T.R.N.C

NEAR EAST UNIVERSITY

HEALTH SCIENCES INSTITUTE

SYNTHESIS AND CHARACTERIZATION OF PHENYL SUBSTITUTED BENZOXAZOLINONE

BLESSING AYEDUN YETUNDE

PHARMACEUTICAL CHEMISTRY

MASTER OF SCIENCES

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PHARMACEUTICAL CHEMISTRY

MASTER OF SCIENCES THESIS

Advisor

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THE DIRECTORATE OF HEALTH SCIENCE INSTITUTE

This thesis work has been accepted by the thesis committee for the degree award in Master of Science in Pharmaceutical Chemistry.

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Director of Institute of Health Science

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DEDICATION

I dedicate this thesis to God Almighty for giving the opportunity to end this program successfully. I also want to appreciate my parents Mr. and Mrs. Ayedun andfor their support towards my education and giving me the best upbringing which are drivers for growth and development that paves way for so many opportunities in life

ABSTRACT

2(3H) benzoxazolone and it derivatives are very important in the field of medicinal chemistry since they have different biological activities, most especially the analgesic and anti-inflammatory activities. Amines such as piperazine as a substituent to benzoxazolone structure is reported to increase the analgesics and anti-inflammatory activities. Different method were used to synthesize the compound **1** (Methylation) and compound **2** (Mannich Reaction). The reactions were monitored by TLC and melting point determination, while the chemical structures of the compound **1** and **2** were determined by FT-IR and ^{1}HNMR analysis.

Keywords: 2(3H)-benzoxazolone, Methylation, Manich reaction, Methylphenylpiperazine, NSAIDs.

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ABBREVIATION

PPA - Polyphosphoric acid

DMF - N, N-dimethylformamide

THF – Tetrahydrofuran

COX - Cyclooxygenase

FT-IR - Fourier Transform - Infrared

UV-VIS - Ultra Violet - Visible Spectroscopy

NMR - Nuclear Magnetic Resonance

ATR - Attenuated Total Reflection

NSAIDs - Non-Steroidal Anti-inflammatory Drugs

TLC - Thin Layer Chromatography

TEA - Triethylamine

ppm- Parts per million

DMSO -Dimethylsulfoxide

1. INTRODUCTION

Benzoxazolinone moieties have attracted special attention in chemistry and biochemistry. Since they possess antifungal, antitumor, anti-inflammatory, antiulcer, anti-tubercular, analgesic activities. [1-3] Furthermore, some of them have found applications as fluorescent whitening agents.

Benzoxazolinone is a heterocyclic compound with a benzene fused oxazole ring structure. Substituted benzoxazolinone derivatives and their analogues such as benzimidazoles and benza thiazoles have been the aim of many researchers for many years, because they constitute an important class of heterocyclic compounds. [4]

Generally, in the pharmaceutical field, new drugs are continuously discovered by molecular modification of lead compound of established activity. Molecular modification can possibly result in augmenting the activity. Molecular modification involves combination of separate group having similar activity in one compound by eliminating, substituting or adding new moiety to parent lead compound. In the survey of literature, it is seen that drug design by molecular modification is a productive source of new drug,among medicinal agents, there is growing interest in the development of newer, effective analgesics and anti-inflammatory agents. Among the variety of compounds studied, benzoxazolinone derivatives form an important class. [5]

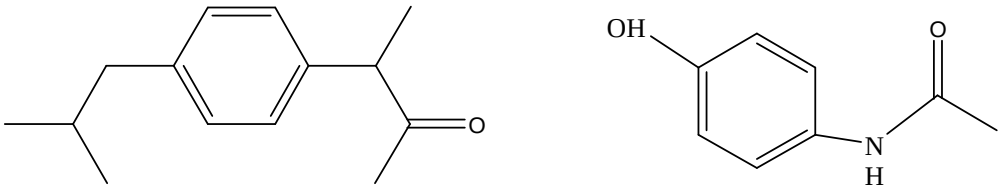
In this research, our focus was on the synthesis of 2-benzaxazolinone derivatives which was discovered to have analgesics and anti-inflammatory activities. Two different methods were used to substitute3 position, which is Methyl and Methylphenylpiperazineused to achieve reaction time.The synthesized compound was characterized by FT-IR and ^{1}HNMR.

2.LITERATURE REVIEW

2.1Analgesics

Pain is a fundamental event that is normally beneficial and work as physiological advice for potentially tissue-damaging situations e.g. the manifestation of inflammatory dysfunctions. [6] However, the very significant emotional and subjective components of human pain and the therapy of chronically depilating pain makes the search for new peripheral analgesics agents. Analgesic is a drug that is used to reduce pain. The two main classification of analgesic are opioids and non-steroidal anti-inflammatory agents (NSAIDs).

Examples of opioids are morphine and codeine WHILE NSAIDs are Aspirin, paracetamol and ibuprofen.



(a) Ibuprofen (b) Paracetamol

Figure2.1. Structure of Ibuprofen and Paracetamol

2.1.1 OpioidsAnalgesics

Opioids analgesics are agents which are active for the relief of pain that are serious [5].the main function is that it act on the central nervous systems which lead to independence, hence limiting their clinical use [6].

Narcotic analgesic may be classified into 4 major categories which are:

1. Narcotic antagonists
2. Natural derivatives of morphine
3. Synthetic agents which resemble the morphine structure
4. Synthetic derivatives of Morphine and Codeine .[8-9]

The narcotic analgesic has effect on the central nervous system, some examples are hydrocodone, methadone, oxycodone and stadol given in Fig 2.1.they can be found in some of the drugs for cough control. [10]

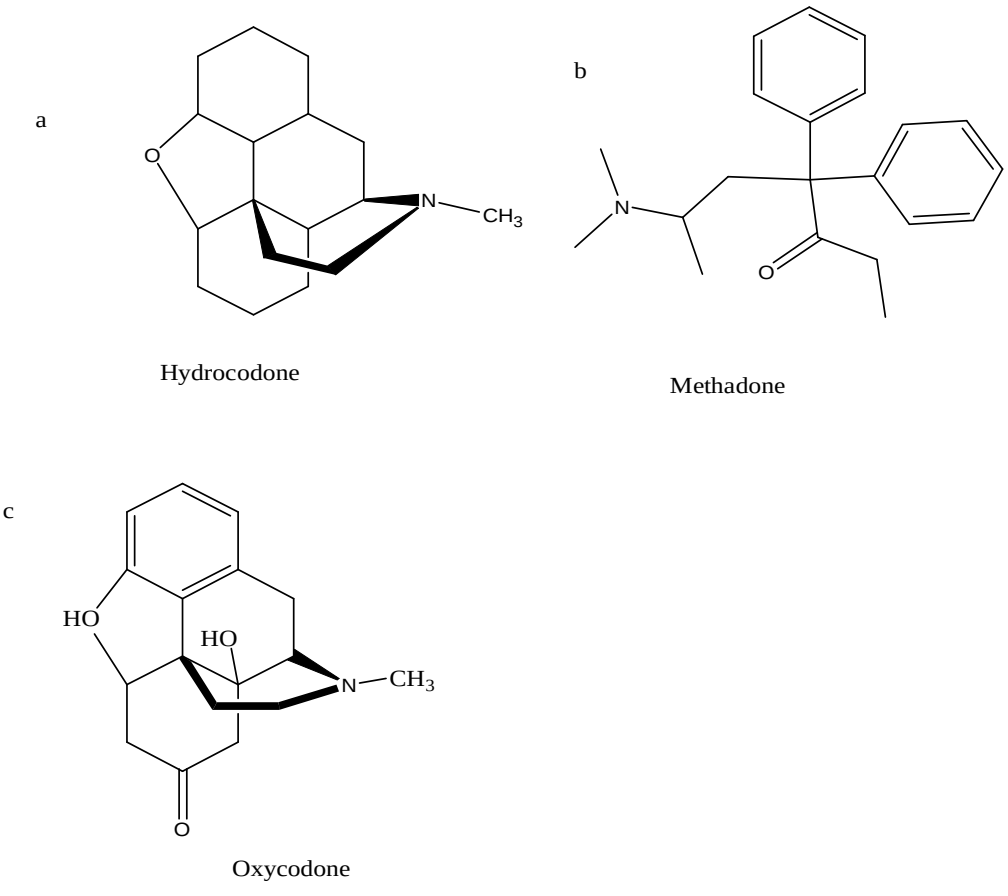
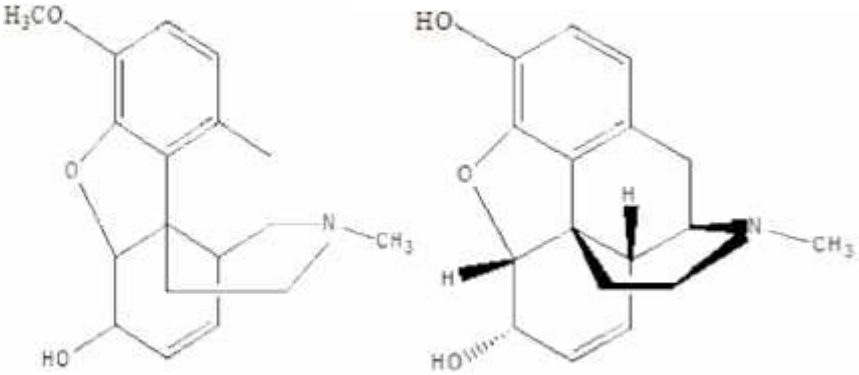


Figure 2.2. Examples of narcotic analgesics drugs



(a) Morphine (b) Codeine

Figure 2.3. Structure of Morphine and Codeine

2.1.2NSAIDS (Non-steroidal anti-inflammatory agents)

Non-steroidal anti-inflammatory drugs are compounds used in clinical anagelsia which act on peripheral nervous system. The drugs agents that provide analgesic, anti-inflammatory, and ant-pyretic effects are used for treatment of a variety of disorders. [11] However, it is not only alleviating inflammation and pain, but also increase gastrointestinal tract damage and bleeding. The most common clinical advantages of Cox-2 NSAIDs are the number of patients chronically treated with, and its selective properties [12]. Furthermore, much of the NSAIDS toxicity, particularly gastrointestinal is associated with Cox-1 inhibition [13].

