SYNTHESIS AND CHARCTERIZATION OF 2-BENZOXAZOLONE AND ITS DERIVATIVES

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ABSTRACT

2(3H)-Benzoxazolone derivatives are compounds that possesses different biological activity particularly analgesic and anti-inflammatory activities according to the literature, in this research two benzoxazolone derivatives were synthesized. Compound 1 was synthesize using Mannich reaction through modification at the 3rd position (under reflux condition). Compound 2 was prepared at room temperature through modification at 6th position. These compounds were prepared to study their effect on analgesic and anti-inflammatory activities of such compounds. The reactions were monitored by TLC and melting point determination, and structural characterization was done by FT-IR and ^{1}H-NMR analysis.

Keywords: *2(3H) benzoxazolone, Piperazine, Mannich reaction, Analgesics, Anti-inflammatory, Reflux condition.*

INTRODUCTION

2-benzoxazolinone derivatives are molecules which are very important and relevant in terms of their biological activities (H. Erdogan, M. Debart and J. cazin, 1991). They play a vital role pharmacologically as they serve as an anti-inflammatory, anti-analgesic, hypnotic, and anti-pyretic agents (E. Palaska, S Unlu, F Ozkanli, G Pillli, H. Erdogan, C Safak, R Demirdamar and Gumusel Z.Z, 1995). Scientific research shows that 2-benzoxazolinone derivatives which have substituent at position 3, 5, 6 and 7 have analgesic activity (which is the ability to reduce pain) (Kithani H., Kurodo, T. Moriguchi, A., Ao, H Hirayarma, F. Ikeda, Y. Kawakita, 1997). 2(3H)-Benzoxazolone having halogenated substituents have been reported to have various biological activities such as anticonvulsant, antioxidant and antimicrobial activities (Plech T, Wujec, M. Siwek, A. Kosikowska, U. Malon,, 2011). Furthermore, 2 (3H)-benzoxazolone and its 5-chloro derivatives possess great biological activities such as anti-tumor, anti-HIV, anti-microbial activities. Also, research have shown that 5-choloro-3-methyl-2(3H)-benzoxazolone rings have antibacterial and antifungal activities (Laufer S., Greim C, Ayoub S. Dehner F, 2008).

The main purpose of this paper is to synthesize some 2-(3H)- Benzoxazolone derivatives that had been modified at the 3rd and 6th positions in effort to prepare COX-2 selective inhibitors with less side effects. These compounds are further purified using recrystallization, melting point, and also TLC was conducted to check the purity of the compounds. They are subsequently characterized using Nuclear magnetic resonance (^{1}H-NMR) and Fourier Transform Infrared (FT-IR).

2. MATERIAL AND METHODS

2.1 Materials

All chemicals used were obtained from Sigma-Adrich(Germany). 2(3H)-benzoxazolone, ethanol, methanol ,dimethylformamide, formaline ,2-methoxyphenyl-piperazine, (4-flourophenyl) piperazine, benzene , triethylamine and chloroform.

2.2 Thin Layer Chromatographic Method

2.2.1 Material

Thin layer chromatography (TLC) was conducted on a silica gel plate and the solvent used were benzene, methanol and chloroform. The spotted silica gel plate was detected under UV-light.

There are two different mobile phases prepared with different solvent at different ratios.

H_1: Benzene- Methanol (9:1)

H_2: Benzene- Methanol (5:1)

2.2.2 Method

The solvent which is the mobile phase is poured into the TLC tank with a depth of about 0.5cm. The tanks were covered and gently swirled and allowed to stand while getting the silica plate. The plates were cut horizontally of about 5 by 3cm and prepared for spotting in three different points while 0.5cm line of origin was gently drawn away from the bottom using a pencil. The starting material and products were dissolved in chloroform and with the aid of capillary spot were made on the TLC plate and the plate was gently placed in the tank, covered and left undisturbed. The solvent was allowed to move through the plate until it reaches the solvent front. The plate was removed and the solvent front was marked with a pencil and then allowed to dry. After drying the spots were viewed under UV light at 254nm and Rf values were calculated.

2.3 Melting Point

The melting point of the compound was detected with Mettler Toledo (FP900) melting point apparatus

2.4 Spectroscopy: Fourier Transform Infrared spectroscopy (FT-IR)

The FT-IR spectra of the compounds were recorded on Agilent Carry 630 spectrometer at Ankara University, Centered Instrumental Analysis Laboratory, and Faculty of Pharmacy.

