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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.

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LIST OF ABBREVIATIONS

NSAIDs Non-steroidal Anti-inflammatory Drugs

PPA Polyphosphoric acid

DMF Dimethylformamide

COX Cyclooxygenase

FT-IR Fourier Transform Infrared

NMR Nuclear Magnetic Resonance

UV-Vis Ultraviolet-visible

TLC Thin Layer Chromatography

DMSO Dimethyl Sulfoxide

1INTRODUCTION

2-Benzoxazolinone derivatives are molecules which are very important and relevant interms of their biological activities. They play a vital role pharmacologically as they serve as an anti-inflammatory, anti-analgesic,hypnotic,and anti-pyretic agents(1-5).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).

2(3H)-Benzoxazolone having halogenated substituents have been reported to have various biological activities such as anticonvulsant, antioxidant and antimicrobial activities. 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 (6-7).

The main purpose of this research is to synthesize some 2-(3H)Benzoxazolone derivatives that had been modified at position 3^{rd} and 6^{th} position in effort to prepare COX-2 selective inhibitors with less side effects.. The compound is 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 LITERATURE REVIEW

2.1. Analgesics

Pain is an unpleasant and unwanted sensation feel in the body due to some weakness in our immune system.Pain can be terminated or reduce with some groups or members of drugs called analgesics.

Analgesics are members or group of drugs that relieve someone from pains due to injury or sickness,they act in various ways in our body in the central nervous and peripheral nerves.The central nervous system (CNS) analgesics cast their effects on the brain and spinal cord example morphine and also theperipheral nervous system(PNS) analgesics act outside the brain and spinal cord exampleNSAIDS (8-9).Analgesic can be categorized into various classes base on their similarity in termsof theirmechanism of action,example; non-steroidal anti-inflammatory drugs and narcotics (opioids), Also analgesic can be classified base on the nature of the pain that is from mild to moderate to severity of the pain example, on-steroidal anti-inflammatory drugs (NSAIDS) andacetaminophen are used for mild to moderate pains, while weak opioids such as codeine are used for moderate to severe pains.

2.1.1 Opioid (Narcotic) Analgesics

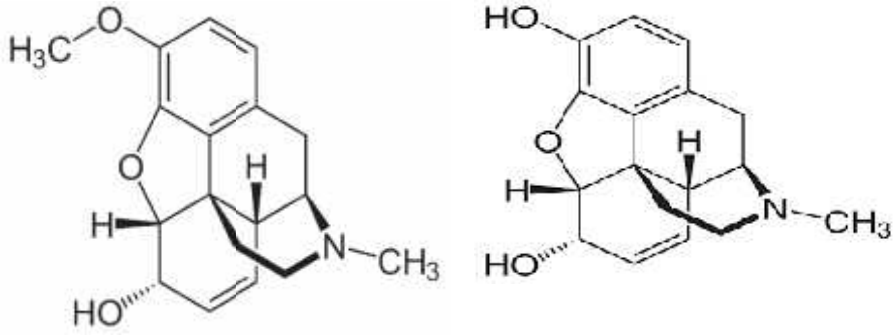
Opioids are derived from opus a greek word which mean Juice' it is obtain from unripe side capsule of poppy plant.This are analgesics that is pain reliever that act on the nervous system by binding to its receptor in brain,spinal cord and other part of the body like the gastrointestinal track to mediate both psychotropic and somatic effects of opioids.Opioidscan be obtain naturally and synthetically base on their nature of production they can be classified into 3 categories:

1. Natural occurring opioid; (found in plants)example morphine and codeine
2. Semisynthetic opioids example;Hydrocodone,buprenorphine, and oxycodone.
3. Synthetic opioids example;Tramadol,Fentanyl,and meperidine.

Some opioids binds to its receptors(mu, kappa, delta, and sigma)activates it and produce a biological responds by reducing the pain, in other words they act as agonist example

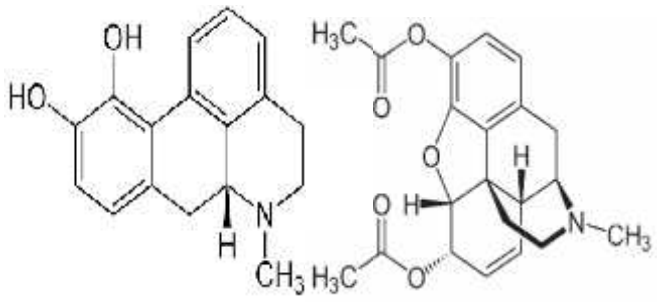
morphine and some gives opposite effect that is blocking the response and also at the same time can provide positive response. Opioids as pain relievers also have some effects when overdosed as they can cause serious effect to the body such as addiction, respiratory depression,seizure, and even death(10)

Figure 2.1 Image of Opium poppy flower and fruit



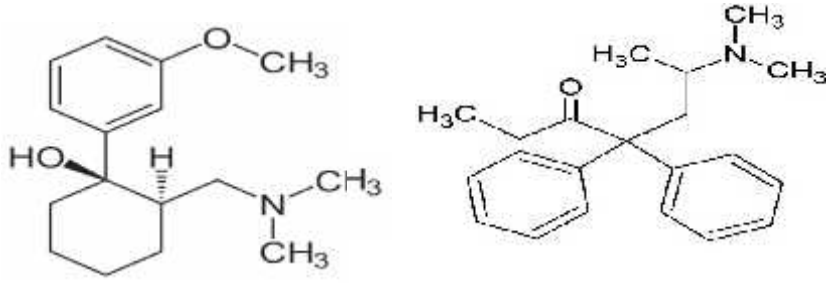
Codeine Morphine

Figure 2.2 Chemical structures of Opioids



Apo morphine Heroin

Figure 2.3 Chemical structures of semi synthetic opioids.



Tramadole Methadone

Figure 2.4 Chemical structures of synthetic derivative opium alkaloid.

2.1.2 Morphine

Pure morphine was first obtained from dried poppy resin in early 1800s by a german scientist called Friedrich W. Serturner. The compound was named "Morphium" which was named after the Greek god of dreams (11). Morphine is a strong analgesic use in the reduction or termination of moderate to severe pains,it manifest its effect on CNS and also smooth muscle. Apart from been a pain reliever,morphine cause effect on the body upon use for long time as it might cause addiction, overdoseslow down breathing and even cause death.Morphine works by binding to and activating a specific receptor involving in controlling of brain functions.The ability of Morphine to reduce pain is enhanced via G-protein coupled with GCPR (heptahelical receptor).

The metabolites of Morphine has the ability to interact with neurons thereby helps in changing neuronal communication, which in turn affect the consciousness, sensation and perception of an individual (12).

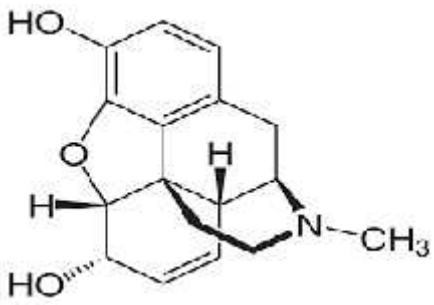


Figure 2.5: Chemical structure of Morphine

2.1.3 Codeine

Codeine is also found in poppy plant but only in minute amounts, Due to its low concentration it is typicallyobtained from codeine. Most of the morphine extracted from opium is normally converted to codeine. Codeine also is used as an analgesics to reduce, eliminate or cure pain in patients. Through metabolism codeine is converted to morphine (13-14)

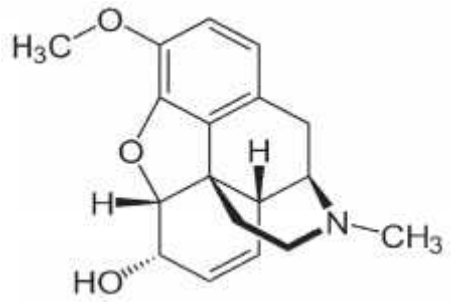


Figure 2.6 Chemical structure of Codeine

2.1.4 Synthetic derivatives of Morphine

Generally there are two compounds that resemble morphine. These compounds have almost the same characteristics with morphine. One of these compounds is methadone (6-(dimethyl amino)-4, 4-diphenyl-3-heptanone) it's a synthetic opioid which is more toxic as well more active than morphine. It has analgesic property, it is used in reducing many kinds of pain. It is also used in place of morphine especially to prevent addiction due to the fact it prevents Morphine abstinence syndrome (15). The structure of methadone is given below.

