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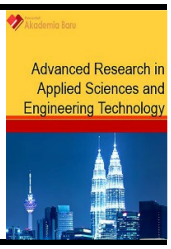

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Study on Synthesis and Characterization of Some 2-Benzoxazolone Derivatives

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ABSTRACT

2-(3H)-benzoxazolone and its derivatives are compounds having different pharmacological activities more especially analgesic and anti-inflammatory. Its ability for modification at different positions makes it be of great interest in medicinal and pharmaceutical chemistry. Consequently they can be used in the development of new drug candidates that are COX-2 selective with less side effects. In this research we synthesized two compounds, Compound 1 via Mannich reaction, under reflux condition which involves modification of the 3rd position of 2-(3H)-benzoxazolone. Compound 2 through a reaction at room temperature which involves the modification of the 6th position of 6-(2-bromo-acetyl)-2(3H)-benzoxazolone. The synthesized compounds were characterized using FT-IR and 1H-NMR spectroscopy. Their purity was checked using melting point determination and thin layer chromatography. From the results obtained it clearly shows the efficiency and efficacy of the two synthesis procedures.

1. Introduction

The basic and fundamental principle for the production of analgesics is to reduce, cure or minimize pain. According to Farlex Medical dictionary, pain is defined as, "An unpleasant sensation associated with actual or potential tissue damage, and mediated by specific nerve fibers to the brain, where its conscious appreciation may be modified by various factors" [1]. Pain is a result of many cases. The usual cause is an injury, even though pain may also be as a result of illness. Pain can further be classified into chronic and acute pain [2].

There are two types of analgesics, namely narcotics and non-steroidal anti-inflammatory drugs but the most used analgesics used globally are Nonsteroidal anti-inflammatory drugs (NSAIDS), and these NSAIDS have great side effects which can result into gastrointestinal bleeding and

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gastroduodenal ulcers. This brings about the idea for the production of new pain relievers with little or no side effects [3].

2-Benzoxazolone derivatives are used for synthesis of new drug candidates [4]. These benzoxazolone derivatives are of great interests due to the fact that they are readily accessible, cheap, and susceptible to structural and chemical modifications and most importantly they have varieties of biological properties. Their pharmacological effects constitute of antifungal, antibacterial, analgesics-anti-inflammatory, anti-cancer, anti-HIV and also used as COX-2 selective inhibitors [6].

The aim of this research is to synthesize some 2-benzoxazolinone derivatives through modification on the 6th position of the compound as well as through modification of the 3rd position using Mannich reaction with less or no side effects such as bleeding as in previous synthesized non-narcotic drugs [5]. The compounds were characterized by Fourier Transform Infrared (FT-IR) and proton Nuclear Magnetic Resonance (H1-NMR) spectroscopy. The purity was also determined using both melting point and thin layer chromatography (TLC).

2. Methodology

2.1 Materials

All the chemicals used in this research work 2 (3H)-benzoxazolone, (4-fluorophenyl) piperazine, (2-metoxyophenyl) piperazine, methanol, 37% formalin solution, n-hexane, ethylacetate, chloroform, triethyl amine, dioxane and ethanol were all purchased from Sigma Aldrich chemical company and used without any further purification.

2.2 Synthesis of Compound 1

1-(4-fluoro phenyl piperazin-1-yl) methyl-2 (3H)-benzoxazolone

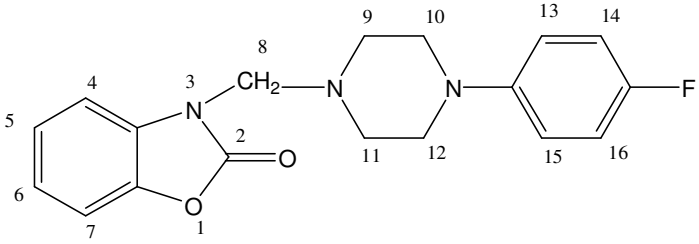


Fig. 1. Chemical structure of compound 1

Reflux

200 mg (0.001 mol) of 2(3H)-benzoxazolone and 267 mg (0.001 mol) of 1-(4-fluorophenyl piperazine) were dissolved in 8 mL of methanol in a 50 ml round bottom flask. 0.2 mL (0.005 mol) of formalin solution 37% (w/v) was mixed with 2 mL methanol and then transferred into the reaction mixture. The mixture was then refluxed for 60 minutes in water bath. After the completion of the reaction, the reaction mixture was poured into crushed ice upon which a precipitate was formed. Later on the product was filtered by 'vacuum filtration' to yield a pure product which was later washed with ethanol and allowed to dry at room temperature. The compound was then recrystallized by using ethanol.