2.4.2. Proton Nuclear Magnetic Resonance (^{1}H-NMR)

The ^{1}H-NMR spectra of the compounds were recorded on a Mercury Varian 400MH NMR spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent at Ankara University, Central Instrumental Analysis Laboratory, Faculty of Pharmacy.

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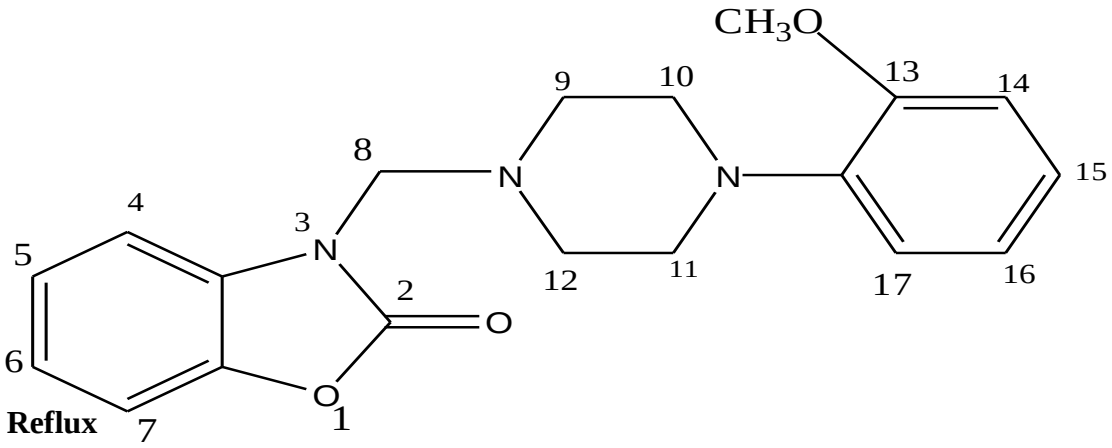
2.5 *Experimental*

2.5.1 Synthesis of compound 1

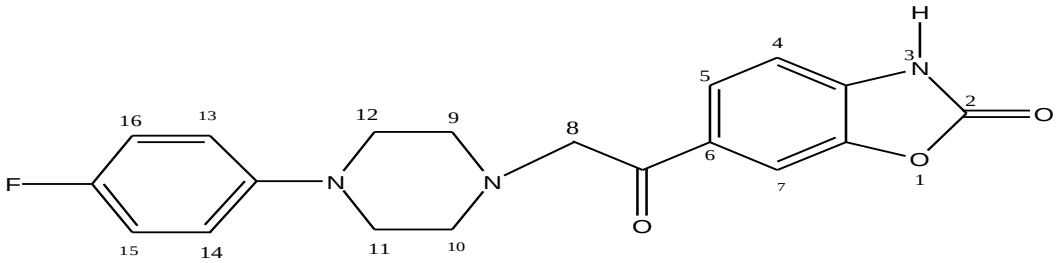
3-(4-(2-methoxy-phenylpiperazin-1-yl) methyl-2(3H) benzoxazolone



200 mg (0.001mol) of benzoxazolone and 0.001mol of 2-methoxy phenylpiperazine were dissolved in 8ml methanol in 50ml round bottom flask. 0.2ml of 37% formalin solution were mixed in 2ml of methanol and then poured into the reaction mixture. The solution was refluxed in a water bath for 60 min. After completion, the mixture was poured into crushed ice where a precipitate was formed. The resulting solid was filtered using vacuum filtration method to yield a crude product which was washed with ethanol and allow to dry at room temperature. After the reaction was checked by TLC and the resulting precipitate was purified by recrystallization with ethanol.

