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Advisor

Assist. Prof. Dr. Yusuf MÜLAZİM

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All praise, be to almighty God, the creator and sustainer of my life, who has given me the wisdom to conduct this thesis, May his blessing and reward be to the last and noble Prophet Muhammad (p.b.u.h.) and his companion.

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DEDICATION

I dedicate this research work to my beloved parent, late Safiyya Mukhtar Bichi and late Yusif Suleiman Bichi and all those who have lost their life due to boko haram insurgency. May their gentle soul rest in perfect peace and Jannatul fir'daus be their final abode.

ABSTRACT

2(3)-Benzoxazolinone and its derivatives are important compounds reported to have diverse biological activity, particularly analgesic and anti-inflammatory. The versatility in its reactivity, made this molecule desirable in medicinal and pharmaceutical research in efforts to develop a drug candidate. Structural modification of it usually occurs at 3-, 5-, 6- and 7-position. In this study, benzoxazolinone was reacted at 3-position with piperazines and piperidine derivatives using Mannich reaction condition. The synthesis was carried out under reflux and microwave assisted heating techniques. The yield obtained, using microwave assisted heating condition, was found relatively higher than that obtained using reflux heating condition. The structures were characterized and confirmed by melting point determination, TLC, FT-IR and ^{1}H NMR spectroscopy.

Keywords: 2(3)-benzoxazolinone, Microwave Assisted Organic Synthesis, Mannich Reaction, Green Chemistry.

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ABBREVIATION

NAISDs – Non steroidal Anti-inflammatory Drugs

COX – Cyclooxygenase

ADME – Absorption, Distribution, Metabolism and Excretion

DMF – N,N-dimethylformamide

PPA – Polyphosphoric Acid

MW – Microwave

DMSO – Dimethyl sulfoxide

FT-IR – Fourier Transform Infra-red

^{1}H NMR – Proton Nuclear Magnetic Resonance

TLC – Thin Layer Chromatography

TMS - Tetramethylsilane

1. INTRODUCTION

Understanding of nature and mechanism of pain are elements for developing analgesics. Pain is defined by the International association for the study of pain as "An unpleasant sensory and emotionally associated with actual or potential tissue damage, or described in terms of such damage" [1].

It is classified based on several ways, but the most commonly used is in terms of therapeutic application, in addition to quantitative measurement based on the victim practical and emotional experiences [2].

From an experimental perceptive, pain is divided into three types, each differed from one another by mechanism; (1) nociceptive tissue pain. (2) Neuropathic pain; originated from injury or irritation to the nerves themselves, like in diabetic neuropath and (3) Inflammatory pain result from inflamed joints or other somatic cells [3].

Pain can be considered as acute or chronic. Acute pain is defined as a pain of recent assault and probable limited duration [4]. It is often associated with a precipitating event for example trauma or surgery.

The symptom is commonly physiologically vital as it can prevent potential tissue damages [5].

There is continues demand to develop effective pain relief (analgesic) drugs with pharmacologically least side effect, led to search for more effective analgesic [6]. It was found Benzoxazolinone compounds shows analgesic and anti-inflammatory activity. Therefore much study needed to exploit its potency.

The aim of this thesis is the synthesis of 2-benzoxazolinone derivatives prepared by mannich reaction with phenylpiperazine, 3-(trifluoromethylphenyl) piperazine and 4-methylpiperidine substituents at 3-position of the ring, using both reflux and microwave reaction. The compounds will be characterized by Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Fourier Transform Infra-Red (FT-IR) spectroscopy. The purity of the compounds was determined by melting point and thin layer chromatography (TLC).

2. LITERATURE REVIEW

2.1 ANALGESIC

Analgesic drugs are compounds that reduce or eliminate pain. It could be through medication or process of suppressing of painful sensation [7].

The major groups of analgesics in the markets are the opioids such as morphine, codeine (figure 2.1) and the non-steroidal anti-inflammatory agents (NSAIDs) including aspirin, paracetamol and Ibuprofen. The opioids perform their functions in central nervous system while non-steroidal anti-inflammatory drugs performs their functions peripherally through inhibiting production of prostaglandin, but reversely causes gastrointestinal problems [8].

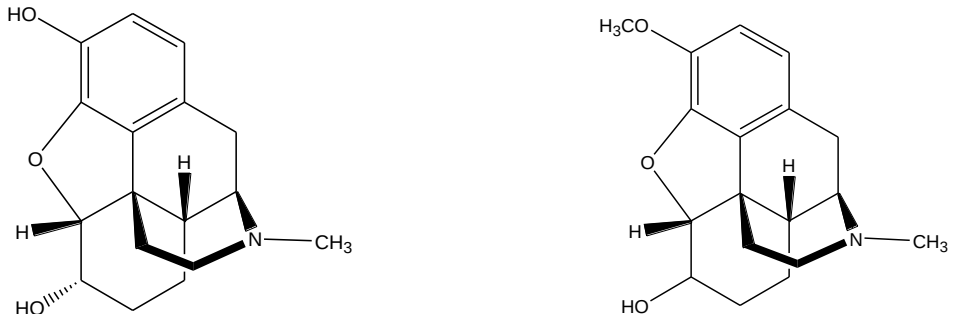
2.1.1 MORPHINE

Morphine is an opiate alkaloid extracted from poppy plant (Papaver Somniferum). It is universally believed by medical historians that, the origin of morphine biological activities was discovered around the 1805 to 1816 by Friedrich Wilhelm Serturner. Owing to addiction and toxicity effects, governments around the world, limit production and mobility of morphine. The ability of morphine metabolites to interact with neuron helps in altering neuronal communication, there by effecting the perception, sensation and consciousness [9].

2.1.2 CODEINE

Codeine is opioid also known as narcotic prodrugs, which is converted to active metabolite morphine [10]. It is sold as a salt, either as codeine phosphate or codeine sulfate in United States. Some countries recommended the use of codeine in very

small concentration and in combination with acetaminophen (as in co-codamol and co-codaphrin [11].



(a) (b)

F**igure 2.1:** Chemical structure of (a) morphine and (b) codeine

2.2 NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

NSAIDs have been reported useful in both veterinary and human medicine as analgesics. It was reported in 1998 that about 50 million U.S people spend $5-10 per year for NSAIDs for treatment and relief of discomfort form diseases and injuries. The ability for NSAIDs to stop inflammation is rest on its ability to inhibit the Cyclooxygenase (cox) enzymes [12]. Based on their mechanism of action NSAIDs were categorized into two major classes:

(1) Non-Selective Cox-1 inhibitors, which can be categorized by chemical families salicylic acid derivatives (e.g. Aspirin, Sodium salicyte); para-amino phenol derivatives; indolacetic acids; heteroaryl acetic acids (e.g. Tolmetin, diclofenac, ketorolac); aryl propionic acid (e.g. Flurbiprofen, ketoprofen, fenoprofen, oxaprofen Ibuprofen, Naproxen,); anthranilic acids (e.g. Mefenamic acid, Meloxifenamic acid); enolic acid (Oxicams) (e.g. piroxicam, Meloxicam, Tenoxicam,Isoxicam), as shown in figure 2.2.

(2) Selective Cox-2 inhibitor, such as Indole acetic acid (Etodolac); sulfonanilide (e.g. Nimesulide); diery substituted furanones (e.g. Refecoxib); Diery substituted Pyrozole (e.g. celecoxib). All of the NSAIDs (figure 2.3) are inhibiting cyclo-oxygenase (Cox) enzymes which causes decreases in production of various prostaglandins and thromboxane as clarified by Sir John Van 1971 [13].

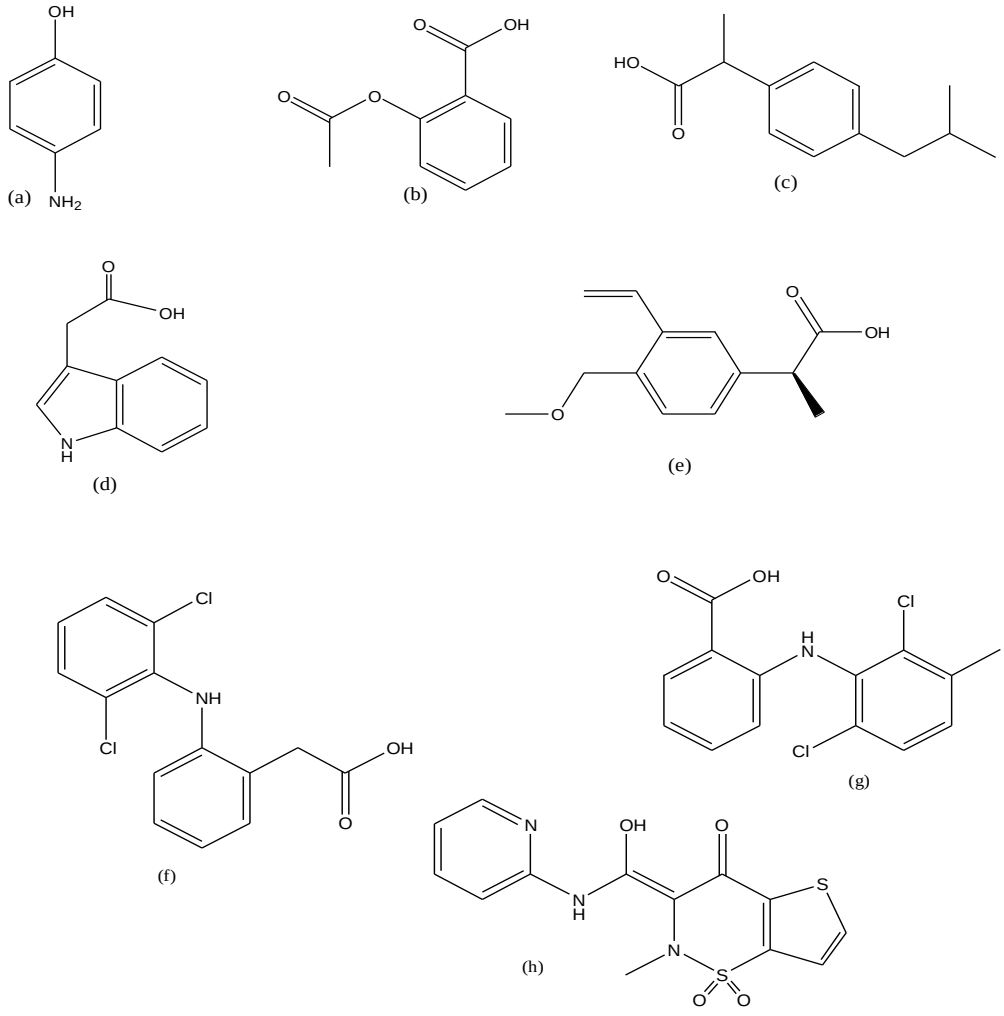


Figure 2.2: Examples of NSAIDs (non-selective Cox-1 inhibitors), structure (a) para-amino phenol, (b) aspirin, (c) ibuprofen, (d) indole acetic acid, (e) naproxen, (f) diclofenac, (g) meloxifenamic acid, (h) tenoxicam.