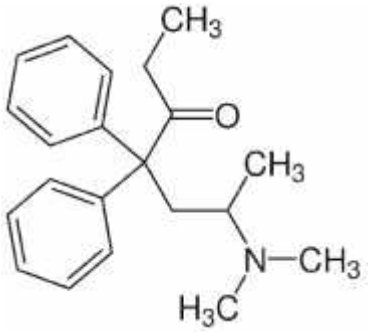


Figure 2.7 Chemical structure of 6-dimethylamino-4, 4-diphenyl -3 heptanone (Methadone).

On the other hand we have Meperidine (1-methyl-4-phenyl-ethyl ester). This is the common derivative of Morphine. The synthetic opioid drug was first synthesized since 1932 by a chemists known as Otto Eishib, it also have many pharmacological activities such as local anesthetic property, mild antihistamine as well as analgesic properties (16). The structure of Meperidine is given below.

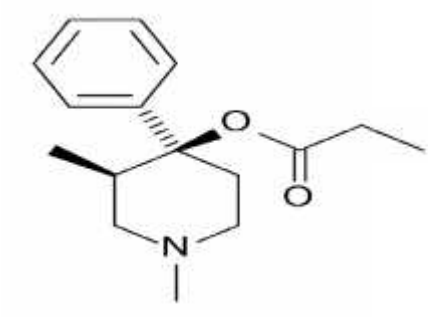


Figure 2.8 Chemical structure of meperidine

2.1.5 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

These drugs are also known as Non-narcotic analgesics and Anti-inflammatory Drugs. This NSAIDs group of drugs includes salicylates and the aspirin. The primary site of action of this drugs is the cyclooxygenase (COX) enzyme, which acts as a catalyst in the conversion of prostaglandin and endoperoxides from arachidionic acid. Non-steroidal anti-inflammatory

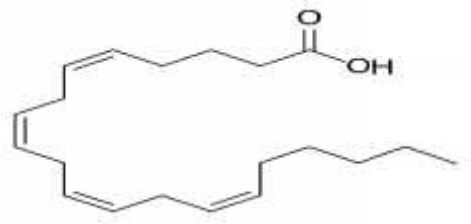
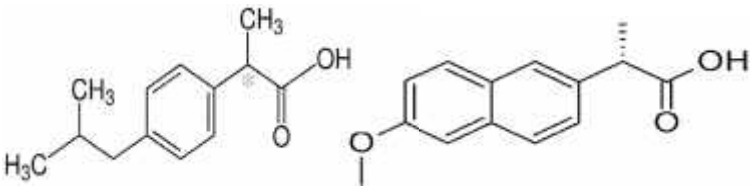


Figure 2.9 Chemical structure of arachidionic acid.

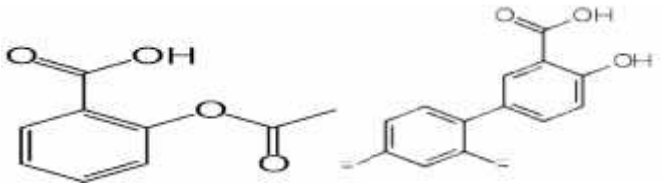
Almost all the NSAIDs including the aspirin have antithrombotic effects, antipyretic effects, analgesic and anti-inflammatory effect. Examples of NSAIDs are ketorolac, ibuprofen, indomethacin, naproxen, mefenamic acid, meloxicam and tolmetin.NSAIDs base on chemical structures can be classified into some classes as follows(17).

1. Propionic acid example ibuorofen and naproxen.
2. Salicylic acid and esters example aspirn and diflnisal.
3. Carbo and Heterocyclic acid example ketorolac and indometacin.
4. Phenylacetic acid example dichlofenac and cateflam.
5. Enoloic acid example meloxicam and piroxicam.
6. Non-acidic acid example nabumetone.



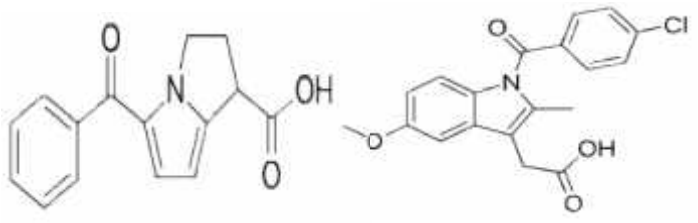
(a) (b)

Propionic acid NSAIDs (a) ibuprofen and (b) naproxen



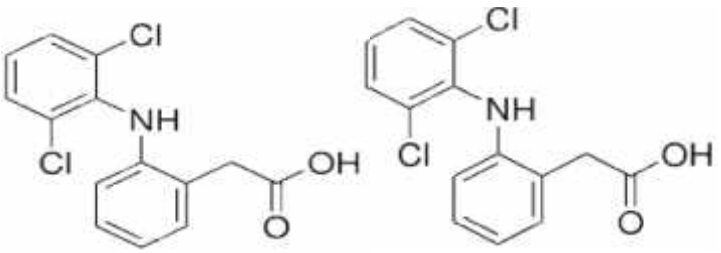
aspirin diflunisal

Structures of salicylic acid NSAIDs.



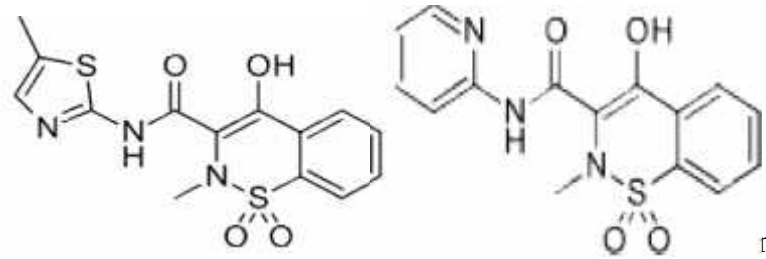
ketorolac indomethacin

Structures of heterocyclic NSAIDs.



dichlofenac meclofenamic acid

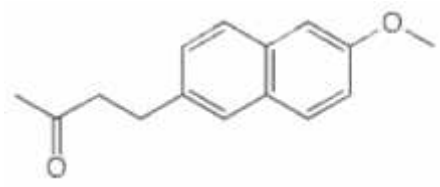
Structures of Phenylacetic acid NSAIDs.



meloxicam

piroxicam

Structures of enoloic acid NSAIDS



Structure of non-acidic NSAIDs nabumetone

Figure 2.10 Chemical structures of some classes of NSAIDs are shown above

2.1.6 Mechanism of Action of NSAIDs

Non-steroidal-inflammatory drugs are drugs that inhibit the cyclooxygenase enzymes COX-1 and COX-2 enzymes which are responsible for catalytic convertion of arachnoids to prostaglandins. COX-1 enzymes produce prostaglandins which found in the body in all tissues and cell, it provides protection to gastrointestinal tracts, blood clots. COX-2 isoenzymes plays a role in pains,inflammation and fever.NSAIDs have a great effect when it inhibit COX-1 leading to complications like ulcer, bleeding and cardiovascular effect (18-19).Depending on the selectivity of the isoenzymes,NSAIDs are categorized into 2 types.

a) Non-selective NSAIDs; This drugs inhibits both COX-1 and COX-2 (dichlofenac and indomethacin) which cause effect in the body.

b) COX-2 selective drugs: Inhibits COX-2 enzymes causing better effects in gastric mucosa and blood clots examples of some of COX-2 selective drugs are Celecoxin and bextra (valdecoxib)

2.1.7 Cyclo-oxygenase-1 (COX-1) Enzyme

This is one of the two isoforms of the cox enzymes that have been identified. Cox-1 enzyme is normally expressed constitutively in many tissues (peripheral nervous system), it produces prostaglandins that protect the gastric mucosa, vasoconstriction of the blood vessels and also enhances blood clotting (20-21). When this enzymes are reduced by non-steroidal anti-inflammatory drugs it leads to ulcers in stomach, bleeding, abdominal pain and also heartburn mayoccur. Therefore selective inhibition of the enzymes by some selective non-steroidal is enhance to avoid the inhibition of COX 1 enzymes.Drugs like aspirin, indomethacin,and piroxicam are selective inhibitors of this enzyme (COX-1),some are slightly selective such as ibuprofen, naproxen and also etodolac.

