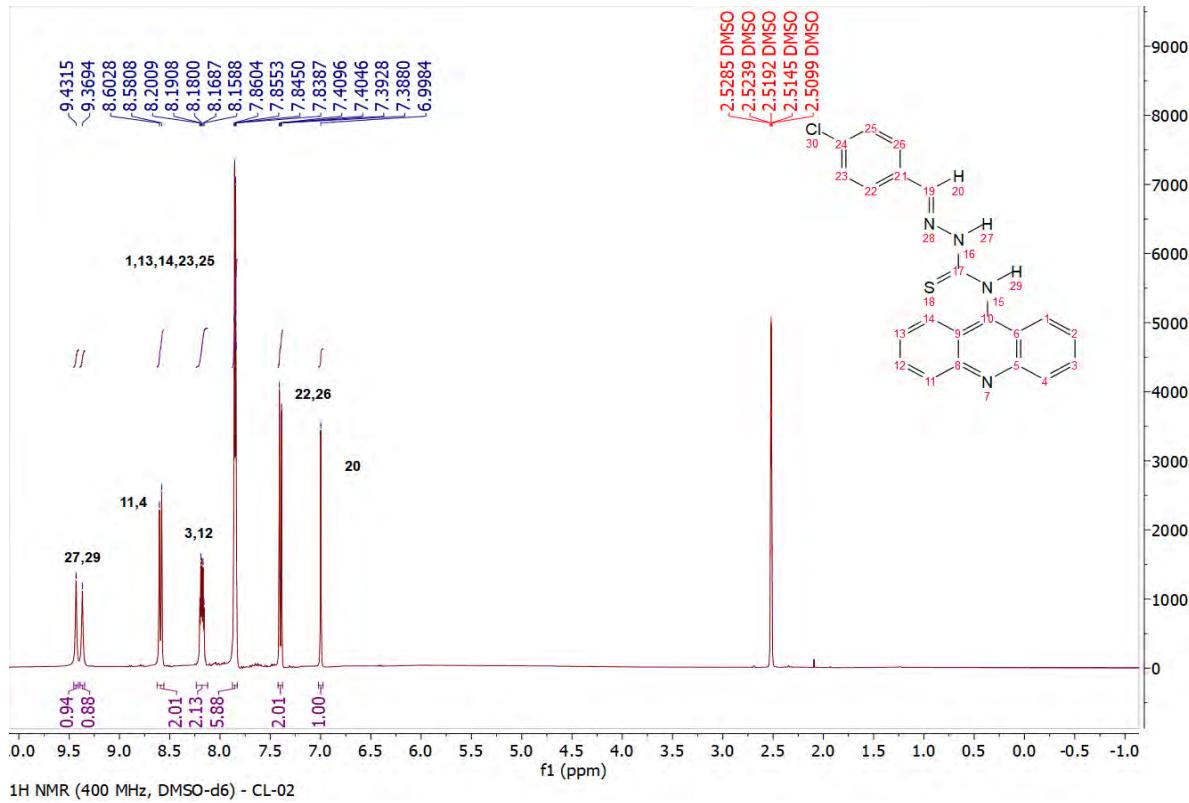


Figura S23. Espectro de RMN ¹H do CL-02.

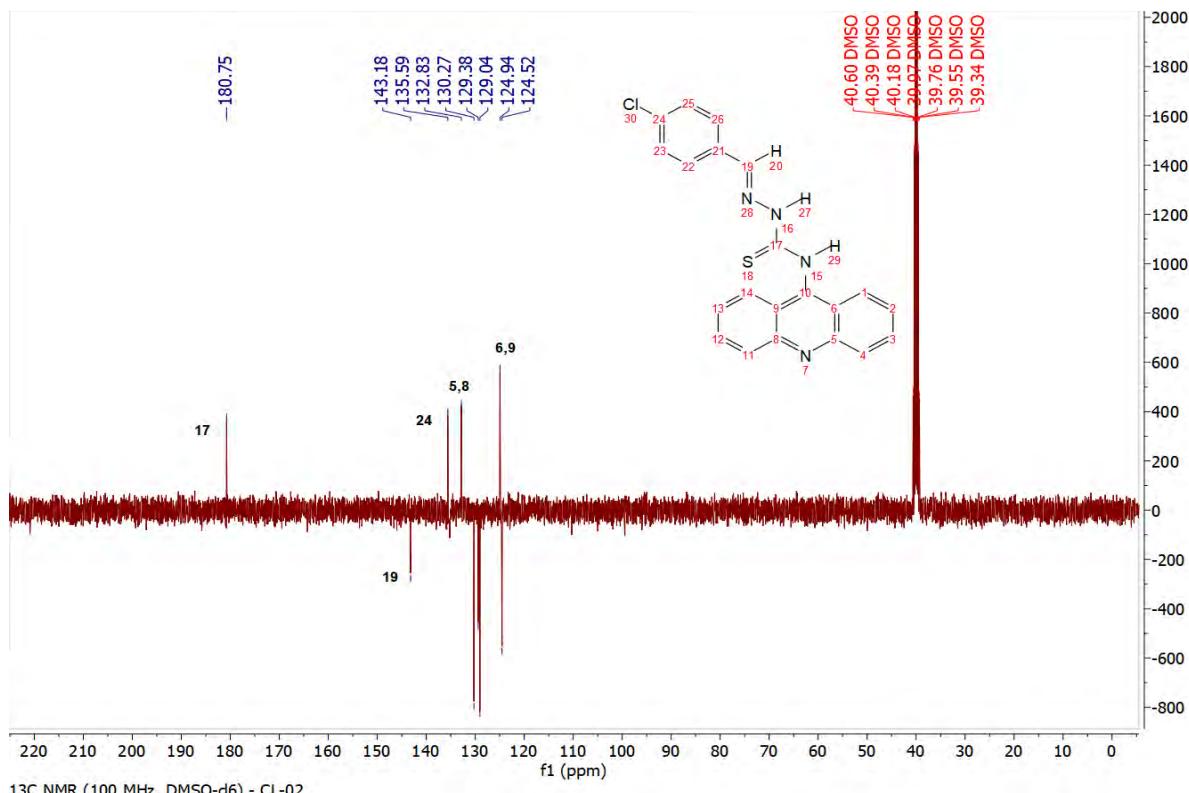


Figura S24. Espectro de RMN ¹³C do CL-02.

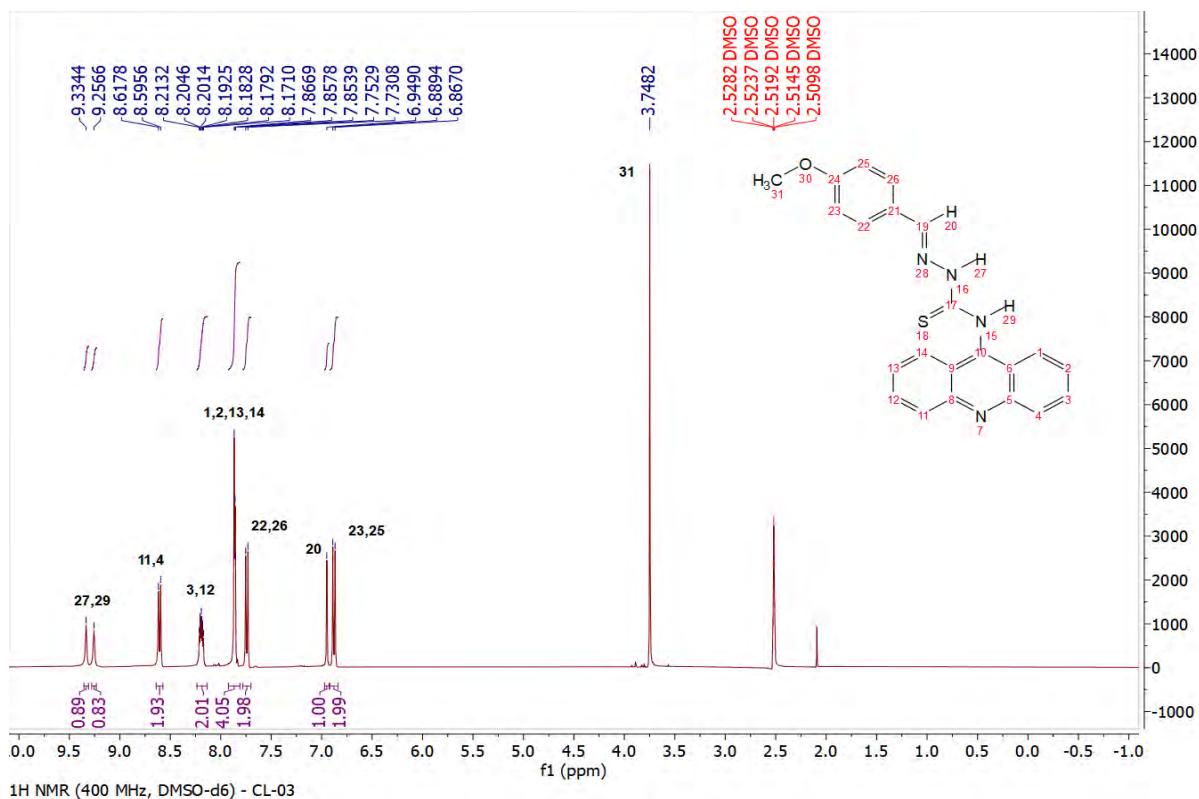


Figura S25. ¹H NMR spectrum of CL-03.

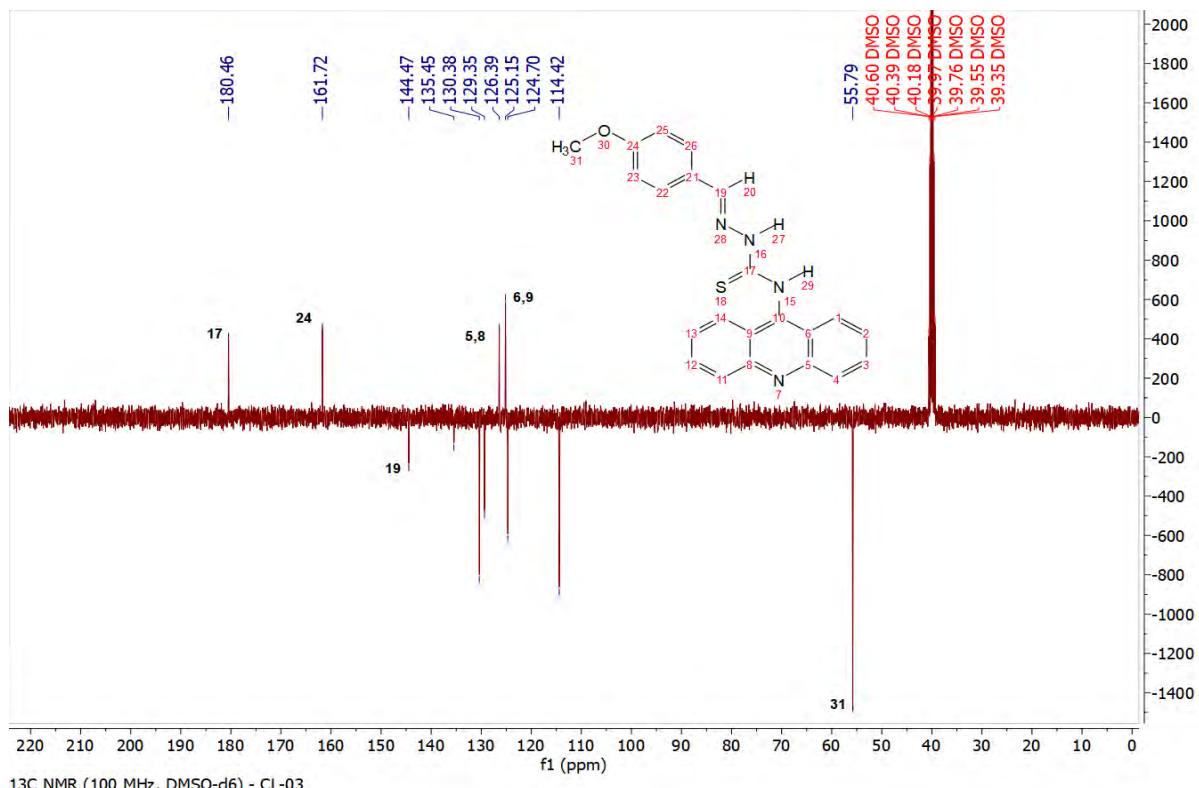


Figura S26. Espectro de RMN ¹³C do CL-03.

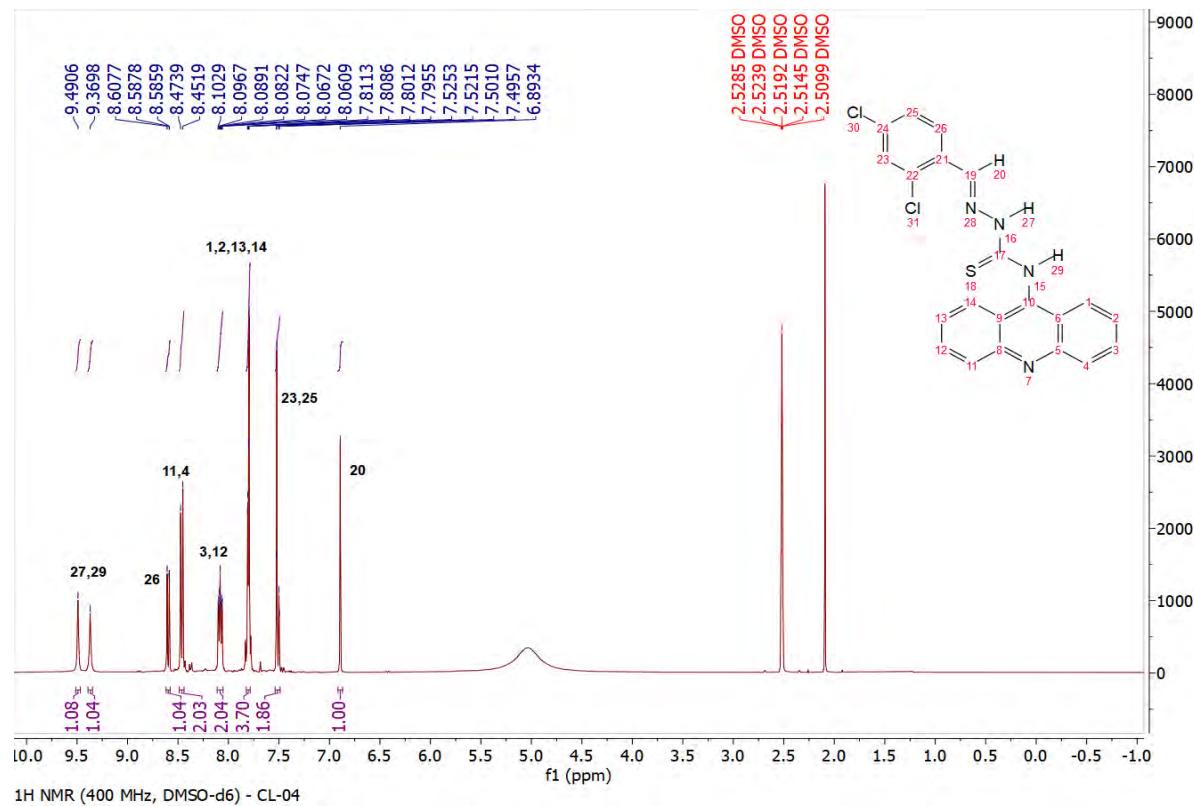


Figura S27. Espectro de RMN ^1H do CL-04.

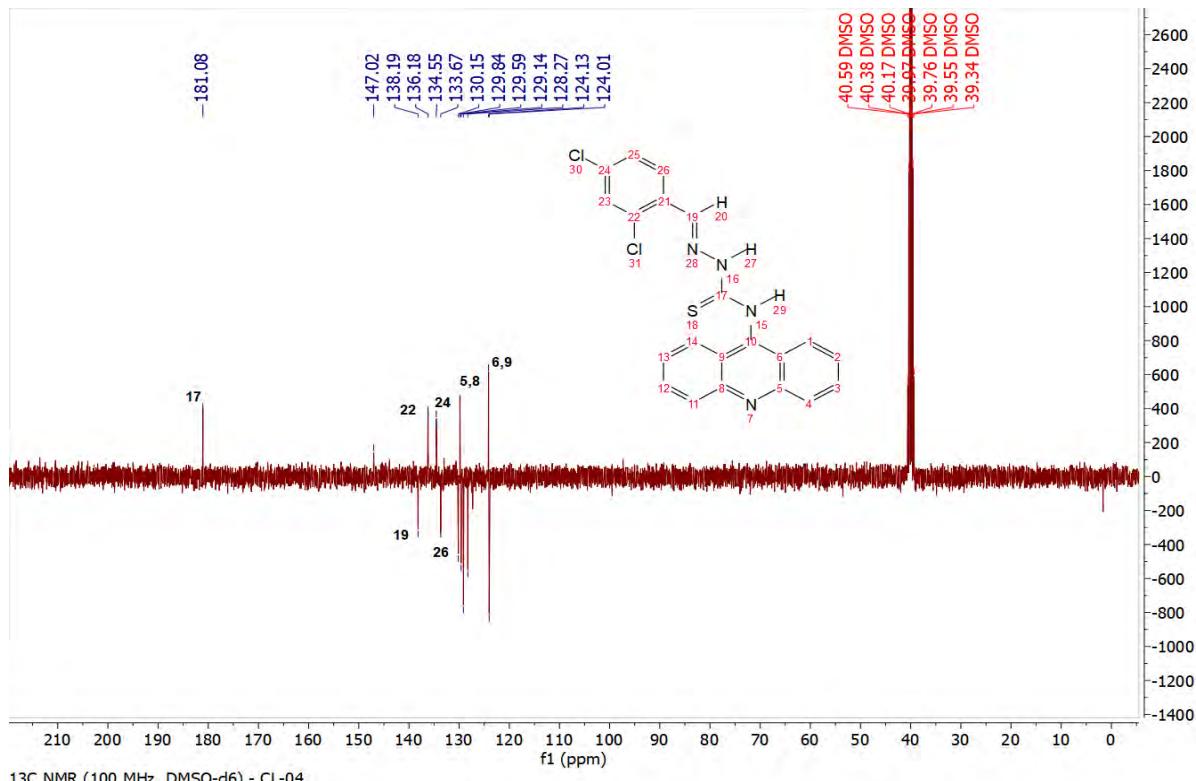


Figura S28. Espectro de RMN ^{13}C do CL-04.

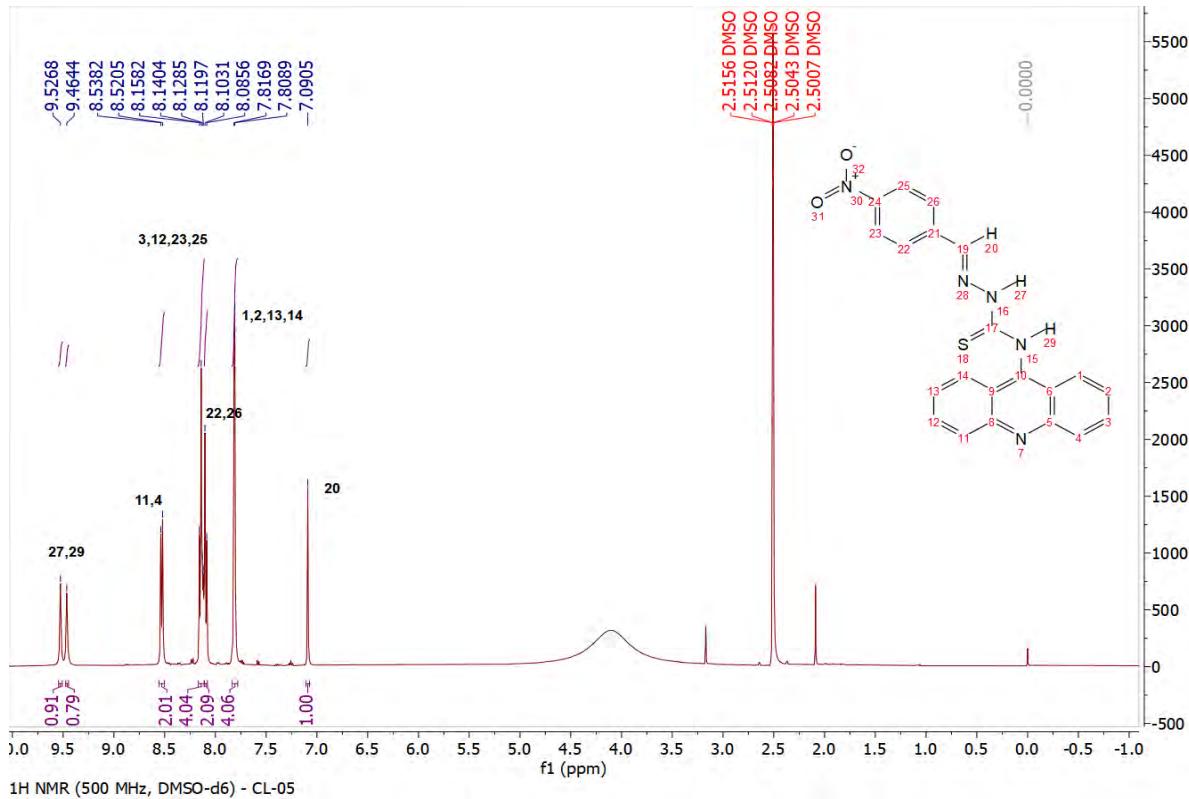


Figura S29. Espectro de RMN ^1H do CL-05.

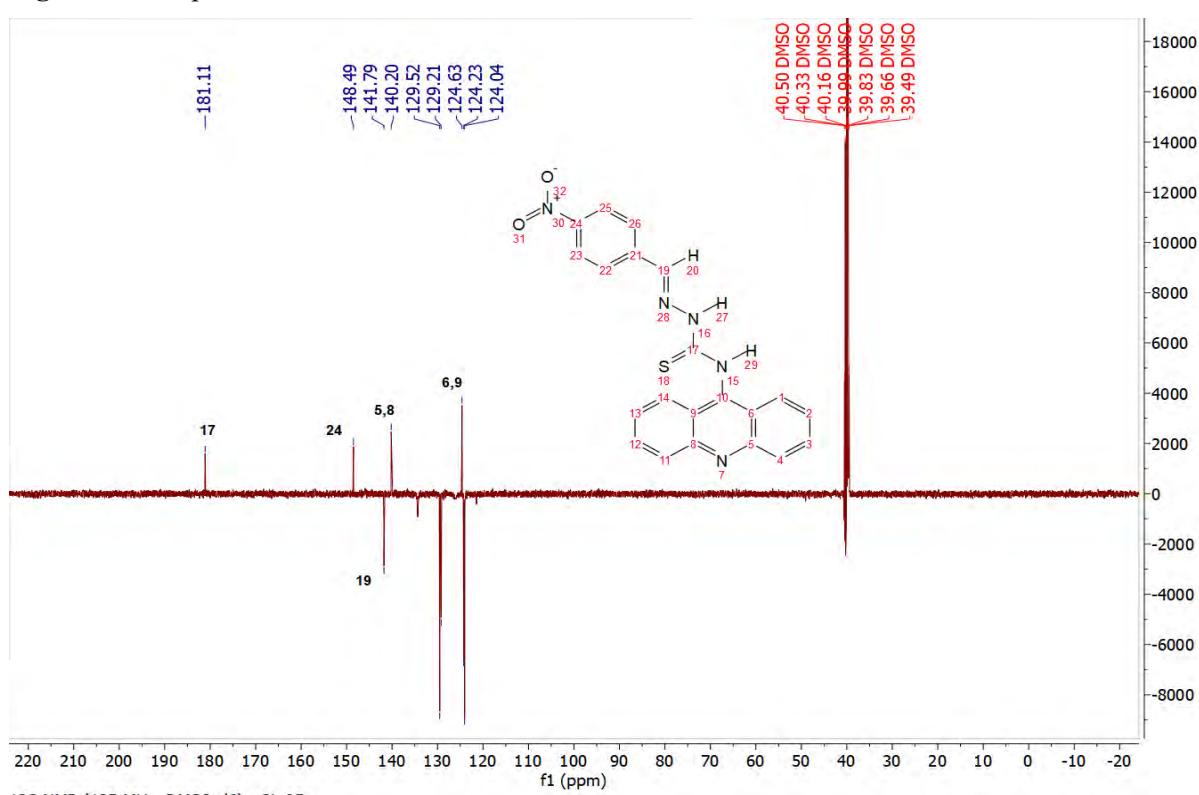


Figura S30: Espectro de RMN ^{13}C do CL-05.

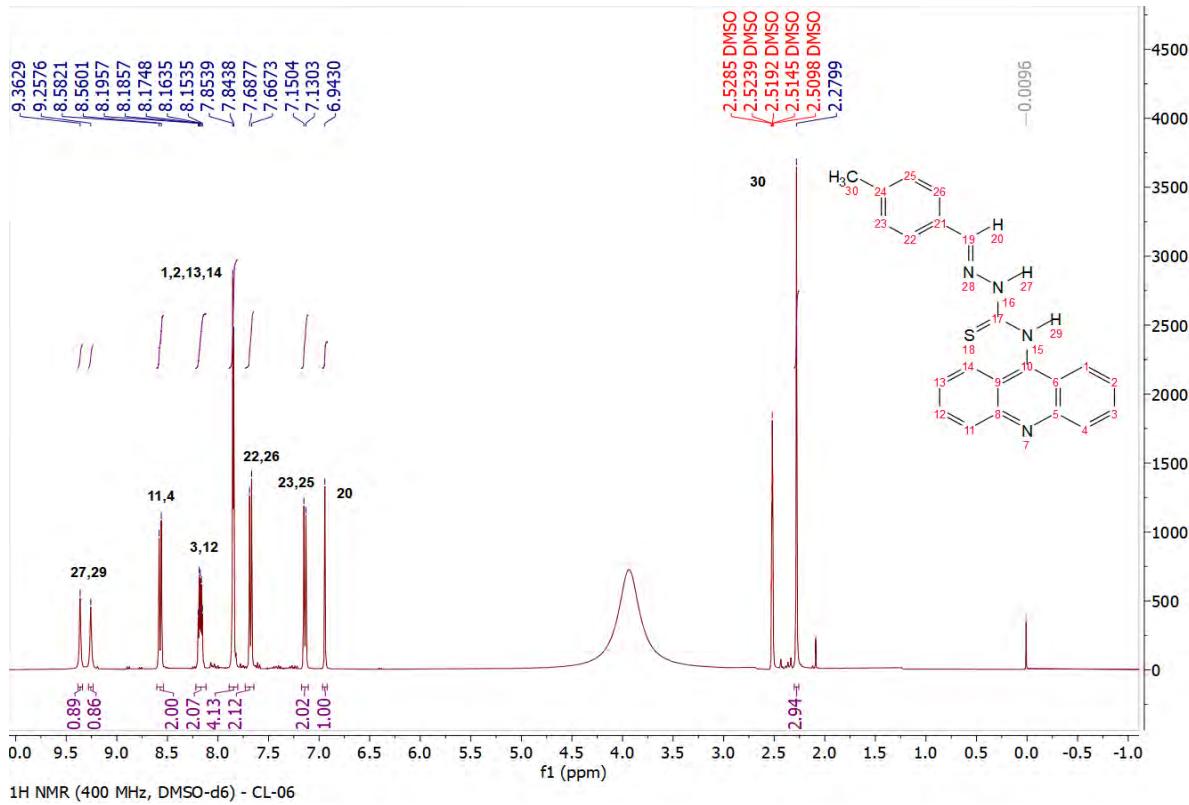


Figura S31. Espectro de RMN ¹H do CL-06.

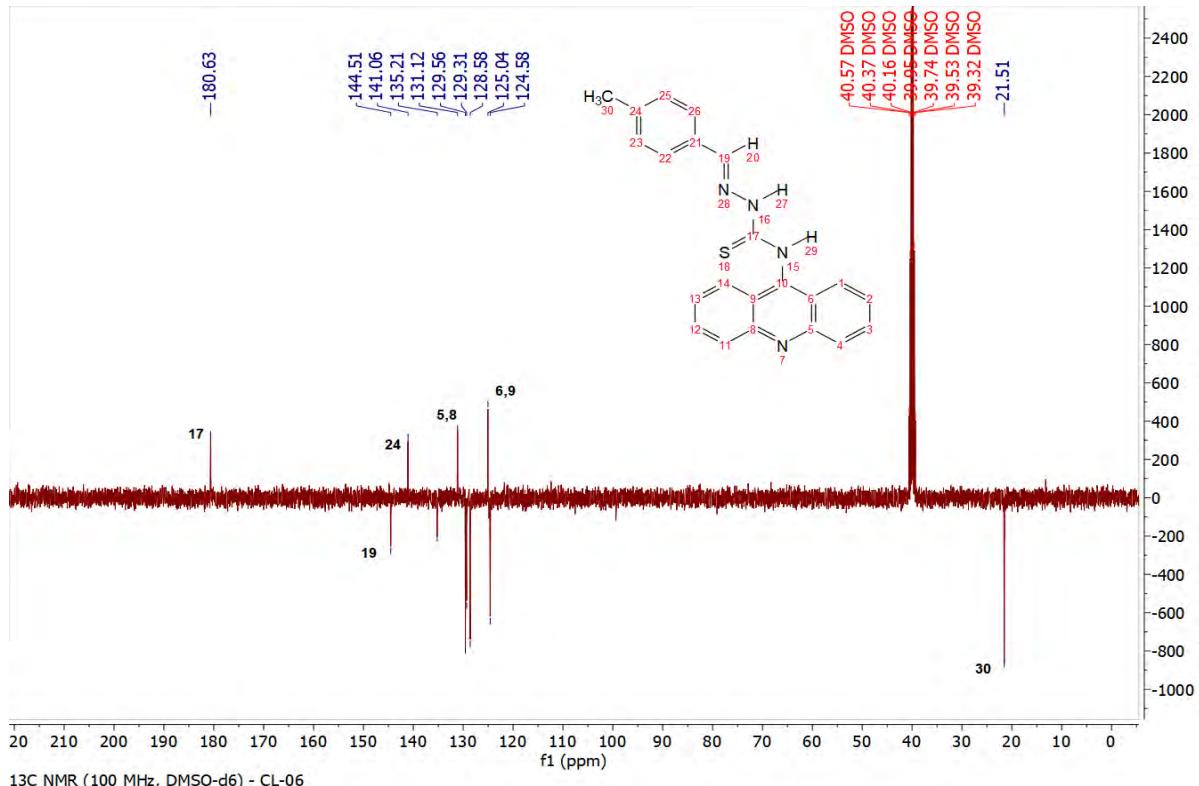


Figura S32. Espectro de RMN ¹³C do CL-06.

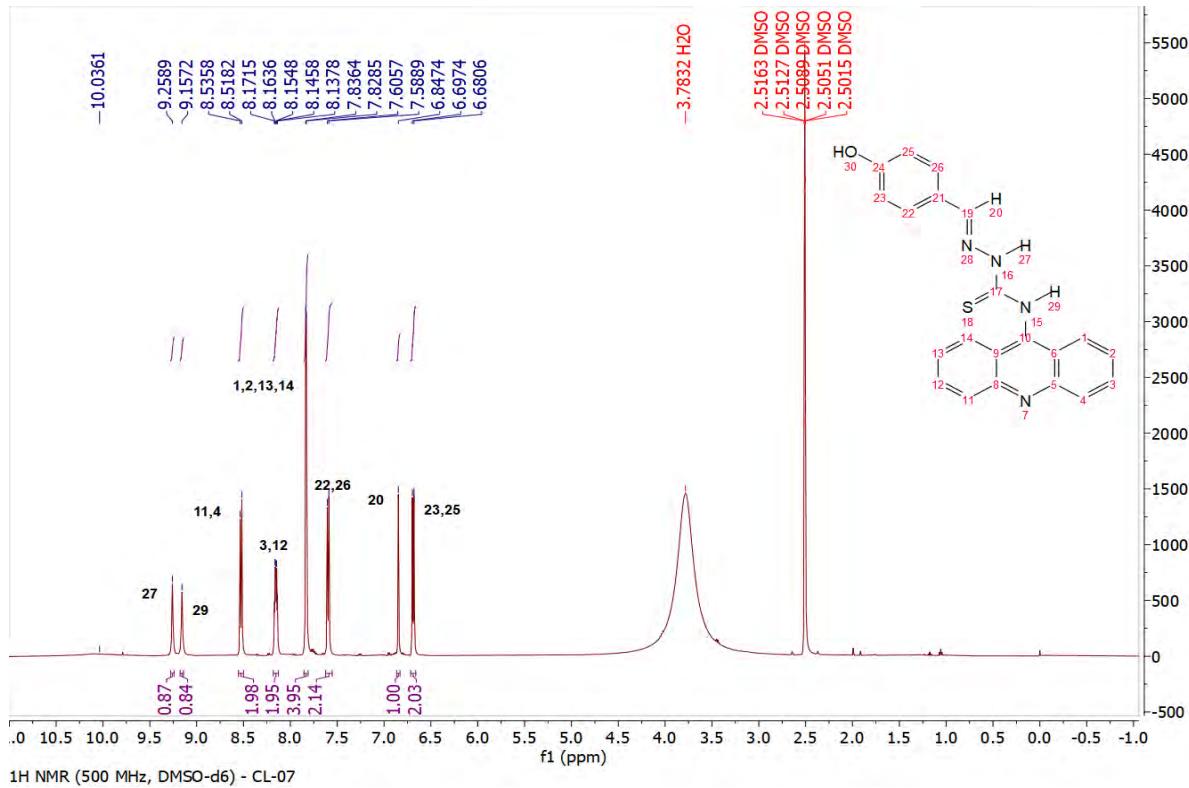


Figura S33. Espectro de RMN ¹H do CL-07.

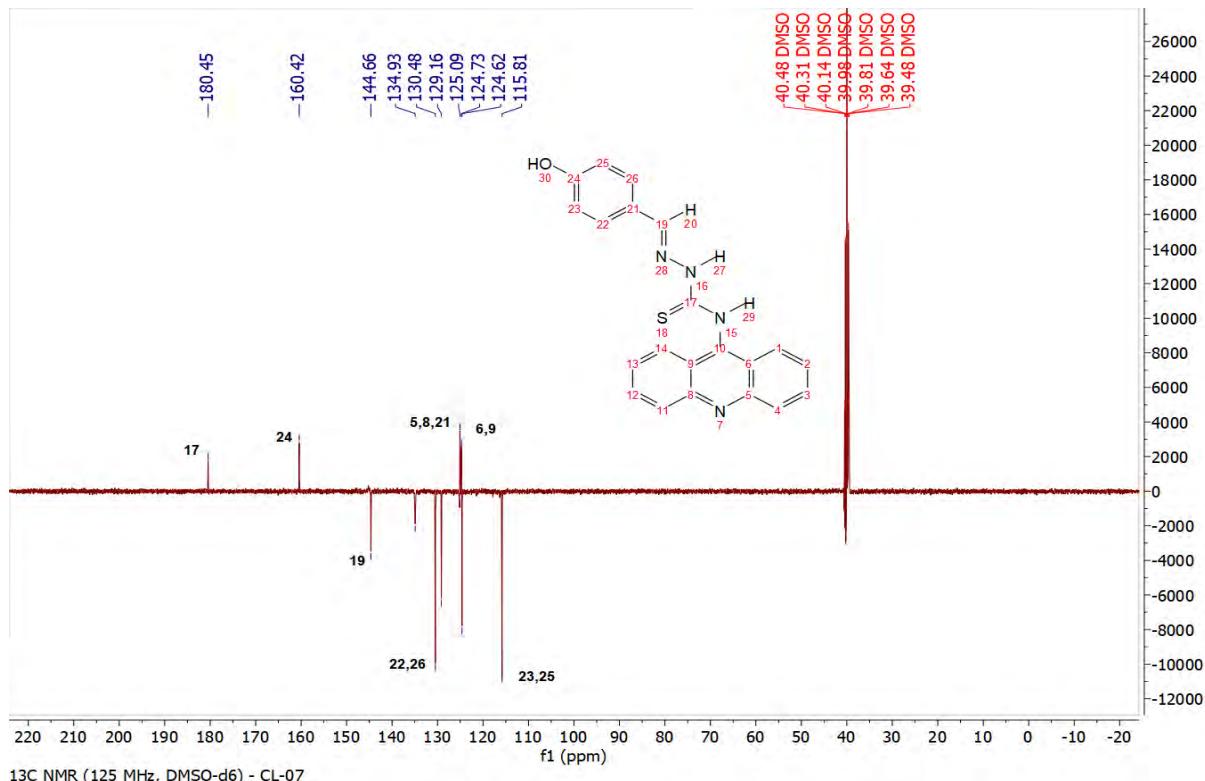


Figura S34. Espectro de RMN ¹³C do CL-07.

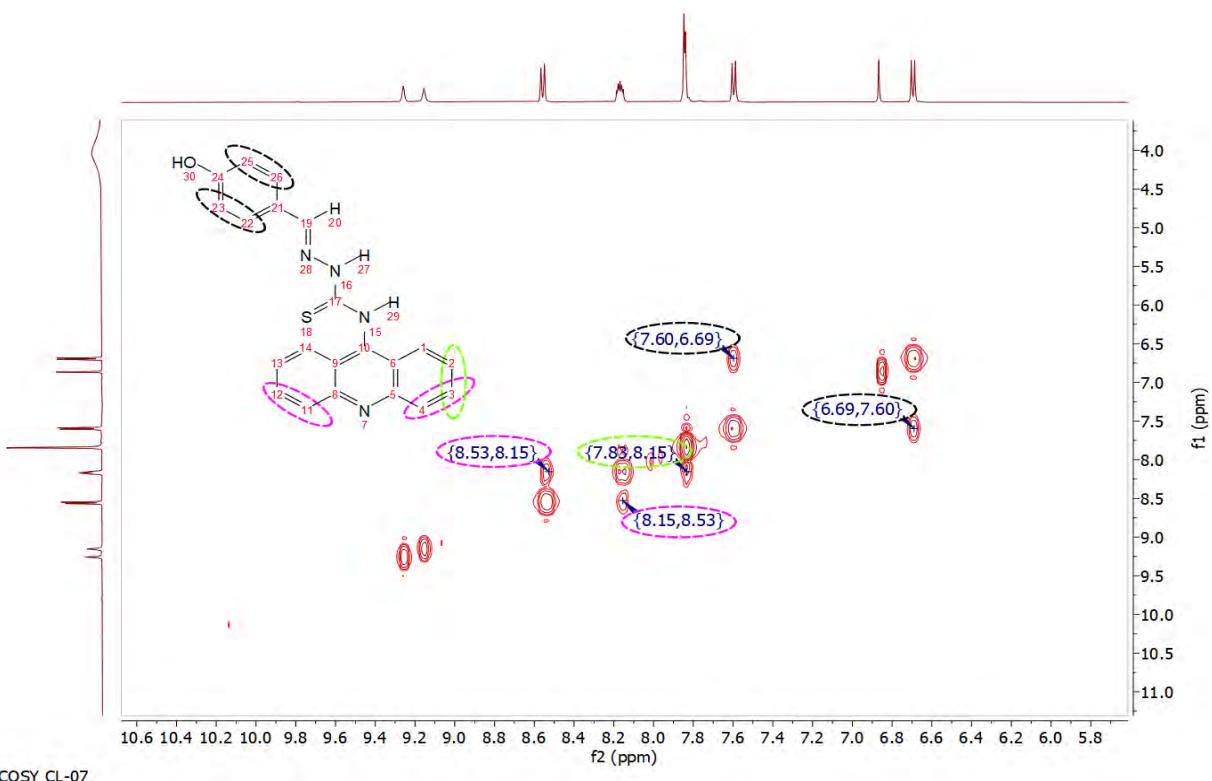


Figura S35. Espectro de correlação COSY do CL-07.

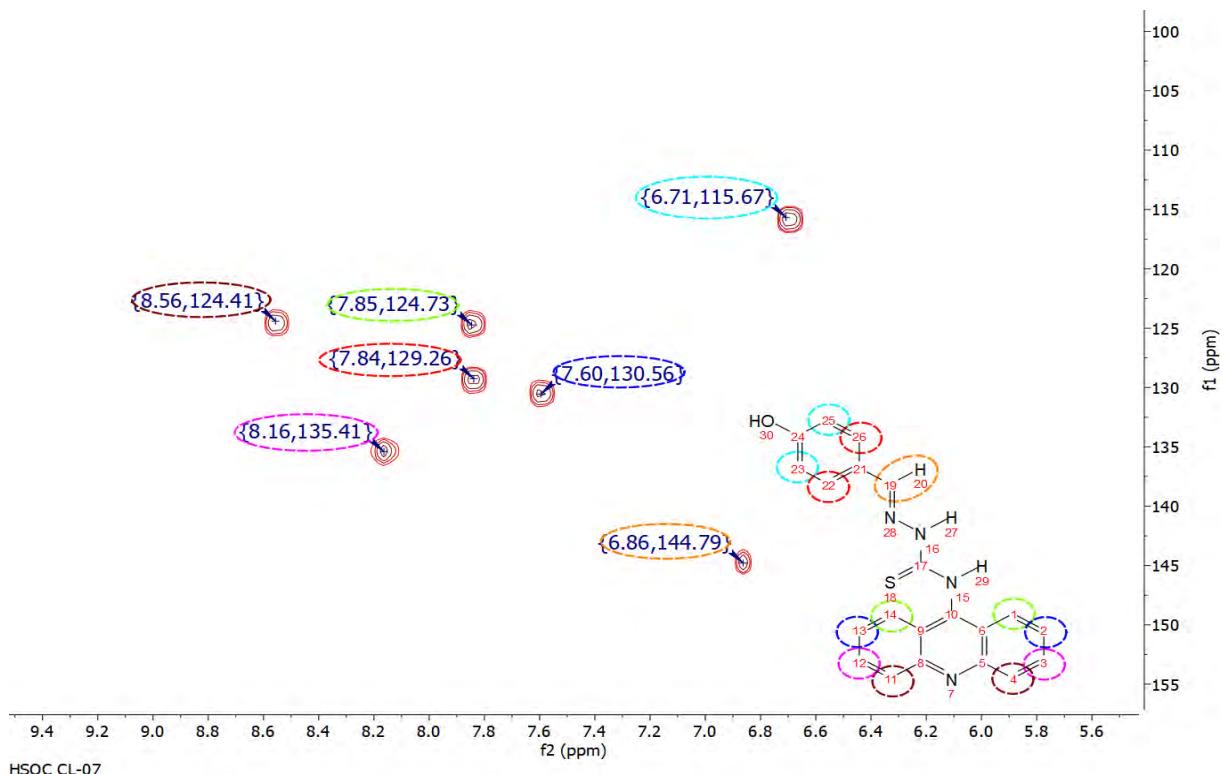


Figura S36. Espectro de correlação HSQC do CL-07.

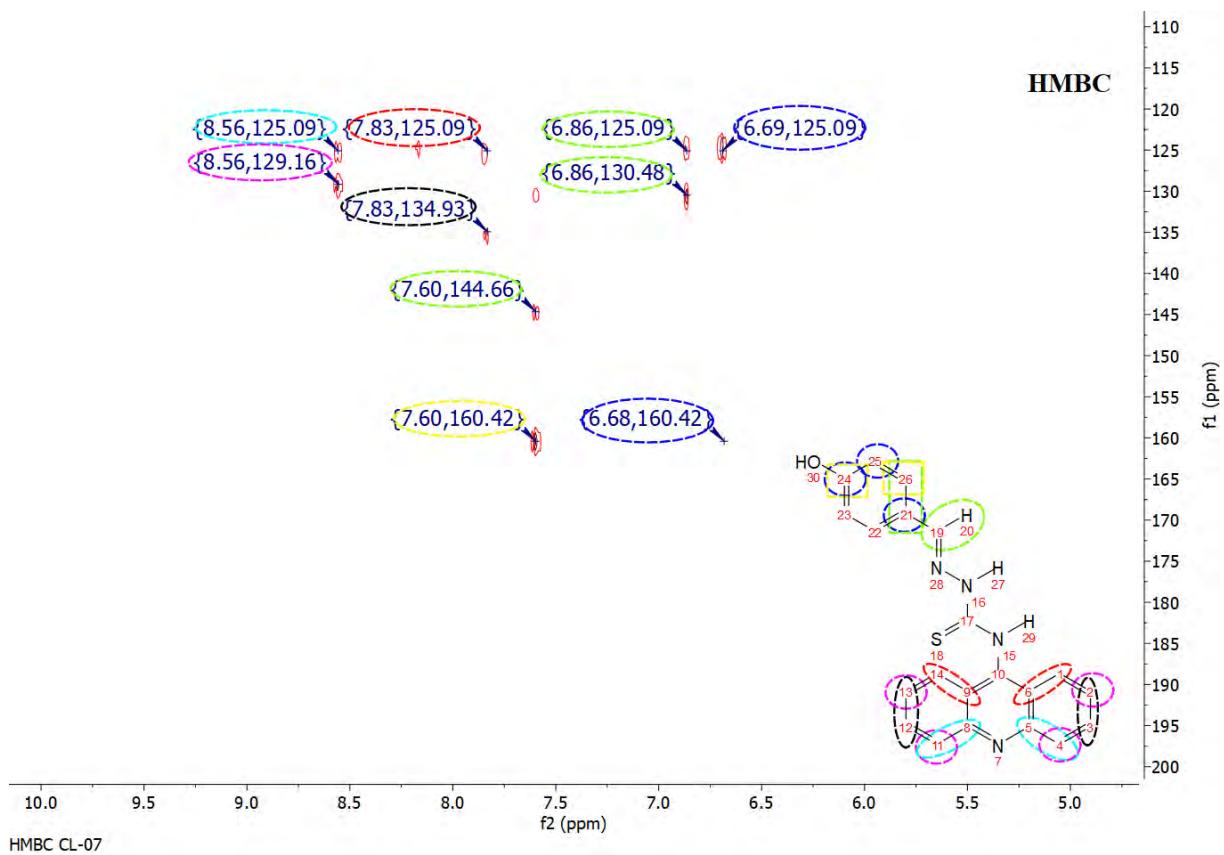


Figura S37. Espectro de correlação HMBC do CL-07.

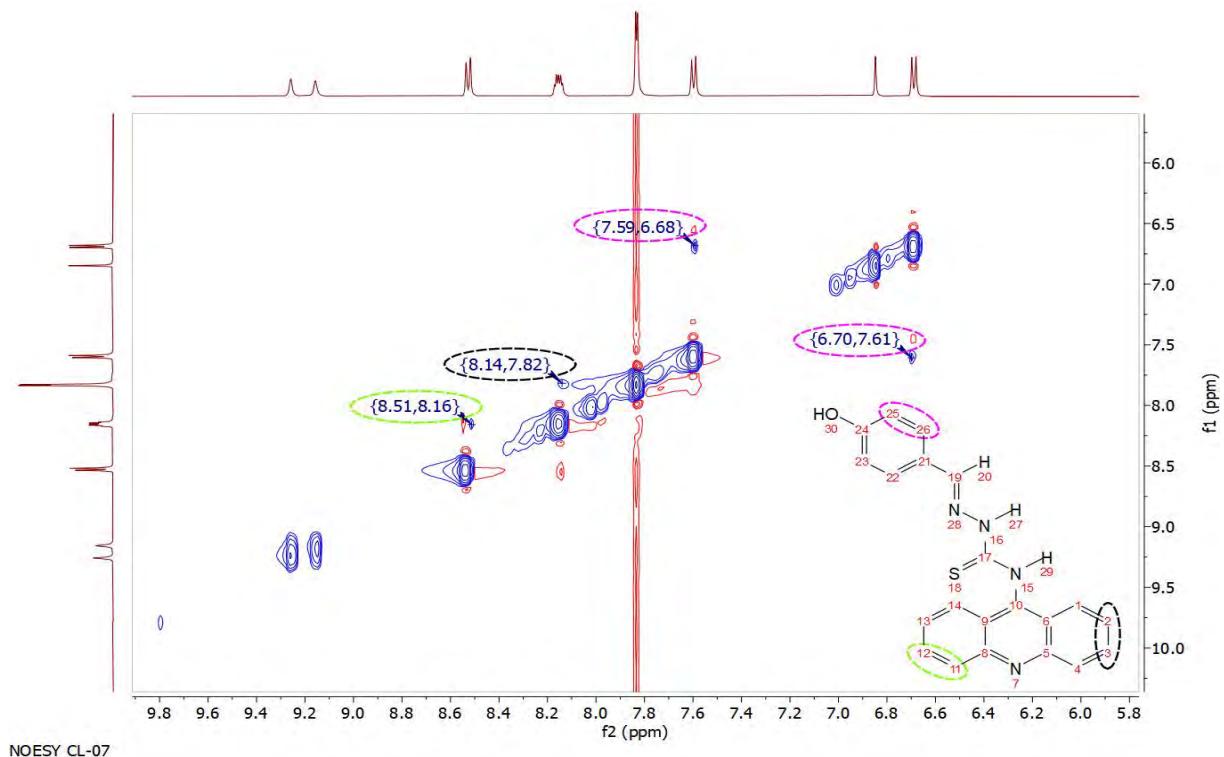


Figura S38. Espectro de correlação NOESY do CL-07.

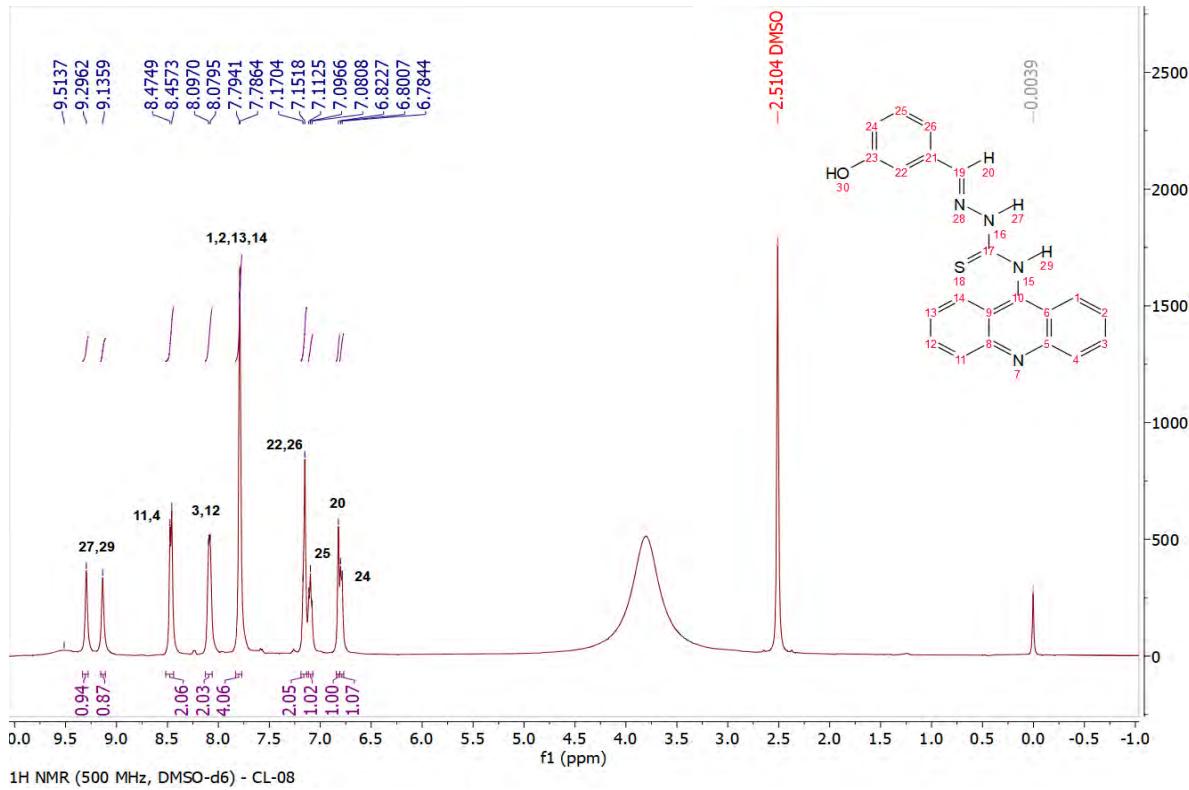


Figura S39. Espectro de RMN ^1H do CL-08.