The NSAIDs inhibit the rate-limiting enzymes cyclooxygenase (COX) in prostaglandin synthesis. Therefore, NSAIDs can be classified into two classes.

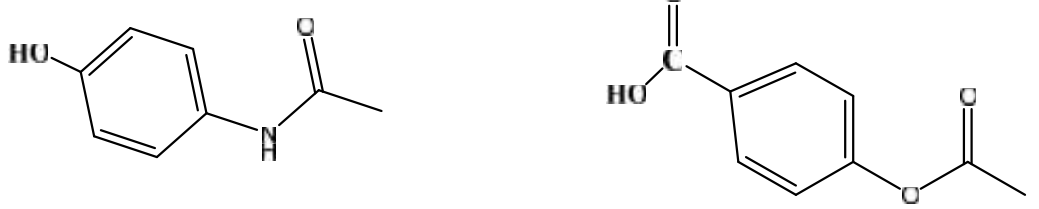
1) Non-selective inhibitors and
2) Selective inhibitors.

Non-selective inhibitors is referred to non-steroidal anti-inflammatory drugs agents that inhibit both cyclooxygenase COX-1 and COX-2.

The inhibition of cyclooxygenase COX-1 by NSAIDs in most caseslead to uncontrolled bleeding or gastrointestinal ulcer formation, while those drugs that are selectively inhibition of cyclooxygenase COX-2 may have less gastrointestinal toxicity.[14]

2.1.3 Non-Steroidal Anti-inflammatory Drugs Non-Selective Inhibitors

Thesearedrug that inhibit the two types of COX enzymes that are associated with an increased risk of gastric ulceration, presumed to be both through the reduction in gastric lining. [15] Examples of Non-selective NSAIDs include: a) para-amino phenol derivatives.e.g paracetamol b) Salicyclic acid derivatives.e.g.aspirin c) Indole and indene acetic acids e.g.Indomethacin d) Propionic acid derivatives e.g. ibuprofen.



(a) Paracetamol (b) Salicyclic acid e.g. aspirin

Figure 2.4: Structure of non-selective drugs (NSAIDs) inhibitors

2.1.4.COX-2 Selective inhibitors

the discovery of second isoform of cyclooxygenase, COX-2 has open a new line of research based on the assumption that pathological prostaglandins are produced by the inducible isoform COX-2 while the physiological prostaglandins are produced by the inducible isoform COX-2.due to this several new inhibitors have been developed and some are now commercially available[16-17]. However, an increased risk of myocardial and cardiovascular thrombotic events associated with the use of some selective COX-2

inhibitors has been observed. The adverse cardiovascular effect which are attributed to a decreased level of the vasolidary PG12 and increased the level of the potent platelet aggregation TxA2, it is primarily responsible for the recent withdrawal of rofecoxib from the market [18]

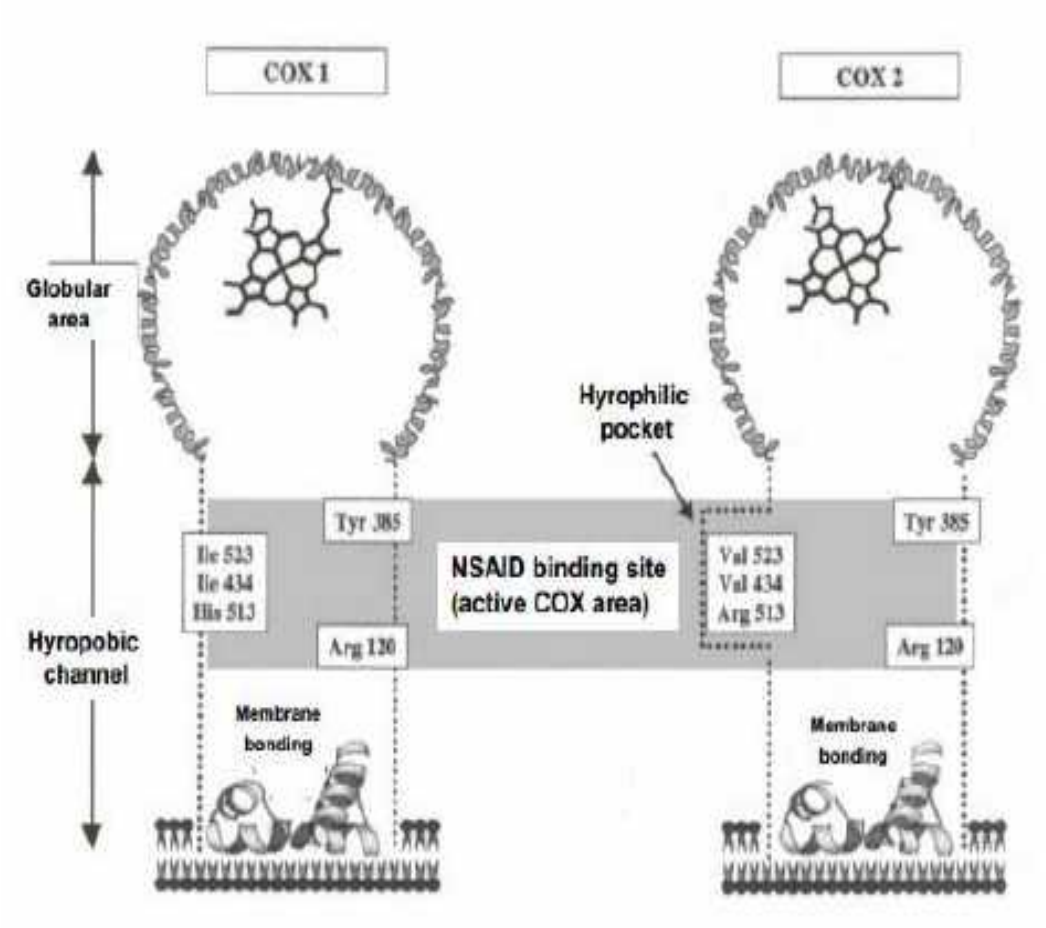


Figure.2.5. Structural differences between COX-1 and COX-2 enzyme

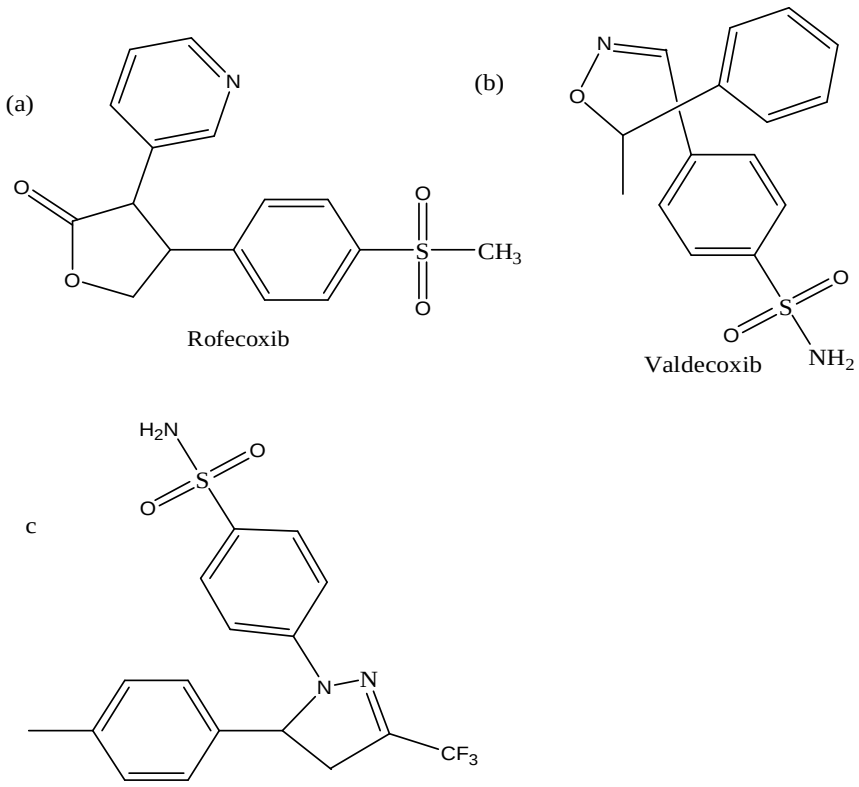


Figure.2.6. The structure above shows selective and non-selective inhibitors that are connected in different ways mentioned COX-1 and COX-2.