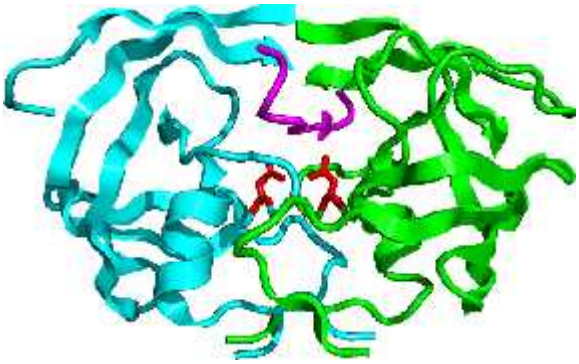


Figure 2.11 Structure of cyclo-oxygenase-1 (COX-1) Enzyme

2.1.8 Cyclo-oxygenase-2 (COX-2) Enzyme

This is the other isoform of the COX enzyme which also produce prostaglandins that promotes pain,fever and also inflammation.They are induce by pro-inflammatory

cytokines,they are different types of drugs use to inhibit COX-2 enzyme known as COX-2 selective drugs.According to some studies COX-2 enzymes also plays a role in angiogenesis.Below is a chart showing the activity of the isoenzymes in Figure 2.24.

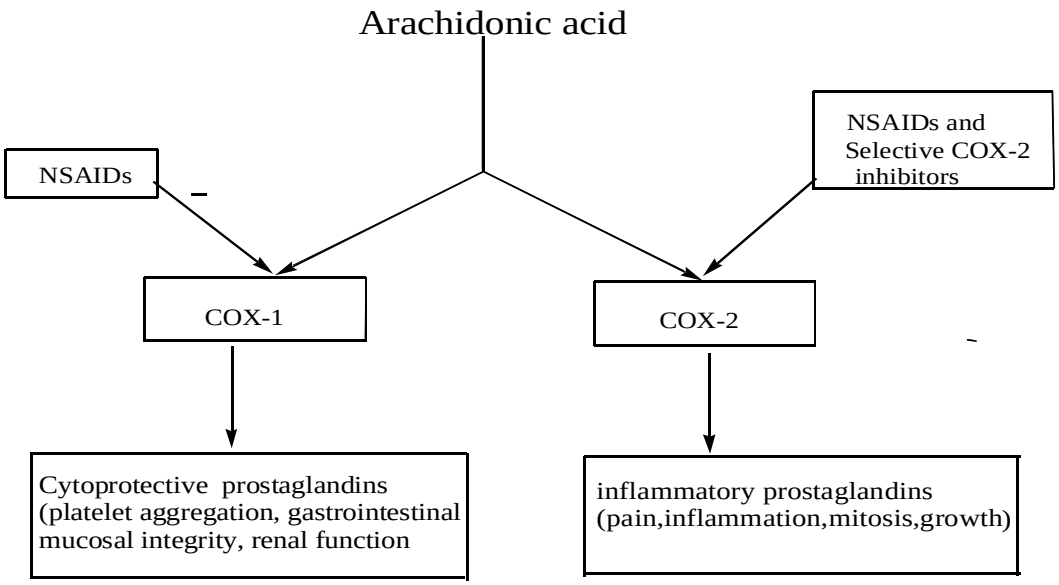


Figure 2.12 Flow chart of arachidionic acid showing both COX-1 and COX -2 enzymes

2.2. Chemistry of Benzoxazolone

This is a heterocyclic bicyclic aromatic ring that composed of a carbamate in conjugation with a benzene ring. It has both hydrophilic as well as lipophilic properties. It has a dipole moment of about 4.47 debye which is one of the reason of its hydrophilic properties. It also have a pka value of 8.7 and it is considered as a slightly weak acid in aqueous solution. 2 (3H)-Benzoxazolone is a compound of biological as well as pharmacological interests because it has been reported to have many pharmacological activities such as antifungal, antibacterial, anticancer, anti-HIV, analgesics and anti-inflammatory effects (22-23).

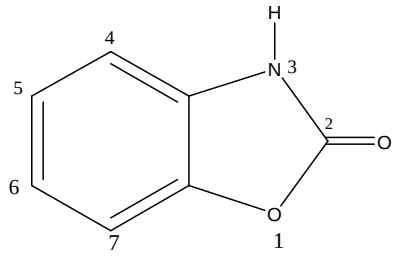


Figure 2.13 Chemical structure of Benzoxazolone

2.2.1 Synthesis of 2(3H) Benzoxazolone;

2(3H) benzoxazolone have various ways of synthesis it can be synthesis by reaction of salicylic acid,ammoniaazide and vilsmeier complex. (24)

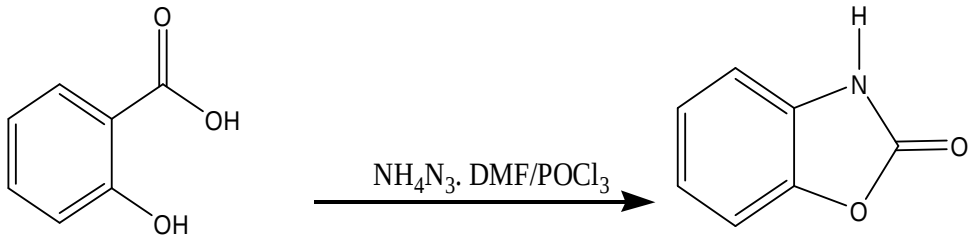


Figure2.14 Synthesis of 2(3H) benzoxazolone from salicylic acid

Derivatives of 2(3H) benzoxazolone as 5-chloro2 (3H) benzoxazolone can be obtain by reaction of 2-Amino-4-Chlorophenol hydrochloride and urea in the presence of 60%sulfuric acid (25)

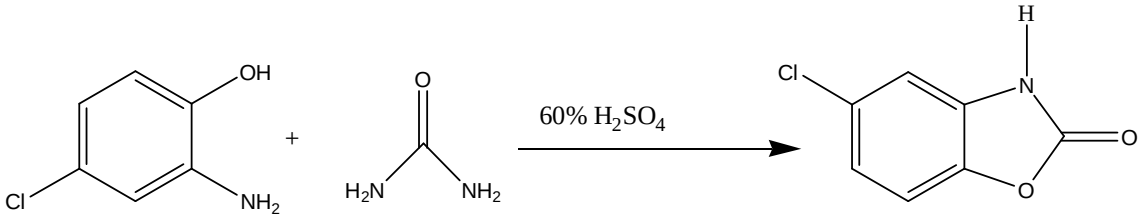


Figure2.15 Synthesis of 5-Chloro-2(3H) benzoxazolone

2(3H) benzoxazolone can also be obtain from synthesizing of 2-aminophenol and carbonyldiimidazole in dry tetrahydrofuran using reflux

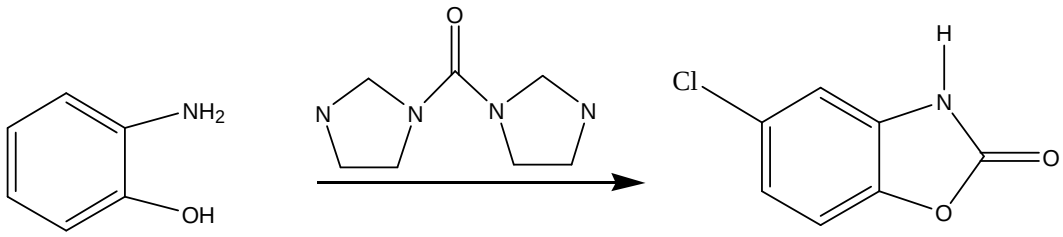


Figure2.16 Synthesis of 2(3H) benzoxazolonefrom 2-Aminophenol.