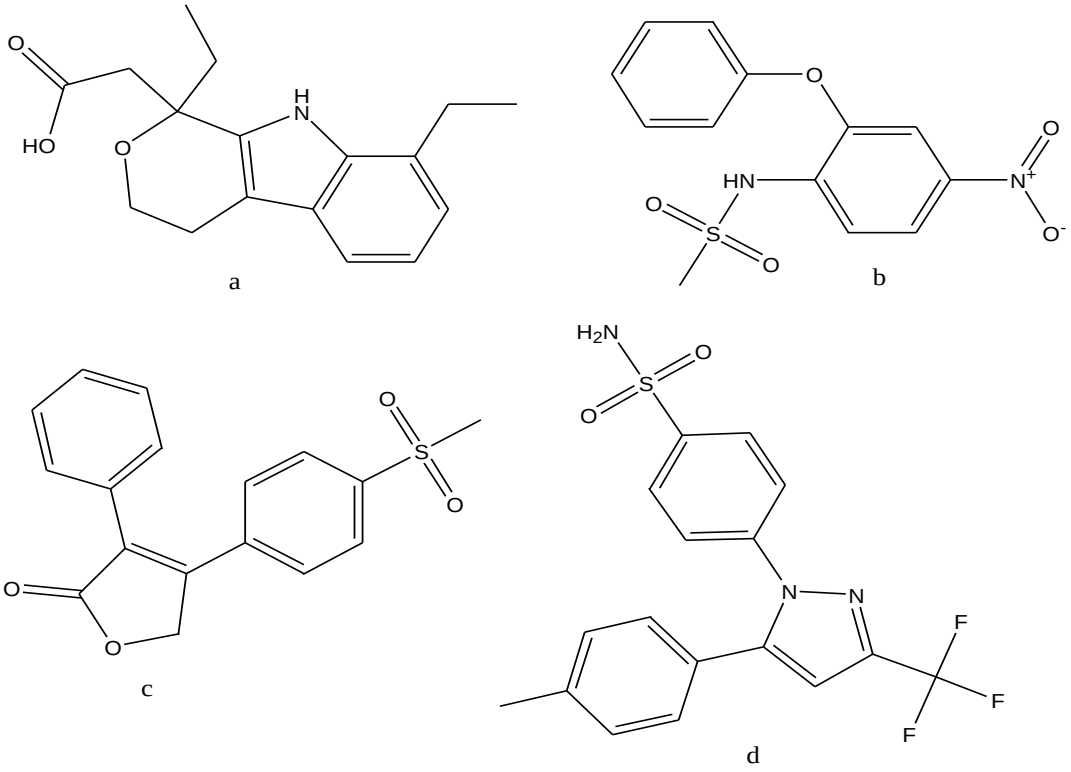


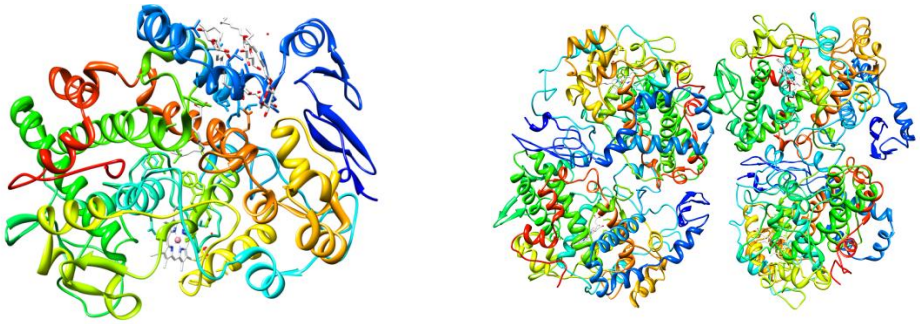
Figure 2.3: Examples of NSAIDs (non-selective Cox-2 inhibitors), structure (a) etodolac, (b) nimesulide, (c) refecoxib, (d) celecoxib.

2.2.1 CYCLOOXYGENASE (COX) ENZYMES

"Inflammation is the consequence of immune system's response to injuries and infections which has been implicated in the pathogeneses of cancer, arthritis, stroke and neurodegenerative as well as cardiovascular disease. The response is inseparably helpful event, since it causes the ejecting of offending factors and regaining of tissue structure and physiological activity" [14].

Cyclooxygenase (cox), enzymes are fundamental enzymes that are responsible for conversion of arachidonic acid (AA) to prostaglandins (PGs). There are two cyclooxygenase isoforms (cox-1 and cox-2) each possessed separate but joined active

site. Human Cox-1 and Cox-2 are homodimer of 576 and 581 amino acids respectively. All of them carry three high mannose oligosaccharide among them one is responsible for the facilitating protein folding. There is fourth oligosaccharide in the cox-2 enzymes which regulates its degradation. Cox-1 gives PGs needed for homeostatic activity such as homostasis and gastric cytoprotection, while Cox-2 plays its role in tumorigenesis and PG synthesis. This Cox-2 supposition catalyzed the rate of developing selective Cox-2 inhibitors that were assumed to have anti-inflammatory activity without causing gastrointestinal disorder, which is known characteristic of some NSAIDs [15].



Cox 1 Cox 2

Figure 2.4: Crystallographic structure of cox 1 complex with flurbiprofen and uninhibited cox 2 enzymes.

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 [16]. Conventionally nonspecific NSAIDs inhibit both Cox-1 and Cox-2.

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 [17]. Furthermore, much of the NSAIDS toxicity, particularly gastrointestinal is associated with Cox-1 inhibition [18].

2.3 2(3H)-BENZOXAZOLINONE

2-(3H)-Benzoxazolinone is a light brown, powdered material, having 138℃ melting point, heterocyclic and bicyclic ring system, composed of a phenyl ring fused to a carbamate [19]. The structure of the Benzoxazolinone possessed two important properties, which attracted the attention of medicinal and pharmaceutical chemists: the hydrophilicity and lipophilicity. Hydrophilicity is attributed to the containing nitrogen and oxygen a term which participate in hydrogen bonding and contributed to high dipole moment of the compound. The bulkiness of the compound is also good factor in lipophilicity of benzoxazolinone. Its lipophilicity helps the structure for proper binding to hydrophobic protein receptor in animal. These properties of benzoxazolinone play a vital role in its absorption, distribution, metabolism, and excretion (ADME) in the body. Many researchers had subjected Benzoxazolinone to bioisosterical optimization at 3-position, and have found to undergo different biological activities which includes; anti-convulsion, antibacterial, anti-fungal, effects etc. [20]. Figure 2.5 below gives the structure of Benzoxazolinone.

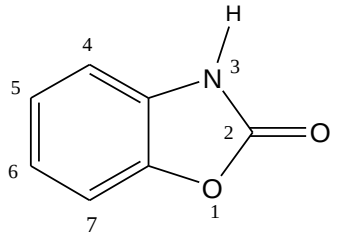
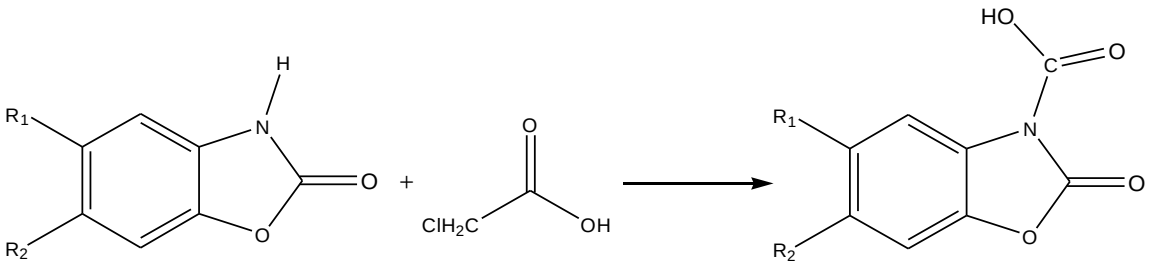


Figure 2.5: Structure and numbering of 2(3H)-benzoxazolinone.

2.3.1 REACTIONS AND REACTIVITY OF BENZOXAZOLINONE

Benzoxazolinone can undergo substitution reaction at 3-, 5- and 6-position, sometime 7-position but is rear, at 3-position qualified it to undergo N-substitution reaction via Friedel Craft alkylation and acylation in addition to its qualification to mannich reaction. Doğruer et al reported the synthesis of Benzoxazolinone derivatives by N-substitution reaction in the presence of sodium ethoxide. The reaction is presented in the figure 2.6 [21].

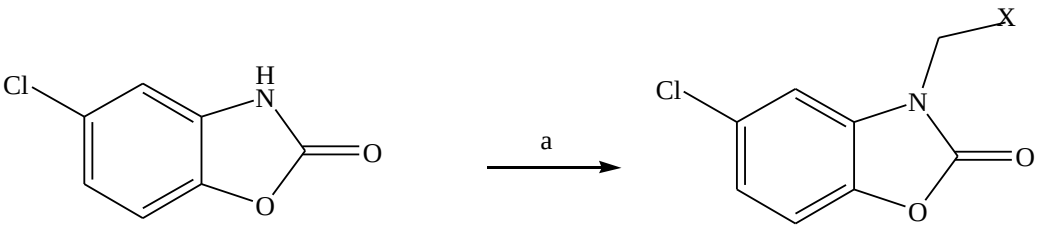


R_1 = Cl, H,

R_2 = H, CH_3, C_6H_5CO, 2-ClC_6H_4CO

Figure 2.6: N-substituted reaction of Benzoxazolinone.

Soyer et al described the synthesis of Benzoxazolinone derivatives via N-substitution reaction by mannich reaction (figure 2.7) [22].

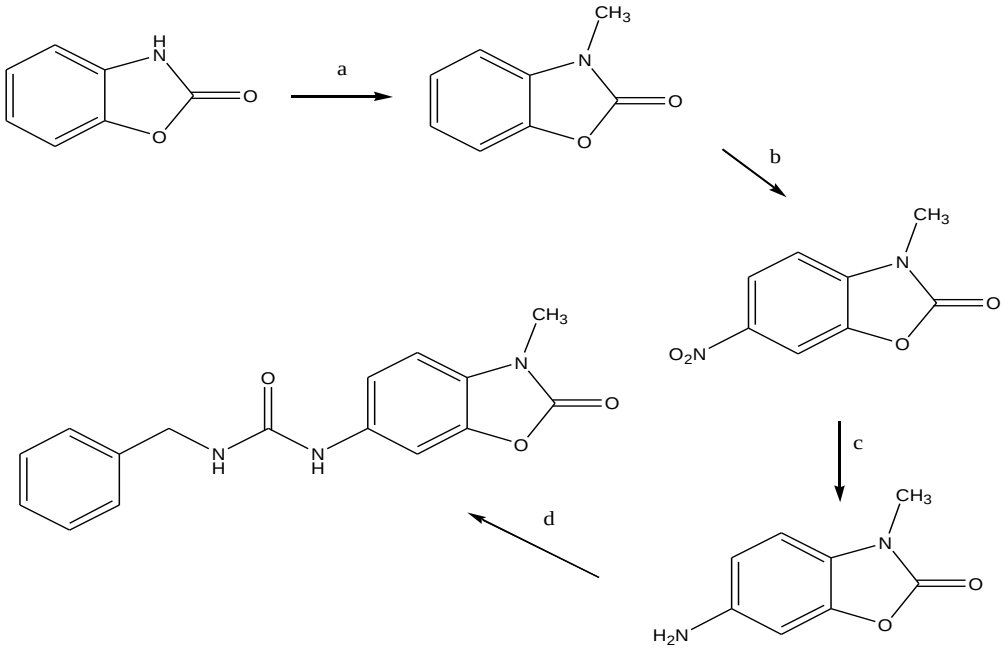


(a) 37% formalin /meOH, amine

X = piperidine, methylpiperidine

Figure 2.7: Example of N-substitution reaction

Y. Gùlkok et al utilized the 6-position and 3-position of Benzoxazolinone in their reaction path to synthesize their target product. The reaction involve N-substitution reaction at 3-position and electrophilic aromatic substitution reaction at 6-position of the structure. The reaction took place according to figure 2.8. [23].



(a) $(CH_3)_2SO_4$, $NaOH/H_2O$
(b) HNO_3
(C) $SnCl_2$
(d) $C_6H_5CH_2$-N=C=O

Figure 2.8: Substitution reaction at 3- and 6-position of Benzoxazolinone.

2.3.2 BIOLOGICAL ACTIVITY OF BENZOXAZOLINONE

Benzoxazolinone derivatives have been reported with different biological activities in both plants and animals, such as antimicrobial, antifungal, anticonvulsant, analgesic anti-inflammatory activity and as allelochemicals in plants [3-11].