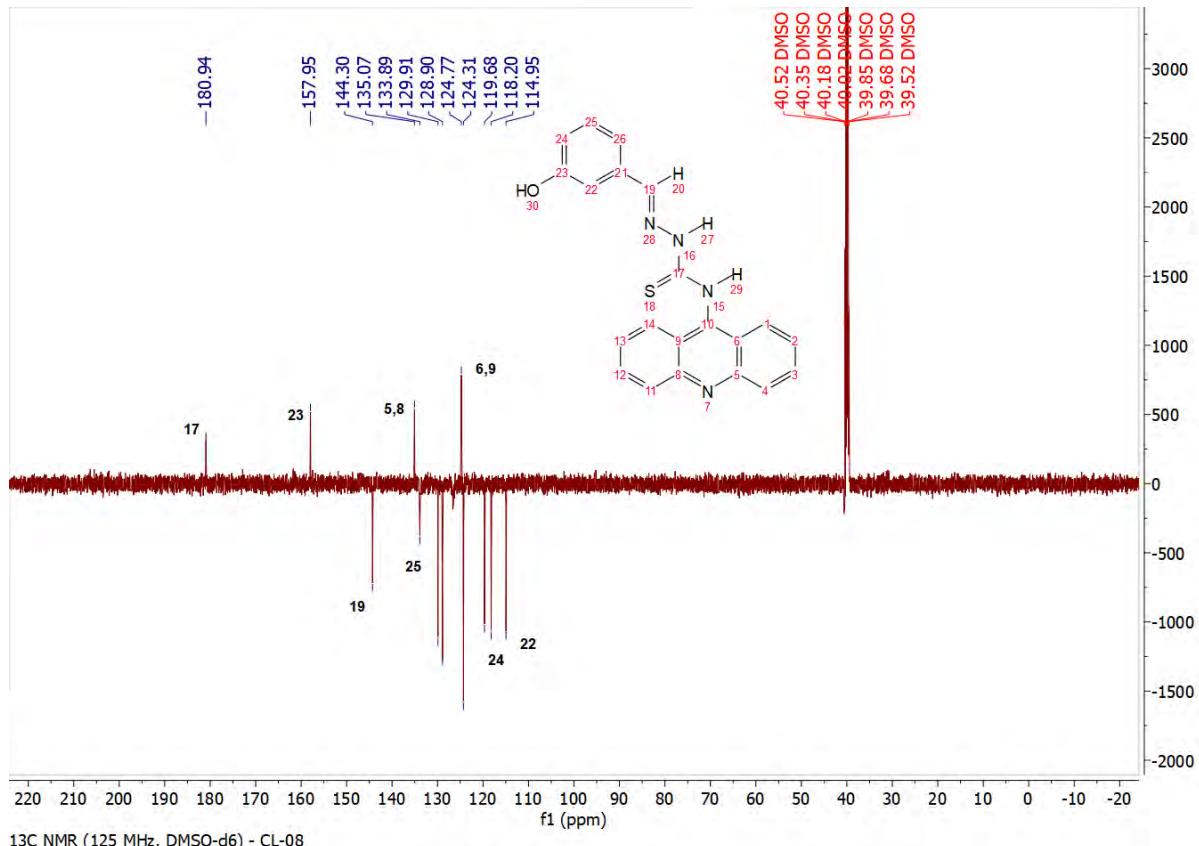


Figura S40. Espectro de RMN ^{13}C do CL-08.

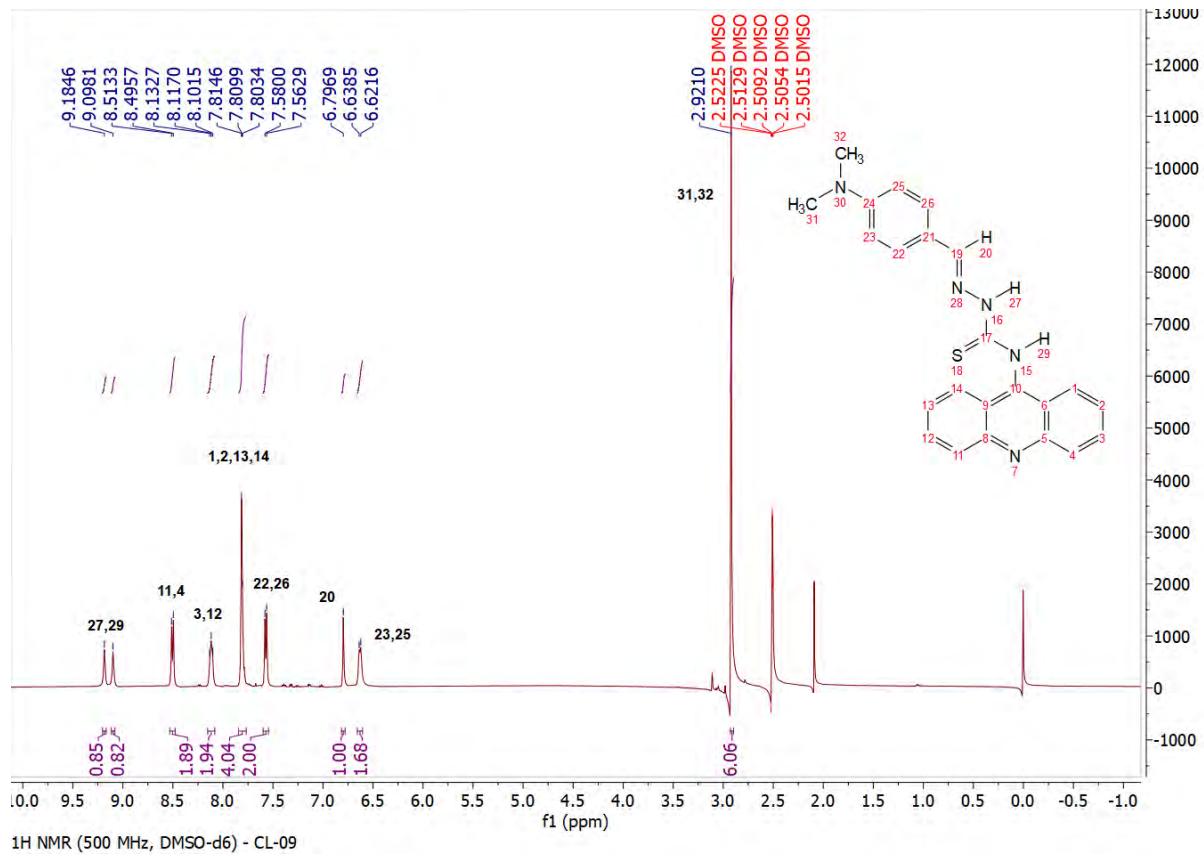


Figura S41. Espectro de RMN ¹H do CL-09.

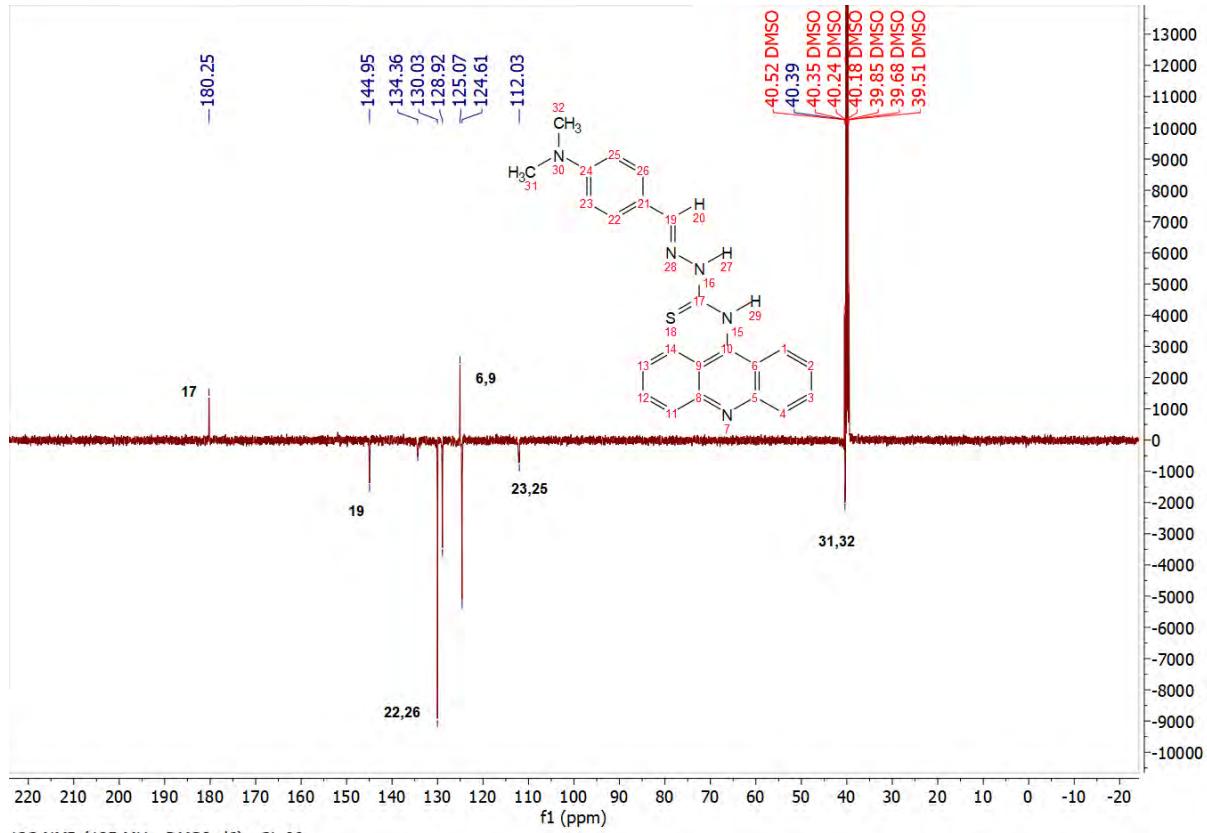


Figura S42. Espectro de RMN ¹³C do CL-09.

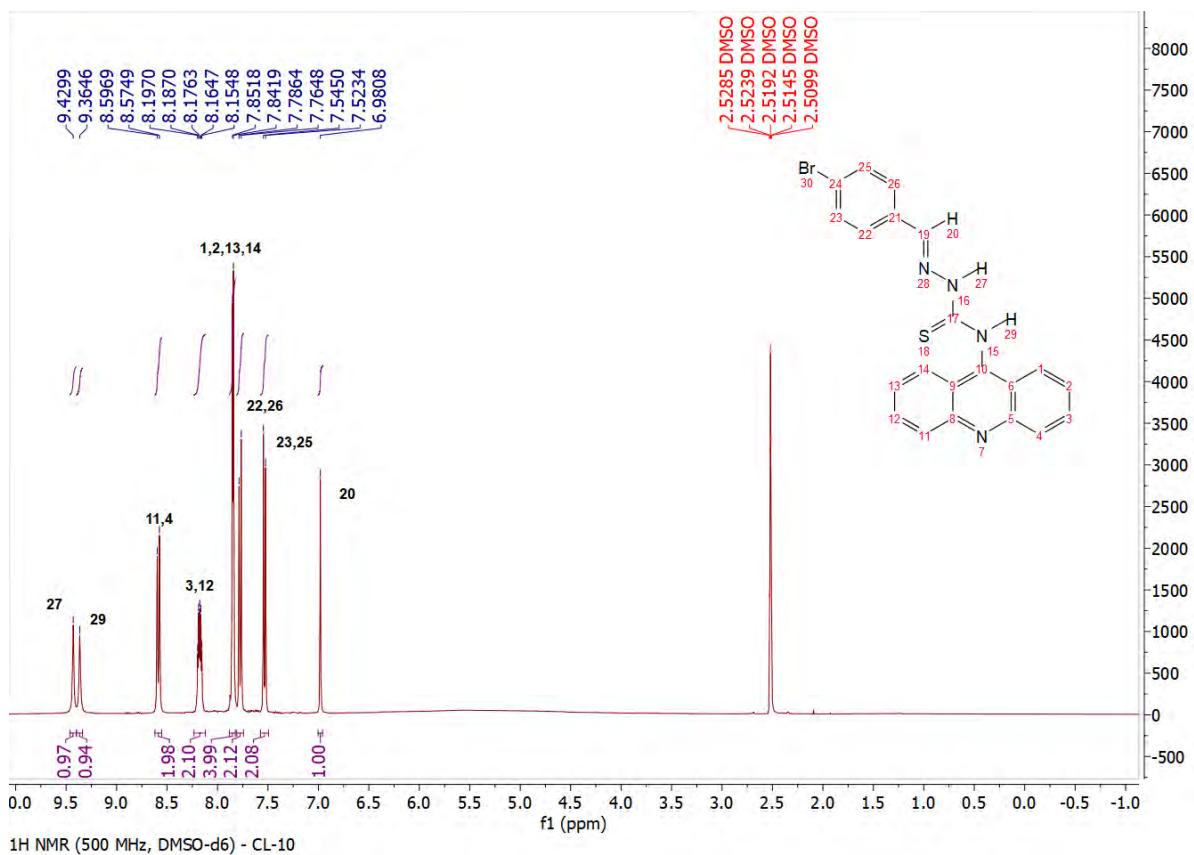


Figura S43. Espectro de RMN ^1H do **CL-10**.

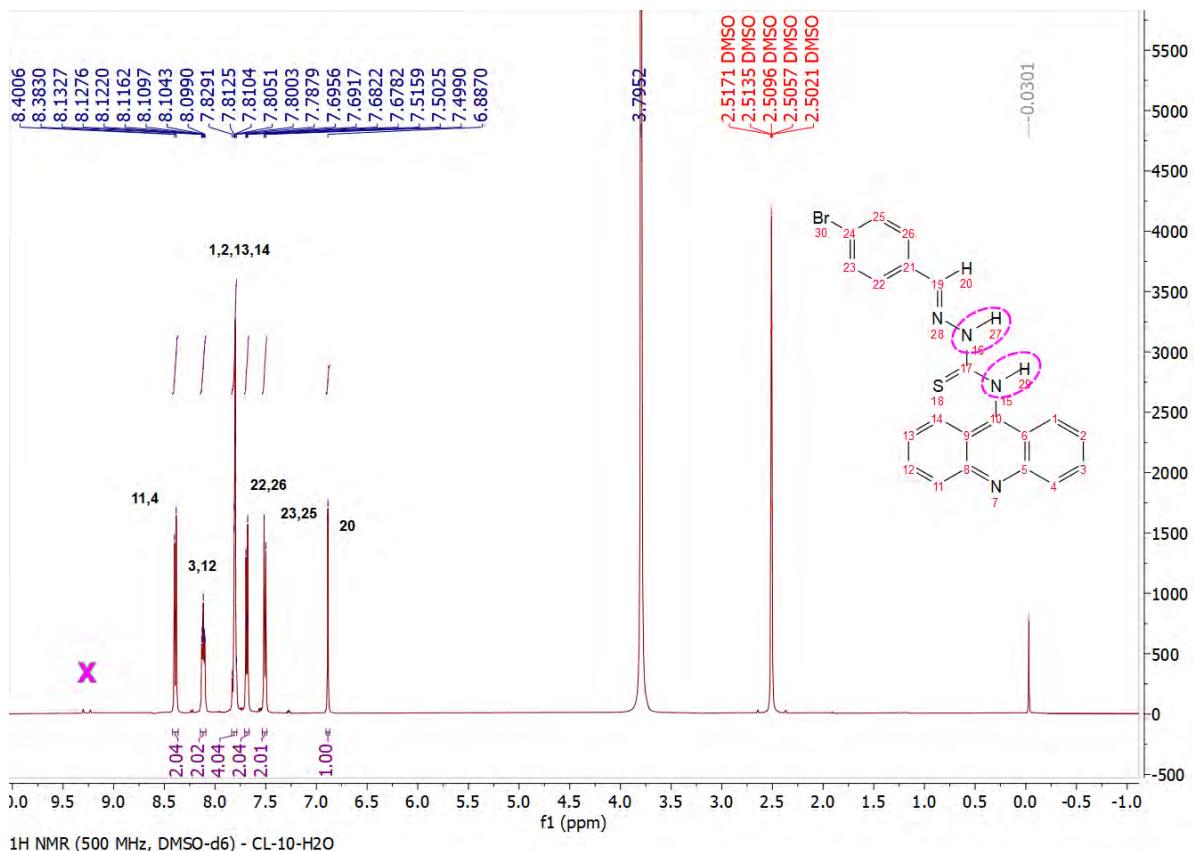


Figura S44. Espectro de RMN ^1H do **CL-10** na presença de D_2O .

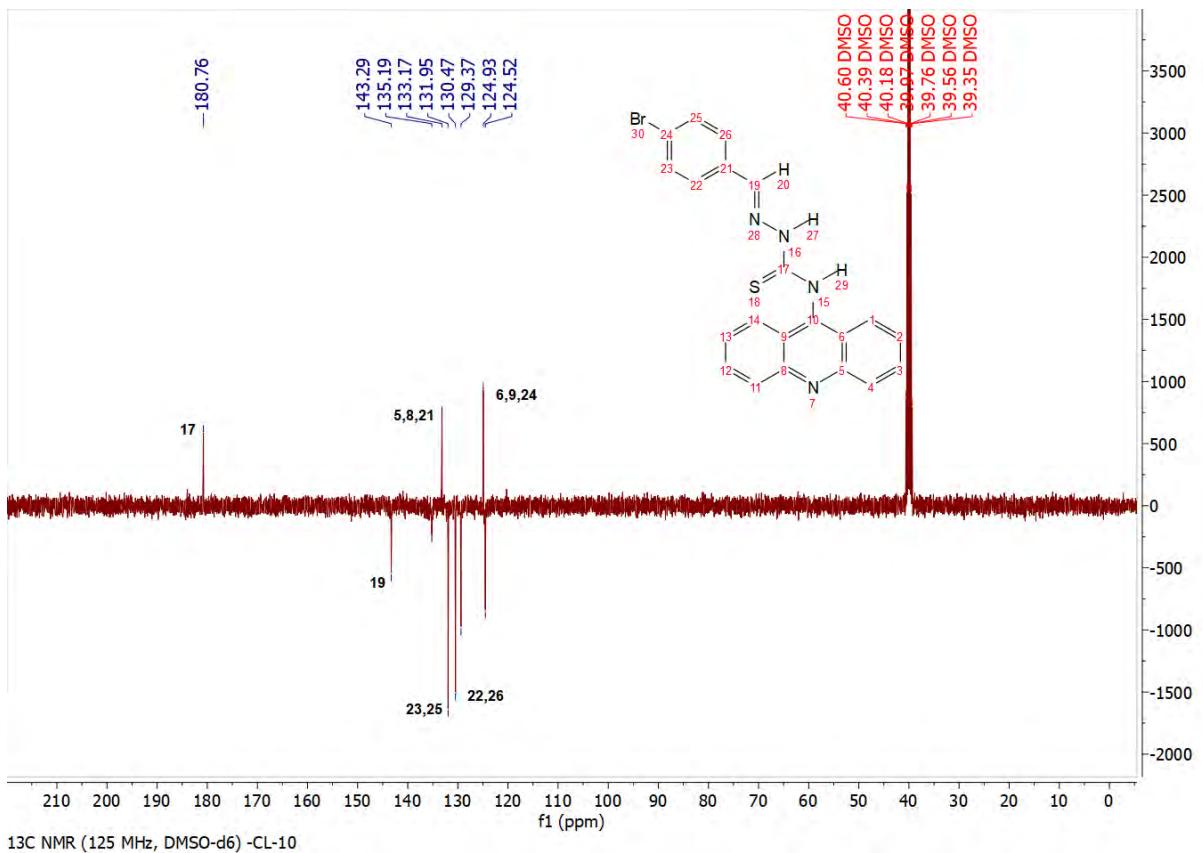


Figura S45. Espectro de RMN ^{13}C do **CL-10**.

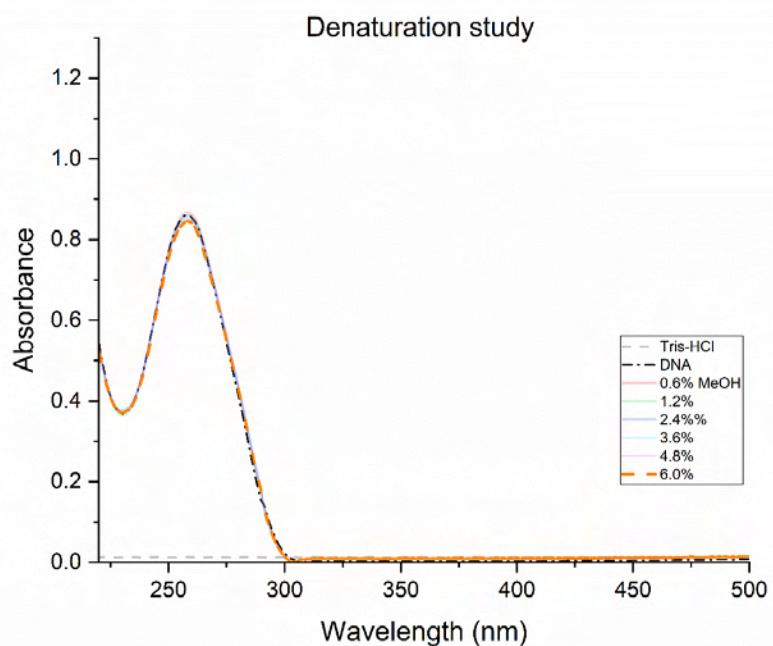


Figura S46. Espectro de absorção do ct-DNA na presença de metanol em diferentes proporções. Metanol = 0, 0.6, 1.2, 2.4, 3.6, 4.8 e 6.0%. ctDNA em uma concentração de $120 \mu\text{mol L}^{-1}$ em tampão Tris-HCl (pH 7.4).

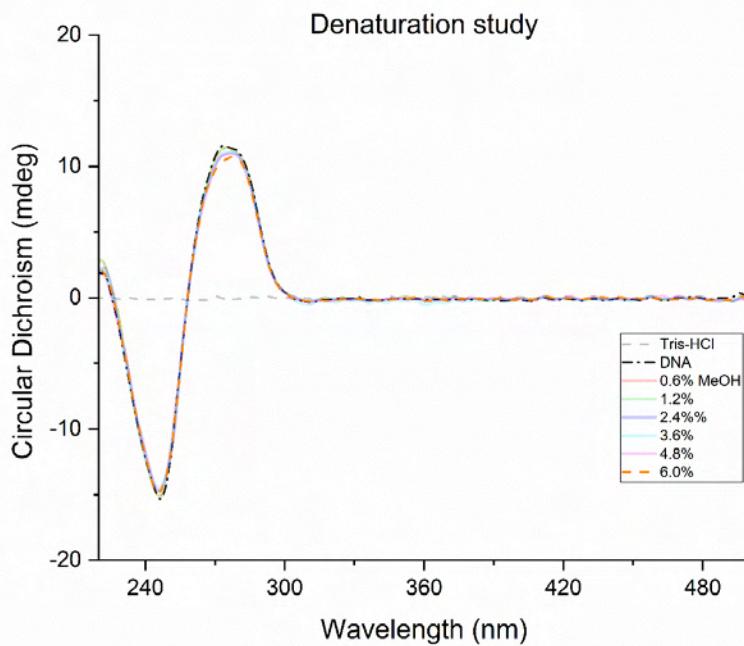


Figura S47. Dicroísmo circular do ctDNA ($120 \mu\text{mol L}^{-1}$) em tampão Tris-HCl buffer (pH 7.4), na presença de proporções crescentes de metanol (0 a 6 %).

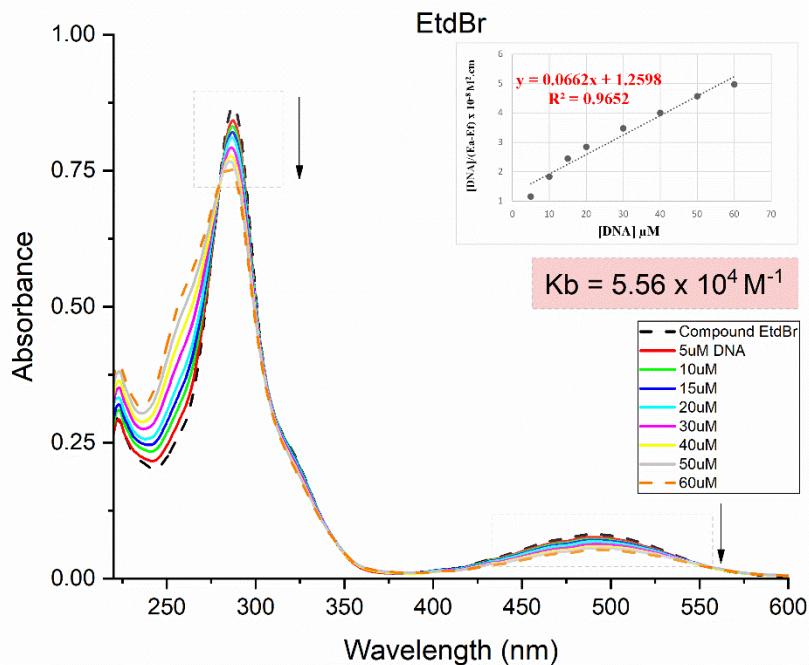


Figura S48. Espectro de absorção do *EtdBr* ($40 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4) na presença de concentrações crescentes de ctDNA (0, 5, 10, 20, 30, 40, 50 e $60 \mu\text{mol L}^{-1}$). λ (K_b) = 489 nm.

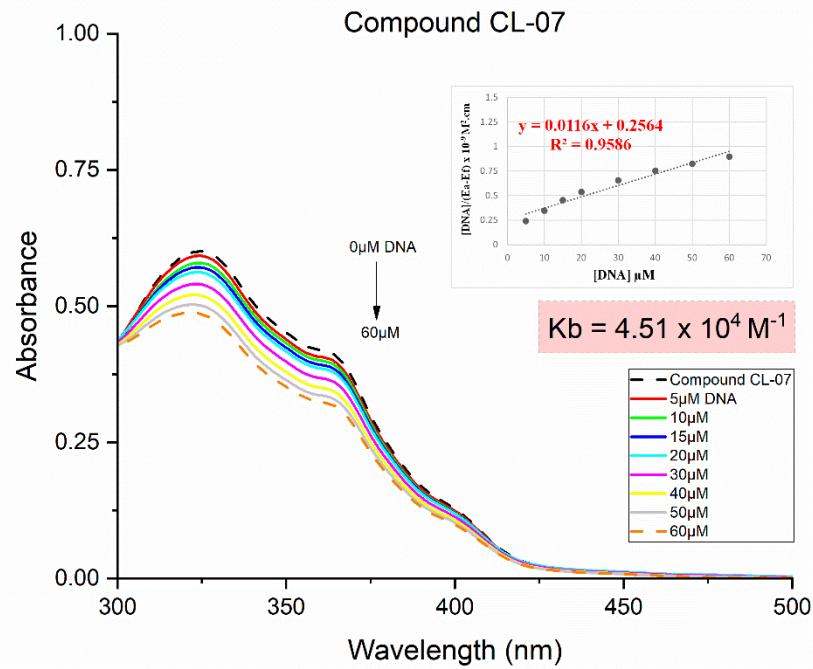


Figura S49. Espectro de absorção do **CL-07** ($40 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4) na presença de concentrações crescentes de ctDNA ($0, 5, 10, 20, 30, 40, 50$ e $60 \mu\text{mol L}^{-1}$). λ (K_b) = 325 nm.

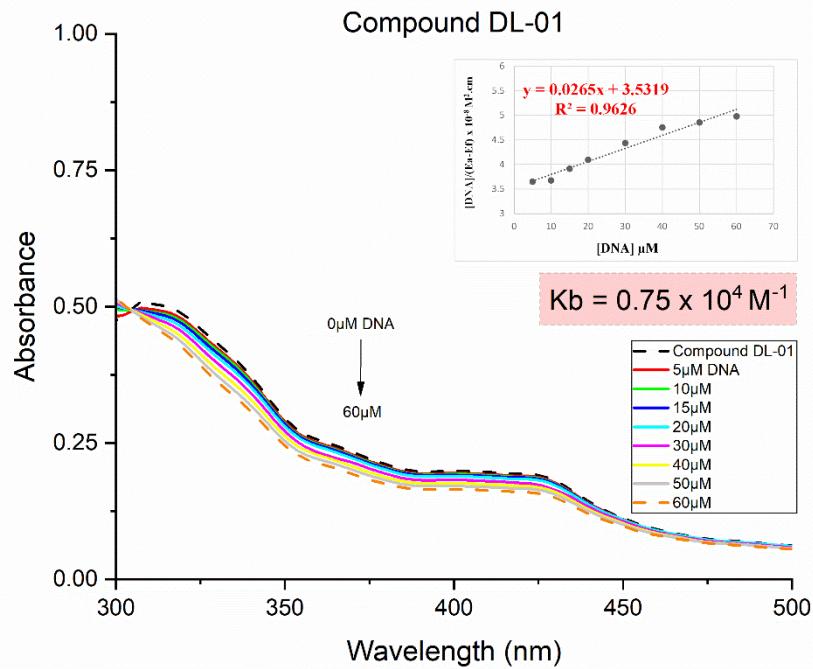


Figura S50. Espectro de absorção do **DL-01** ($40 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4) na presença de concentrações crescentes de ctDNA ($0, 5, 10, 20, 30, 40, 50$ e $60 \mu\text{mol L}^{-1}$). λ (K_b) = 320 nm.

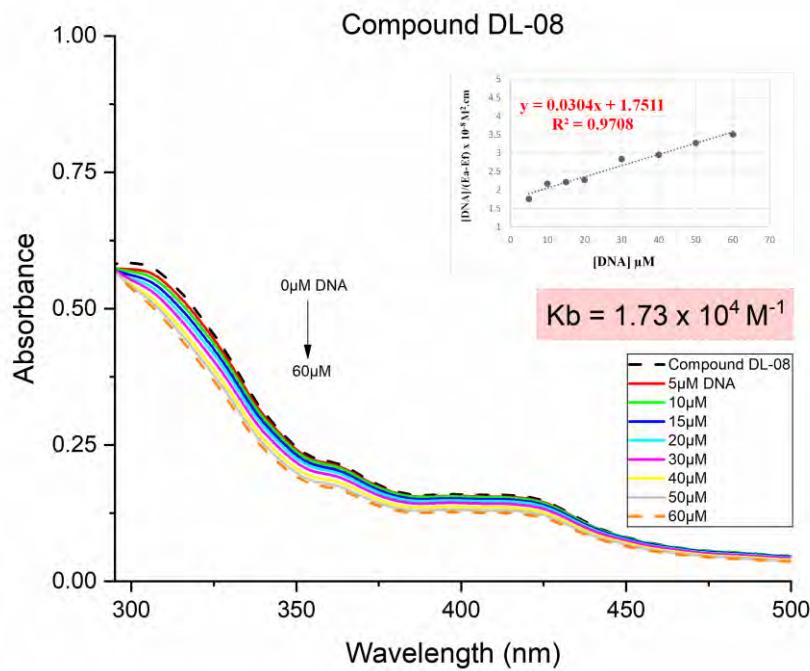


Figura S51. Espectro de absorção do **DL-08** ($40 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4) na presença de concentrações crescentes de ctDNA ($0, 5, 10, 20, 30, 40, 50$ e $60 \mu\text{mol L}^{-1}$). λ (K_b) = 305 nm.

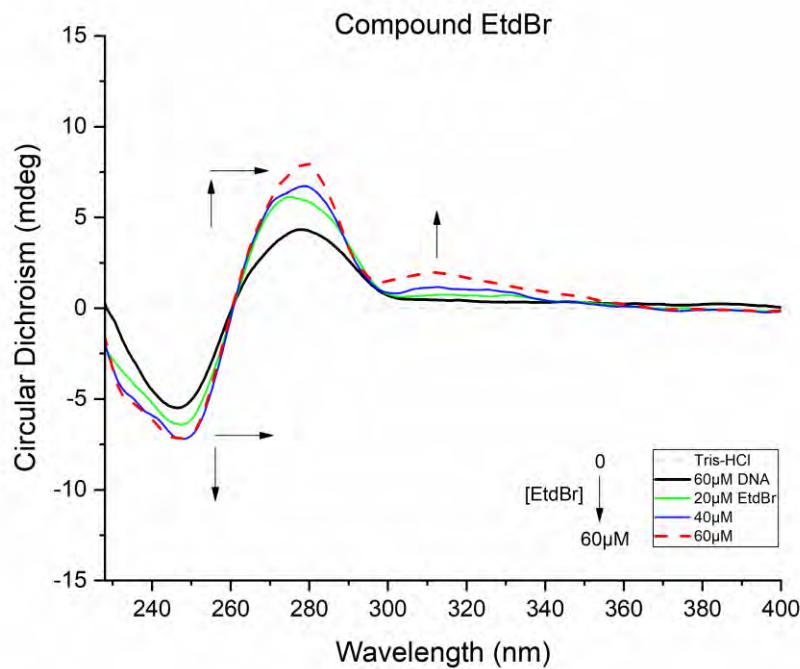


Figura S52. Dicroísmo circular do ctDNA ($60 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4), na presença de concentrações crescentes do **EtdBr** ($20, 40$ and $60 \mu\text{mol L}^{-1}$).

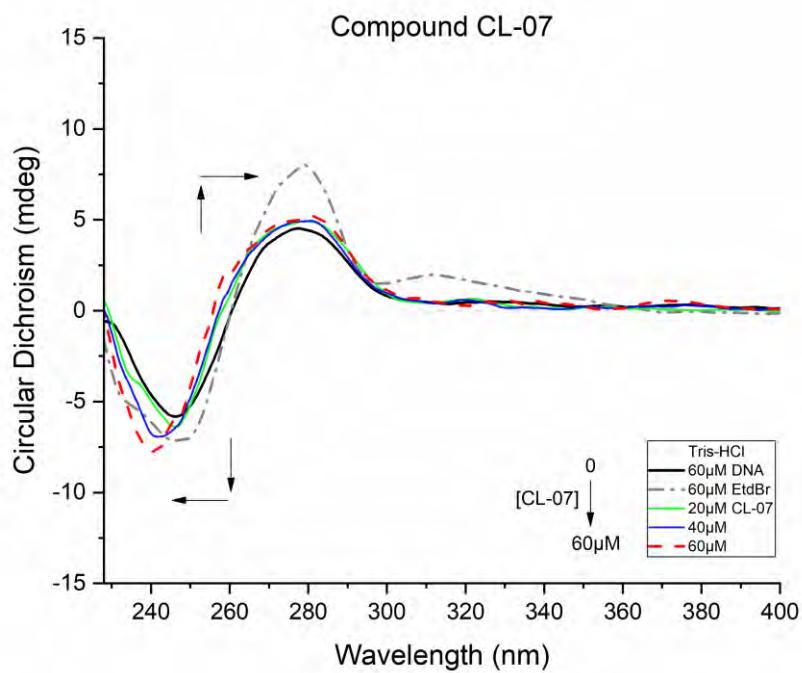


Figura S53. Dicroísmo circular do ctDNA ($60 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4), na presença de concentrações crescentes do **CL-07** (20, 40 and $60 \mu\text{mol L}^{-1}$).

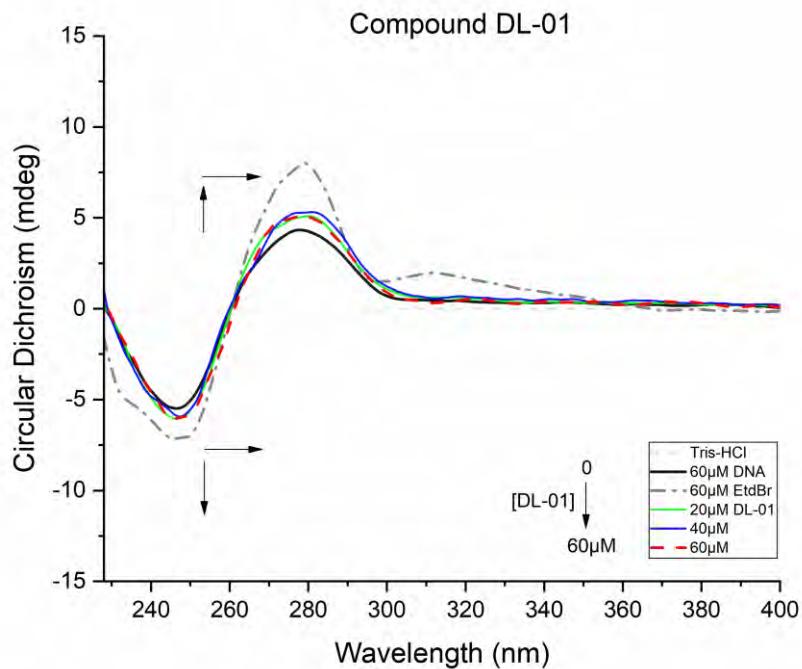


Figura S54. Dicroísmo circular do ctDNA ($60 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4), na presença de concentrações crescentes do **DL-01** (20, 40 and $60 \mu\text{mol L}^{-1}$).

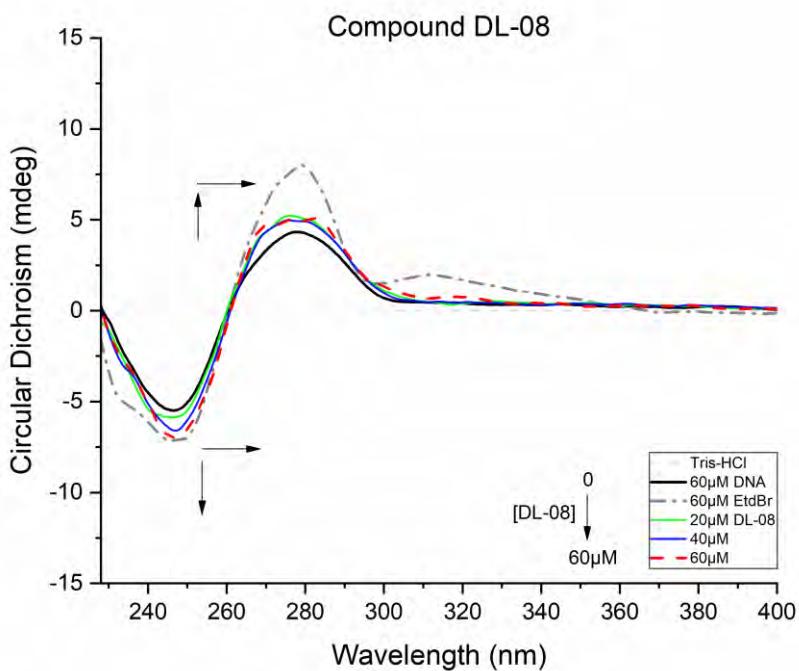


Figura S55. Dicroísmo circular do ctDNA ($60 \mu\text{mol L}^{-1}$) em tampão Tris-HCl (pH 7.4), na presença de concentrações crescentes do **DL-08** (20, 40 and $60 \mu\text{mol L}^{-1}$).

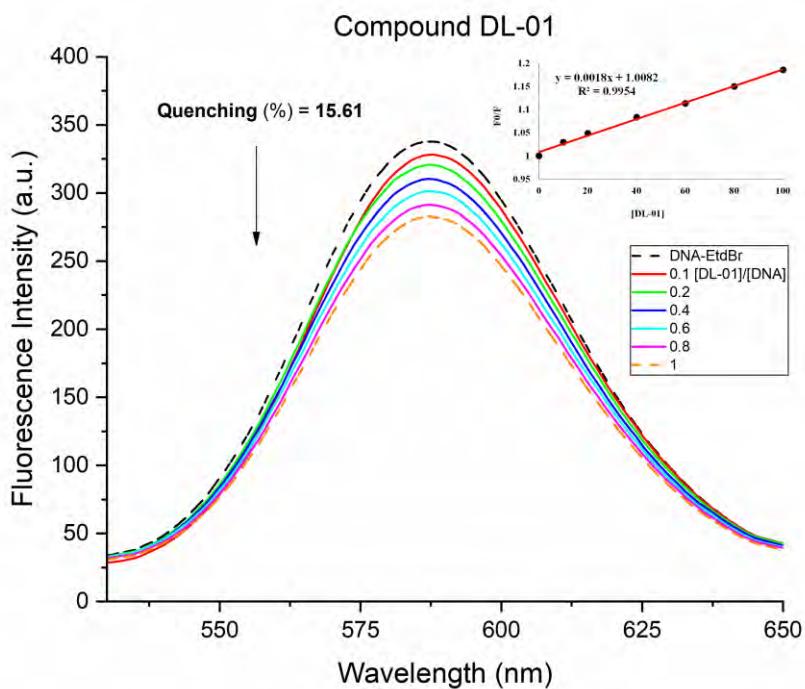


Figura S56. Curvas de extinção da emissão de fluorescência EtdBr-ctDNA pelo composto **DL-01** ($[\text{EtBr}] = 20 \mu\text{mol L}^{-1}$, $[\text{ctDNA}] = 100 \mu\text{mol L}^{-1}$, $[\text{DL-01}] = 0 - 100 \mu\text{mol L}^{-1}$).

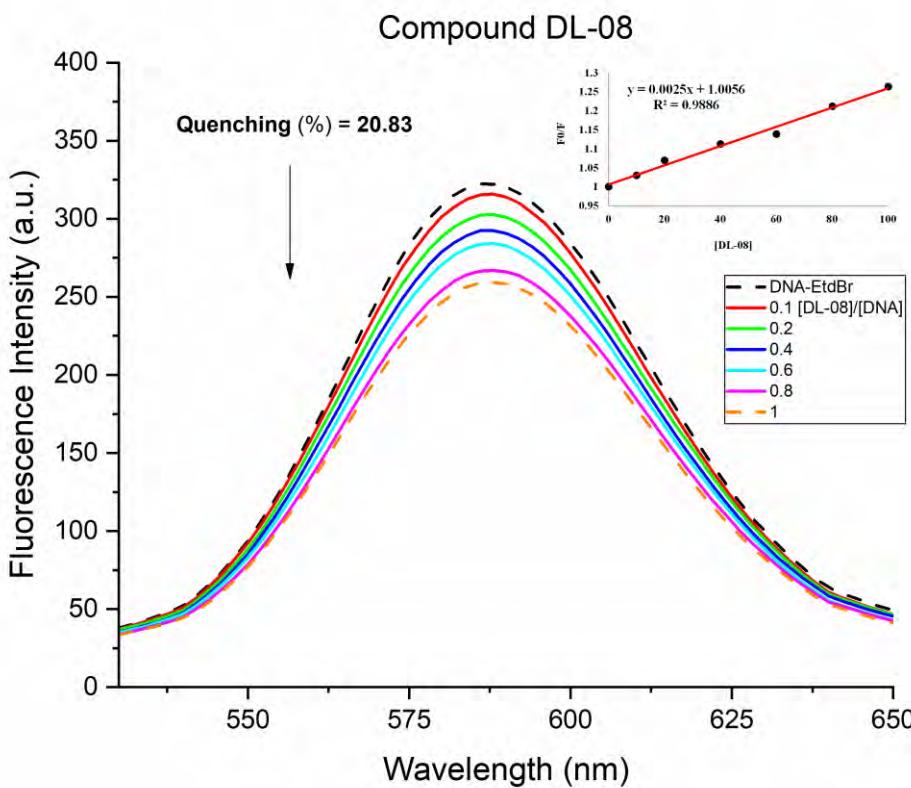


Figura S57. Curvas de extinção da emissão de fluorescência EtdBr-ctDNA pelo composto **DL-08** ($[EtBr] = 20 \mu\text{mol L}^{-1}$, $[ctDNA] = 100 \mu\text{mol L}^{-1}$, $[DL-01] = 0 - 100 \mu\text{mol L}^{-1}$).

Tabela S1. Efeitos de derivados de acridinas em animais submetidos a estudo de toxicidade aguda.

Estudo de toxicidade	DA/TA	Mortalidade (%)	Sinais de toxicidade
CL-07	0/3	0	Nenhum
DL-01	0/3	0	Consumo de ração reduzido
DL-08	0/3	0	Esteatose hepática
NC	0/3	0	Nenhum

Grupo controle (NC), animais mortos (DA), total de animais (TA).

Tabela S2. Massa absoluta e relativa de órgãos de animais tratados com derivados de acridina após um estudo de toxicidade aguda.

Compostos	Órgãos				
	Fígado (g)	Pulmão (g)	Baço (g)	Coração (g)	Rins (g)
CL-07	6,135±0,287 ^a	0,619±0,089 ^b	0,574±0,061 ^c	0,417±0,038 ^d	1,308±0,099 ^e
DL-01	5,257±0,610 ^a	0,640±0,057 ^b	0,551±0,037 ^c	0,410±0,039 ^d	1,338±0,091 ^e
DL-08	5,619±0,259 ^a	0,646±0,032 ^b	0,412±0,033 ^c	0,427±0,035 ^d	1,355±0,062 ^e
NC	4,959±0,191 ^a	0,628±0,027 ^b	0,408±0,037 ^c	0,409±0,040 ^d	1,284±0,040 ^e

Grupo controle (NC). Na mesma categoria e tratamento, as médias seguidas de letras desiguais, diferem estatisticamente entre si pelo teste *T de Student* ($p<0.05$), em relação aos grupos tratado e controle.

Tabela S3. Massa relativa aos animais tratados com derivados de acridina após um estudo de toxicidade aguda.

Compostos	Dados fisiológicos		
	Consumo de ração (g)	Consumo de água (mL)	Ganho de peso (g)
CL-07	14,57±1,78 ^a	23,57±1,34 ^c	1,33±0,27 ^e
DL-01	12,35±1,39 ^b	23,71±1,26 ^c	0,69±0,58 ^f
DL-08	15,21±0,97 ^a	25,28±0,46 ^d	0,76±0,43 ^f
NC	18,64±3,52 ^a	23,14±1,51 ^c	1,00±0 ^f

Grupo controle (NC). Na mesma categoria e tratamento, as médias seguidas de letras desiguais, diferem estatisticamente entre si pelo teste *T de Student* ($p<0.05$), em relação aos grupos tratado e controle.

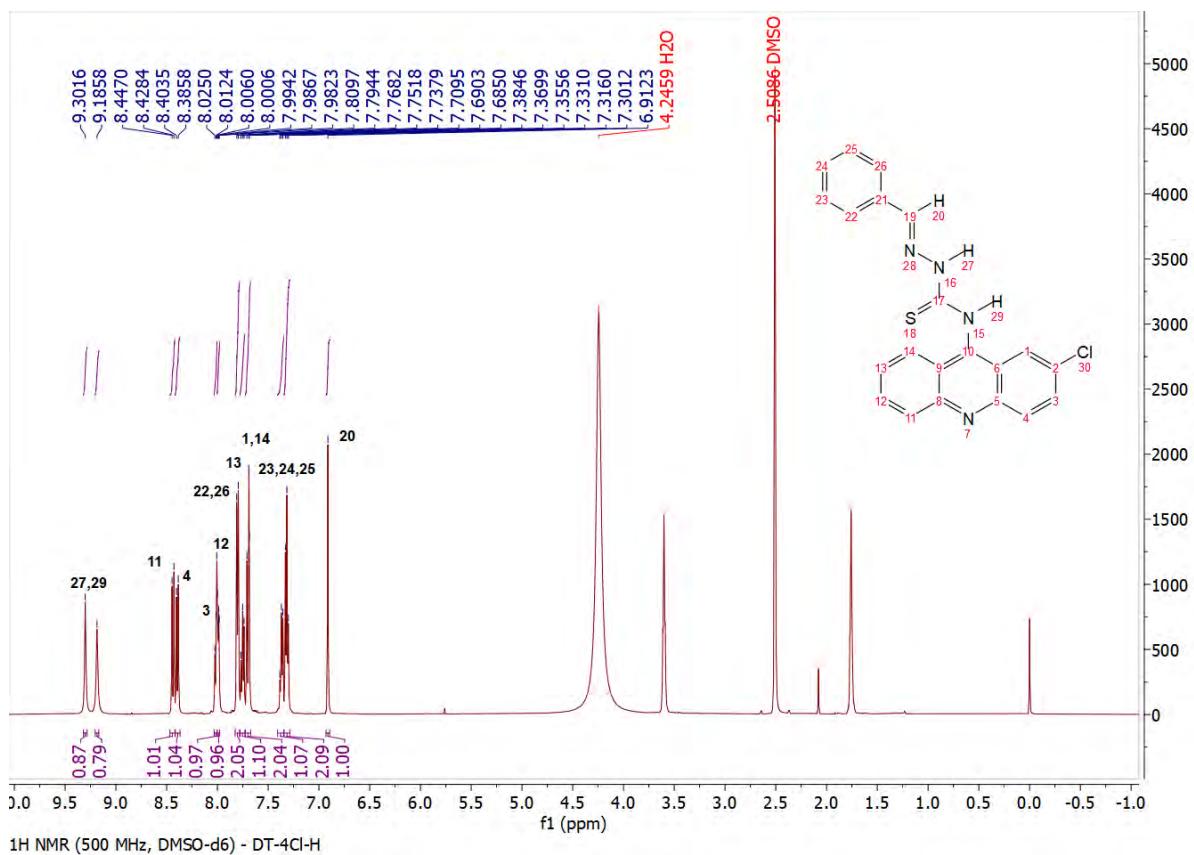


Figura S58. Espectro de RMN ¹H do DT-4Cl-H.

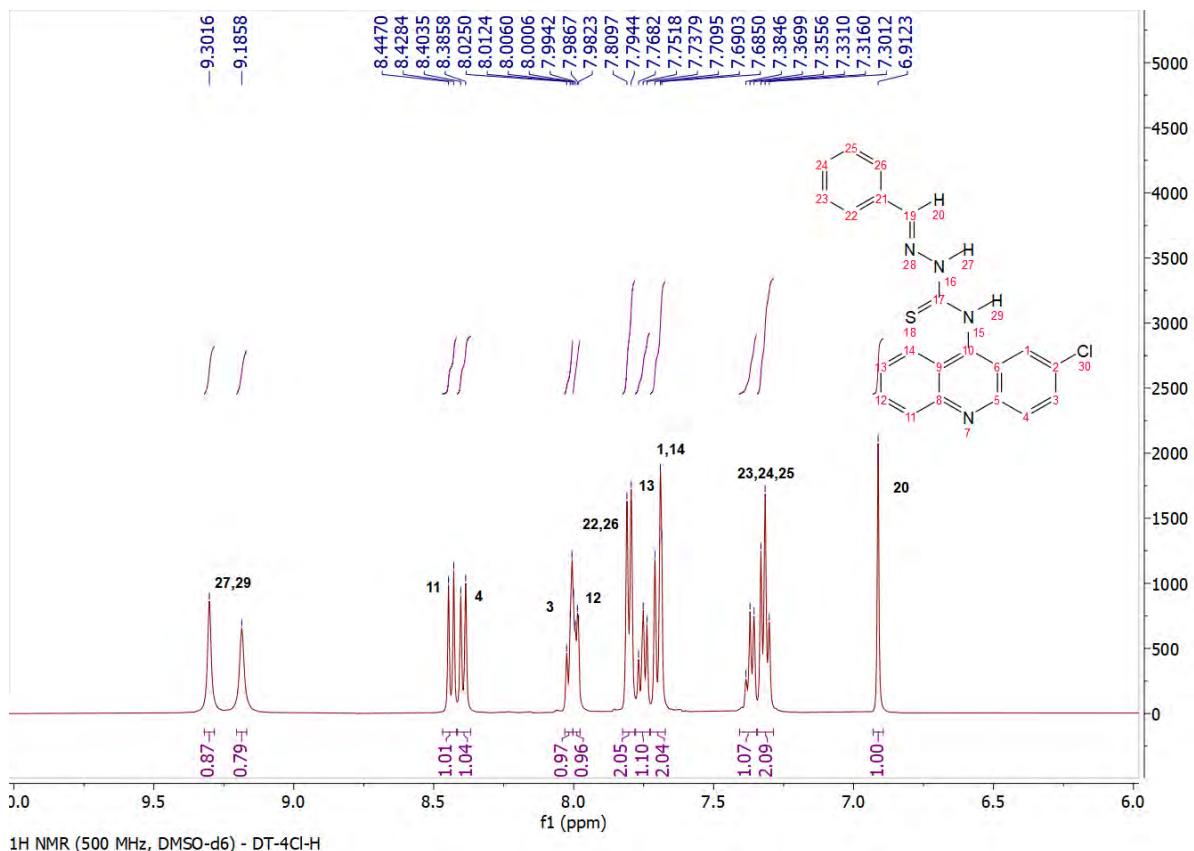


Figura S59. Expansão do espectro de RMN ¹H do DT-4Cl-H.