2.2.2 Chemical Reactivity of Benzoxazolone

2- (3H)-benzoxazolone has the ability to undergo mainly three kinds of chemical reactions which includes:-

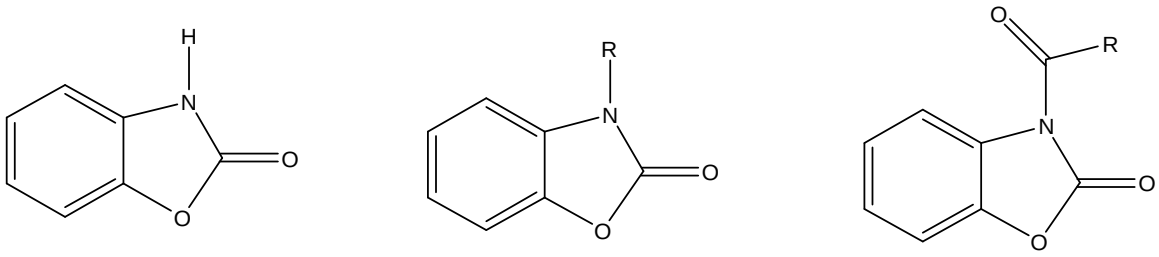
1) N-Substitution

2) Electrophilic aromatic substitution.

3) Ring opening and expansion.

2.2.3N-Substitution

This N-substitution occurs at position 3 where the amide permit vital transformation due to its ability to be converted into enol or enolate.The alkylation reaction is conducted under basic-catalyze condition whereas the acylation is conducted under acidic –base catalyze condition. Alkylation of2(3H) benzoxazolone under base-catalyzed condition generate (b), and under acid-base catalysis generates(c) which is the N-acylation. (26)



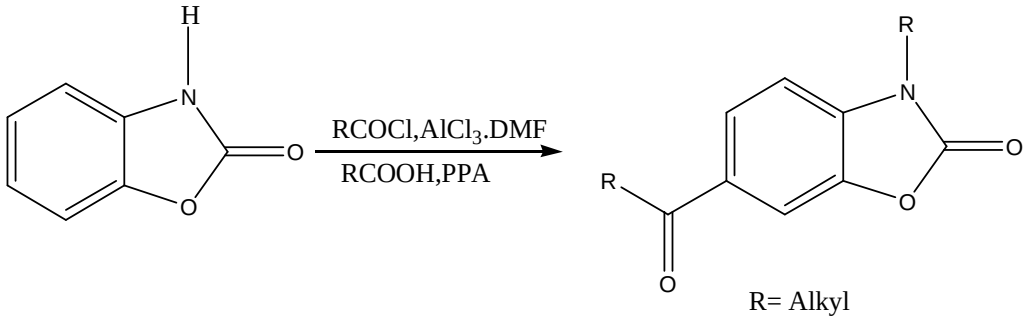
(**a**) (b) (c)

Fig 2.17 showing (b)alkylated benzoxazolone and (c) acylated benzoxazolone

2.2.4Electrophilic Aromatic Substitution

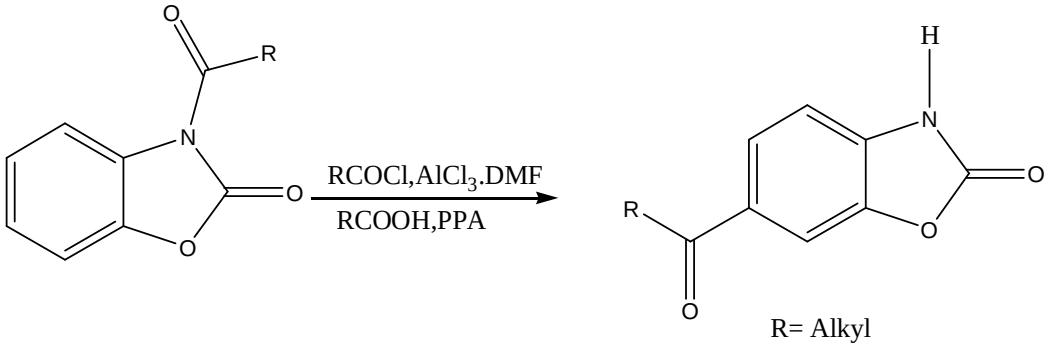
The electrophilic aromatic substitution reaction occurs mostly at 6 position in which reactions sulfonation, halogenation,nitration,and chloro-sulfonation can be observed. This process is not only for the above mentioned reactions which are easy and straight forward ,Aromatic electrophilic substitution also can be done on more difficult Friedel Craft reactions(27).Because of the electron-rich nature of 2(3H) benzoxazolone,it is further protonated by Lewis acid present in the reaction media,which serves as electrophilic attack of acylium ion.To tackle this problem, the reaction can be done using a less reactive electrophilic species as (PPA) or by using $AlCl_3$.DMF complex to give the 6-acyl derivatives.

(A)



R= Alkyl

(B)

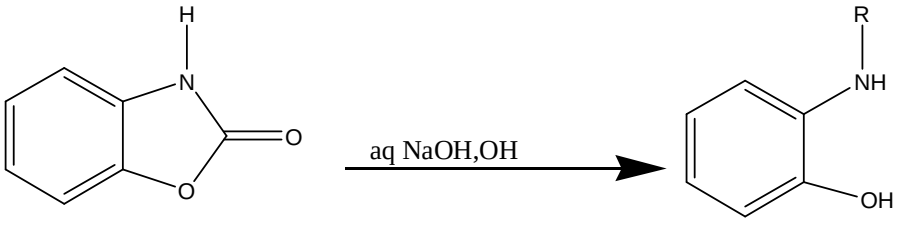


R= Alkyl

2.2.5Ring Expansion and Opening

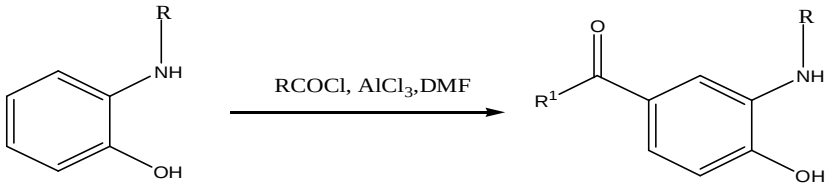
This is a series of opening and closing of the ring process firstly 2(3H)benzoxazolone is hydrolyze in basic media fastly due to it fairly or poorly stability in acidic media(28) The steps are as follows.

Step1;2(3H) benzoxazolone is hydrolyzed in the basic media leading to opening of the ring forming 2-Amino Phenol.

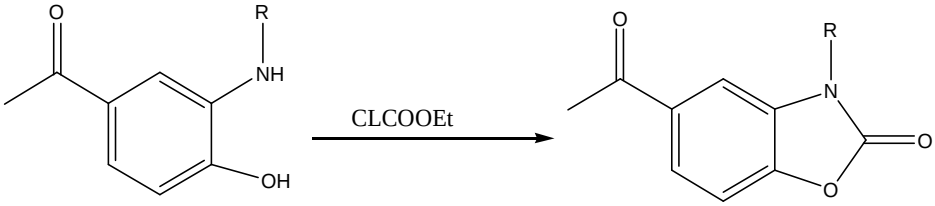


2(3H)Benzoxazolone 2-AminoPhenol

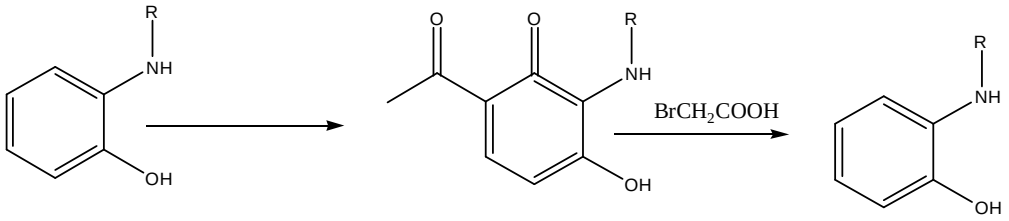
Step 2 The 2-Amino Phenol undergoes acylation at the 4 position to form 4-acetobenzoxazolone derivatives.



Step 3 So also the closure of 4-Acyl benzoxazolone derivatives leads to the formation of 5-Acyl-2(3H) benzoxazolone derivatives.



Step 4; Ring expansion can also be done at the acylated 4-position of 2(3H)benzoxazolone derivative forming a ketone derivative of benzoxazinoneand also some path can be obtain from 2-amino phenol.



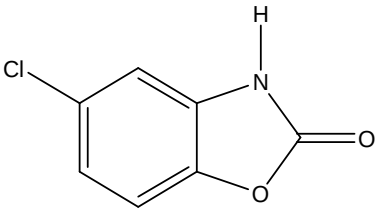
2.2.6 Therapeutic Application of 2(3H) Benzoxazolone

2-(3H) benzoxazolone is found widely distributed in natural plants and is of great interest for various pharmacological activities such as anti-inflammatory, analgesics, anti-HIV, anti-detoxification(29,30 31). Benzoxazolone and its bioisoteres have been of great interest in medicinal chemistry due to its capacity to behave like a phenol or catechol moiety in a

metabolically stable template and assumed as a structure when incorporated in a pharmacological probes (32).

