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# Synthesis and Characterization of Enaminone Derivatives of Barbituric Acid

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**ABSTRACT:** In this study, four enaminones derived from barbituric acid were synthesized with the reaction of 5-formylbarbituric acid and selected primer amines with high yield. The structures of all compounds were proved by using ATR-FTIR, $^{1}H$ and $^{13}C$ NMR spectroscopy. Also, $^{19}F$ NMR spectroscopy was used for characterization of **2d**. The obtained spectroscopic results have complied with reported similar derivatives in literature.

**Keywords:** Barbituric acid, Enaminone, Condensation reaction, Spectroscopy

# Barbitürik Asitin Enaminon Türevlerinin Sentezi ve Karakterizasyonu

**ÖZET:** Bu çalışmada barbitürik asitten türeyen dört enaminon türevi 5-formilbarbitürik asit ve seçilen birincil aminlerin reaksiyonu ile yüksek verimle sentezlenmiştir. Sentezlenen bütün bileşiklerin yapıları ATR-FTIR, $^{1}H$ ve $^{13}C$ NMR spektroskopileri kullanılarak kanıtlanmıştır. Bileşik **2d**'nin yapısal karakterizasyonun da ayrıca $^{19}F$ NMR spektroskopisi kullanılmıştır. Elde edilen spektroskopik sonuçlar literatürdeki rapor edilmiş benzer türevler ile uyumludur.

**Anahtar Kelimeler:** Barbitürik asit, Enaminon, Kondenzasyon reaksiyonu, Spektroskopi

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## INTRODUCTION

Enaminones are a significant subclass of organic compounds which contain conjugated N-C=C-C=O fragment owing to fact that they include both nucleophilic and electrophilic moieties at same skeleton (Castro-Alvarez et al., 2017). These active sites help to synthesis of linear or cyclic hetero atom containing organic compounds (Negri et al., 2004; Kumar et al., 2018). Both enaminones and the organic compounds derived from them have biological activity against the most harmful microorganisms (Negri et al., 2004; Baldwin et al., 2018). Therefore, there is still a demand for synthesis of new enaminone derivatives. The most common way for preparation of enaminone derivatives is the condensation of a β-diketone and a primary amine at mild condition in an organic solvent (Elassar and El-Khair, 2003). Barbituric acid is more convenient candidate for reach enaminones so it contains β-diketone fragment in the six-membered ring (Mahmudov et al. 2014). Barbituric acid derivatives have been widely used in syntheses of different type complexes because they have three oxygen and two nitrogen atoms which can bind to transition metal center (Fırıncı et. al, 2017). Also, an active methylene group is presented in the skeleton of barbiturates for preparation of organic compounds. On the other hand, the compounds derived from barbituric acid have attracted much interest as many barbiturate derivatives are pharmacologically active (Neumann et al, 2014). In this context, the barbiturate bearing enaminones were synthesized by reaction of 5-formylbarbituric acid and selected primer amines in presented study. The structures of the prepared compounds were elucidated by ATR-FTIR, $^{1}$H and $^{13}$C NMR spectroscopy.

## MATERIAL AND METHODS

### Materials and Physical Measurements

All chemical reagents were obtained commercially and used without further purification. 5-formyl barbituric acid was synthesized according to literature (Neumann et al, 2014). Melting points were measured with a Stuart SMP30 melting point apparatus. Infrared spectra were measured on an ATR Spectrum-II, Perkin Elmer spectrometer. Elemental analyses were performed by ODTU Microlab (Ankara, Turkey). $^{1}$H, $^{13}$C and $^{19}$ F NMR spectra were measured on a Varian 400 spectrometer and referenced internally to residual protio-solvent ($^{1}$H) or solvent ($^{13}$C) resonances in $(CD_3)_2S$. $^{19}$F NMR spectra were referenced to $CFCl_3$.

### Experimental

### General procedure for synthesis of enaminones (2)

5-formyl barbituric acid (**1**, 5.0 mmol) and aniline derivative (5.0 mmol) were mixed in 20 mL of methanol than the mixture was refluxed for 4h in presence of catalytic amount of acetic acid. The suspension was cooled down at room temperature and the precipitate was filtered. The solid product was washed with diethyl ether and dried (Figure 1).

### Synthesis of 2a

Pale orange powder, 0.52 g, Yield: 53.2%, m.p.: 262-264 °C (decom.), IR (ν cm$^{-1}$): 3245, 3174, 3082, 3005, 2825, 1721, 1640, 1633, 1609. Anal. Calc. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53; found: C, 49.27; H, 4.58; N, 21.62. $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 4.10 (t, 2 H, HNC*H*$_2$CH), 5.18 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.93 (m, 1 H, CH$_2$C*H*=CH$_2$), 8.08 (d, 1 H, NHC*H*=C, *j*: 14.5 Hz), 10.16 (m, 1 H, N*H*CH=C), 10.56 (br. s, 1 H, O=CN*H*), 10.65 (br. s, 1 H, O=CN*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 51.2 (HN*C*H$_2$CH), 89.8 (NHCH=*C*), 117.5 (HNCH$_2$*C*H), 134.4 (CH$_2$CH=*C*H$_2$), 150.9 (*C*=O), 158.7 (NH*C*H=C), 163.9 (*C*=O), 165.9 (*C*=O).