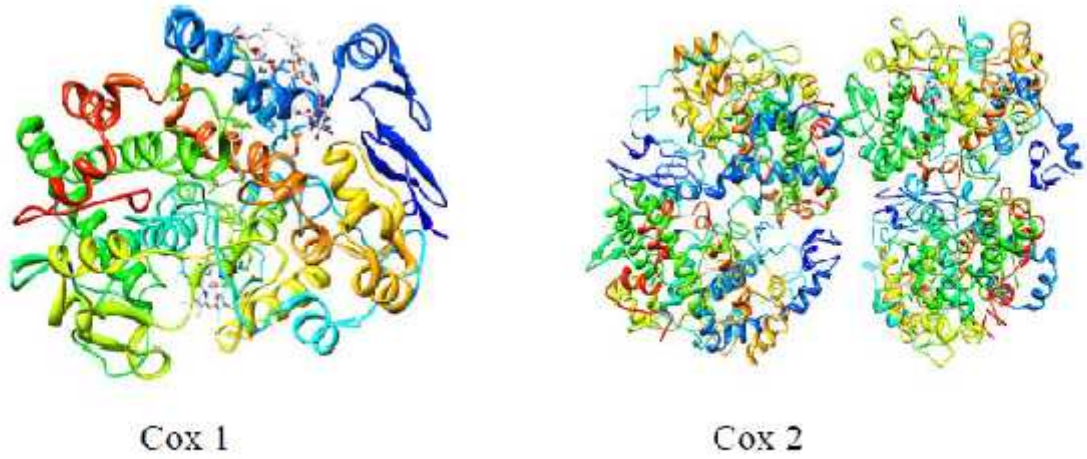


Figure.2.7. Crystallographic structure of Cyclooxygenase 1 and 2

Prostaglandins are lipid compounds obtained for derivatization of arachidonic acid (AA). They all serves as homeostatic sustenance and mediate pathogenic mechanisms for instance, the inflammatory response. They are procreated from arachidonate by the function of cyclooxygenase (COX) isoenzymes and their biosynthesis is prevented by non-steroidal anti-inflammatory drugs including those selective for inhibition of COX-2. In spite of the clinical efficacy of NSAIDs, prostaglandins may act in promotion and resolution of inflammation. The two cyclooxygenase isoform, COX-2 and COX-1 are the target of NSAIDs and they competes the active site of the both COX-1 and COX-2 [19-20]. Conventionally nonspecific NSAIDs inhibit both COX-1 and COX-2.

2.2.Nature of Benzoxazolinone

Benzoxazlinone is known to be a powder material which is light brownish in color, with the melting point of 138^{o}C. It is known to be heterocyclic compound with a bicyclic ring system, which has a phenyl ring attached to a carbon, From the structure of benzoxazolinone, Two attributes that caught the attention of medicinal and pharmaceutical chemist:

1 hydrophilicity
2 lipophility

Talking about hydrophilic we are talking about the presence of hydrogen and oxygen which take part in the hydrogen bonding and contribute greatly to the dipole moment of the compound. The lipophility help the structure for proper binding to hydrophobic protein receptors, the bulkiness of the compound is a good factor in lipophilicity of benzoxazolinone which is very important because it plays a vital role in distribution, absorption, metabolism and excretion in the body. Due to this properties it shows it possess biological activities which includes the analgesic and anti-inflammatory effects [22]

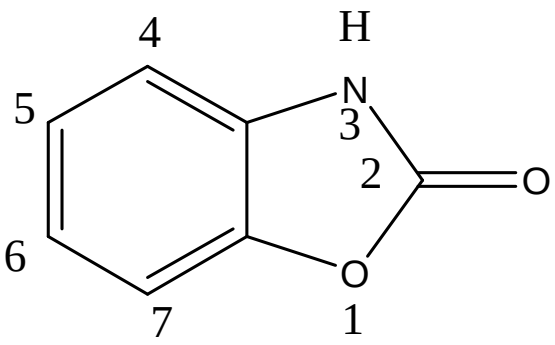


Figure 2.8: Structure of benzoxazolinone

2.2.1. Synthesis Of Benzoxazolinone

There are different ways to synthesize benzoxazlinone, for example the synthesis with yield from 2-aminophenol throughreflux method [21] with the present of carbonyl dilmidazole and in dry tetrahydrofuran(THF) in 4 hour is given in fig. 2.7.

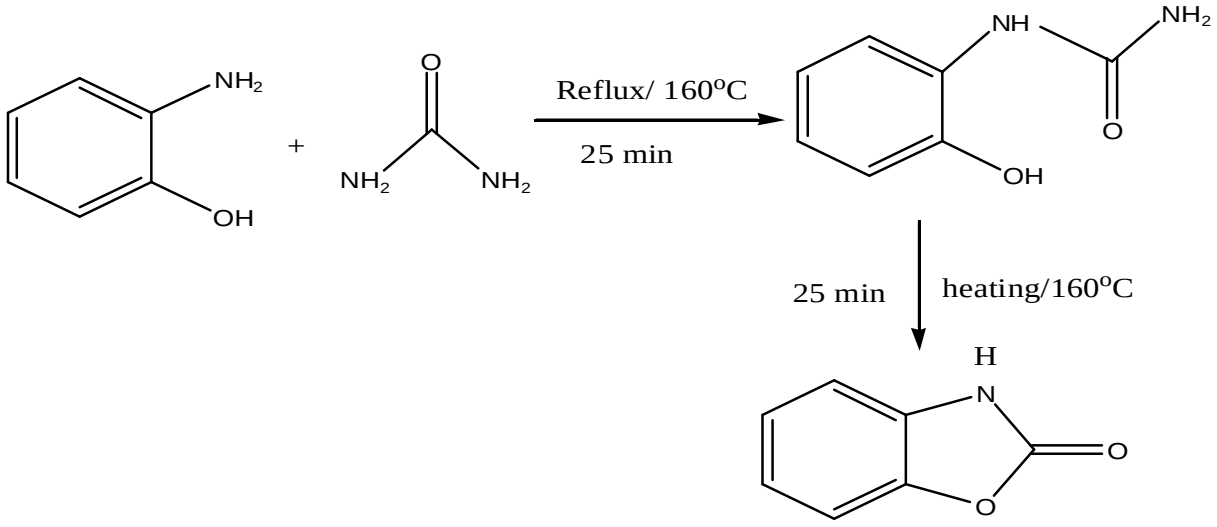


Figure 2.9. Synthesis of benzoxazolinone under reflux condition

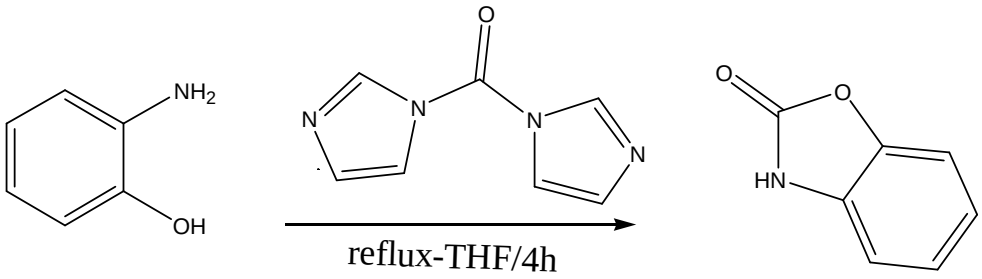


Figure 2.10. Synthesis of benzoxazolin 2(3H) ones from 2 aminophenol

2.2.2.Chemical Reactivity of Benzoxazolinone

Due to the heterocyclic form of benzoxazolinone, they are considered to have high versatility in chemical modification; mostly the function of the nitrogen atom is always at the 3rd position which is very important for a biological activity. [23]The chemical reactivity of benzoxazolinone occur in 3 different reactions which are:

N-substitution reaction (it may be alkylation or acylation)

Electrophilic substitution and ring opening or expansion reaction [24].

2.2.2.1 N- substitution reaction

The N- substitution reaction undergo base- catalyzed conditions of which the result gives N-akyl derivatives while the N- acylation, acid-base catalysis is carried out .

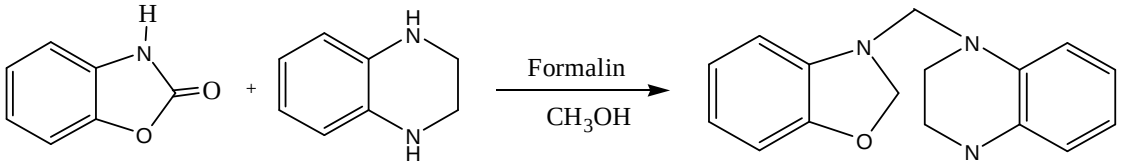


Figure 2.11. General synthesis of N-alkyl derivative of 2-(3H)benzoxazolone.