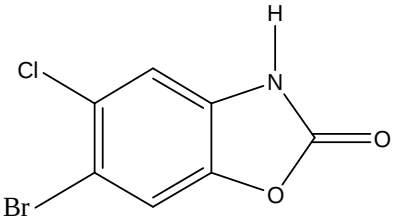
As stated earlier in the literature on the importance of benzoxazolone in analgesic activity made by modification at position 3, 5, and 6 was conducted in order to screen their antinociceptive properties.

5-chloro-3H-benzooxazole(Paraflex): This is a benzoxazolone derivative which is a central muscle relactant with sedative properties(33) .



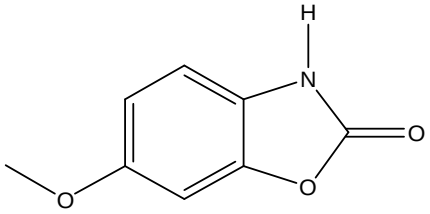
5-chloro-3H-benzooxazole

6-Bromo-5-chloro-3H-benzooxazole-2-one(vinizine) :2(3H)-benzoxazolonederivative use for repallant and prevention of germs, bacteria, parasite, and other diseases .



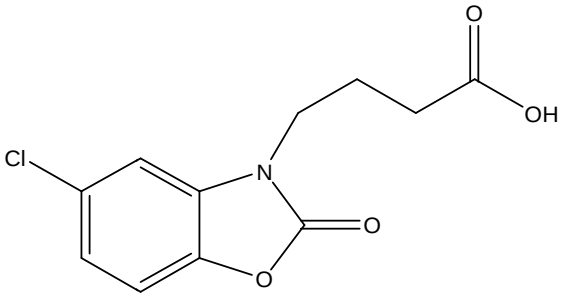
6-Bromo-5-chloro-3H-benzooxazole-2-one

6-methoxy benzoxazolone : A benzoxazolonederivztive possessing anti-fungal, anti-microbial, and also insecticide properties.



6-methoxy benzoxazolone

4-(5-Chloro-2-oxo-1,3-benzooxazole -3(2H)-yl) butanoic acid: It ethyl ester and amide are found as most potent antinoceptive and anti-inflammatory agent(34).

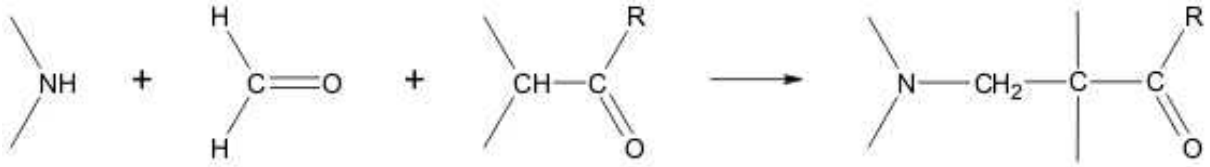


4-(5-Chloro-2-oxo-1,3-benzooxazole-3(2H)-yl)butanoic acid

Figure 2.18 Some examples of therapeutic active benzoxazolone

2.3 Mannich Reaction

Mannich reaction is a kind of reaction which involve the condensation of ammonia or primary/secondary amine with a formaldehyde and a hydrogen atom of pronounced activity(35).In other words it involve the condensation of three compounds an aldehyde,amino methylation from an amine and another compound with an acidic methylene moiety (36).This type of reaction is used in the synthesis of organic chemical as well as many range of pharmaceutical precursors(37).

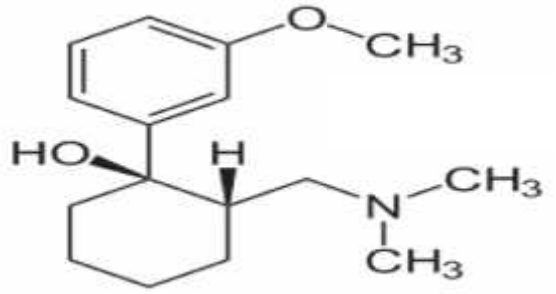


Amine formalin ketone Amino alkyl derivatives, R=phenyl, H, alkylgrp

Figure 2.19 Mannich Reaction of Amino-Alkyl derivatives

2.3.1 Applicationof Mannich Reaction

Mannich reaction is one of the reactions that explores new findings especially in organic synthesis,specifically in the production of compounds with biological activities,while sometimes the kind of reaction plays an important role in the modification of an existing bioactive compounds.This mannich reaction is the most important reaction involve in the formation carbon-carbon bond,it can be involve in varieties of functional group especially in the preparation of amino carbonyl and other derivatives .The amino carbonyl is useful in the production of beta-lactam and beta-peptides, ,which are frequently present in varieties of bioactive molecules such as taxol (anti-tumor agent),tramol(analgesic agent),moban(neuroleptic agent),zelpiden(hypnotic agent),and ferroceric aminohydroxy naphthoquinone (anti-microbial agent).



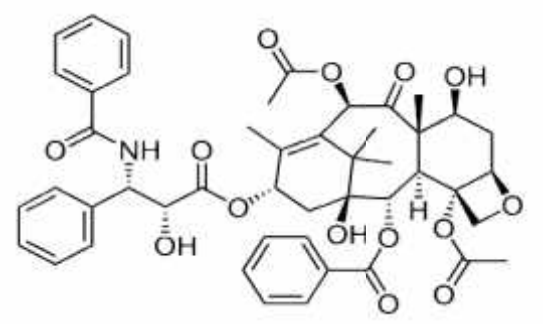
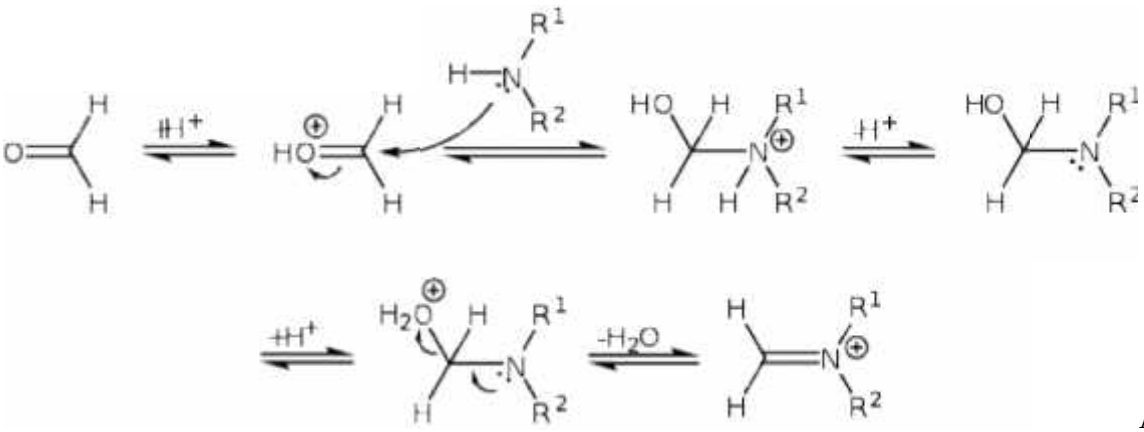


Figure 2.20 Tramol andTazol

First step in mechanism of mannich reaction is the formation of iminium ion obtain from amine and formaldehyde,



Alkyl or Aryl group

The compound with the carbonyl functional group can be tutomerise the enol form, after which it can attack the iminium ion.