Benzoxazolinone derivative known as 1-phenyl-3-(3-methyl-2-benzoxazoline-6-yl)-1H-pyrazol-4-carboxyaldehyd was designed and synthesized using Vilsmeier reaction condition [24] to be used as starting material to produces the target product 1,3-diaryl substituted 1H-pyrazole derivatives (figure 2.9) as bifunctional inhibitors of cyclo-oxygenase and thromboxane synthase enzymes [25].

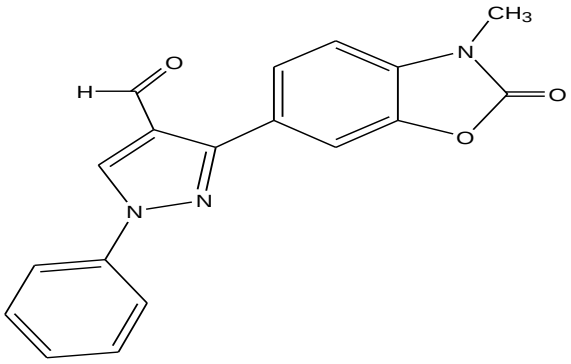
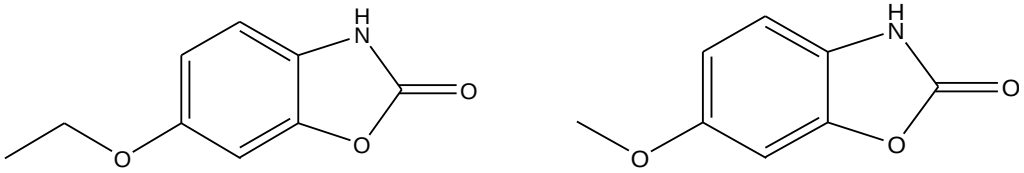


Figure 2.9: 1,3-diaryl substituted 1H-pyrazole product

Due to common side effects, such as ulceration and gastrointestinal hemorrhage of NSAIDs, numbers of Benzoxazolinone derivatives were synthesized of which some were found with anti-oxidant activity and can also work as free radical scavengers, due to their possession of analgesic anti-inflammatory impact. Some Benzoxazolinone compounds exist and produce naturally in wheat, rye and corn as

allelochemicals [26]. 2-Benzoxazolinone, 6-methoxy-2-benzoxazoline and 6-ethoxy-2-benzoxazolinone (figure 2.10) had revealed auxine inhibitory property. However, the transformation of the pharmacophore moiety on given position in the structural formula played an important role in changing the bioactivity of the compounds for example, as it is found, when methyl chain at position C-6 on 2-benzoxazolinone [27-28].



a b

Figure 2.10: Structures of (a) 6-ethoxy-2-benzoxazolinone and (b) 6-methyl-2-benzoxazolinone.

Moreover, Benzoxazolinone was reported to have inhibited the stem length of same plant with a significant value [28].

Krawiecka et al synthesized a novel biological agent of N-substituted 1,3-benzoxazol-2-(3H)-one; 5-chloro-1-3-benzoxazol-2(3H)-one; and 6-bromo-1,3-benzoxazol-2(3H)-one. All the compounds were tested for anti-microbial activity against a selective of Gram-positive and gram-negative bacteria and yeast. The compound below in figure 2.11, have shown antimicrobial activity against Gram-positive Cocci represented by E. coli. The compound inhibits the growth of bacteria at 512mg/L concentration [29-30].

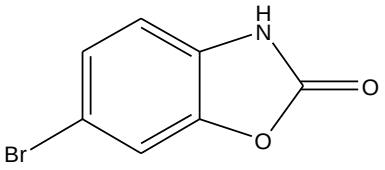


Figure 2.11: 6-Bromo-2(3H)-benzoxazolinone compound that have shown antimicrobial activity.

As it is in literature, the structural activity relationship of Benzoxazolinone in plant depends on the active pharmacophore present at position 6-position. Series of investigation disclosed that, dissociation of proton from the molecule take place at Nitrogen atom of the 2-(3H)-benzoxazolinone ring system and, the analgesic/ anti-inflammatory activities of the named benzoxazolinone derivatives compound decrease when pKa values of the compound decrease and vice versa [27,31].

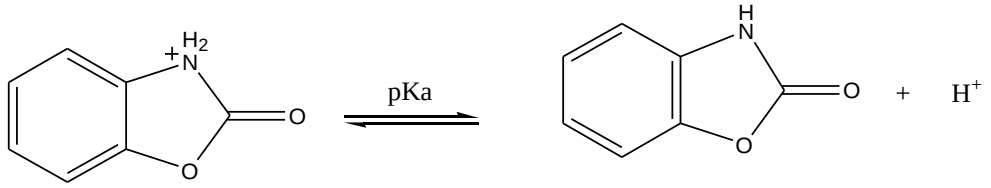
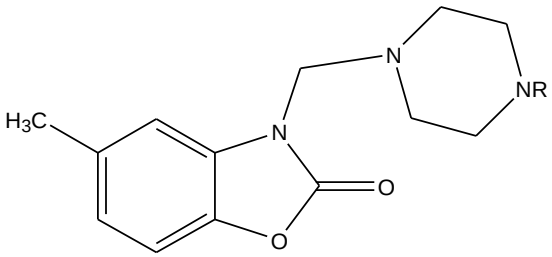


Figure 2.12: Deprotonation at quaternary amine moiety.

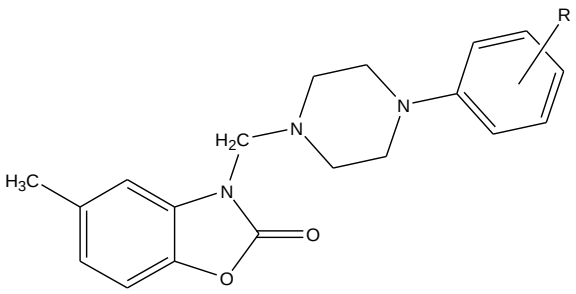
In their effort to discovered better analgesic, anti-inflammatory compounds, Gokhan and coworker have synthesized derivatives of 5-methyl-3-substituted piperazinomethyl-2-benzoxazolinone (figure 2.13). The most interesting property of the subject compounds synthesized is their basic natures, which have made them to differ from other acidic non-steroidal anti-inflammatory compounds [32].



R = acetylphenyl, 2-pyrimidinyl, 3-trifluoromethylphenyl, 2-pyridyl, benzyl, piperonyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl.

Figure 2.13: 5-methyl substituted benzoxazolinone.

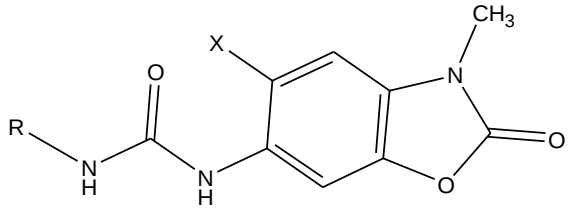
In the same study, it was observed from the result that non substituted 2-benzoxazolinone comparatively produced weak antinociceptive activity. It is also worthy to note that in this study the pronounced analgesic activity was observed from the products obtained with substituents (phenylpiperazine) having electron-withdrawal atoms at 4-position of phenyl substituents. Moreover, the presence of electron-donating group, example methoxy, or methyl on the 3-position of the phenyl nucleus nullified the analgesic properties of the compound (figure 2.14) [32].



R = 4-fluorophenyl, 4-chlorophenly, 3-methoxyphenyl, 3-methylphenyl

Figure 2.14: 5-position substituted benzoxazolinone shown antimicrobial activity

In another research to discover new anti-microbial compounds Tuba and coworker synthesized benzoxazolinone containing derivatives. Antimicrobial against pathogenic strains, found compounds (I-IV) (figure 2.15) possess inhibitory activity against E. coli. [33].



(I) R = benzyl, X = H,

(II) R = 4-chlorobenzyl, X = H,

(III) R = 2-phenylethyl, X = Cl,

(IV) R = benzyl X = Cl,

Figure 2.15: Examples of compounds containing substituents at 5-position, which shown antimicrobial activity.

Considering the structural activity of the above mentioned compounds, it was found out that chloro substituent at 5-position in the 3-methyl-2-(3H)-benzoxazolone have shown no effect in the antibacterial activity of the studied compounds [33].

In another approach by H. Erdogan in 2007 finding an improved analgesic anti-inflammatory active compound 5-nitro-3-piperazinomethyl-benzoxazolinone (figure 2.16) was synthesized. The compounds demonstrate an attractable basic property which is a good determinant factor in predicting its hydrophilicity [34] and [35].

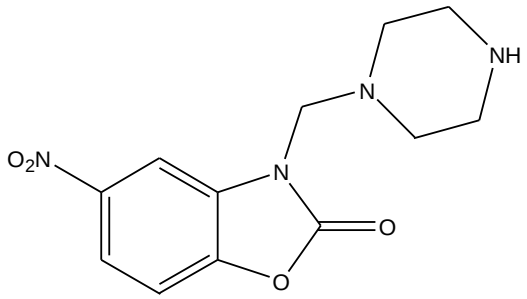


Figure 2.16: Structure of 5-nitro-3-piperazinomethylbenzoxazolinone

Gokhan et al reported the synthesis of Benzoxazolinone derivatives containing acyl and halo group at 6 and 5-position of benzoxazolinone structure respectively [36]. The reaction took place according to the figure 2.17 given below.

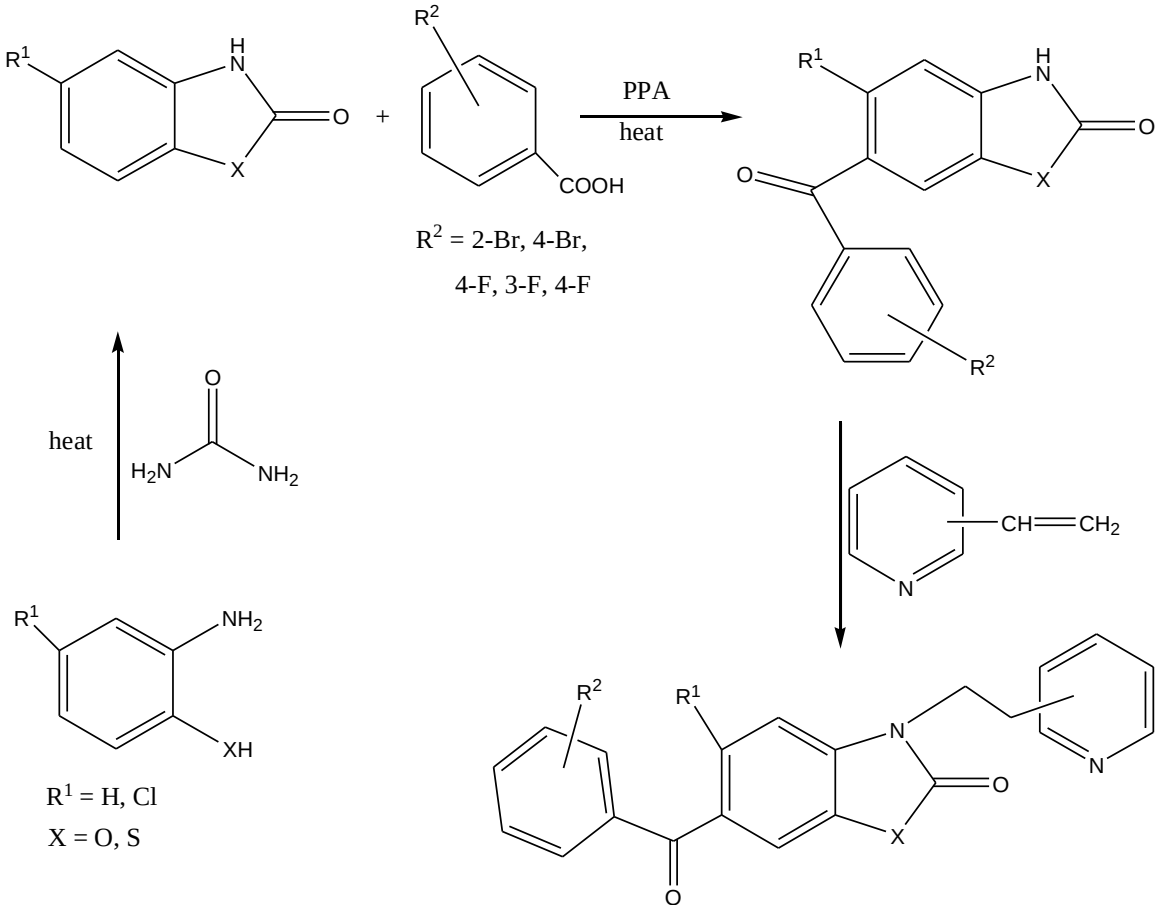
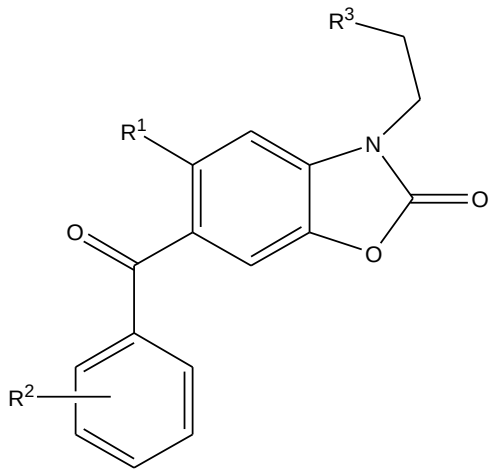


