Preparation, characterization, and evaluation cytotoxic of some urea/thiourea derivates of Oxymetazoline against HepG2 cell line

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Abstract :
This study includes the synthesis, characterization, and cytotoxicity evaluation of 1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethyl benzyl)-4,5-dihydro-1H-imidazole-1-yl)methyl) urea, thiourea compounds (1-16) as N-Mannich imidazoline bases. The compounds (1-16) performed by the condensation of the Oxymetazoline with urea, thiourea and various aldehydes. The products (1-16) confirmed by mean of their IR, ^{1}H-NMR, ^{13}C-NMR, spectra and elemental analysis. The toxicity effect against HepG2 cell line assessed for some of the prepared compounds use the MMT method. The tested compounds showed improved results in comparison with the target drug.

KEYWORDS: N-Mannich base; Cytotoxic effects; MTT assay

1. Introduction

Oxymetazoline is a sympathomimetic amine drug containing an imidazoline ring. It is potentially used to relieve nasal congestions or as an inhibitor for pro-inflammatory reactions. In order to increase efficiency and reduce a side effect of this drug on patients researchers are encouraged to prepare new derivatives of it and studied their biological and therapeutic effects for instance [1-7].

Urea and thiourea derivatives have a significant role in many agricultural and medical fields due to their multi-dynamic effectiveness such as insecticidal, herbicidal [8-12], antioxidants[13], anticancer agents [14-17], antiviral [18], anticonvulsant[19], anti-inflammatory [20,21], urease inhibitory[22], antimalarial, antimicrobial [23-28].

N-Mannich bases known as potentially useful prodrugs, therefore several pharmaceutical compounds contain NH group modified by N-aminomethylation and experienced as possible therapeutic agents [29-35].

The aminomethylation of urea/thiourea by formaldehyde or substituted benzaldehyde and secondary amines have not involved so much work [36-39], Although the first report on this subject has appeared more than many years ago. Because of the possibility of obtained different condensations involving urea/thiourea and aldehyde as aside reactions [40,41].

On the bases of these facts, the aim of this work to prepare new derivatives of Oxymetazoline by aminomethylation of urea/thiourea, on three-component condensation and studying their cytotoxicity efficacy against HepG2 cells line and comparing them with the same drug.

2.1. **Materials and methods**

Melting points determined on (SMP3) apparatus in open capillary tubes and them uncorrected. All the chemical materials purchased from Merck which used without any purification. The purity of products was carried out on TLC plates coated with

Silica gel 0.30 cm which already made 6x6 cm and spots visualized under UV light used (1:2:5) cyclohexane ,ethyl acetate and ethanol as eluent . The IR spectra recorded on FT-IR 8400S Shimadzu spectrophotometer as potassium bromide discs at the (Chemistry department/ College of education / University of Samarra). The ^{1}H, ^{13}C NMR and DEPT NMR spectra were recorded on Bruker spectrometer (400 MHz) in DMSO-d6 as a solvent with (TMS) as an internal reference at (Jordan University for science and technology /Jordan). The Elemental analysis (CHN) was carried out on a Perkin Elmer 2400 Series analyzer. The experiment of cytotoxic effects done at the biotechnology research center / Al Nahrain University.

2.2. A general method for the syn thesis of N-Mannich base compounds (1-16)

The synthesis of the compounds (1-16) performed according to previous literature[36-39]:

To a solution of Oxymetazoline (0.001mol), aldehyde (0.001 mol), and urea or thiourea (0.001mol) in ethanol (25 ml) added few drops of glacial acid and the crude refluxed for 6-10 hours. On completion of reaction as monitored by TLC. The mixture kept overnight, the solvent removed by vacuum. The crude products were collected, washed with hot water, followed by washing with acetone or diethyl ether, dried on air and recrystallized from ethanol.

2.2.1. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethyl benzyl)-4,5-dihydro-1H-imidazol-1-yl)methyl)urea* , 1

Off white powder, m.p. (245–247 ^{o}C);Yield: 69.5% ; FTIR (cm^{-1}) : 3311 (O-H str.), 3278 (NH,NH_2 str.), 3062 (arom. C–H stretch), 2954,2914 (aliph. C–H str.), 1647 (NHC=O amide-I), 1604 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 9.88 (s, 1H, N<u>H</u>), 9.11 (s, 2H, N<u>H_2</u>), 8.01 (s, 1H, O<u>H</u>), 6.89 (s, 1H, Ar–<u>H</u>), 4.91 (s, 2H, C<u>H_2</u> –NH), 3.77-3.85 (d,4H, imidazoline ring), 3.34 (s,2H,C<u>H_2</u> brig) , 2.10-2.17(d,6H, methyl group) , 1.34 (s,9H, t-butyl group);^{13}C NMR, δ (ppm): 170.7 (<u>C</u>=O), 168 (<u>C</u>=N), 150.33 (<u>C</u>-OH) , 125.65 -136.32 (Ar– <u>C</u>), 66.76 (<u>C</u>H_2 –NH), 46.76(<u>C</u>H_2, imidazoline ring), 30.32 (<u>C</u>H_2 brig),34.65(<u>C</u> ,t-butyl carbon),30.65(<u>C</u>H3,t-butyl group), 19.19,13.54(<u>C</u>H_3,methyl group) ;DEP135 :124.43 (↑,CH) ,65.45 ,45.87 ,29.62 (↓,CH_2) ,29.31,19.55,12.91(↑,CH_3) .

2.2.2. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethyl benzyl)-4,5-dihydro-1H-imidazol-1-yl)-(phenyl)methyl)urea,* 2

Light gray powder, m .p. (143–145^{o}C), Yield: 61.1%;FTIR (cm^{-1}) :3307 (O-H stretch) ,3265,3251 (NH,NH_2 stretch), 3066 (arom. C–H stretch), 2952 (aliph. C–H stretch), 1689 (NHC=O amide-I), 1596 (NHC=O amide-II) ; ^{1}H NMR,δ (ppm): 8.78 (s, 1H, N<u>H</u>), 8.11 (s, 2H, N<u>H_2</u>), 8.06 (s, 1H, O<u>H</u>), 7.63-7.87 (m, 5H, Ar–<u>H</u>), 7.05 (s, 1H, Ar–<u>H</u>),5.63 (s, 1H, C<u>H</u> –NH), 3.93-4.01 (d,4H, imidazoline ring) , 3.52(s,2H,C<u>H_2</u> brig) , 2.26-2.34(d,6H, methyl group) , 1.50 (s,9H, t-butyl group) ; ^{13}C NMR, δ (ppm) : 169.54 (<u>C</u>=O), 167.24 (<u>C</u>=N), 151.58 (<u>C</u>-OH) , 125.50- 136.54 (Ar– <u>C</u>), 61.16 (<u>C</u>H –NH), 44.11 (<u>C</u>H_2, imidazoline ring), 34.17 (<u>C</u>, t-butyl carbon), 29.39 (<u>C</u>H3, t-butyl group), 27.39 (<u>C</u>H_2brig) ,19.80 ,13.16 (<u>C</u>H_3 ,methyl group) ;DEPT135 :129.12 , 128.88 ,128.79,128.16,125.43,61.55(↑,CH),43.84,27.12(↓,CH_2),29.31,19.55,12.91(↑,CH_3).

2.2.3. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethyl benzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-fluorophenyl)methyl)urea,* 3

Oily crude, Yield: 45.4%;FTIR (cm^{-1}) :3315 (O-H stretch) ,3275,3177 (NH,NH_2 stretch), 3060 (arom. C–H stretch), 2923,2858 (aliph. C–H stretch), 1670 (NHC=O amide-I), 1604 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 9.94 (s, 1H, N<u>H</u>), 8.63 (s, 2H, N<u>H_2</u>), 8.05 (s, 1H, O<u>H</u>), 7.23 (m, 4H, fluoro phenyl), 7.01 (s, 1H, Ar–<u>H</u>),5.34 (s,

1H, CH –NH), 3.67-3.74 (d,4H, imidazoline ring) , 3.39(s,2H,CH_2 brig) , 2.13-2.16(d,6H, methyl group) , 1.33 (s,9H, t-butyl group).

2.2.4. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethyl benzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-chlorophenyl)methyl)urea,*** **4**

White powder, m.p. (191–193ºC), Yield: 54.5% ; FTIR (cm^{-1}) :3438 (O-H stretch) ,3307,3207 (NH,NH_2 stretch), 3060 (arom. C–H stretch), 2950 (aliph. C–H stretch), 1660 (NHC=O amide-I), 1600 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 9.84 (s, 1H, NH), 9.19 (s, 2H, NH_2), 8.19(s, 1H, OH), 7.19-7.44 (dd, 4H, chloro phenyl), 6.90 (s, 1H, Ar–H),5.60 (s, 1H, CH –NH), 3.71-3.75 (d,4H, imidazoline ring) , 3.51(s,2H,CH_2 brig) , 1.99-2.07(d,6H, methyl group) , 1.23 (s,9H, t-butyl group) .

2.2.5. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethyl benzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-nitrophenyl)methyl)urea,*** **5**

Light brown powder, m.p. (138–140ºC), Yield: 50.1%;FTIR (cm^{-1}) :3433 (O-H stretch) ,3315,3199 (NH,NH_2 stretch), 3083 (arom. C–H stretch), 2952,2927 (aliph. C–H stretch), 1660 (NHC=O amide-I), 1604 (NHC=O amide-II) ; ^{1}H NMR ,δ (ppm): 10.33 (s, 1H, NH), 9.97 (s, 2H, NH_2), 8.34-8.36 (d, 2H, Ar–H nitrophenyl) 8.19 (s, 1H, OH), 7.73-7.75 (d, 2H, Ar–H nitrophenyl), 7.06 (s, 1H, Ar–H),5.64 (s, 1H, CH –NH), 3.94-4.01 (d,4H, imidazoline ring) , 3.55(s,2H,CH_2 brig) , 2.27-2.34(d,6H, methyl group) , 1.51 (s,9H, t-butyl group) ;^{13}C NMR, δ (ppm) :169.75 (C=O), 167.41 (C=N), 157.82 (C-NO_2) , 151.77 (C-OH) , 123.36 -136.75 (Ar– C), 58.78 (CH –NH), 44.31(CH_2, imidazoline ring), 34.37 (C, t-butyl carbon), 29.77 (CH3,t-butyl group), 27.59 (CH_2brig) ,19.99, 13.35 (CH_3,methyl group) ;DEPT135 :126.95 ,125.44 , 122.90,58.31(↑,CH),43.85,27.13(↓,CH_2),29.31,19.53,12.90(↑,CH_3) .

2.2.6. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-hydroxyphenyl)methyl)urea,*** **6**

Light pink powder, m.p. (184–186 ºC), Yield: 66.4%;FTIR (cm^{-1}) : 3433 (O-H stretch),3311,3209 (NH,NH_2 stretch), 3060 (arom. C–H stretch), 2950 (aliph. C–H stretch), 1660 (NHC=O amide-I), 1596 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 9.92 (s, 1H, NH), 9.47 (s, 1H, OH) , 8.17 (s, 1H, OH), 7.90 (s, 2H, NH_2), 6.88-7.11 (m, 5H, Ar–H), 5.59 (s, 1H, CH –NH), 3.92-3.98 (d,4H, imidazoline ring) , 3.51(s,2H,CH_2 brig), 2.24-2.32(d,6H, methyl group) , 1.49 (s,9H, t-butyl group) ; ^{13}C NMR, δ (ppm):171.15 (C=O), 165.01 (C=N), 161.18 (C-OH) , 153.22 (C-OH) 138.17-117.02 (Ar– C,Ar-CH), 77.45 (CH –NH), 45.82 (CH_2, imidazoline ring), 35.83 (C, t-butyl carbon), 31.23 (CH3, t-butyl group), 29.07 (CH_2 brig), 21.45,14.80 (CH_3,methyl group));DEPT-135: 129.54 , 125.44, 115.11,74.31 (↑,CH), 43.84, 27.13(↓,CH_2), 29.32, 19.54 ,12.90 (↑,CH_3) ; Anal. Calc. ($C_{24}H_{32}N_4O_2$): C, 67.90, H, 7.60, N, 13.20, O, 11.31, S, 9.20; Found :C, 67.87,H ,7.72, N,13.44%.

2.2.7. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(2-hydroxyphenyl)methyl)urea,*** **7**

Light gray powder, m.p. (278ºC dec.), Yield: 47.6% ;FTIR (cm^{-1}) :3438 (O-H stretch) ,3298,3180 (NH,NH2 stretch), 3080 (arom. C–H stretch), 2985,2954 (aliph. C–H stretch), 1687 (NHC=O amide-I), 1647 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 9.94 (s, 1H, NH), 8.53 (s, 2H, NH_2), 8.01 (s, 1H, OH), 7.88 (s, 1H, OH), 6.86-7.37 (m, 5H, Ar–H), 5.34 (s, 1H, CH –NH), 3.89-3.77 (d,4H, imidazoline ring) , 3.37(s,2H,CH_2 brig) , 2.15-2.17(d,6H, methyl group) , 1.35 (s,9H, t-butyl group) ; Anal. Calc. ($C_{24}H_{32}N_4O_3$): C, 67.90, H, 7.60, N, 13.20, O, 11.31; Found :C, 67.79 ,H , 7.49, N, 13.16% .