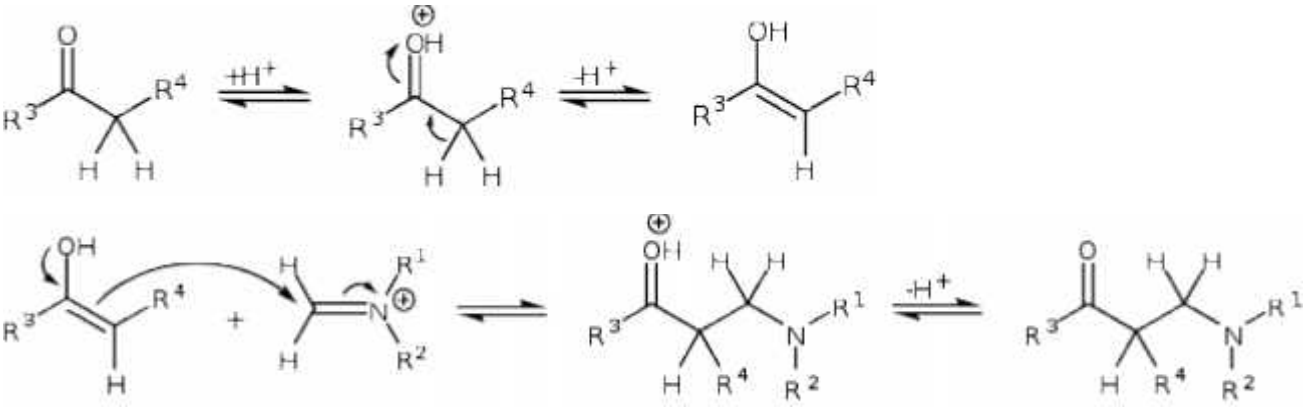


Figure 2.21;Mechanism of mannich reaction

2.3.2 Mannich Base

This is a beta-amino ketone produced in a mannich reaction during the condensation of ammonia or a primary lsecondary amine,formaldehyde (or an aldehyde)with an activated hydrogen in a carbon acid or its derivatives(38).This mannich bases are found to be bioactive molecules

example indolin-2,3-dione which is known as isatin and its derivatives have been investigated to have many biological properties such as anti-fungal,anti-HIV, anti-bacterial properties(39-40).

Thiazole also have been found to have anti-bacterial,anti-HIV,and anti-fungal properties, also isatin-beta-thio-semi-carbazone have anti-microbial properties.

Some derivatives of amino-pyridine-2-carboxaldehyde-thio-semi-carbazone have been reported to posses anti-tumor properties.Just a recent discoveries has shown that mannich bases of chalcones possess cytotoxic activities.

3 MATERIAL AND METHOD

3.1 Materials

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

3.2 Thin Layer Chromatographic Method

3.2.1 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

3.2.2 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 dissolve 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.

3.3 Melting Point

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

3.4 Spectroscopy

3.4.1. 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, Faculty of Pharmacy.

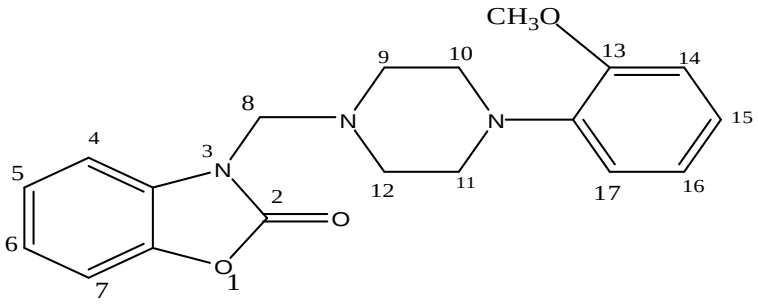
3.4.2. Proton Nuclear Magnetic Resonance (^{1}H-NMR)

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, Centered Instrumental Analysis Laboratory, Faculty of Pharmacy.

3.5 Experimental

3.5.1 Synthesis of compound 1

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

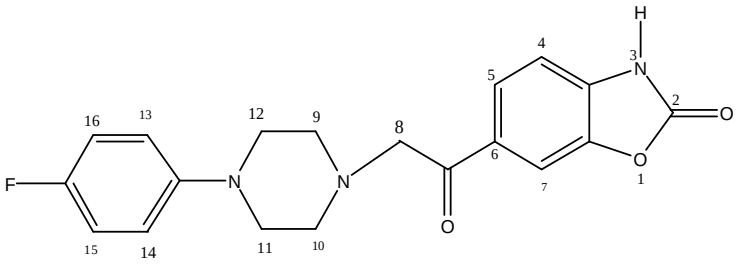


Reflux

200mg(0.001mol) of benzoxazolone and 0.001mol of 2-methoxy phenylpiperazinewere dissolved in 8ml methanol in 50ml round bottom flask. 0.2ml (0.05 mol) 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

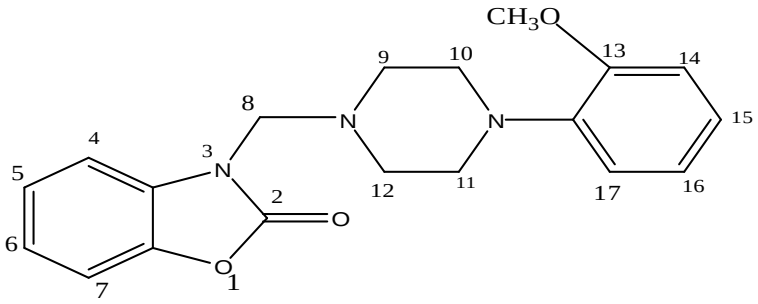
Reaction at room temperature

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

4.0 RESULTS AND DISCUSSION

4.1. Results

Compound 1

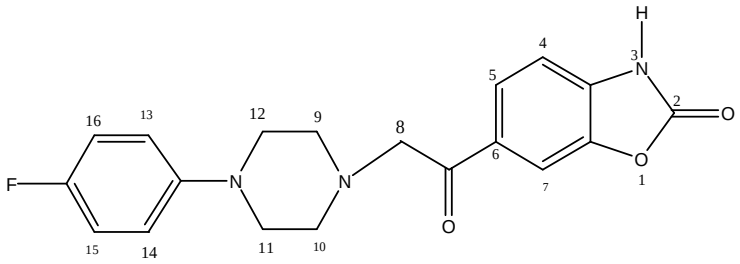


Reflux

- Yellowish crystalline was observe with a melting point of 165.8^0 C
- TLC theH_1 and H_2 mobile phases gave R_f values of 0.42 and 0.59 respectively.
- 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).

- The ^{1}H-NMR spectra shows chemical shift at 6.9-7.2ppm (7H,m, Ar-H), 4.8 ppm (2H, s,H^8), 3.8pm(3H,s,-O-CH_3) , 2.8-3.2ppm(8H,d,protons of pip peaks).

Compound 2



compound 2

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

- TLC theH_1 and H_2 mobile phases gave R_f values of0.24 and 0.48 respectively.

- 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).

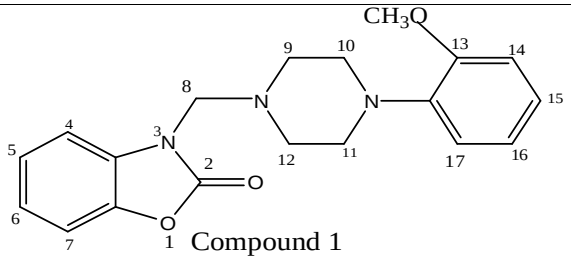
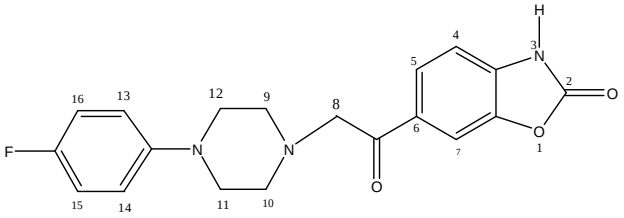
-The ^{1}H-NMR spectra shows chemical shift around 7.0-8.0ppm (7H,m,Ar-H), 3.8ppm (2H-s-CH_2)

3.5-4.4ppm(8H,d,H^{9}-H^{12}).