2.3 Synthesis of compound 2

6-{2-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-acetyl}-2-(3H)-benzoxazolone

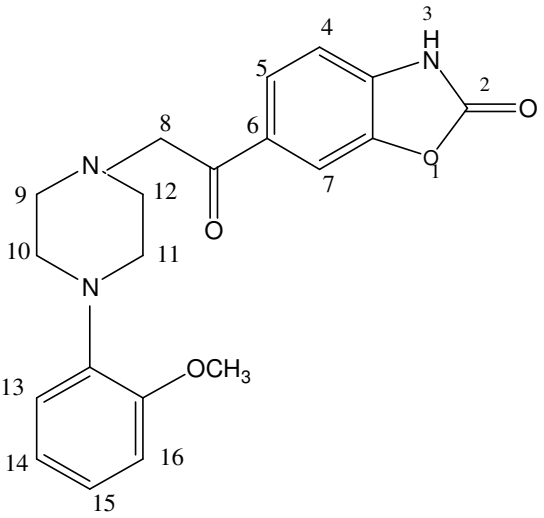


Fig. 3. Chemical structure of compound 2

Reaction at Room Temperature (Modification of 6th position)

350 mg (0.001 moles) of 6-(2-bromoacyl)-2-(3H)-benzoxazolone was disssoved in 7 ml of dimethylformamide (DMF) solution. 0.25ml (0.001 moles) of 2-metoxyphenylpiperazine was mixed with 0.4ml (0.002 moles) of triethyl amine solution in 3 ml dimethyl formamide. And then the mixture containing 6-(2-bromoacyl)-2(3H)-benzoxazolone in DMF was added dropwise into the reaction mixture. The mixture was stirred at room temperature for 30 hours and then poured into crushed ice and then filtered using vacuum filtration method. The synthesized compound was then washed with water and dried.

2.4 Thin Layer Chromatography

This process was carried out on silca gel-plates having a fluorescent indicator at 254 nm to check the progress of the reaction using chloroform as the stationary phase. Three different mobile phases were prepared and used. Which are:

A1- Benzene/ methanol: (9:1)
A2- Benzene/ methanol: (5:1)

Both the starting material and product were dissolved in chloroform as the stationary phase. The mobile phase was transferred into the TLC chamber and gently swirled. The silica gel plate containing spots made with the aid of micro capillary of both the starting material solution and the solution of the product was carefully transferred into the mobile phase chamber. It is then allowed to move undisturbed up to the desired height and then gently removed and allowed to dry. It was then visualize under a UV-light having a wavelength of 254nm and the spots were marked with a pencil. The retention factor values (R_F values) were then calculated.

2.5 Melting Point Determination

This process was conducted using Mettler Toledo (FP90 central processor) melting point apparatus to determine the melting points of the compounds synthesized.

2.6 Spectroscopy
2.6.1 Fourier Transform infra-Red (FT-IR) (IR υ max)

The FT-IR spectra of the product was recorded on Agilent carry 630 spectrometer at Ankara University, Central Instrumental Analysis Laboratory, Faculty of Pharmacy

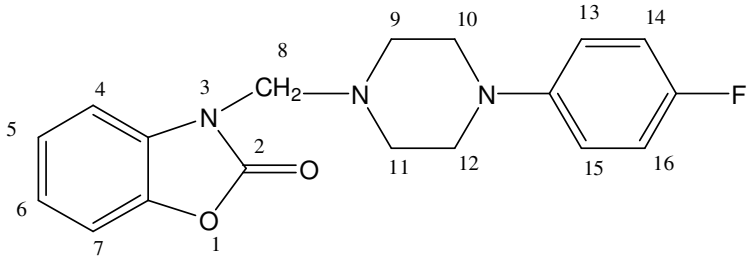
2.6.2 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

The ^{1}H-NMR spectra of the product was recorded on a Mercury Varian 400 MHz Spectrometer where deuterated solvent of dimethyl sulfoxide (DMSO) was used. The test was conducted at Ankara University, Central Instrumental Analysis Laboratory, Faculty of Pharmacy. Chemical shift (**δ**) values were reported in parts per million (ppm).