2.2.8. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(2-methoxyphenyl)methyl)urea,*** **8**

Light green powder, m.p. (125–127ºC), Yield: 70.6%;FTIR (cm^{-1}) :3367 (O-H stretch) ,3215 (NH,NH_2 stretch), 3072 (arom. C–H stretch), 2954,2867 (aliph. C–H stretch), 1677 (NHC=O amide-I), 1600 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 10.45 (s, 1H, NH), 7.67 (s, 1H, OH), 7.50 (s, 2H, NH_2), 6.81-7.08 (m, 5H, Ar–H), 5.68 (s, 2H, CH_2 –NH), 3.87 (s, 3H, O-CH_3), 3.61-3.67 (d,4H, imidazoline ring) , 3.39(s,2H,CH_2 brig) , 2.27-2.33(d,6H, methyl group) , 1.50 (s,9H, t-butyl group) ; ^{13}C NMR, δ (ppm) : 174.79 (C=O), 166.73 (C=N), 159.89 (C-OCH_3) 151.52 (C-OH) , 116.05- 135.99 (Ar– C, Ar– CH), 72.25 (CH –NH), 58.25(O-CH_3), 48.07 (CH_2, imidazoline ring),34.23 (C, t-butyl carbon), 29.87 (CH_3, t-butyl group), 29.36 (CH_2brig),20.09,13.25 (CH_3, methyl group));DEPT-135: 128.54,127.73,124.79, 119.06,116.07,72.07(↑,CH),58.17 (↑,OCH_3) 47.59, 28.89(↓,CH_2), 29.41, 19.64 ,12.80 (↑,CH_3) .

2.2.9. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)methyl)thiourea,* 9

White powder, m.p. (216–218ºC), Yield: 65.5%;FTIR (cm^{-1}) :3313 (O-H stretch) ,3269,3188 (NH,NH_2 stretch), 3053 (arom. C–H stretch), 2954,2916 (aliph. C–H stretch), 1217 (C=S stretch) ; ^{1}H NMR, δ (ppm): 9.91 (s, 1H, NH), 8.43 (s, 2H, NH_2), 8.05 (s, 1H, OH), 6.91 (s, 1H, Ar–H),5.04 (s, 2H, CH_2 –NH), 3.87-3.79 (d,4H, imidazoline ring) , 3.39(s,2H,CH_2 brig) , 2.19-2.12(d,6H, methyl group) , 1.34 (s,9H, t-butyl group); ^{13}C NMR, δ (ppm) : 170.1 (C=O),166.77 (C=N), 151.22 (C-OH),124.55-135.32 (Ar– C, Ar–CH), 64.76 (CH_2–NH), 48.33 (CH_2, imidazoline ring) ,30.32 (CH_2brig),33.65(C ,t-butyl carbon),30.25(CH3, t-butyl group),19.19,13.54(CH_3,methyl group);DEPT135:124.43 (↑,CH) , 63.45,47.88 , 29.62(↓,CH_2) , 29.31 , 19.43 ,12.94 (↑,CH_3) .

2.2.10. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(phenyl)methyl)thiourea,* 10

white powder, m.p. (178–180 ºC), Yield: 42.1%;FTIR (cm^{-1}) :3323 (O-H stretch) ,3285,3221 (NH,NH_2 stretch), 3058 (arom. C–H stretch), 2950,2910 (aliph. C–H stretch), 1222 (C=S stretch); ^{1}H NMR, δ (ppm): 9.91 (s, 1H, NH), 8.43 (s, 2H, NH_2), 8.05 (s, 1H, OH), 6.91 (s, 1H, Ar–H),5.04 (s, 1H, CH –NH), 3.87-3.79 (d,4H, imidazoline ring) , 3.39(s,2H,CH_2 brig) , 2.19-2.12(d,6H, methyl group) ,1.34 (s,9H, t-butyl group) .

2.2.11. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-fluorophenyl)methyl)thiourea,* 11

Light yellow powder, m.p.(201–203ºC),Yield:53.7% ;FTIR (cm^{-1}) :3371 (O-H stretch) ,3265,3176 (NH,NH_2 stretch), 3060 (arom. C–H stretch), 2923,2858 (aliph. C–H stretch), 1224 (C=S stretch); ^{1}H NMR: δ (ppm), 9.49 (s, 1H, NH), 8.89 (s, 2H, NH_2), 7.89 (s, 1H, OH), 7.15 (s, 4H, fluoro phenyl), 6.77 (s, 1H, Ar–H),5.47 (s, 1H, CH –NH),3.32-3.36(d,4H, imidazoline ring) ,3.09(s,2H,CH_2 brig) ,2.08-2.15 (d,6H,methyl group),1.32(s,9H,t-butyl group); ^{13}CNMR,δ(ppm) :185.45(C=S), 167.10 (C=N) , 161.11(C-F),152.74(C-OH),116.74-136.32(Ar– C),71.67(CHNH),44.23(CH_2, imidazoline ring),35.64(C, t-butyl carbon),31.36(CH_3,t-butyl group) , 30.32 (CH_2 brig) , 21.60 ,14.67(CH_3,methyl group) ;DEPT135 :129.29 ,126.22 ,119.2 ,71.77 (↑,CH) , 44.23 ,29.87(↓,CH_2),31.07,21.32,14.39(↑,CH_3) .

2.2.12. *1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-chlorophenyl)methyl)thiourea,* **12**

White powder, m.p. (134–136ºC), Yield: 55.7%;FTIR (KBr ,cm^{-1}) :3367 (O-H stretch) ,3282,3170 (NH,NH2 stretch), 3066 (arom. C–H stretch), 2952,2869 (aliph. C–H stretch), 1222 (C=S stretch) ; ^{1}H NMR, δ (ppm): 9.91 (s, 1H, NH), 8.43 (s, 2H,

NH_2), 8.05 (s, 1H, OH), 6.91 (s, 1H, Ar–H),5.04 (s, 1H, CH –NH), 3.87-3.79 (d,4H, imidazoline ring) , 3.39(s,2H,CH_2 brig) , 2.19-2.12(d,6H, methyl group) , 1.34 (s,9H, t-butyl group) .

2.2.13. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-nitrophenyl)methyl)thiourea,*** **13**

Dark orange powder, m.p. (211-213ºC dec.), Yield: 61.4%;FTIR (cm^{-1}) :3411 (O-H stretch) , 3382 (NH,NH_2 stretch), 3043 (arom. C–H stretch), 2958 (aliph. C–H stretch), 1132 (C=S stretch) ; ^{1}H NMR, δ (ppm): 9.48 (s, 1H, NH), 8.99 (s, 2H, NH_2), 8.48 (s, 1H, OH), 7.19,8.10 (d, 4H, Ar–H nitro phenyl), 6.83 (s, 1H, Ar–H),5.47 (s, 1H, CH –NH), 3.40-3.44 (d,4H, imidazoline ring) , 3.35(s,2H,CH_2 brig) , 2.07-2.16(d,6H, methyl group) , 1.33 (s,9H, t-butyl group); ^{13}C NMR ,δ (ppm) : 184.07 (C=S), 168.10 (C=N), 159.67 (C-NO_2),151.43 (C-OH) , 125.20-136.03 (Ar– C, Ar–CH), 73.33 (CH –NH), 48.13 (CH_2, imidazoline ring), 34.31 (C, t-butyl carbon), 30.02 (CH3,t-butyl group),29.33(CH_2 brig),20.25,13.33(CH_3,methyl group); DEPT135: 129.62, 127.25,124.65,72.77(↑,CH),45.37,29.33(↓,CH_2),29.43,19.69,12.77 (↑,CH_3) .

2.2.14. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(4-hydroxyphenyl)methyl)thiourea,*** **14**

Oily crude, Yield: 43.7%;FT-IR (cm^{-1}) :3310 (O-H stretch) ,3245,3190 (NH,NH_2 stretch), 3066 (arom. C–H stretch), 2951 (aliph. C–H stretch), 1125 (C=S stretch) ; ^{1}H NMR, δ (ppm): 9.91 (s, 1H, NH), 8.43 (s, 2H, NH_2), 8.05 (s, 1H, OH), 6.91 (s, 1H, Ar–H),5.04 (s, 2H, CH_2 –NH), 3.87-3.79 (d,4H, imidazoline ring) , 3.39(s,2H,CH_2 brig) , 2.19-2.12(d,6H, methyl group) , 1.34 (s,9H, t-butyl group) .

2.2.15. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl) -(2-hydroxyphenyl)methyl)thiourea,*** **15**

Dark gray powder, m.p. (252 ºC dec.), Yield: 64.1%;FT-IR (cm^{-1}) :3396 (O-H stretch) , 3284 (NH,NH_2 stretch), 3047 (arom. C–H stretch), 2964 (aliph. C–H stretch), 1122 (C=S stretch) ; ^{1}H NMR, δ (ppm): 9.87 (s, 1H, NH), 9.09 (s, 2H, NH_2), 8.21 (s, 1H, OH), 7.78 (s, 1H, OH), 6.76-7.27 (m, 5H, Ar–H),5.44 (s, 1H, CH –NH), 3.47 (s,4H, imidazoline ring) , 3.39(s,2H,CH2 brig) , 2.08-2.15(d,6H, methyl group) , 1.33 (s,9H, t-butyl group) .

2.2.16. ***1-((2-(4-(t-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)-(2-methoxyphenyl)methyl)thiourea,*** **16**

Orange powder, m.p. (151–153ºC), Yield: 71.8%; FTIR (cm^{-1}) :3357 (O-H stretch) , 3282,3143 (NH,NH_2 stretch), 3050 (arom. C–H stretch), 2950,2871 (aliph. C–H stretch), 1226 (C=S stretch) ; ^{1}H NMR, δ (ppm): 9.61 (s, 1H, NH), 8.65 (s, 2H, NH_2), 8.02 (s, 1H, OH), 6.81-7.21 (m, 5H, Ar–H), 5.64 (s, 1H, CH –NH), 3.67-3.58 (d,4H, imidazoline ring) , 3.36(s,2H,CH_2 brig) , 2.19-2.21(d,6H, methyl group) , 1.32 (s,9H, t-butyl group) .

2.2.17. ***1-((2-(4-(tert-butyl)-3-hydroxy-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazol-1-yl)methyl)-3-(hydroxymethyl)urea,*** **17**

To a solution of Oxymetazoline (0.002mol), formaldehyde (0.002 mol), and urea (0.001mol) in ethanol (25 ml) added few drops of glacial acid and the crude refluxed for 8 hours. On completion of reaction as monitored by TLC. The mixture kept overnight, the solvent removed by vacuum. The crude products were collected,

washed with hot water, followed by washing with diethyl ether, dried on air and recrystallized from ethanol.

Off white powder, m.p. (233–235 ºC);Yield: 75.5% ; FTIR (cm^{-1}) :3352 (O-H, NH str.), 3070 (arom. C–H stretch), 2966 (aliph. C–H str.), 1641 (NHC=O amide-I), 1500 (NHC=O amide-II) ; ^{1}H NMR, δ (ppm): 10.15 (s, 1H, NH), 9.48 (s, 1H, NH), 8.25 (s, 1H, OH), 7.03 (s, 1H, Ar–H), 5.02 (s, 2H, CH_2 –NH), 4.66 (s, 2H, CH_2 –NH), 4.24 (s, 1H, OH –CH_2), 3.80-3.90 (d,4H, imidazoline ring), 3.52 (s,2H,CH_2 brig) , 2.23-2.33(d,6H, methyl group) , 1.48 (s,9H, t-butyl group).

2.3. Cytotoxic effects of some synthesize compound against HepG2 Cell line using MTT assay

2.3.1. The Culture of cell lines:

HepatocarcinomaHepG2 Cell cultured in DMEM medium supplemented with 10% fetal bovine serum, L-glutamine. Cells were grown as a monolayer at 37 °C with 5% CO_2. The experiments performed when cells were in the logarithmic phase of growth. The cell line incubated with different concentrations of some synthesizers compounds. The four prepare concentrations were used in triplicate to investigate their cytotoxic effects.

2.3.2 Concentrations preparation:

The concentration of the synthesizes compounds test (25,50,75,100) µg/ml prepared according to the formula: $C_1V_1=C_2V_2$, where, C_1 is a concentration of a stock solution, V_1 is volume obtained from the stock solution, C_2 is final concentration and V_2 is final volume. DMSO(dimethyl sulfoxide) the solvent which used as a diluent solution.

2.3.3. Cytotoxic effect using MTT assay

The experiment was done at the biotechnology research center / Al Nahrain University. The cytotoxic effect of Oxymetazoline and some synthesizes compounds against HepG2 Cell evaluated using MTT assay. At first, 100 µL/well of HepG2 cells (106 cell/ ml) cultured in 96-well tissue culture plate. Four concentrations of synthesizes compounds (25,50,75,100) µg/ml prepared use DMSO as a solvent. Then, 100 µL of each prepared concentrations was added to each well and incubated at 37°C for 24h. After the incubation, 10µL of MTT solution (5 mg/ ml) added to each well and incubated at 37°C for 4 hours. Finally, 50 µL of DMSO added to each well and incubated for 10 min.HepG2 cells cultured in complete medium without synthesizes compound solution as a control. The absorbance measured for each well at 620 nm using an ELISA reader. The live cells, the percentage of viability and inhibition ratio calculated according to the formula:

GI%=(OD of control wells-OD of test walls)/OD of control wells ×100

2.3.4. Statistical analysis

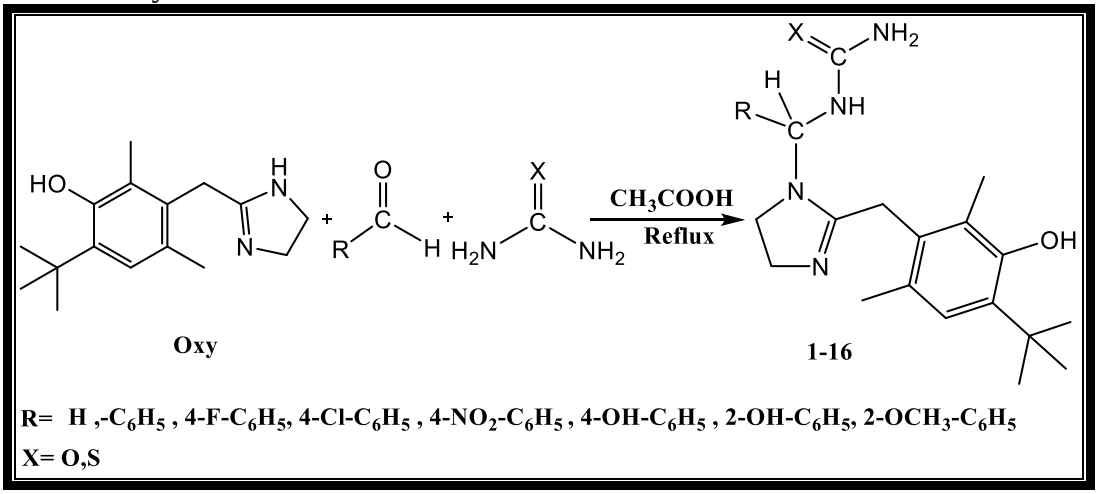
The statistical evaluation of the results performed using Analysis System-Microsoft SAS (2012). The chi-square test was used to compare the significance between the growth inhibition percentages.