4.2 Discussion

In this research, two compounds of benzoxazolone derivatives were synthesized at 3rdand 6th position respectively. This synthesized compounds were obtained using mannich reaction which is the modification at3rd position and at room temperature modification at 6th, 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

4.2.1 The general reactions use for the synthesis of the target compounds

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

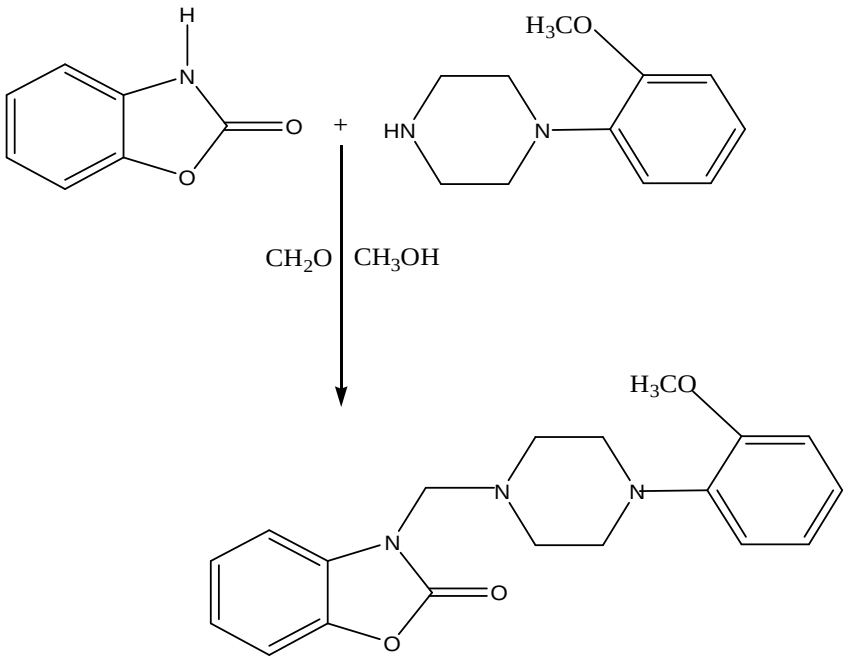


Figure 2.22 General synthesis of 3-(4-(2-methoxyphenyl piperazine-1-yl) methyl-2(3H) benzoxazolone.

Compound 2was synthesized at room temperature, where the modification was done at the 6^{th}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.

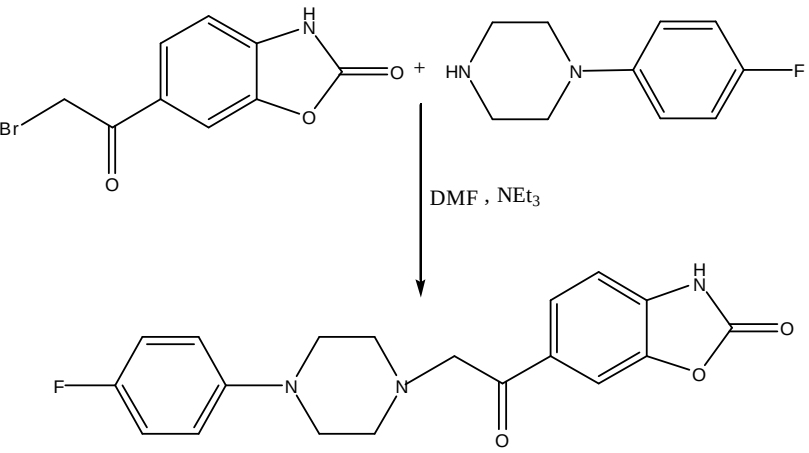
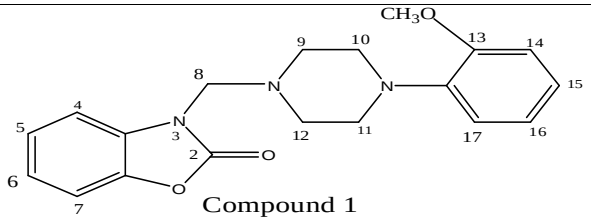
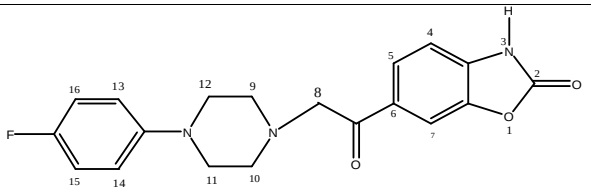


Figure 2.23 Synthetic pathway of 6-(2-(4-flourophenyl piperazine-1-yl)acetyl-2(3H)-benzoxazolone

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

Table 4.2 The above table compares the melting point and Rf values of both the two synthesize

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

The FT-IR spectrrum 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

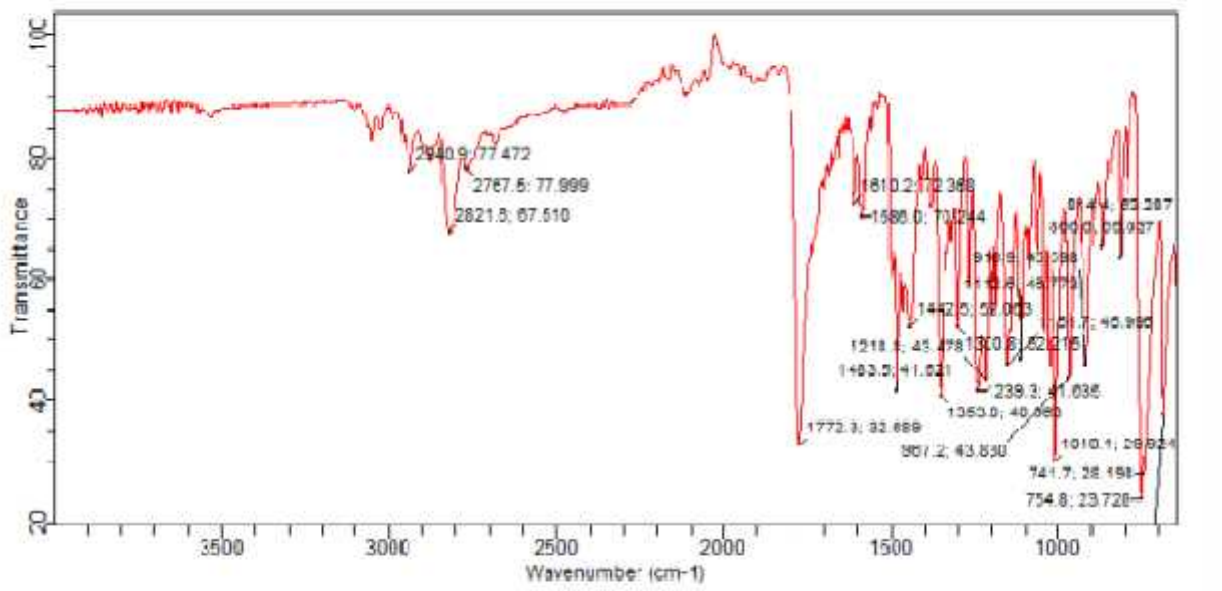


Figure 2.24 FT-IR spectrum of 3-(4-(2-methoxyphenyl piperazine-1yl) methyl-2(3H) benzoxazolone

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 around1770cm^{-1}(C=O) appears as expected. Fig 2.36shows the FT-IR spectra of synthesized compound.

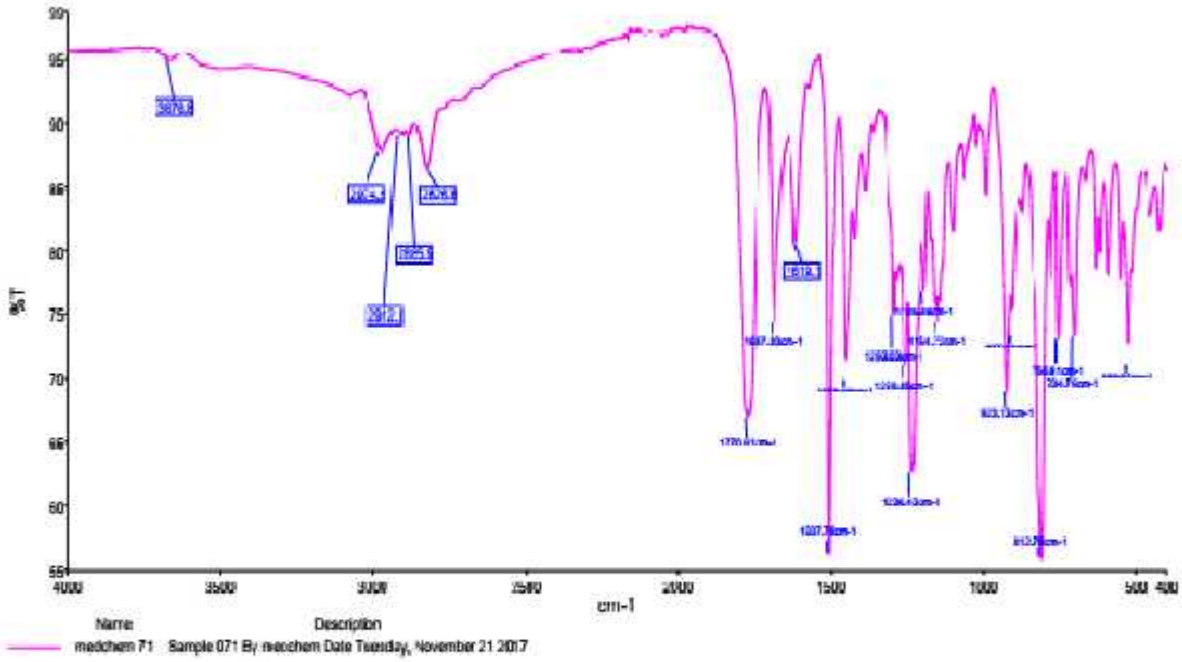


Figure 2.25 FT-IR spectrum of 6-(2-(4-floro phenylpiperazine -1-yl) acetyl 2(3H) benzoxazolone

^{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.