Figure 2.17: Benzoxazolinone substituted at 3-, 5- and 6-position

The authors explains that the Nitrogen of the benzoxazolinone have been the director of the substitution and the product obtained with bromobenzoyl moiety substituents shows best analgesic activity compared to the products resulted from fluorobenzoyl moiety as substituents (figure 2.18). It was also found out that presence of Cl atom at 5-position of the benzoxazolinone derivatives (a, b, c and d) exhibit better analgesic activity than the unsubstituted derivatives (e, and f) figure 2.18 [36].



a : R^1 = H, R^2 = 2-Br, R^3 = 4-pyridyl

b : R^1 = H R^2 = 2-Br R^3 = 2-pyridyl

c : R^1 = Cl, R^2 = 2-Br R^3 = 4-pyridyl

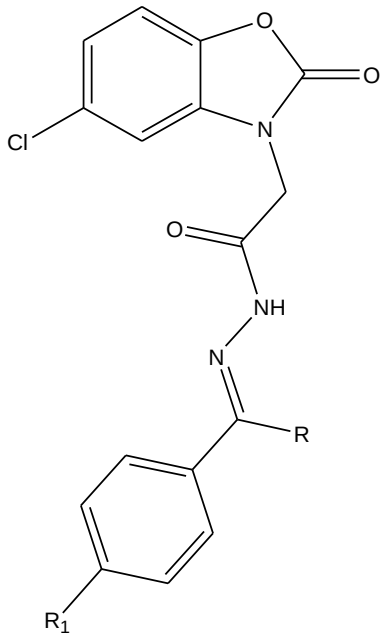
d : R^1 = Cl, R^2 = 2-Br R^3 = 2-pyridyl

e : R^1 = Cl, R^2 = 4-F R^3 = 4-puridyl

f : R^1 = Cl, R^2 = Cl, R^3 = 2-pyridyl

Figure 2.18: Benzoxazolinone containing substituents at 5-position.

Modiya et al in their recent article presented six benzoxazol-2-one derivatives with various substituents at 3-position. These substituents were reported been potent anti-microbial agents. Therefore, incorporating them with azole made them more active (figure 2.19) [37].



Where R = H, CH_3.

R_1 = H, F, Cl, Br, OH, OCH_3.

Figure 2.19: Example of benzoxazolinone derivatives containing azole group.

2.4 MANNICH REACTION

Mannich reaction provides important pathway for researchers in their efforts to discover new drug candidates [35-37]]. It is among the most basic and noted method for synthesis of β-amino carbonyl compounds and has been also the very useful in organic chemistry because of its diverse application in various pharmaceutical production [38].

Mannich bases were synthesized using Mannich reaction as reported in uncountable number of researches, such as 1,3-dihydroxyxanthone which has revealed inhibitory activity against Acetylcholinesterase(AChE) and Butyrylcholinesterase (BuChE) [39-40]. The Mannich base serves as paramount pharmacophore or bioactive leads

compound, which were used for preparation of highly valued medicinal agents with amino alkyl chain as it is common in fluoxetine, (a); cocaine, (b); Trihexyphenidyl, (c); atropine, (d); Biperiden, (e); procyclidine, (f); Ranitidine, (g); (figure 2.18). Below is the representation of Mannich reaction (figure 2.20) [41-42].

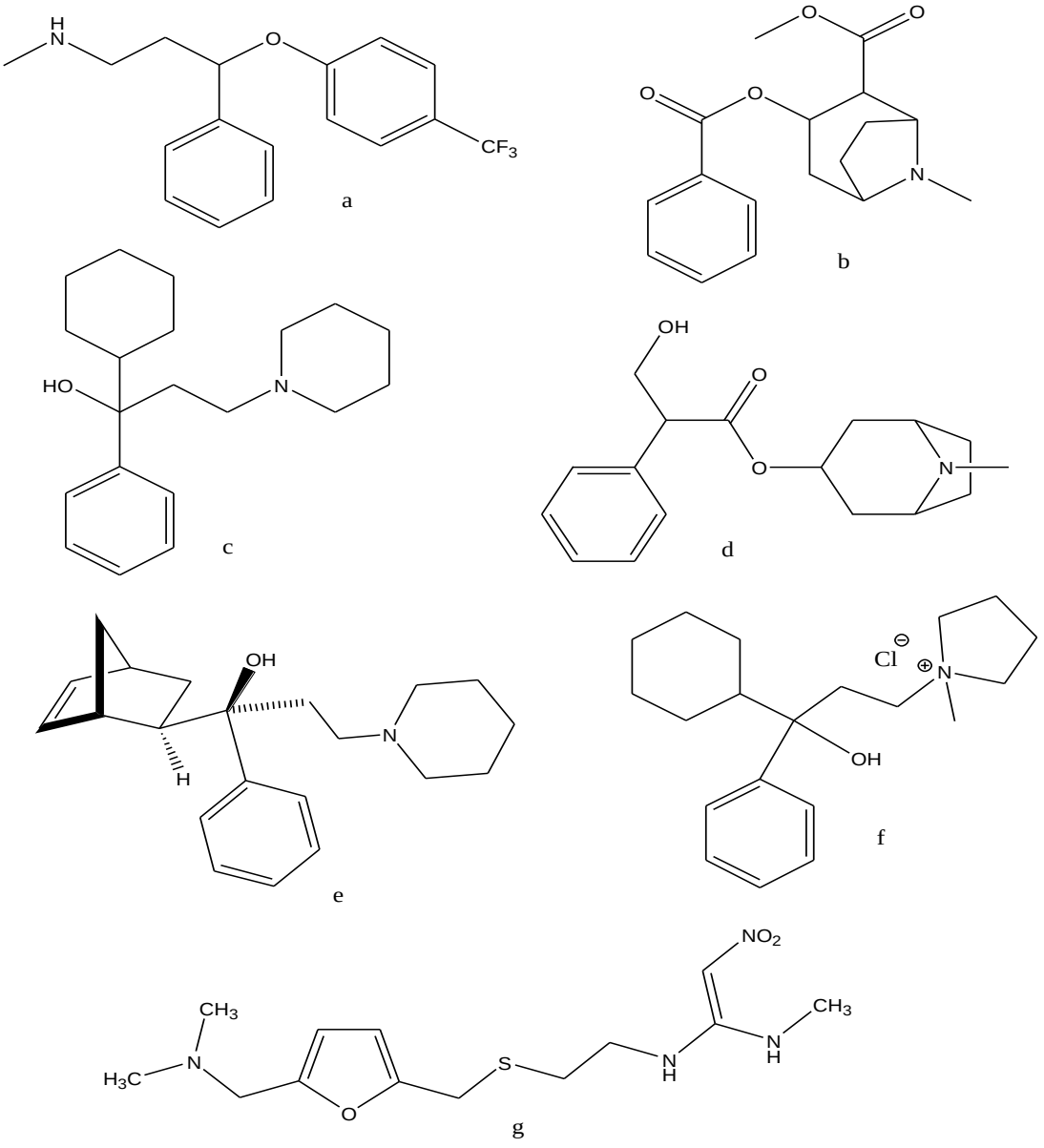
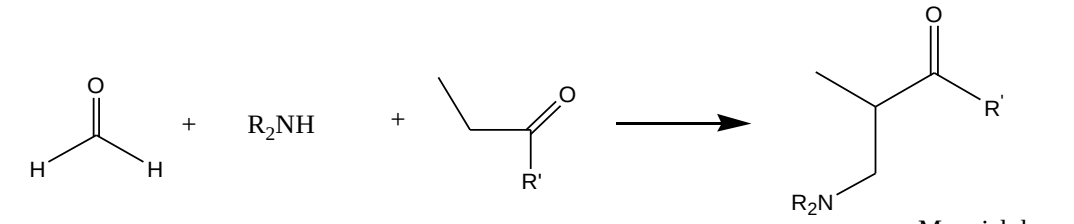


Figure 2.20: Example of compounds containing Mannich base.



Non enolizable aldehyde | 1^0 or 2^0 amine | Enolizable ketone | Mannich base

R and R′ = alkyl, or aryl

Figure 2.21: Representation of mannich reaction.

Mannich reaction also played a vital role in optimizing bioisostere of Artemisinin derivatives. The existence of Mannich side chain in the structure enhances lipophilicity and thus bioavailability of the drugs active ingredients in the body. The increase popularity and widespread of Mannich reactions has been due to properties of physiological and psychological properties of Nitrogen containing compounds in synthetic and natural products [37,43-44].

2.5 GREEN CHEMISTRY

The green chemistry is defined as “the discovery, design and utilizing chemical product and processes to minimize or to eliminate the use and generation of hazardous substances”. Centuries ago, chemist thought that chemical reaction occurs only in liquid state or if dissolved. This has made solvent paramount in chemical synthesis, despite its environmental impact [45].

Historically, chemists have been using different heating method in chemical laboratory. Heating process was first invented by Robert Bunsen in 1855, when he invented Burner which act as energy resource for heating in endothermic reaction.

Isomantle, oil bath or plate (figure 2.22) superseded the burner, but the heating process remains the same [46].