3. Results and discussion

3.1. Chemistry

The N-mannich bases 1-16 (Scheme 1) contained urea or thiourea group were designed and synthesized in the present study, and prepared by the three-component condensations method. Previously it was reported that the substrate (urea or thiourea) inters aminomethylation reaction to give N-Mannich base proceeds either direct or by reaction them first with formaldehyde to give intermediate compound (N-hydroxymethyl derivative) then condensate with a secondary amine [40,41]. Herein,

which carried out by the direct method, mixing a substrate as the acidic component, Oxymetazoline as a secondary amine and (formaldehyde, benzaldehydes, or substituted benzaldehydes) in one pot, in equimolar amounts with few drops of glacial acid as catalyst media under mild reflux.



Scheme 1. Synthesis route to formation compounds (1-16)

In most experiments, a gummy product obtained treated with diethyl ether and acetone and left for several days in the air, to obtain a dry precipitate, For compounds 3 and 14 several attempts made to settle the product, but they remained greasy no powder product separated even after a long period(up to four weeks).

The yielded percentage of prepared compounds was about 41.6-71.8. The lack of production is due to the prediction of by-products of this type of reaction. Such as the condensation between substrate and aldehyde to give R-CH_2OH or formation of bis-derivatives R-CH_2-R [40,41].

Physicochemical data of the compounds (1-16) given in Table 1. Assignment of all 16 structures based on their IR, ^{1}H NMR, ^{13}C NMR, DEPT-135, and elemental analysis data given in the experimental part in detail.

Table 1: Physicochemical data for compounds (1-16)

Compd. NO.	X	R	m.p. °C	M.W g/mol	Yield %	M.F.	Elemental analysis Calculated,(found)(%)		
							C	H	N
1	O	H	245-247	332.45	69.5	$C_{18}H_{28}N_4O_2$	65.03 (64.98)	8.49 (8.41)	16.85 (17.05)
2	O	C_6H_5	143-145	408.55	61.1	$C_{24}H_{32}N_4O_2$	70.56 (70.32)	7.90 (7.78)	13.71 (13.89)
3	O	p-F-C_6H_4	oily	426.54	45.4	$C_{24}H_{31}FN_4O_2$	67.58 (67.39)	7.33 (7.21)	13.14 (13.29)
4	O	p-Cl-C_6H_4	191-193	442.99	54.5	$C_{24}H_{31}ClN_4O_2$	65.02 (65.00)	7.05 (7.01)	12.65 (12.57)
5	O	p-NO_2-C_6H_4	138-140	453.54	50.1	$C_{24}H_{31}N_5O_4$	63.56 (63.47)	6.87 (6.79)	15.44 (15.58)
6	O	p-OH-C_6H_4	184-186	424.55	66.4	$C_{24}H_{32}N_4O_3$	67.90 (67.87)	7.60 (7.72)	13.20 (13.44)
7	O	o-OH-C_6H_4	278 dec.	424.55	47.6	$C_{24}H_{32}N_4O_3$	67.90 (67.79)	7.60 (7.49)	13.20 (13.16)
8	O	o-OCH_3-C_6H_4	125-127	438.57	70.6	$C_{25}H_{34}N_4O_3$	68.47 (68.38)	7.81 (7.72)	12.78 (12.83)
9	S	H	216-218	348.51	65.5	$C_{18}H_{28}N_4OS$	62.04 (61.93)	8.10 (8.05)	16.08 (16.04)
10	S	C_6H_5	178-180	424.61	42.1	$C_{24}H_{32}N_4OS$	67.89 (67.79)	7.60 (7.53)	13.20 (13.42)
11	S	p-F-C_6H_4	201-203	442.60	53.7	$C_{24}H_{31}FN_4OS$	65.13 (65.03)	7.06 (7.04)	12.66 (12.78)
12	S	p-Cl-C_6H_4	134-136	459.05	55.7	$C_{24}H_{31}ClN_4OS$	62.80 (62.65)	6.81 (6.63)	12.21 (12.29)
13	S	p-NO_2-C_6H_4	211-213	469.60	61.4	$C_{24}H_{31}N_5O_3S$	61.38	6.65	14.91

							(61.24)	(6.59)	(15.03)
14	S	p-OH-C_6H_4	oily	440.61	43.7	$C_{24}H_{32}N_4O_3S$	65.42 (65.25)	7.32 (7.25)	12.72 (12.79)
15	S	o-OH-C_6H_4	252 dec.	440.61	64.1	$C_{24}H_{32}N_4O_2S$	65.42 (65.37)	7.32 (7.31)	12.72 (12.61)
16	S	o-OCH_3-C_6H_4	151-153	454.63	71.8	$C_{25}H_{34}N_4O_2S$	66.05 (66.01)	7.54 (7.46)	12.32 (12.26)

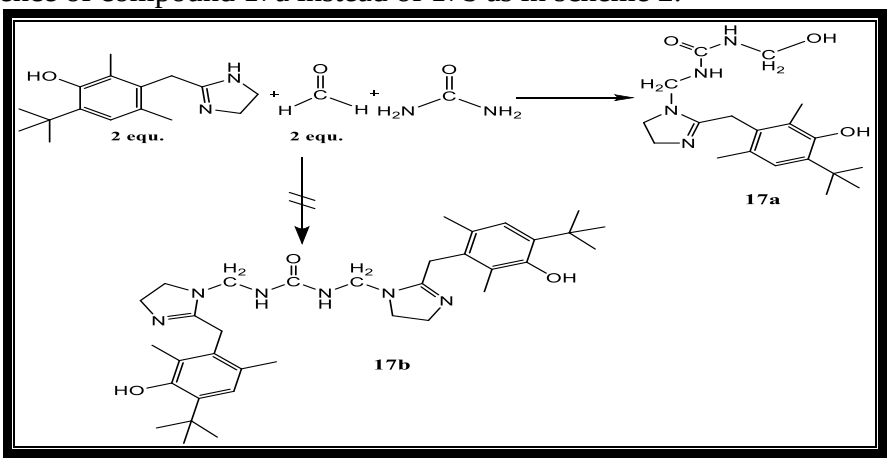
In general, the IR spectra of all compounds showed absorption bands at around 3477 to 3307$cm^{-1}$for OH stretching and bands at around 3382 to 3170$cm^{-1}$for NH, NH_2 stretching. The compounds(1-8) showed bands at around1689-1569$cm^{-1}$for HNC=O amide-I, II. Also, the compounds (9-16) showed bands for C=S stretching around 1224 to 1114 cm^{-1}.

The ^{1}H NMR spectrums of prepared products agreed with corresponding structures. All compounds showed signals at around δ 10.54 to 9.48ppm for NH and signals around δ 9.91 to 7.90 ppm for NH_2 which referred to urea and thiourea groups. Also showed signals at around δ 5.68-4.91 ppm for methylene and methine protons (N-CH_2-N, N-CH-N).

The ^{13}C NMR spectrum of some prepared compounds showed peaks at around: 184.07,185.45 ppm for -C=S, 169.54-174.79 ppm for -C=O, 165.01-168.22 ppm for C=N–,150.33-161.18 ppm for C-OH, 116.05-138.17 ppm for aromatic carbon, 58.78-77.45 ppm for N-CH_2-N ,N-CH-N ,44.11-48.13 ppm for imidazoline methylene carbons, 27.39-35.32 ppm, for methylene bridge, 31.23-13.16 ppm for methyl groups carbons.

The Regarding DEPT-135 spectrum for compounds (1,9)showed the incidence of methylene carbons (N-CH2-N) moiety as a negative signal and showed the presence of methine carbons (N-CH-N) moiety as a positive signal.

An attempt to condensation urea with 2 equiv of formaldehyde and Oxymetazoline to obtain either 17a or 17b compounds. According to ^{1}HNMR data, there are two different signals for the NH proton at δ 10.15, 8.48 ppm and δ 5.02,4.66 ppm signals for CH_2-NH. Also showed a signal at δ 4.24 ppm for CH_2-OH. This is the evidence of the existence of compound 17a instead of 17b as in scheme 2.



Scheme 1. Synthesis route to formation compounds (17)

3.2. Cytotoxic evaluation

The results of the cytotoxic effect in four concentrations of some synthesized compound display in a table -2, And the results show a significant difference between the value of cytotoxicity to each compound with probability value p≤0.05, also show a significant difference between concentrations to each compound. In general, the 100µg/ml concentrations of compounds and Oxymetazoline show the high percentage

of cytotoxicity when compared with other concentrations, while the lowest concentrations 25µg/ml and 50µg/ml of the synthesized compound and Oxymetazoline show lower cytotoxic effects against HepG2 cell line that's may be related to its safety in pharmaceutical use.

Statistical analysis show comp.15 the high cytotoxic effect reach to 85±29 at the concentration 100µg/ml while comp. 8 and 9 show the lowest cytotoxic effects at the concentrations 100µg/ml the cytotoxic effects reach to 65±25 to the two compounds when compared with control.

The results of cytotoxicity against HepG2 cell line show that the cytotoxic effect of each studied compound and drug increase gradually with the increase of prepared compound concentrations.

Table 2: Cytotoxic effects Percentage of some synthesized compounds against HepG2 cell line using Mtt assay%

comp. no.	25µg/ml	50µg/ml	75µg/ml	100µg/ml
1	0. 1±15	2±18	76±22	81±27
2	0. 8±77	3±17	55±0	80±27
6	0. 8±77	3±72	34±12	75±22
8	0. 1±25	4±53	38±12	65±25
9	0. 3±37	2±18	24±13	65±25
11	0. 2±24	2±95	72±18	78±0
13	0. 4±24	13±37	67±30	73±0
15	0. 1±15	11±0	76±22	85±29
16	0. 2±24	14±34	65±25	71±0
Oxymethazoline	1.0±25	4±0	38±0	75±22
control	0.0±0	0.0±0	0.0±0	0.0±0

mean0.0±SE
P value ≥0.05

4. Conclusions

In the light of the results obtained in this research, it is possible to prepare the N-mannich bases for Oxymethazoline having urea, thiourea groups with different aldehyde by a satisfactory product and mild reaction conditions. The toxicity of the derivatives was found to be similar to the toxicity of Oxymetazoline so it could be used as a pharmaceutical.

The outcome of this research encourages the expansion of future studies of these compounds, such as the study of pharmaceutical properties and their biological efficiency.