3.5.2 Synthesis of compound 2

6-(4-flouro phenyl piperazine -1-yl) acetyl-2(3H) -benzoxazolone



compound 2

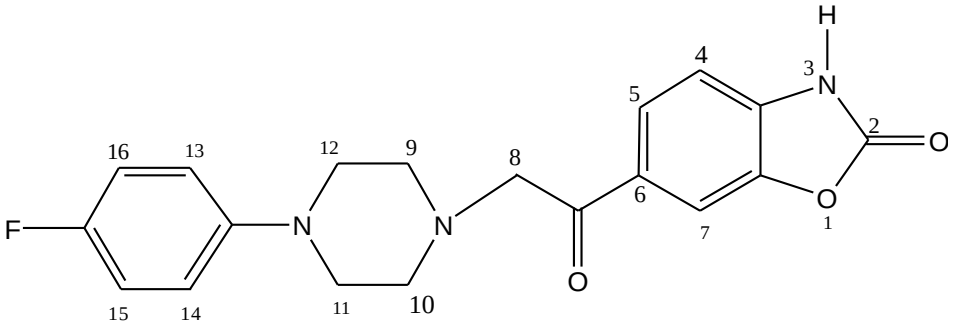
Reaction at room temperature

350 mg (0.01mol) of 6-(2-bromoacyl)-2(3H)-benzoxazolone was dissolved in 7ml of dimethyl formamide (DMF), 0.25ml 4-flourophenyl piperazine was mixed with 0.4ml (0.06mol) of triethylamine in 3ml DMF, then the solution of 6-(2-bromoacyl)-2(3H) benzoxazolone was added dropwise. The mixture was stirred at room temperature for 30 hrs. The reaction mixture was poured into crushed ice and then filtered using vacuum filtration, washed with water and dried at room temperature.

3. RESULTS AND DISCUSSION

4.1. Results

Compound 1



Reflux

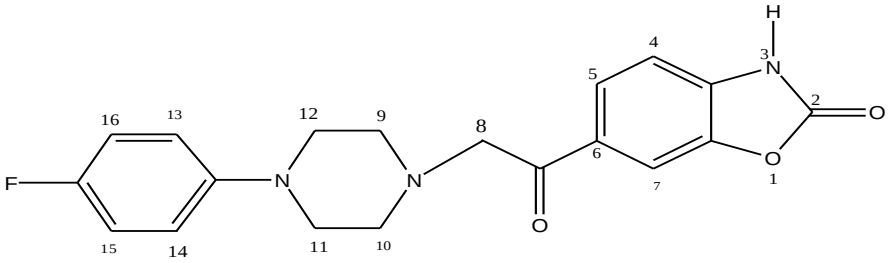
I. Yellowish crystalline was observe with a melting point of 165.8 ^{0}C

II. TLC the H_1 and H_2 mobile phases gave R_f values of 0.42 and 0.59 respectively.

III. Fourier Transform Infrared (FT-IR) spectroscopy (V_{max}): FT-IR shows absorption band of aromatic and aliphatic peak at 2768-2941 cm $^{-1}$(C-H stretch), and carbonyl group at 1772 cm^{-1} (C=O stretch).

IV. The ^{1}H-NMR spectra shows chemical shift at 6.9-7.2 ppm (8H,m, Ar-H), 4.8 ppm (2H,S H^{8}), 3.8pm (3H,s,-O-CH_3) , 2.8-3.2 ppm (8H, d ,protons of pip peaks) .

Compound 2



compound 2

I. White solid was observed and melting point of 141.9^{0}C.

II. TLC the H_1 and H_2 mobile phases gave R_f values of 0.24 and 0.48 respectively.

III. Fourier Transform Infrared (FT-IR) spectroscopy (V_{max}): FT-IR shows absorption peak at 3676 cm^{-1} (N-H stretch), 2974-2826(C-H stretch), 1770 carbonyl group (C=O stretch).

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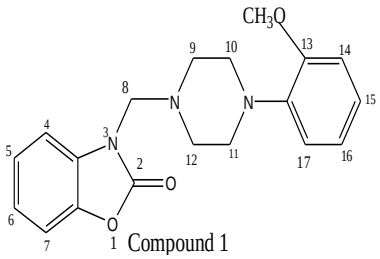
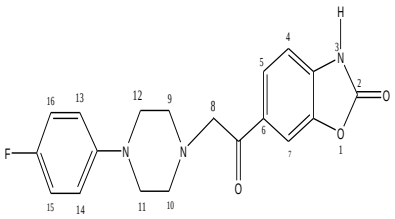
IV. The ^{1}H-NMR spectra shows chemical shift around 7.0-8.0ppm indicating an aromatic proton (7H, m, Ar-H), chemical shift at 3.8ppm indicates a methyl proton (2H-s-CH_2), chemical shift around 3.5-4.4ppm (8H, d, H^9-H^{12}) indicates piperazine protons.