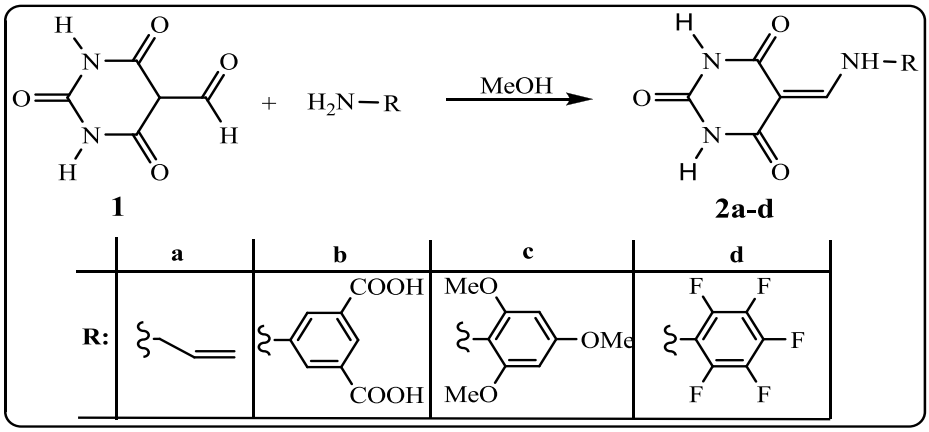


**Figure 1.** Synthesis of Enaminone Derivatives

**Synthesis of 2b**

White powder, 1.59 g, Yield: 99.5%, m.p.: 376-378 °C (decom.), IR (ν $cm^{-1}$): 3528, 3166, 3111, 3003, 2832, 1734, 1724, 1697, 1615. Anal. Calc. for $C_{13}H_9N_3O_7$: C, 48.91; H, 2.84; N, 13.16; found: C, 48.87; H, 2.92; N, 13.13. $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 8.19 (s, 2 H, *o-H*-$C_6H_3$), 8.27 (s, 1 H, *p-H*-$C_6H_3$), 8.54 (d, 1 H, NHC*H*=C, *j*: 9.4 Hz), 10.90 (s, 1 H, O=CN*H*), 11.03 (s, 1 H, O=CN*H*), 11.87 (d, 1 H, N*H*CH=C, *j*: 9.4 Hz), 13.47 (br. s, 2H, COO*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 93.4 (NHCH=*C*), 123.3 (*C*$_6$H$_3$), 126.7 (*C*$_6$H$_3$), 132.7 (*C*$_6$H$_3$), 139.7 (*C*$_6$H$_3$), 150.7 (*C*=O), 151.8 (NH*C*H=C), 163.6 (*C*=O), 165.7 (*C*=O), 166.0 (*C*=O).

**Synthesis of 2c**

Bright yellow powder, 1.41 g, Yield: 87.9%, m.p.: 300-302 °C (decom.), IR (ν $cm^{-1}$): 3123, 3075, 3040, 2854, 1750, 1716, 1688, 1662. Anal. Calc. for $C_{14}H_{15}N_3O_6$: C, 52.34; H, 4.71; N, 13.08; found: C, 52.37; H, 4.62; N, 13.12. $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 3.63 (s, 3H, *p*-OC*H*$_3$-$C_6H_2$), 3.82 (s, 6H, *o*-OC*H*$_3$-$C_6H_2$), 6.86 (s, 2H, *m-H*-$C_6H_2$), 8.58 (d, 1 H, NHC*H*=C, *j*: 14.1 Hz), 10.84 (s, 1 H, O=CN*H*), 10.98 (s, 1 H, O=CN*H*), 11.88 (d, 1 H, N*H*CH=C, *j*: 14.1 Hz). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 56.2 (O*C*H$_3$), 60.1 (O*C*H$_3$), 92.2 (NHCH=*C*), 96.3 (*C*$_6$H$_2$), 134.5 (*C*$_6$H$_2$), 135.4 (*C*$_6$H$_2$), 150.7 (*C*$_6$H$_2$), 151.6 (*C*=O), 153.6 (NH*C*H=C), 163.6 (*C*=O), 166.3 (*C*=O).

**Synthesis of 2d**

White powder, 0.64 g, Yield: 40.0%, m.p.: 290-292 °C (decom.), IR (ν $cm^{-1}$): 3258, 3183, 3070, 2810, 1721, 1685, 1640, 1615. Anal. Calc. for $C_{11}H_4N_3O_3F_5$: C, 41.14; H, 1.26; N, 13.08; found: C, 41.17; H, 1.22; N, 13.02. $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 8.34 (d, 1 H, NHC*H*=C, *j*: 13.3 Hz), 10.98 (s, 1 H, O=CN*H*), 11.05 (s, 1 H, O=CN*H*), 11.46 (d, 1 H, N*H*CH=C, *j*: 13.3 Hz). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 94.8 (NHCH=*C*), 150.5 (*C*=O), 155.8 (NH*C*H=C), 163.1 (*C*=O), 166.1 (*C*=O). $^{19}$F NMR (376 MHz, DMSO-$d_6$, δ ppm): -167.15 (t, 2F, *m-F*-$C_6F_5$, *J:* 52.6), -163.06 (t, 1F, *p-F*-$C_6F_5$ , *J:* 45.1), - 155, 24 (d, 2F, *o-F*-$C_6F_5$ , *J:* 45.1).

## RESULTS AND DISCUSSION

The barbiturate enaminone derivatives were synthesized by the condensation of 5-formyl barbituric acid and selected primary amine in methanol. The structural characterizations of the compounds were done by ATR-FTIR and NMR spectroscopy.