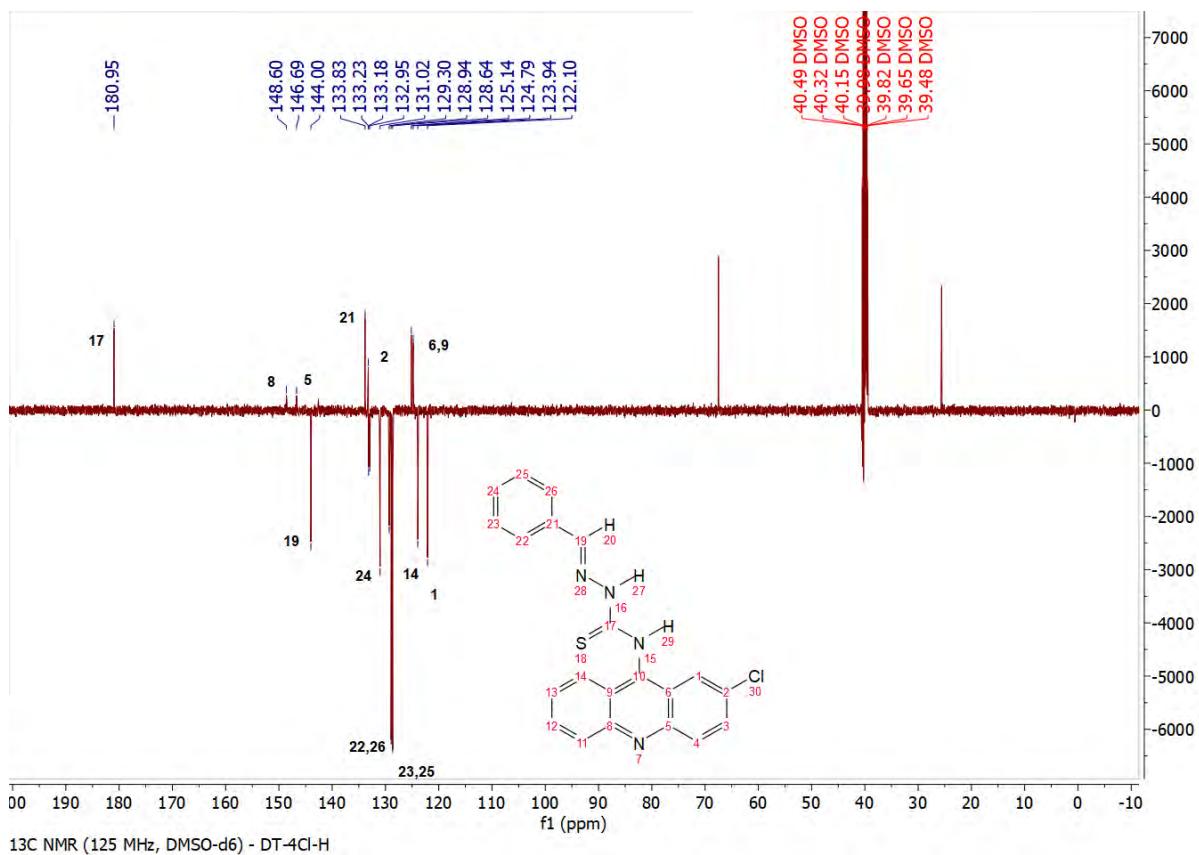


Figura S60. Espectro de RMN ^{13}C do DT-4Cl-H.

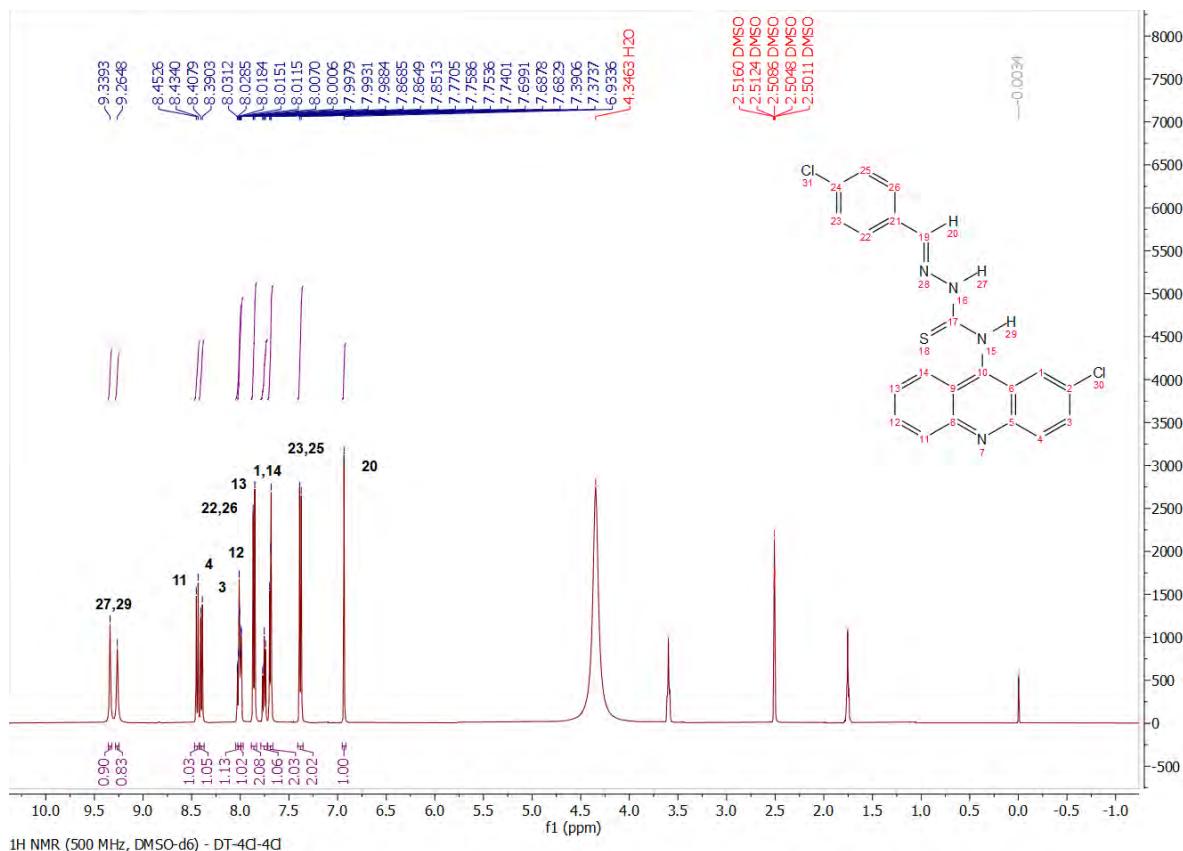


Figura S61. Espectro de RMN ^1H do DT-4Cl-4Cl.

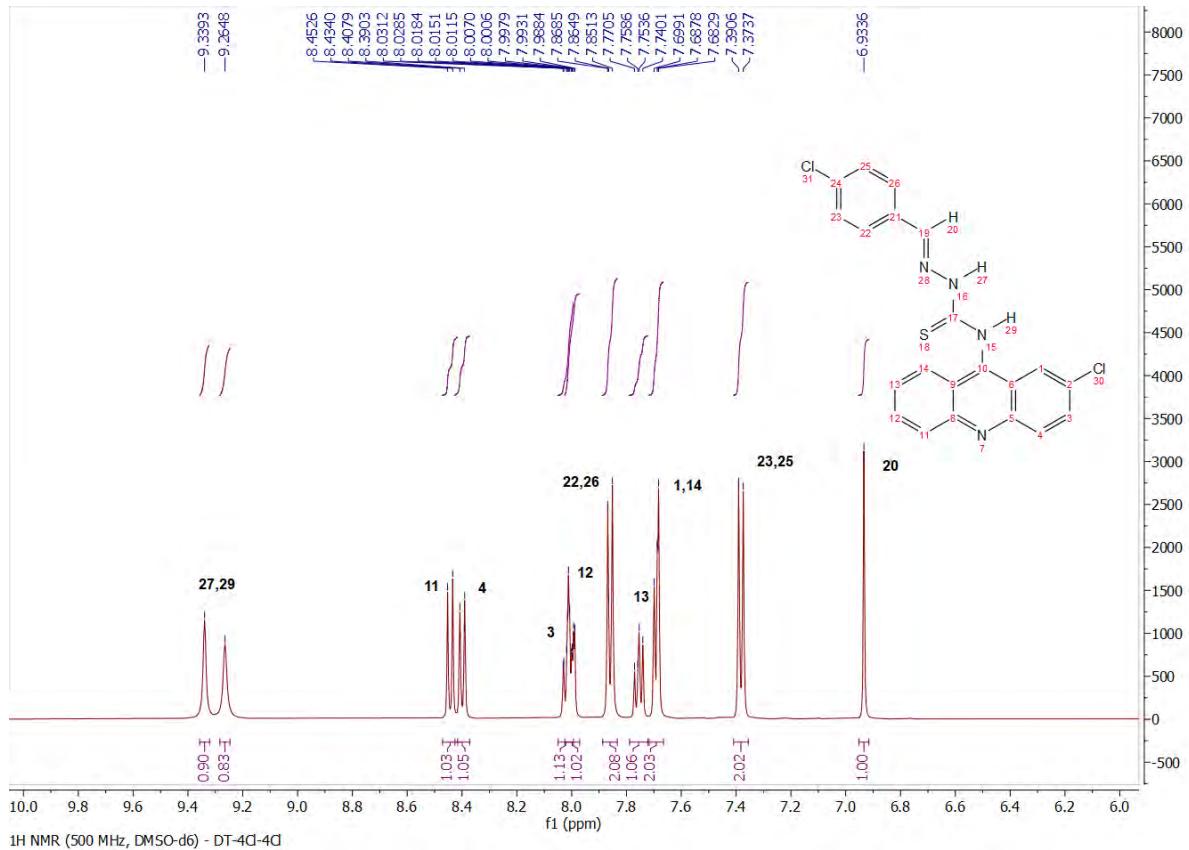


Figura S62. Expansão do espectro de RMN ¹H do DT-4Cl-4Cl.

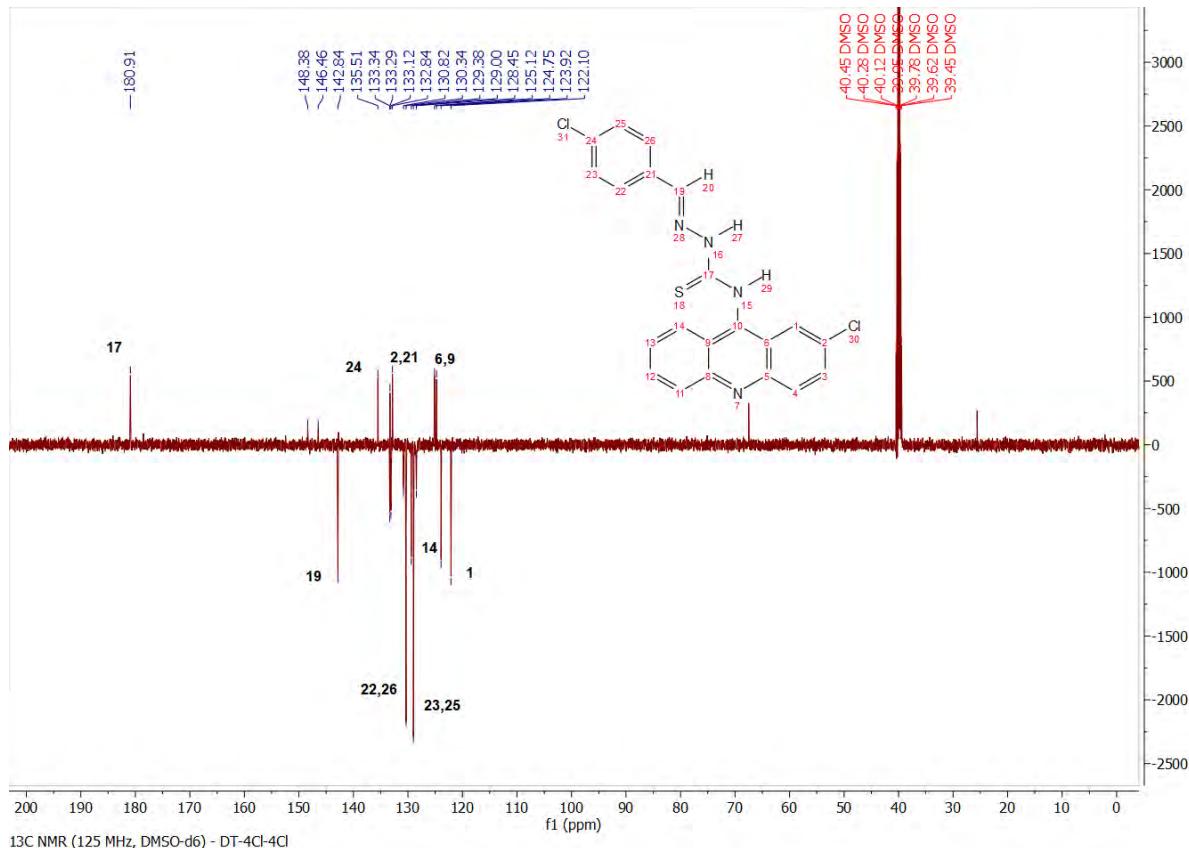


Figura S63. Espectro de RMN ¹³C do DT-4Cl-4Cl.

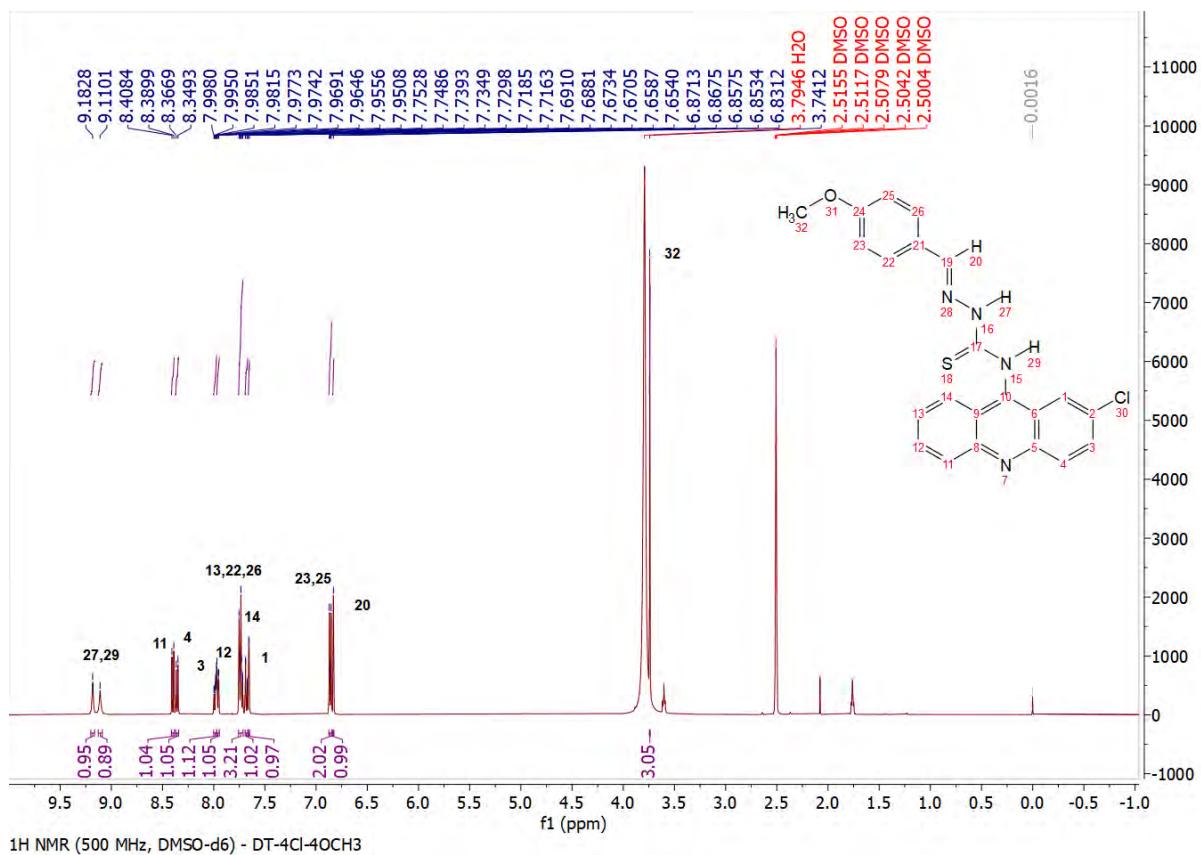


Figura S64. Espectro de RMN ¹H do DT-4Cl-4OCH₃.

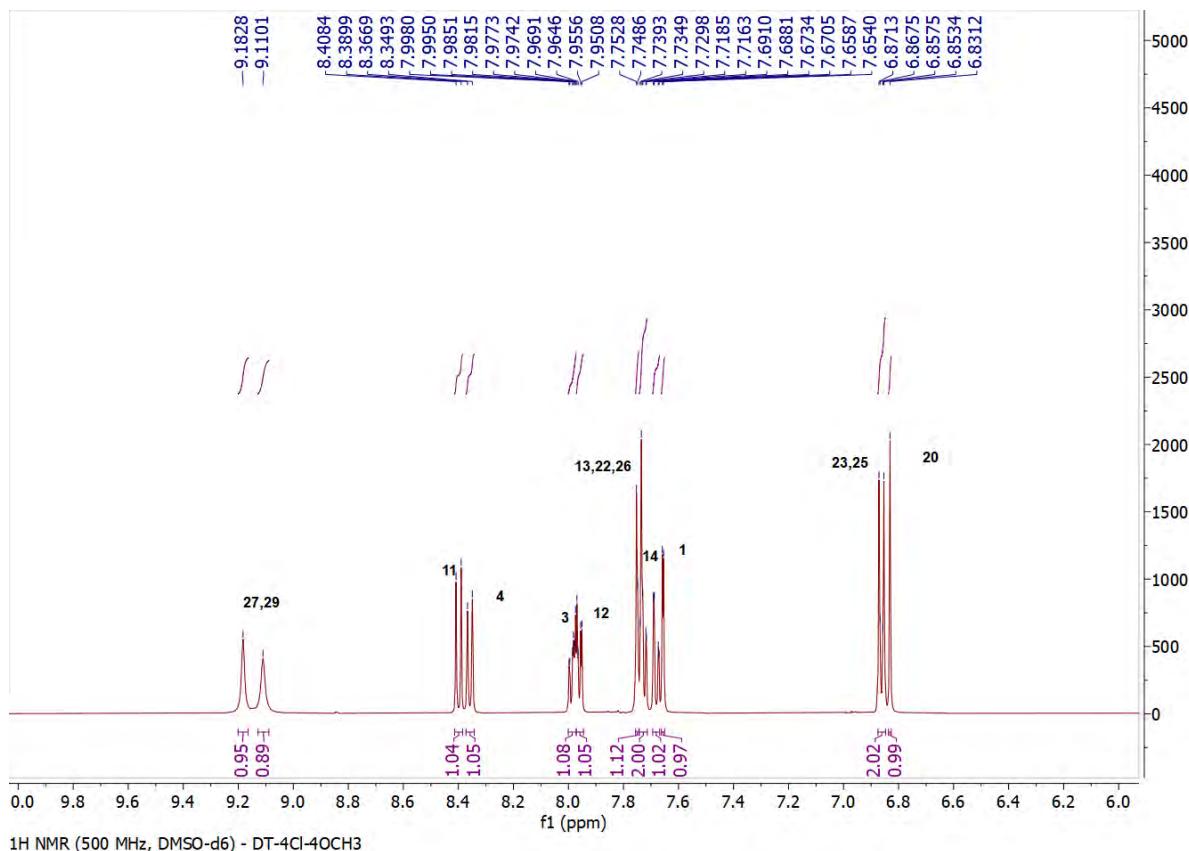


Figura S65. Expansão do espectro de RMN ¹H do DT-4Cl-4OCH₃.

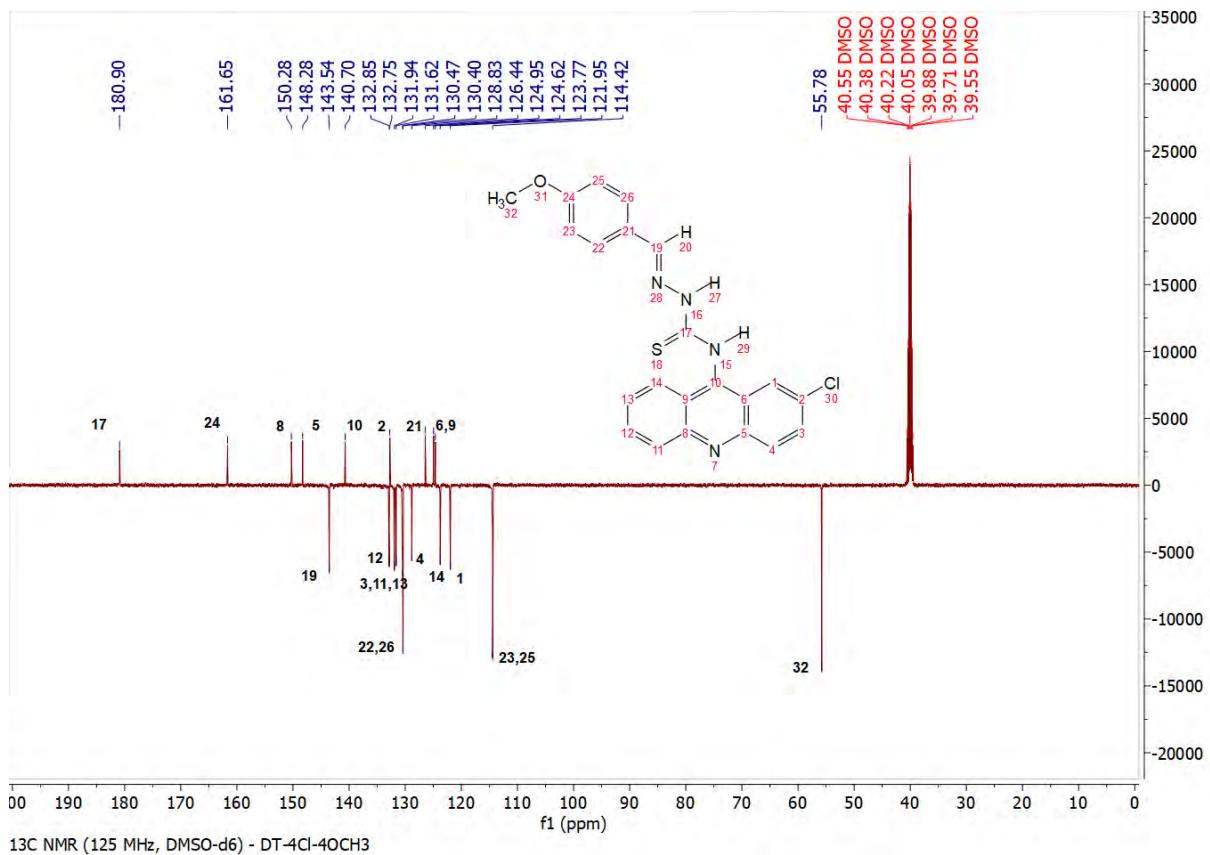


Figura S66. Espectro de RMN ^{13}C do DT-4Cl-4OCH₃.

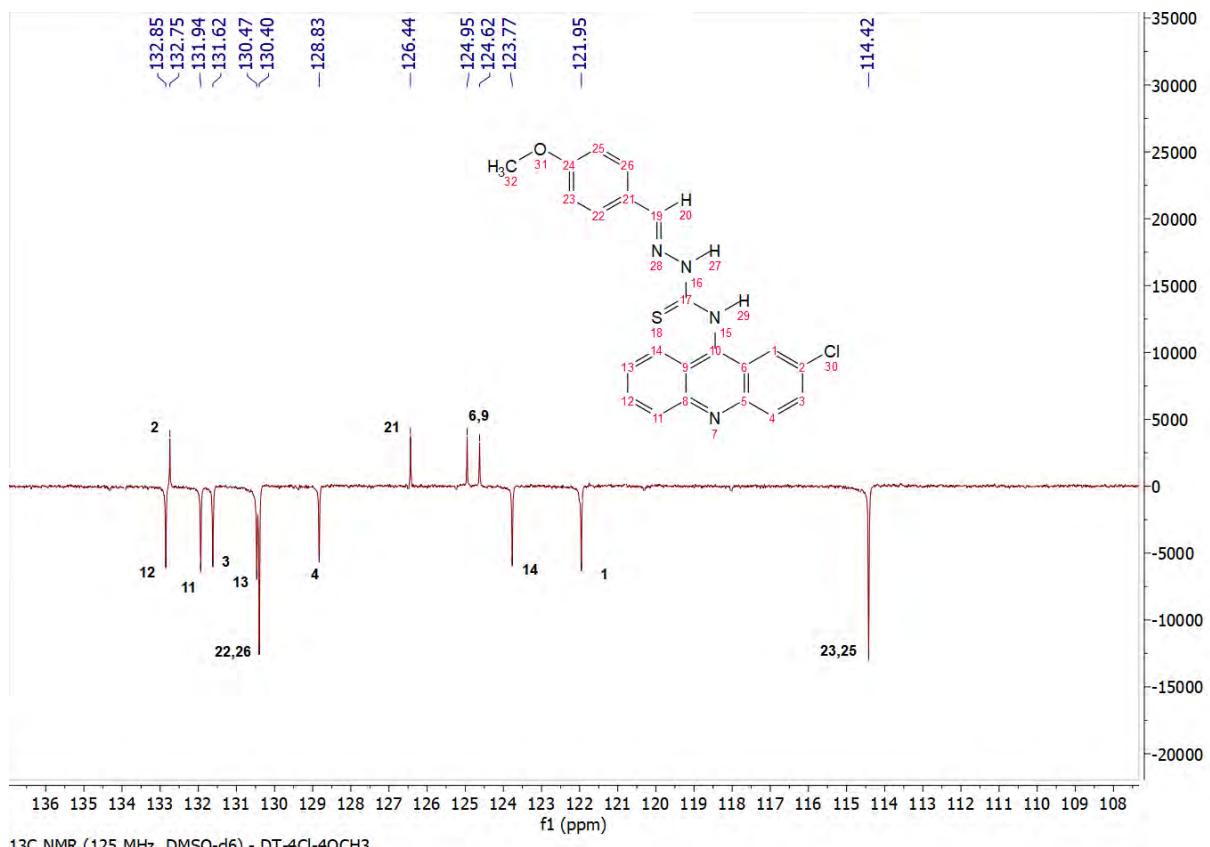
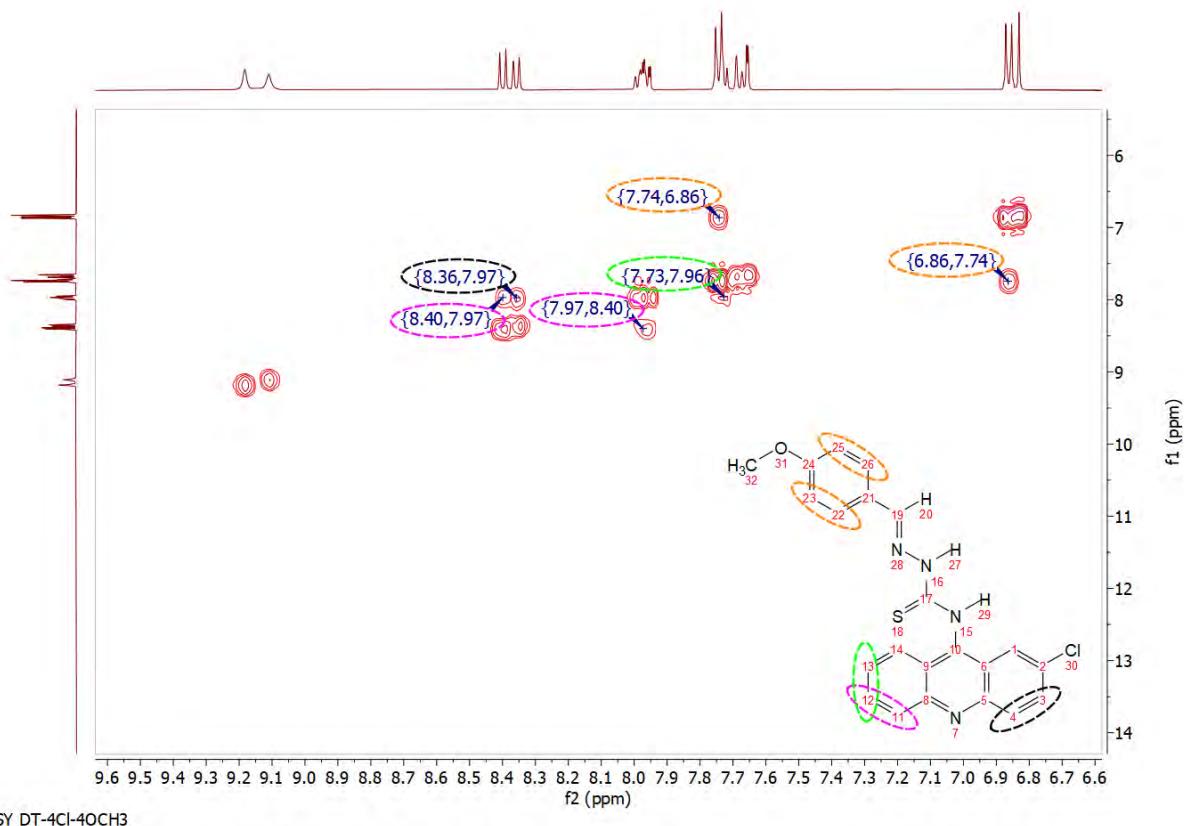
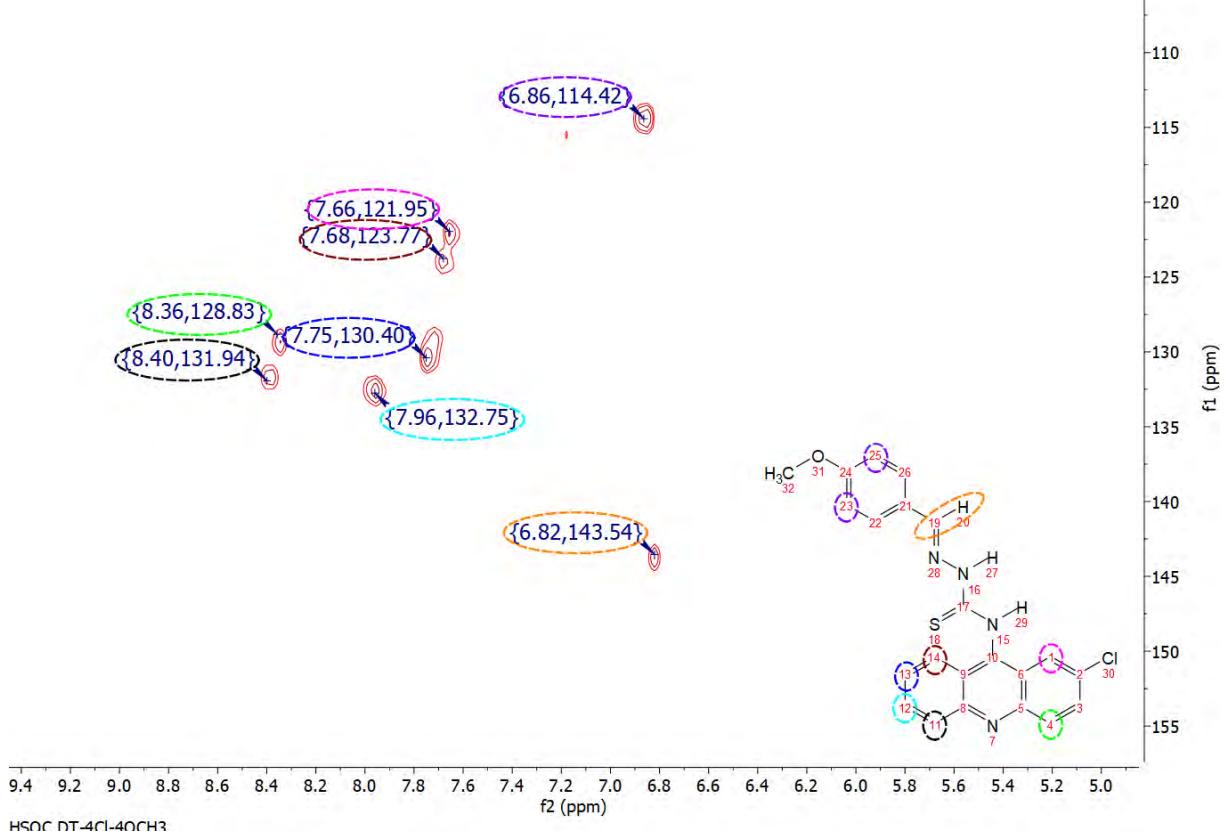


Figura S67. Expansão do espectro de RMN ^{13}C do DT-4Cl-4OCH₃.



COSY DT-4Cl-4OCH₃

Figura S68. Espectro de correlação COSY do DT-4Cl-4OCH₃.



HSQC DT-4Cl-4OCH₃

Figura S69. Espectro de correlação HSQC do DT-4Cl-4OCH₃.

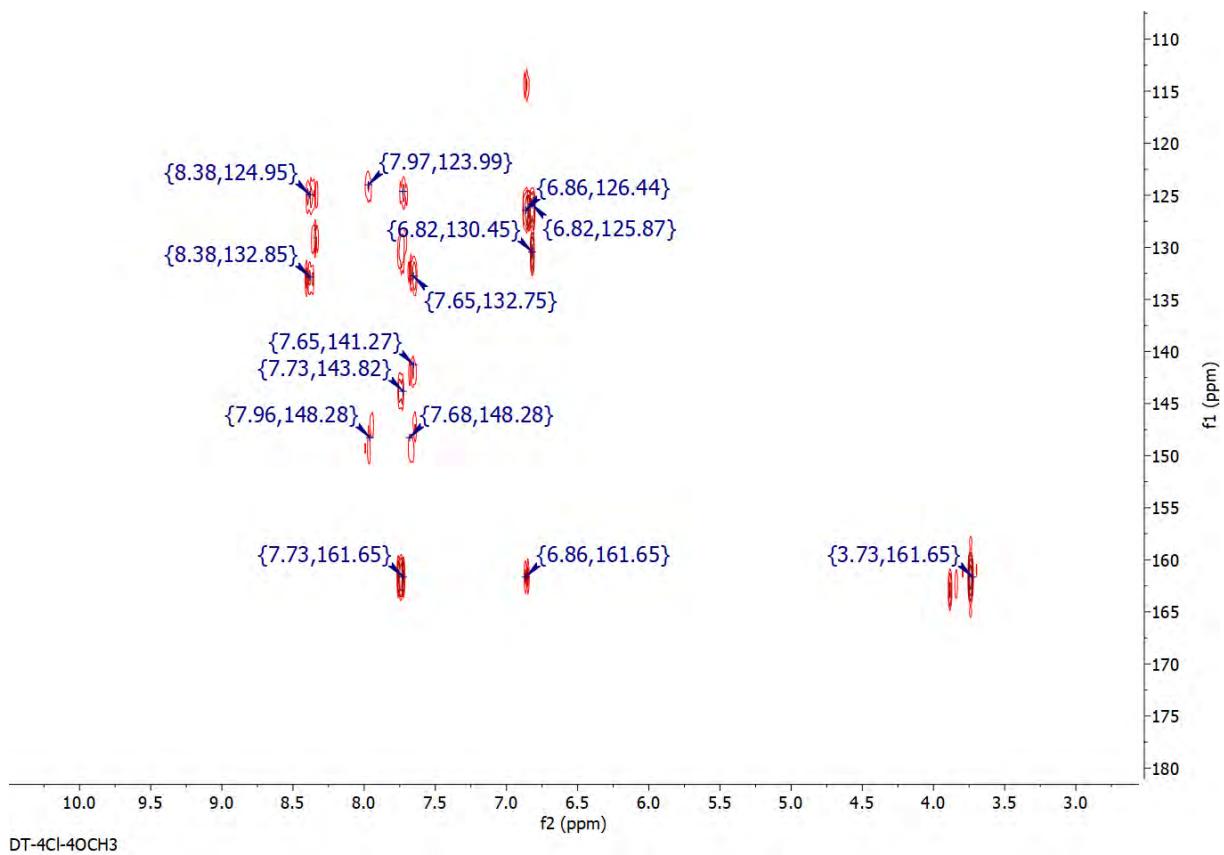


Figura S70. Espectro de correlação HMBC do DT-4Cl-4OCH₃.

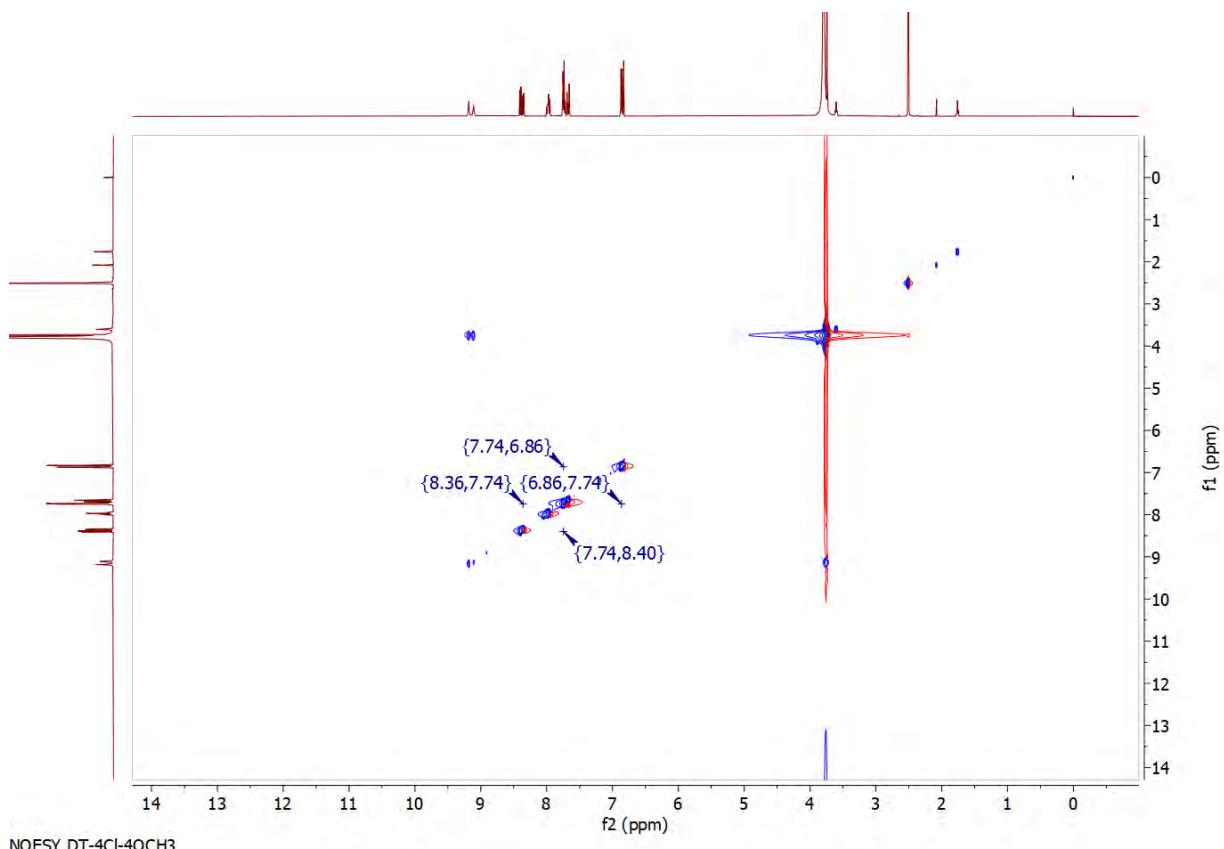


Figura S71. Espectro de correlação NOESY do DT-4Cl-4OCH₃.

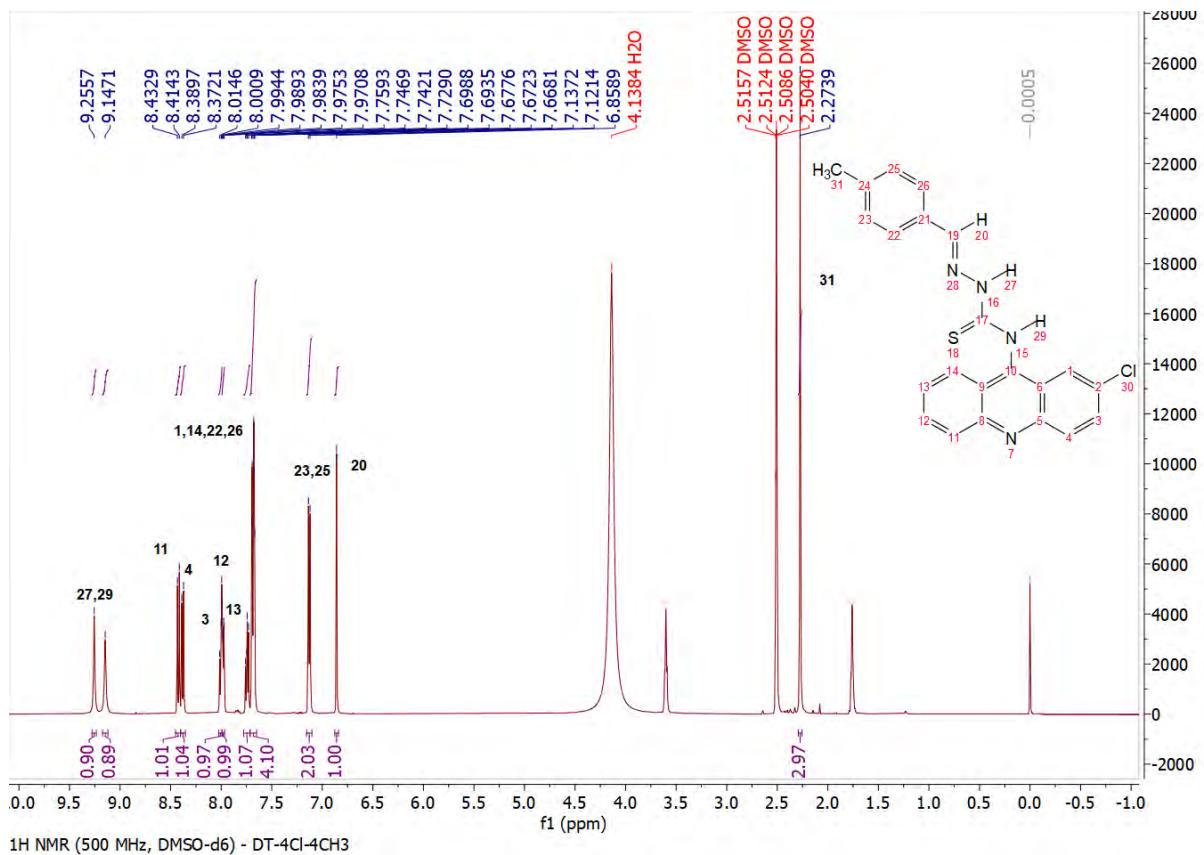


Figura S72. Espectro de RMN ^1H do DT-4Cl-4CH₃.

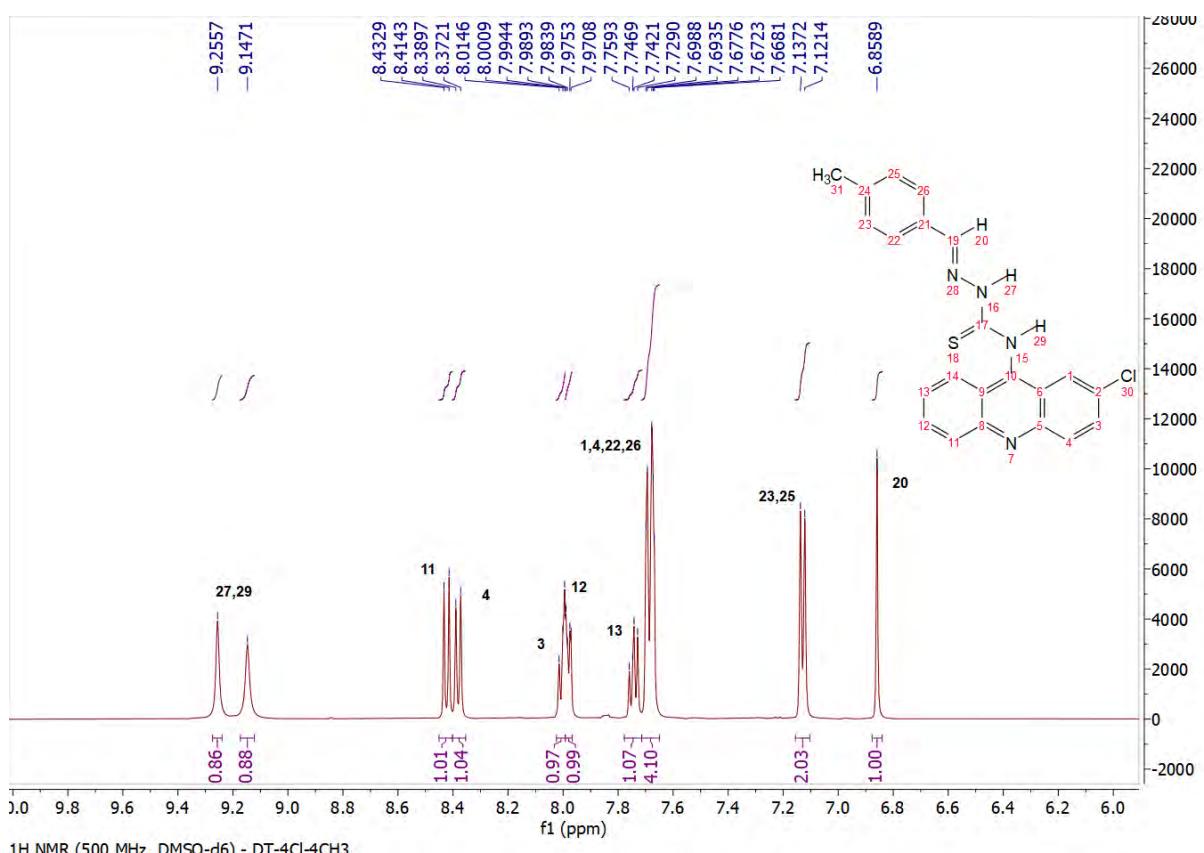


Figura S73. Expansão do espectro de RMN ^1H do DT-4Cl-4CH₃.

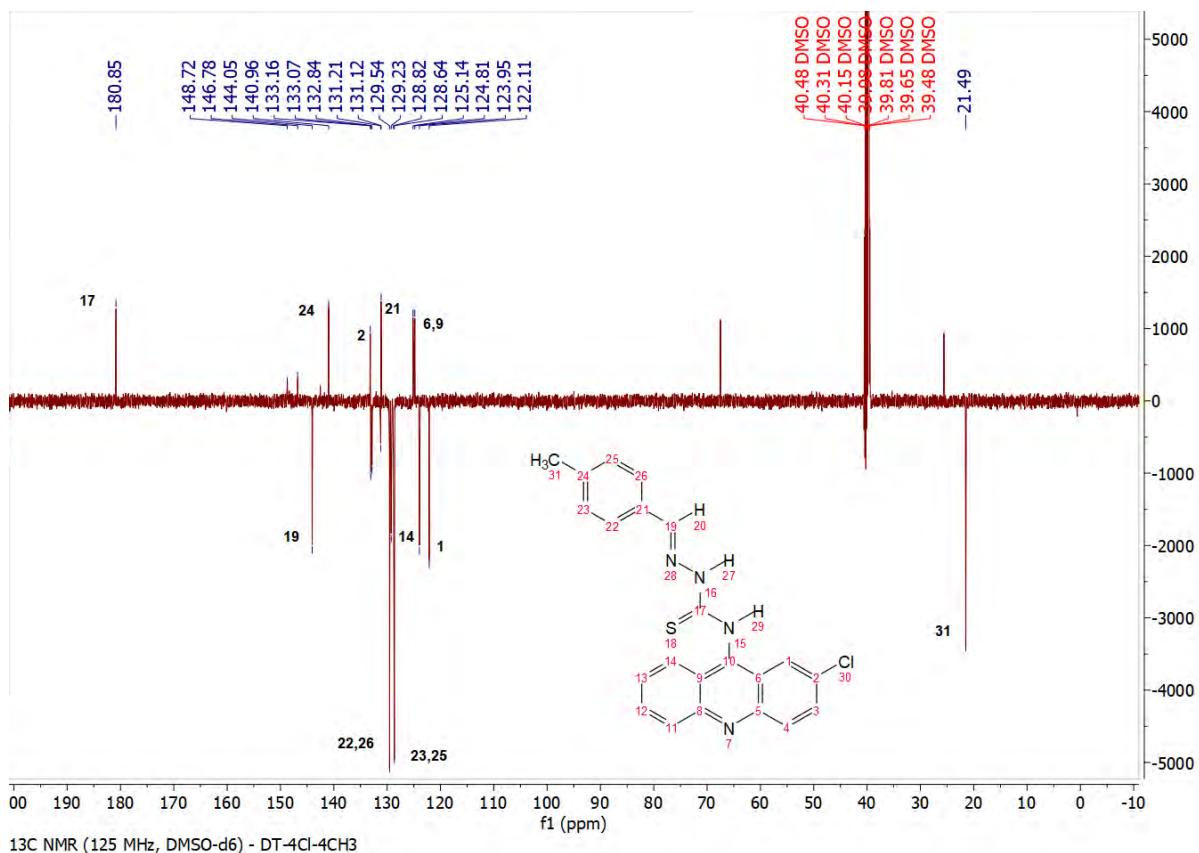


Figura S74. Espectro de RMN ^{13}C do DT-4Cl-4CH₃.