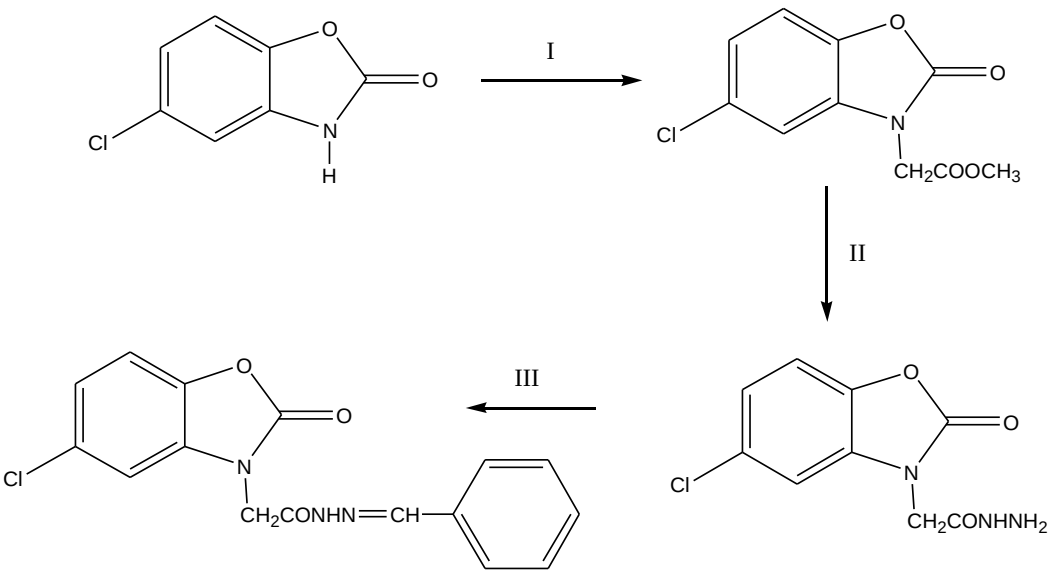
flame oil bath heating mantle

Figure 2.22: Example of conventional heating devices

Green chemistry sufficiently and efficiently utilizes available raw material (preferably renewable), eliminate waste, and vanishes the use of hazardous solvents and reagents in synthesis of new compounds [47]. Microwave reactors could be used to replace traditional heating methods as they reduce waste, time needed thus less environmental effect.

2.5.1 MICROWAVE ASSISTED ORGANIC SYNTHESIS

Microwave assisted organic synthesis has emerged as opportunity to carry out synthesis that is historically not feasible by time. The technique involves clean, simple, efficient, fast and economically desirable, in synthesis [48].



(I) $ClCH_2COOCH_3, K_2CO_3$/Acetone

(II) $HNNH_2.H_2O$

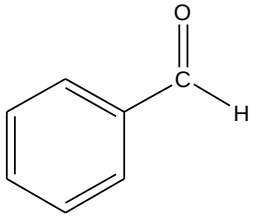
(III)  (400 W, 76-78 °C) for 15 min.

Figure 2.23: Example of microwave reaction

.

Microwave heating principle involves the use of electromagnetic energy having lower frequency at the end of electromagnetic spectrum (300-300000MHz) [49].

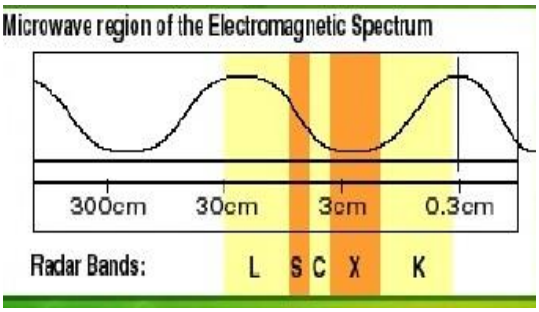
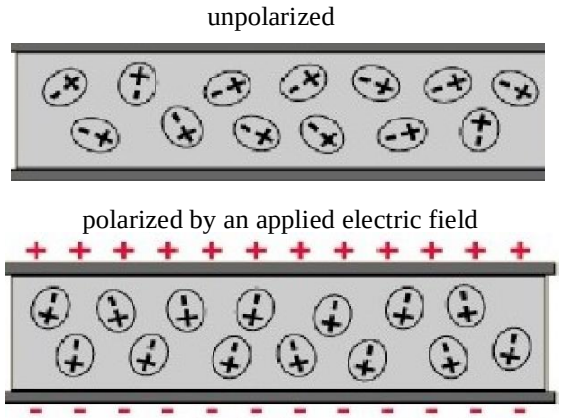


Figure 2.24: Microwave region of electromagnetic spectrum.

2.5.2 TECHNIQUES OF MICROWAVE ASSISTED ORGANIC SYNTHESIS

The fundamental principle of the microwave assisted organic heating technique is due to interaction of charged particle of the reaction material with the electromagnetic wavelength of a fixed frequency. The technique involves, transmitting of thermal energy by electromagnetic irradiation either by conduction or collision, in some cases by both. All the wave energy convert its polarity to negative with each cycle of the wave, as a result of such, rapid orientation and reorientation occurs, and thus, heating by collision (figure 2.25) [50].



Figures 2.25: Dipole orientation according to electric field

Moreover, for the material to be heated, substance has to possess a dipole moment, since the dipole is influencing in external electric field by rotation. When subjected to an alternative current, electric field is reversed at each alterant and this dipole and thus dipole tends to move simultaneously to the inversed electric field, due to this rotation and friction of the molecules occurs which dissipates as internal homogeneous heating. The electric field often used irradiation frequency of 2450MHz which produced $4.9x10^9$ oscillators per second. Therefore, microwave heating is directly dependents upon dielectric constant (ε′) and dielectric loss (ε″) gıves ın equatıon 1. The relation given below explains the ability of the material to generate heat energy from electromagnetic energy at a given temperature and frequency [50-51].

$$\varepsilon''/\varepsilon' = \tan\delta \qquad \text{eqn (1)}$$

Where δ defined as “dissipation factor” or “loss tangent” of the sample, ε′ is the dielectric constant, and ε″ is the dielectric loss. And higher value of δ shows larger probability to microwave energy [52].

2.5.3 LOSS ANGLE

Microwave heating needed polar solvent and/or ions. The microwave heating effects vary with the solvent use. The Dielectric polarization occurs due to ability of dipole to re-orientate in an applied field. It is also known that, more polar solvent do have higher dielectric constant, which is more readily microwave irradiation to be absorbed and convert it into heat energy hence, attaining higher temperature, . This scenario is observed in microwave heating of dioxane and water. (figure 2.26) [53].

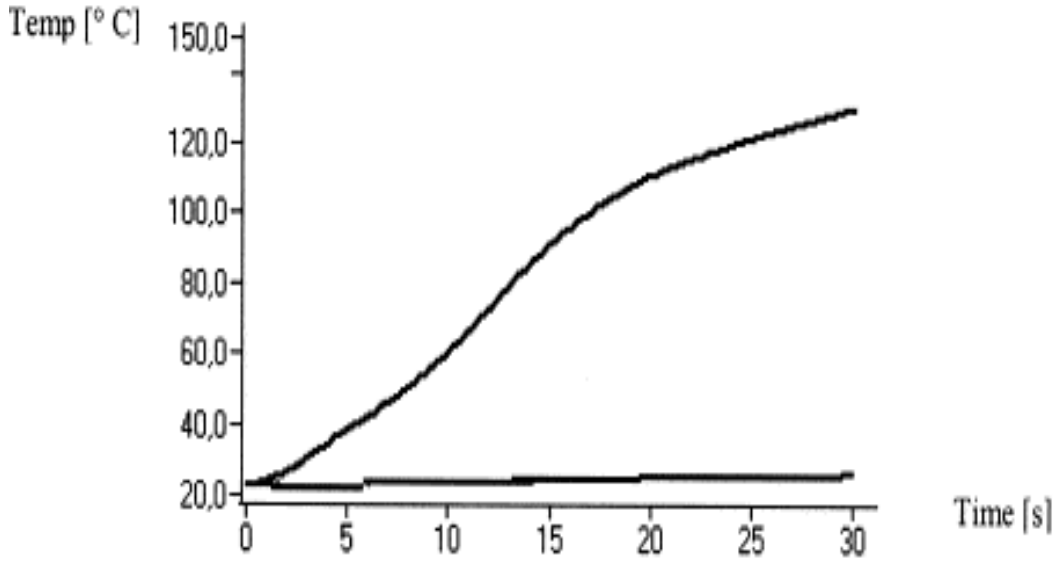


Figure 2.26: The temperature increase of water and dioxane, respectively, at 150W irradiation, the upper curve represents water and the lower plot represents dioxane.

However, the heat generated by conduction mechanism due to presence of ions that formed hydrogen bonding in water, add to heat generated by dipolar mechanism, resulting the higher final temperature of the water than dioxone [52-53].

Table 2.1: Dielectric constants and loss tangent values for some solvents relevant to organic synthesis, the values were determined at 2.45GHz and room temperature.

SOLVENTS	DIELECTRIC CONSTANT, (ε′)	LOSS TANGENT $(tan\ \delta)^a$
Hexane	1.9	
Benzene	2.3	
Carbon tetrachloride	2.2	
Chloroform	4.8	
Acetic acid	6.1	0.091
Ethylacetate	6.2	0.174
THF	7.7	0.059
Methylene chloride	9.1	0.047
Acetone	20.6	0.042
Ethanol	24.6	0.054
Methanol	32.7	0.941
Acetonitrile	36.7	0.069
Dimethylformamide	36.7	0.062
DMSO	47	0.161
Formic acid	58	0.722
Water	80.4	0.123

2.5.4 TEMPERATURE-TIME RELATIONSHIP IN MICROWAVE HEATING

According to Arrhenius equation," time of reaction decrease by half value when the reaction temperature increases by 10℃ ". For example when a polar solvent, (ethanol) at 80℃ is run in 8 hours. If the Arrhenius law is applied, time will reduce in a pattern given in the table 2.2, [54].

Table 2.2: Table of temperature-time dependence.

Temperature (℃)	time	Temperature (℃)	Time
80	8hrs	120	30mins
90	4hrs	130	15mins
100	2hrs	140	8mins
110	60mins	150	4mins

Looking at the above table, one may understand that, the time is reduced from 8 hours (480 minutes) to 4 minutes, when reaction temperature is increase by 70℃ .This procedure is applicable to all reaction. Moreover, when a new reaction is carrying out which has never been conducted in both conventional and microwave assisted heating, the temperature is fixing 30-40℃ higher than the solvents boiling point and reaction is run for about 10 minutes [55].

The first publication on microwave irradiation has been done by group of Gedye, more than 5000 article have been published. Lots of compounds had reported synthesized using microwave techniques [56-57]. Smita et al had published brief review on microwave assisted organic reaction [58].

In 2006 Balm reported a proline-catalyzed direct asymmetric Mannich reaction using Microwave irradiation. The synthesis consumed very short time and the products obtained with only 0.5mol% of catalyst and up to 98% *ee* (figure 2.27) [59-60].

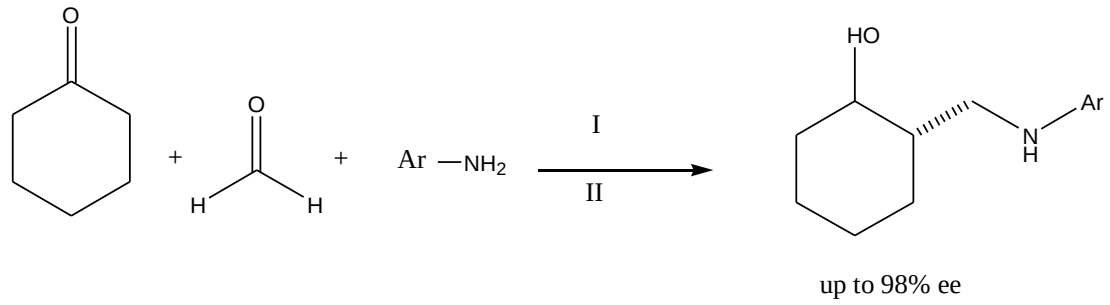


Figure 2.27: Microwave assisted asymmetric Mannich reaction, (I) 0.5% L-proline/mw, DMSO and (II) $NaBH_4$

Ravichandran S. reported, the calcium chloride catalyzed, solvent-free organic reaction under microwave (figure 2.28) [61].