The IR spectra of **2a**, the broad absorption bands for ν(N-H) of barbiturate amides and enamine appeared at 3250-2825 $cm^{-1}$. Also, ν(C-H) absorption bands of ally moiety overlapped in the same region. The strong sharp bands from 1750 to 1600 $cm^{-1}$ were attributed to C=O stretching vibrations.

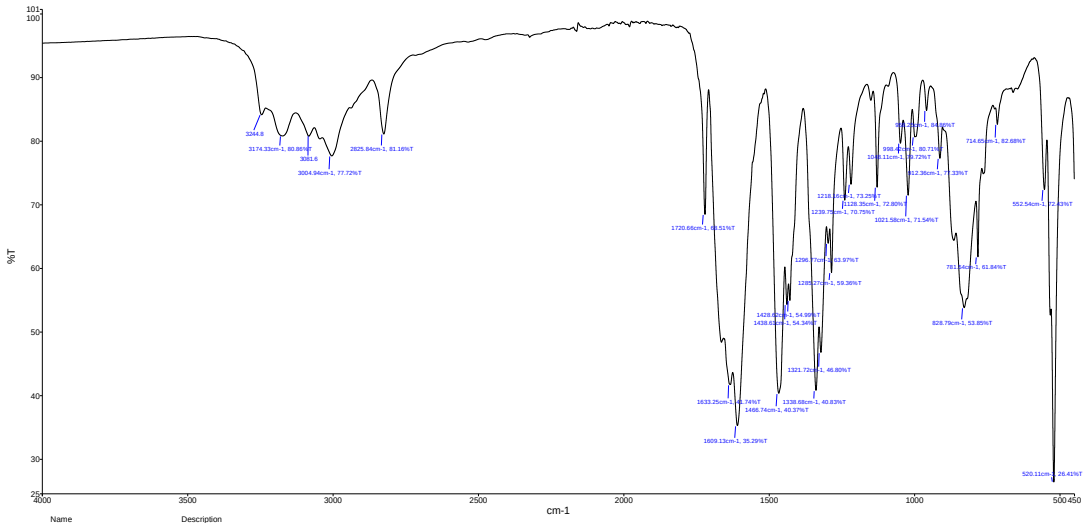


**Figure 2.** IR spectra of **2a**

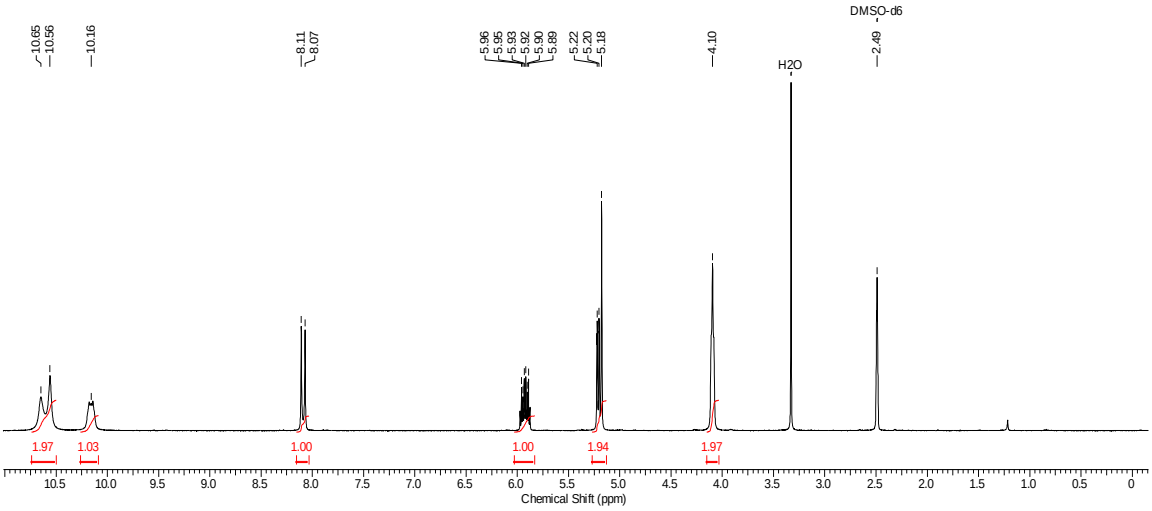


**Figure 3.** $^{1}$H NMR spectra of **2a**

The NH proton of enaminone moiety appeared at 10.16 ppm as multiplet in $^{1}$H NMR spectra of **2a**. The doublet peak at 8.08 ppm was assigned to CH proton of enaminone moiety. The barbiturate amide protons gave two broad singlet peaks at 10.56 and 10.65 ppm, respectively. The multiplet signals at 4.10, 5.18 and 5.93 ppm belonged to the ally fragment. Also, the found integration areas of protons are compatible with number of protons in **2a**.

There are eight carbon atoms in **2a** which have different chemical environment each other and they have been detected by $^{13}$C NMR spectroscopy (Figure 4). The $^{13}$C NMR spectrum showed that the vinylic carbon atoms of *C*=*C*H-NH-$CH_2$ gave two peaks at 89.8 and 158.7 ppm. The chemical shift of the carbonyl carbons of **2a** were observed at 150.9, 163.9 and 165.9 ppm in the $^{13}$C NMR spectra.