2.2.2.2 Aromatic electrophilic substitution reaction

The aromatic electrophilic reaction is controlled by the complete defeat of the 6-positionmention acylation which is nitration,sulfonation and chlorosulfonation reaction [25].2(3H) benzoxazolone is complexed (protonated)by the Lewis acid present in the reaction medium, which acts as an electrophilic attack of acylium ions. In order to avoid this, the reaction can be run by using less reactive electrophilic species e.g phosphoric acid [26] AlCl3,

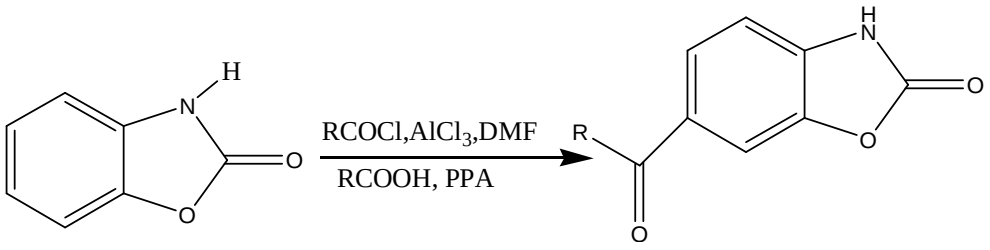
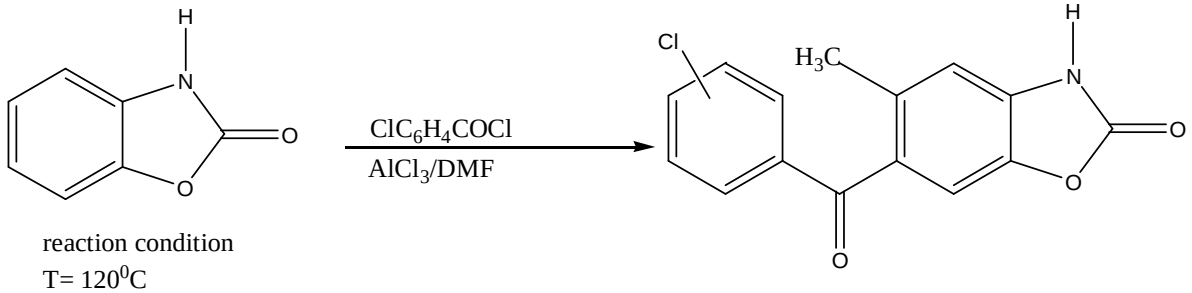


Figure 2.12. Aromatic substitution reaction of N- acyl benzoxazolone 6- acyl derivative

2.3 Ring opening or Expansion reaction

In the ring opening system 2(3) benzoxazolone are fairly stable in the acid medium, they are quickly hydrolysed in basic medium, which lead to an opening ring products e.g. 2-aminophenols. The 2-aminophenols can be acylated at 4^{th} position(route b), subsequent ring closure leads to the otherwise inaccessible 5-akyl-2(3H) benzoxazolone derivatives route(c). the ring expansion of 2(3H) benzoxazolone to become benzoxazinones can be effected with the same 2- aminophenols[28]



reaction condition
T= 120^0C
t= 6h

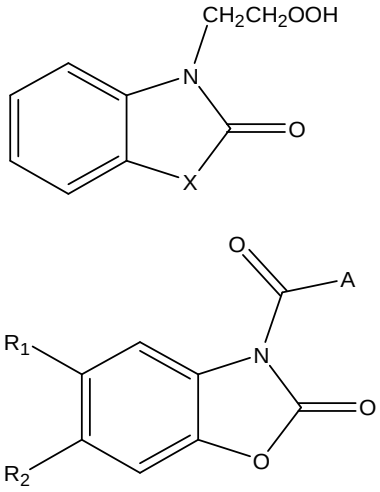
General synthesis of 5-acyl-2(3H) benzoxazolone and benzoxazinone derivatives method

(a) aq.NaOH (b)RCOCL,ALCL3.DMF,(c)ClOOEt, Triethylamine(TEA) (d)$BrCH_2COOEt$,Triethylamine(TEA).

Figure 2.13: Synthesis of 5-acyl-2(3H) benzoxazolone

2.2.3 Biological activity of benzoxazolinone

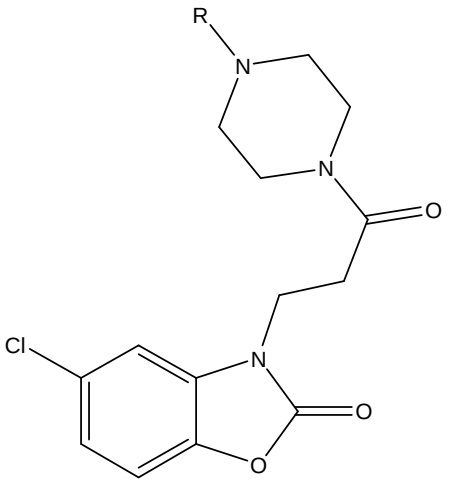
The biological important of 2-3H benzoxazolone is of various types but is mainly on the analgesic and the anti-inflammatory activity, and the medical value of 5-chloro-2(3H)benzoxazolone prompted to the investigation of 3-substituted 2(3H) benzoxazolone.Lespagnol and co-workers carried out or investigate tested number of 2(3H) benzoxazolone derivatives for their anti-convulsive, hypnotic, antipyretic and analgesic properties 2(3H)benzoxazolones have emerged during the last two decades as a very important analgesics and anti-inflammatory agents. When they carried out the test, from their investigation 2(3H)benzoxazolones was structurally modified the position 3,5 and 6 in order to screen for their antinoiceptive properties.[29](6 Acyl-2(3Hbenzoxazolone 3-yl) alkanoic acid and ethyl ester derivatives also exhibit analgesicproperty.



X = O ,S , R1= H,Cl
R= H ,CH_3 ,C_6H_5 -CO ,2-CLC6H_4-CO
A=1-Morpholinyl, 1-Pyrrolidinyl diethylamino OCH_3 ,OC_2H_5OH

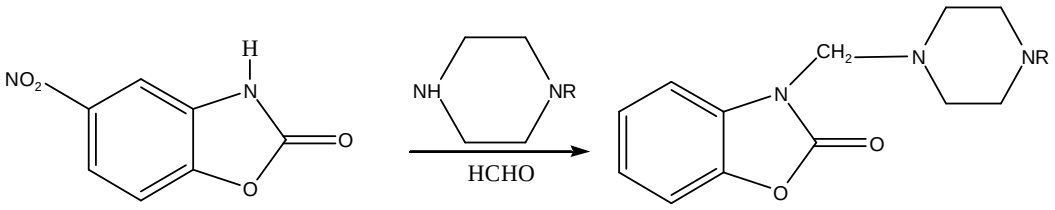
Figure 2.14. Examples 2(3H) benzoxazolone 3yl procainamide derivatives

Onkol et al, [30-31] synthesized (5-chloro2 (3H-benzoxazolinone-3-yl)propanamide derivatives as potent antinociceptive agents.Shown in Fig.2.13.



R = C_6H_5,2-OCH_3-C_6H_4 ,3-Cl-C_6H_4 ,4-Cl-C6H4
3-CF_3-C_6H_4 ,2-F-C_6H_4 ,4-F-$C_6H_4CH_2$-C_6H_5 ,2-Pyrindyl

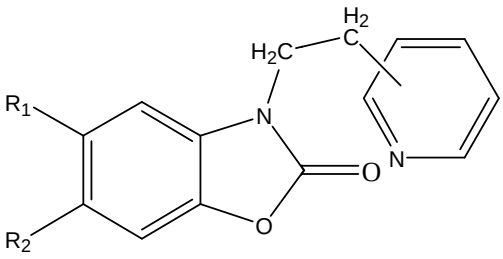
Figure 2.15: Examples of 6- acyl-3-piperazomethyl-2- benzoxazolinone derivatives



R=4-Flourophenyl, 4-Chlorophenyl, 2-Florophenyl and 3-Methoxyphenyl

Figure 2.16: Synthesis of 5-nitro-3-piperazinomethyl-2-benzoxazolinone.

Safak et al. synthesized 3-(2-pyridylethyl)benzoxazolone(figure 2.15) derivatives as potent analgesic and anti-inflammatory compounds inhibiting prostaglandins E2 All the synthesized compounds showed the anti-inflammatory activities compared to indomethacin. Those without substituents on 6^{th} position ring were significantly more active than the rest of the members. [32-33]



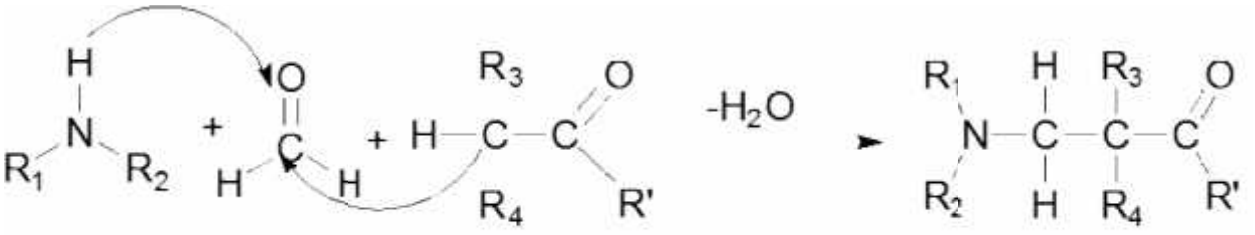
R1= -H, -Cl

R2= $-C_6H_4Cl$ (O), $-C_6H_4OCH_3$ (p)

Figure 2.17. Structure of 3-[2-(2 and 4-pyridylethyl)] benzoxazolones.

2.3 Manich Reaction

Mannich reaction entails the synthesis of two carbonyl compounds with amine groups to give a beta-amino carbonyl compound and has been in use in organic chemistry because of the different ways it was applied in pharmaceutical industries [34]



Amine | Aldehyde | Ketone

B –amino-carbonyl

R= Ph, H, Alkyl groups

Figure.2.18: Manich Reaction of Amino-Alkylated derivatives

Mannich bases were synthesized using manich reaction in different report from many researchers, such as 1, 3-dihydroxyxanthone which has shown clearly the activity against Acetylcholinesterase¸(AChE) and Butyrycholinesterase (BUChE) [35] The

reaction is used for preparing medicinal agents that are valuable with amino alkyl chain as it is common in fluocetine.