Acknowledgments

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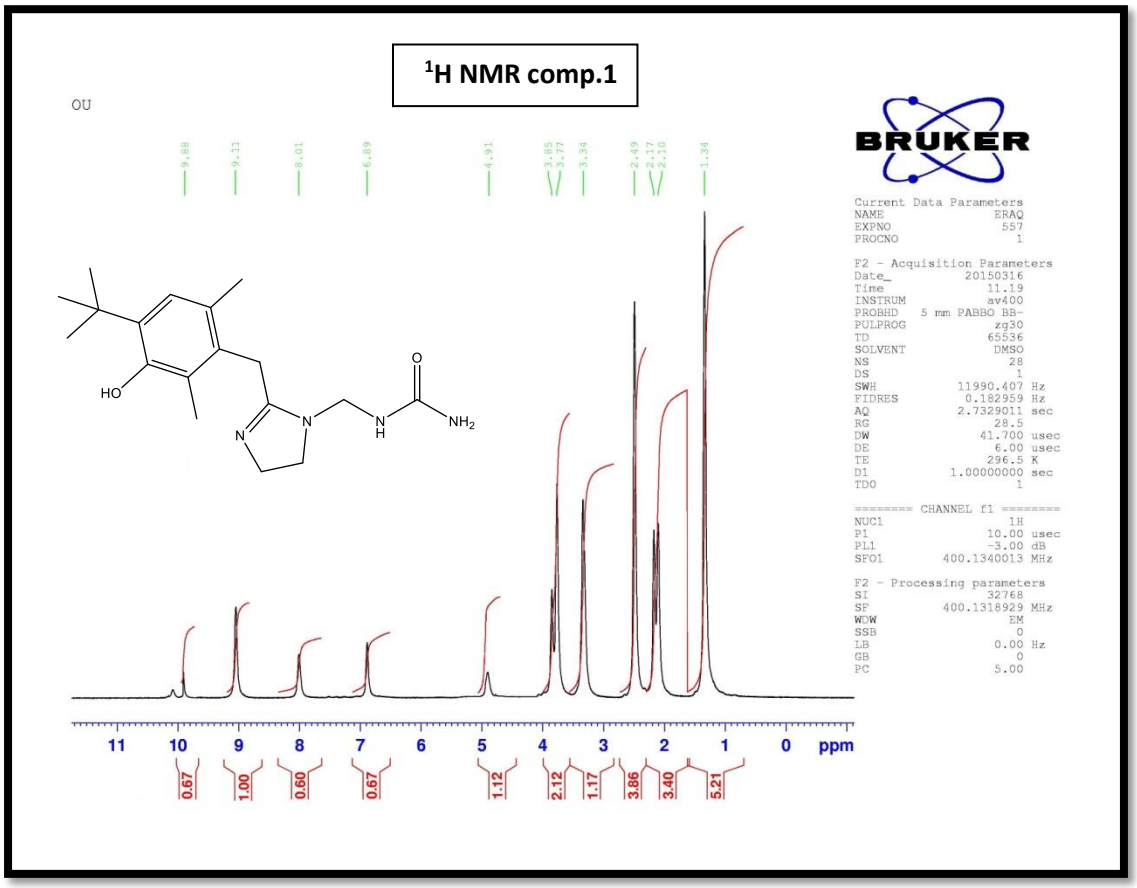
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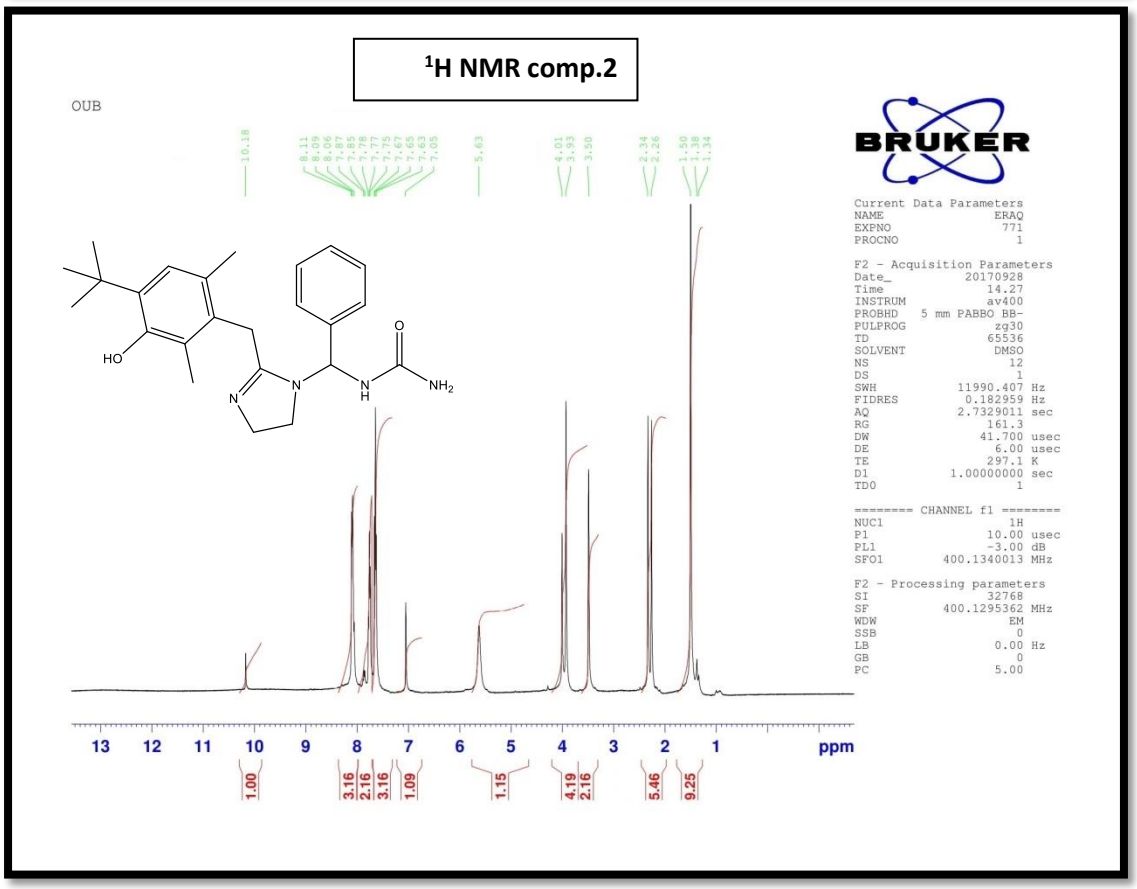
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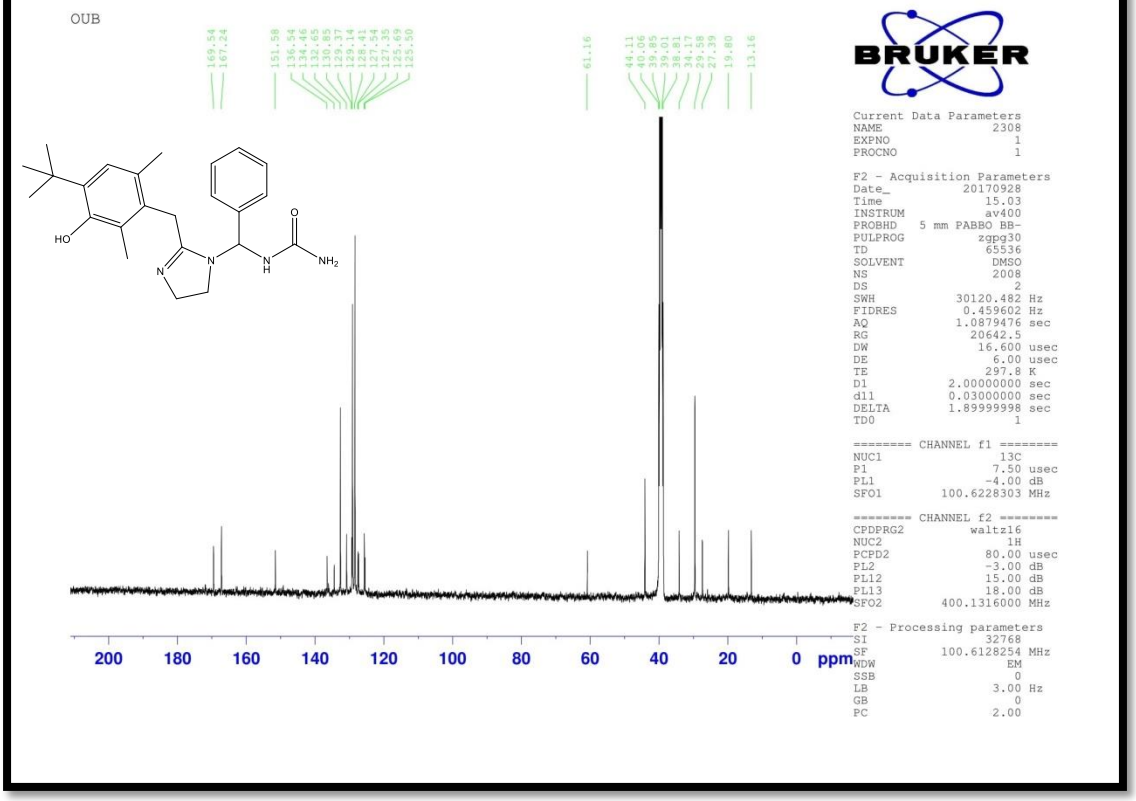
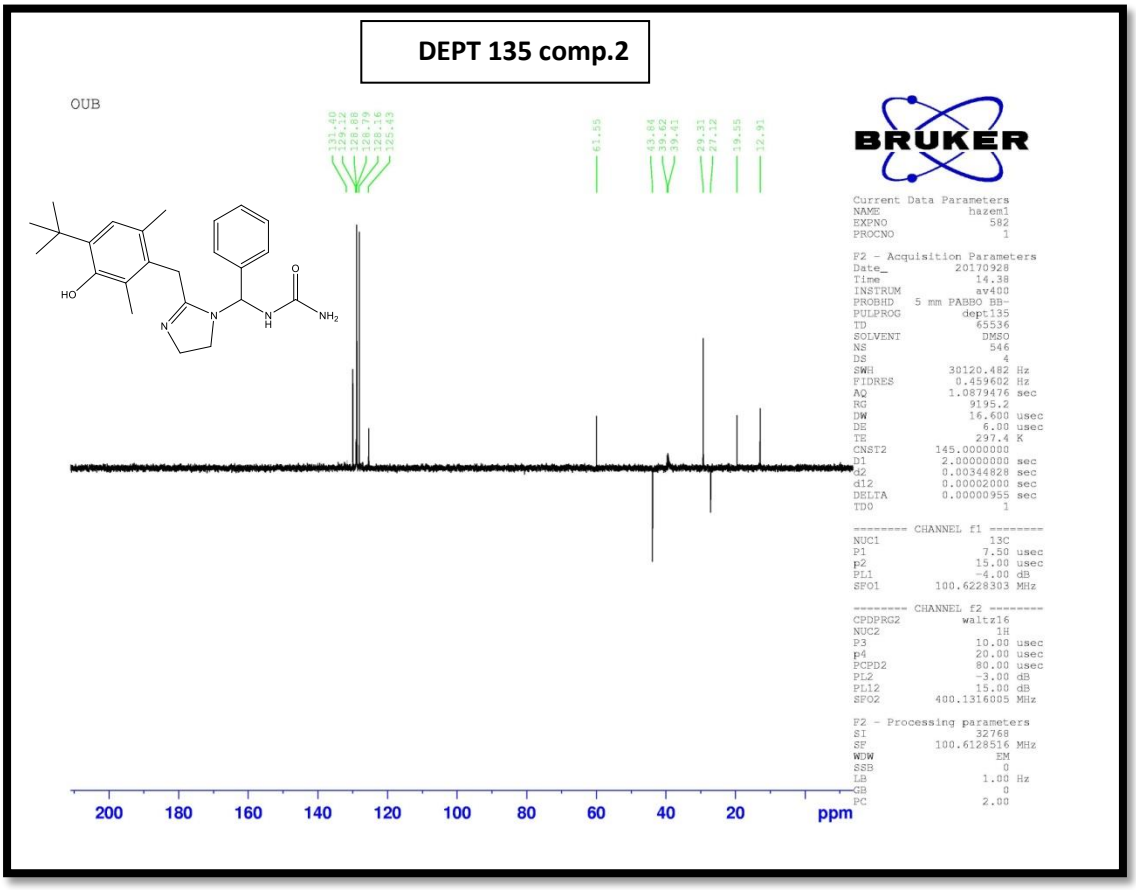
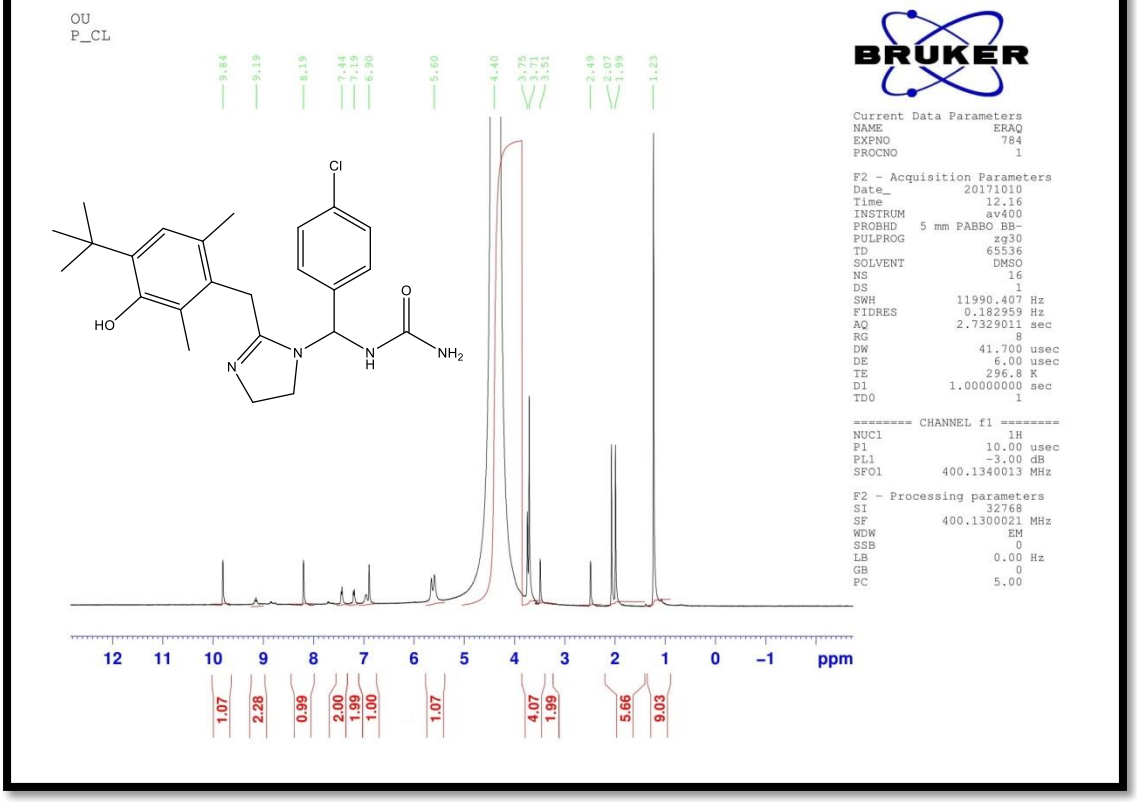
^{13}C NMR comp.2