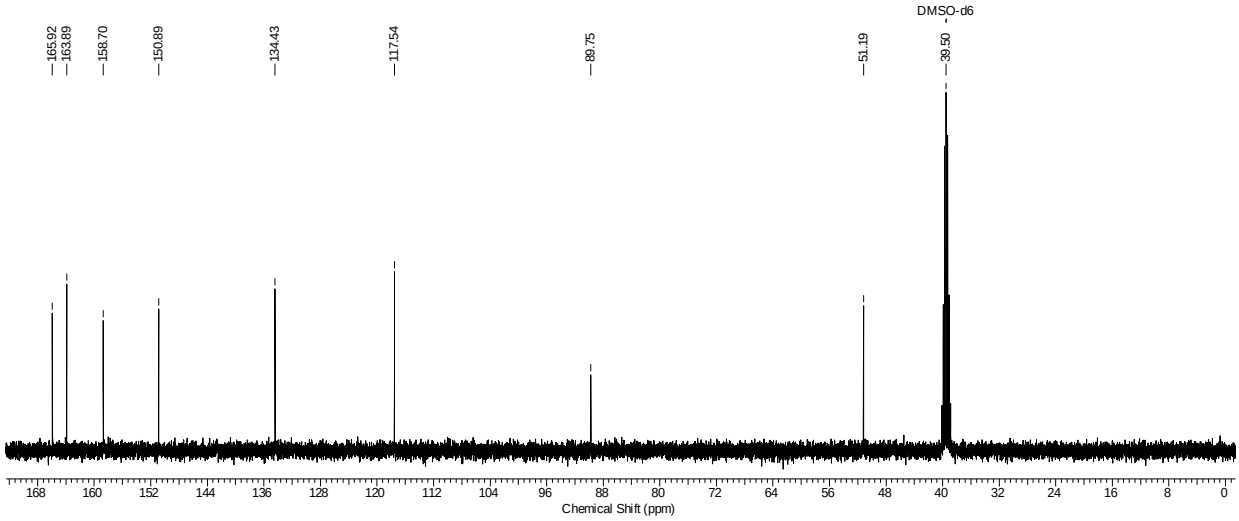


**Figure 4.** $^{13}$C NMR spectra of **2a**

For **2b**, the broad medium band at 3528 cm$^{-1}$ was assigned to the stretching vibrations of ν(O-H) from carboxylic acids. The strong peaks around at 3200-2850 cm$^{-1}$ belonged to ν(N-H) and ν(C-H) vibrations. The characteristic sharp bands of C=O stretching vibrations were observed from 1740 to 1600 cm$^{-1}$ (Figure 5).

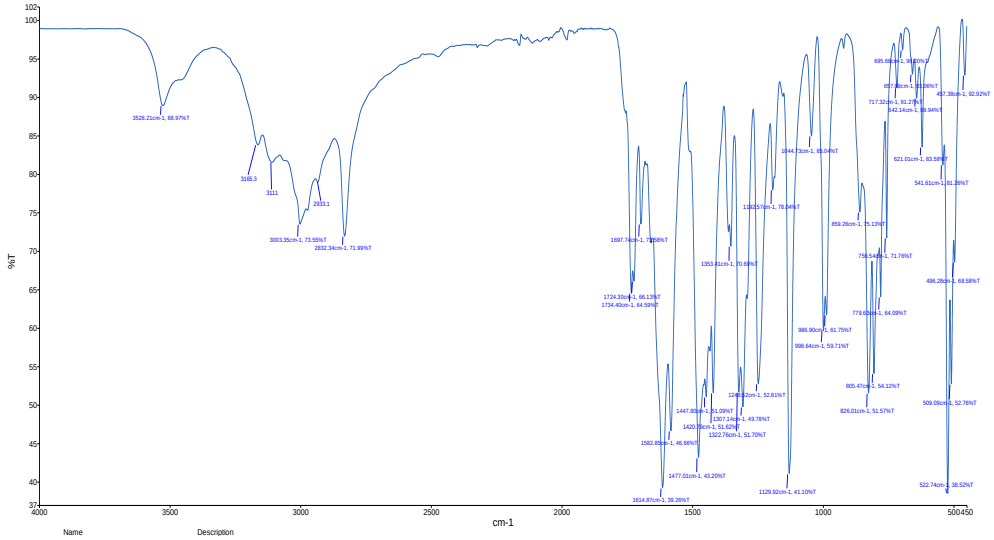


**Figure 5.** IR spectra of **2b**

The broad singlet peak at 13.47 ppm was assigned to COOH protons of **2b** in the $^{1}$H NMR spectra. The CH and NH protons of enaminone moiety gave douplet at 8.54 and 11.87 ppm, respectively. The NH protons of barbiturate ring appeared at 10.90 and 11.03 ppm as singlet. Two singlets at 8.19 and 8.27 ppm belonged *ortho* and *para* protons of aromatic ring respectively according to the integration areas of peaks.