3. Results

Compound 1

1-(4-fluorophenylpiperazin-1-yl) methyl-2 (3H)-benzoxazolone



The above compound was synthesized by reflux method, mentioned in the experimental section using the procedure from the literature [5].

Reflux

- Brown crystalline solid was obtained
- Melting point: 147°C.

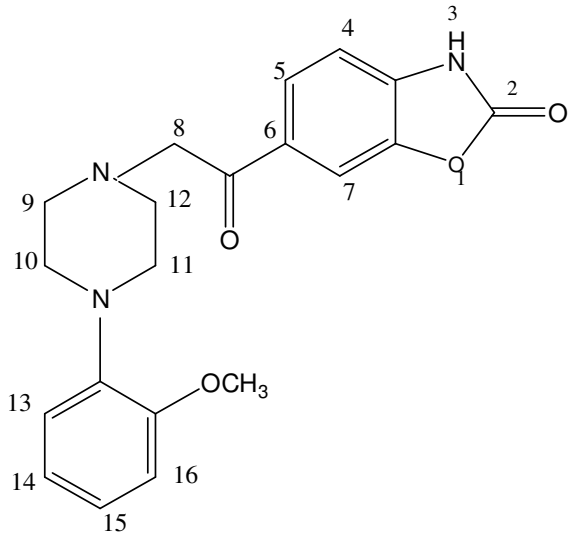
Thin layer chromatography:
The TLC in A1 and A2 mobile phases gave a retention factor values (R_f values) of 0.48 and 0.55 respectively.

Fourier Transforms Infrared (FT-IR) spectroscopy (IR υ max)
FT-IR showed absorption band at 2823-2956 cm^{-1} for aromatic and aliphatic (C-H) stretches and 1753cm^{-1} carbonyl group (C=O stretch).

Proton Nuclear Magnetic Resonance spectroscopy (^{1}H-NMR in DMSO-d6)
^{1}H-NMR showed chemical shift at 7.2-6.8 (8H, m; Ar-H), 4.7 (2H, s; CH_2), 2.8-3.2 (8H, t; pip H^9-H^{12}) ppm.

Compound 2

6-{2-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-acetyl}-2-(3H)-benzoxazolone



Reaction at Room Temperature (Modification of 6th position)

- Pale yellow solid was formed
- Melting point: 200.4 ̊C.

Thin layer chromatography:
The TLC in A1 and A2 mobile phases gave a retention factor values (R_f values) of 0.22 and 0.29 respectively.

Fourier Transforms Infrared (FT-IR) Spectroscopy (IR υ max)
FT-IR showed a single stretch at 3352 indicating the presence of an amine (N-H), an absorption band at 2827-2988 for aromatic and aliphatic (C-H) stretch and 1777cm-^{1} carbonyl group (C=O stretch).

Proton Nuclear Magnetic Resonance spectroscopy (^{1}H-NMR in DMSO-d6)
^{1}H-NMR showed chemical shift at 12 (1H, s; N-H), 6.8-8.0 (7H, m; Ar-H), 4.8 (2H, s; CH_2), 3.8 (3H, s; OCH_3), 2.5-3.2 (8H, t; pip H^9-H^{12}) ppm.

3.1 Discussion

In this research two compounds were synthesized following procedures from literature [5] based on 2-(3H)-benzoxazolone and 2-bromoacyl-2-(3H)-benzoxazolone. The **compound 1** was synthesized involving the modification of the 3rd position through employing Mannich reaction method. On the other hand, **Compound 2** was made by a reaction at room temperature which involves the modification of the 6th-position of 2-bromoacyl-2-(3H)-benzoxazolone. These reactions were conducted to check the reactivity of 2-(3H)-benzoxazolone at different positions

(3rd and 6th-positions) as stated in the literature. 4-Flourophenylpiperazine was studied for molecule with substitution at 3rd position of 2-(3H)-benzoxazolone via Mannich reaction to produce the target compound.

The synthesized compounds were characterized using Fourier Transform Infra-Red (FT-IR) and Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H-NMR).

In **compound 2,** 2-metoxyphenylpiperazine was attached to the 6th position of 2-bromoacyl-2-(3H)-benzoxazolone at room temperature to give the target compound.

The core structure of the two compounds are the same. They only differs in the amine moiety attached on the 3rd and 6th positions respectively.