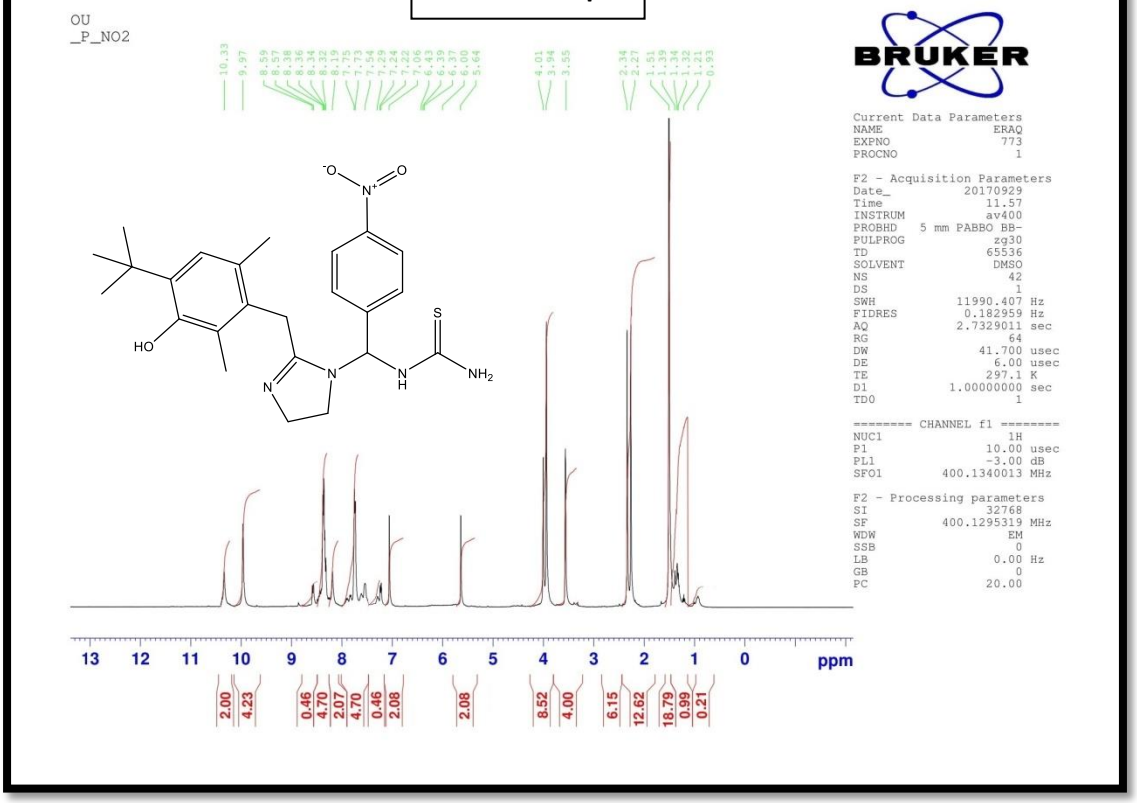
DEPT 135 comp.2



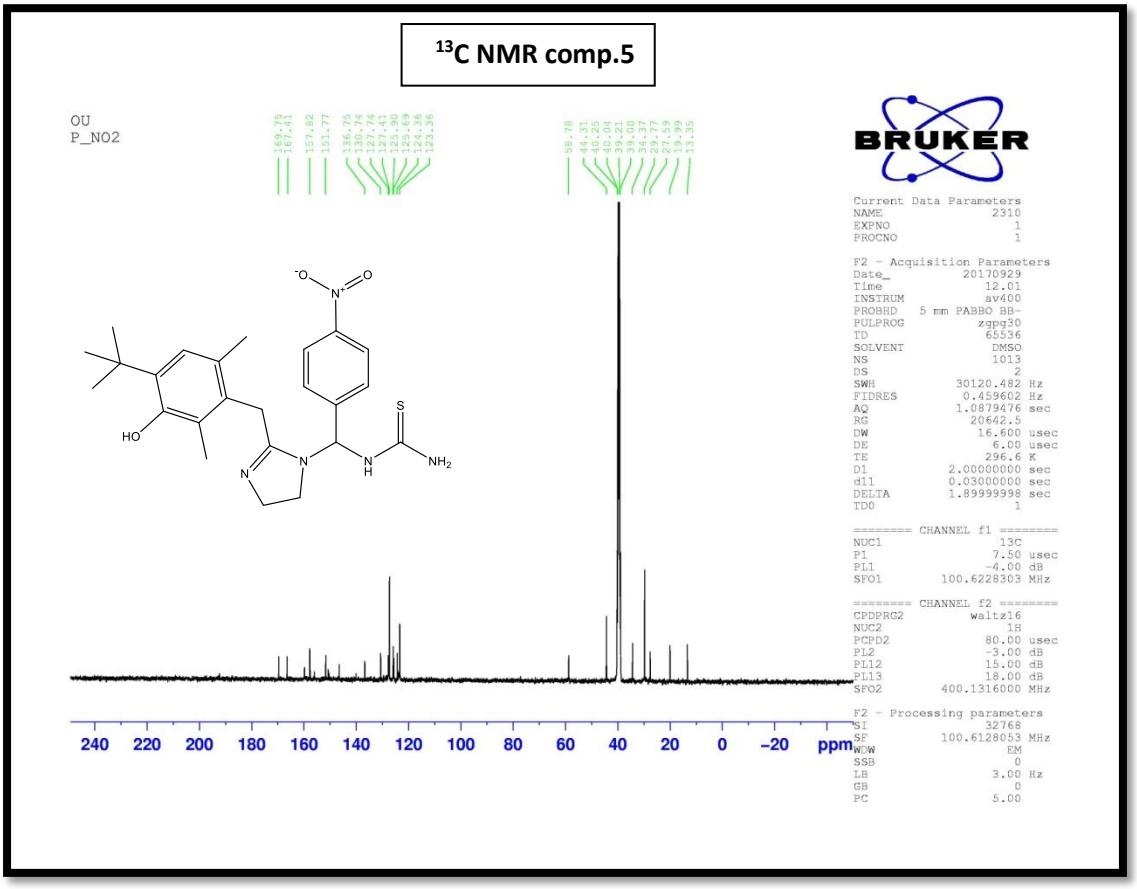
^{1}H NMR comp.4



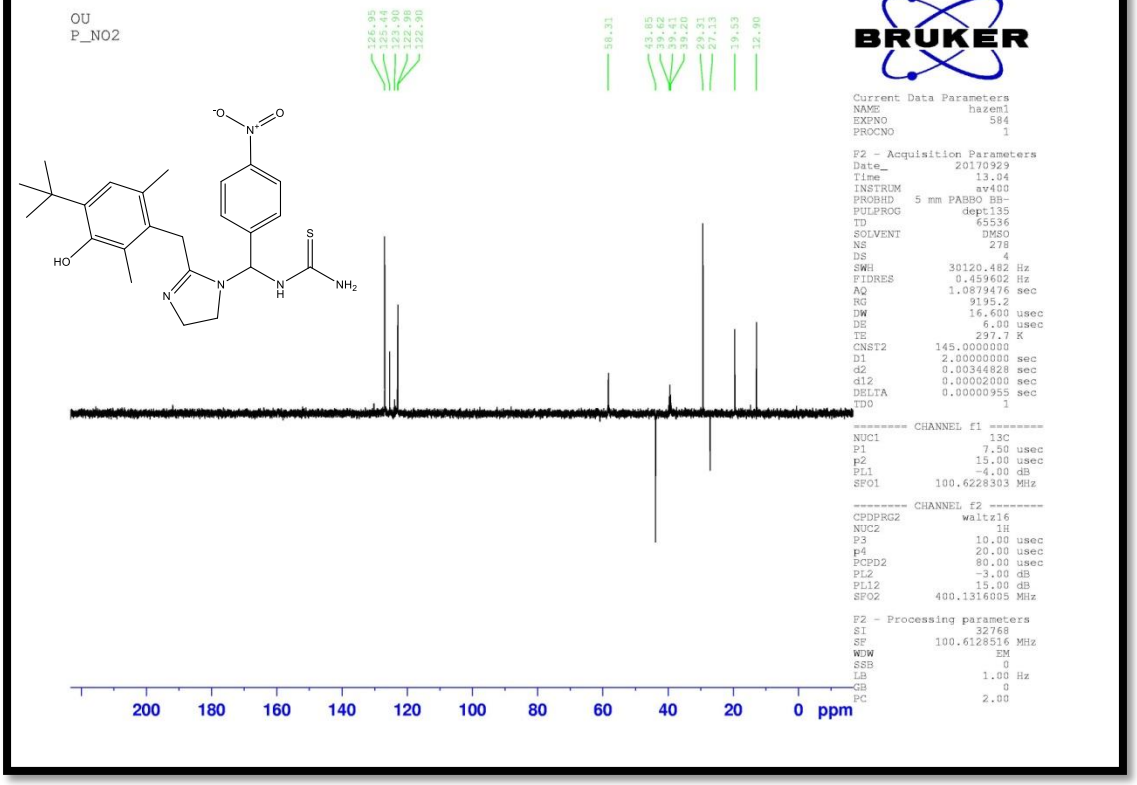
^{1}H NMRcomp.5

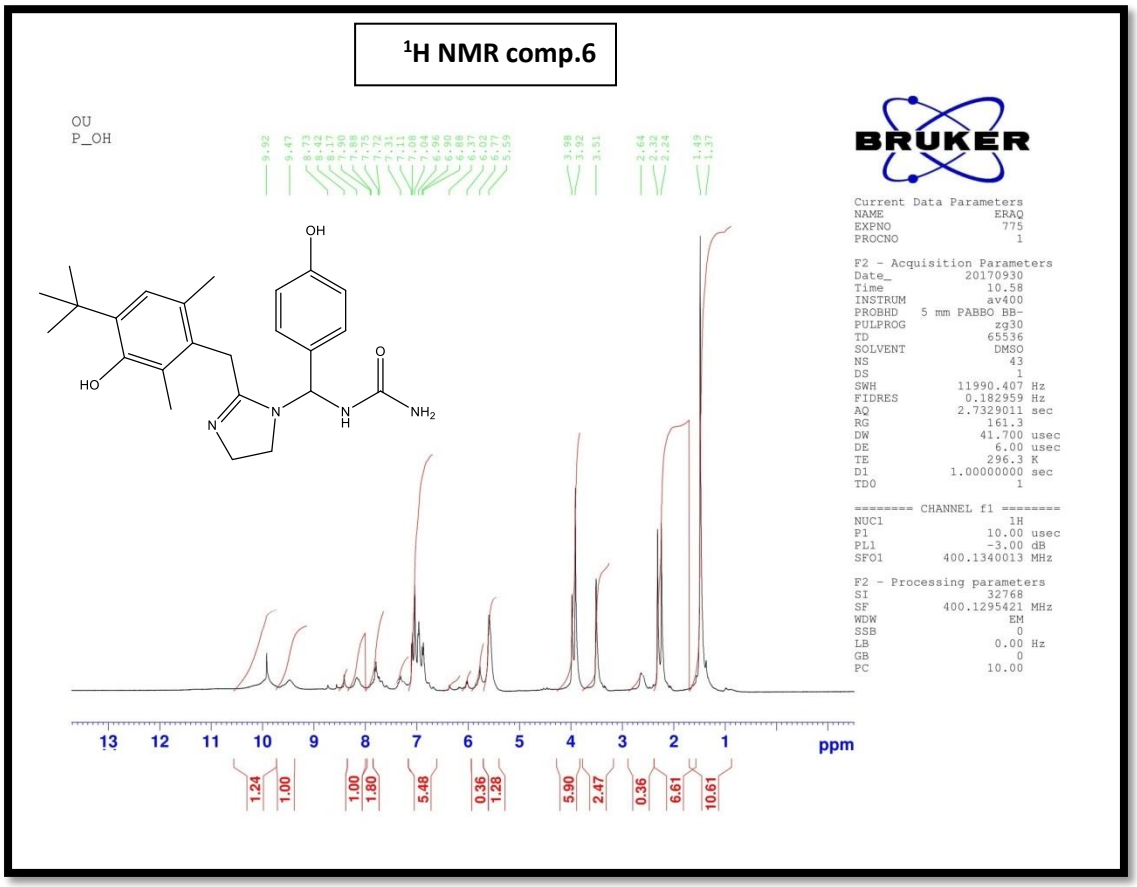


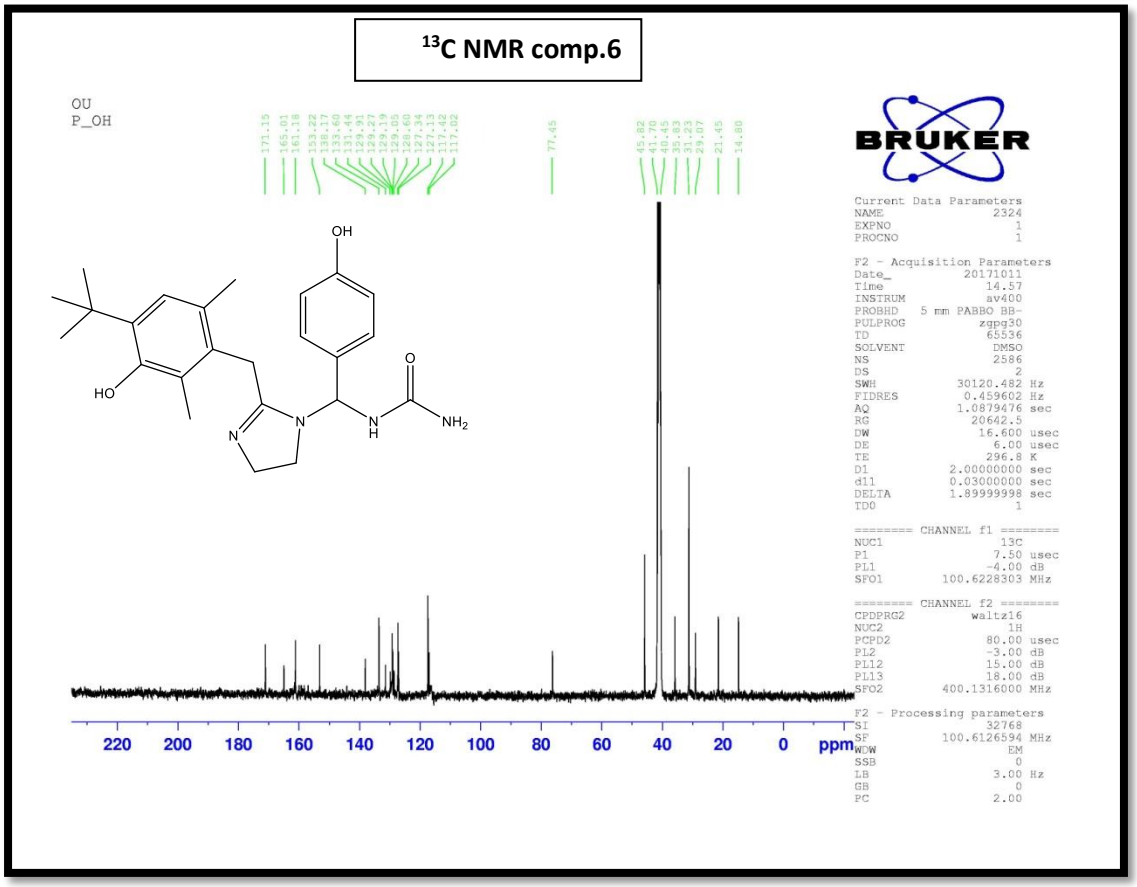
^{13}C NMR comp.5

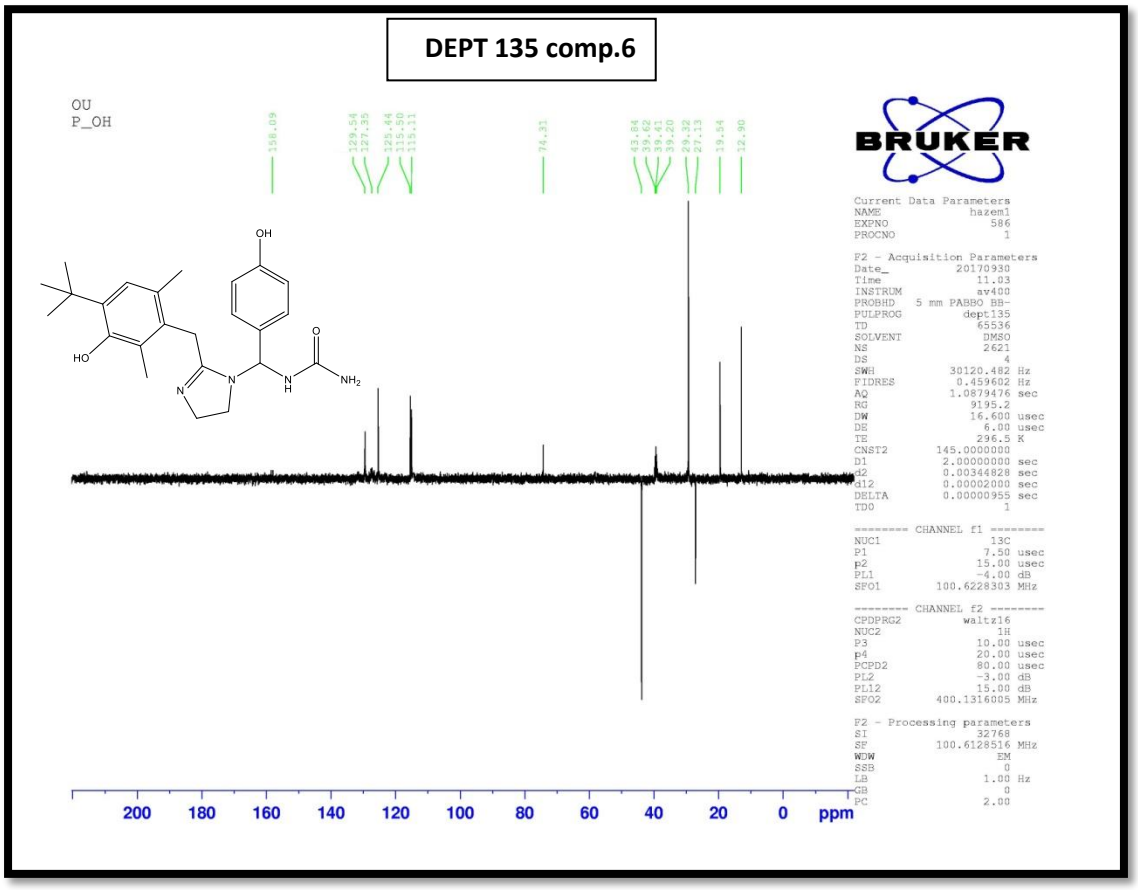


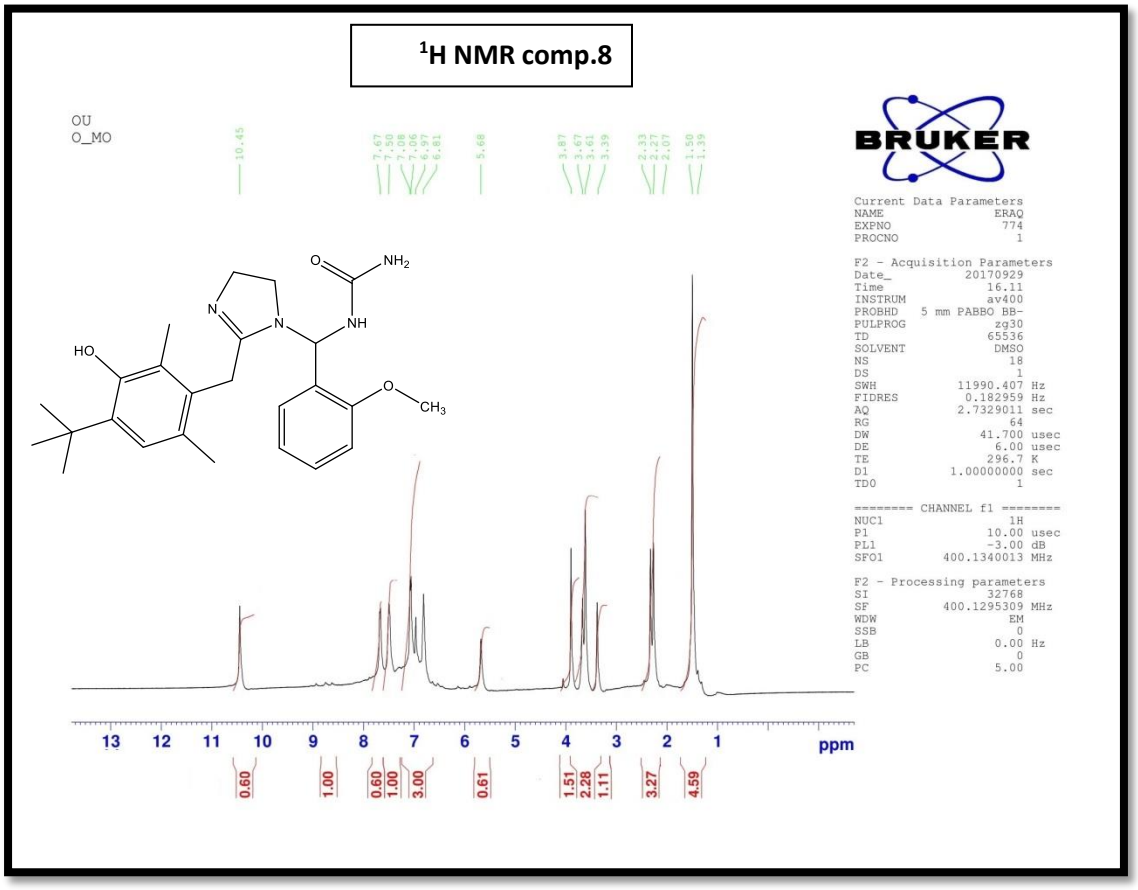
DEPT 135 comp.5



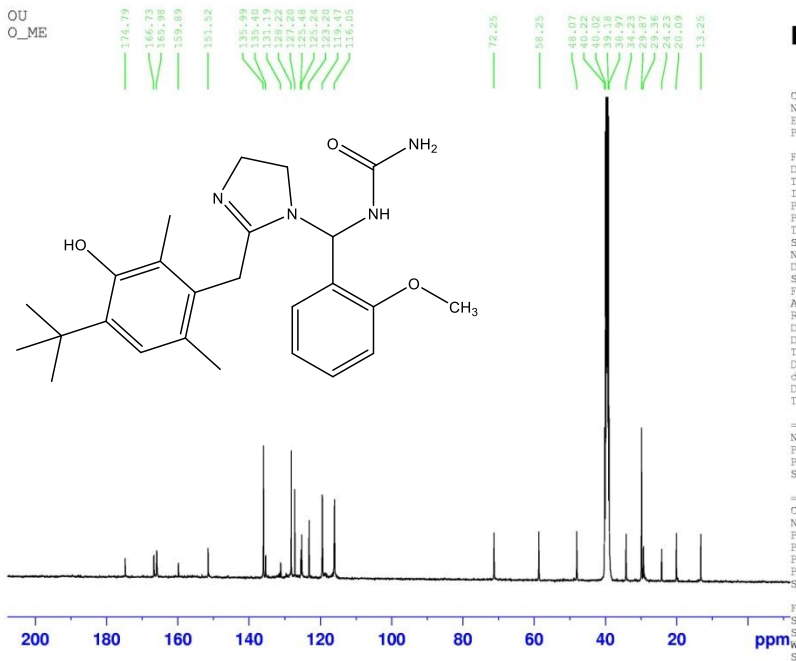

^{1}H NMR comp.6
OU
P_OH
BRUKER
Current Data Parameters
NAME ERAQ
EXPNO 775
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170930
Time 10.58
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 43
DS 1
SWH 11990.407 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 161.3
DW 41.700 usec
DE 6.00 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1340013 MHz
F2 - Processing parameters
SI 32768
SF 400.1295421 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 10.00
ppm


^{13}C NMR comp.6
OU
P_OH
BRUKER
Current Data Parameters
NAME 2324
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171011
Time 14.57
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2586
DS 2
SWH 30120.482 Hz
FIDRES 0.459602 Hz
AQ 1.0879476 sec
RG 20642.5
DW 16.600 usec
DE 6.00 usec
TE 296.8 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.50 usec
PL1 -4.00 dB
SFO1 100.6228303 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 15.00 dB
PL13 18.00 dB
SFO2 400.1316000 MHz
F2 - Processing parameters
SI 32768
SF 100.6126594 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 2.00
ppm


DEPT 135 comp.6
OU
P_OH
158.09
129.54
127.35
125.44