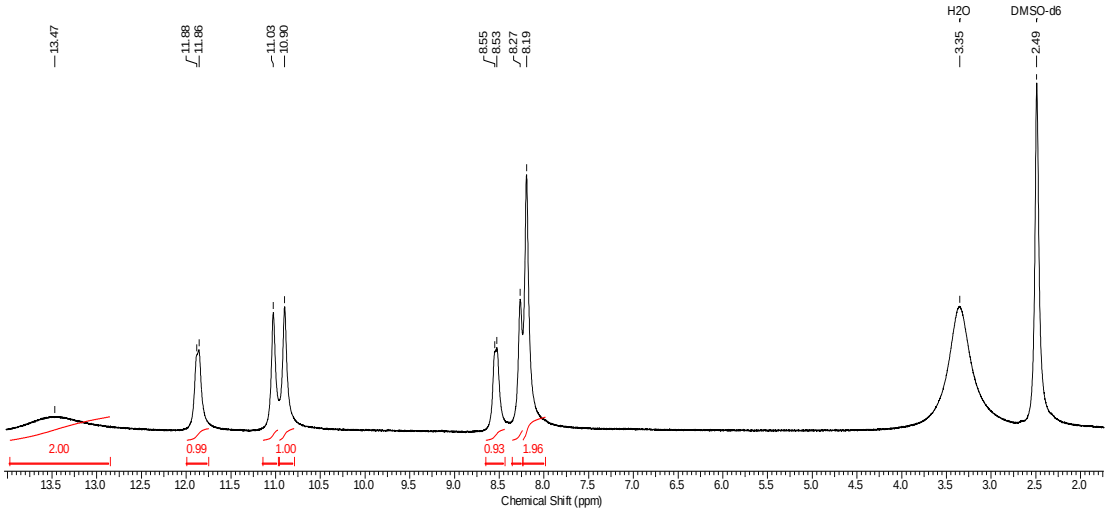


**Figure 6.** $^{1}$H NMR spectra of **2b**

The signals at 93.4 and 151.8 ppm belonged to the vinylic carbon atoms of **2b** in the $^{13}$C NMR spectra (Figure 7). The four peaks at 150.7, 163.6, 165.7 and 166.0 ppm were assigned to the carbonyl carbons of barbiturate moiety and carboxylic acid. Also, the number of observed carbon atom signals in the $^{13}$C NMR spectra complies with the expected.

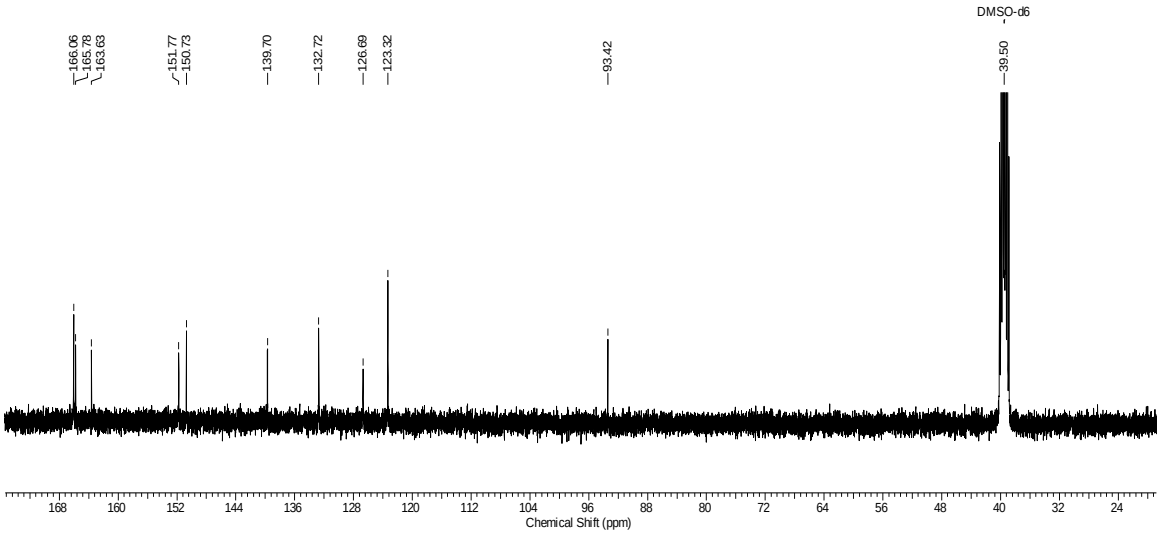


**Figure 7.** $^{13}$C NMR spectra of **2b**

In the IR spectra of **2c**, the broad absorption bands at 3200-2850 cm$^{-1}$ were assigned to ν(N-H) of barbiturate amides and enamine. Also, ν(C-H) absorption bands overlapped in the same region. The strong sharp bands from 1750 to 16500 cm$^{-1}$ were attributed to C=O stretching vibrations.