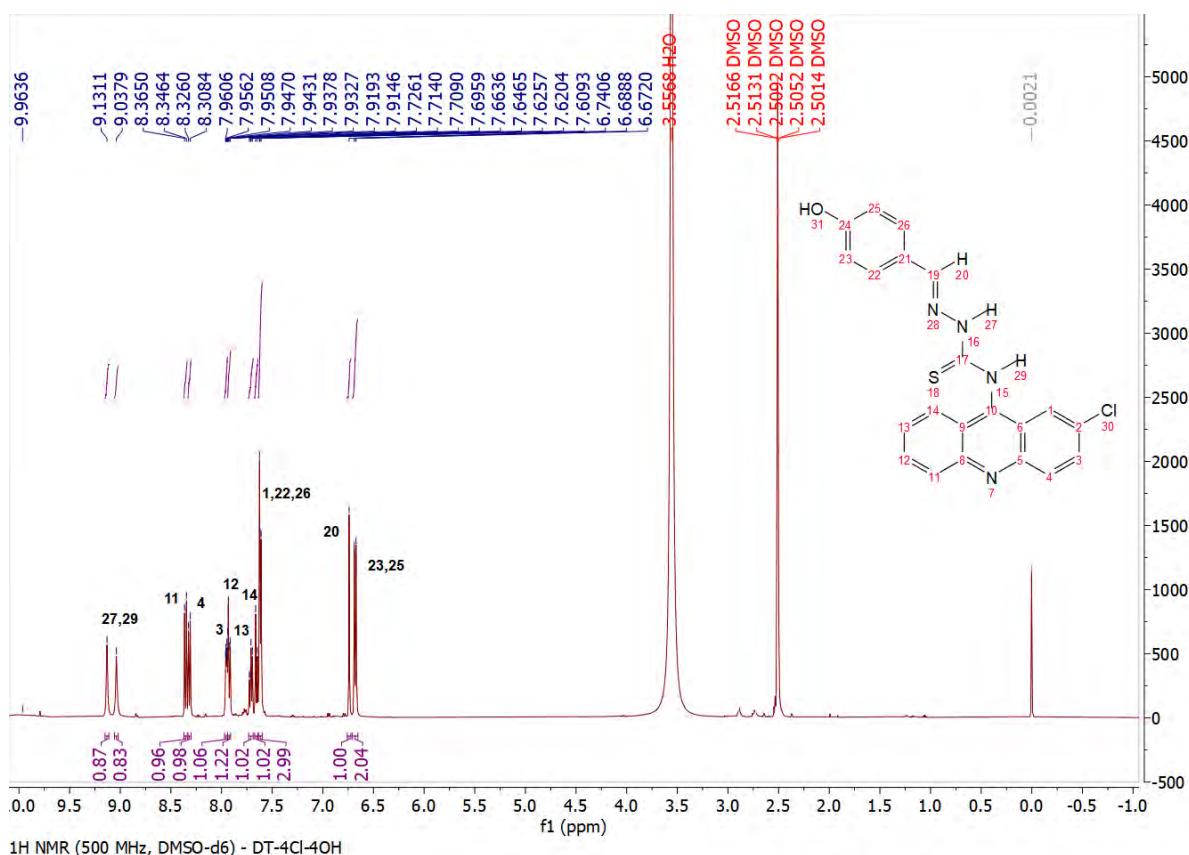


Figura S75. Espectro de RMN ^1H do DT-4Cl-4OH.

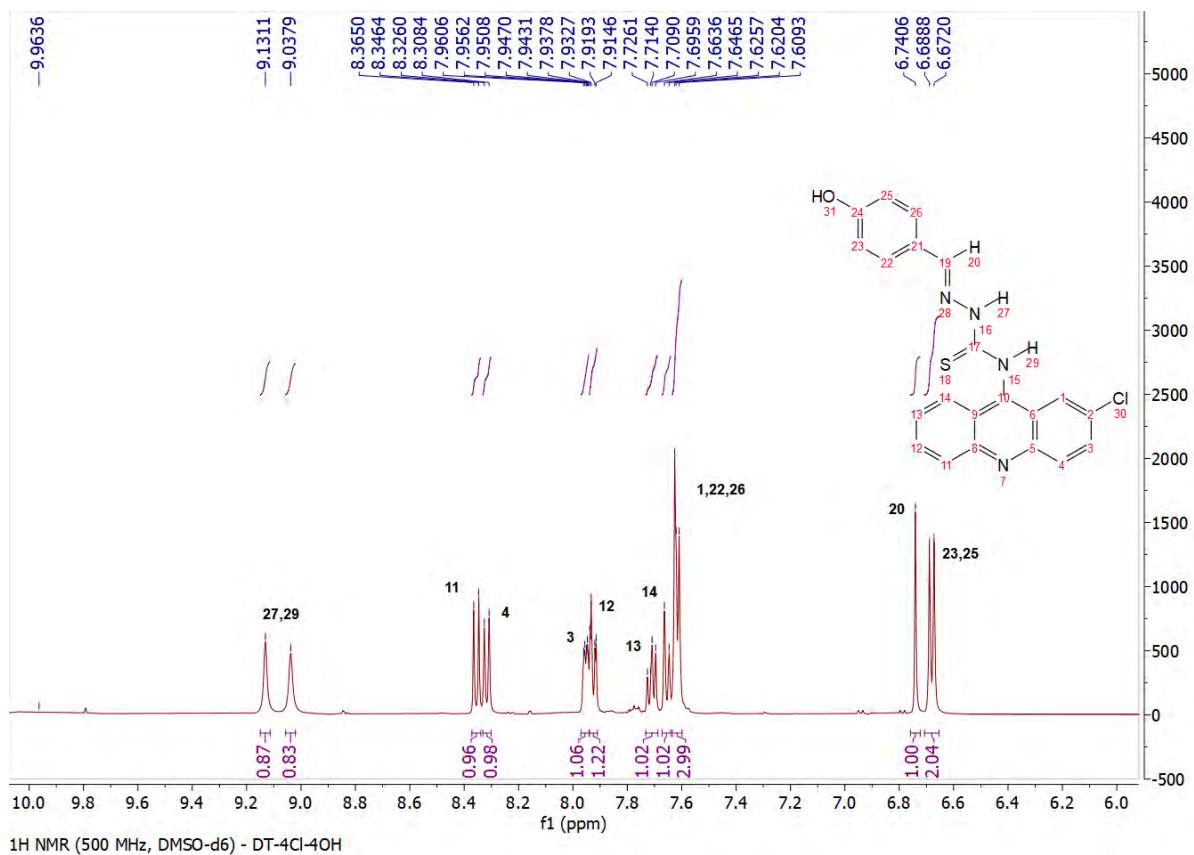


Figura S76. Expansão do espectro de RMN ¹H do DT-4Cl-4OH.

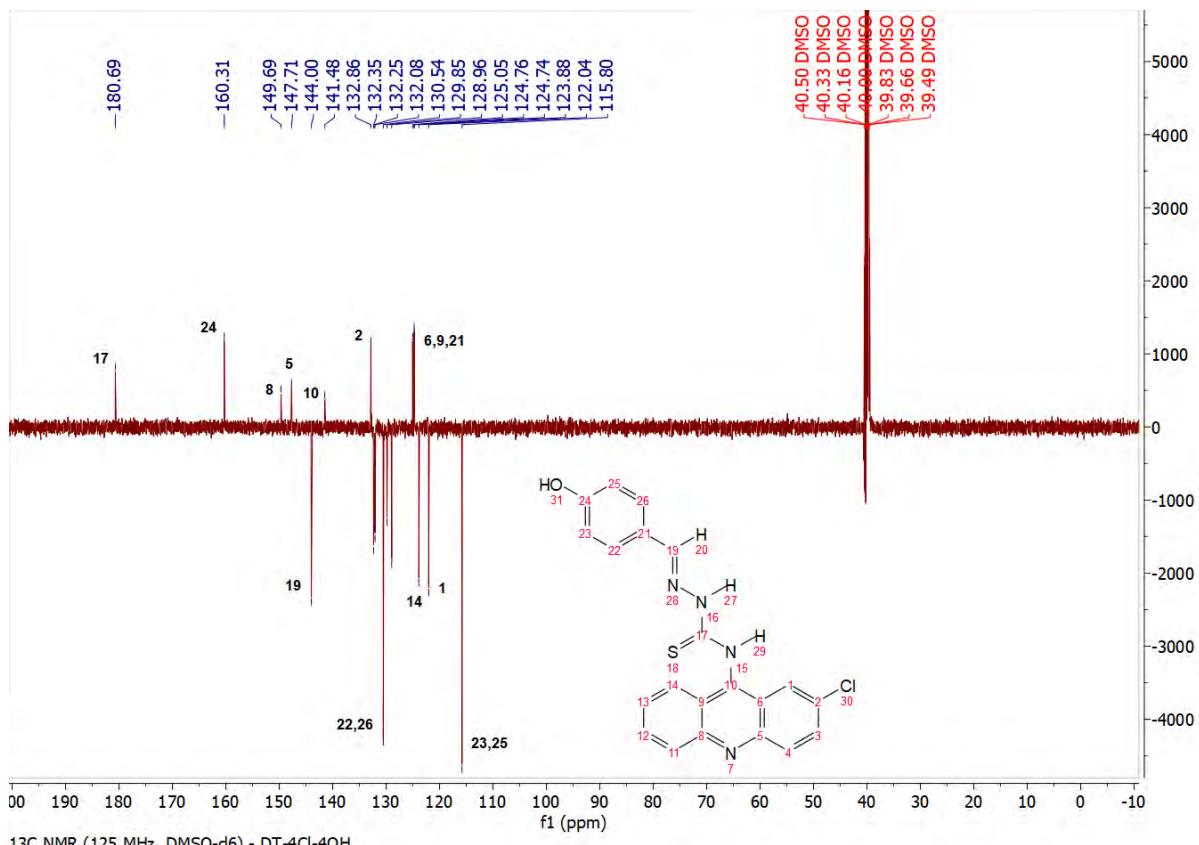


Figura S77. Espectro de RMN ¹³C do DT-4Cl-4OH.

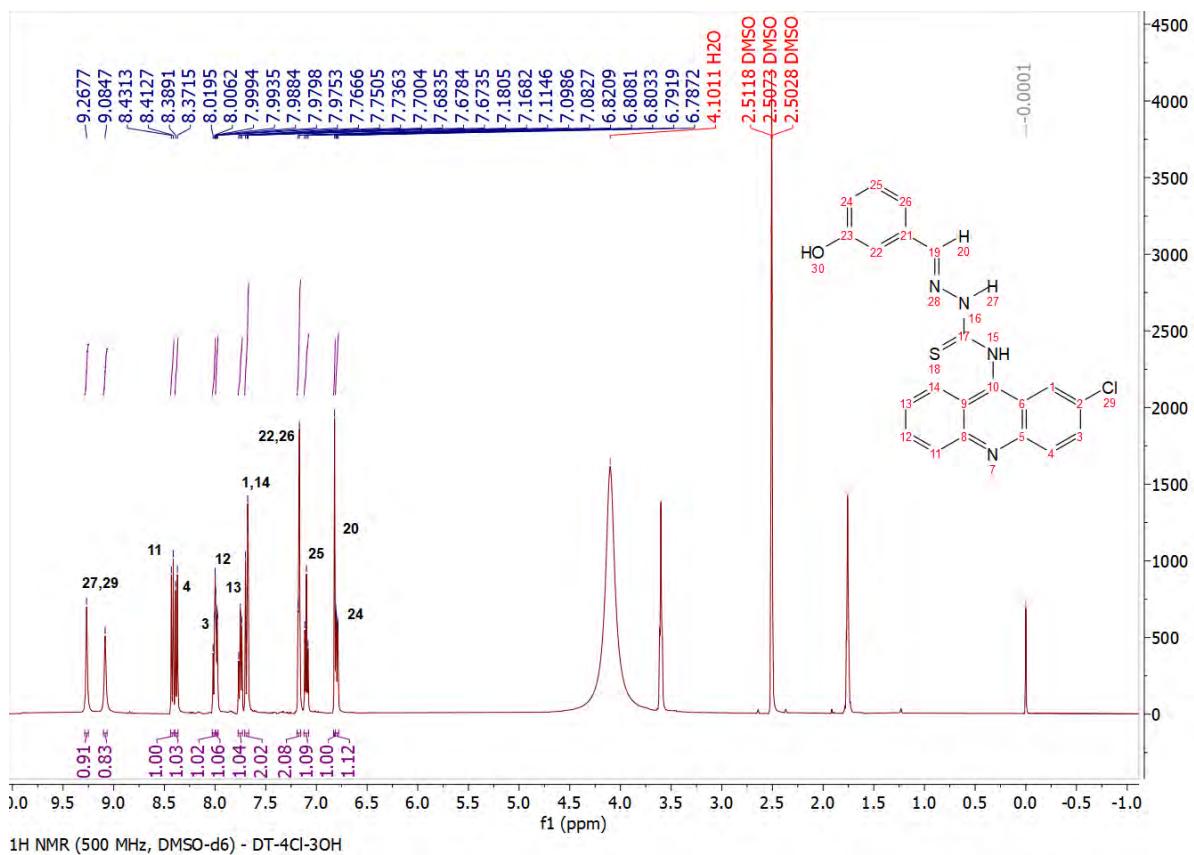


Figura S78. Espectro de RMN ^1H do DT-4Cl-3OH.

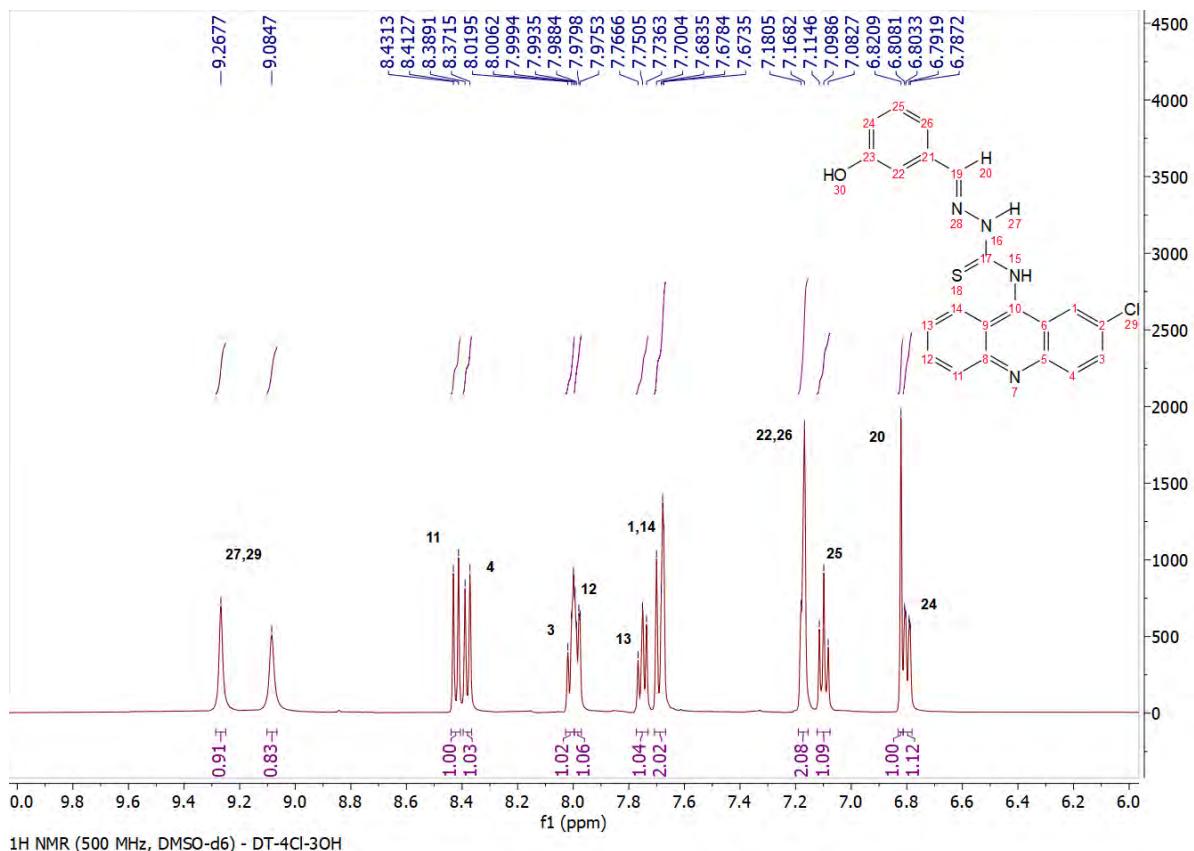


Figura S79. Expansão do espectro de RMN ^1H do DT-4Cl-3OH.

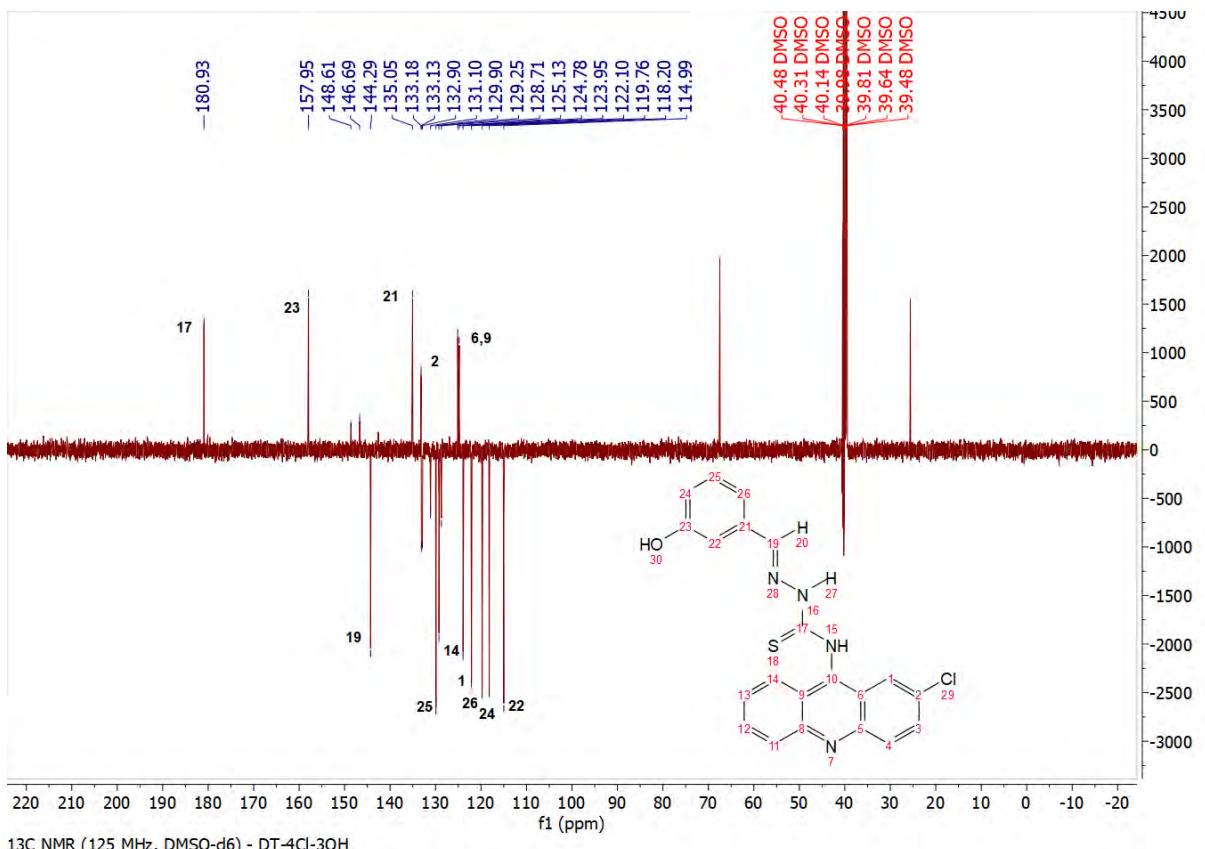
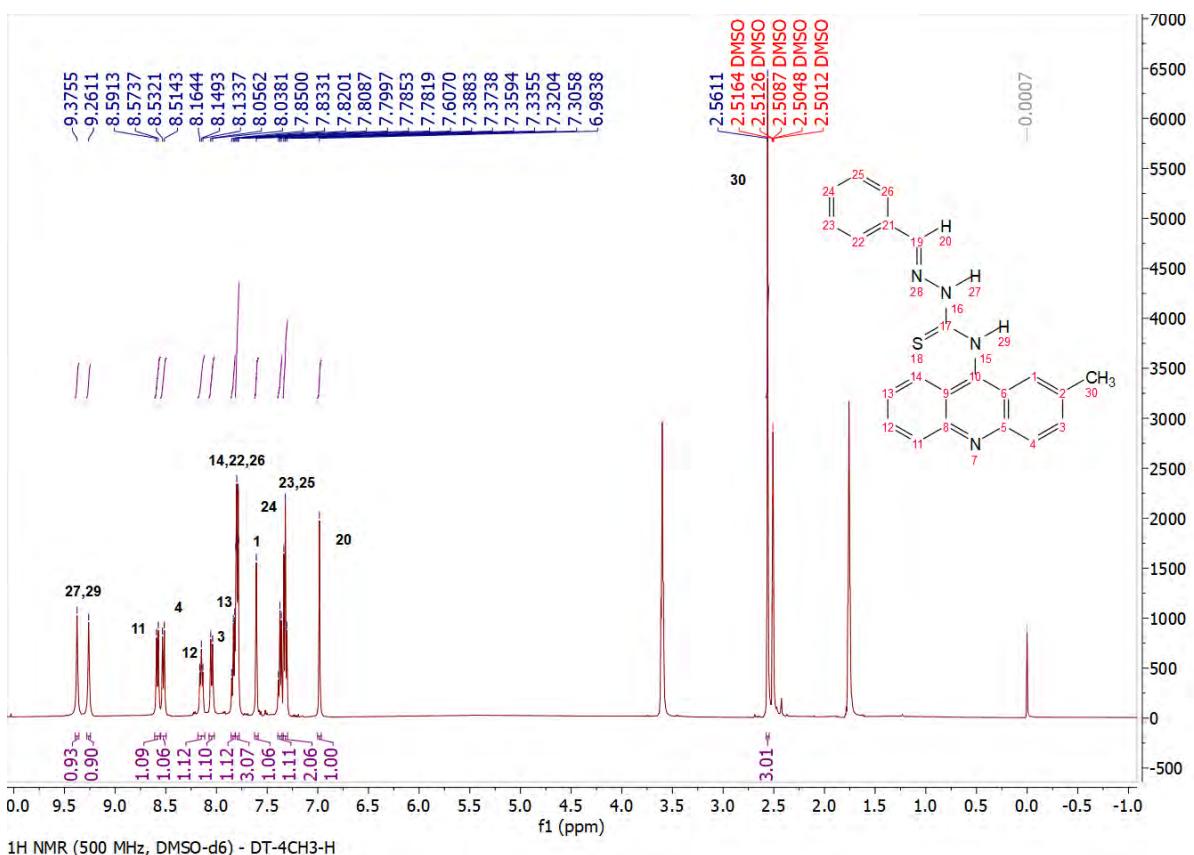


Figura S80. Espectro de RMN ¹³C do DT-4Cl-3OH.



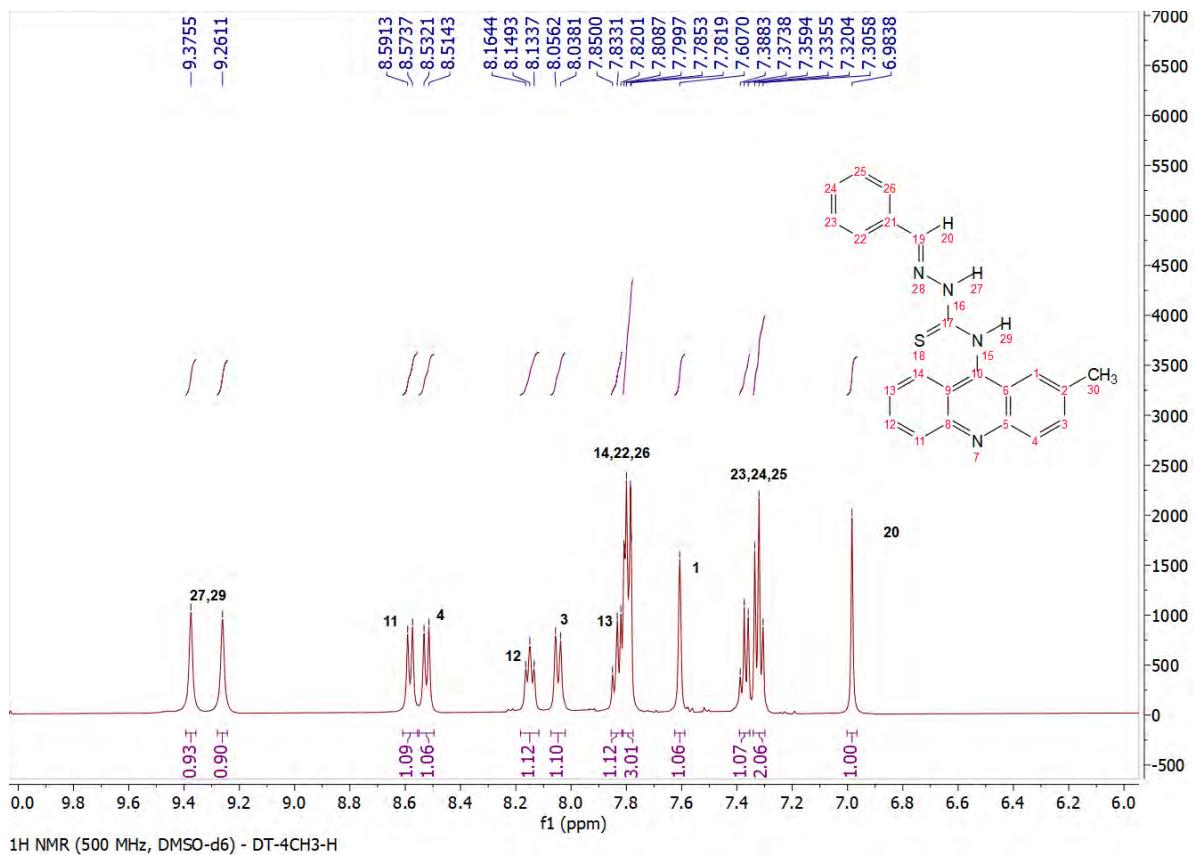


Figura S82. Expansão do espectro de RMN ^1H do DT-4CH₃-H.

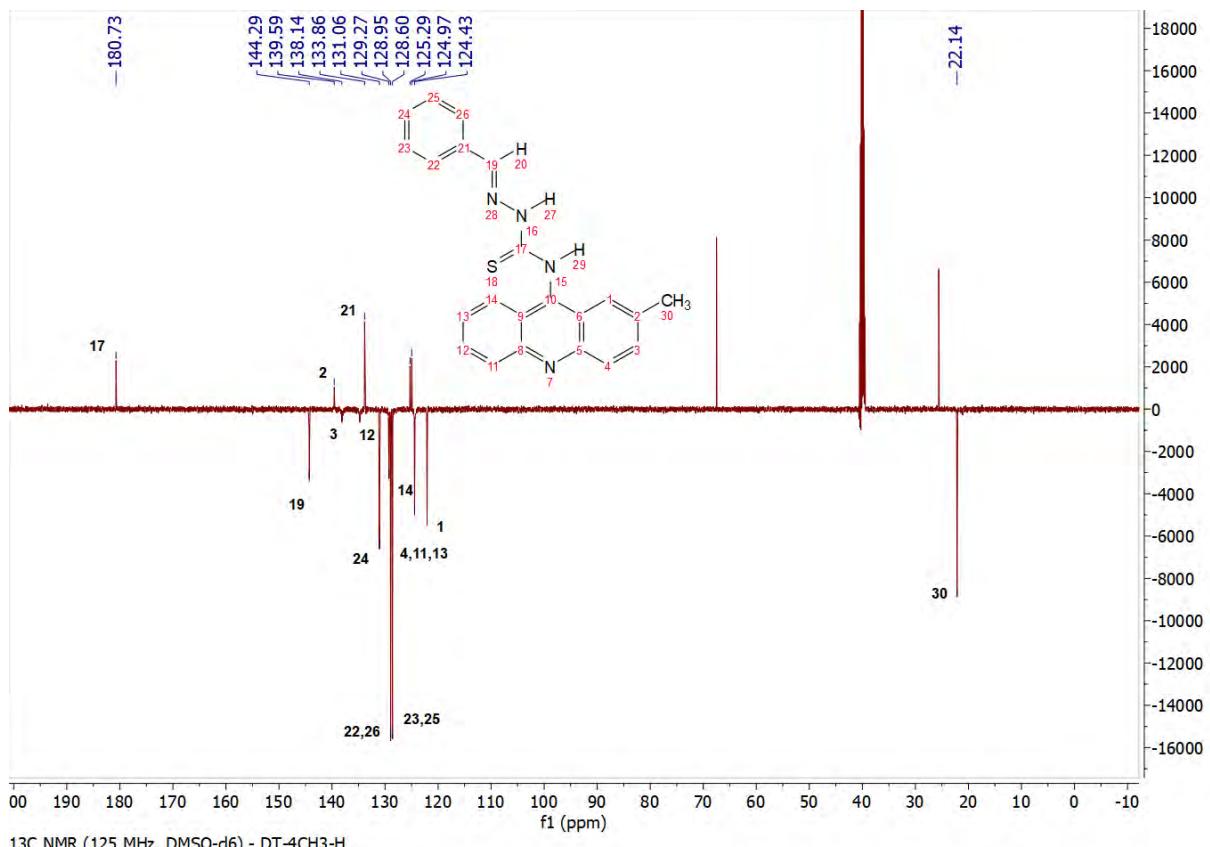


Figura S83. Espectro de RMN ^{13}C do DT-4CH₃-H.

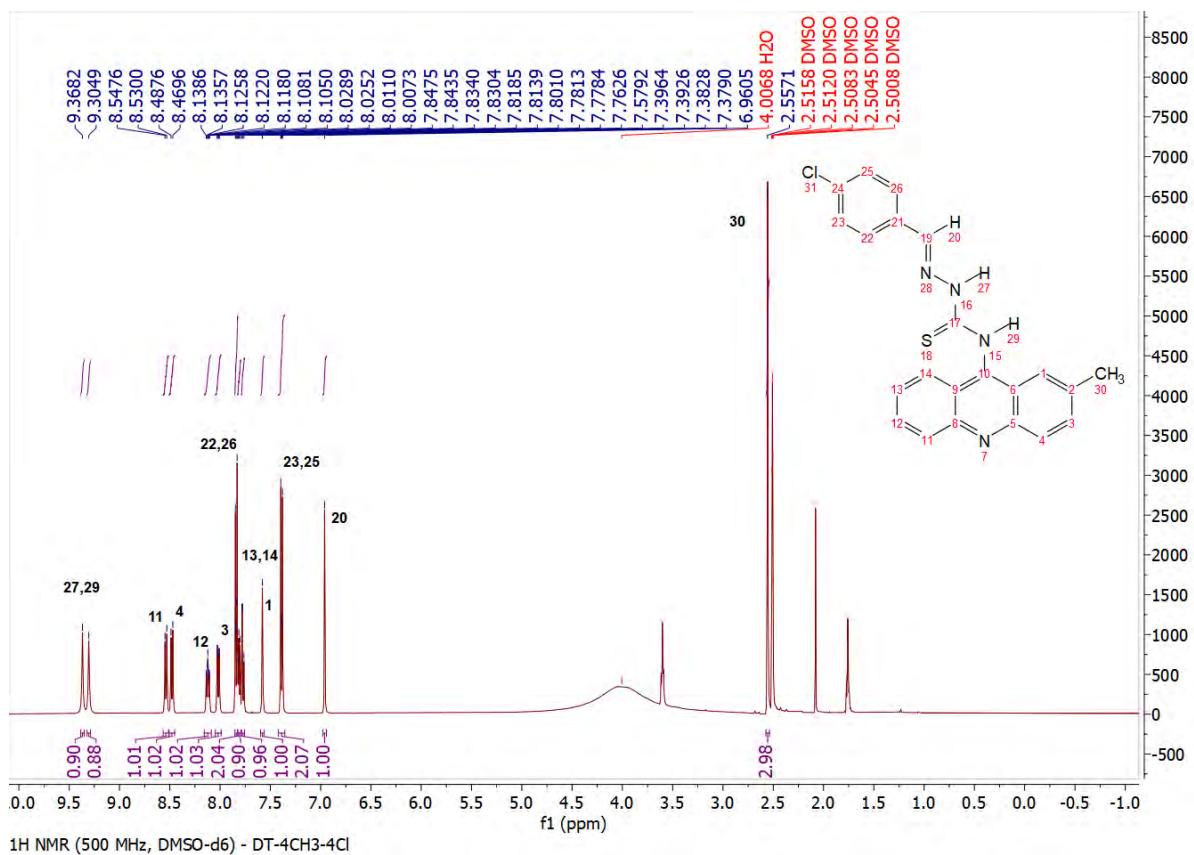


Figura S84. Espectro de RMN ^1H do DT-4CH₃-4Cl.

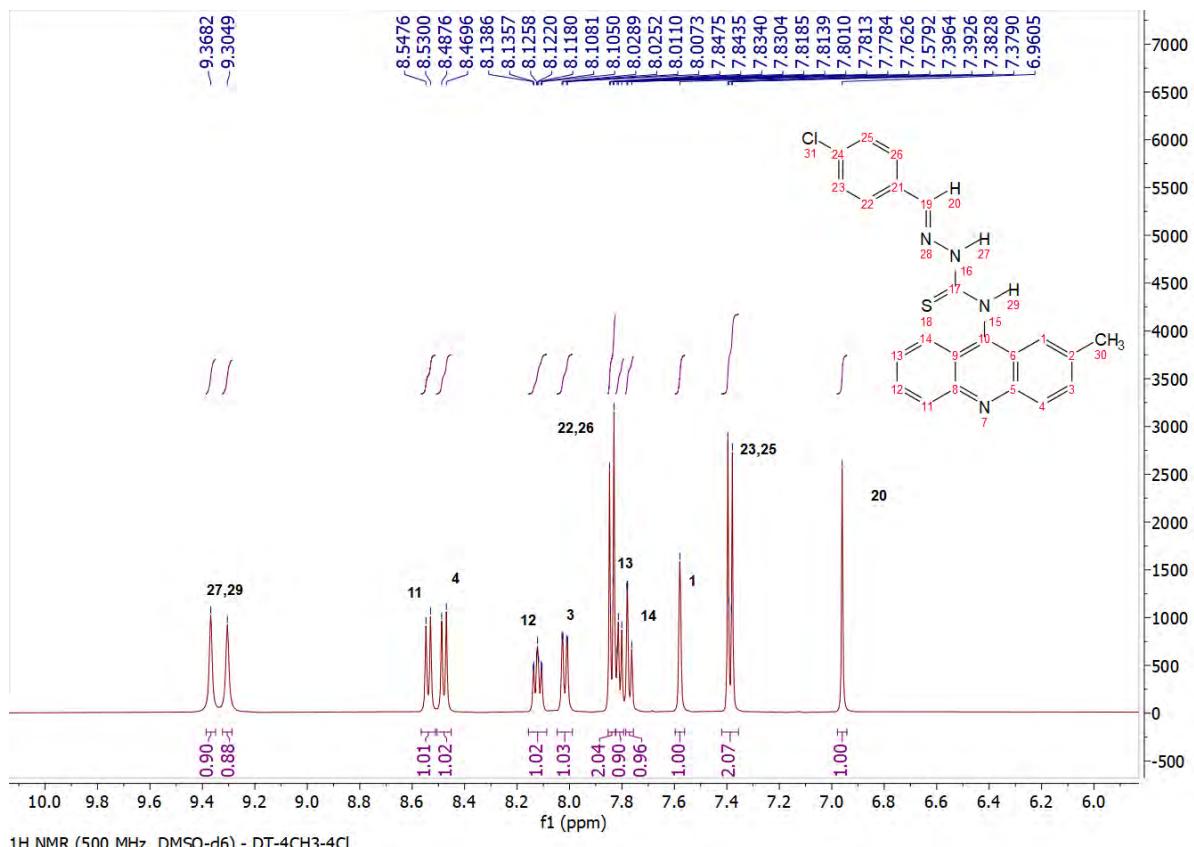


Figura S85. Expansão do espectro de RMN ^1H do DT-4CH₃-4Cl.

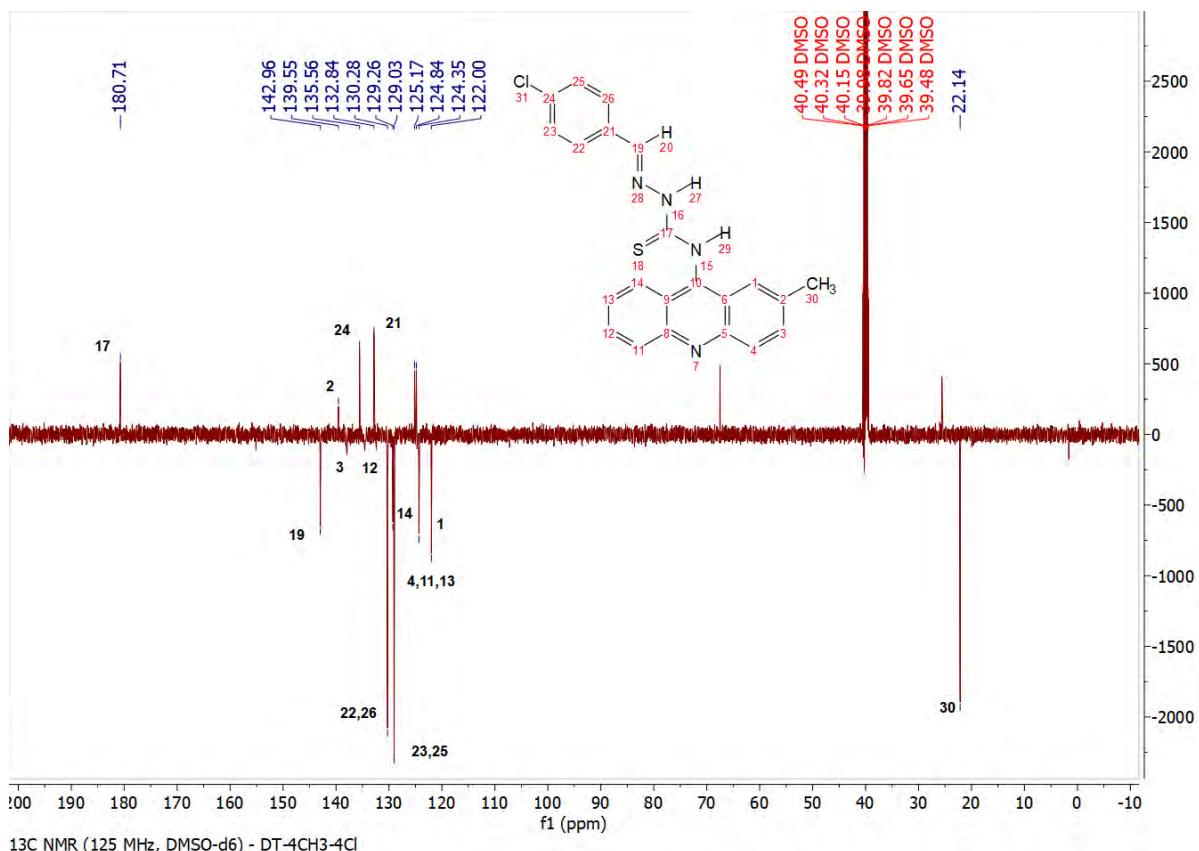


Figura S86. Espectro de RMN ^{13}C do DT-4CH₃-4Cl.

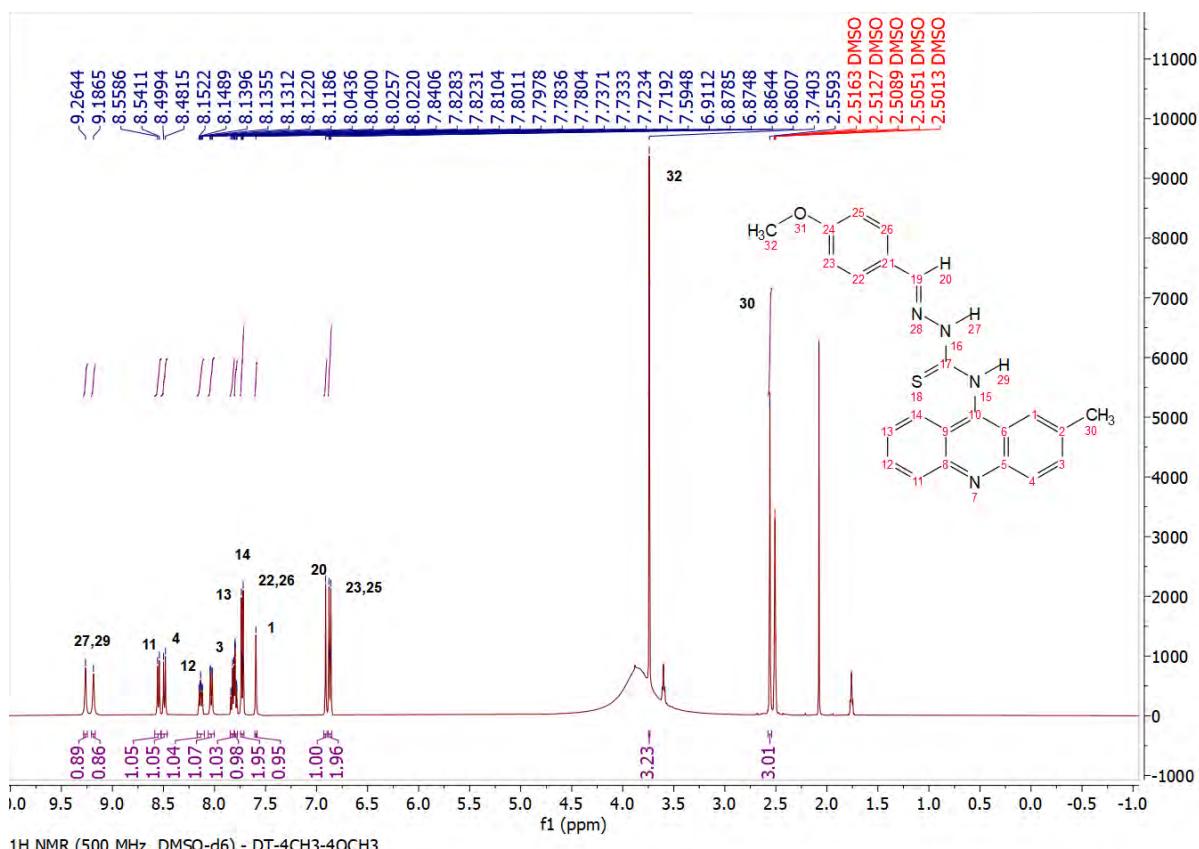


Figura S87. Espectro de RMN ^1H do DT-4CH₃-4OCH₃.

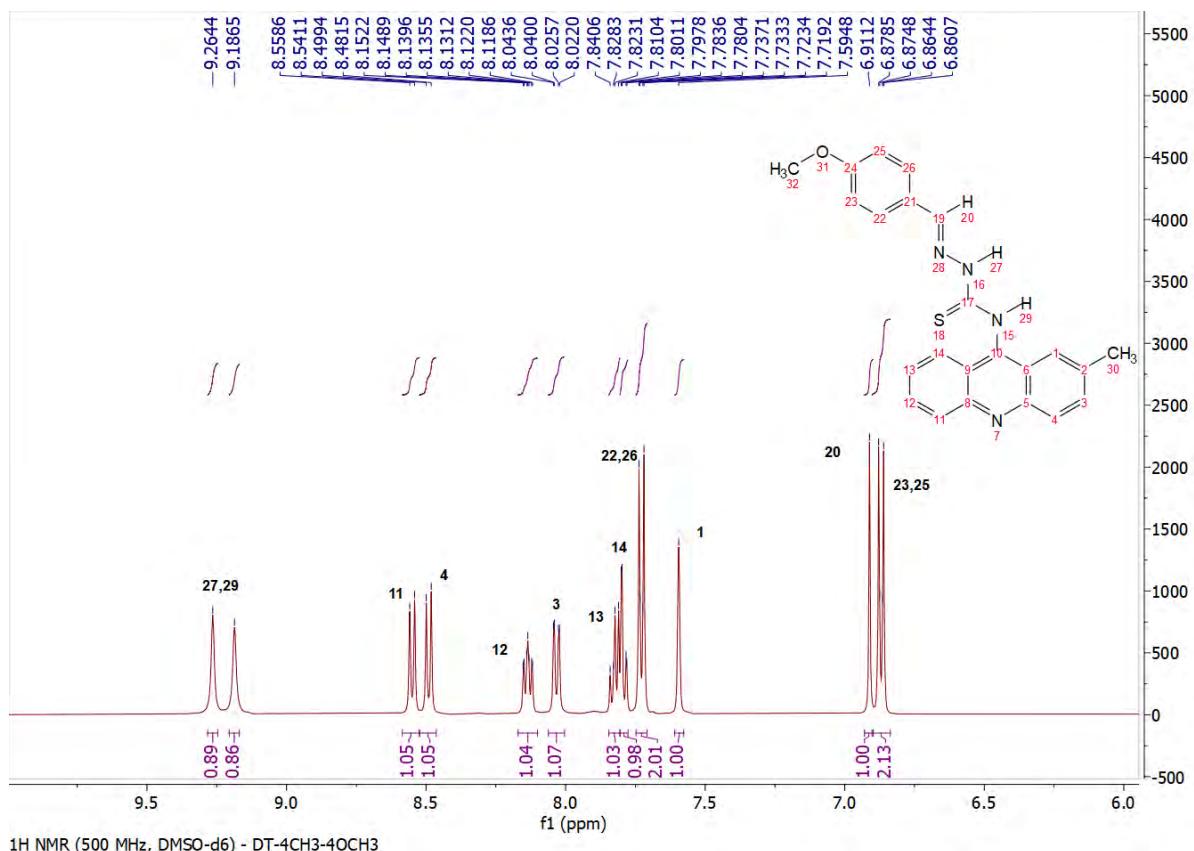


Figura S88. Expansão do espectro de RMN ^1H do **DT-4CH₃-4OCH₃**.

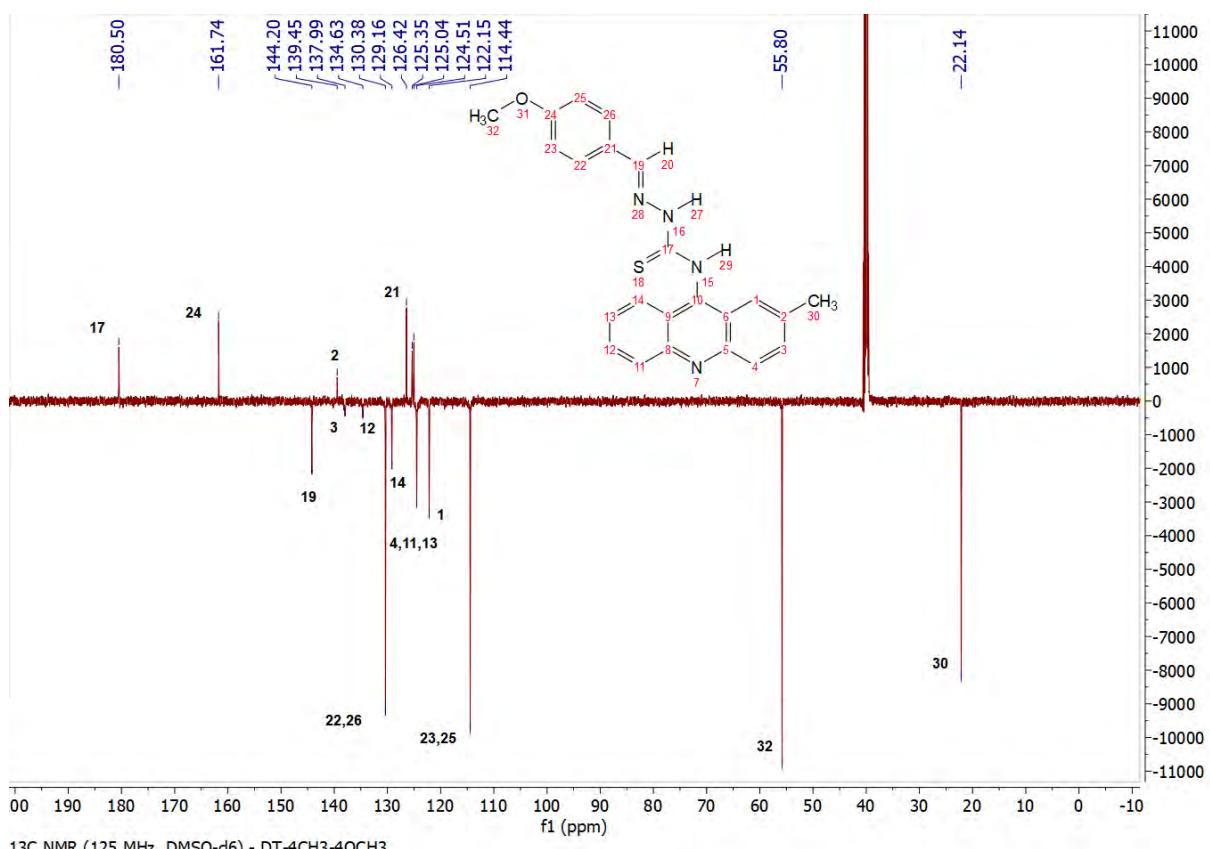


Figura S89. Espectro de RMN ^{13}C do PT-4CH₃-4OCH₃.

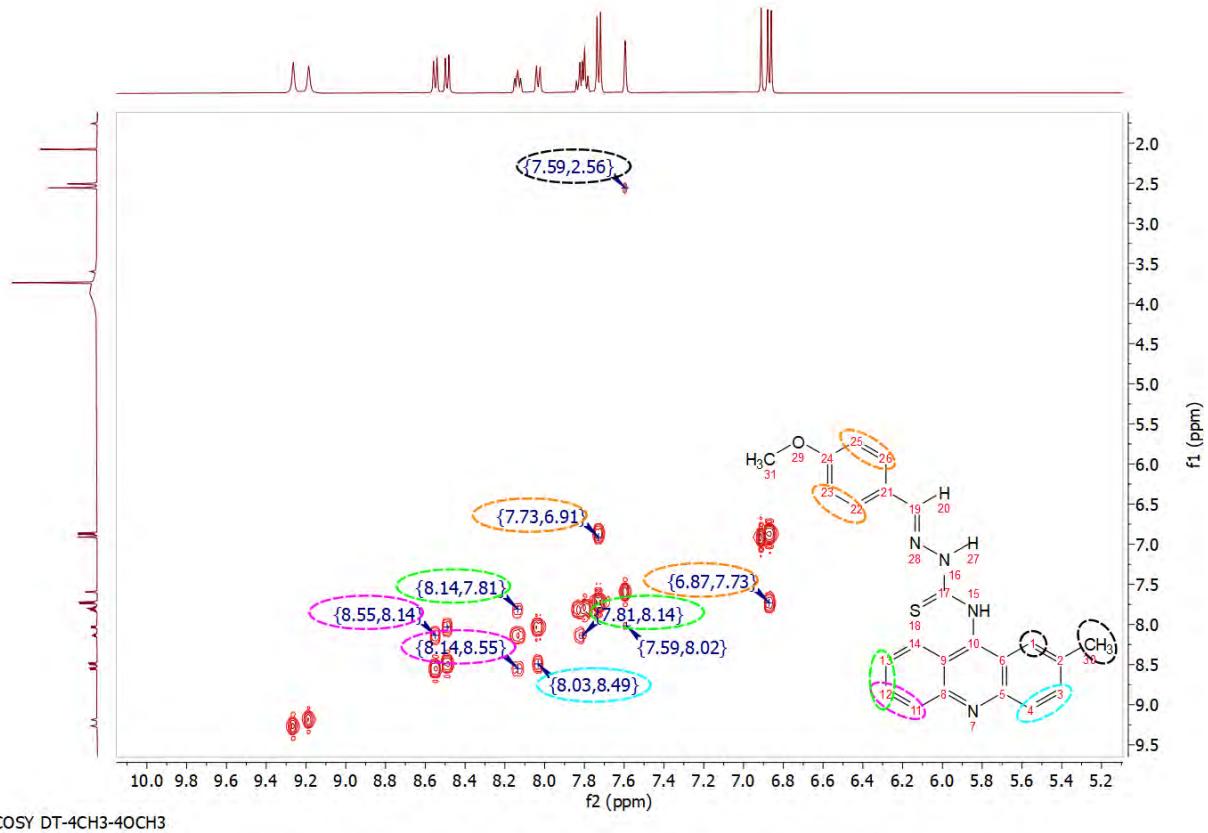


Figura S90. Espectro de correlação COSY do DT-4CH₃-4OCH₃.