115.50
115.11
74.31
43.84
39.62
39.41
39.20
29.32
27.13
19.54
12.90
OH
HO
N
N
N
H
O
NH2
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME hazem1
EXPNO 586
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170930
Time 11.03
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG dept135
TD 65536
SOLVENT DMSO
NS 2621
DS 4
SWH 30120.482 Hz
FIDRES 0.459602 Hz
AQ 1.0879476 sec
RG 9195.2
DW 16.600 usec
DE 6.00 usec
TE 296.5 K
CNST2 145.0000000
D1 2.00000000 sec
D2 0.00344828 sec
d12 0.00002000 sec
DELTA 0.00000955 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.50 usec
p2 15.00 usec
PL1 -4.00 dB
SFO1 100.6228303 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
P3 10.00 usec
p4 20.00 usec
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 15.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128516 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00


1H NMR comp.8
OU
O_MO
10.45
7.67
7.50
7.08
7.06
6.97
6.81
5.68
3.87
3.67
3.61
3.39
2.33
2.27
2.07
1.50
1.39
O
NH2
NH
N
N
HO
O
CH3
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.60
1.00
0.60
1.00
3.00
0.61
1.51
2.28
1.11
3.27
4.59
BRUKER
Current Data Parameters
NAME ERAQ
EXPNO 774
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170929
Time 16.11
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 18
DS 1
SWH 11990.407 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 64
DW 41.700 usec
DE 6.00 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1340013 MHz
F2 - Processing parameters
SI 32768
SF 400.1295309 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 5.00