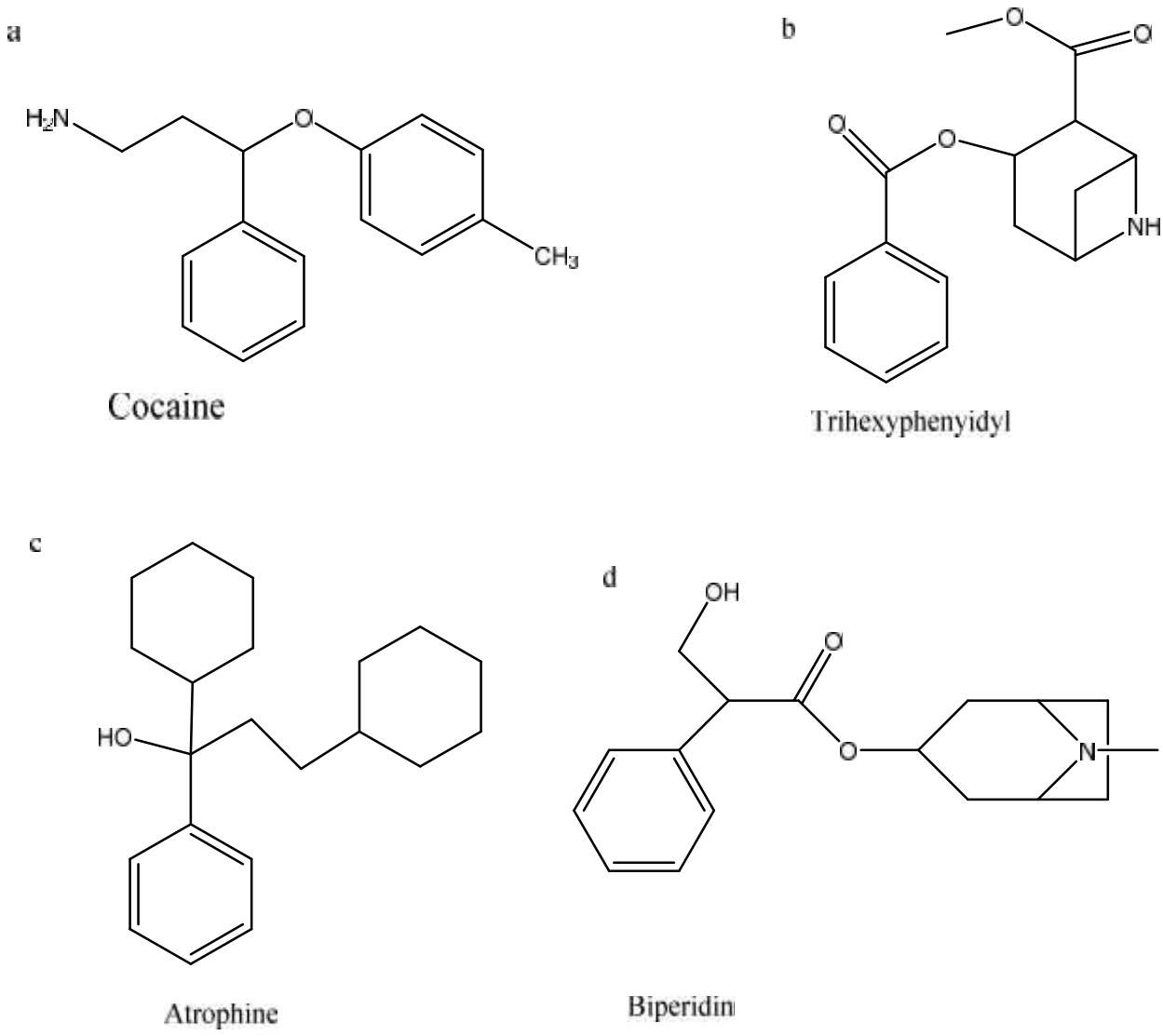


Figure 2.19. Examples of compounds containing mannich base

R and R1= akyl or aryl

3. MATERIALS AND METHODS

3.1 Materials

All reactions were carried out using standard laboratory equipment and standard laboratory glassware. All chemicals such methylphenylpiperazine, benzoxazolinone, ethylacetate,cyclohexane, n-hexane,methanol and ethanol were used in this research work which was purchased by Sigma Aldrich chemical company and were used as received, no further

3.2. Methods

3.2.1. Thin Layer Chromatography (TLC).

In TLC, the plate was made of silica gel/TLC plates and the solvent used are benzene, ethyl acetate, hexane and methanol. Silica gel plate were detected under UV light 254 nm wavelength.

Three different mobile phases were prepared with different solvent at different reaction

S-1: Benzene/Methanol (9:1)

S-2: Benzene/Methanol (5:1)

The solvent was poured into the glass tank to a depth of 0.5cm, swirled gently and allowed to stand while the TLC plate is prepared. The starting material and product were put into two different test tubes, after which chloroform was added. The silica plate were spotted with the two different solution and was placed into different mobile phases. The silica gel were allowed to develop until the solvent got to a certain marked point, which was later removed from the solvent and the covered distance were marked with pencil, the silica gel was allowed to dry. The spots were viewed under UV light at 254nm. The Rf values were calculated using the equation below;

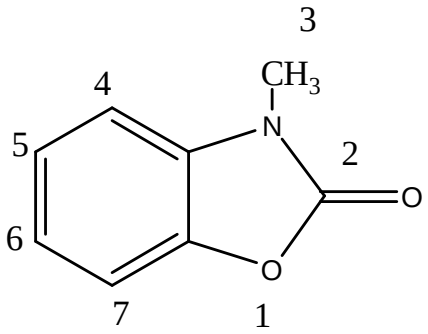
Rf = distance travelled by the sample/ Distance travelled by the solvent [36]

3.2.2. Melting Point Determination

The melting point of the synthesized compound was carried with Mettler Toledo (FP90 Central Processor) melting point apparatus

3.2.3. Methylation Compound 1

200 mg (0.001mol) of 2- benzoxazolone was dissolved in 9ml of 10% NaOH, and 15 ml of water was added. The solution was cooled in ice bath;0.2ml (0.001 mol) dimethyl sulfate was added dropwise, and mixed for 2h. The precipitate was crystallized using ethanol.



3- Methylbenzoxazolinone

Figure 3.1. Structure of Compound **1**

3.2.4. Mannich Reaction Compound 2

200mg (0.001mol) of benzoxazolone was dissolved in 8ml of methanol, followed by the addition of 0.26 grams of methyphenylpiperazine in round bottom flask, then 0.2ml of 37% (w/v) formalin solution was mixed with 2ml of methanol and poured into this reaction mixture. The solution was refluxed in a water bath for one hour. After completion, the reaction mixture was then poured onto crushed ice and resulting precipitate was filtered off, using vacuum filtration method to yield crude products

which was subsequently washed with methanol and allowed to dry at room temperature.the reactions were monitored by TLC and resulting precipitate was purified by recrystallization using ethanol.

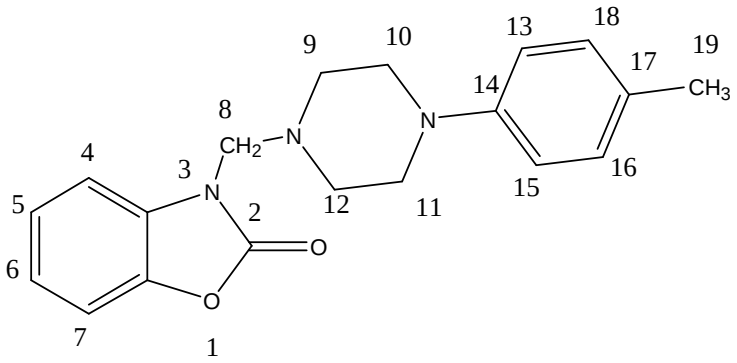


Figure.3.2. Structure of Compound 2

3.3.1. Fourier Transform Infra-Red (FT-IR)

The FT-IR spectra of the product were recorded on Agilent Carry 650 Spectrometer at Ankara University, Central Instrumental Analysis Laboratory, Faculty of Pharmacy.

3.3.2. 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-*d*6) was used. The test was conducted at Ankara University, Central Instrumental Analysis Laboratory, and Faculty of Pharmacy. Chemical shift (δ) values were reported in parts per million (ppm).

4. RESULTS AND DISCUSSION

4.1.Results

The above compound was synthesized by Methylations mentioned in the experimental part. [35]

Compound 1

Compound 1 was synthesized using method (A), described in the experimental section.

Appearance: Product was obtained as brownish powder form

M_p: The melting point of the product:84.2^0C

TLC Result: The mobile phases of S1 and S2 were calculated with Rf value; 0.45 and 0.51 respectively by FT-IR, NMR.

Fourier Transform Infrared (FT-IR) Spectroscopy (IR.V_{max}): FT-IR showed stretches at 2900 cm-1 (C-H Stretch), 1735-1782 cm-1 carbonyl group(C=O stretch)

Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR): shows peaks at 7.2 ppm (m; 8H; Aromatic-H); 3.2 ppm (CH_3)

Compound 2

Compound **2** was synthesized using method (B) described in the experimental section.

Appearance: Product was obtained as white crystals.

M_P: The melting point of the product: 176^0C

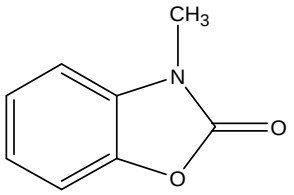
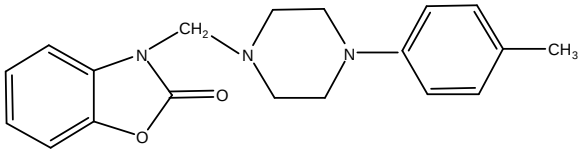
TLC Result: the mobile phase S1 and S2 were calculated with Rf value; 0.38 and 0.48 respectively.