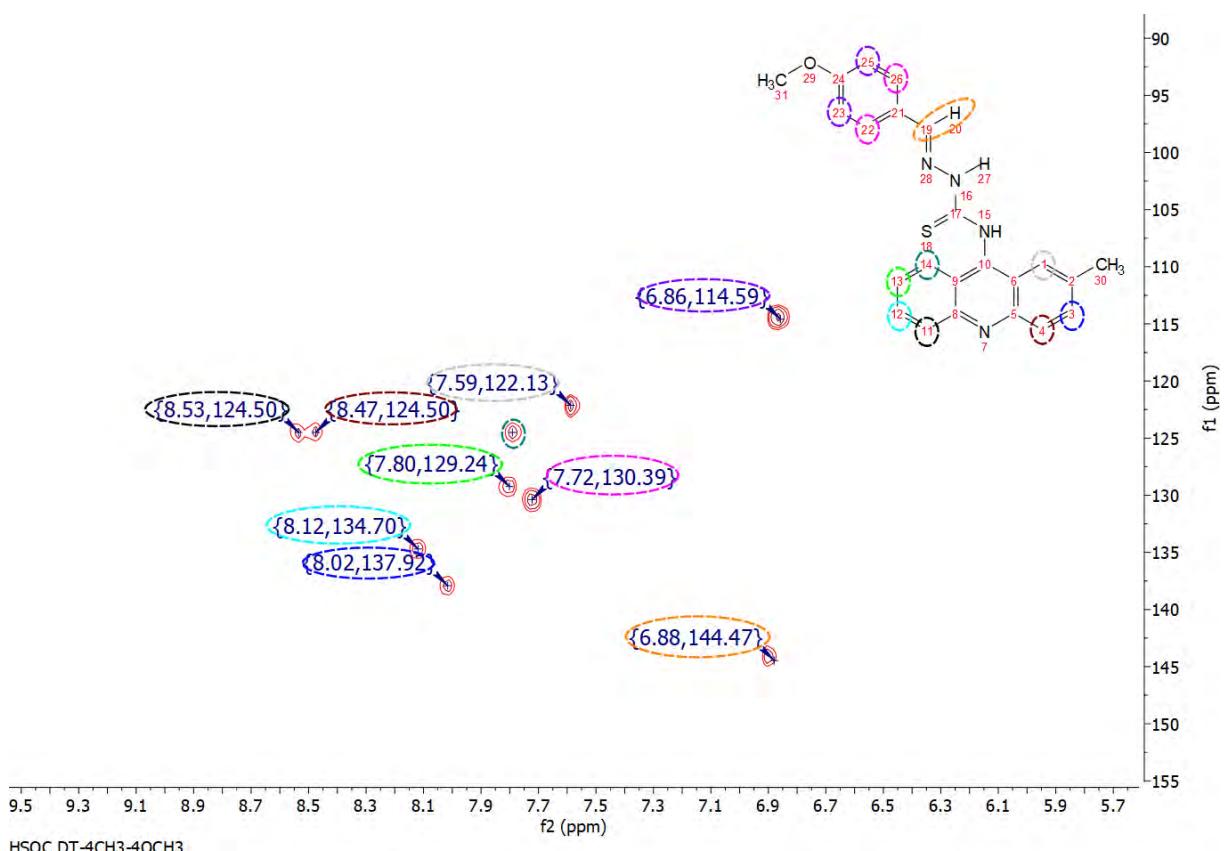


Figura S91. Espectro de correlação HSQC do DT-4CH₃-4OCH₃.

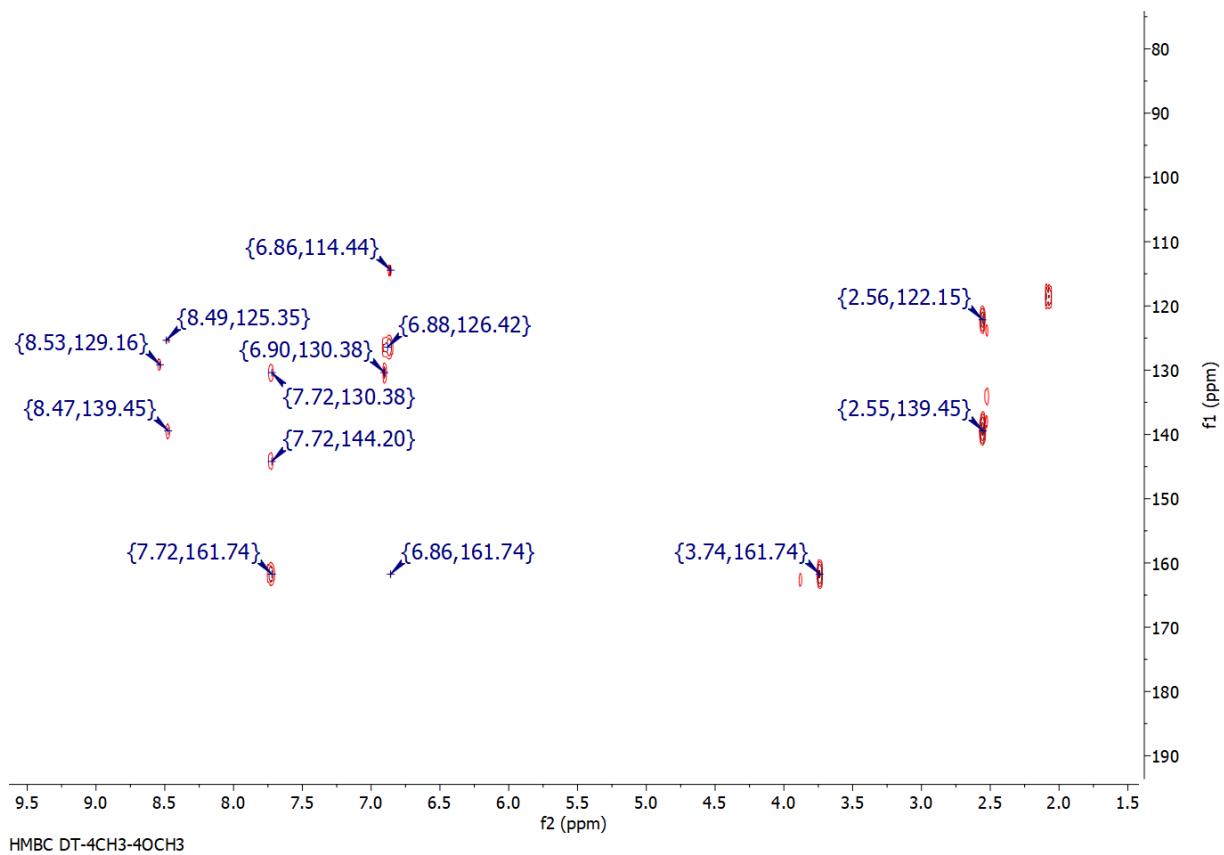


Figura S92. Espectro de correlação HMBC do DT-4CH₃-4OCH₃.

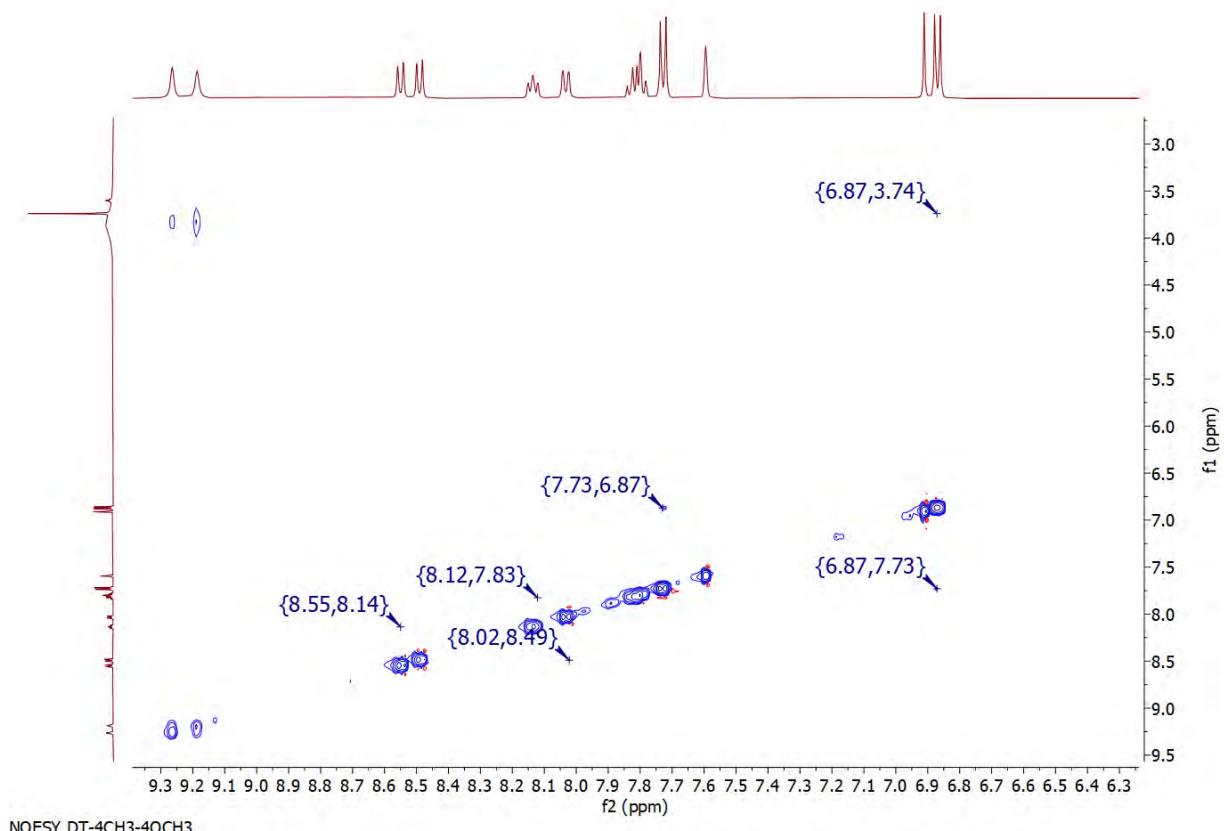


Figura S93. Espectro de correlação NOESY do DT-4CH₃-4OCH₃.

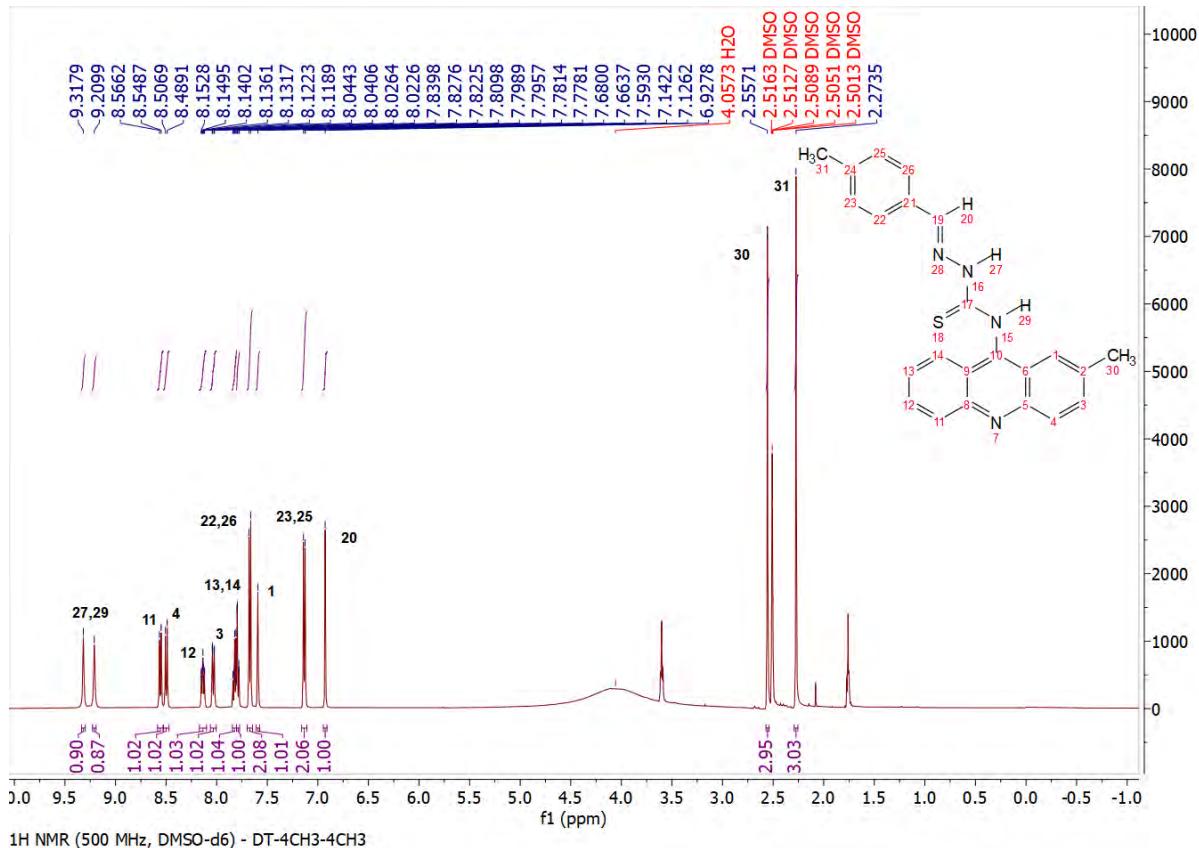


Figura S94. Espectro de RMN ¹H do DT-4CH₃-4CH₃.

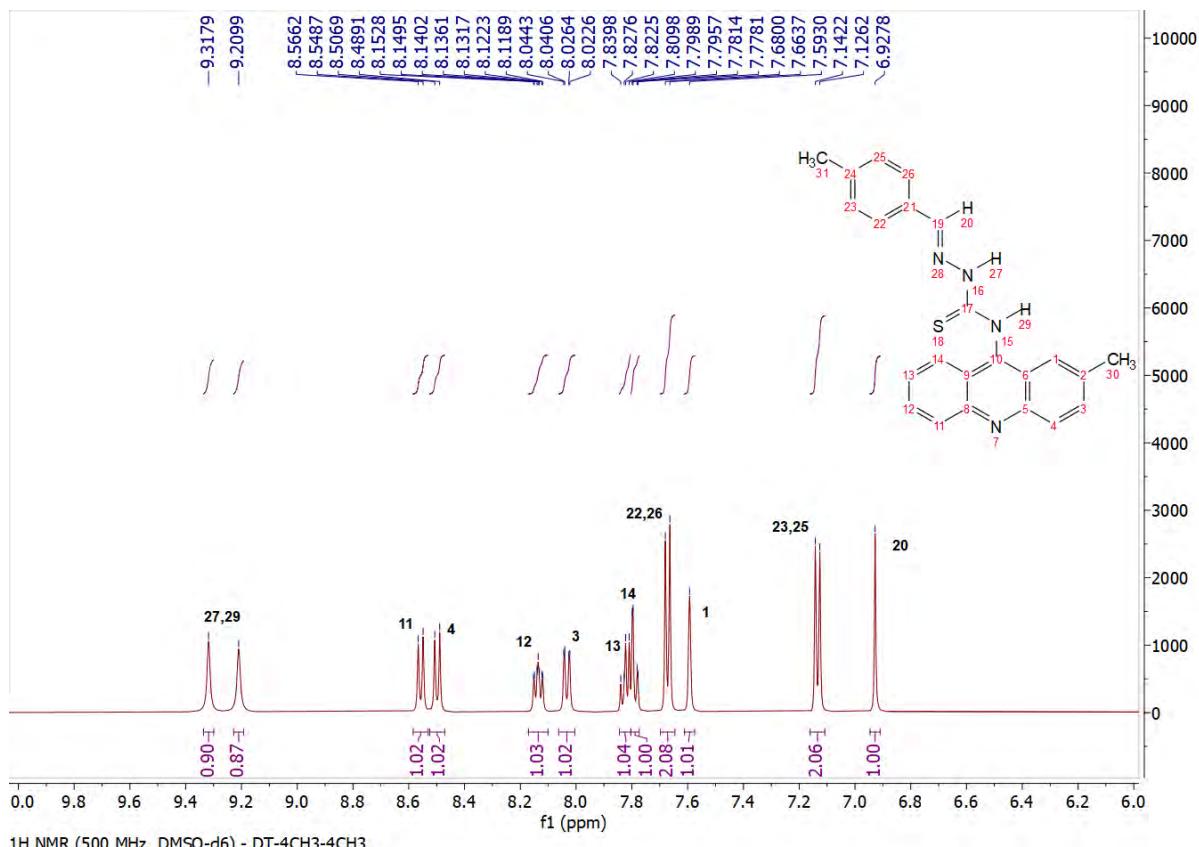


Figura S95. Expansão do espectro de RMN ¹H do DT-4CH₃-4CH₃.

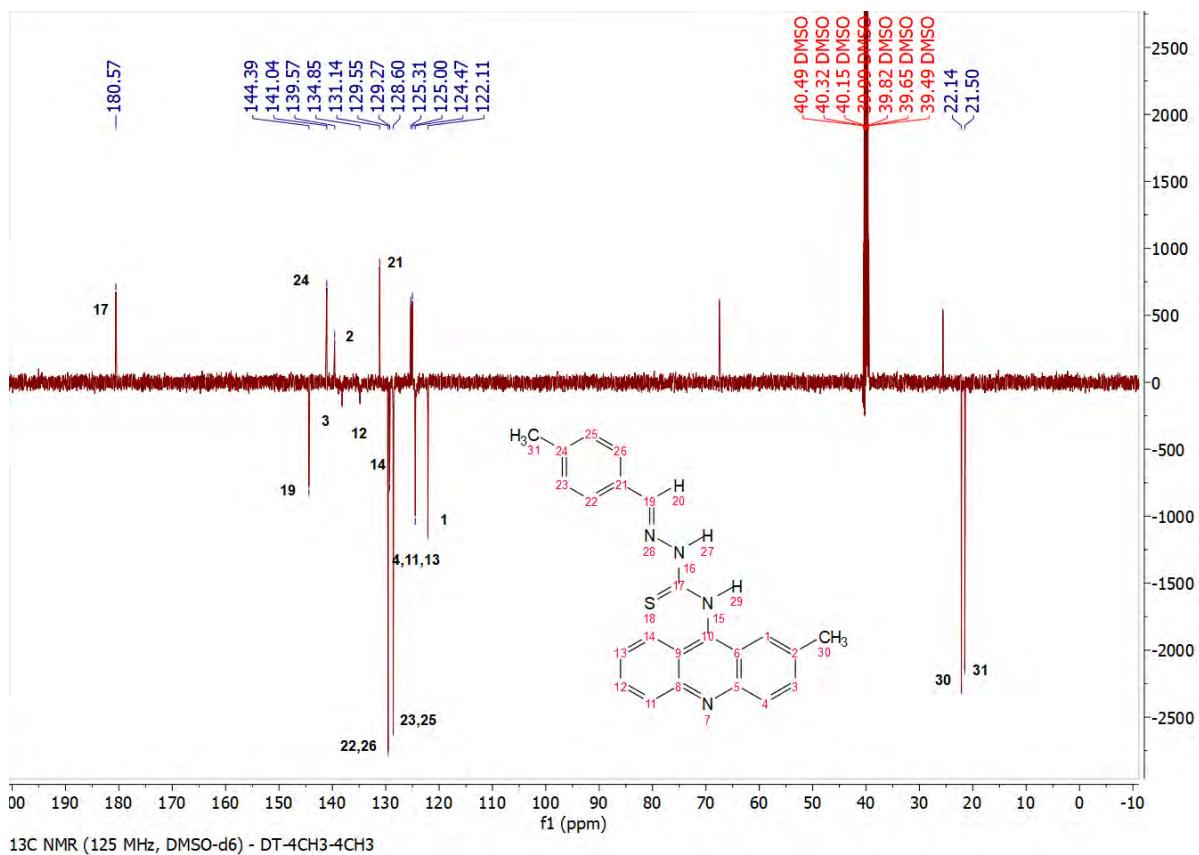


Figura S96. Espectro de RMN ^{13}C do DT-4CH₃-4CH₃.

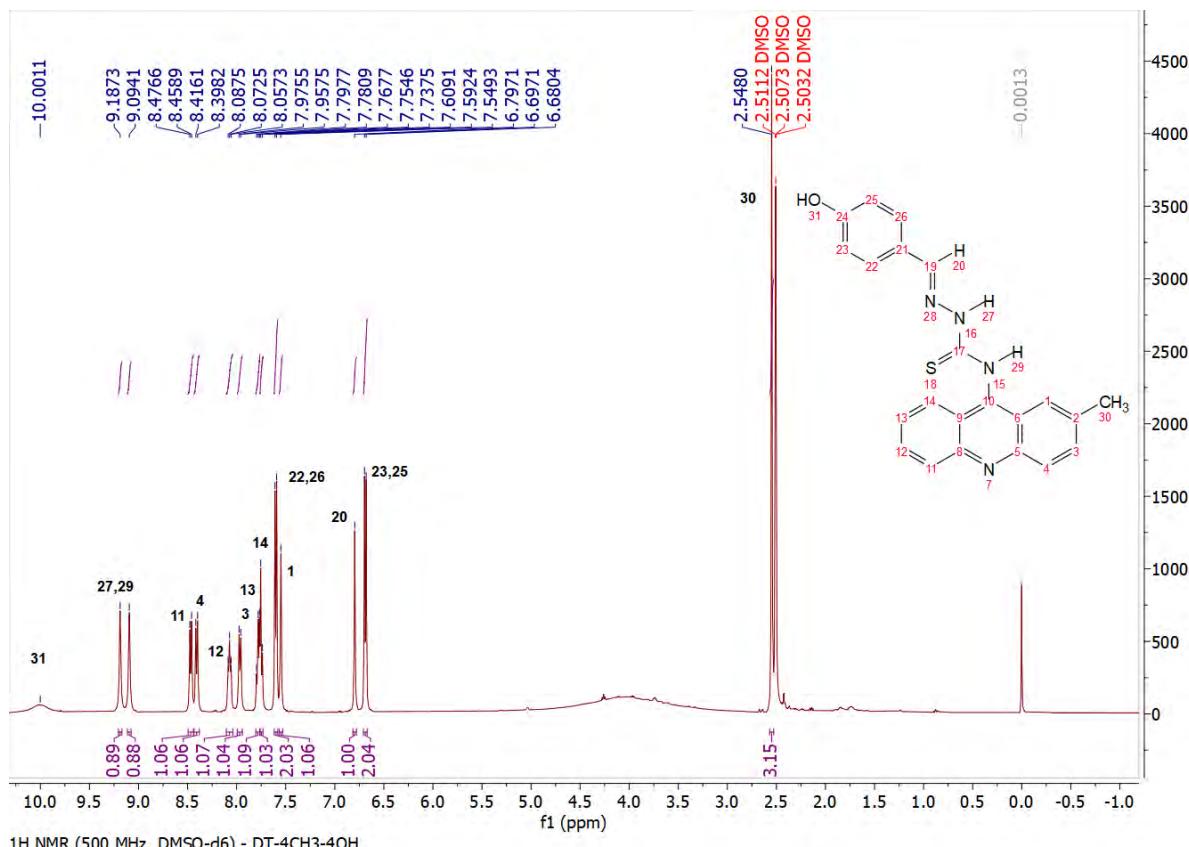
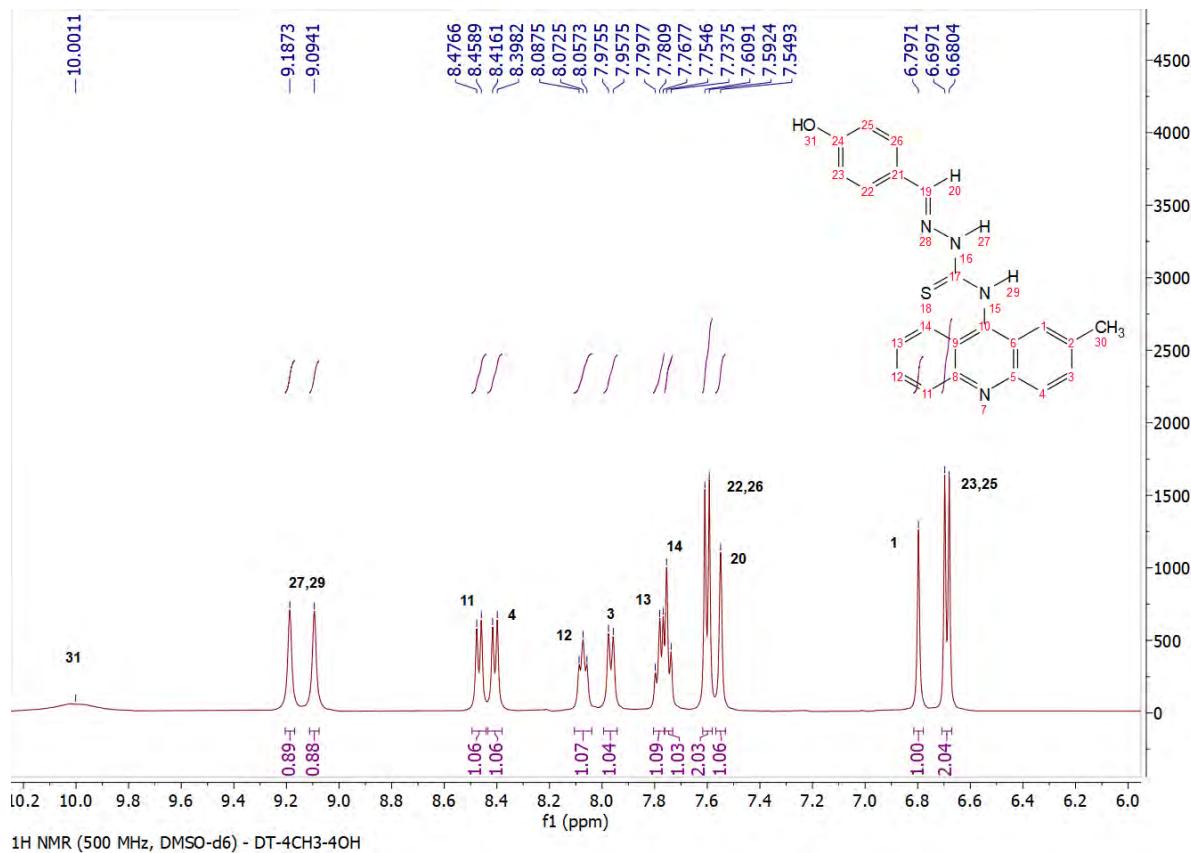
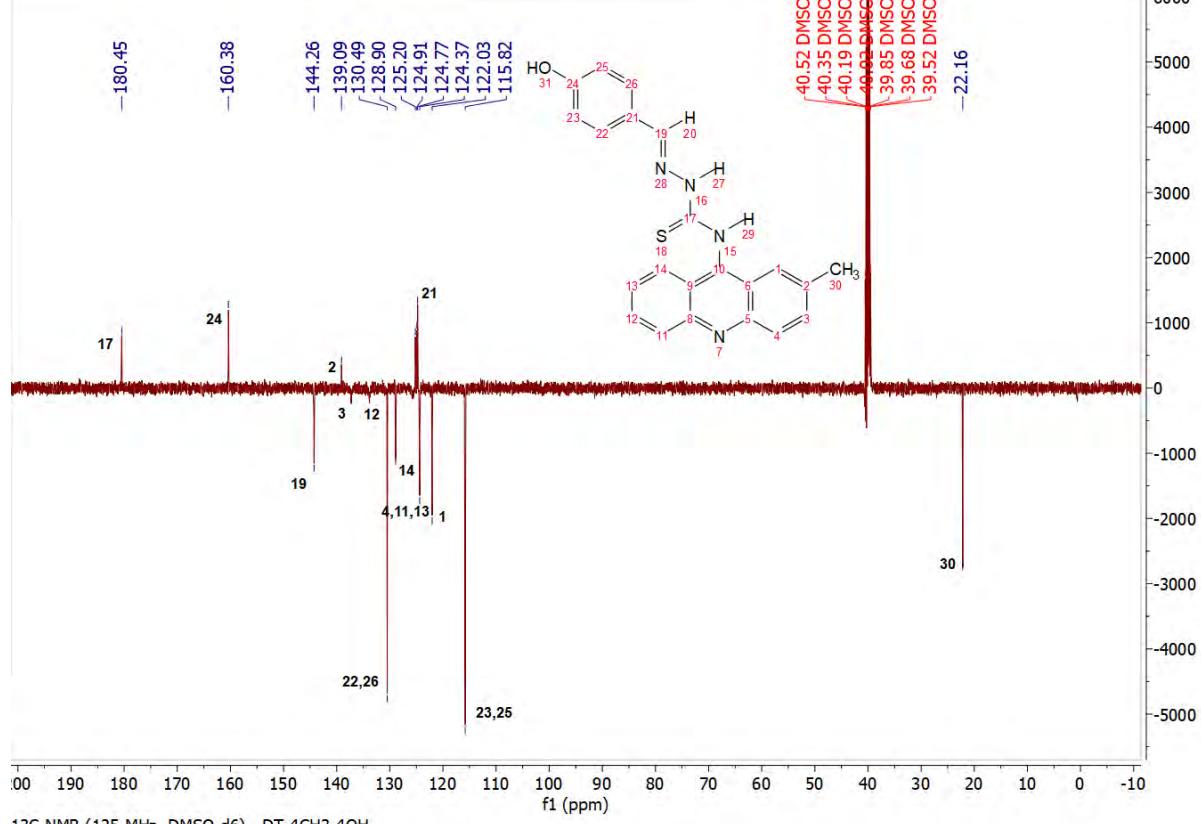


Figura S97. Espectro de RMN ^1H do DT-4CH₃-4OH.



1H NMR (500 MHz, DMSO-d6) - DT-4CH₃-4OH

Figura S98. Expansão do espectro de RMN ¹H do DT-4CH₃-4OH.



13C NMR (125 MHz, DMSO-d6) - DT-4CH₃-4OH

Figura S99. Espectro de RMN ¹³C do DT-4CH₃-4OH.

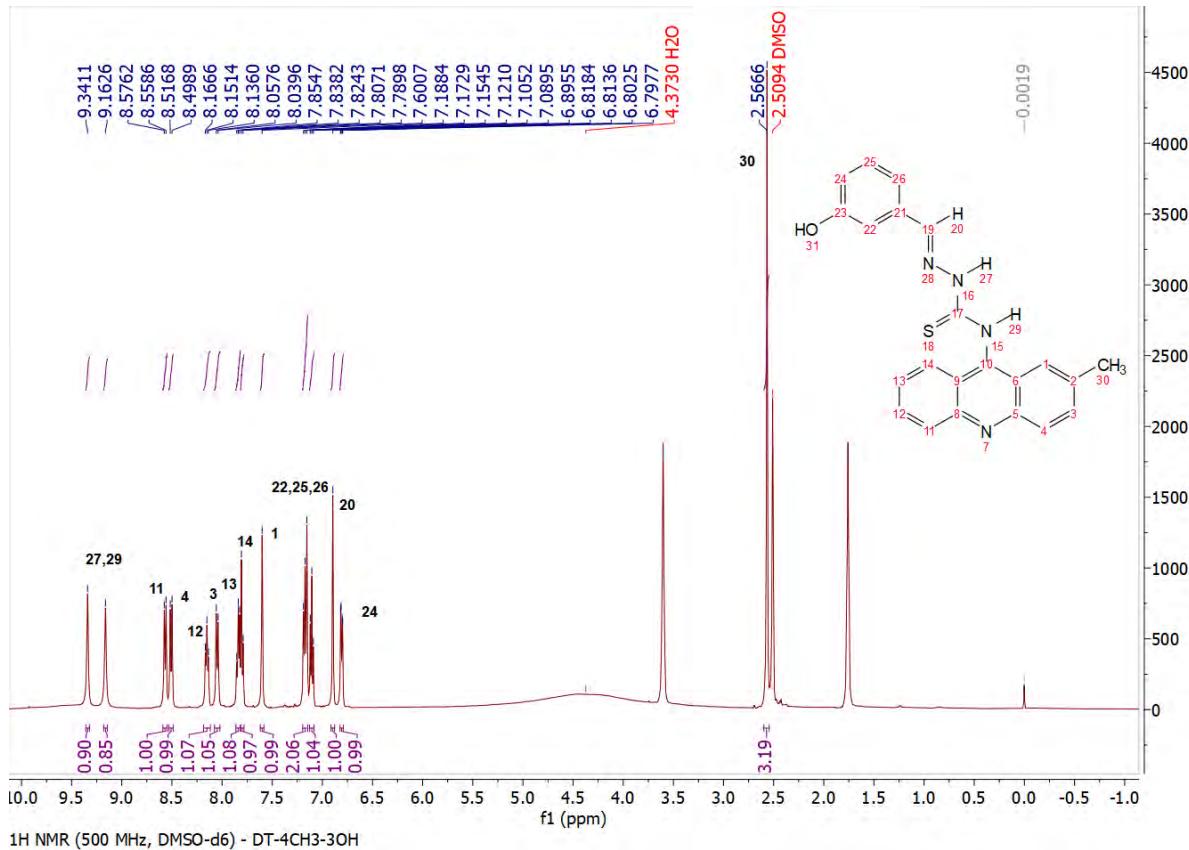


Figura S100. Espectro de RMN ¹H do DT-4CH₃-3OH.

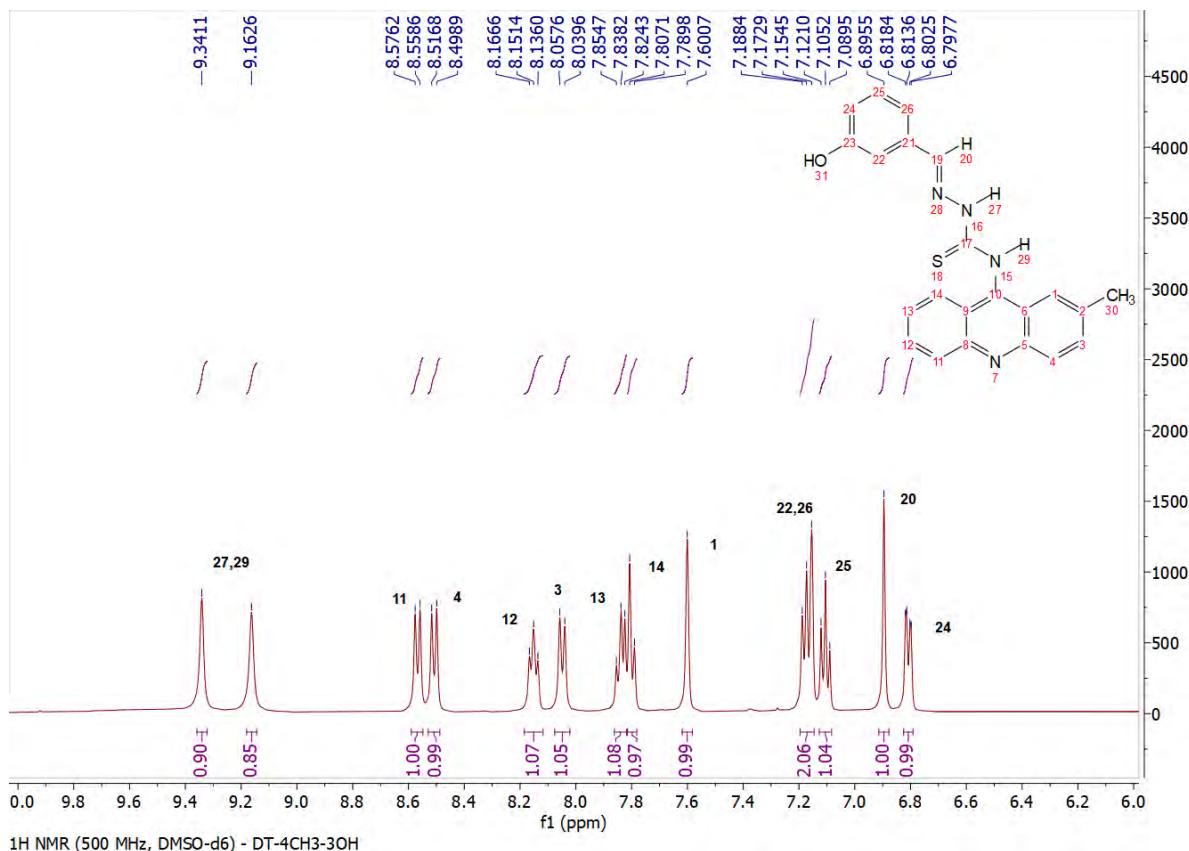


Figura S101. Expansão do espectro de RMN ¹H do DT-4CH₃-3OH.

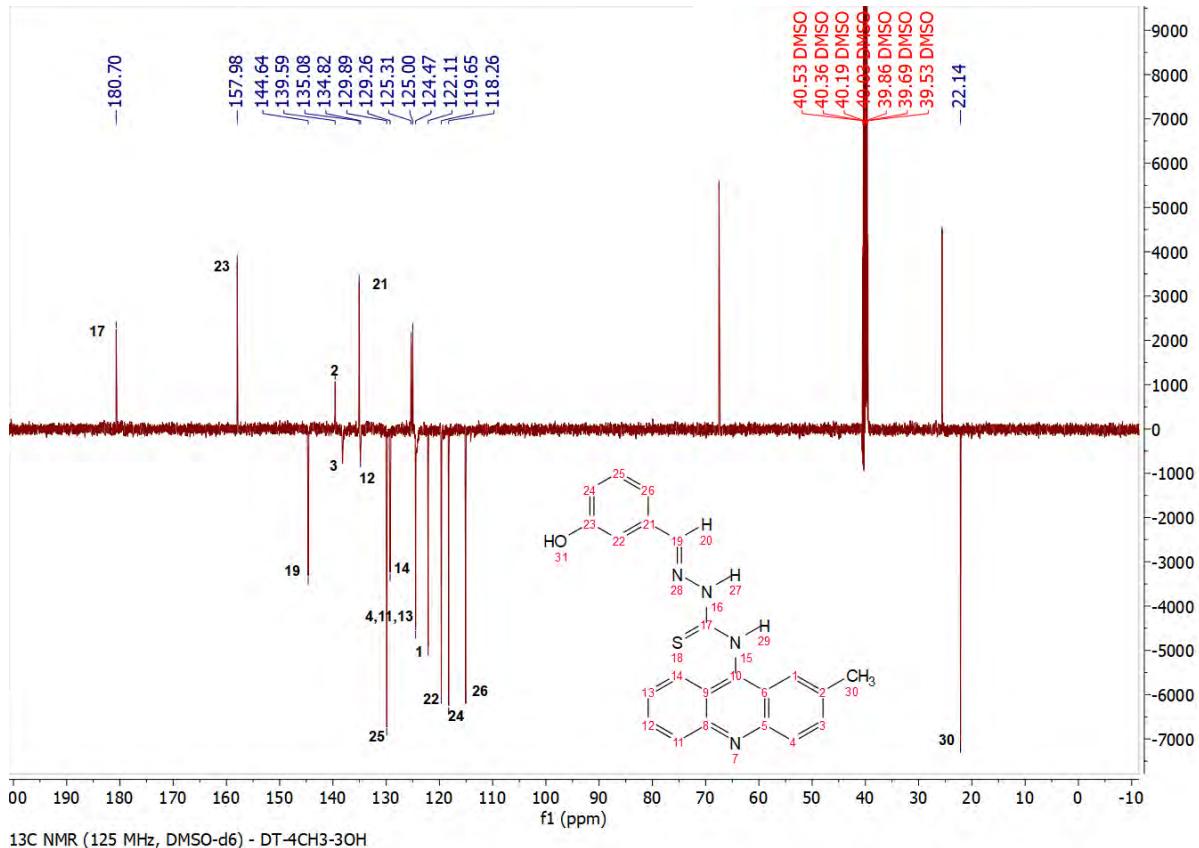


Figura S102. Espectro de RMN ^{13}C do DT-4CH₃-3OH.

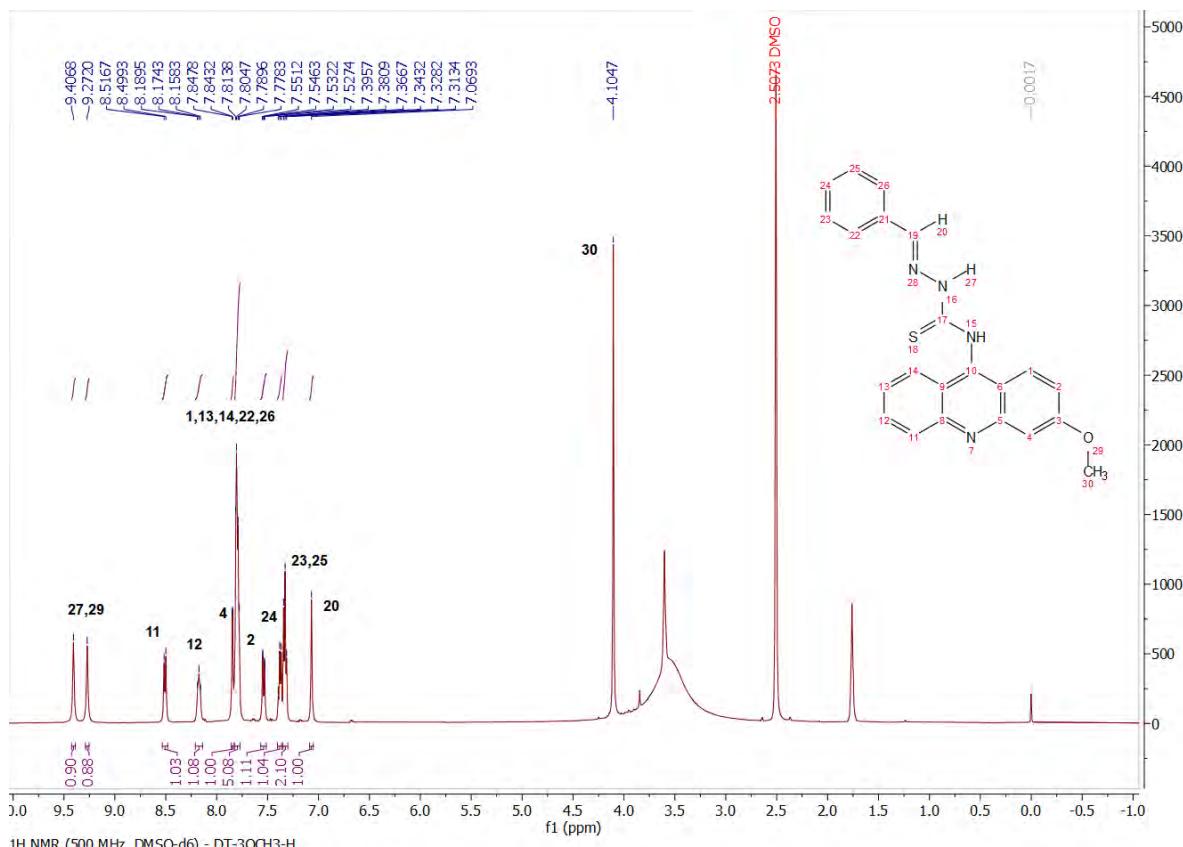


Figura S103. Espectro de RMN ^1H do PT-3OCH $_3$ -H.

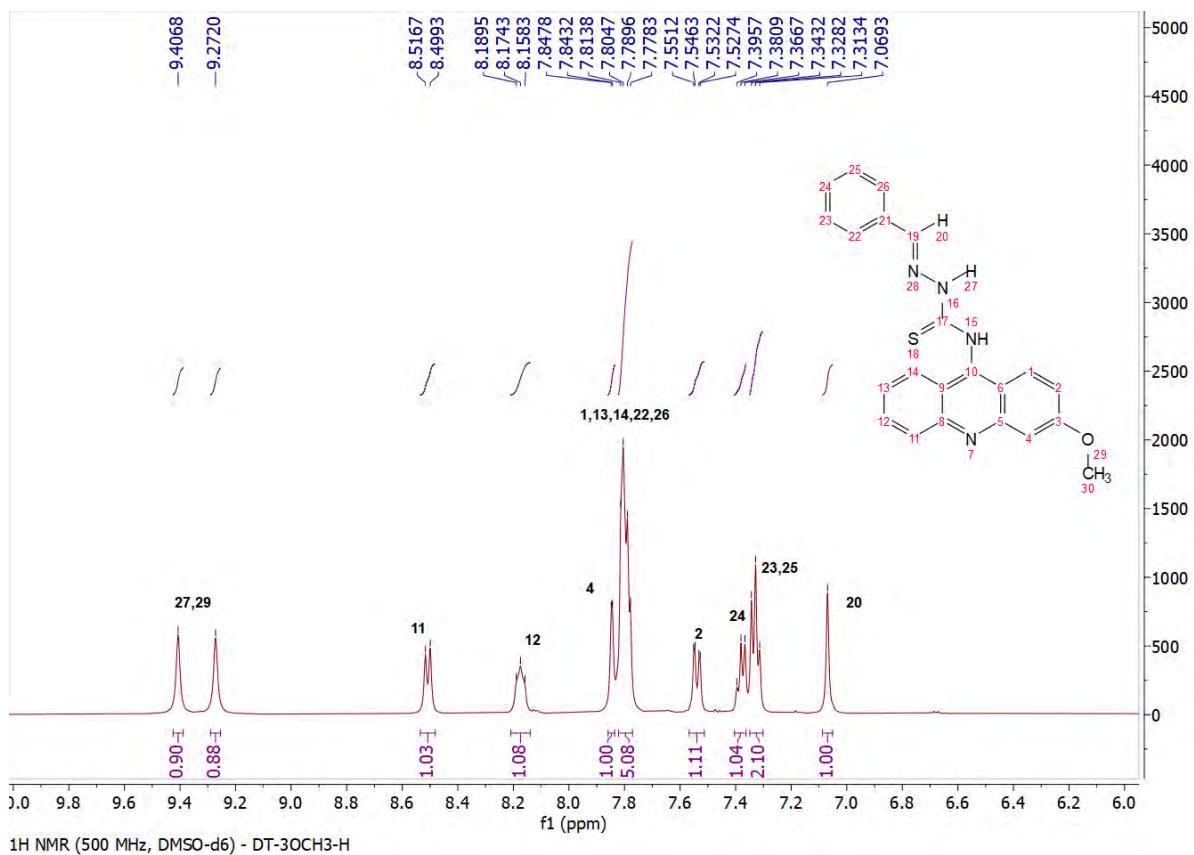


Figura S104. Expansão do espectro de RMN ¹H do DT-3OCH₃-H.

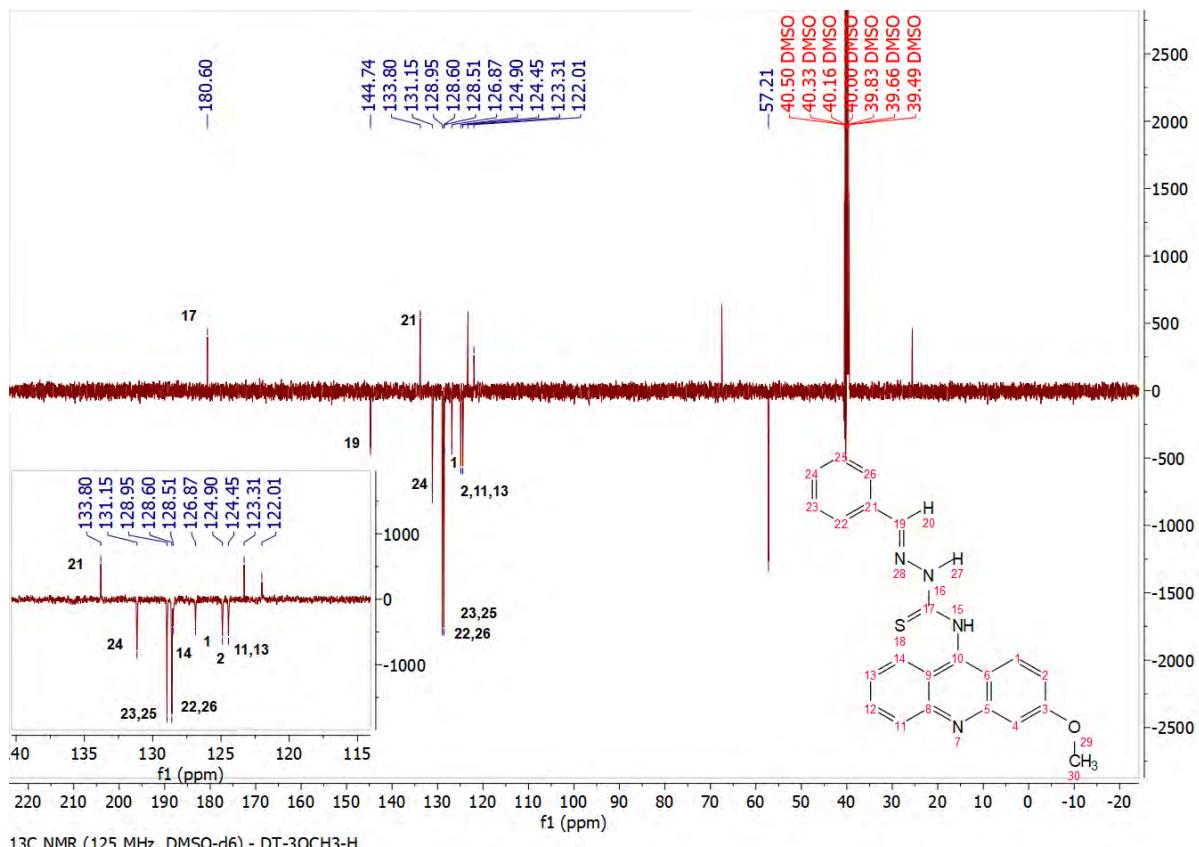


Figura S105. Espectro de RMN ¹³C do DT-3OCH₃-H.