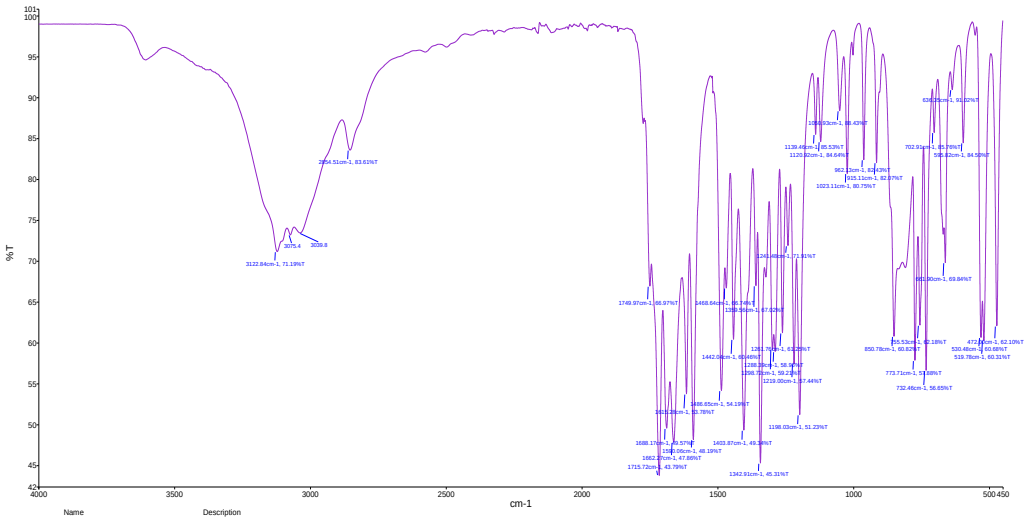


**Figure 8.** IR spectra of **2c**

The $^{1}$H NMR spectra of **2c**, two singlets at 3.63 and 3.82 ppm belonged *para* and *ortho* methoxy protons according to the integration areas of peaks. The singlet peak at 6.86 ppm was assigned to phenyl protons. The CH and NH protons of enaminone moiety gave douplet at 8.58 and 11.88 ppm, respectively. The NH protons of barbiturate ring appeared at 10.84 and 10.98 ppm as singlet.

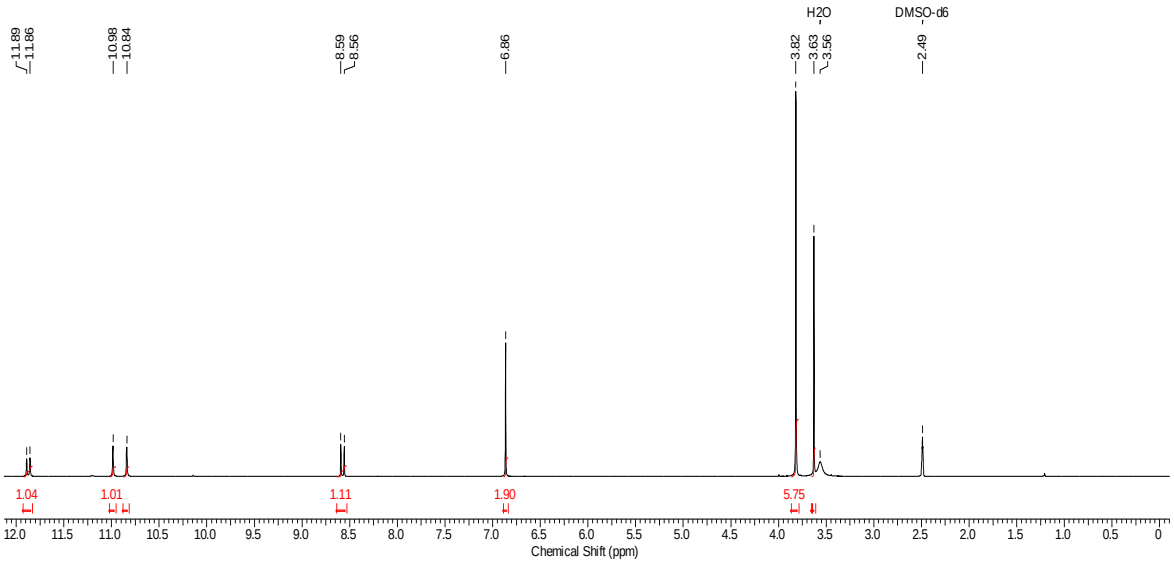


**Figure 9.** $^{1}$H NMR spectra of **2c**

The peaks of methoxy carbons appeared at 56.2 and 60.1 ppm. The vinylic fragment displayed two signals at 92.2 and 153.6 ppm **2c** in the $^{13}$C NMR spectra (Figure 10). The three distinct resonances at 151.6, 163.6 and 166.3 ppm were assigned to the carbonyl carbons of barbiturate moiety. Also, the number of observed carbon atom signals in the $^{13}$C NMR spectra is consistent with the expected.

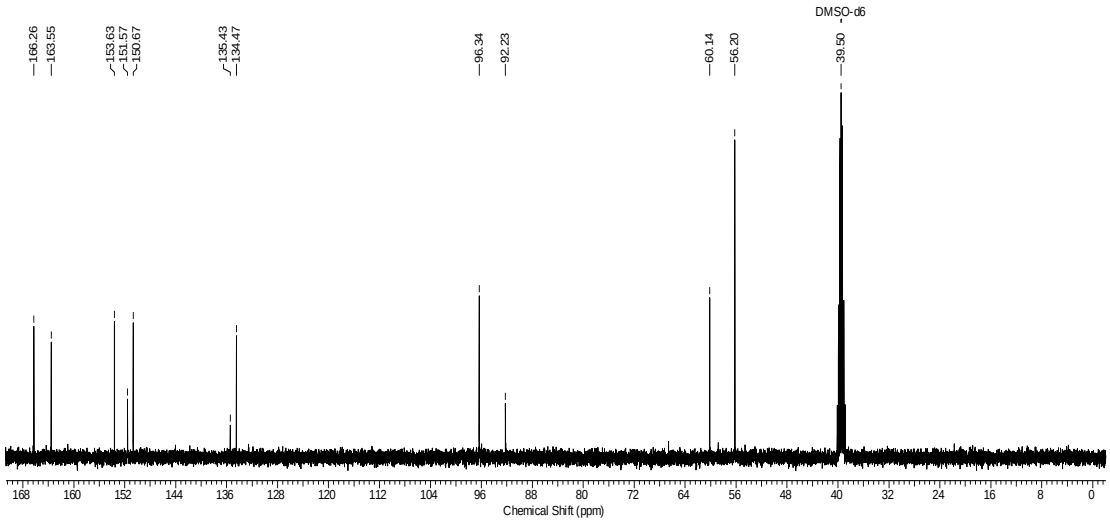


**Figure 10.** $^{13}$C NMR spectra of **2c**

The ν(N-H) and ν(C-H) bands of **2d** appeared at between 2800 and 3260 cm$^{-1}$. The strong sharp bands from 1720 to 1600 cm$^{-1}$ were assigned as C=O stretching vibrations (Figure 11).