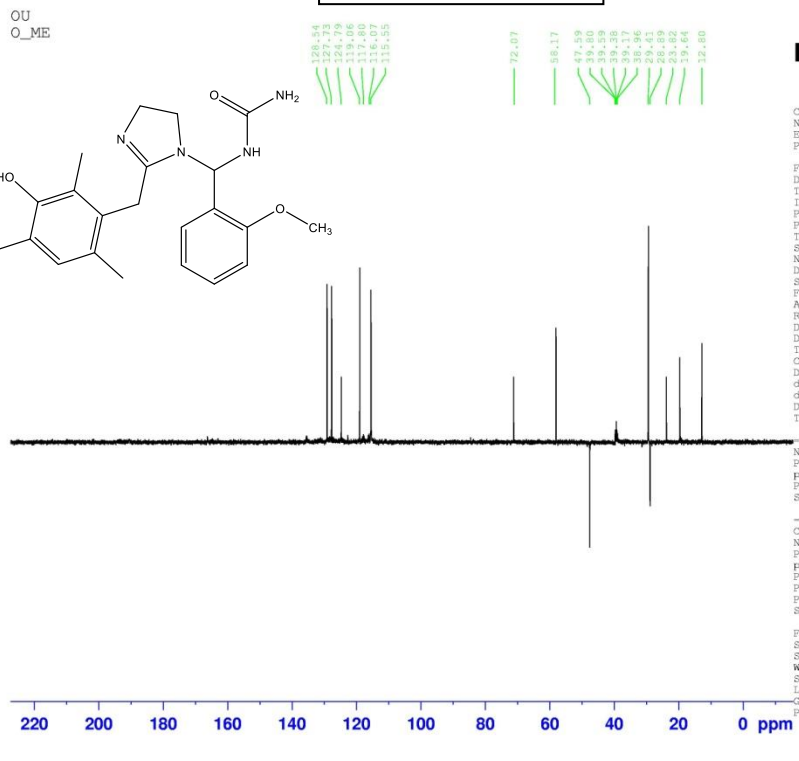
^{13}C NMR comp.8



BRUKER

```
Current Data Parameters
NAME                  2311
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20170930
Time                   8.25
INSTRUM               av400
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                   18531
DS                       2
SWH             30120.482 Hz
FIDRES           0.459602 Hz
AQ               1.0879476 sec
RG                 20642.5
DW                16.600 usec
DE                 6.00 usec
TE                298.4 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  7.50 usec
PL1                -4.00 dB
SFO1          100.6228303 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2              80.00 usec
PL2                -3.00 dB
PL12               15.00 dB
PL13               18.00 dB
SFO2          400.1316000 MHz

F2 - Processing parameters
SI                   32768
SF            100.6128053 MHz
WDW                     EM
SSB                      0
LB                  3.00 Hz
GB                       0
PC                   10.00
```

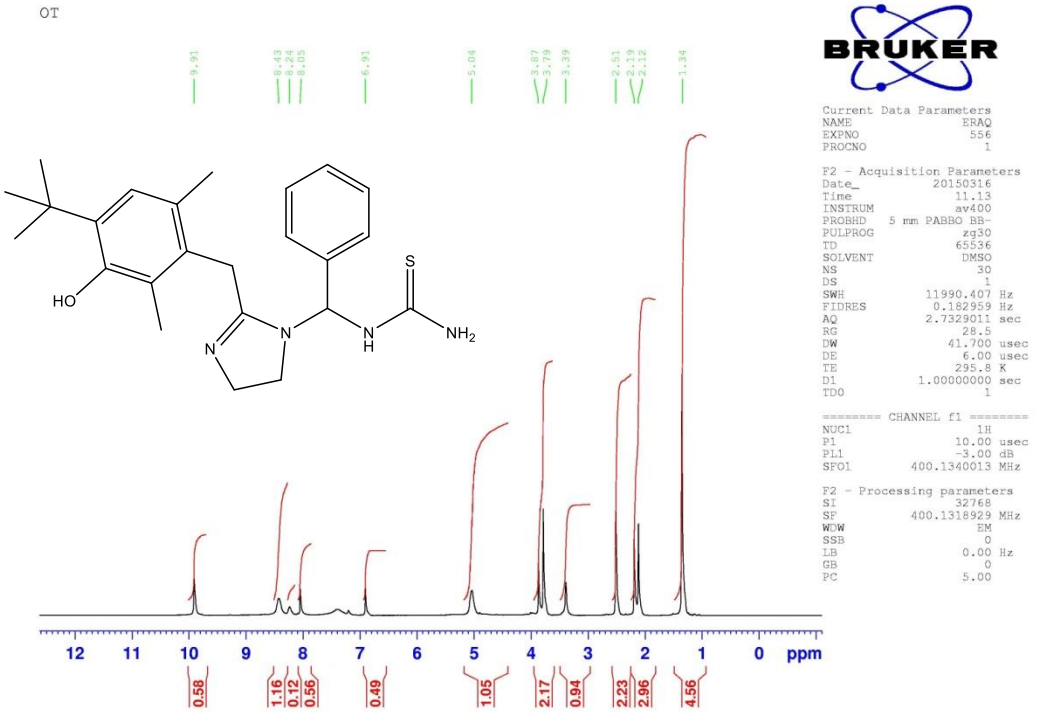
DEPT 135 comp.8



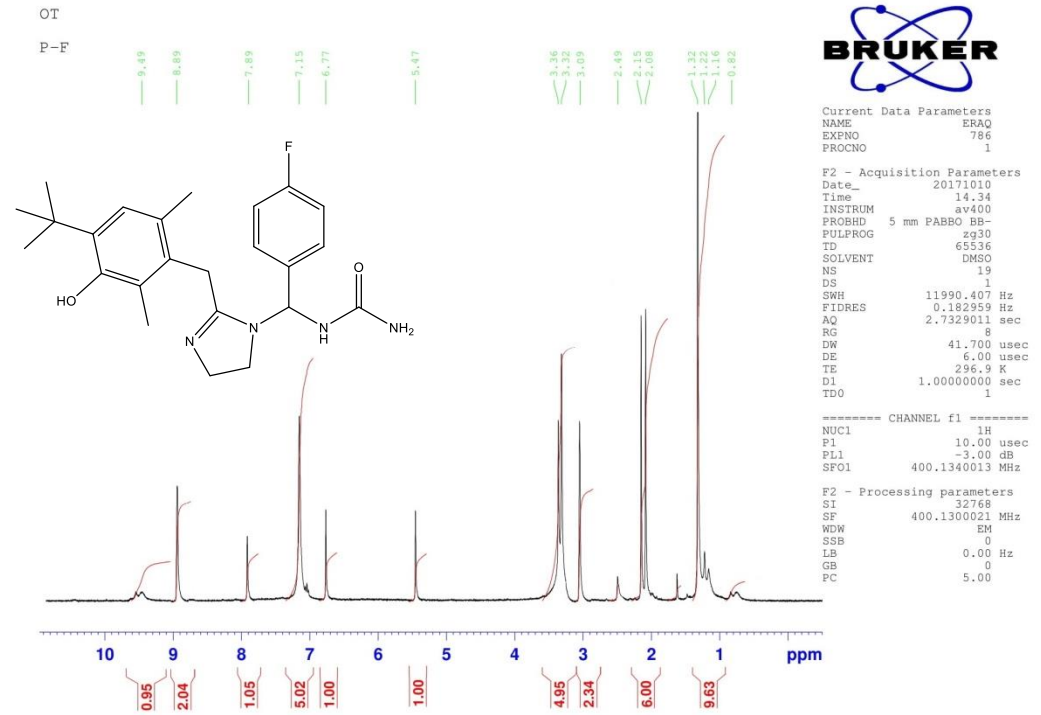
BRUKER

```
Current Data Parameters
NAME                 hazem1
EXPNO                   585
PROCNO                    1

F2 - Acquisition Parameters
Date_              20170930
Time                  10.33
INSTRUM               av400
PROBHD   5 mm PABBO BB-
PULPROG            dept135
TD                   65536
SOLVENT               DMSO
NS                    2704
DS                       4
SWH             30120.482 Hz
FIDRES           0.459602 Hz
AQ               1.0879476 sec
RG                  9195.2
DW                16.600 usec
DE                 6.00 usec
TE                297.7 K
CNST2         145.0000000
D1             2.00000000 sec
d2             0.00344828 sec
d12            0.00002000 sec
DELTA          0.00000955 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  7.50 usec
p2                 15.00 usec
PL1                -4.00 dB
SFO1          100.6228303 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
P3                 10.00 usec
p4                 20.00 usec
PCPD2              80.00 usec
PL2                -3.00 dB
PL12               15.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF            100.6128516 MHz
WDW                     EM
SSB                      0
LB                  1.00 Hz
GB                       0
PC                    2.00
```

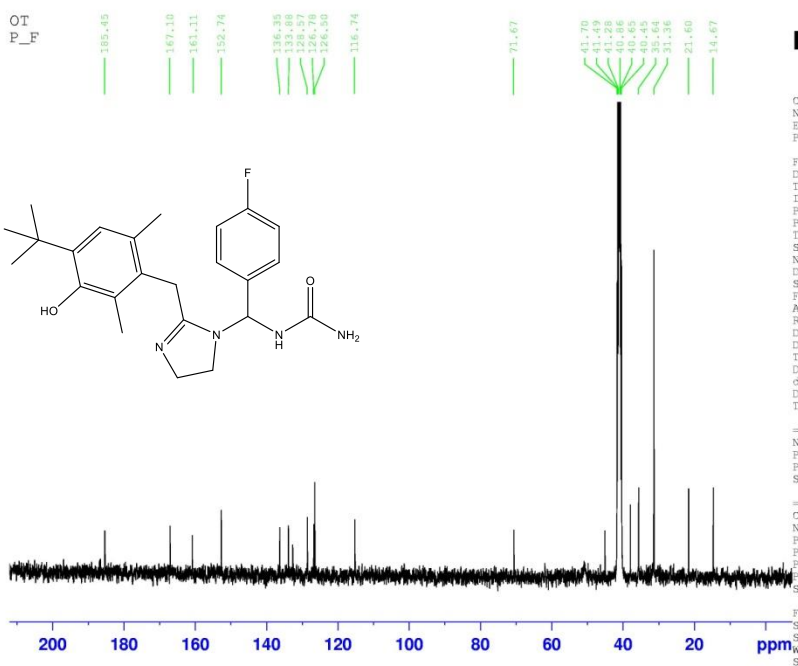
^{1}H NMR comp.9



^{1}H NMR comp.11



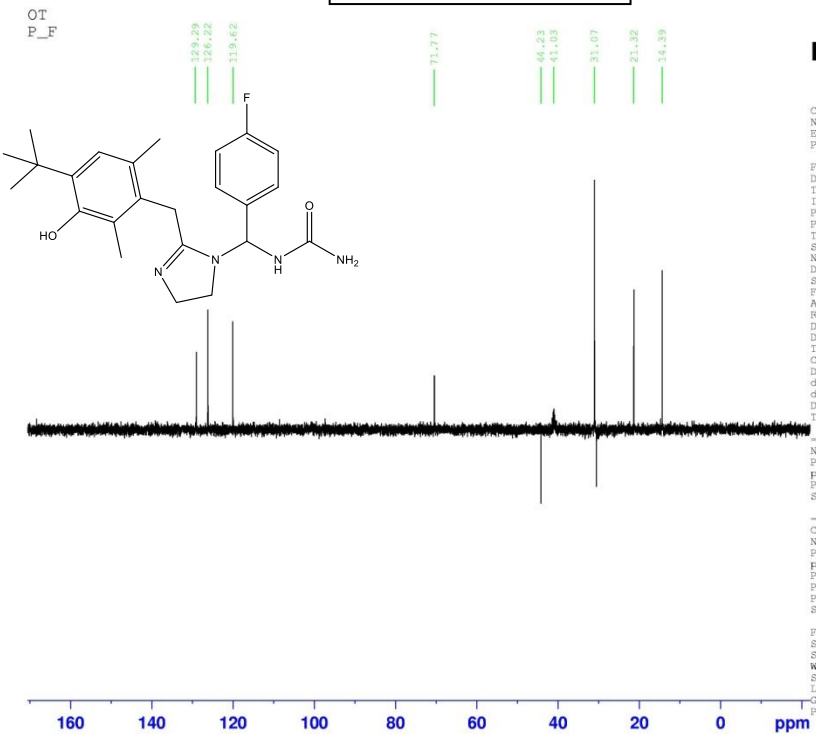
^{13}C NMR comp.11



BRUKER

```
Current Data Parameters
NAME                  2322
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20171010
Time                 15.00
INSTRUM              av400
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                     966
DS                       2
SWH             30120.482 Hz
FIDRES          0.459602 Hz
AQ              1.0879476 sec
RG                20642.5
DW                16.600 usec
DE                 6.00 usec
TE                296.9 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    7.50 usec
PL1                  -4.00 dB
SFO1          100.6228303 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -3.00 dB
PL12                 15.00 dB
PL13                 18.00 dB
SFO2          400.1316000 MHz

F2 - Processing parameters
SI                     32768
SF            100.6126594 MHz
WDW                       EM
SSB                        0
LB                    3.00 Hz
GB                         0
PC                      2.00
```