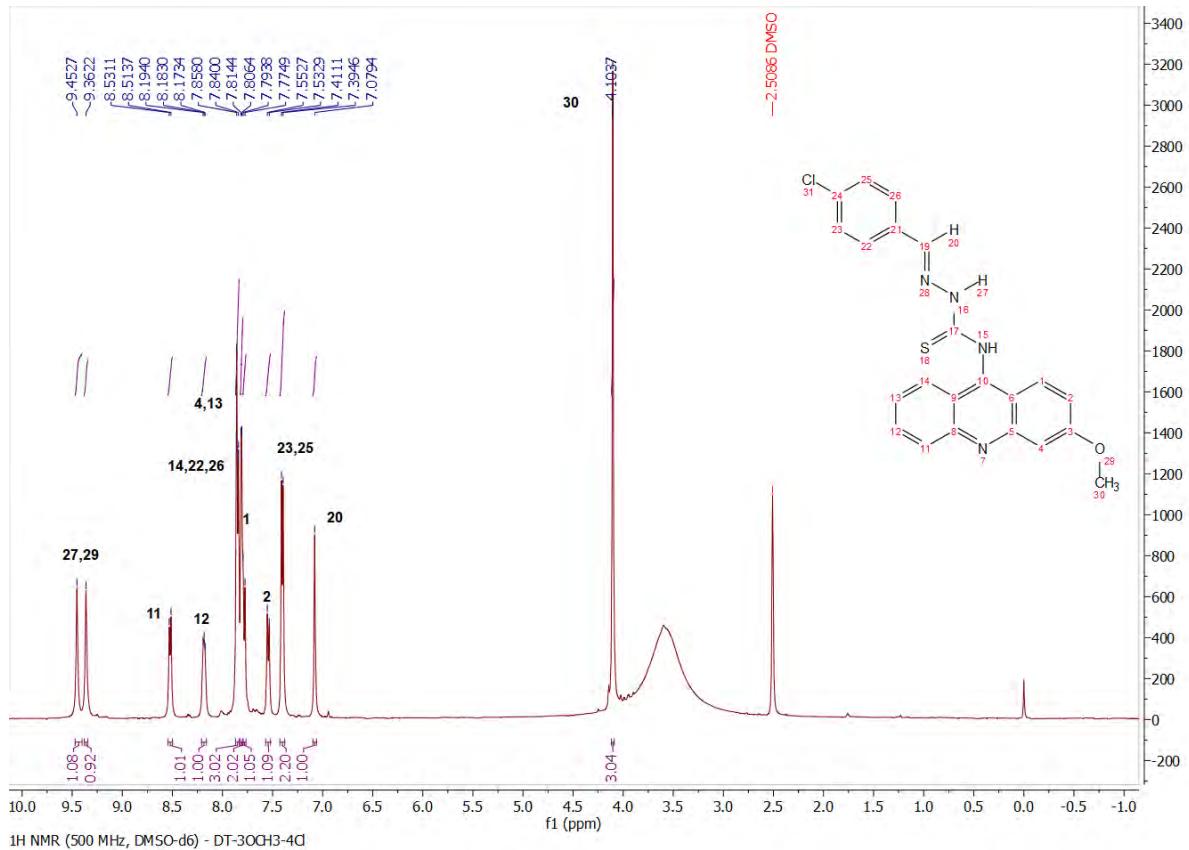


Figura S106. Espectro de RMN ^1H do DT-3OCH $_3$ -4Cl.

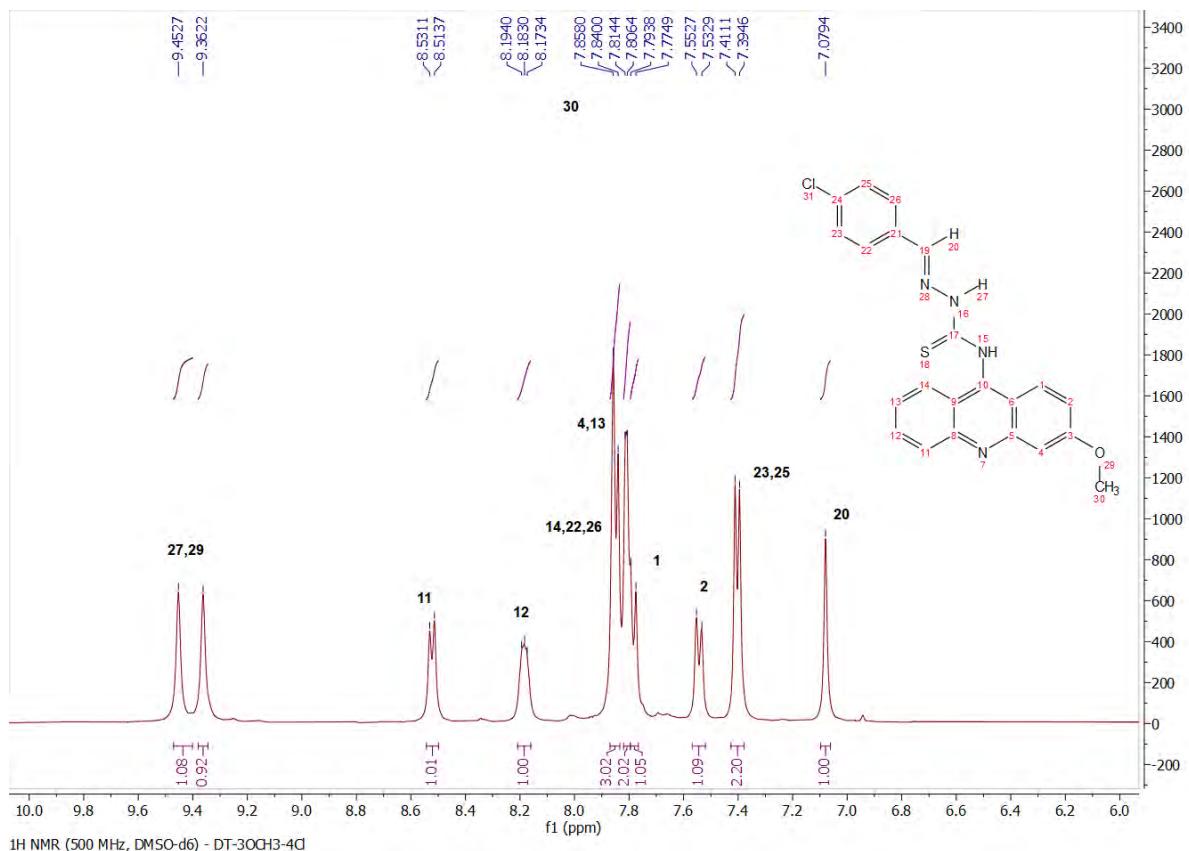


Figura S107. Expansão do espectro de RMN ^1H do DT-3OCH $_3$ -4Cl.

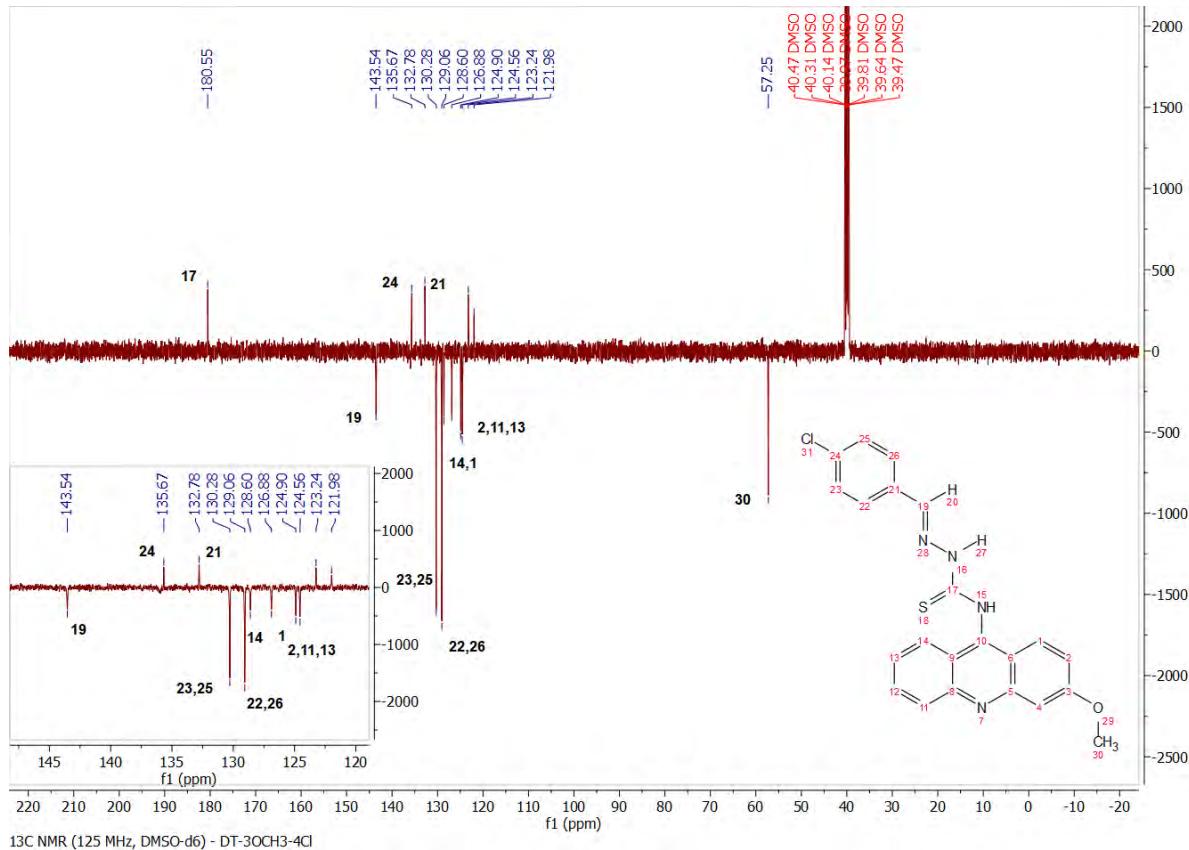


Figura S108. Espectro de RMN ^{13}C do DT-3OCH₃-4Cl.

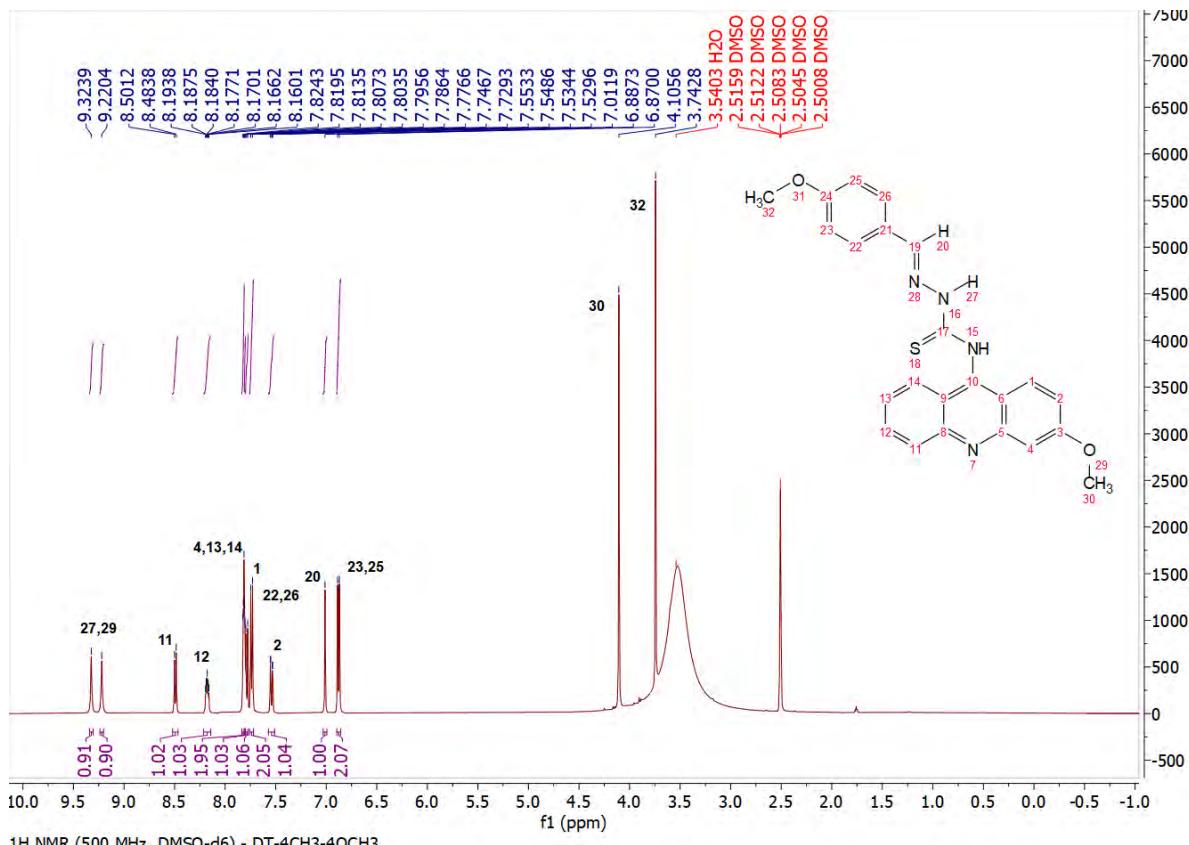


Figura S109. Espectro de RMN ^1H do DT-3OCH₃-4OCH₃.

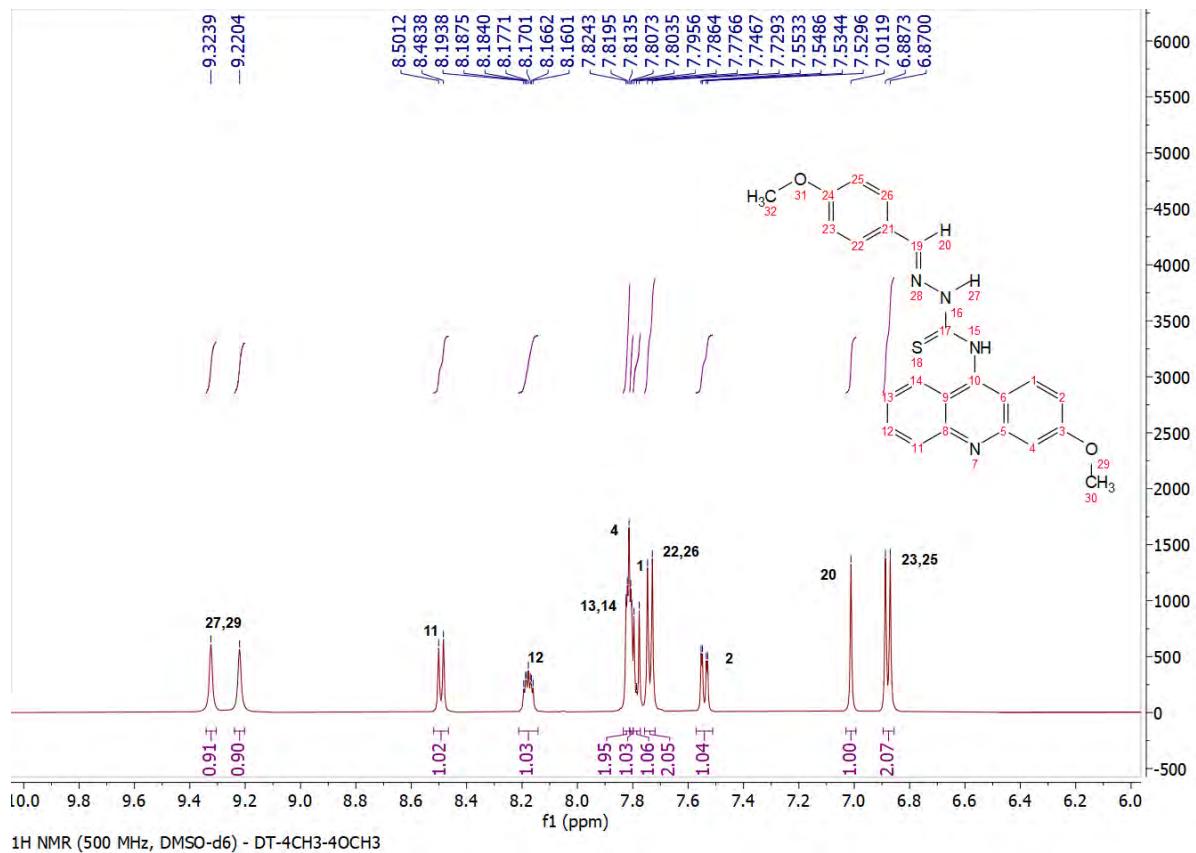


Figura S110. Expansão do espectro de RMN ¹H do DT-3OCH₃-4OCH₃.

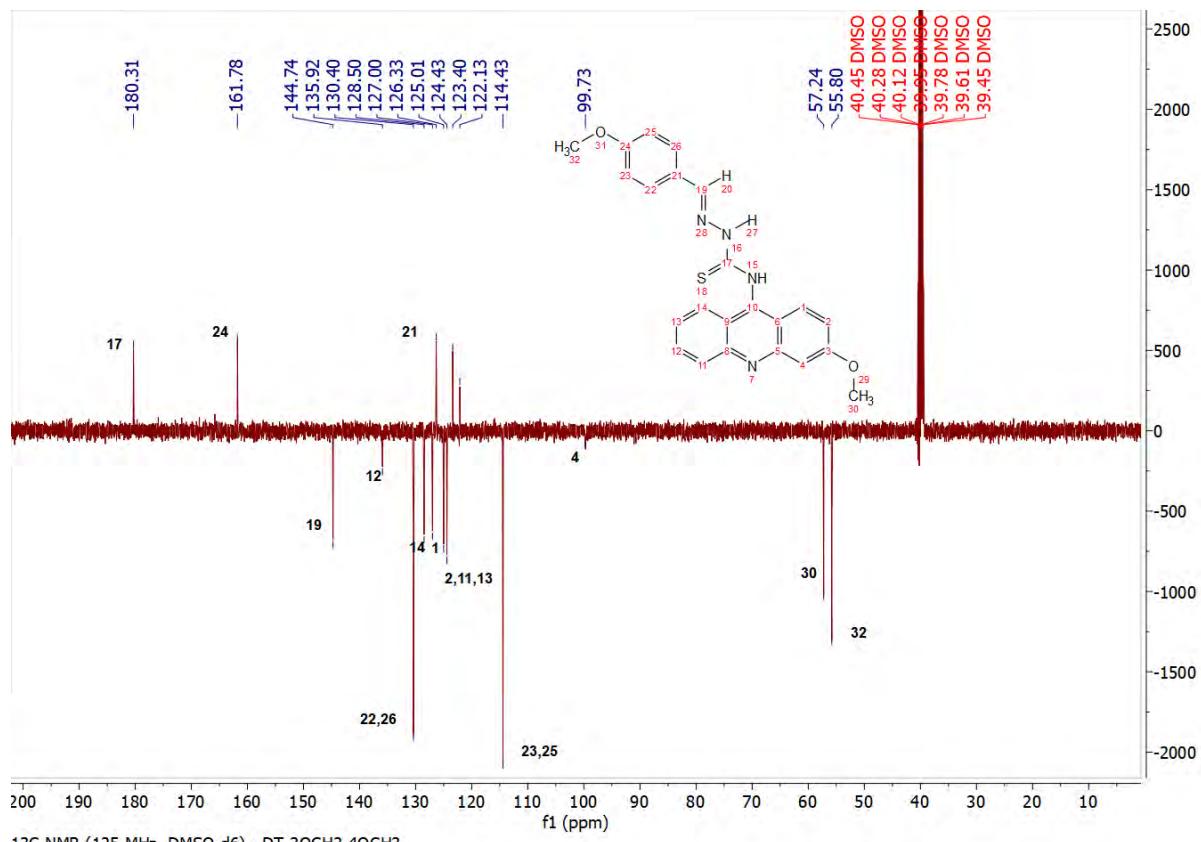


Figura S111. Espectro de RMN ¹³C do DT-3OCH₃-4OCH₃.

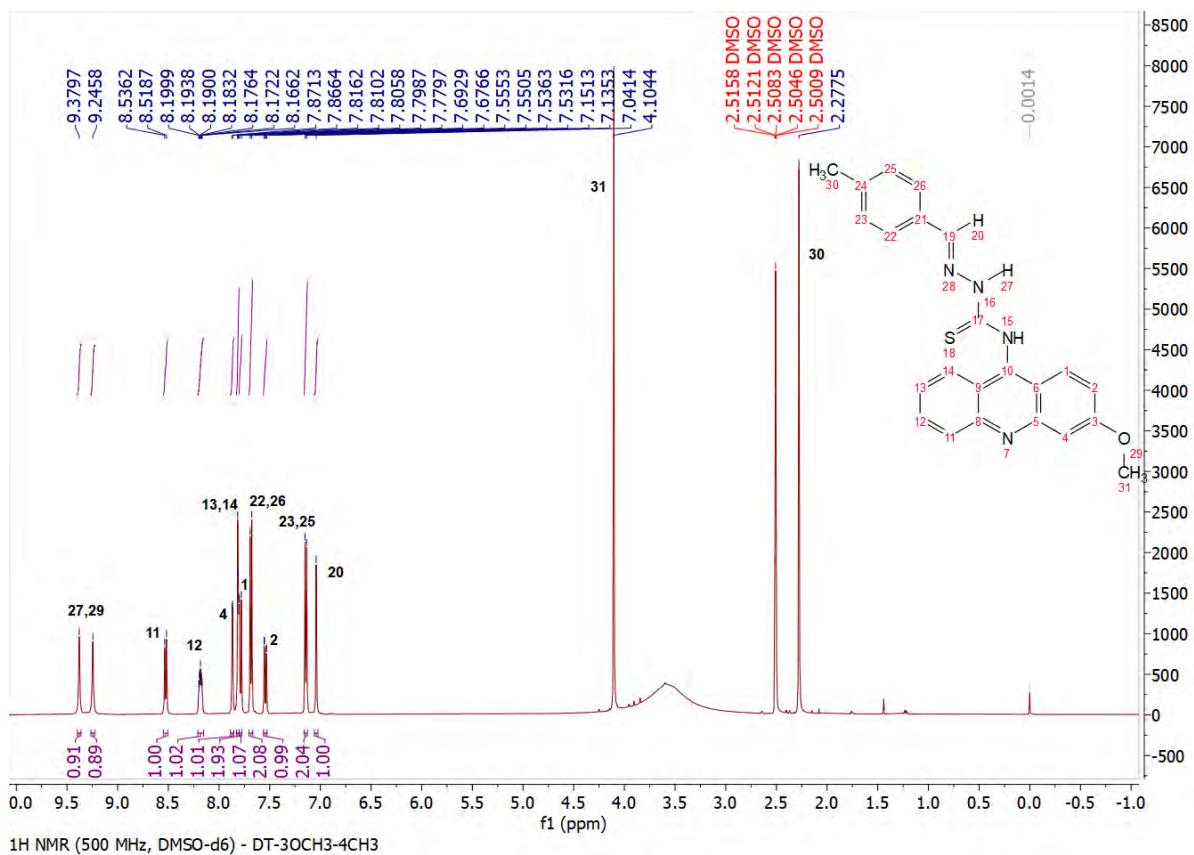


Figura S112. Espectro de RMN ^1H do DT- 3OCH_3 - 4CH_3 .

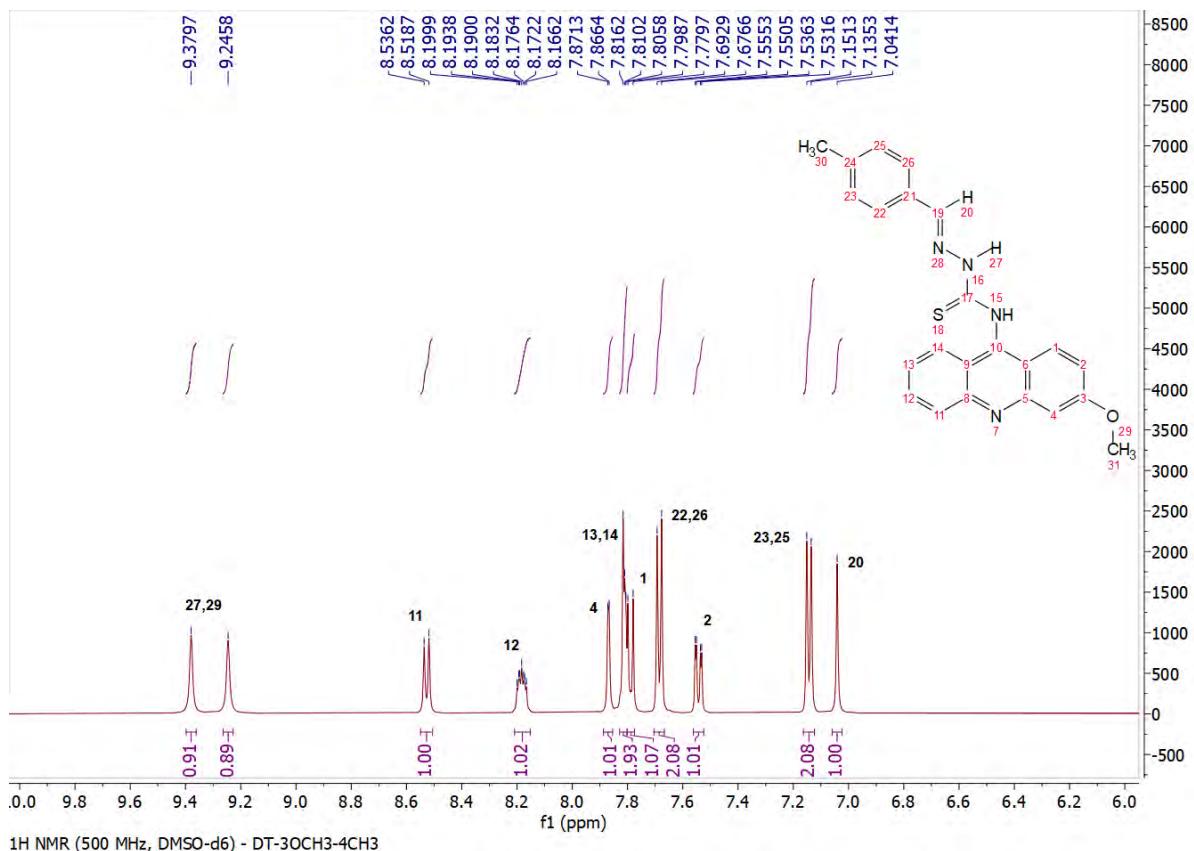
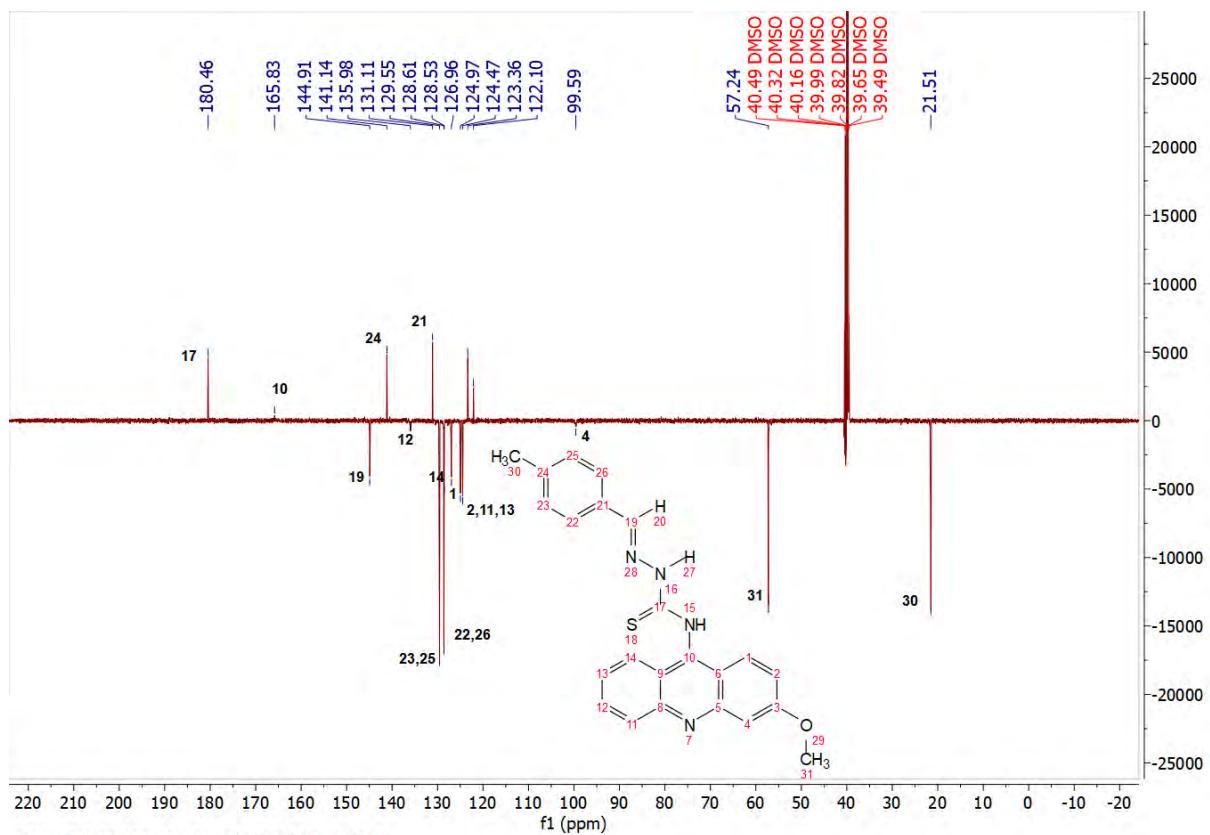
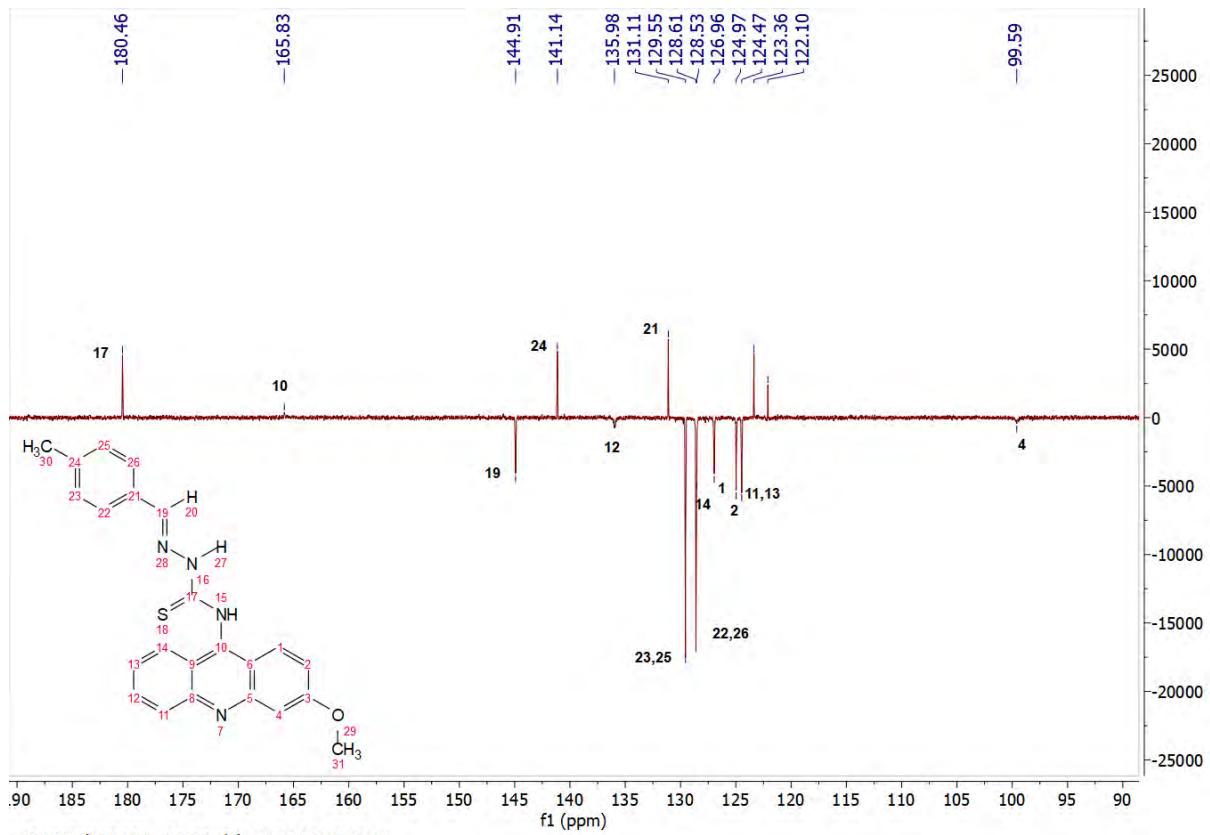


Figura S113. Expansão do espectro de RMN ^1H do DT- 3OCH_3 - 4CH_3 .



13C NMR (125 MHz, DMSO-d6) - DT-3OCH₃-4CH₃

Figura S114. Espectro de RMN ¹³C do DT-3OCH₃-4CH₃.



13C NMR (125 MHz, DMSO-d6) - DT-3OCH₃-4CH₃

Figura S115. Expansão do espectro de RMN ¹³C do DT-3OCH₃-4CH₃.

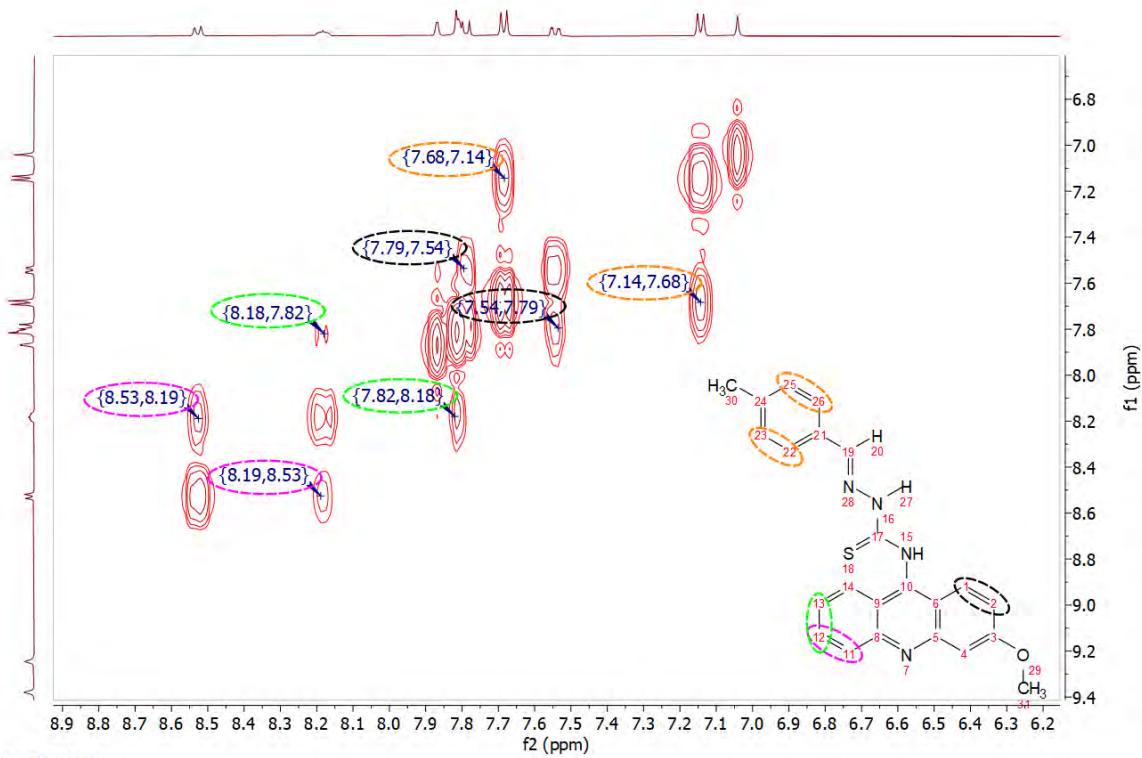


Figura S116. Espectro de correlação COSY do DT-3OCH₃-4CH₃.

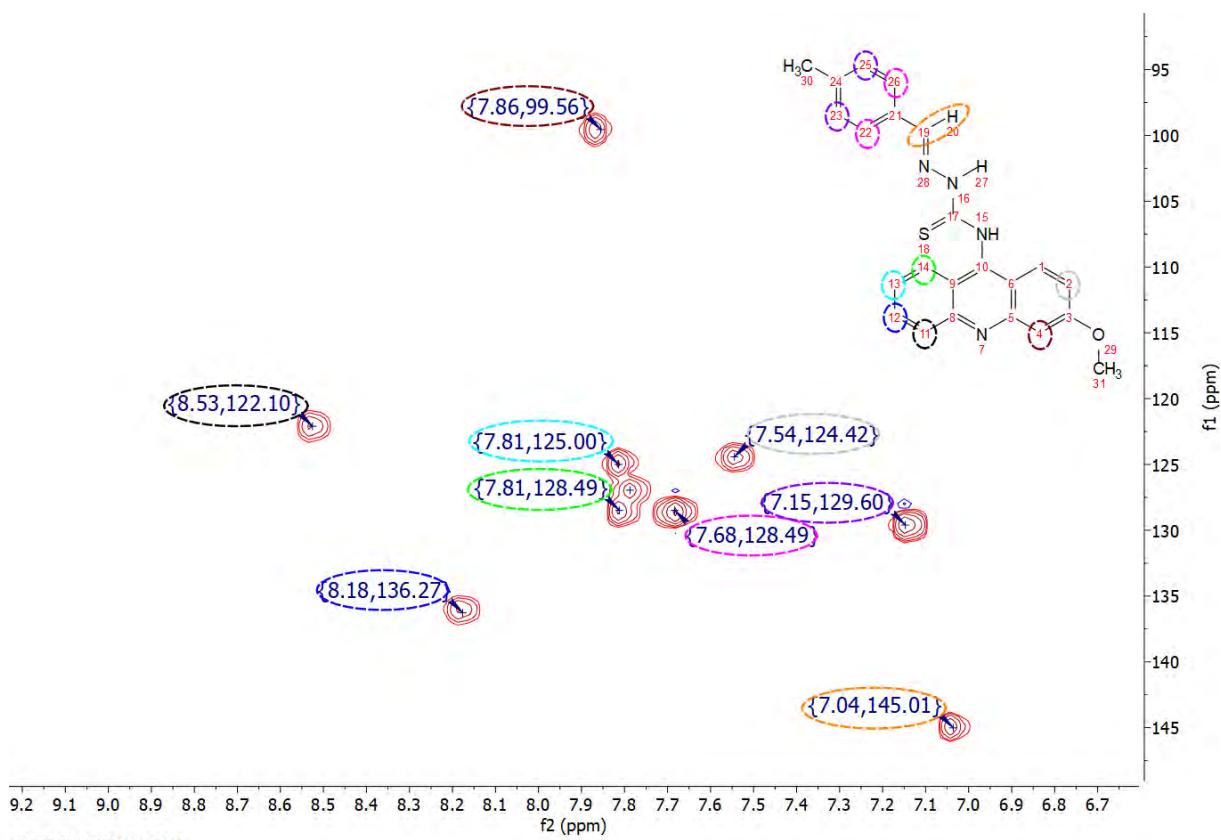


Figura S117. Espectro de correlação HSQC do DT-3OCH₃-4CH₃.

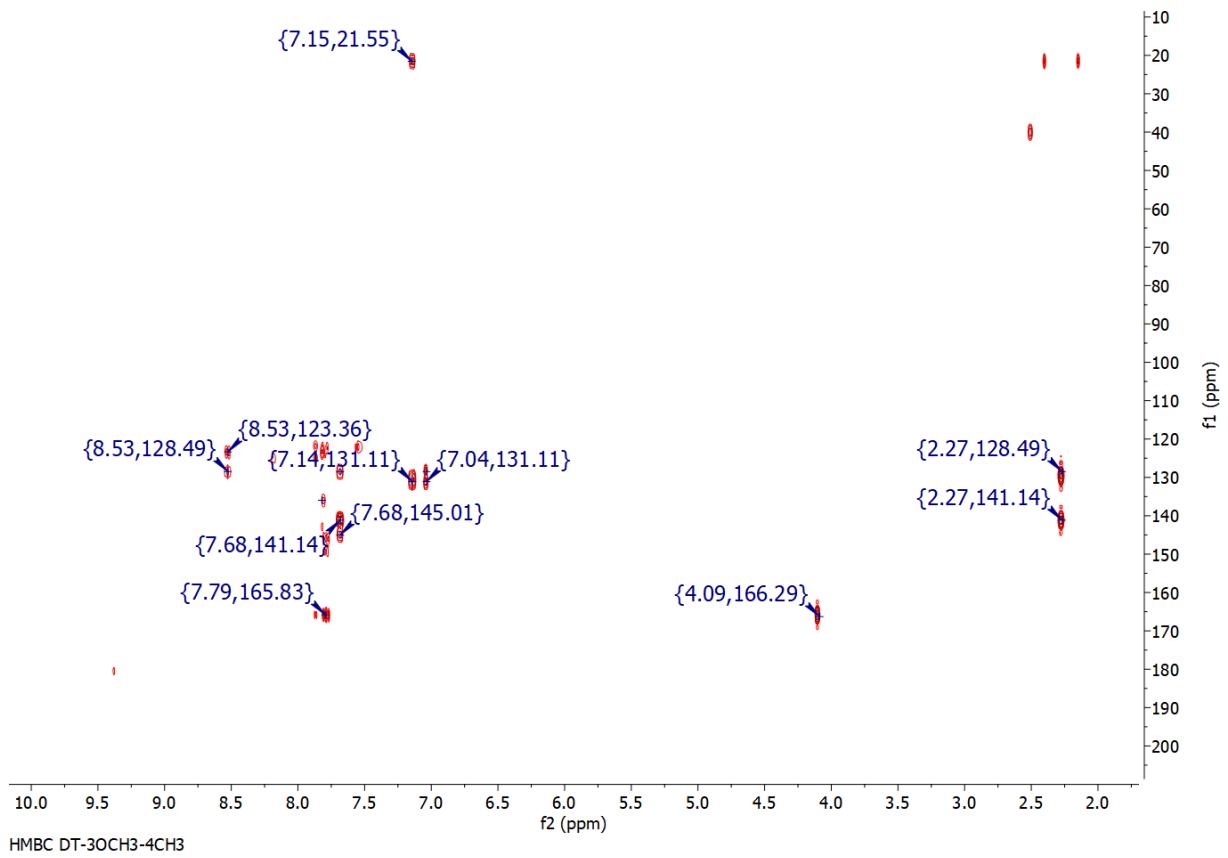


Figura S118. Espectro de correlação HMBC do DT-3OCH₃-4CH₃.

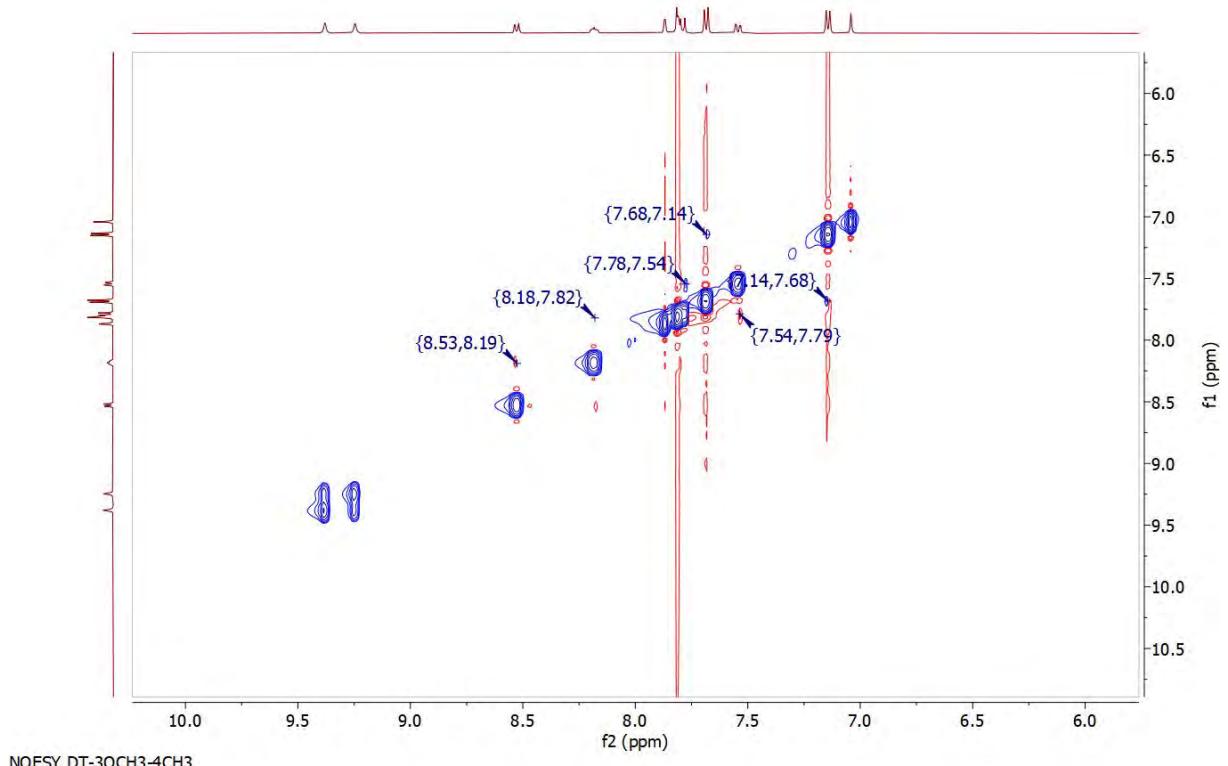


Figura S119. Espectro de correlação NOESY do DT-3OCH₃-4CH₃.

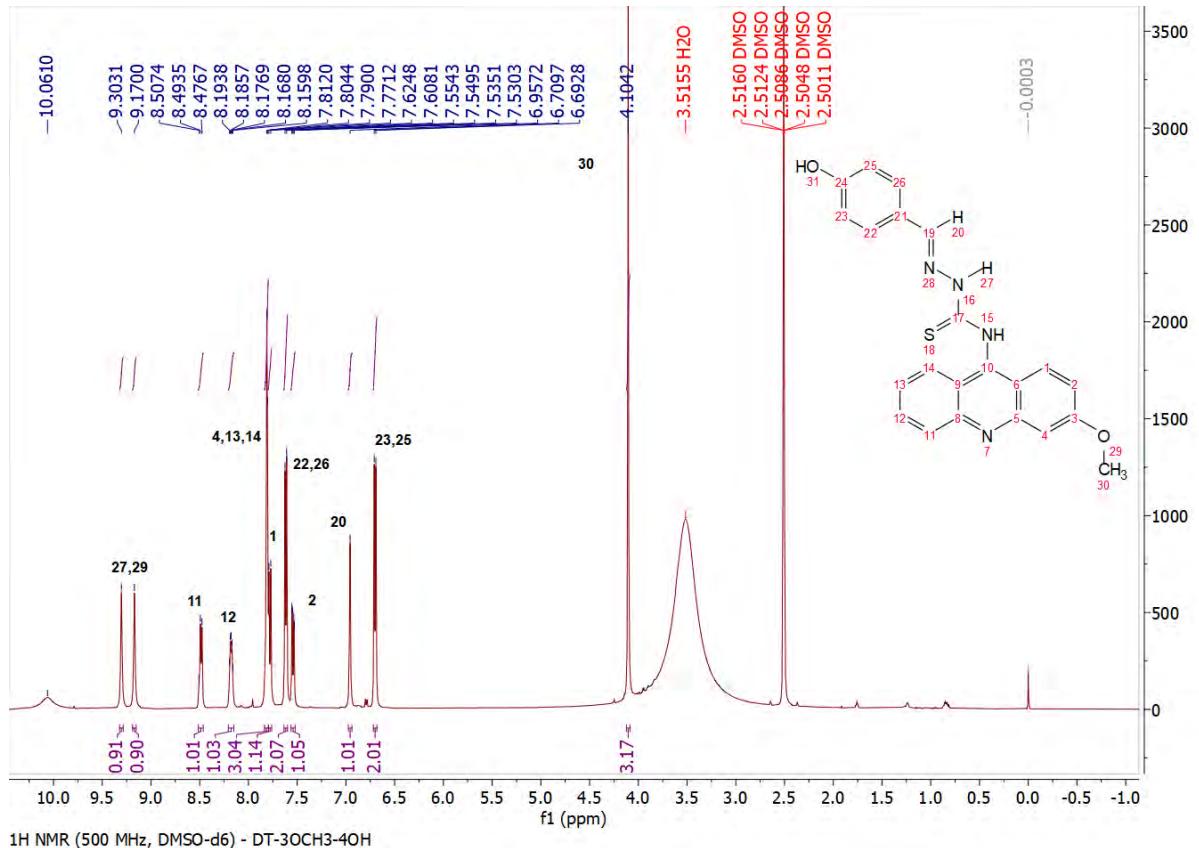


Figura S120. Espectro de RMN ^1H do DT-3OCH $_3$ -4OH.

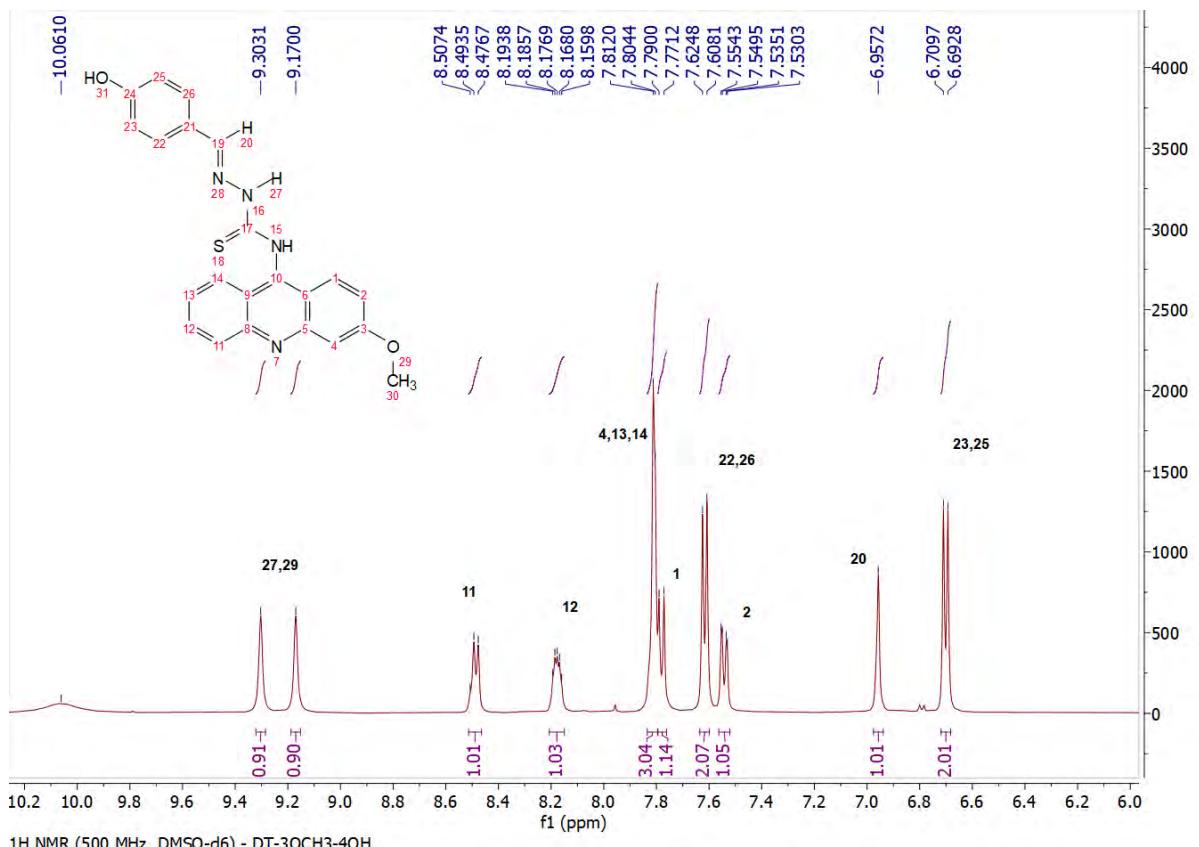


Figura S121. Expansão do espectro de RMN ^1H do DT-3OCH₃-4OH.