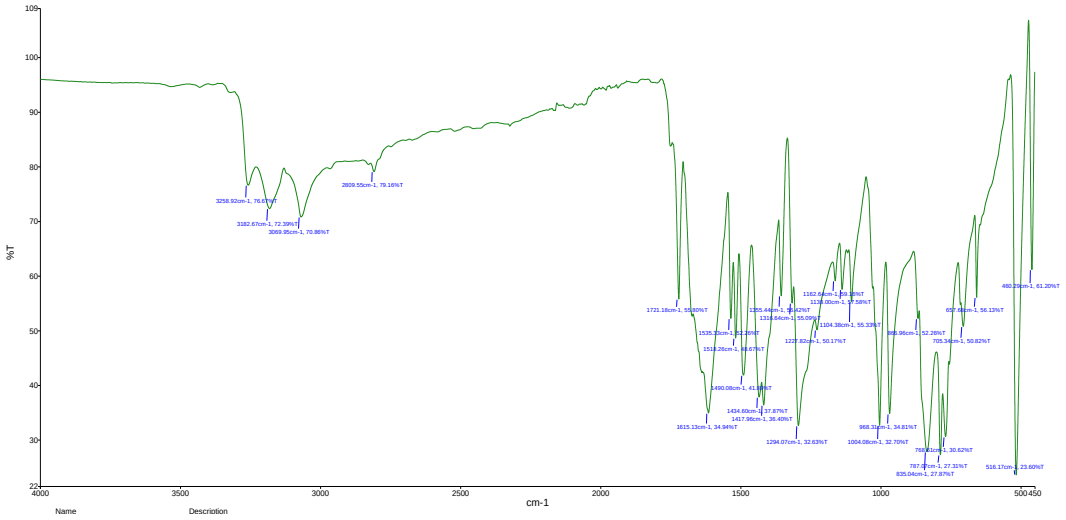


**Figure 11.** IR spectra of **2d**

The $^{1}$H NMR spectra of **2d** showed that The NH and CH protons of enaminone moiety gave rise to doublet peaks at 8.34 and 11.46 ppm, respectively. The barbiturate amide protons gave two singlet peaks at 10.98 and 11.05 ppm.

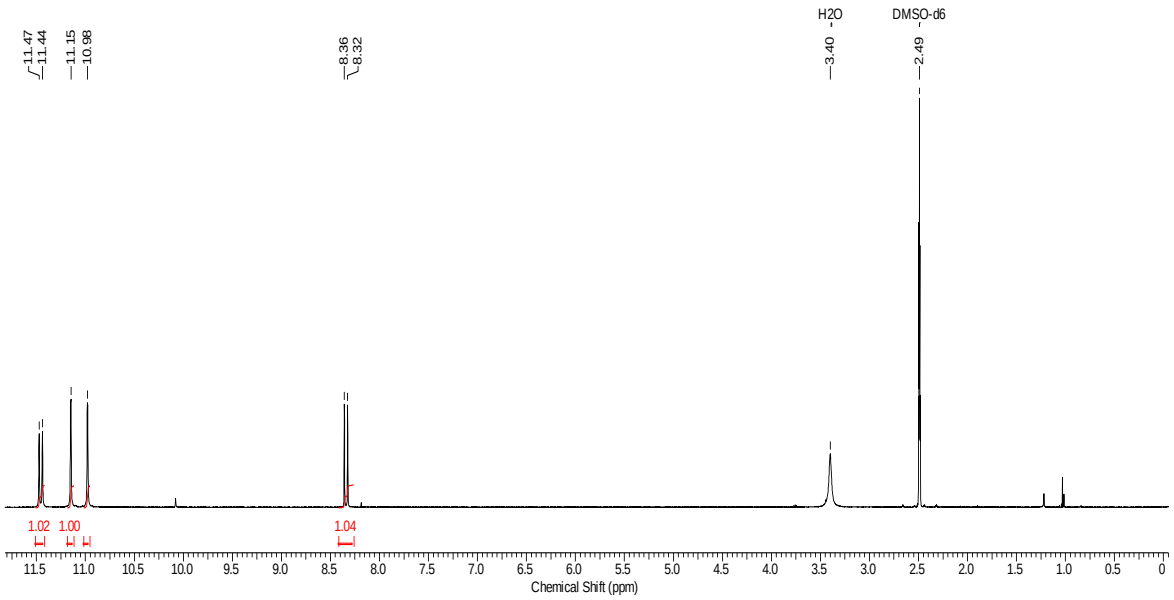


**Figure 12.** $^{1}$H NMR spectra of **2d**

The carbons of C=C appeared at 94.8 and 155.8 ppm in the $^{13}$C NMR spectra of **2d** (Figure 13). The three signals at 150.5, 163.1 and 166.1 ppm were assigned to the carbonyl carbons of barbiturate moiety. Unfortunately, fluoride bounded carbon atoms of phenyl could not be detected in the $^{13}$C NMR spectra.