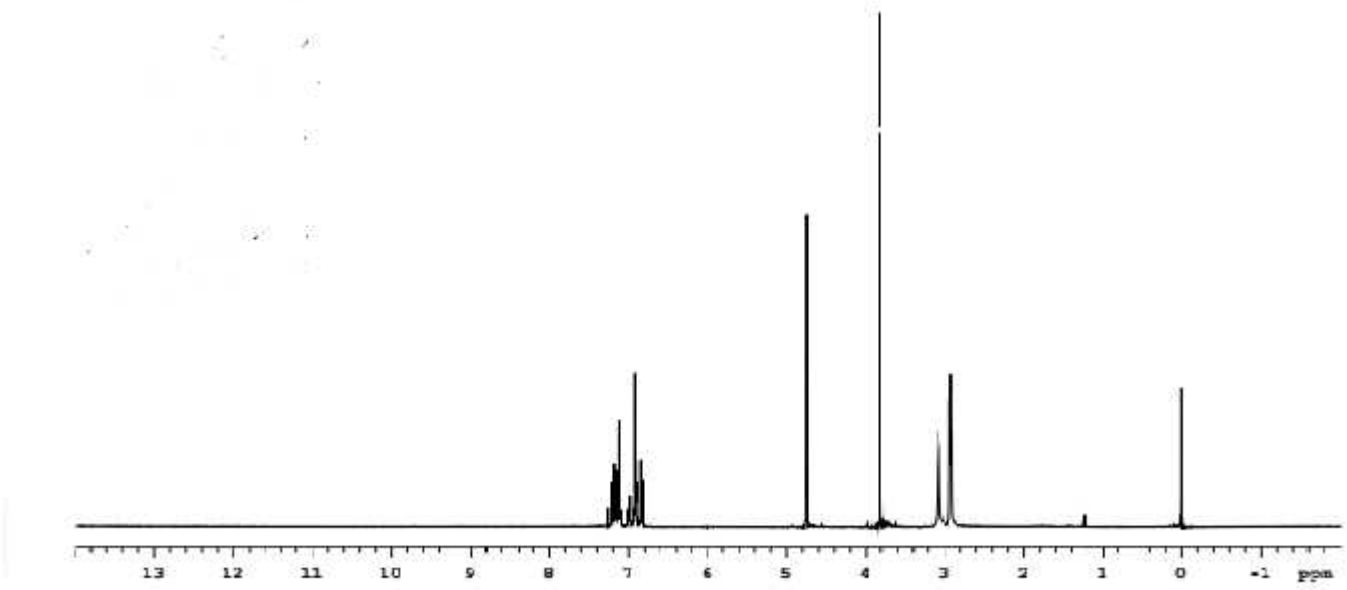


Figure2.26 ^{1}H-NMR spectrum of 3-(4-(2-methoxy-phenylpiperazine-1-yl)methyl 2(3H)benzoxazolone.

^{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.

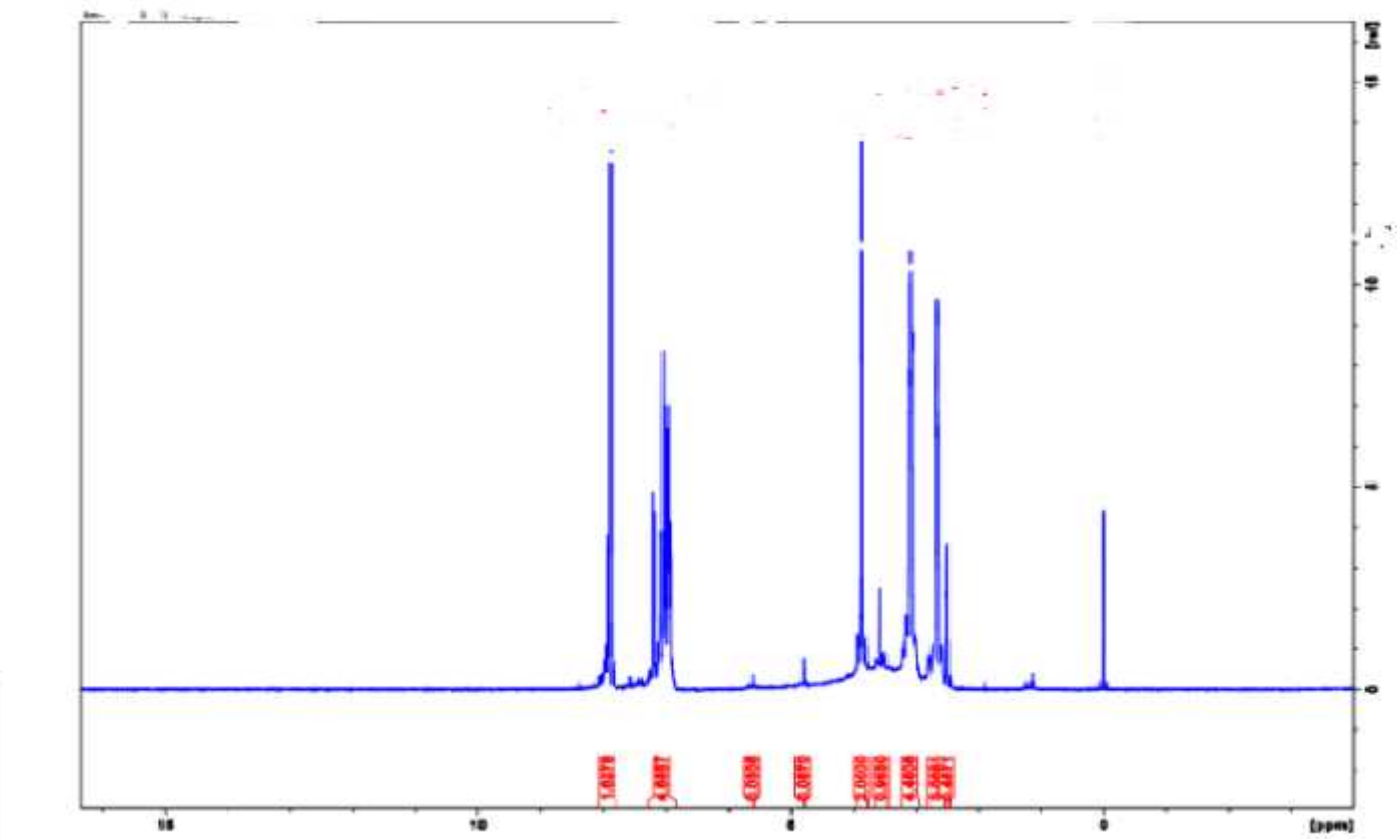


Figure 2.27 H-NMRspectrum of 6-(2-(4-floro phenylpiperazine -1-yl) acetyl 2(3H) benzoxazolone

5 CONCLUSION

Modification of 2-(3H)-benzoxazolone at 3rdand 6th position was conducted using two different reaction methods namely ; mannich reaction and reaction at room temperature,respectively. The aim of this reach 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 constrain,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 core structure, Thiscould potentially cause change in the biological activities of these types of compounds.

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This study has been accepted by the thesis committee for the degree of Master of Science in pharmaceutical chemistry.

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According to the relevant articles of the Near East University Postgraduate study-Education and Examination Regulations, this thesis has been approved by the members of the thesis committee and decision of the Board of Directors of the institute

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Solely dedicated to my parents (Haj Hauwa and Alh Ammani)