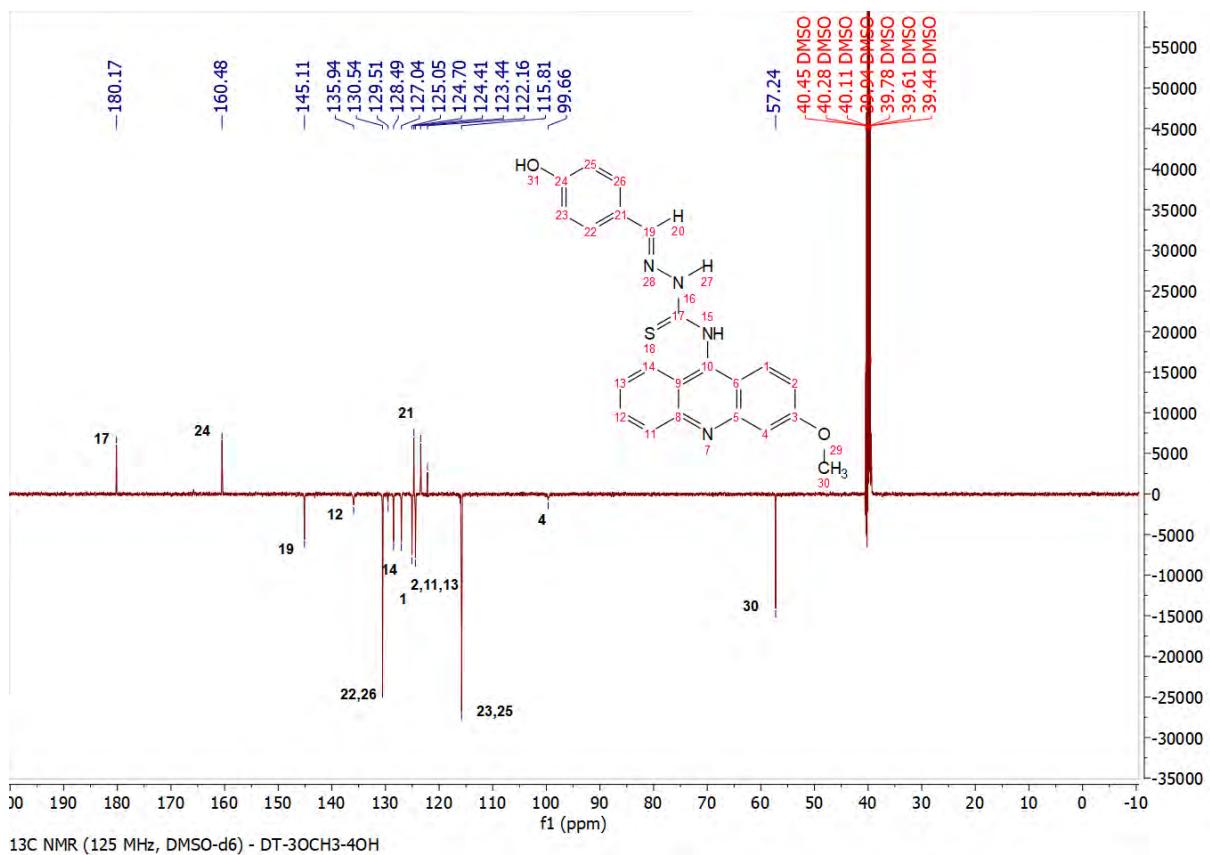


Figura S122. Espectro de RMN ¹³C do DT-3OCH₃-4OH.

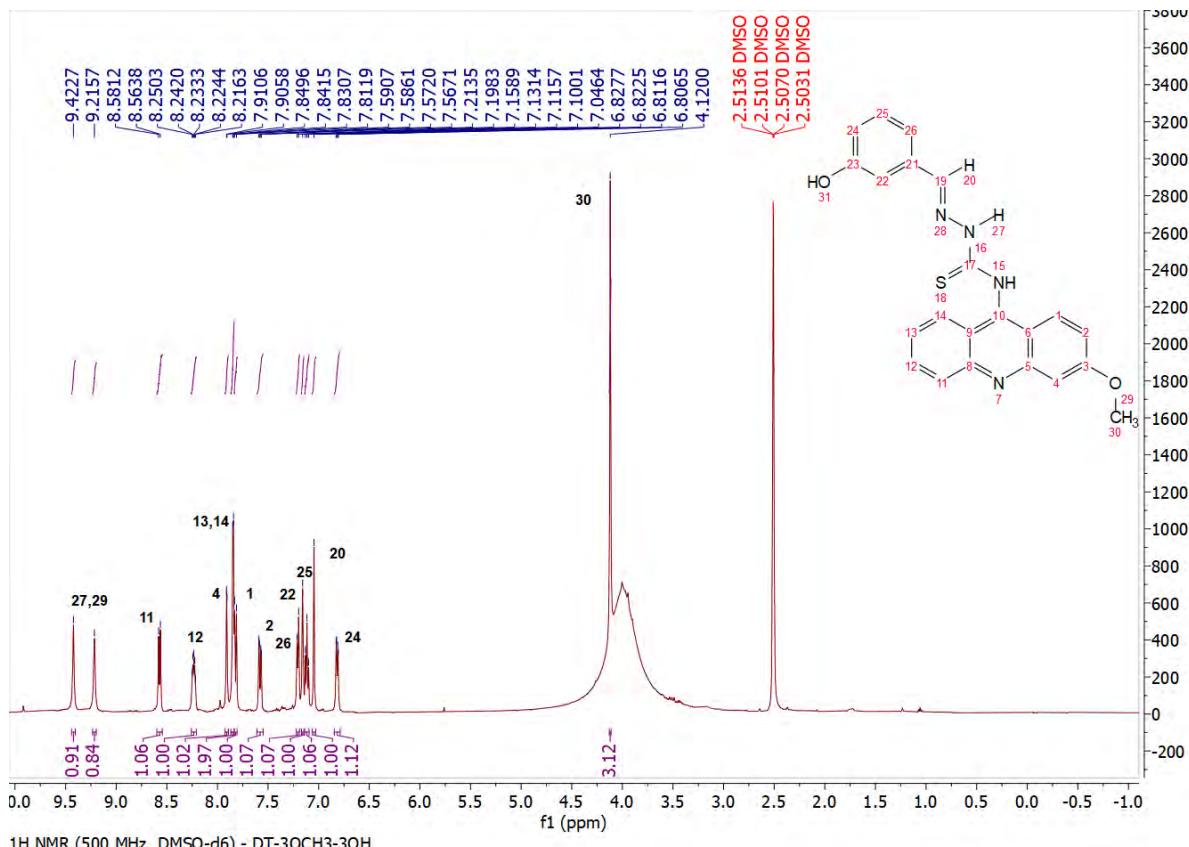


Figura S123. Espectro de RMN ¹H do DT-3OCH₃-3OH.

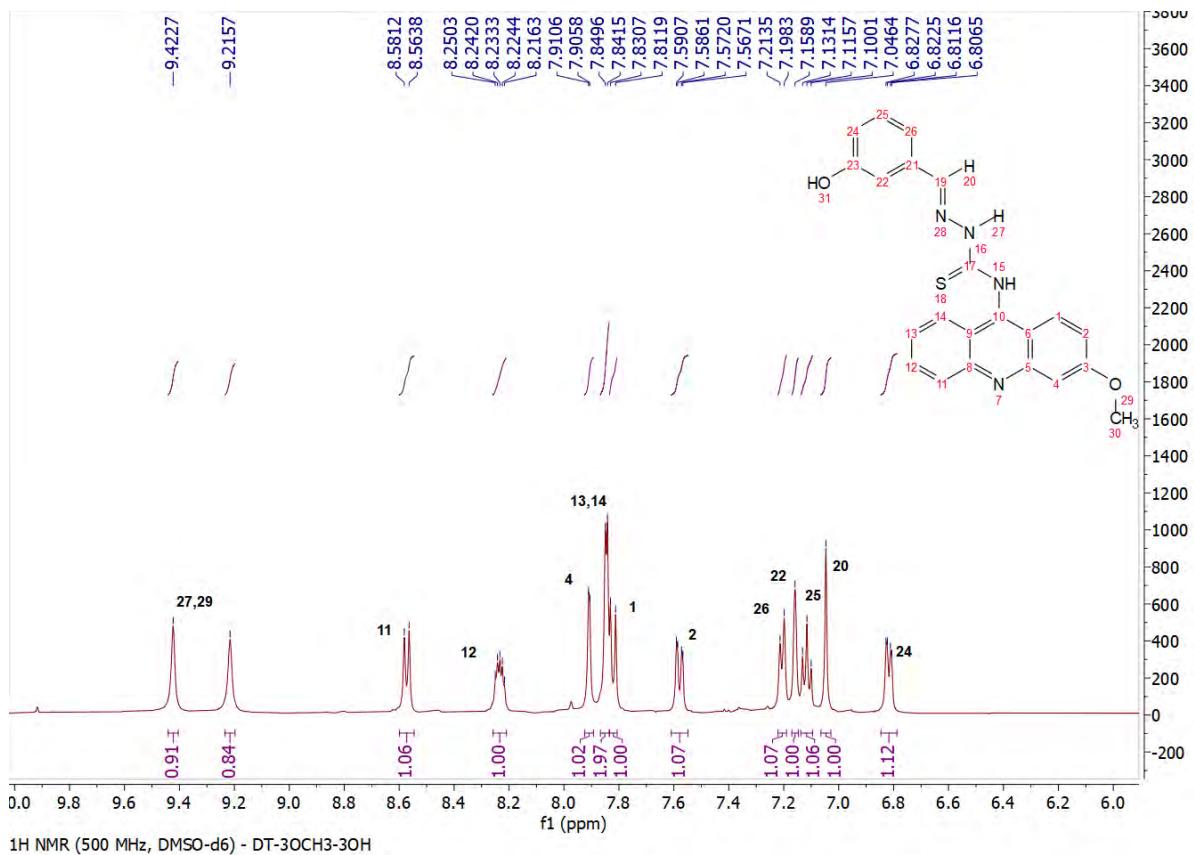


Figura S124. Expansão do espectro de RMN ¹H do DT-3OCH₃-3OH.

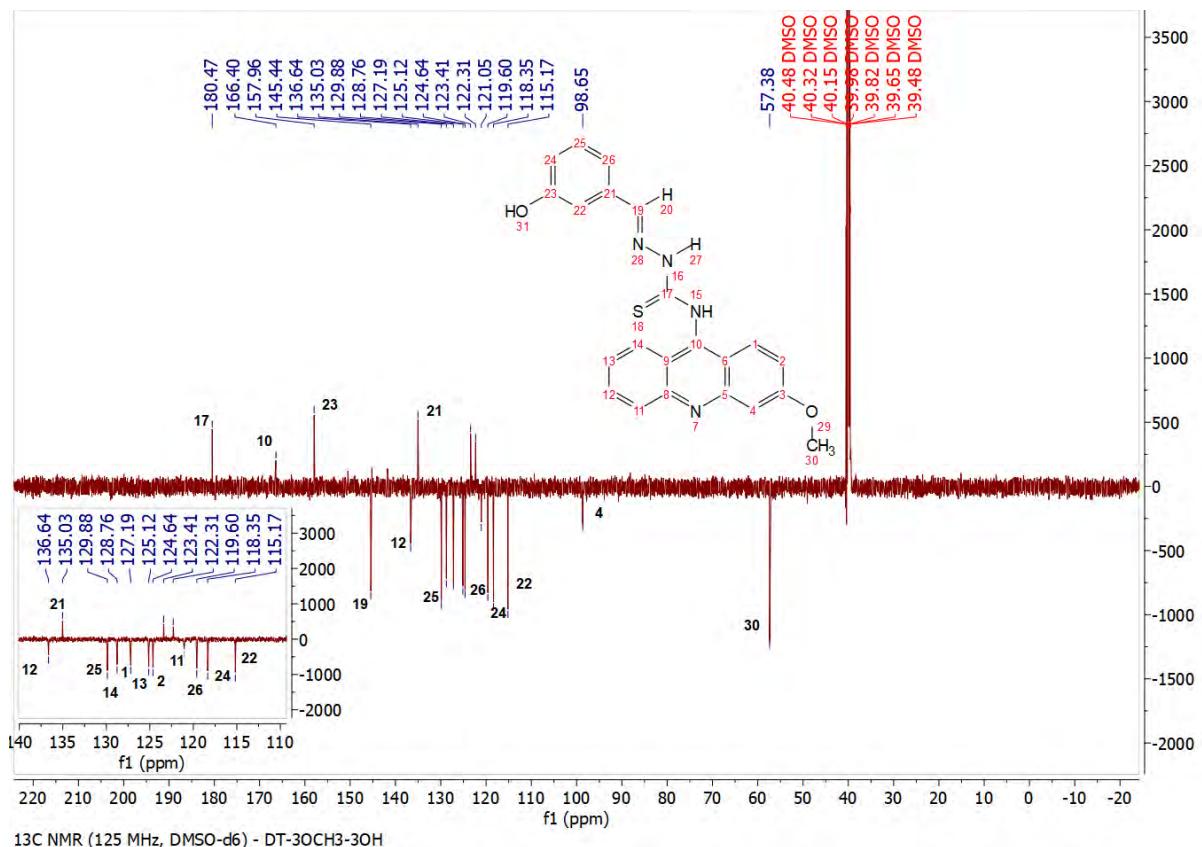


Figura S125. Espectro de RMN ¹³C do DT-3OCH₃-3OH.

Tabela S4. Efeitos de derivados de acridinas em animais submetidos a estudo de toxicidade aguda.

Estudo de toxicidade	DA/TA	Mortalidade (%)	Sinais de toxicidade
DT-3OCH₃-4OH	0/3	0	Consumo de ração reduzido
NC	0/3	0	Nenhum

Grupo controle (NC), animais mortos (DA), total de animais (TA).

Tabela S5. Massa absoluta e relativa de órgãos de animais tratados com derivados de acridina após um estudo de toxicidade aguda.

Compostos	Órgãos				
	Fígado (g)	Pulmão(g)	Baço(g)	Coração(g)	Rins (g)
DT-3OCH₃-4OH	5,257±0,610 ^a	0,640±0,057 ^b	0,551±0,037 ^c	0,410±0,039 ^d	1,338±0,091 ^e
NC	4,959±0,191 ^a	0,628±0,027 ^b	0,408±0,037 ^c	0,409±0,040 ^d	1,284±0,040 ^e

Grupo controle (NC). Na mesma categoria e tratamento, as médias seguidas de letras desiguais, diferem estatisticamente entre si pelo teste *T de Student* ($p<0.05$), em relação aos grupos tratado e controle.

Tabela S6. Massa relativa aos animais tratados com derivados de acridina após um estudo de toxicidade aguda.

Compostos	Dados fisiológicos		
	Consumo de ração (g)	Consumo de água (mL)	Ganho de peso (g)
DT-3OCH₃-4OH	13,78±1,18 ^a	22,78±1,05 ^c	1,00±0 ^d
NC	18,64±3,52 ^b	23,14±1,51 ^c	1,00±0 ^d

Grupo controle (NC). Na mesma categoria e tratamento, as médias seguidas de letras desiguais, diferem estatisticamente entre si pelo teste *T de Student* ($p<0.05$), em relação aos grupos tratado e controle.

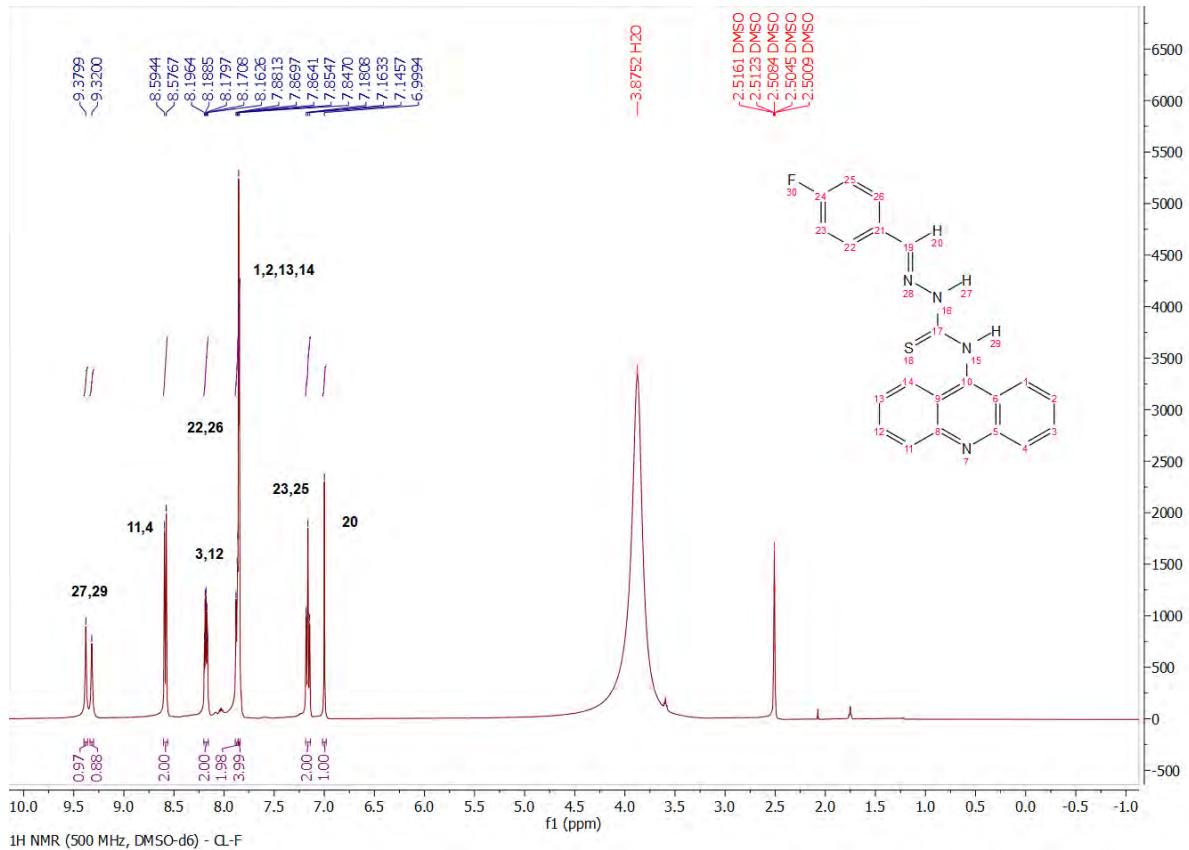


Figura S126. Espectro de RMN ^1H do CL-F.

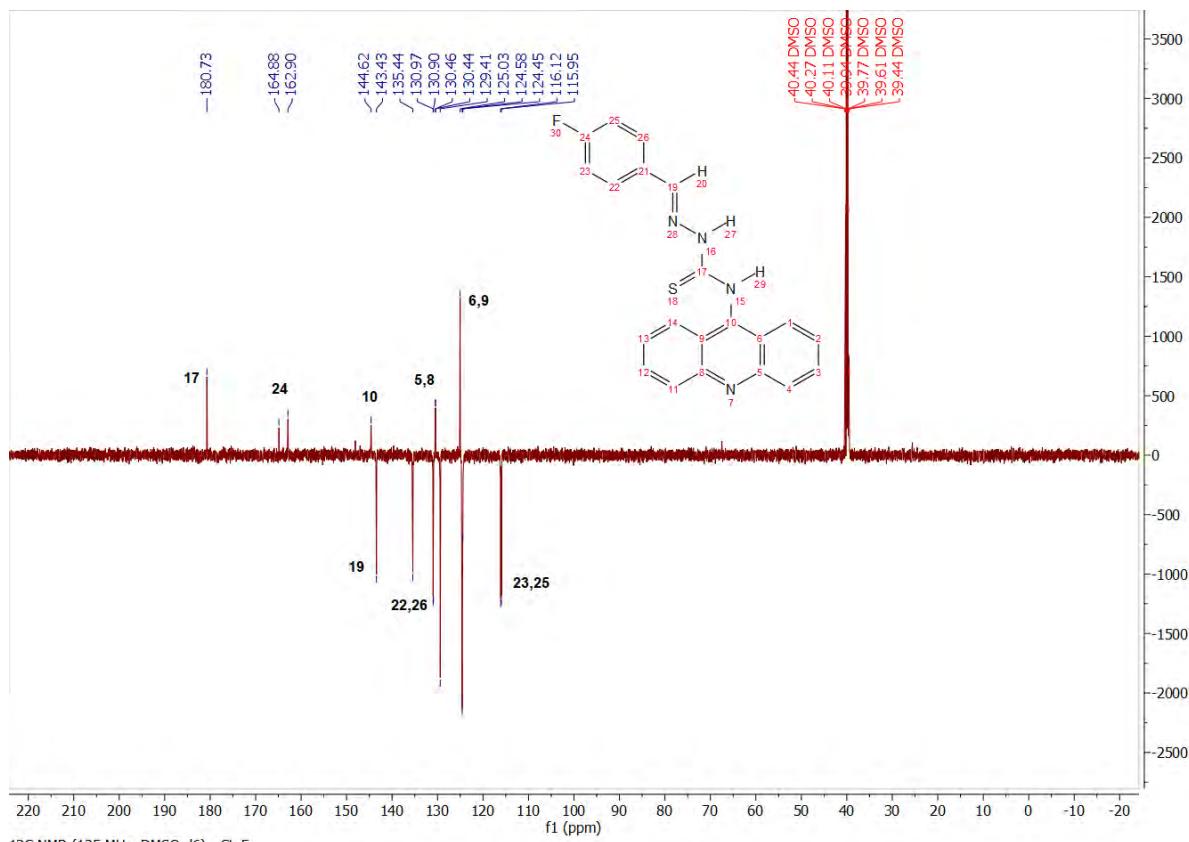


Figura S127. Espectro de RMN ^{13}C do CL-F.

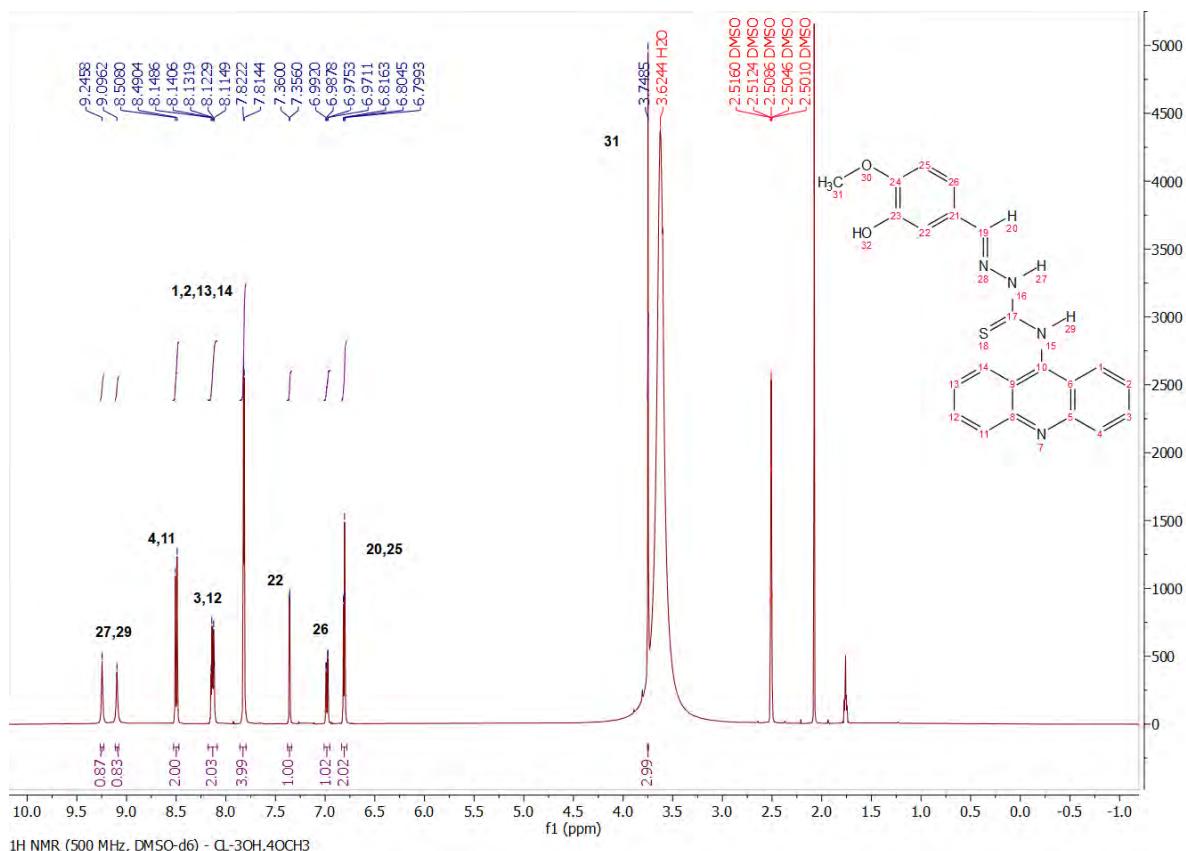


Figura S128. Espectro de RMN ^1H do **CL-3OH,4OCH₃**.

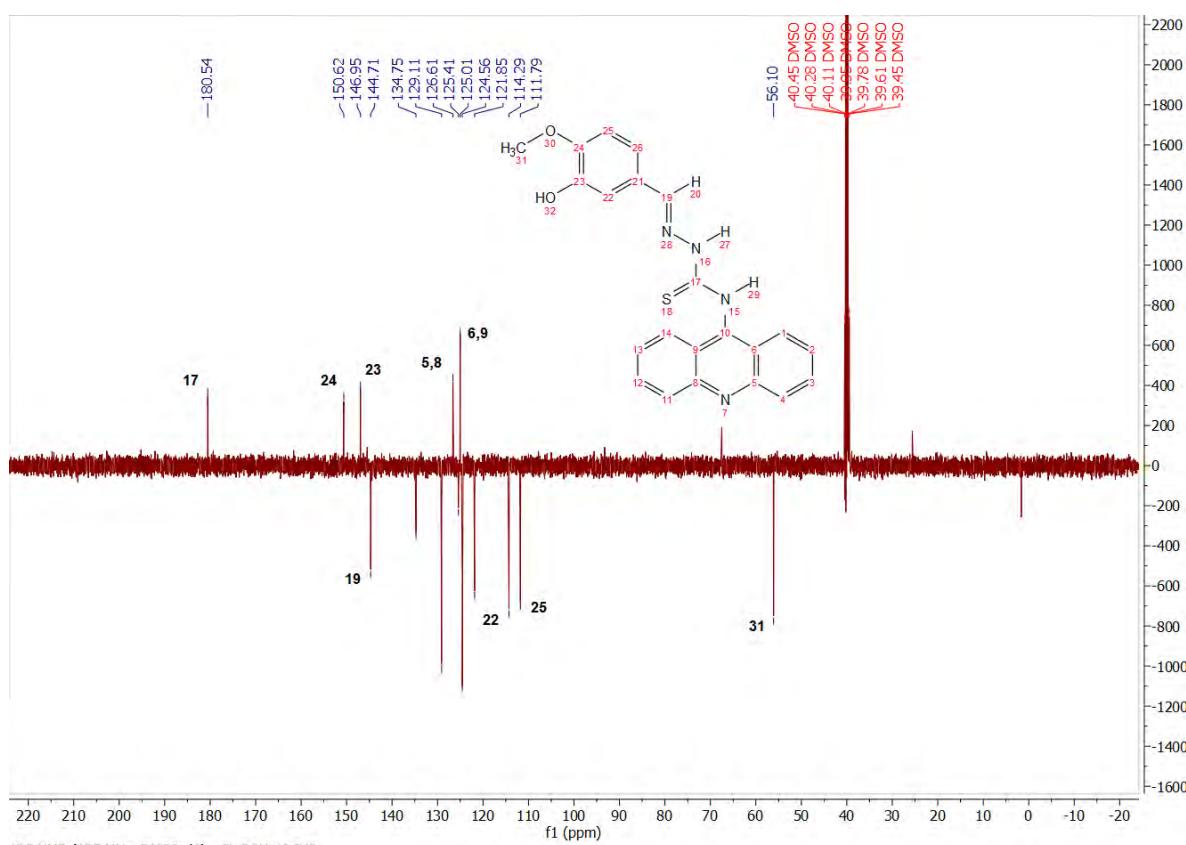


Figura S129. Espectro de RMN ^{13}C do CL-3OH 4OCH₃.

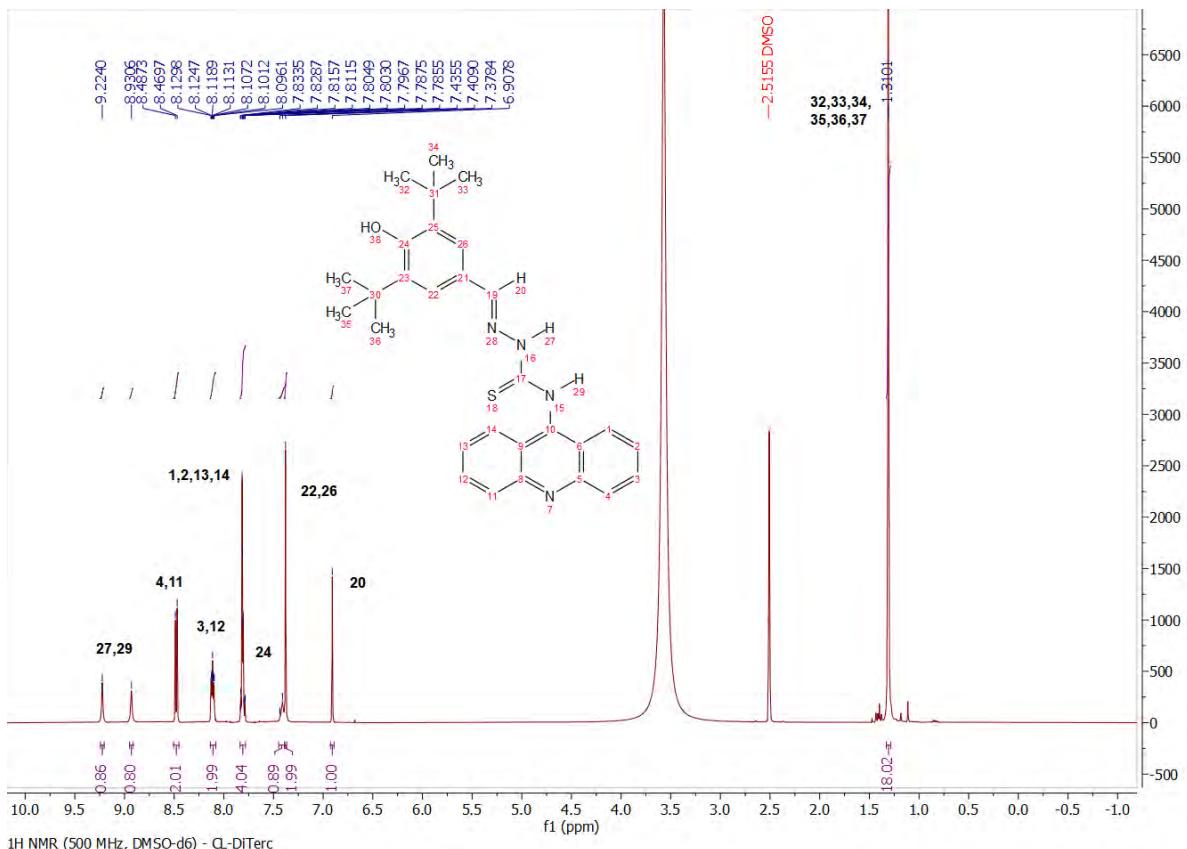


Figura S130. Espectro de RMN ^1H do CL-DiTerc.

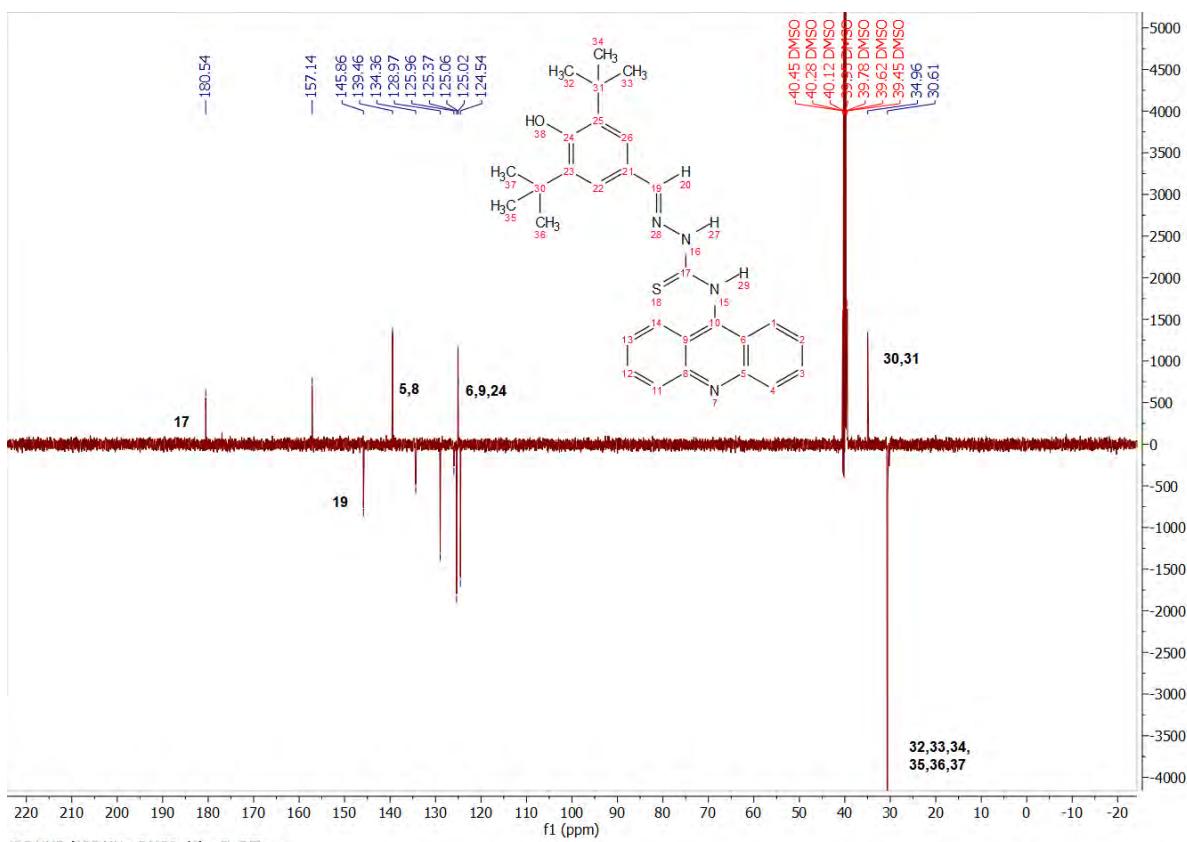


Figura S131. Espectro de RMN ^{13}C do CL-DiTerc.

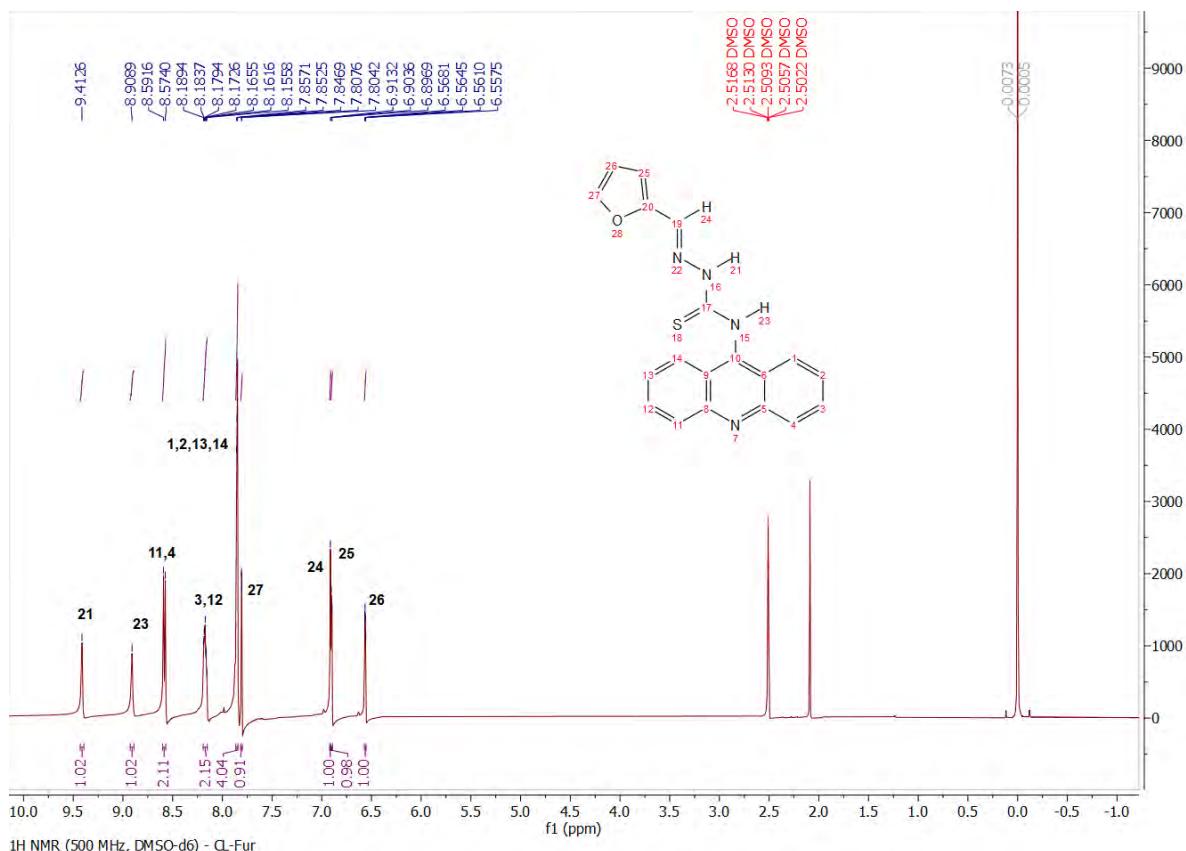


Figura S132. Espectro de RMN ^1H do CL-Fur.

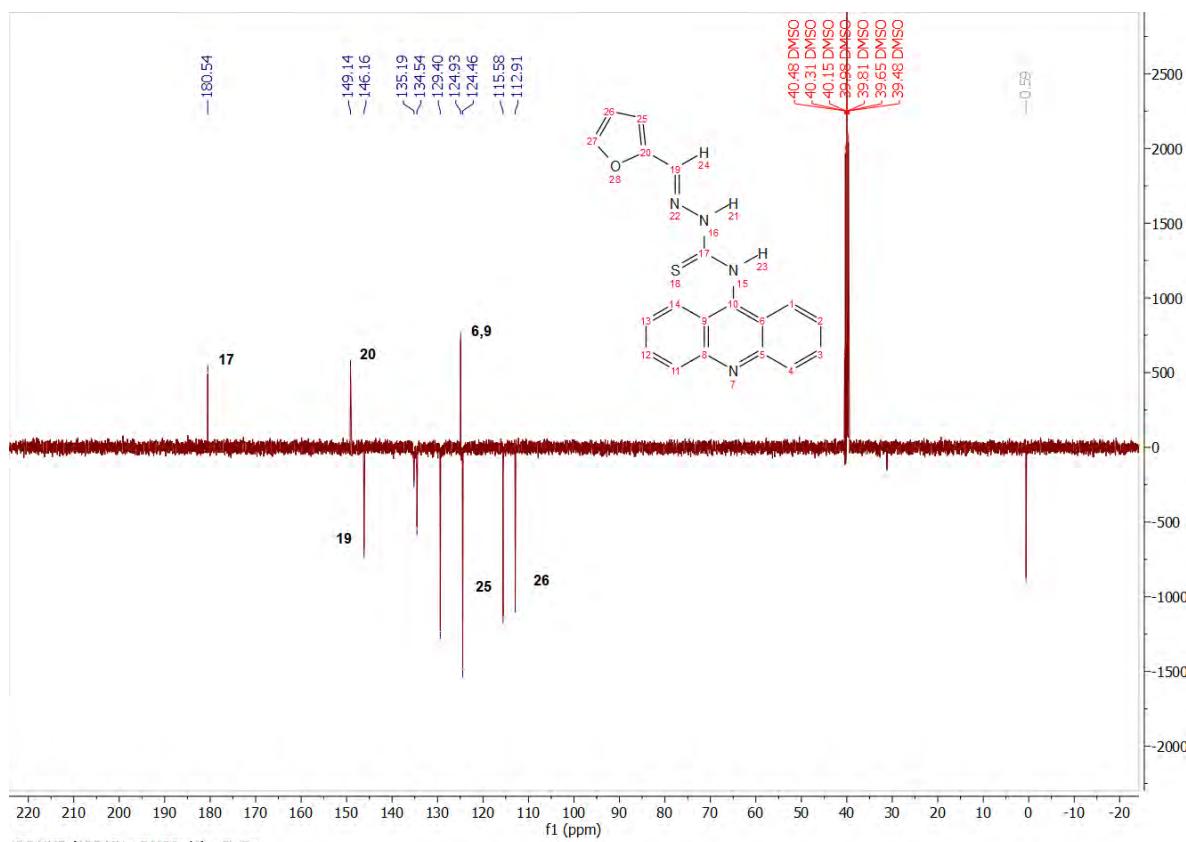


Figura S133. Espectro de RMN ^{13}C do CL-Eur

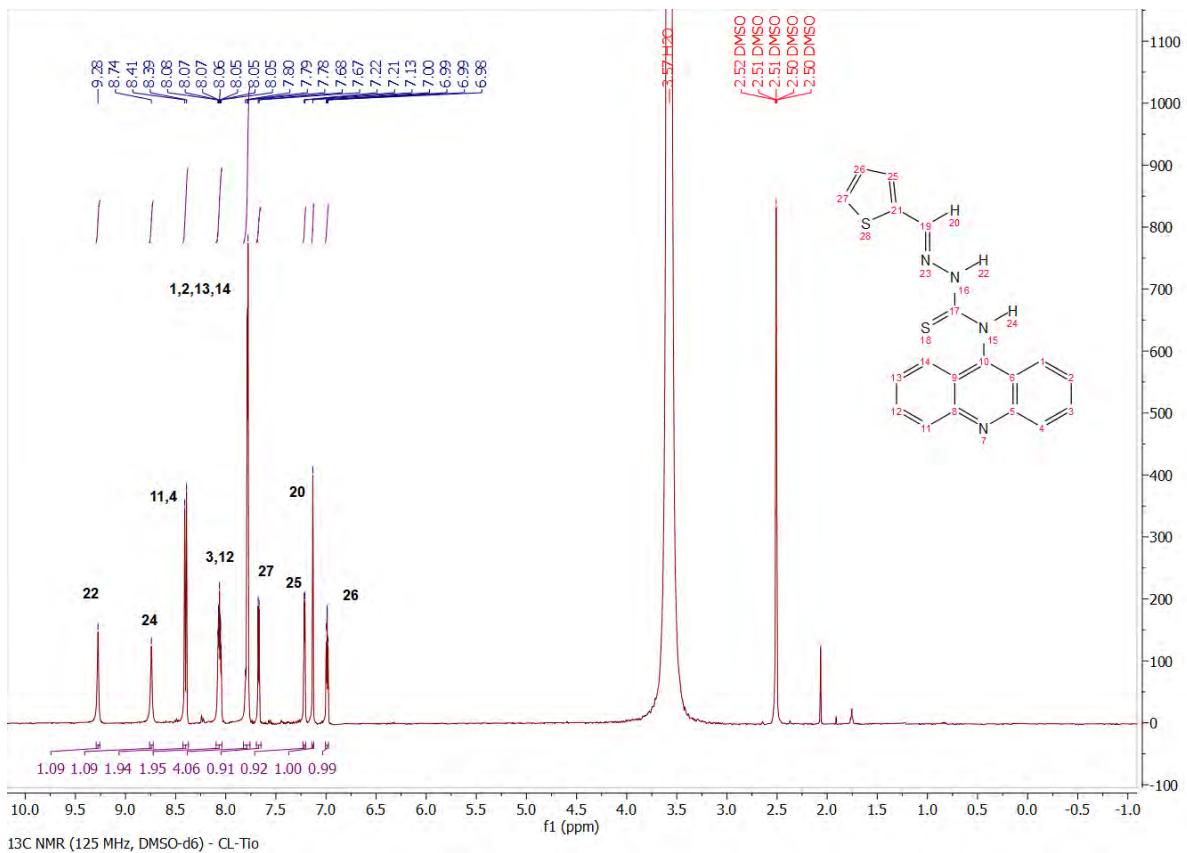


Figura S134. Espectro de RMN ^1H do CL-Tio.

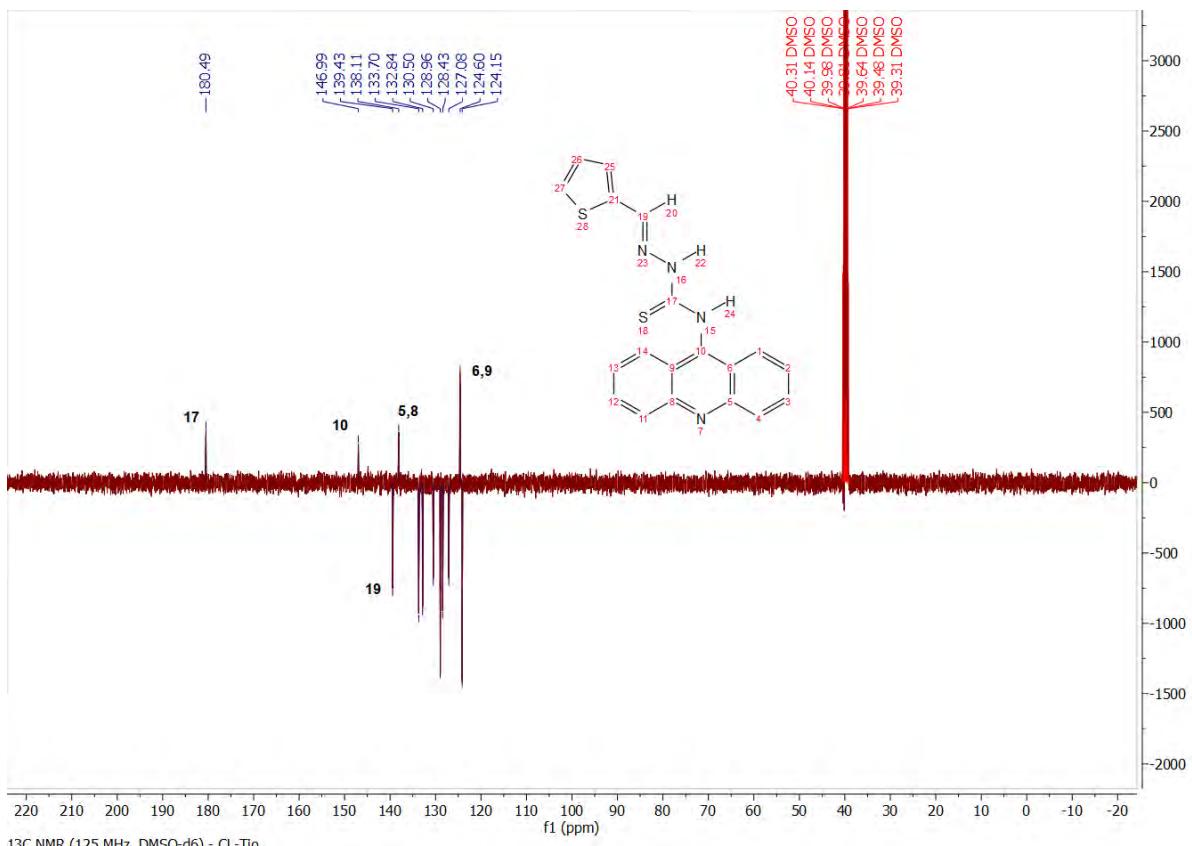


Figura S135. Espectro de RMN ^{13}C do CL-Tio.

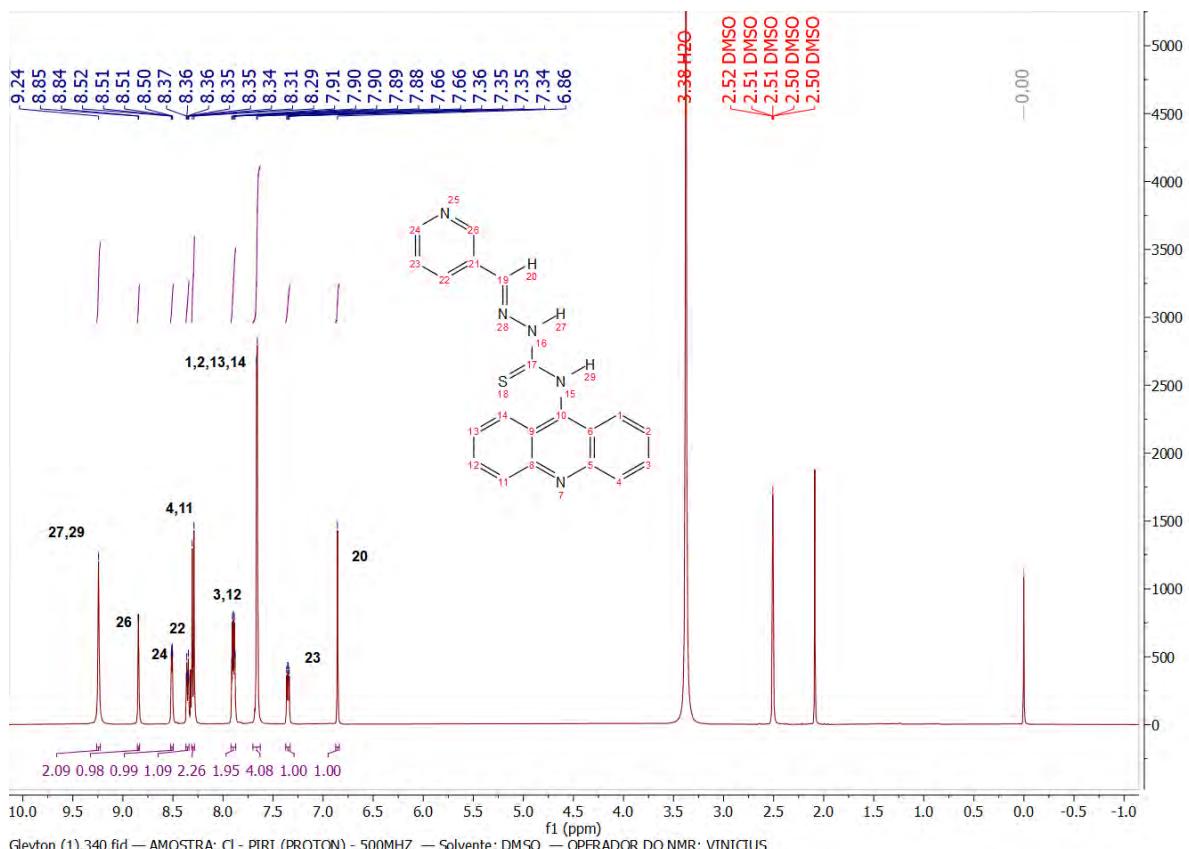


Figura S136. Espectro de RMN ^1H do CL-3PIRI.