4.2 Discussion

In this research, two compounds of benzoxazolone derivatives were synthesized at 3rd and 6th position respectively. These synthesized compounds were obtained using mannich reaction which involves the modification at 3rd position and at room temperature which involves modification at 6th position, these reactions were conducted to check the reactivity of 2-(3H) benzoxazolone at various positions. Table 4.2 below shows the structure, numbering and naming of the compounds.

Table 1. The chemical name, numbering and the structures of synthesized compounds

Chemical name	Structure
3(4-(2-methoxyphenyl piperazine-1-yl) methyl-2(3H)-benzoxazolone	 Compound 1
6-(2-(4-floro phenylpiperazine-1-yl) acetyl-2(3H) Benzoxazolone.	 compound 2

Compound 1 was synthesize using Mannich reaction with a modification on Nitrogen atom of the benzoxazolone with 2-methoxy-piperazine as the heterocyclic amine. The synthesis pathway of the reaction is given below in fig 2.34

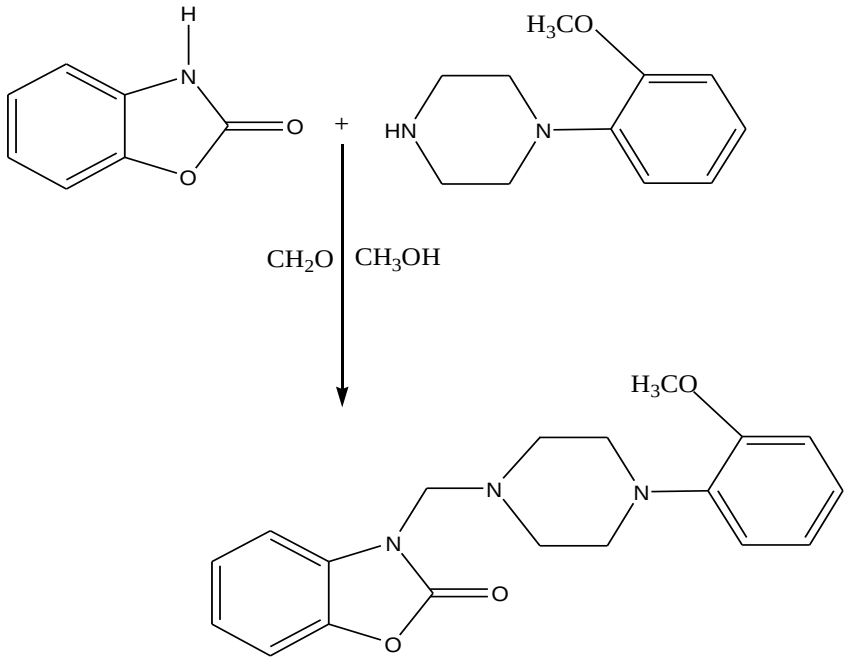


Figure 2.22 General synthesis of 3-(4-(2-methoxyphenyl piperazine-1-yl) methyl-2(3H) benzoxazolone.

Compound 2 was synthesized at room temperature, where the modification was done at the 6th position of benzoxazolone with 4-floro-phenylpiperazine. The synthesized compound was characterized by Fourier Transform Infra-red (FT-IR) and Proton Magnetic Resonance Spectroscopy (^{1}H-NMR). Thin layer chromatography and melting point were used to check the purity of the compound.