Fourier Transform Infra-Red (FT-IR) Spectroscopy (IR.V_{max}): FT-IR shows stretches at 2816 cm^{-1} (C-H stretch),1753 cm^{-1}carbonyl group(C=O stretch).

Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR):shows peaks at 7.2(m;8H;Aromatic-H) ,4.6-4.9(s;2H;H^4),3.0(t;4H;pip H^6-H^7),2.3(t;4H;pip H^5-H^8) ppm.

In this thesis, facile method are given for the synthesis of compound 1 and 2 Shown in Table **4.2**

Table 1: Structure and name of compound **1-2**

Name of compound	Structure	Condition Time (hrs/mins)	Melting point
Compound 1		120 mins	84.2
Compound 2		60 mins	176.8

The structures of the synthesized compound were confirmed by Fourier Transform Infra-Red (FT-IR) and Proton Nuclear Resonance (^{1}HNMR) Spectroscopy. The melting was used to determine the purity of the compound, while thin layer chromatography was used to check the progress of the reaction.

Fourier Transforms Infra-Red (FT-IR) Spectroscopy (IR Vmax) Compound 1:

The FT-IR spectra synthesize compound shows absence of N-H stretch which is around 3100-3400cm^{-1}, which shows that the reaction has taken place at position 3 of benzoxazolinone and it indicate that the substitution has taken place at 3rd position. The strong C=O stretch bond of 2-benzoxazolinone are visible at 1735cm^{-1}-1782cm^{-1}, the C-H stretch for the product also appear at 2900cm^{-1} as expected in the spectra.

Fourier Transforms Infra-Red (FT-IR) Spectroscopy (IR Vmax) Compound 2:

The FT-IR spectra synthesize compound shows absence of N-H stretch which is around 3100-3400cm^{-1}, which shows that the reaction has taken place at position 3 of benzoxazolinone and it indicate that the substitution has taken place at 3rd position. The strong C=O stretch bond of 2-benzoxazolinone are visible at 1753cm^{-1} , the C-H stretch for the product also appear at 2816cm^{-1} as expected in the spectra.

FT-IR spectra of the synthesized compound 1 and 2 made under different conditions are given below.

^{l}HNMR spectra of the synthesized compound shows peaks at the expected chemical shift. **Compound 1** ^{1}HNMR showed aromatic proton (H) chemical shift at **7.2 ppm**(m, 7H,Aromatic H) methyl (-CH_3-) shift at 3.2 ppm which indicate the accuracy of the substitution of heteroatomic at position 3.

,^{1}HNMR spectra of Compound **2** shows peaks at expected chemical shift at 7.2 ppm(m, 7H,Aromatic H), methyl group(-CH_2-) chemical shift at 4.6-4.9 ppm which shows the accuracy of the substitution at heteroatomic nitrogen at position 3 and phenyl chemical shift at 3.0 ppm and piperazine shift at 2.3 ppm (m, 10H, -CH_2-CHOH-,piperazine$H^2H^3H^5H^6$)

4.2 DISCUSSION

Both of the synthesized compounds have the same substitution on 3rd position of 2(3H) benzoxazolone ring. In this Study, two different reaction conditions have been used for the synthesis of these compounds, namely, low temperature and Methylation in Mannich reaction.

The reaction for the synthesis of the target compound is carried out according to manich reaction condition, in which menthylphenylpiperazine reacted with 2(3H) benzoxazolone at 3-position, which is the reactive site for mannich reaction. At room temperature, a moderate yield was formed from the product. The general reaction used for the synthesis of the target compound is shown in figure 4.2.

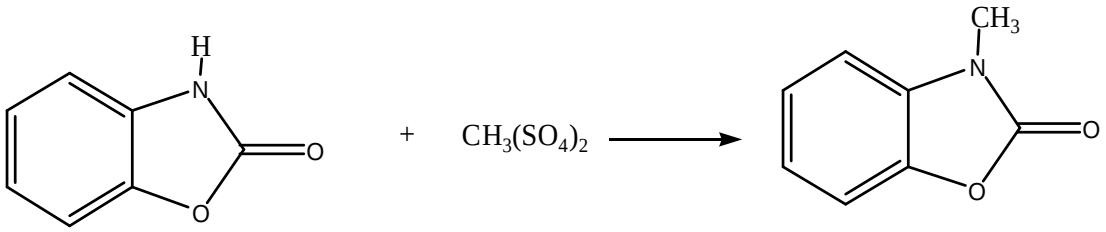


Figure 4.1: Synthesis of Compound 1

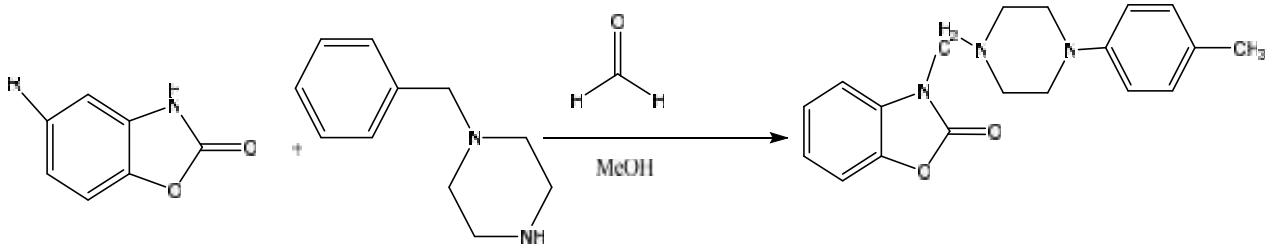


Figure 4.2. General synthesis of target Compound

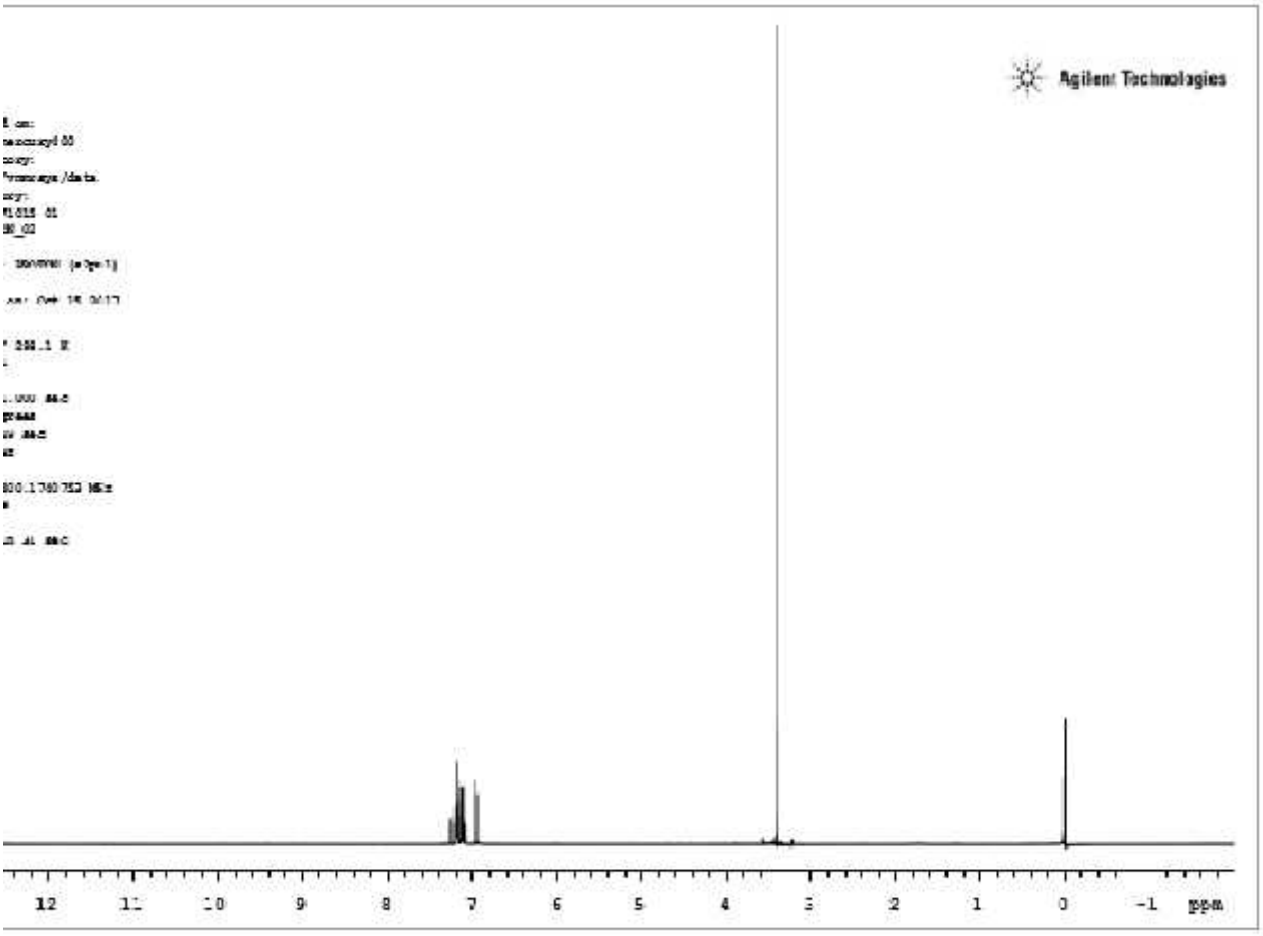


Figure 4.3. ^{1}HNMR spectrum of Compound **1**

The 1HNMR spectra of compound 1 shows peak at around 6.8-7.4 ppm which shows the presence of the aromatic ring. And shows a peak at 3.4 ppm showing the presence of CH_3. The absence of N-H peak in the ^{1}HNMR spectra shows that the reaction has taken place