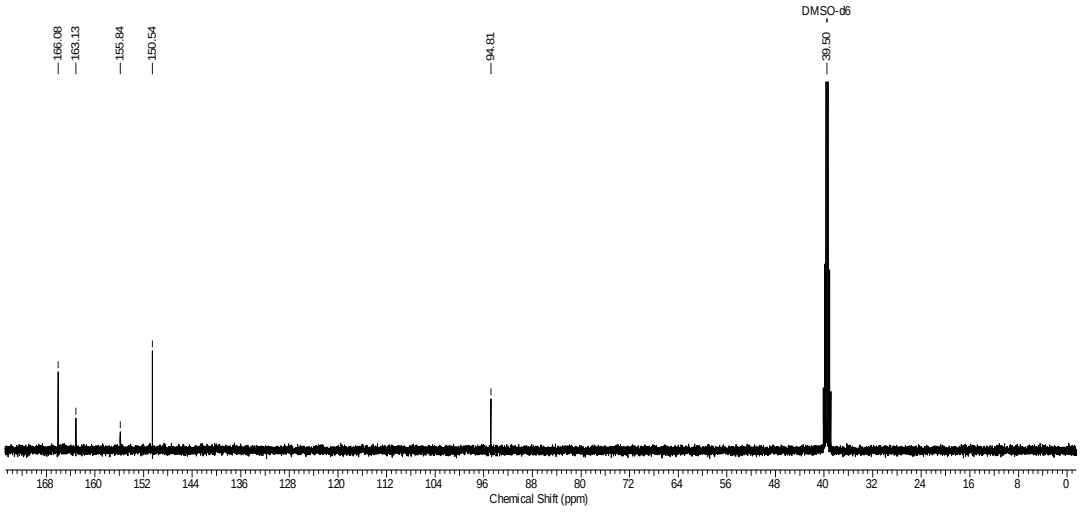


**Figure 13.** $^{13}$C NMR spectra of **2d**

On the other hand, the existence of penta-fluoride bounded phenyl in **2d** was proved by $^{19}$F NMR spectroscopy. The observed three signals (Figure 14), which were appeared at -167.15, -163.06 and -155, 24 ppm, were justified that symmetric penta-fluoride bounded phenyl group. The values are consistent with the penta-fluoride phenyl containing compounds in literature (Vidovic et al, 2007).

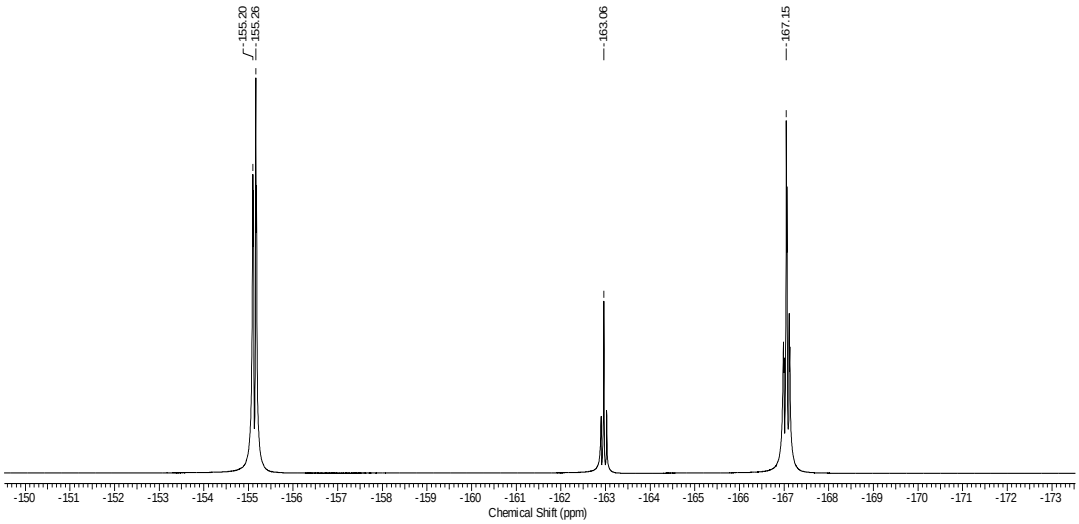


**Figure 14.** $^{19}$F NMR spectra of **2d**

## CONCLUSION

Four enaminones derived from barbituric acid were prepared from the condensation reaction of 5-formyl barbituric acid and selected primer amines with high yield in present study. The structures of the prepared compounds were explained by ATR-FTIR, $^{1}$H and $^{13}$C NMR spectroscopy. Also, $^{19}$F NMR spectroscopy was used for characterization of **2d**. The integration areas of protons in $^{1}$H NMR spectra of **2a-d** and the number of the carbon atoms in $^{13}$C NMR spectra of **2a-d** cohere with the expected. Also, the obtained data from spectroscopic instruments comply with the previously reported similar enaminones (Neumann et al., 2014; Rauf et al., 2015; Fırıncı et al, 2017). The prepared enaminone derivates can be estimated both versatile ligand for preparation transition metal complexes and synthesis of hetero atom containing organic compounds. The prepared enaminones have potential the being biological active owing to fact that they include barbiturate fragment.

## ACKNOWLEDGMENTS

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