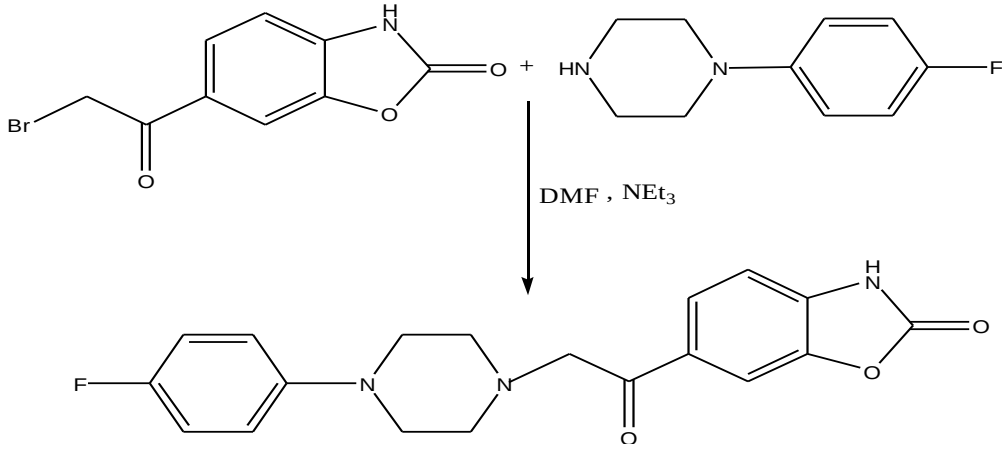


Figure 2.23 Synthetic pathway of 6-(2-(4-flourophenyl piperazine-1-yl)acetyl-2(3H)-benzoxazolone

Table 2. Comparison of the R_f Values and melting point of the starting materials and the synthesize compounds.

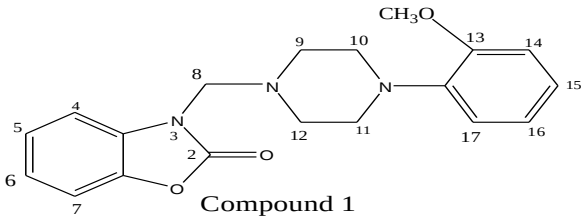
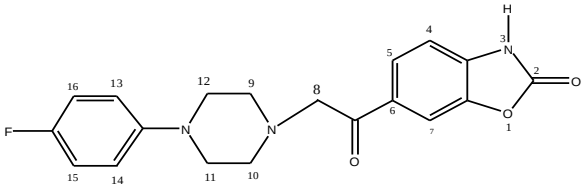
Methods	Chemical Structures	Melting Points (^{0}C)	R_f Values
Reflux (modification at 3rd position)	 Compound 1	165^{0}C	A_1=0.42 A_2=0.59
Reaction at room temperature (modification at 6th position)	 compound 2	141^{0}C	A_1=0.24 A_2=0.48

Table 2 above table compares the melting point and R_f values of both the two synthesize

The FT-IR spectrum of the compound **1** shows the absence N-H stretch around 3100-3400cm^{-1}, indicating the occurrence of the reaction at position 3 of 2(3H) benzoxazolone. Aromatic and aliphatic stretches are visible around 2768-2941 cm^{-1}(C-H) stretch. A strong carbonyl (C=O) stretch appears at 1772 cm$^{-1.}$as expected.