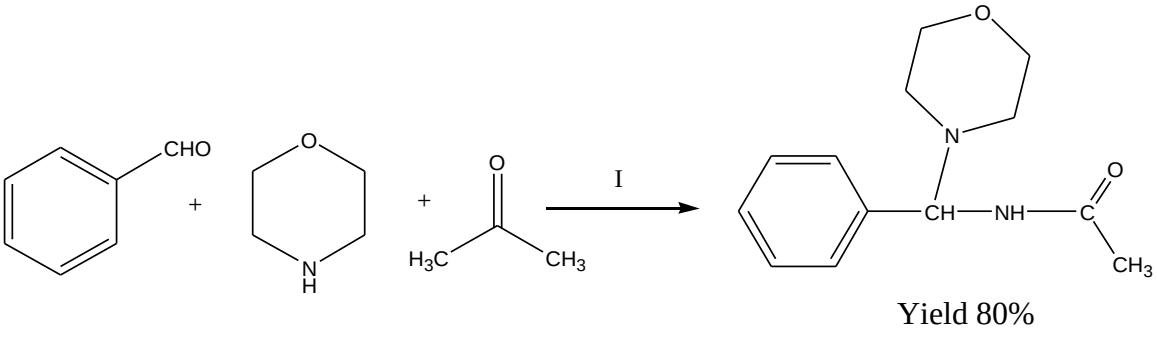


Figure 2.28: Calcium chloride catalyzed microwave Synthesis of mannich bases, (I) 1:1:1 mol ratio, mw (130℃/2min).

2.5.4 CONVENTIONAL VS MICROWAVE HEATING

Microwave heating is unique in relation to conventional heating for numerous regards. The mechanism of heating behind microwave is completely distinctive. Enlisted in table 2.3, are the points that differentiates Microwave heating method from that of conventional heating method [62-63].

Table 2.3: Differences between Conventional heating and Microwave heating.

No.	CONVENTIONAL HEATING	MICROWAVE HEATING
1	Heating take place by thermal or electric source.	Heating is by electromagnetic wave.
2	Heating mechanism involves conduction.	Heating mechanism involves dielectric polarization conduction.
3	Vessels must to be in physical contact with higher heating source (e.g. heating mantle, sand, oil bath, steam bath, etc).	There is no need of physical contact between the reaction vessels and the higher temperature sources.
4	There is transfer of heat from the wall surface of the vessel, to the mixture and eventually to the reactants	The core mixture is heated directly while the vessel wall is source of loss heat.
5	The reaction mixture heating is continuous from a surface often inside the reaction vessels.	Reaction mixture is heated directing is continuous directly inside the mixture.

6	Compounds in a mixture are heating equally.	There could be selective heating of the compounds in the same mixture.
7	Heating rate is less.	Heating rate is several folds high.
8	Highest temperature is achieved by boiling point of the solvent or mixture.	Temperature of the mixture can proceeds beyond boiling point of the solvents by super heating.

3. MATERIAL AND METHOD

3.1 MATERIALS

All reactions were carried out using standard laboratory equipment and standard laboratory glassware. All the chemicals such as phenylpiperazine, 3-(trifluoromethylphenyl)piperazine, 4-methylpiperidine, benzoxazolinone, ethylacetate, cyclohexane, n-hexane, methanol and ethanol the used in this research work were purchased from Sigma Aldrich chemical company and were used as received no further purification was carried out.

3.1.1 Microwave Reaction

Microwave reactions were carried out utilizing Milestone Microsynth (microwave lab-station for synthesis). The reaction temperature and time were varied to get optimum conditions.

3.1.2 Melting Point Determination

The melting point determination of the synthesized compounds was carried out with Mettler Toledo (FP90 central processor) melting point apparatus.

3.2 METHOD

3.2.1 General method for reflux reaction (**method A**)

Solution of 2-benzoxazolinone (0.001mol) in 8ml of methanol was added in 50ml round bottom flask followed by 0.001mol of phenylpiperazines/piperidines. Solution

of 0.2ml of formalin 37% w/w in 2ml of methanol was transfer into this mixture. The mixture was refluxed for 60 minutes in water bath, after which was poured into the crush ice, upon which a precipitate formed. The ice was allowed to melt in the reaction mixture. The crude product obtained was filtered off, washed, dried in oven and purified by crystallization method using appropriate solvent. The product was allowed to recrystallize and then filtered off, washed and dried.

3.2.2 General method for microwave reaction (**method B**)

Solution of 2-benzoxazolinone (0.001mol) in 8ml of methanol and 0.001mol of piperazines/piperadines were added in 50ml round bottom flask. 0.007mol formalin 37% w/w in 2ml of methanol was added to this mixture, placed in a microwave and irradiated (65°C/100W) for 8 minutes. After completion of reaction, it was poured into crush ice. The ice was allowed to melt in the reaction mixture; a resulting precipitate was filtered off, washed, dried and purified by crystallization using appropriate solvent. The product was allowed to recrystallize and then filtered, washed and dried.

3.3 Thin layer chromatography

Thin layer chromatography (TLC) was used to monitor the progress of the reaction using Silica gel with fluorescent indicator 254nm and 0.2mm thickness, as stationary phase. Three different mobile phases were prepared and used. These are:

$S_1 -$ Benzene/methanol: (9:1).

$S_2 -$ Benzene/methanol: (5:1).

$S_3 -$ Ethylacetate/hexane: (1:2).

The products and starting material were dissolved in chloroform and methanol respectively. The silica gel containing spots of both product solution and starting material solutions were well prepared and carefully put in mobile phase chamber. The mobile phase was allowed to move undisturbed on the silica gel plate up to the desired height, and gently removed from, distance covered by the solvent was marked and the plate was allowed to dry. Spots were viewed under UV light of 254nm. The R_f values were calculated.

3.4 SPECTROSCOPY

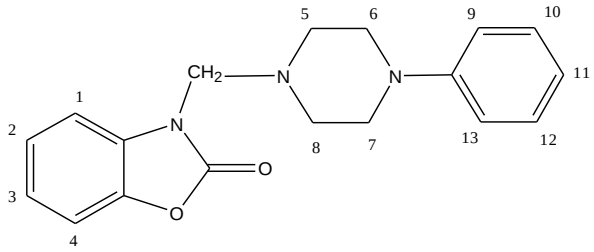
3.4.1 Fourier Transform Infra-Red (FT-IR): It was conducted at Marmara University Faculty of Science and Arts, Chemistry Department. The spectra of the compounds were recorded on a Perkin Elmer spectrum 100 spectrometer with attenuated total reflection (ATR), in wave number (cm^{-1}).

3.4.2 Proton Nuclear Magnetic Resonance (^{1}H NMR): It was conducted at Boğaziçi University, Research and Development Laboratories. The compounds ^{1}H NMR spectra were recorded on Mercury Varian 400MH_z. ^{1}H-NMR spectrometer using deuterated chloroform ($CDCl_3$) solvent, chemical shift were recorded in part per million (ppm) downfield from TMS as internal standard.

4. RESULT AND DISCUSSION

4.1 Results

Compound 1



3-[(4-phenylpiperazin-1-yl)-methyl]-2-benzoxazolinone.

The above compound was synthesized by the both methods (method A and method B) mentioned in experimental section, using the procedure taken from literature [60].

Method A: 200mg (0.001mol) of 2(3H)-benzoxazolinone, and 162mg (0.001mol) 1-phenyl piperazine were dissolved in 8ml of methanol and 0.2ml (0.007mol) of 35% formalin was added to the mixture then refluxed in a water bath for 60 minutes, the mixture started precipitating toward last 10 mins of the heating, but complete precipitate was formed when it was poured onto crushed ice, resulting precipitate was filtered off and purified by crystallization using ethanol as solvent, upon which off-white crystalline compound was obtained: Yield: 55.4% (171.5mg).

TLC in S_1 and S_2 solvent system gave R_f values of 0.68 and 0.49 respectively. The percentage yield and melting point were given in the table 4.2.

Method B: 200mg (0.001mol) of 2(3H)-benzoxazolinone, and 162mg (0.001mol) 1-phenyl piperazine were dissolved in 8ml of methanol and added to 50ml round bottom flask 0.2ml (0.007mol) of 35% formaldehyde was added to the mixture, placed in a microwave and irradiated (65°C /150W for first and 65°C /100W for

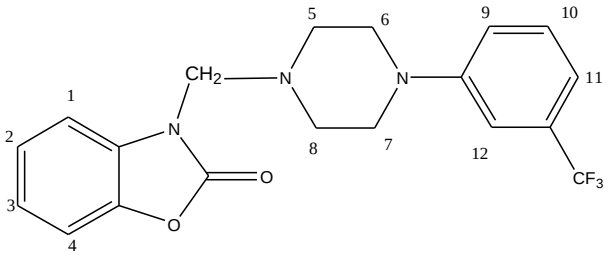
second heating step respectively) for 8 minute, the mixture started precipitating toward the last 2mins of the irradiation, but complete precipitate was formed when it was poured onto crushed ice, resulting precipitate was filtered off and purified by crystallization using ethanol as solvent, upon which off-white crystalline compound was obtained; Yield: 86.5% (267.7mg).

Thin layer chromatography: in S_1 and S_2 solvent system gave R_f values of 0.67 and 0.48 respectively.

Fourier Transforms Infra-Red (FT-IR) Spectroscopy (IR v_{max}): FT-IR showed absorption band at 2846-3071cm^{-1} aromatic (C-H Stretch), 1758cm^{-1} (C=O of carbonyl).

Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR in $CDCl_3$): ^{1}H NMR showed chemical shift at 7.2-6.8 (9H, m, Ar-H); 4.7 (2H, s;CH_2); 2.8 (4H, t; pip $H^6 - H^7$); 3.2 (4H, t; pip$H^5 - H^8$) ppm.

Compound 2



3-[4-(3-trifluoromethylphenyl)piperazinylmethyl]-2-benzoxazolinone.

The above compound was synthesized by the both methods (method A and method B respectively), mentioned in experimental section.

Method A: 200mg (0.001mol) of 2(3H)-benzoxazolinone, 340.78mg (0.001mol) 3-(trifluoromethyl)phenylpiperazine were dissolved in 8ml of methanol, added to round bottom flask and 0.2ml (0.007mol) of 35% formalin in 2ml of methanol was added to the mixture then refluxed in a water bath for 60 minutes, then it poured onto crush ice, where a brown precipitate was formed. When the precipitate filtered off and purified by crystallization using methanol as solvent, a brown crystalline compound was obtained; Yield: 62% (235.3mg).

TLC in S_1 and S_3 solvent system gave R_f values of 0.74 and 0.77 respectively. The percentage yield and melting point were given in table 4.2.

Method B: 200mg (0.001mol) of 2(3H)-benzoxazolinone, and 340.78mg (0.001mol) 3-(trifluoromethyl)phenylpiperazine were dissolved in 8ml of methanol and 0.2ml (0.007mol) of 35% formaldehyde was added to the mixture, placed in a microwave and irradiated (150/100W, 65°C for first and second heating step respectively) for 8 minute, after it was allowed for 10 minute to cooled, it was poured onto crush ice, where a brown precipitate was formed. When the precipitate filtered off and purified

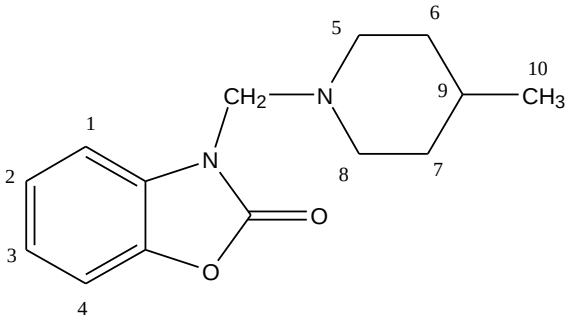
by crystallization using methanol as solvent, a brown crystalline compound was obtained. Yield: 80% (303.0mg).

TLC in S_1 and S_3 solvent system gave R_f values of 0.74 and 0.75 respectively.

Fourier Transforms Infra-Red (FT-IR) Spectroscopy (IR V_{max}): FT-IR showed absorption band at 2822-3065cm^{-1} aromatic (C-H Stretch), 1747cm^{-1} (C=O of carbonyl).

Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR in $CDCl_3$): ^{1}H NMR showed chemical shift at 7.2-7.0 (8H, m, Ar-H); 4.2 (2H, s, N-CH_2-N); 2.3 (4H, t; pip $H^6 - H^7$); 3.2 (4H, t; pip$H^5 - H^8$) ppm.

Compound 3



3-[(4-methylpiperidin-1-yl) methyl]-2-benzoxazolinone

The compound 3 was synthesized by both method A and method B described in experimental part respectively.

Method A: 200mg (0.001mol) of 2(3H)-benzoxazolinone, 146.79mg (0.001mol) p-methylpiperidine were dissolved in 8ml of methanol and 0.2ml (0.007mol) of 37% formalin in 2ml of methanol was added to the mixture then refluxed in a water bath for 60 minutes, after which poured onto crushed ice where light yellow precipitate formed. The resulting precipitate was filtered off and purified by crystallization, using

cyclohexane as solvent. Light yellow crystalline compound was obtained: Yield; 30.7% (75.5mg).

TLC in S_1, S_2 and S_3 solvent system gave R_f values of 0.43, 0.48 and 0.42 respectively. The percentage yield and melting point were given in table 4.2.

Method B: 200mg (0.001mol) of 2(3H)-benzoxazolinone, and 146.79mg (0.001mol) p-methylpiperidine were dissolved in 8ml of methanol and 0.2ml (0.007mol) of 37% formaldehyde was added to the mixture, placed in a microwave and irradiated (150/100W, 65°C for first and second heating step respectively) for 8 minute, it was allowed to for 10 mins to cooled, then poured onto crushed ice where light yellow precipitate formed. The resulting precipitate was filtered off and purified by crystallization, using cyclohexane as solvent. Light yellow crystalline compound was obtained. Yield; 36.7% (90.5mg).

TLC in S_1 solvent system gave R_f value of 0.42.

.

Fourier Transforms Infra-Red (FT-IR) Spectroscopy (IR V_{max}): FT-IR showed stretching peaks at 2759-2949cm^{-1} aromatic (C-H Stretch), 1759cm^{-1} (C=O of carbonyl).

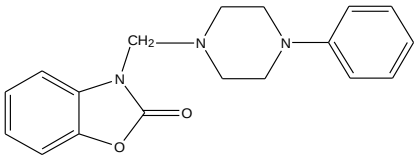
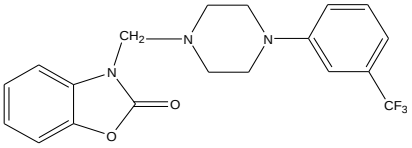
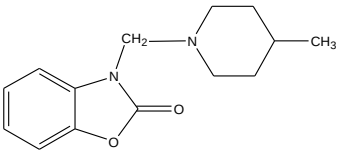
Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR in $CDCl_3$): ^{1}H NMR showed chemical shift at 7.2 (4H, m, Ar-H); 4.6 (2H, s, methylene H) 3.0 and 1.6 (4H, dd, $H^5 - H^8$); 2.3 (4H, t, $H^6 - H^7$); 1.2 (1H, s; H^9) 0.9 (3H, d; H^{10}) ppm.

.

4.2 DISCUSSION

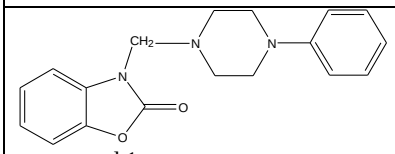
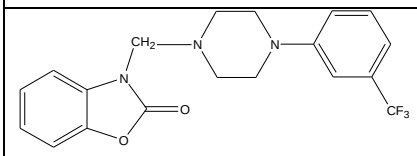
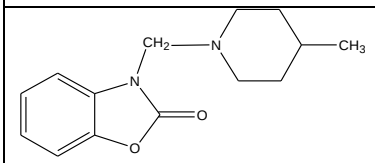
In this thesis, facile methods for synthesis of compound 1.2 and 3, given in table 4.1 below, have been developed.

Table 4.1: Structure and name of compound 1- 3

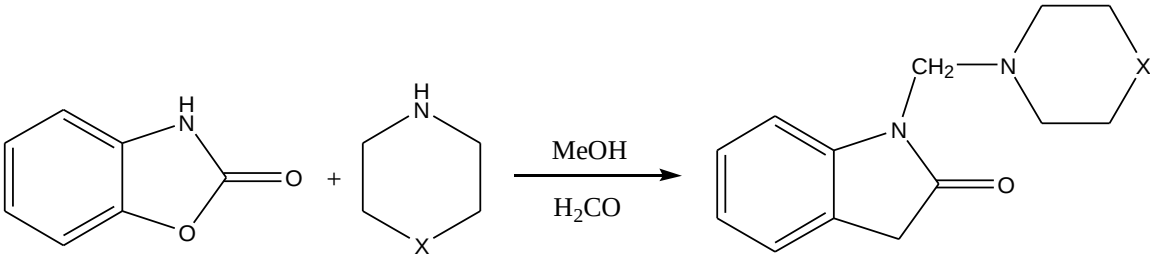
Name	Structure
3-[(4-phenylpiperazin-1-yl)-methyl]-2-benzoxazolinone	 Compound 1
3-[4-(3-trifluoromethylphenyl)-piperazinylmethyl]-2-benzoxazolinone	 Compound 2
3-[(4-methylpiperidin-1-yl)methyl]-2-benzoxazolinone	 compound 3

The comparison between conventional (reflux) and microwave irradiation for preparations of 3-[(4-phenylpiperazin-1-yl)-methyl]-2-benzoxazolinone (compound 1), 3-[4-(3-trifluoromethylphenyl)-piperazinylmethyl]-2-benzoxazolinone (compound 2) and 3-[(4-methylpiperidin-1-yl)methyl]-2-benzoxazolinone (compound 3) have been utilized for the first time in this thesis. According to literature survey, the compounds were reported initially but none synthesized by microwave irradiation [64]. It is obvious that microwave assisted heating approach for the synthesized compounds gives relatively high yield, minimized time consuming from 60mins to 8mins. However, the techniques provided an efficient simple path for avoiding undesirable (impurities) particles, as proved by the melting point of the synthesized compounds. Table 4.1 summaries yield and melting point by reflux versus microwave assisted heating technique.

Table 4.2: Summaries yield and melting point of compound 1-3, by reflux versus microwave assisted heating technique.

Structures of compound 1-3	Condition/time (hrs/mins)	Yield (%)	Melting point (℃)
 compound 1	Reflux/1hr	55.4	180.0
	Mw/8mins	86.5	180.0
 compound 2	Reflux/1hr	62.0	136.4
	Mw/8mins	80.0	136.0
 compound 3	Reflux/1hr	30.7	104.4
	Mw /8mins	36.7	104.6

All the compounds (1, 2 and 3) synthesized according to mannich reaction condition, in which piperazines and piperidine substituents reacted with 2(3H)-benzoxazolinone at 3-position, which is the reactive site for mannich reaction. The general synthetic pathway involved, is given in the figure 4.1



Compound 1: X = C_6H_5N

Compound 2: X = (m-$CF_3C_6H_4$)N

Compound 3: X = CH_2-CH_3

Figure 4.1: Stepwise synthetic pathway for preparation of compound 1-3.

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

In the IR spectra, there is absence of N-H stretching band at 3300-3500cm^{-1} in all the IR spectra of the compounds proves that the substitution took place at 3-position of the 2(3H)-benzoxazolinone as expected. the C=O stretching band of the 2(3H)-benzoxazolinone group were observed between 1747-1759cm^{-1} and those bands were confirmative signals for the carbonyl functional group of the named above compounds and the values were consisted with the C=O stretching of 2(3)-benzoxazolinone derivatives that had been previously reported [40]. Moreover, C-H stretching was also observed between 2759-3091cm^{-1} in all the spectra as expected.

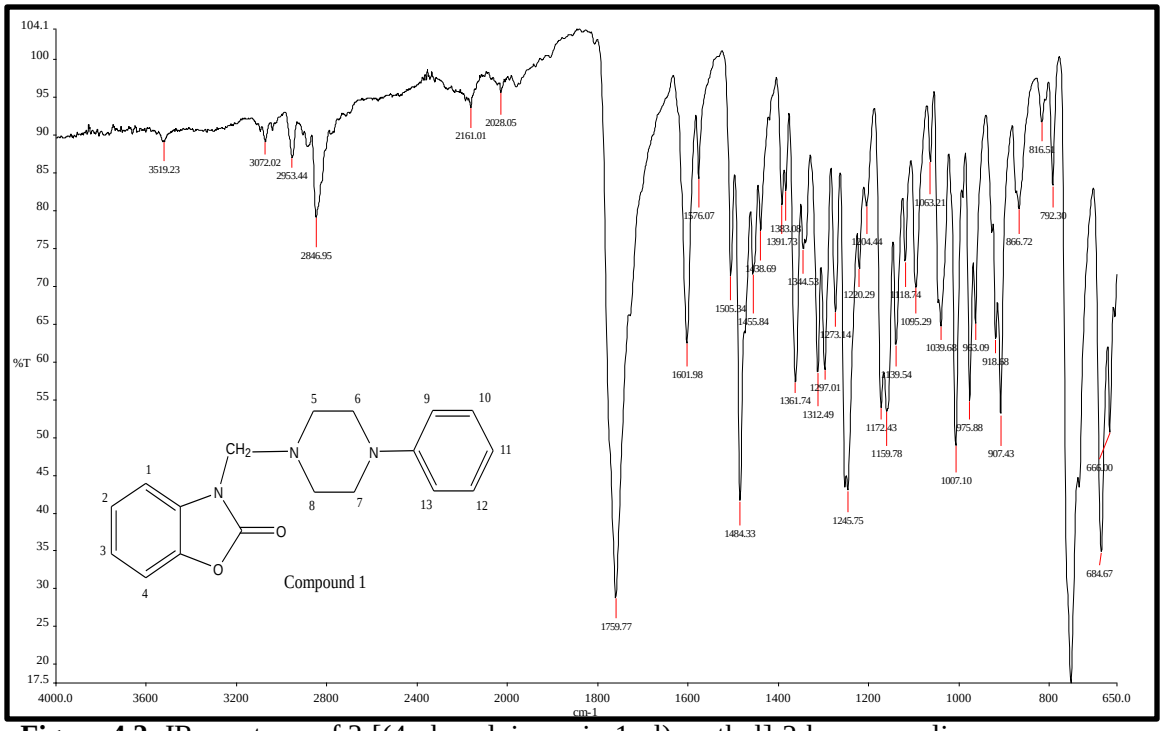


Figure 4.2: IR spectrum of 3-[(4-phenylpiperazin-1-yl)-methyl]-2-benzoxazolinone.