Compound 1 has 4-fluorophenylpiperazine attached to the 3rd position of 2-(3H)-benzoxazolone while **compound 2** has 2-metoxyphenylpiperazine attached on the 6th position of 2-bromoacyl-2-(3H)-benzoxazolone. Fig. 4.3 and 4.4, give the general synthesis in this research.

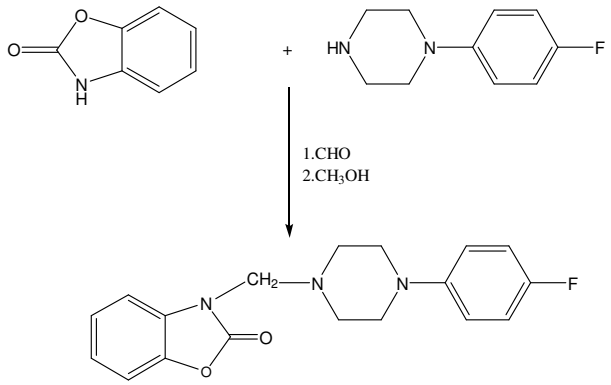


Fig. 4. Synthesis of compound 1 via Mannich reaction

The general mechanism of this reaction involves two major steps; formation of iminium ion and attacking of iminium ion by the substrate (2(3H)-Benzoxazolone nucleus) as a nucleophile.

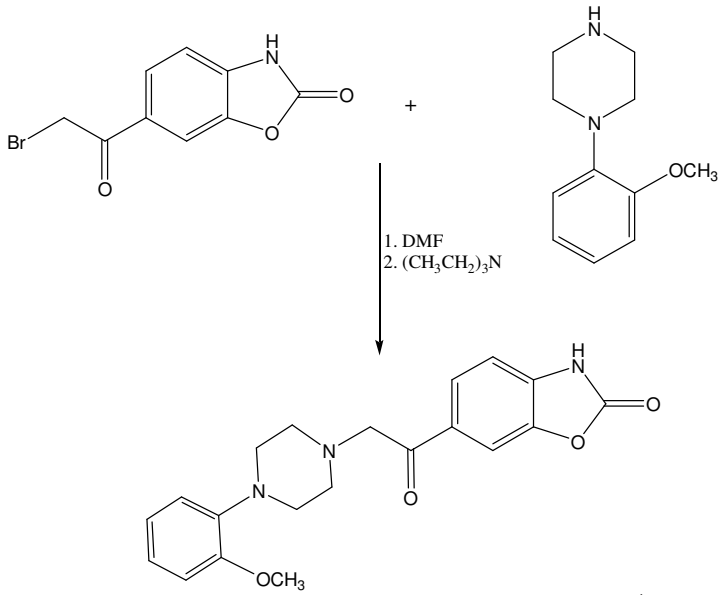
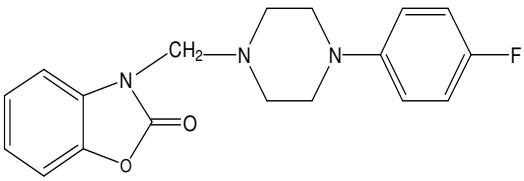
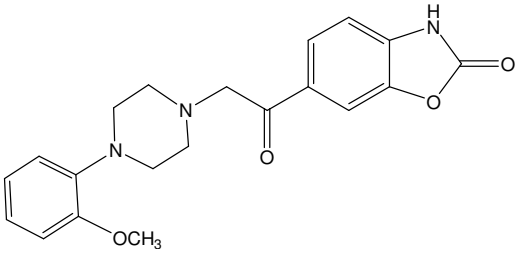


Fig. 5. Synthesis of compound 2 through modification of 6th position

The chemical structure of the compounds synthesized and their starting materials, methods of preparation, R_f values and melting points are shown in the table 4.1 below.

Table 1
Comparison of the R_f values and melting points of the starting materials and the compounds synthesized

Method	Chemical structure	Melting point (^{0}C)	R_f values
Reflux (Modification at 3rd-position)	 Compound 1	147	A1=0.48 A2=0.55
Reaction at room temp. (Modification at 6th-position)	 Compound 2	200.4	A1=0.22 A2=0.29

Compound 1 and 2 were characterized using Fourier Transform Infra-Red (FT-IR) and Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H-NMR). The FT-IR of **compound 1** shows absence of N-H stretch which has been reported to be around 3146 cm^{-1} this shows the reaction has taken place at the 3rd position of 2(3H)-benzoxazolone as expected. The C=O stretch appears at 1754 and C-H stretches are seen at around 2958-2824 cm^{-1} as expected. The FT-IR spectrum of compound 1 synthesized is shown in fig. 6 below.