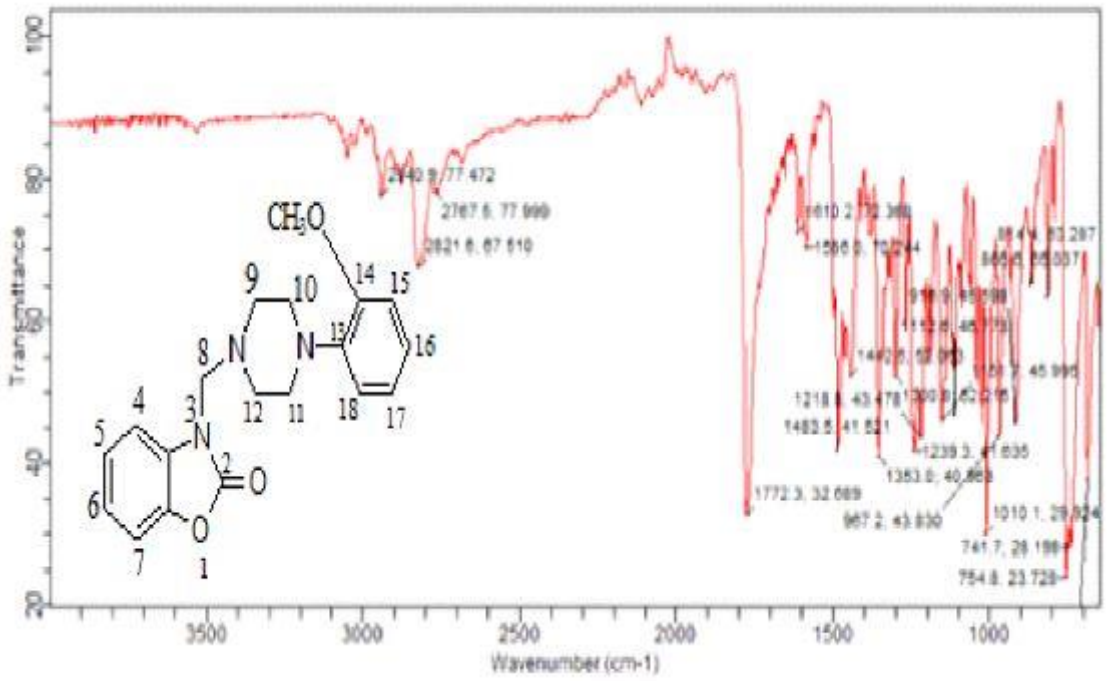


Figure 2.24 FT-IR spectrum of 3-(4-(2-methoxyphenyl piperazine-1yl) methyl-2(3H) benzoxazolone

The FT-IR of **compound 2** shows the presence of N-H stretch around 3676cm^{-1} revealing that reaction did not occur at 3-position, Both aromatic and aliphatic (C-H) stretch around 2826-2974 cm^{-1},A strong absorption band of carbonyl group around 1770cm^{-1}(C=O) appears as expected. Fig 2.36 shows the FT-IR spectra of synthesized compound.

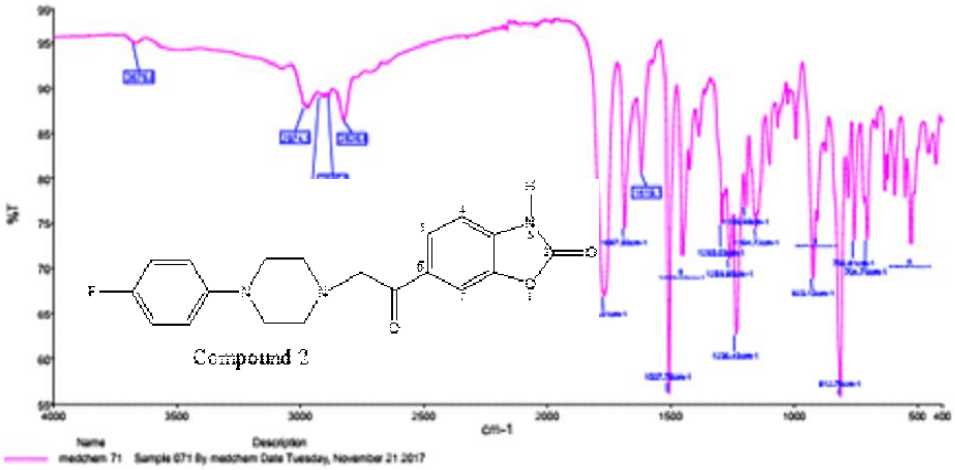


Figure 2.25 FT-IR spectrum of 6-(2-(4-fluoro phenylpiperazine -1-yl) acetyl 2(3H) benzoxazolone

^{1}H-NMR spectrum of **compound 1** shows aromatic peak at around 6.9-7.2 ppm ppm, methylene signal was observed at a chemical shift around 4.8 ppm, a methoxy proton at a chemical shift around 3.8 ppm, piperazine proton shows a chemical shift around 2.8-3.2 ppm.