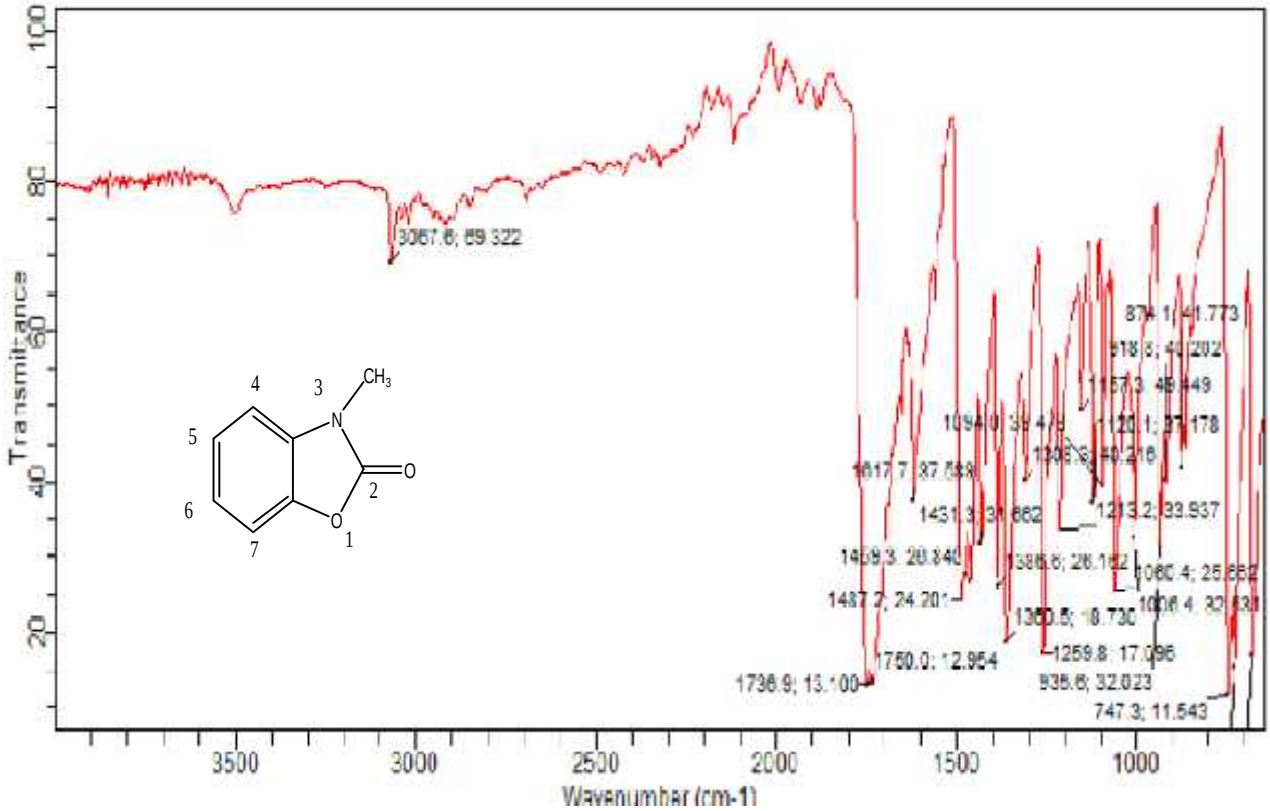


Figure 4.4.FT-IR spectrum of Compound **1**

The FT-IR of compound 1 shows some stretches at 3067 cm-1 and C=O stretch as expected was seen at 1760cm-1. The FT-IR spectra shows absence of N-H stretch that should be around 3100 -3400cm-1 which shows that the reaction has taken place at position 3.

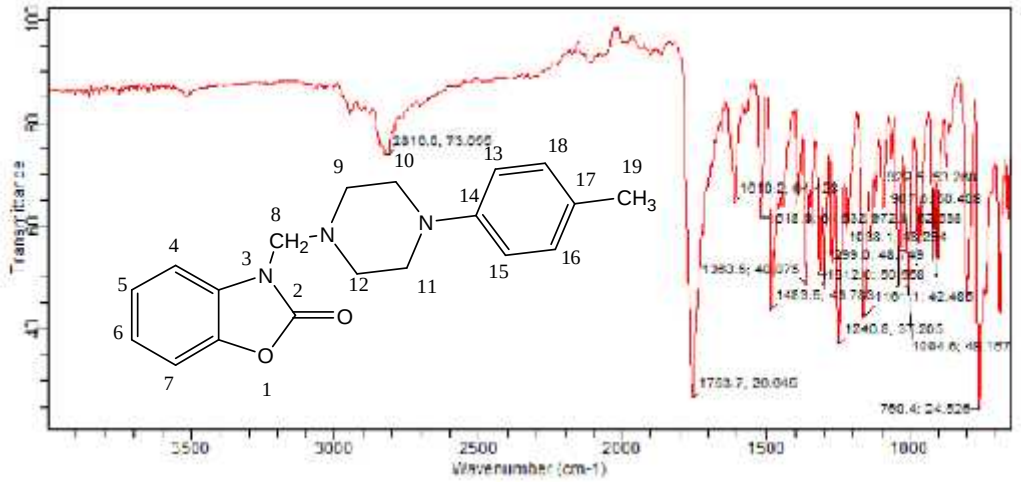


Figure 4.5: TheFT- IR spectra of Compound **2**

The FT-IR of compound 2shows a C-H stretch at 2816 cm-1 as expected and a sharp peak at 1753 cm-1 showing the presence of C=O group.

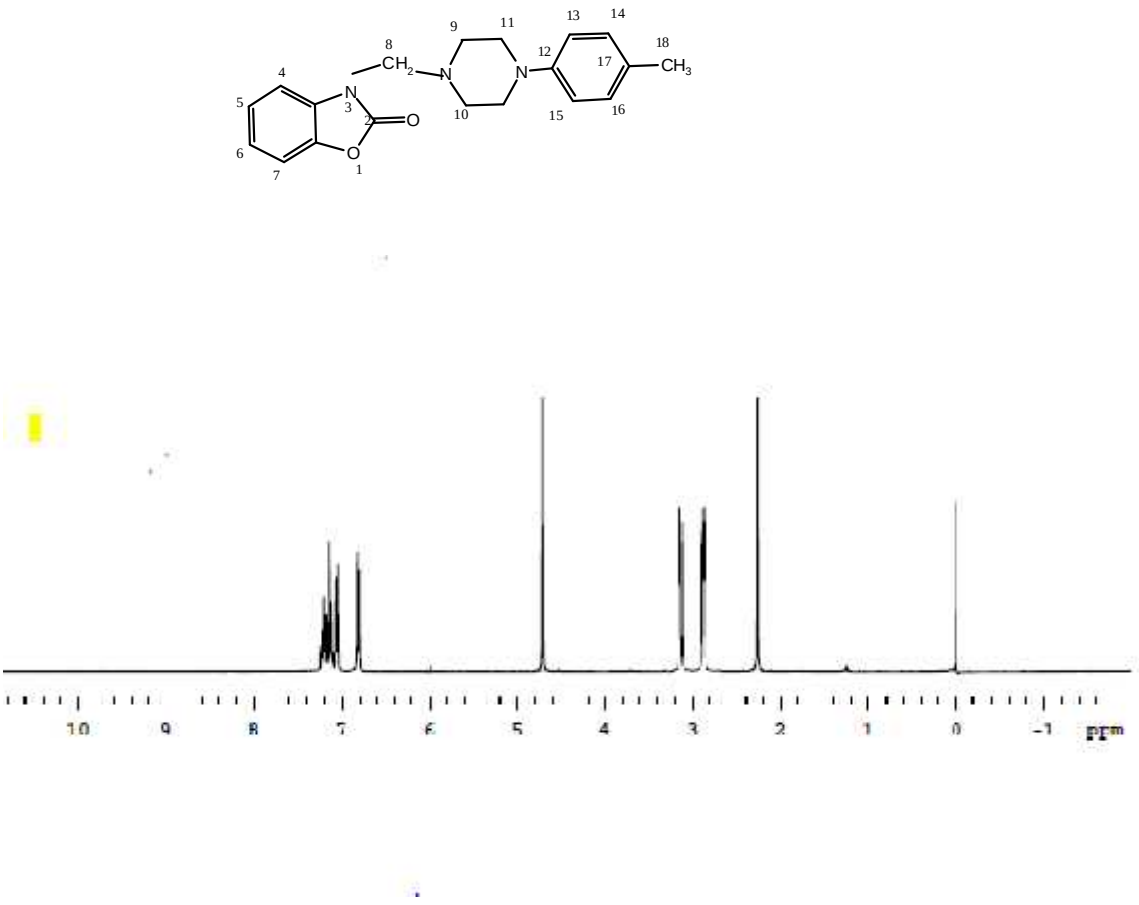


Figure4.6: [1]HNMR Spectrum of Compound 2

[1]HNMR Spectrum of Compound **2**

The FT-IR spectra of the two synthesized compounds shows the absence of N-H peaks which is reported to come around 3100 cm-1, this indicates that the reaction have actually taken place at position 3of 2-benzoxazolinone.

The ^{1}HNMR of compound 2 shows the aromatic peaks from 6.8-7.2 ppm. A singlet peak at 4.6 ppm showing the presence of methylene (CH2), a doublet signal from 2.5 -3.6 ppm showing the presence of piperazine and singlet peak at 2.2 ppm showing the of methyl (CH3).