^{1}H-NMR spectra of **compound 1** in DMSO-*d6* shows peaks at the expected chemical shifts values, which is relative to the starting material (2-(3H)-benzoxazolone), there is additional CH_2 (methylene) peak as a singlet observed at 4.7 ppm of the compound. This shows that the reaction has taken place at the N-atom in the 3rd position and the piperazine derivative is bounded to 2 (3H)-benzoxazolone through the CH_2 bridge. Further analysis of the ^{1}H-NMR spectra reveals the presence of aromatic

peaks as multiplets between 6.8-7.3ppm as expected. The piperazine protons (H^9-H^{12}) were seen as triplets at 2.8-3.2 ppm for **compound 1.**

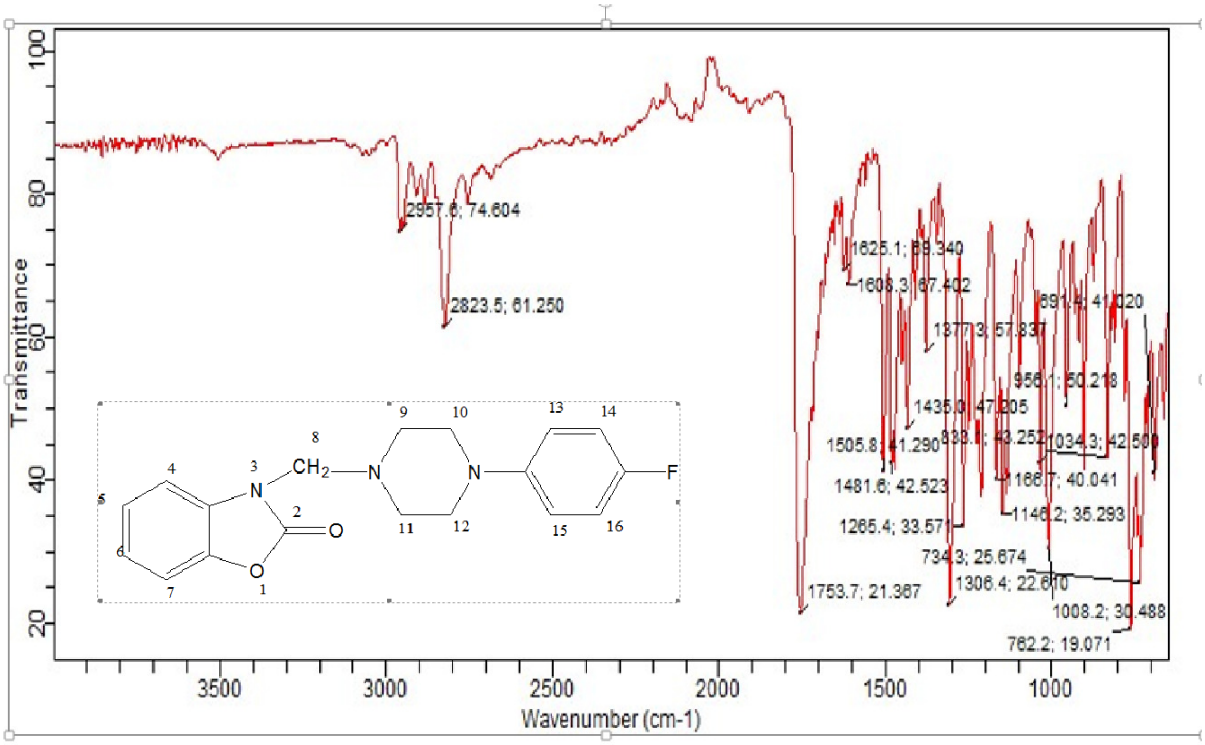


Fig. 6. FT-IR spectrum of 1-(4-fluorophenylpiperazin-yl) methyl-2(3H)-benzoxazolone