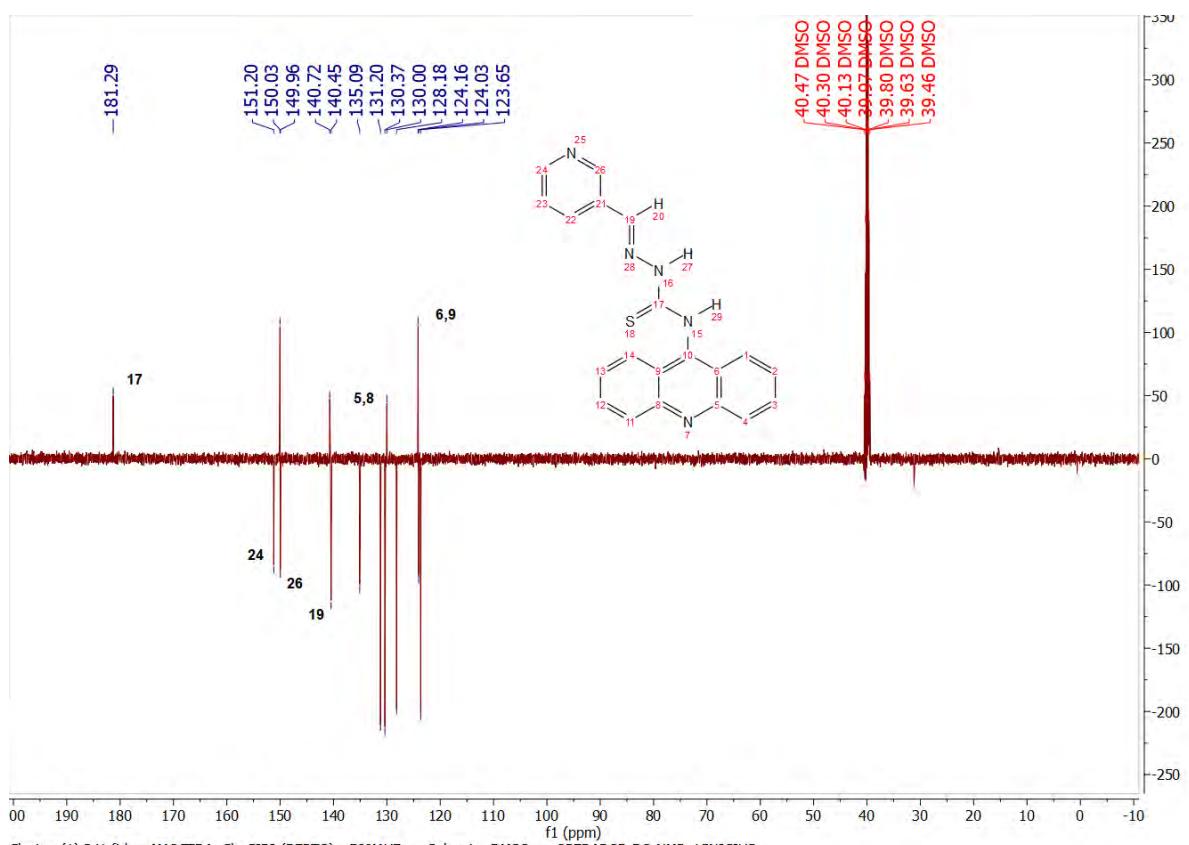


Figura S137. Espectro de RMN ^{13}C do CL-3PIRI.

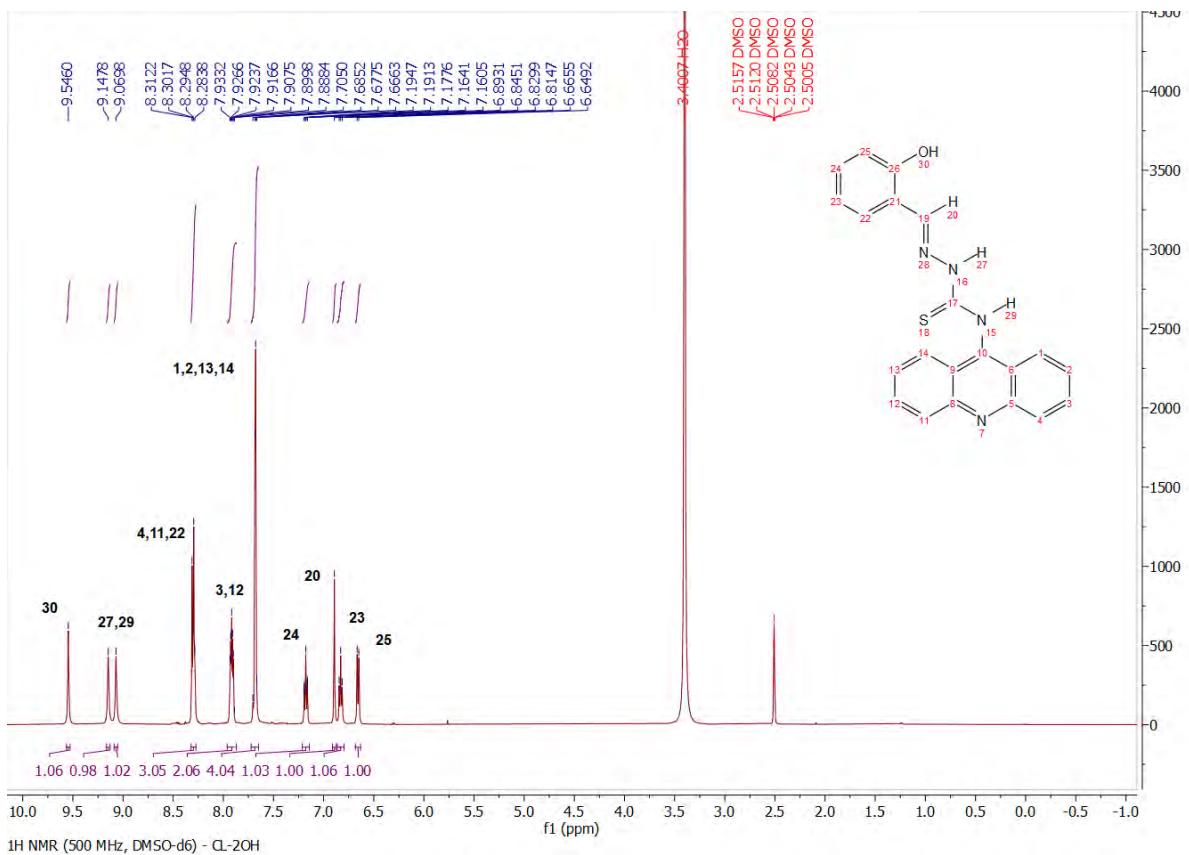


Figura S138. Espectro de RMN ¹H do CL-2OH.

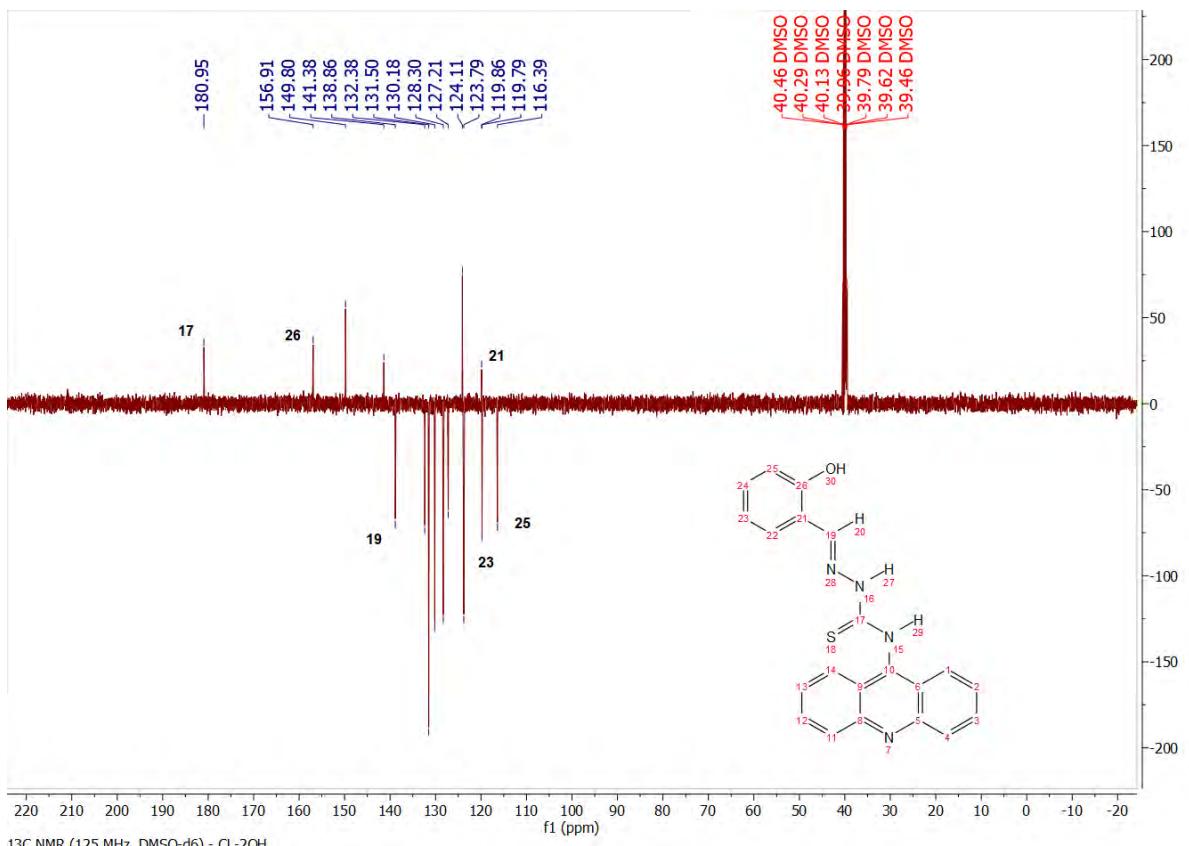


Figura S139. Espectro de RMN ¹³C do CL-2OH.

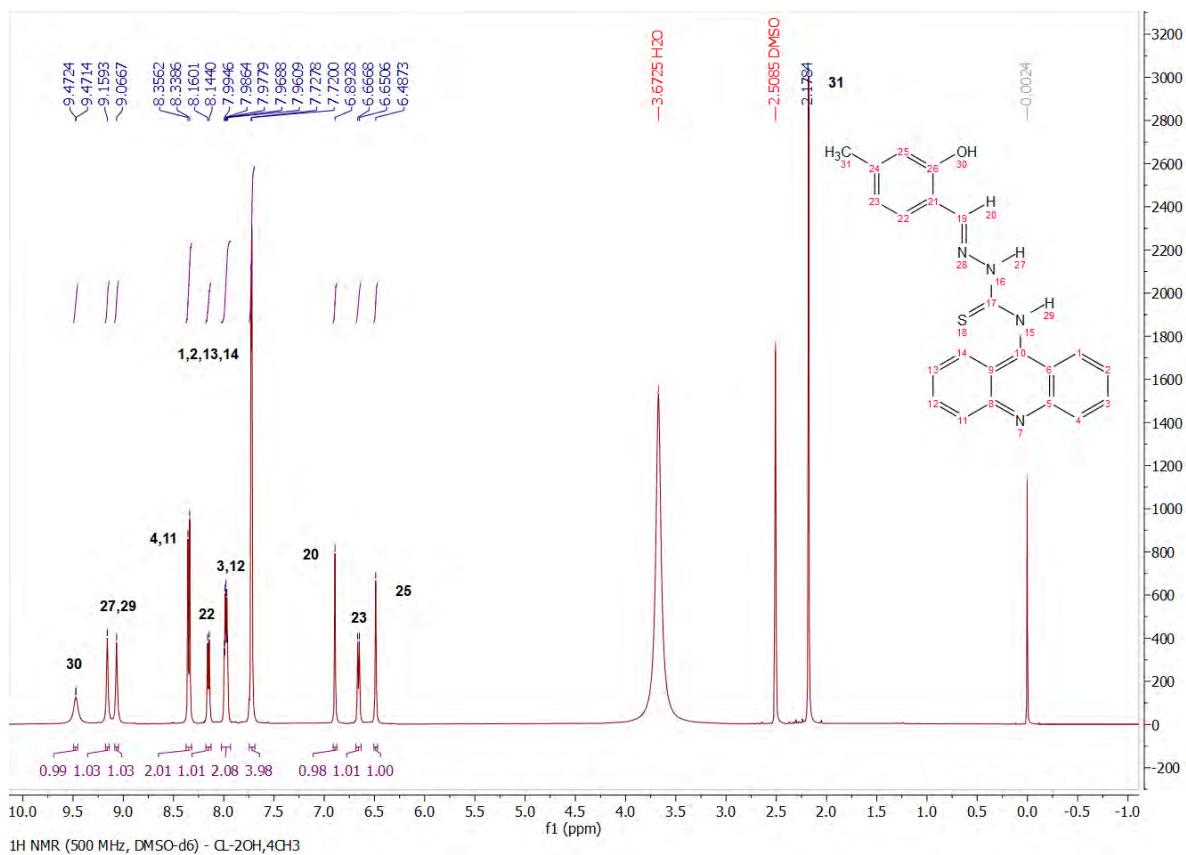


Figura S140. Espectro de RMN ¹H do CL-2OH,4CH₃.

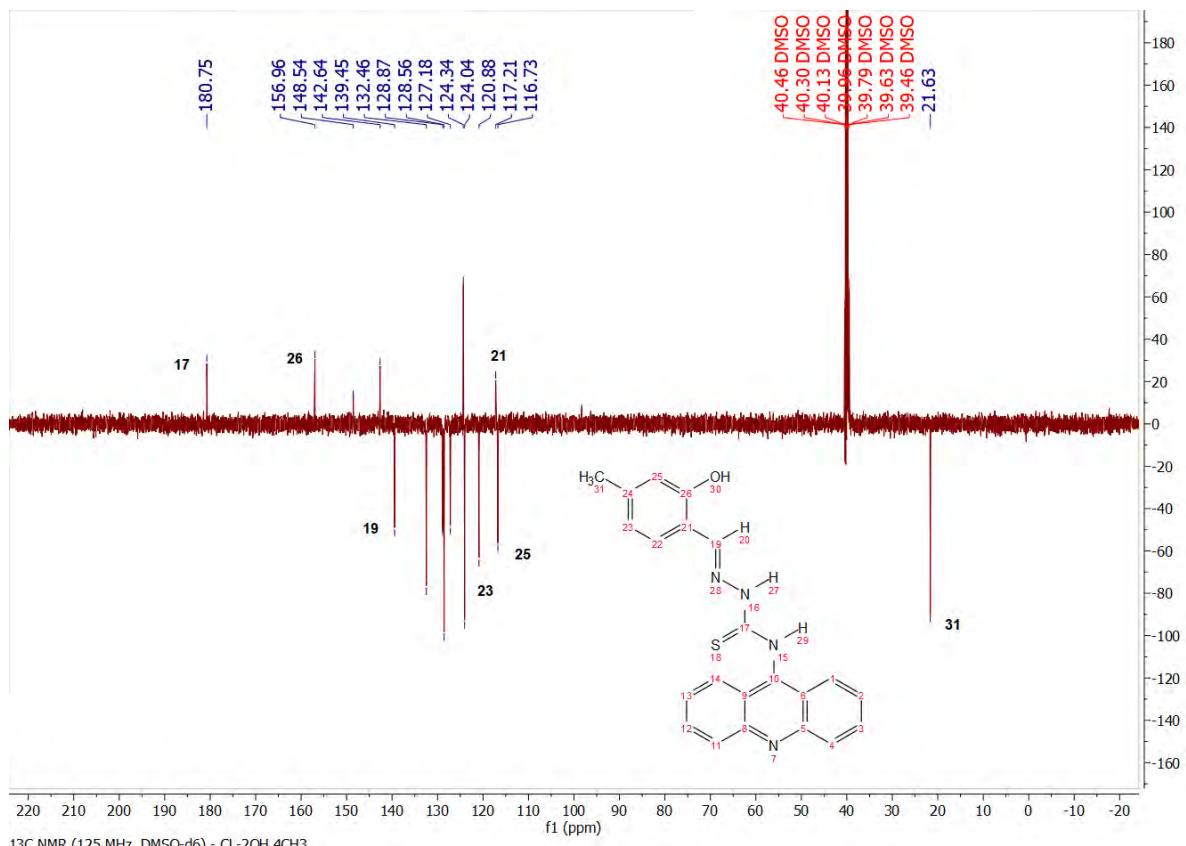


Figura S141. Espectro de RMN ¹³C do CL-2OH,4CH₃.

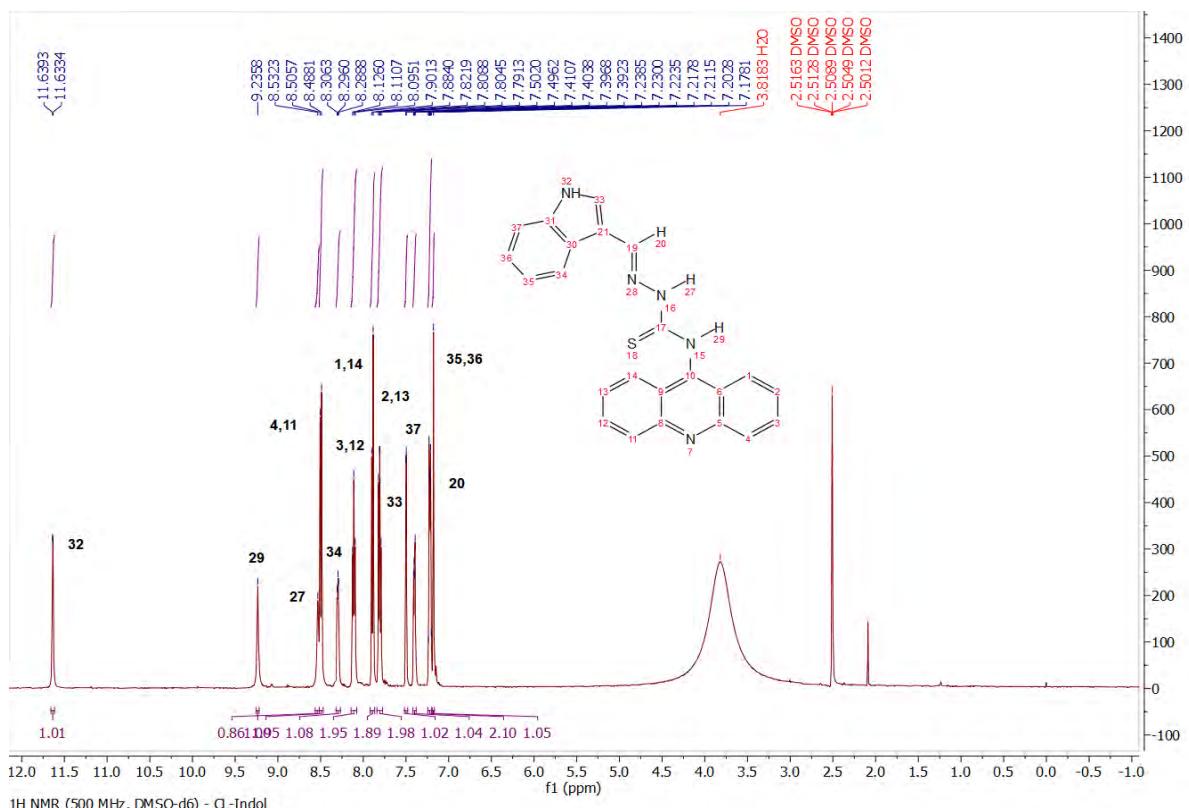


Figura S142. Espectro de RMN ^1H do CL-Indol.

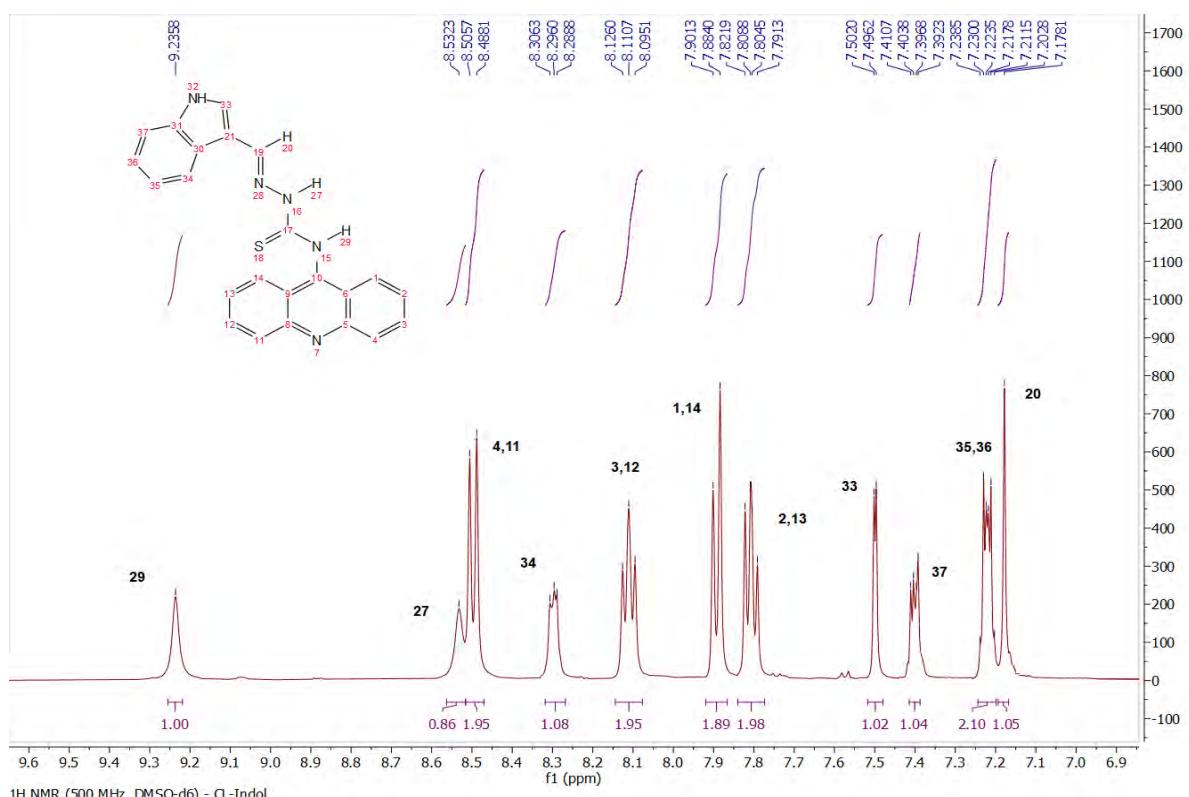


Figura S143. Expansão do espectro de RMN ^1H do CL-Indol.

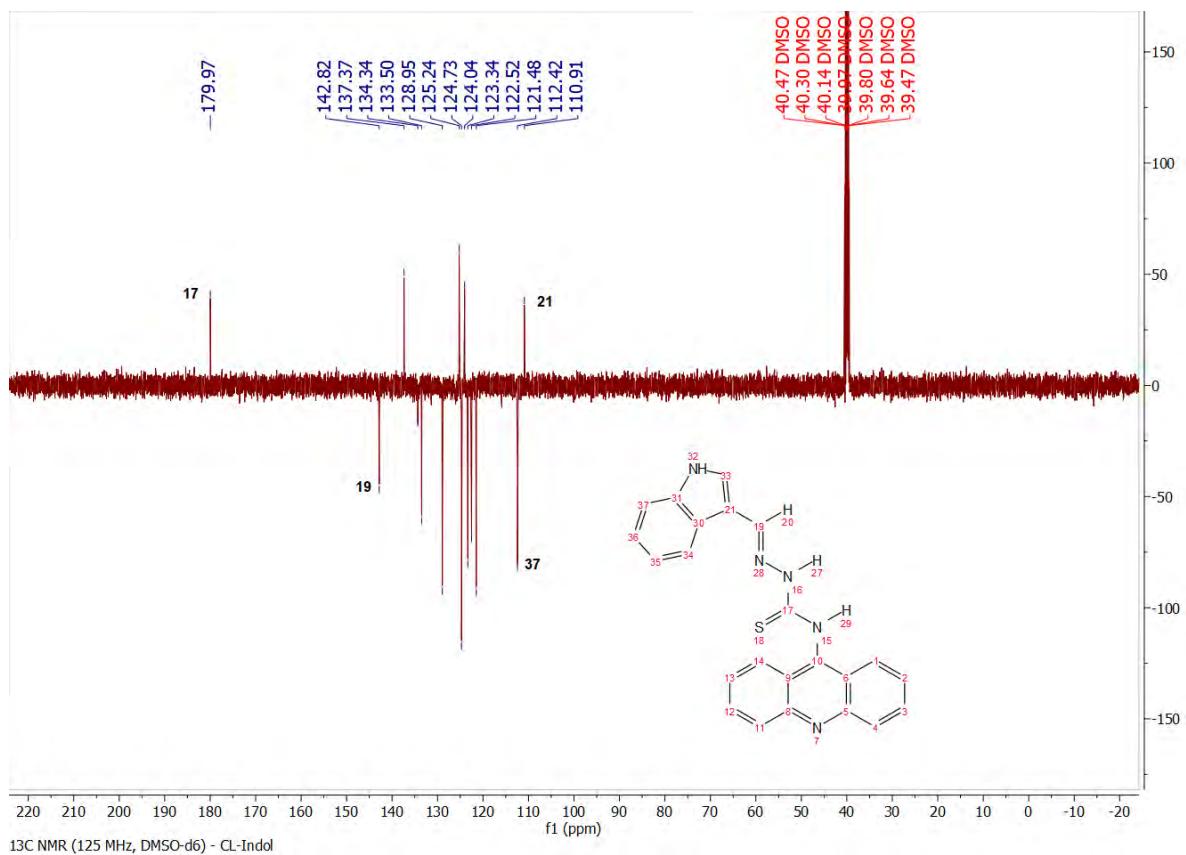


Figura S144. Espectro de RMN ¹³C do CL-Indol.

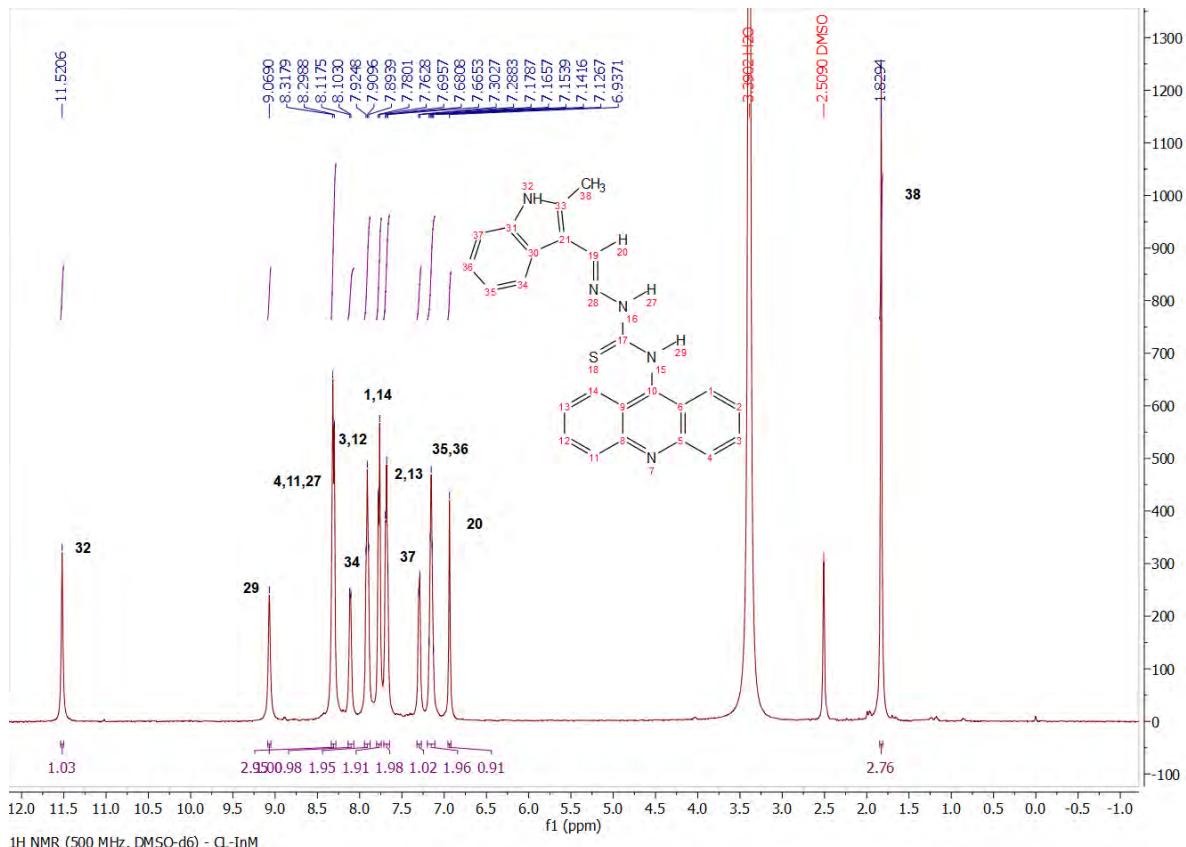


Figura S145. Espectro de RMN ^1H do CL-InM.

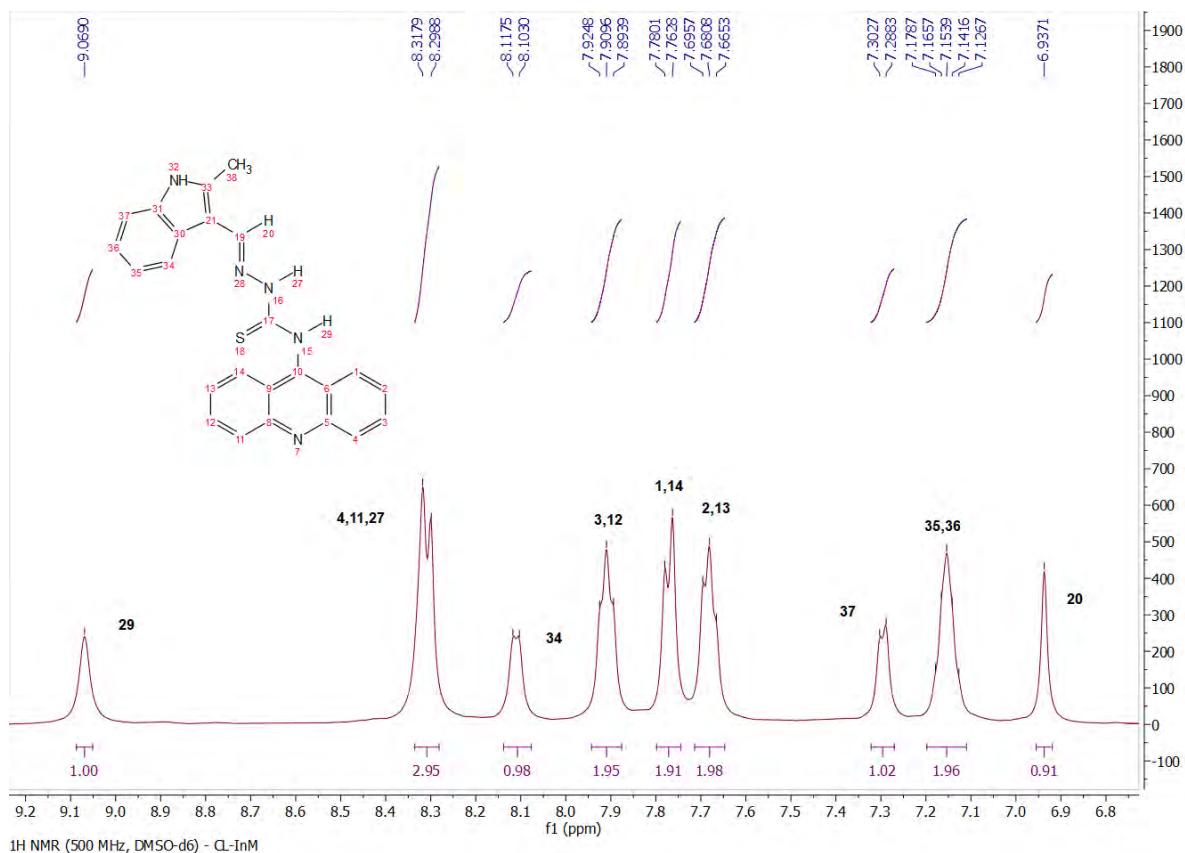


Figura S146. Expansão do espectro de RMN ^1H do CL-InM.

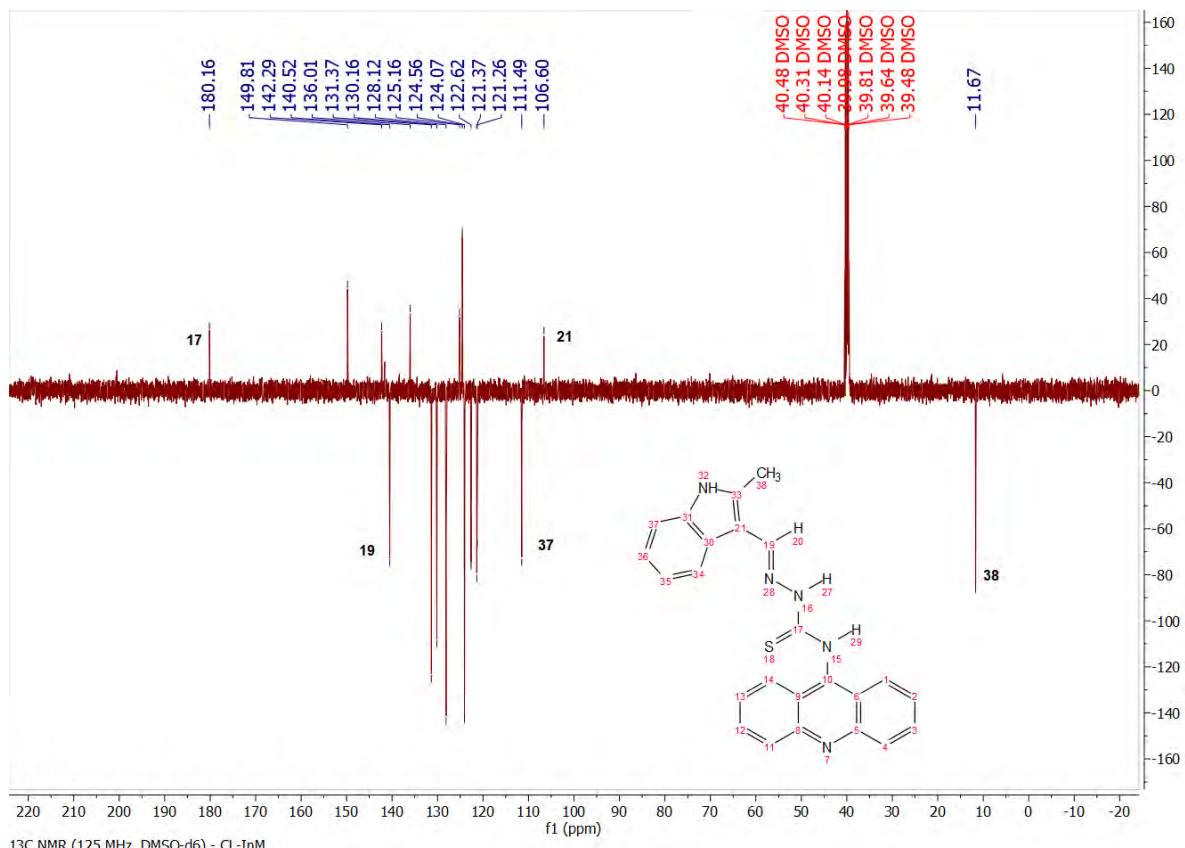


Figura S147. Espectro de RMN ^{13}C do CL-InM.

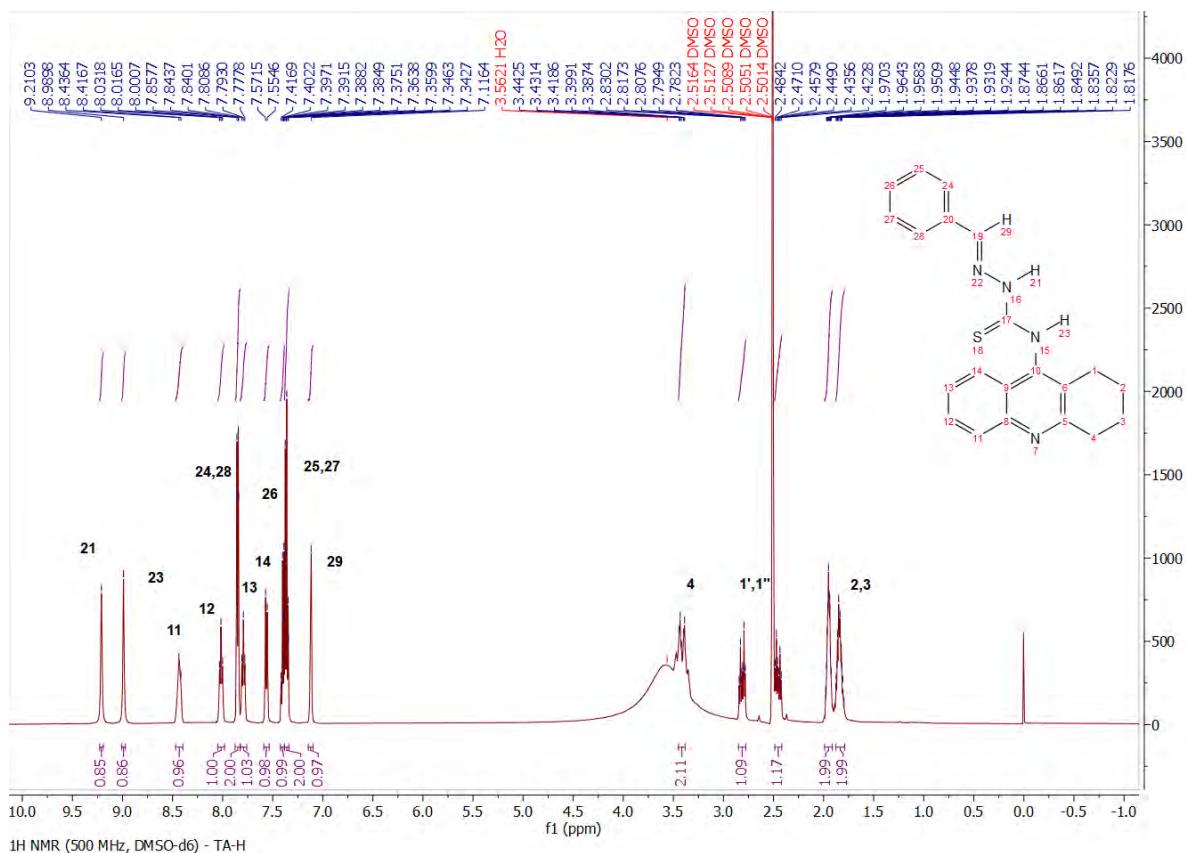


Figura S148. Espectro de RMN ^1H do TA-H.

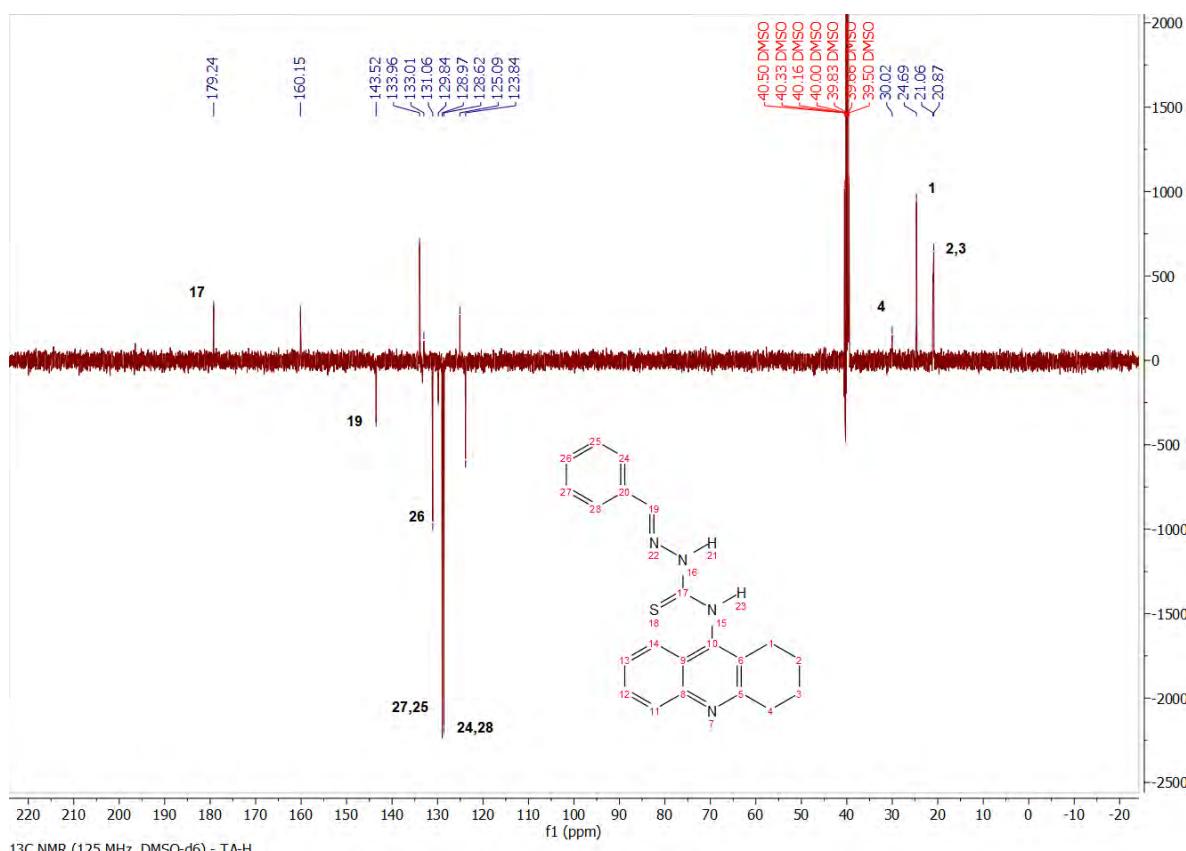


Figura S149. Espectro de RMN ^{13}C do TA-H.

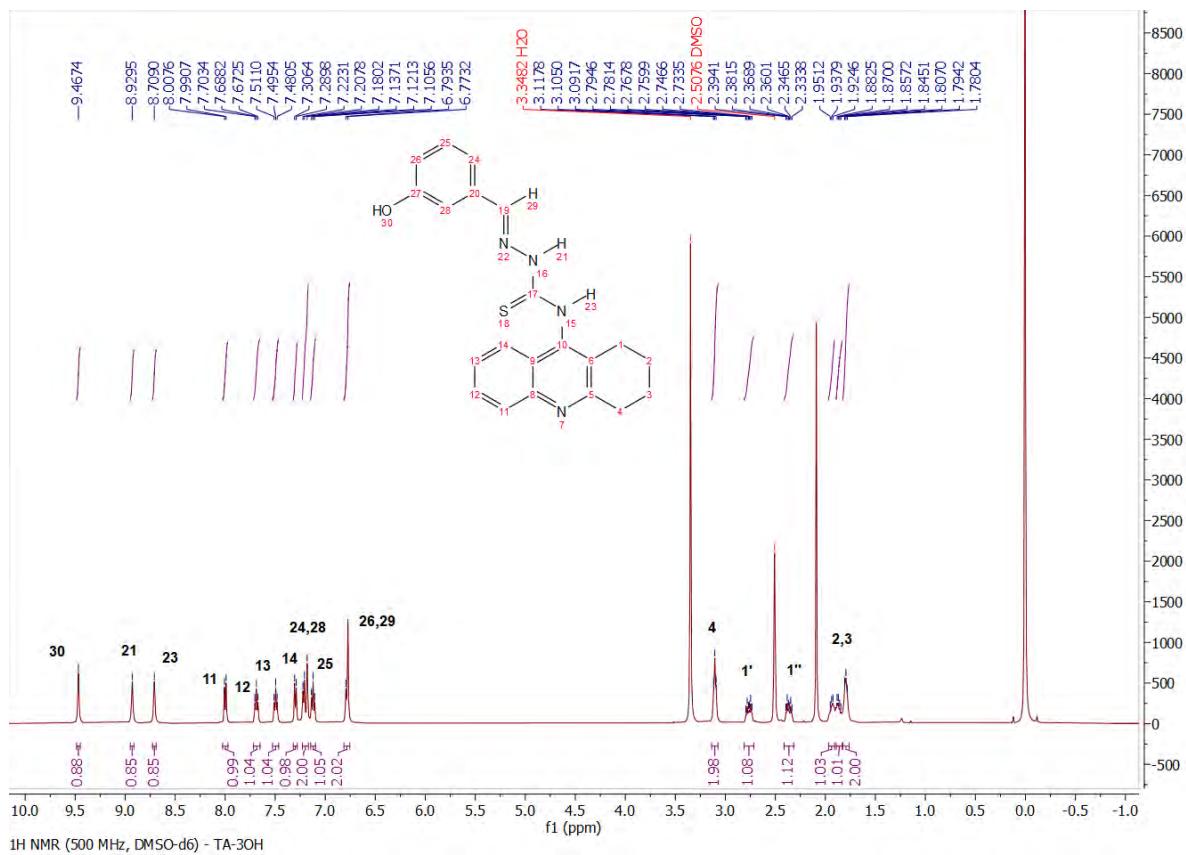


Figura S150. Espectro de RMN ^1H do TA-3OH.

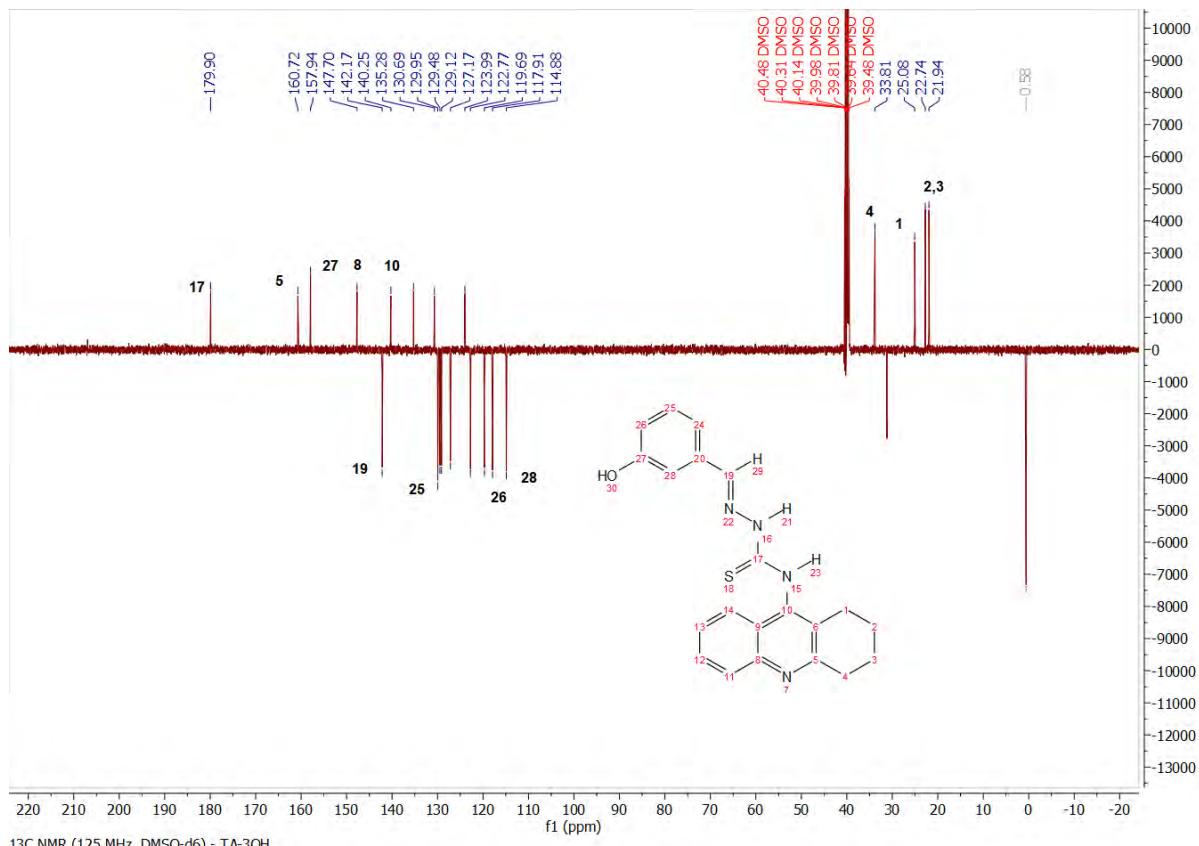


Figura S151. Espectro de RMN ^{13}C do **TA-3OH**.

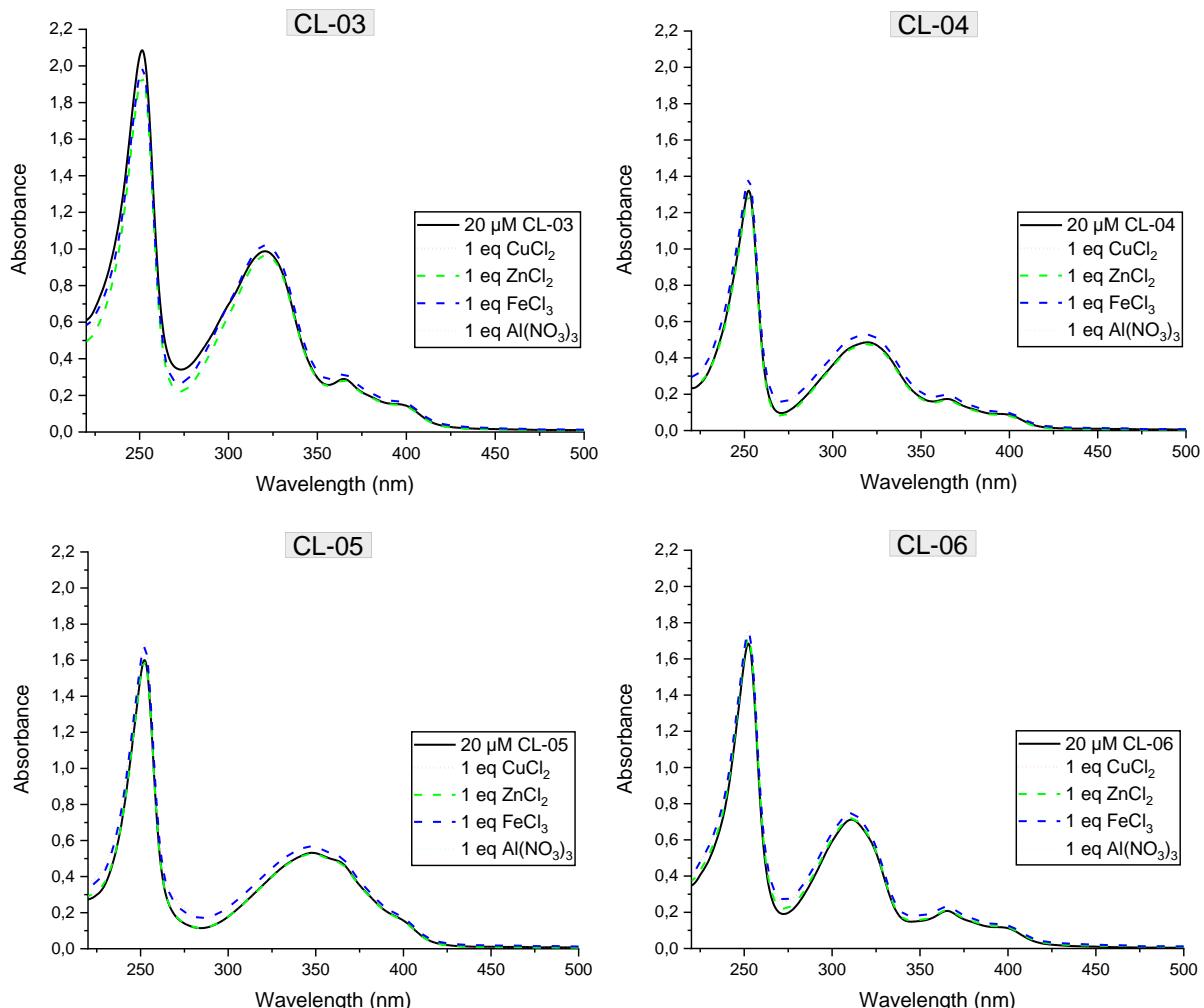


Figura S152. Espectro de absorbância dos derivados avaliados (20 μM) em $\text{MeOH}/\text{H}_2\text{O}$ (50/50, v/v, Tris-HCl pH= 7,5) antes e após adição de Cu^{2+} , Zn^{2+} , Al^{3+} e Fe^{3+} .