^{1}HNMR spectra of the compound 1 and 2 in DMSO shows peak at expected chemical shifts values. In all spectra, relative to the starting material (2-benzoxazolinone) there is an additional CH_2 (methylene) peak as singlet observed at 4.6 ppm in compound 2, in compound 1 the CH_3peaked as singlet is seen at 3.4 ppm. This also proves that the reaction has taken place at N-atom in position 3 and piperazine is bonded to 2-benzoxazolinone via CH_2 bridge.

Further investigations of ^{1}HMNR spectra reviews the presence of aromatic peaks around 6.8 to 7.4 ppm which is expected as similar to the literature. The piperazine protons (H^6 and $H^{7)}$ were seen as triplets at 2.5-3.6 ppm respectively for compound 1. This indicated that, less shielded protons (H^6 and H^7) are closer to the piperazine nitrogen next to electron releasing group (CH_2-).

Additional peaks are observed in compound 2 due to assymmetric hydrogen of piperazine. ^{1}HNMR of compound **1** and **2** is shown below shown in fig. 4.3 and 4.6.

5CONCLUSION

This study shows the synthesis of 2-benzoxazolone using two different methods of reaction, methylation and Mannich reaction. It is possible to do substitution at different sites of benzoxazolone structures and furthermore, it is easier to synthesize a lot of compounds through the substitution of different amines. This type of molecules could be good candidates for biologically active molecules since similar ones have been reported to be active in literature.

REFERENCES

[1]Turker L., Sener E., Yakin L., Akbulut U., Kayalidere I.,QSAR of some antifungal-active benzoxazole using the quantum chemical parameters, *Scientia Pharmaceutica*, 58,107-113, **(1990)**.

[2]. Rajogopal, M. R. Pain-Basic consideration, *indian journal of Anaesthsia* Vol. 50 (5) page (331-334). **(2006)**

[3] Henry L. James,Rashig, D. Schlopflocher, P. Taenzer. E. Johnson, Wiley – Blackwell Pathophysiology of chronic pain, Rashig, D. *Weinhein*, Germany page (59-66). **(2008)**Ed S.

[4] Modi, C. M., Mody, S. K., Patel, H.B., Dudhatra, G.B., Avinash, K., Madhavi, A.; Toxicopathologial overview of Analgesic and Anti-inflammatory Drugs in Animals. *Journal of Applied Pharmaceutical Science*, 2(1): 149-157**(2012)**

[5] Dinakaran VS, fused pyrimidines. The heterocycle of diverse biological and pharmacological significance .*Der pharm Chem* 4(1):255-65.**(2012)**

[6] Deniz, S, Dorguer.,S, Unlu.M , Fethi S, Erdem, Y.. Anti-noiceptive and anti-inflammatory activity of some (2-benzoxazolinone 3-yl) acetic acid derivatives *II famaco* 53, 80, 84.) **(1998)**

[7] Wang,C.H.,Lee,S.Y.,.Under treatment of cancer pain. *Journal of Acta Anaesthesia Taiwan*, 53, pp 58-61.**(2015)**

[8] Laura, T, keran, R., Lucy, M...Opioids in management of persistent non-cancer pain.*J. MPAIC*, 17,552-554.**(2016)**

[9] Shen H, He M.M, Liu H, Comparative metabolic capabilities and inhibitory Profiles of CYPED6.1 CYP2D6.10, and CYP2D6.17 *Drug Metab. Dispos* ; 35 (8) page (1292-300). **(August 2007)**

[10] Busse G, Drugs the straight facts "Morphine ", *Chelsea house Publisher*, NY.**(2006)**,

[11] Hanks G, Cherny N, Calcman K; Opioids Analgesic therapy, *oxford Textbook of palliative Medicine,* Third Edition **(2005).**

[12] Jaffe JH, martins W., Opioids anagelsics and antagonists. In the pharmacological basic of therapeutics(Goodman LS,Gilman A.Rail.T.W, Nits A.S,Target whole body assay for rapid and routine testing of non-steroidal anti-inflammatory drugs(NSAIDS)) on cyclo-oxygnase-2-activity. *Inflamom-pharmacology*, 16 page (155-161). **(2008)**

[13] Kumar et al, Toxic pathological overview of analgesic and anti-inflammatory drugs in animals, *journals of applied pharmaceutical science* 02(61); pp149-189.**(2012),**

[14]http://health.ccm.net/fag/1105-analgesic-definition

[15] Nalhan C. Point of control in inflammation, Nature, 420 pp 845-885. Pubmed: 124909507.**(2012)**

[16] Rouzer and Marnet , cyclooxygenase, structural and functional insight journal of lipid research, 50,s29-34**.(2009)**

[17]Ricottti and Fitzgerald , prostaglandin and inflammatory, Arteriosclethromb vasc Biol.31(5): pp 986-1000.**(2012)**

[18] Ghosi R. Targhi A, Daraei B, Hedayati M.Design,synthesis and biological evaluation of new 2,3- dearylquinonine derivatives as selective cyclooxygenase 2 inhbitors.Bioorg.med.chem., 18: 1029-1030**.(2010)**

[19] Simmons DL, Botting RM. Hla T. COX isozymes: the biology of prostaglandin

Synthesis and inhibition. *Pharmacol*; Rev.56. Page (387-437).(**2006)**

[20] Ricottti and Fitzgerald , prostaglandin and inflammatory, *Arteriosclethromb vascBiol*.31(5): pp 986-1000**.(2012)**

[21] .Urban Mk, cox-2 specific inhibitors of the improved advantage over traditional NSAIDS, *Orthopedic*.2000.July; 23.**(2000)**

[22] Suman, B, Minaxi, S, Sunil K,. Methods for synthesis of oxazolones, areview. Info,*J,Chem.Tech.Res*, 3(3), 1102-1118.**(2011)**

[23] Kim V,Marie E. Migaud Org. Lett., 6 (20), pp 3461–3464 (2004)

[24] Lespagnol C.; Mahidulla S.; Marcincal-L.A.; La Benzoxazolinone et ses Derives Considers *Sous I'angle de la Chimie Therapeutigue. Bull. ChimTher*.; .2 (5): p 395.**(1967)**

[25] Ucar,H. et al . 'Fries liked' rearrangement: A novel and efficient method of synthesis of 6-ayl-2(3H) –benzoxazolone and 6-acyl-2(3H)- benzoxazolone tetrahedron,54g; 1763-1772**(1998)**.

[26] Umut, S and Nesna,, G. et al). 1-Acylthiosemi carbazides, 1, 2, 4- triazole-5(4H)-theories. Synthesis of analgesic- anti-inflammatory and anti- microbial activities. Journal of bio organic and medicinal chemistry, 75, 5738-5751.**(2007)**

[27] Ucar H., Derpoorten K.V., Depovere P., Leiseur D., Isa M.,et al.; "Fries Like" Rearrangement a Novel and Efficient Method for the Synthesis of 6-Acyl-2(3H) benzoxazolones and of 6-Acyl-2(3H) benzoxazolones. Tetrahedron, . 54: page (1763-1772). **(1998)**

[28] Lesspagnol A., Warembourg, H., Lespagnol, Ch., Butaeye, P.; *Lille-Medical* , 6, 8. 60.**(1951)**

[29] George W. Parshall Acc. *Chem. Res*., 3(4), pp 139–144**(1970)**

[30] Aichaoui H. , Poupaert J.H. Lesieur D., Henichart J.P., AlCl3-DMF Reagent in The Friedel-Crafts Reaction. Application to 2(3H)- Benzoxazolinones in The *Haworth Reaction. Bull. Soc. Chim. Belk.* ,. 101(12): p. 1053**(1992.)**

[31] Safak C, Erdogan H. Palaska E. Sunal. R, Duru S. Synthesis of 3-(2-pyr-idylethyl) Benzoxazolone derivatives. Potent Analgesics and Anti-inflammatory Compound. Inhibiting prostaglandin E2 *J. Med. Chem* 35, 1296. **(1992)**

[32] Onkol,T. ahin,M,F, Yildriem,E, Erol K. Ito,S; Arch.Pharm Res. ,27,1086 (2004)

[33]. Gokhan N. et al, Synthesis of some new pyridylethylated Benzoxa(thia)zolinones with analgesic activity, *Turk J. chem* 28: pp 123-132**(2004),**

[34]Safak C., Erdogan H., Palaska E., Sunal R., Duru S., Synthesis of 3-(2-Pyridylethyl) Benzoxazolinone Derivatives: Potent analgesic and anti-inflammatory Compounds Inhibiting Prostaglandin E2 *J.Med. Chem.*, 1992 35;1296**(1992)**

[35] Qin et al, synthesis and biological Evaluation of 1,3 – dihyroxyxanthone Mannich base derivatives as anticholinesterase agents; *Chemistry central journal*, 7:78 (http://journal.chemistrycentral.com/content/7/78)**(2013).**

[36] Zaho G and Lu M; one pot green procedure for the Mannich Reaction catalyzed by a test – specific ionic liquid, *chiang mai journal of science*: 39 (1).**(2012)**

[37]. Erdoğan H., Analgesic and antiinflammatory activity of some new mannich bases of 5-nitro-2-benzoxazolinone, *Arch pharm. Res*. 30(4); pp 419-424 **(2007)**

[38]. Suman, B., Neha., S., Kajal, A., Sunil, K., Vipin, S.; Mannich bases: An important pharmacophore in the present scenario. *International Journal of Medicinal Chemistry*, **(2014),**

[39] Arzinem.-Forsh. / Drug Res. 41 (I), 1, 73-76 **(1991)**