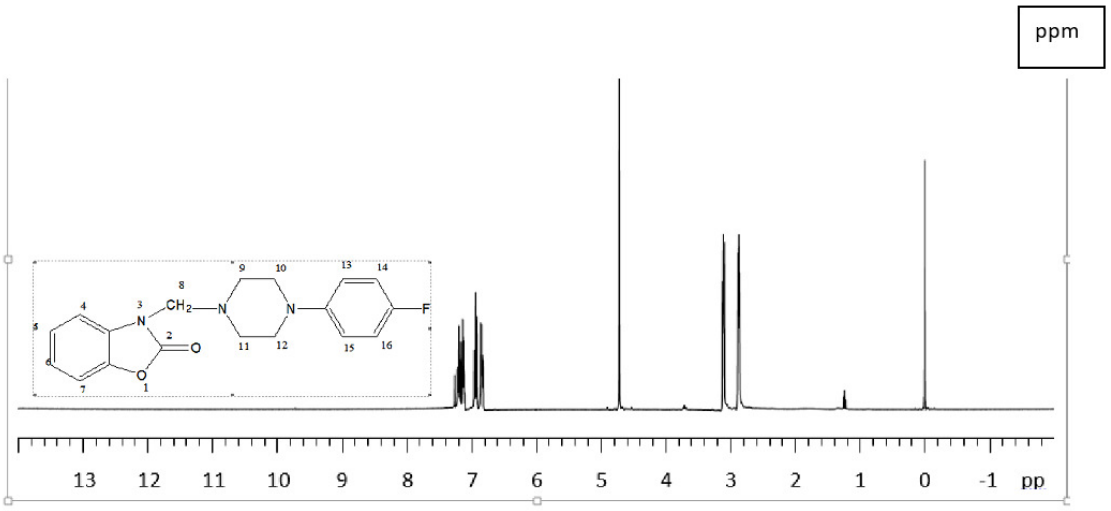


Fig. 7. ^{1}H-NMR spectrum of 1-(4-fluorophenylpiperazin-yl) methyl-2(3H)-benzoxazolone

The FT-IR of **compound 2** shows presence of N-H stretch at 3351.9 cm^{-1} as expected. The C=O stretch also appears at 1777.67 cm^{-1} and C-H stretch are seen at around 2988-2827 as expected. Presence of N-H indicates the reaction did not take place at the 3rd position.The FT-IR spectra of **compound 2** synthesized is shown in fig. 3.5 below.

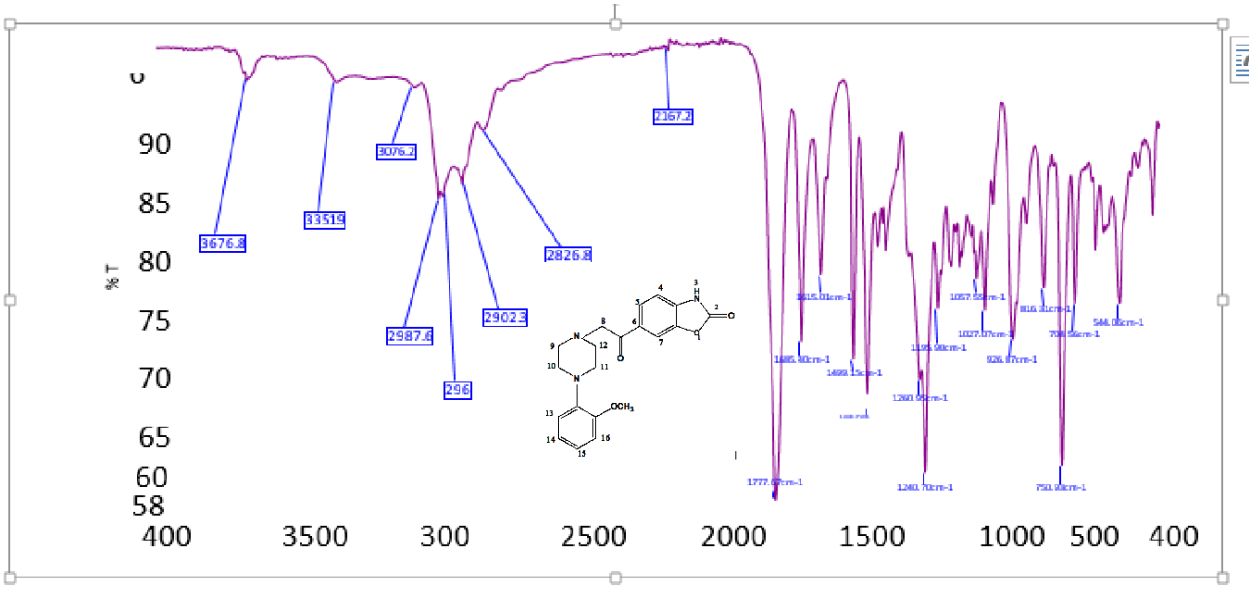


Fig. 8. FT-IR spectrum of 6-{2-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-acetyl}-2-(3H)-benzoxazolone