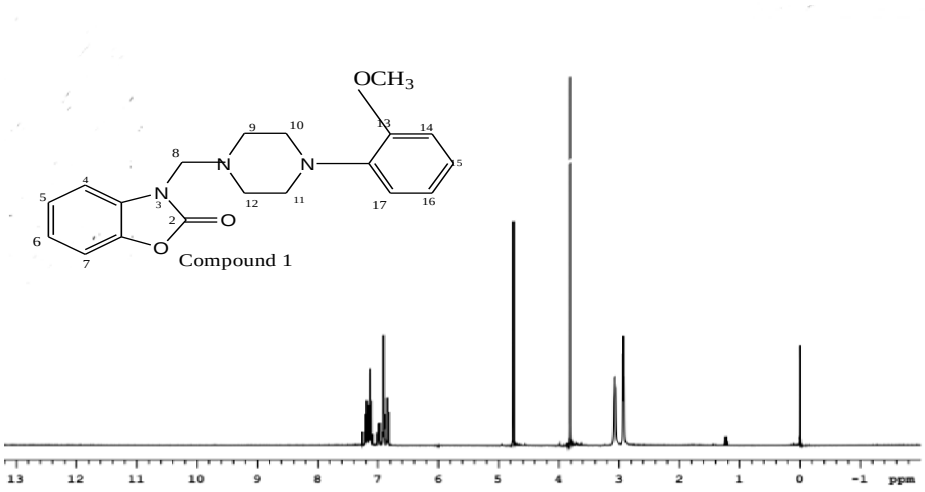


Figure2.26 ^{1}H-NMR spectrum of 3-(4-(2-methoxy-phenylpiperazine-1-yl)methyl 2(3H)benzoxazolone.

^{1}H-NMR spectra of **compound 2** shows a chemical shift 7.0-8.0 ppm indicating an aromatic proton, chemical shift at 3.8 ppm indicates a methyl proton and chemical shift at 3.5-4.4 ppm indicates a piperazine proton.

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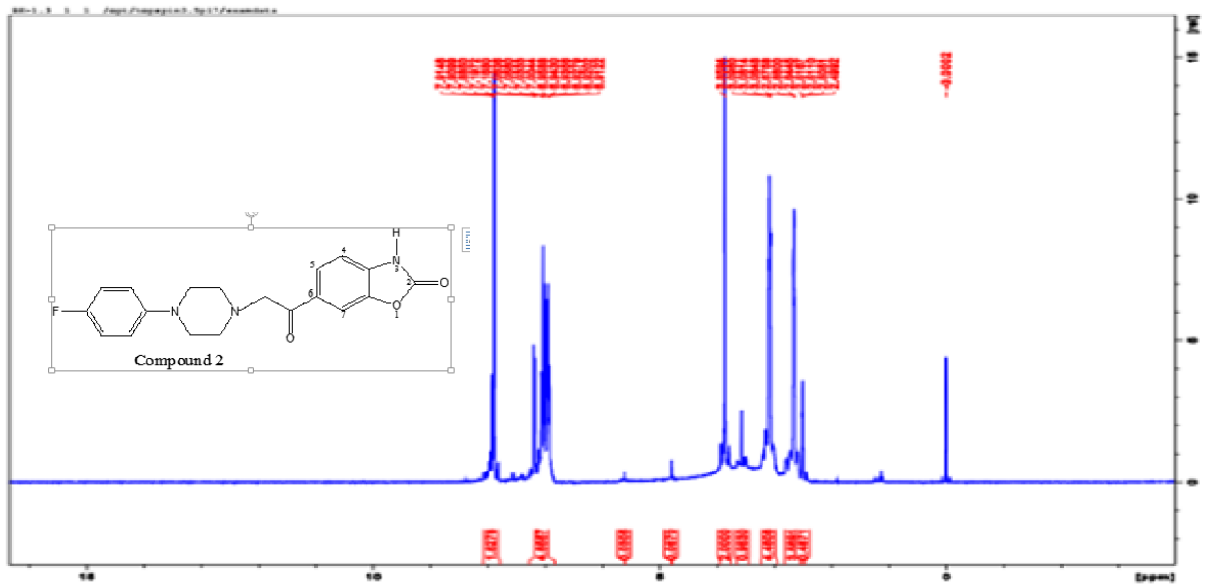

Figure 2.27 H-NMR spectrum of 6-(2-(4-floro phenylpiperazine -1-yl) acetyl 2(3H) benzoxazolone

CONCLUSION

Modification of 2-(3H)-benzoxazolone at 3rd and 6th position was conducted using two different reaction methods namely; mannich reaction and reaction at room temperature. The reaction time taken in modification at 3rd position is much shorter than at 6 position which was conducted at room temperature. The aim of this paper is to synthesize compound possessing analgesic and anti-inflammatory activity, especially COX-2 selective analgesics. Biological activities of the synthesized compounds were not conducted due to time constrained, however the future studies will involve the biological activities. Activity studies apart from analgesic and anti-inflammatory activities are intended to be made in the future since it is possible to substitute different amine at various position of benzoxazolone, this will potentially cause change in the biological activities of these types of compounds.

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