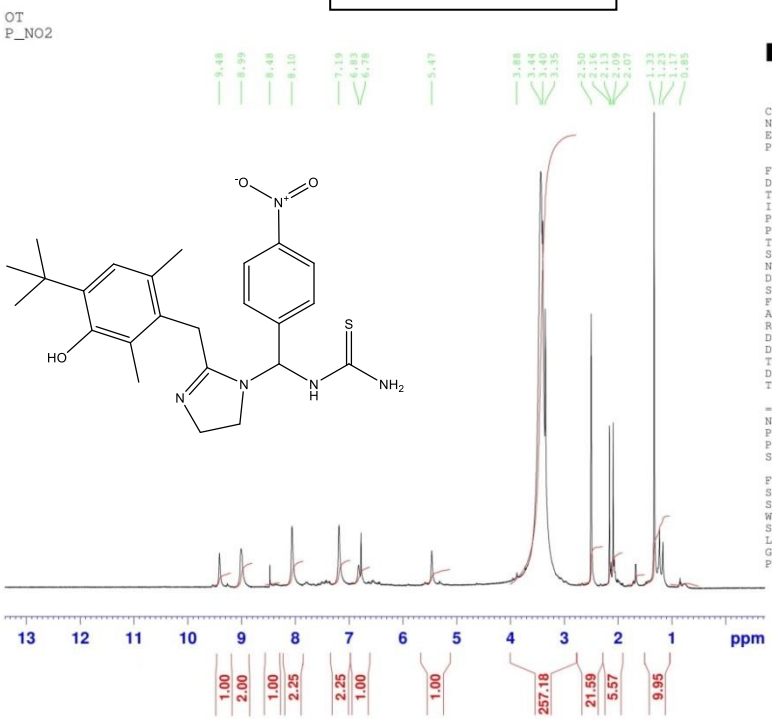
DEPT 135 comp.11



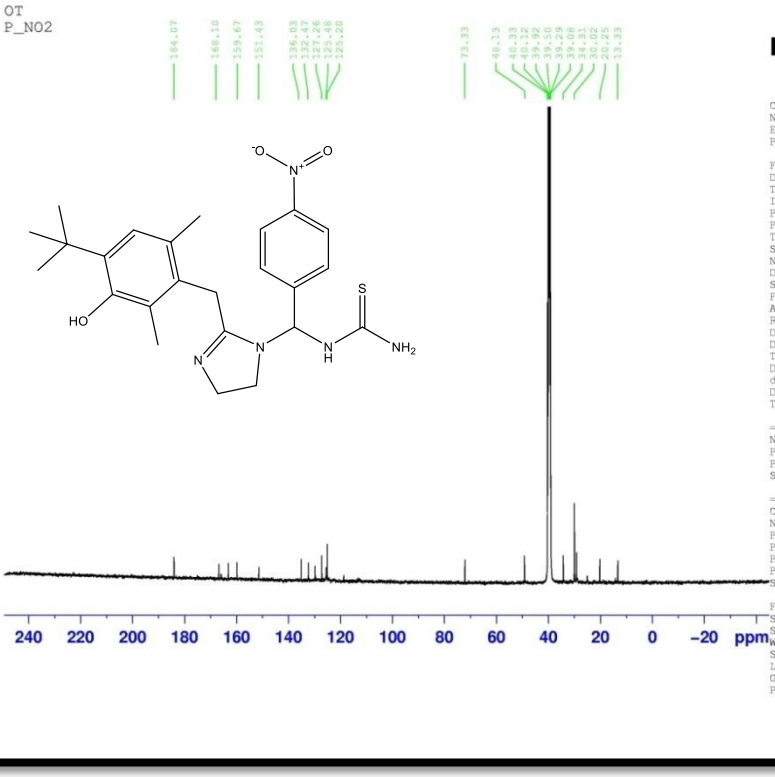
BRUKER

```
Current Data Parameters
NAME                 hazem1
EXPNO                   595
PROCNO                    1

F2 - Acquisition Parameters
Date_              20171012
Time                 11.23
INSTRUM              av400
PROBHD   5 mm PABBO BB-
PULPROG            dept135
TD                   65536
SOLVENT               DMSO
NS                     1351
DS                        4
SWH             30120.482 Hz
FIDRES          0.459602 Hz
AQ              1.0879476 sec
RG                 9195.2
DW                16.600 usec
DE                 6.00 usec
TE                296.8 K
CNST2          145.0000000
D1             2.00000000 sec
d2             0.00344828 sec
d12            0.00002000 sec
DELTA          0.00000955 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                   13C
P1                    7.50 usec
p2                   15.00 usec
PL1                  -4.00 dB
SFO1          100.6228303 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
P3                   10.00 usec
p4                   20.00 usec
PCPD2                80.00 usec
PL2                  -3.00 dB
PL12                 15.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                     32768
SF            100.6126880 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                      2.00
```

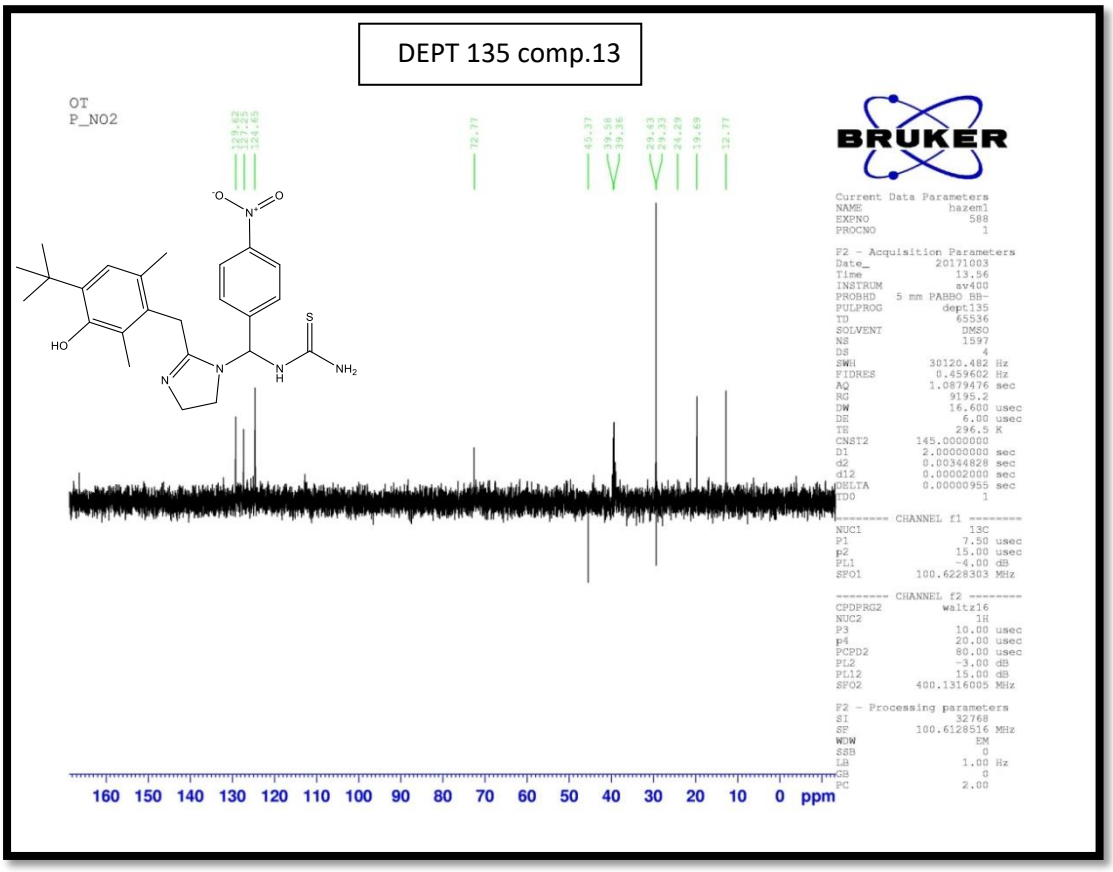
^{1}H NMR comp.13



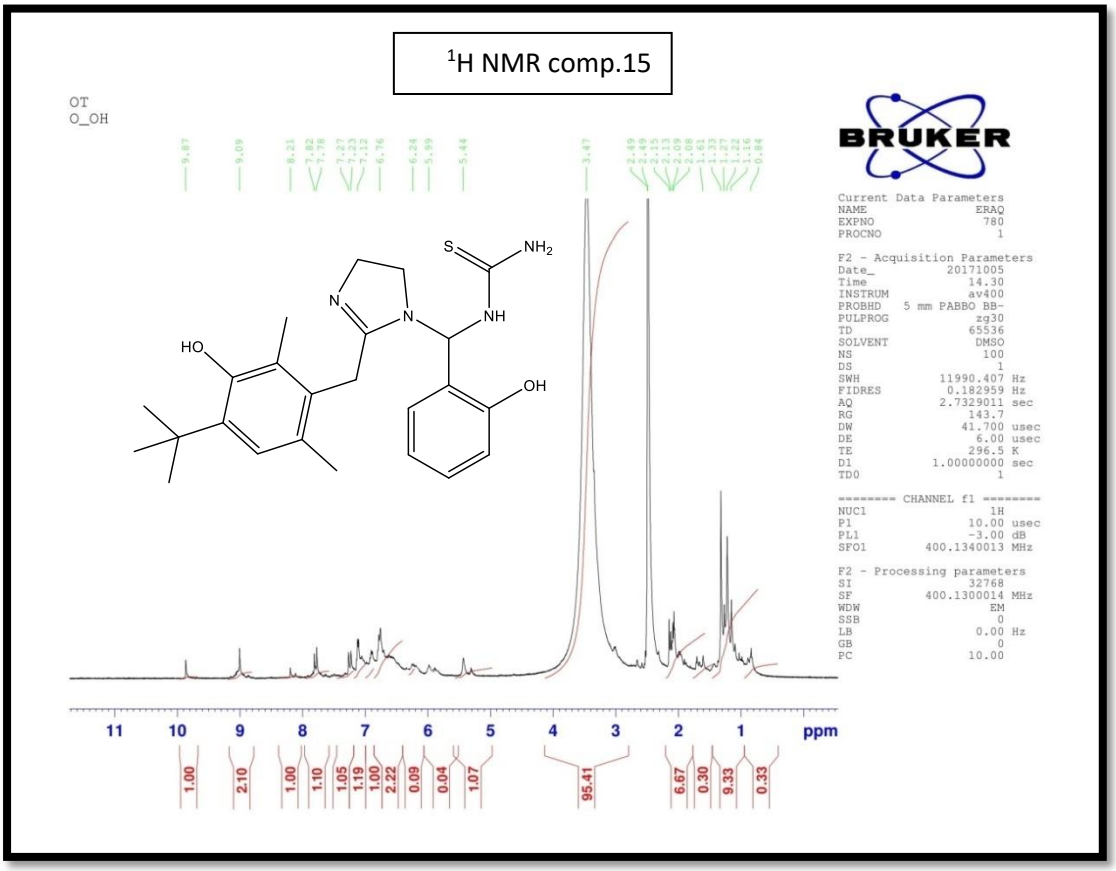
^{13}C NMR comp. 13

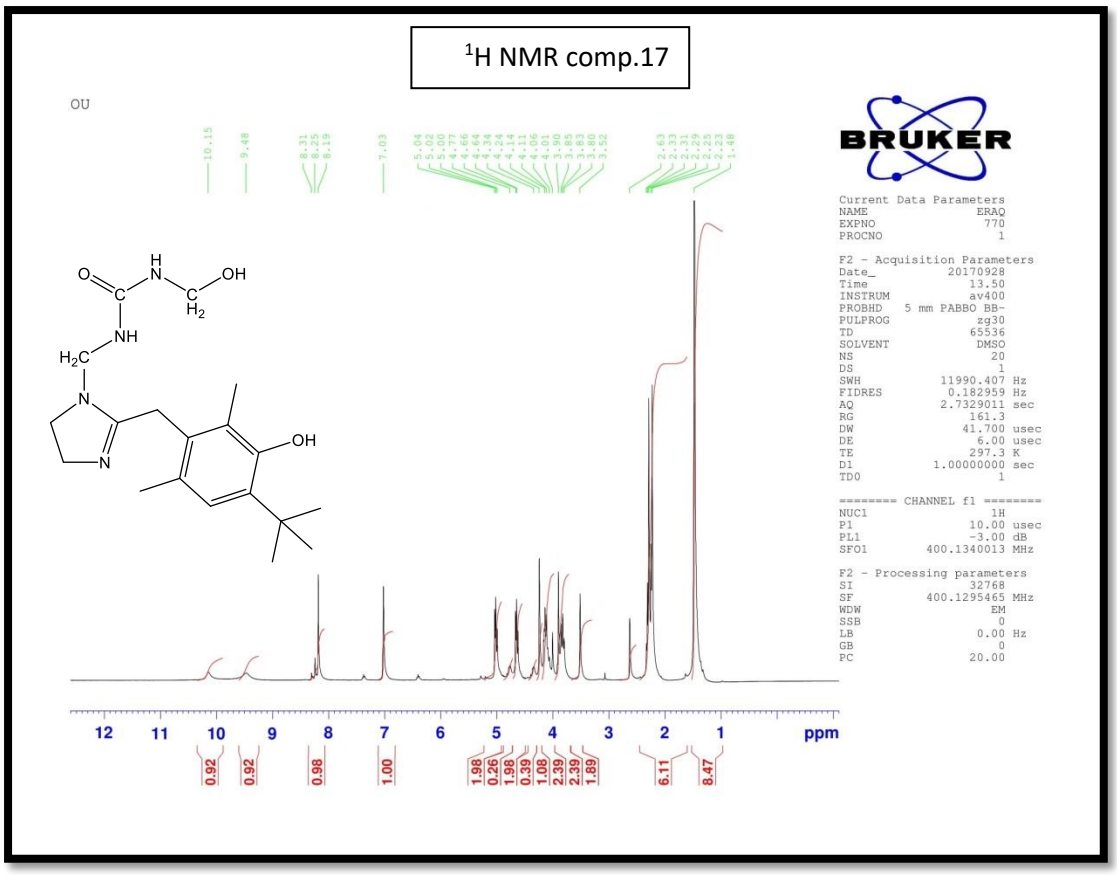


DEPT 135 comp.13



^{1}H NMR comp.15




^{1}H NMR comp.17
OU
BRUKER
Current Data Parameters
NAME ERAQ
EXPNO 770
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170928
Time 13.50
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 20
DS 1
SWH 11990.407 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 161.3
DW 41.700 usec
DE 6.00 usec
TE 297.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1340013 MHz
F2 - Processing parameters
SI 32768
SF 400.1295465 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 20.00
12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.92 0.92 0.98 1.00 1.98 0.26 1.98 0.39 1.08 2.39 2.39 1.89 6.11 8.47