^{1}H-NMR spectra of **compound 2** in DMSO-*d6* shows peaks at the expected chemical shifts values, which is relative to the starting material 6-(2-bromo-acetyl)-2-(3H)-benzoxazolone, there is additional piperazine protons (H^{8}-H^{11}) peaks as triplets observed at 2.5-3.2. Further analysis of the ^{1}H-NMR spectra reveals the presence of CH_2 (methylene) peak as a singlet at 3.8 ppm, aromatic peaks as multiplets between 6.8-8.0 ppm as expected and O-CH_3 (methoxy) peak as singlet at around 3.7 ppm also as expected. Presence of N-H peak as singlet at 12ppm This shows that the reaction has taken place at the 6th position of and the piperazine derivative is bounded to 6-(2-bromo-acetyl) 2-(3H)-benzoxazolone.

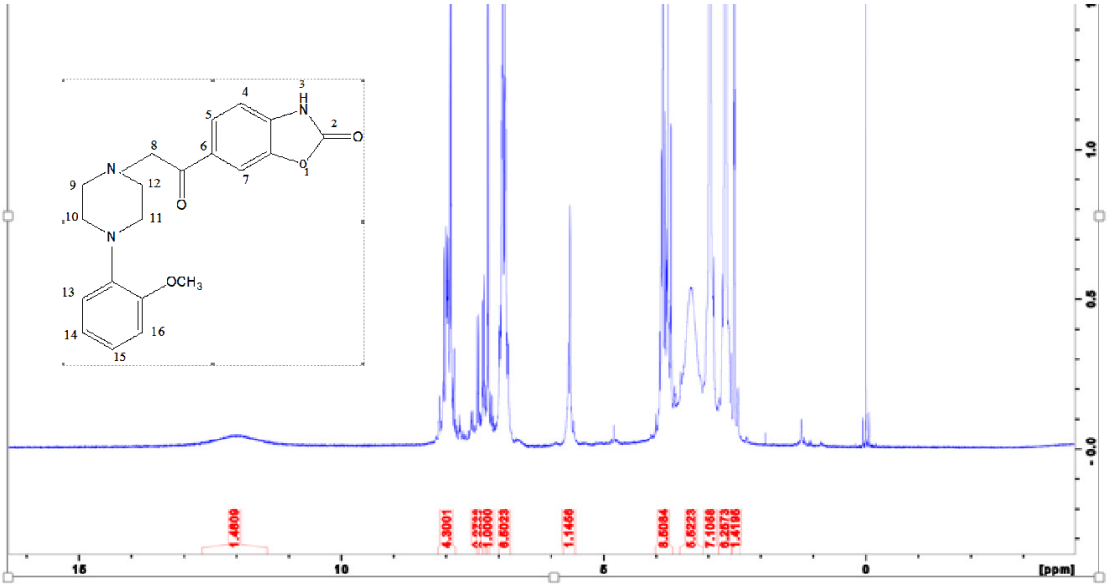


Fig. 9. ^{1}H-NMR spectrum of 6-{2-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-acetyl}-2-(3H)-benzoxazolone

4. Conclusions

This research studies the modification of 2-(3H)-benzoxazolone since it's possible to do substitution at different positions. It involves the modification of the 3rd position 2-(3H)-benzoxazolone via Mannich reaction and also modification of the 6th position of 6-(2-bromo-acetyl) 2-(3H) benzoxazolone using reaction at room temperature with different piperazine substituents. Biological activity of the synthesized compounds were not conducted due to time constrains, though based on the literature the two compounds might have some biological activities. Since, it's possible to do substitution at different positions of the starting material, by using different amine groups to do substitution at the 3rd and 6th positions which can change the biological activities of these types of compounds. Moreover, **compound 1 and 2** could be studied for COX-2 selectivity inhibition.

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