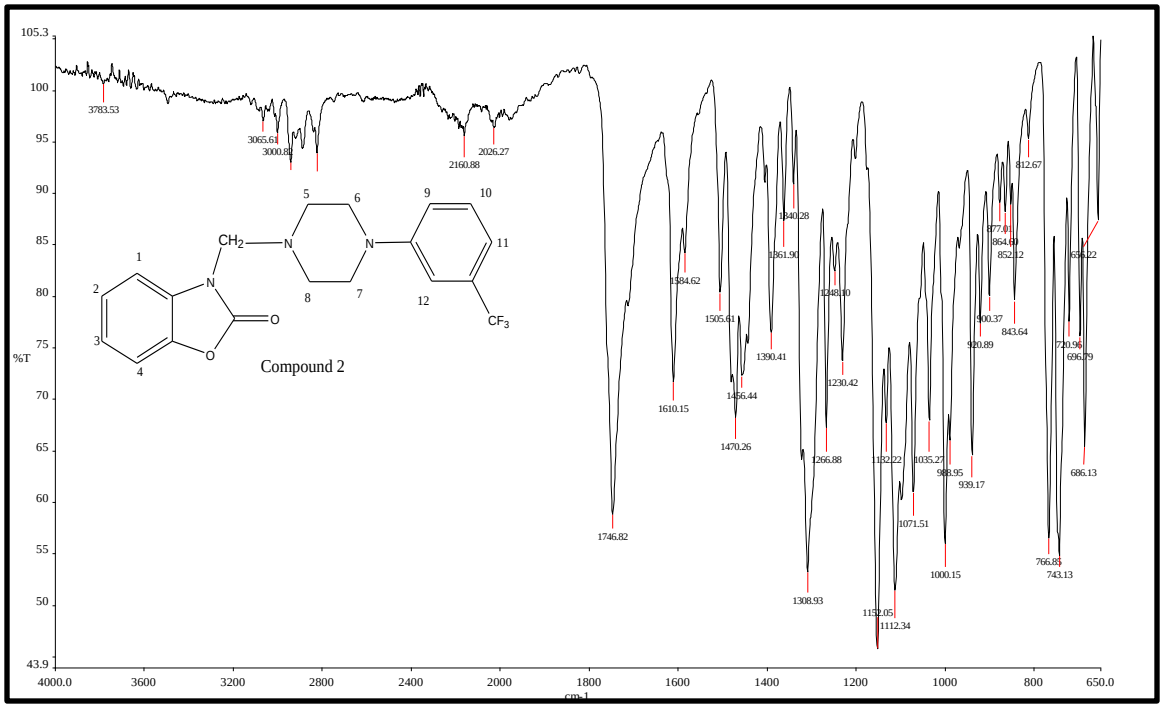


Figure 4.3: IR spectrum of 3-[4-(3-trifluoromethylphenyl)-piperazinylmethyl]-2-benzoxazolinone.

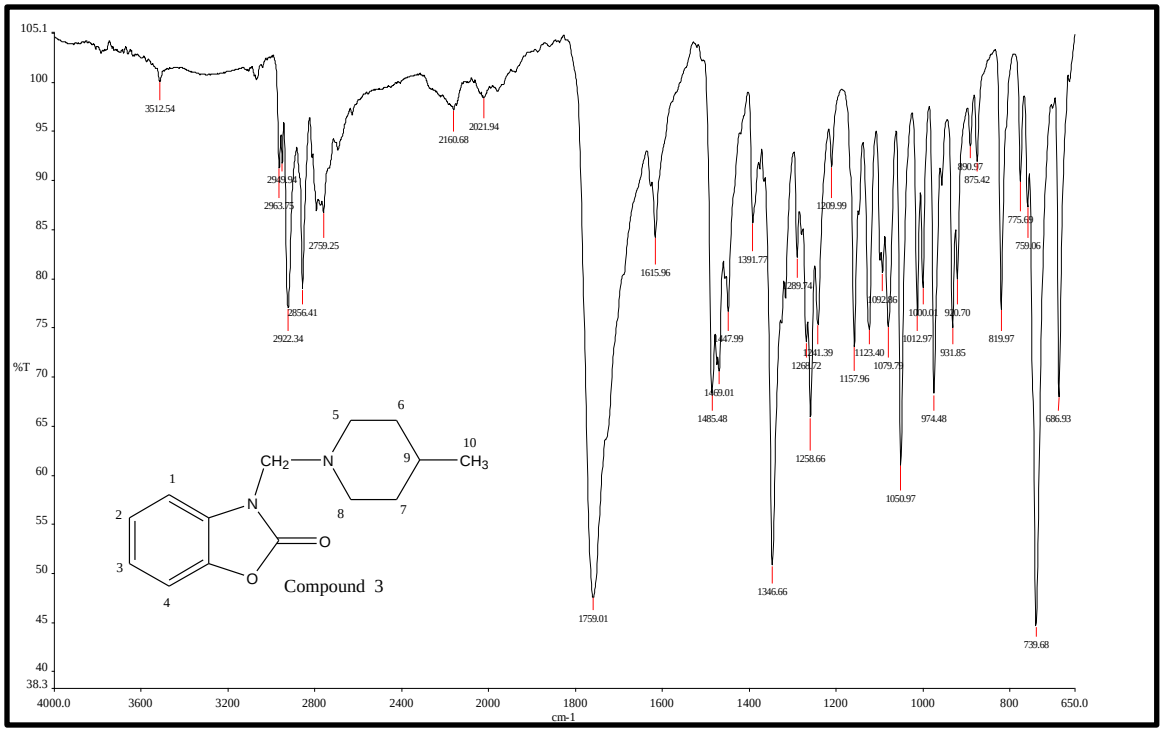


Figure 4.4: IR spectrum of 3-[(4-methylpiperidin-1-yl)methyl]-2-benzoxazolinone.

In the ^{1}H NMR spectra of the synthesized compounds 1-2 were more similar with the expected in terms chemical shift [40].

The methylene-proton signal of the compound 1, 2 and 3 observed as singlet signals at 4.7, 4.2 and 4.6 ppm respectively confirmed, the expected compounds were formed.

The down field resonance signals at 7.2-6.8 and 7.2-7.0 ppm correspond to aromatic protons of compound 1 and 2 respectively. While 7.2 ppm shows presence of aromatic protons of compound 3.

Piperidine proton are different than piperazine less symmetrical, the resonance at 2.8-3.2; 2.3-3.2 and 2.3-3.0 ppm shows the presence of piperazines (compound 1 and 2) and piperidine ($C_5N_2H_8$) protons respectively. However, the values of the peaks on

the proton NMR of the compounds corresponded to the number of protons in the proposed structures of all the compounds.

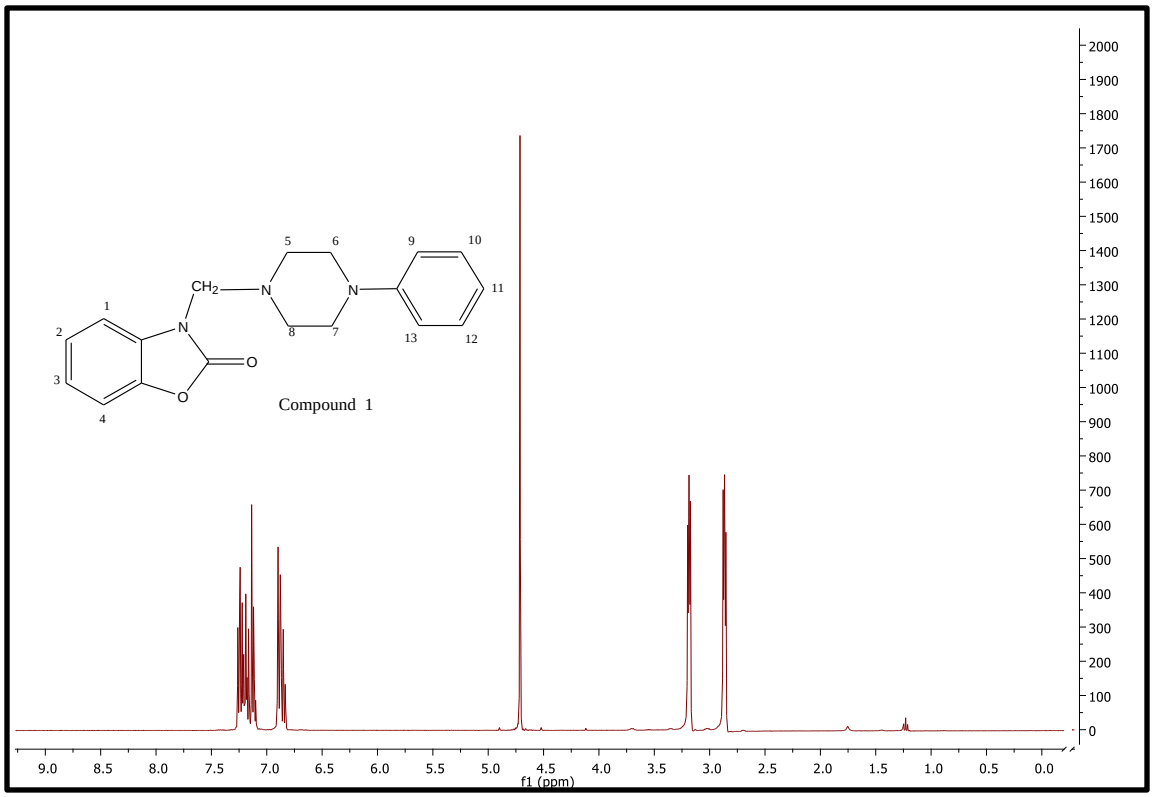


Figure 4.5: ^{1}H NMR spectrum of 3-[(4-phenylpiperazin-1-yl)-methyl]-2-benzoxazolinone.

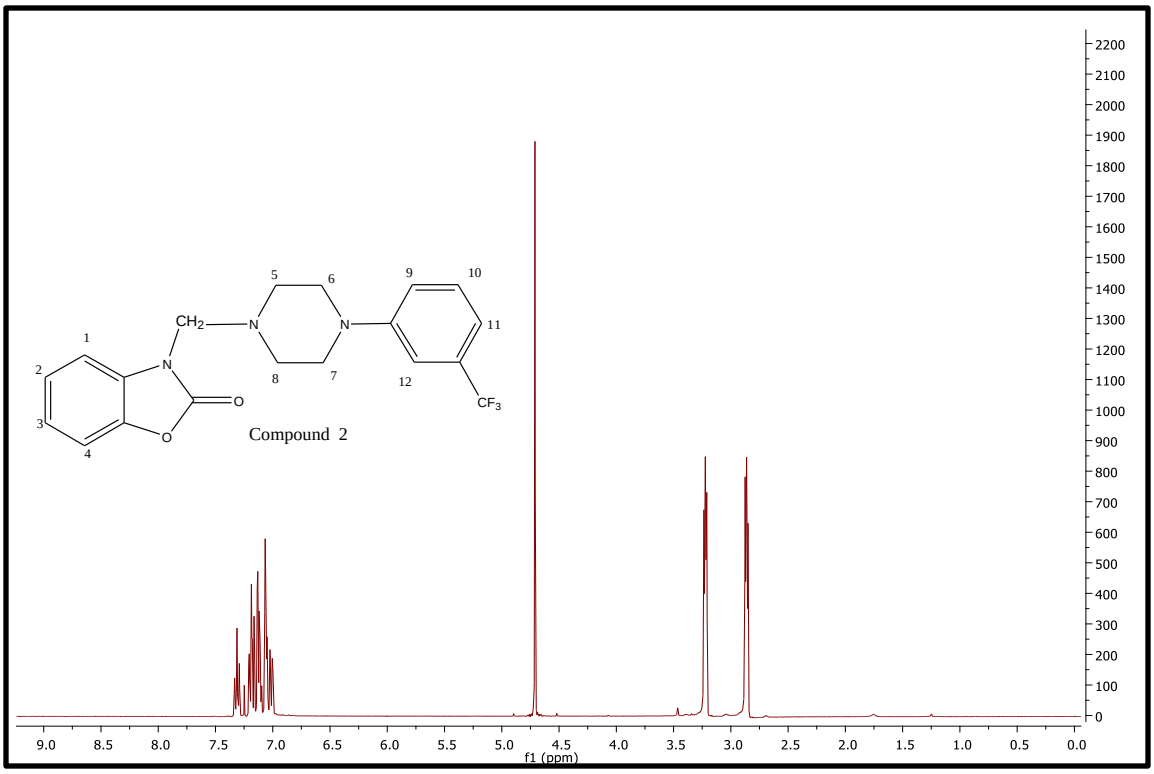


Figure 4.6: ^{1}H NMR spectrum of 3-[4-(3-trifluoromethylphenyl)-piperazinylmethyl]-2-benzoxazolinone.

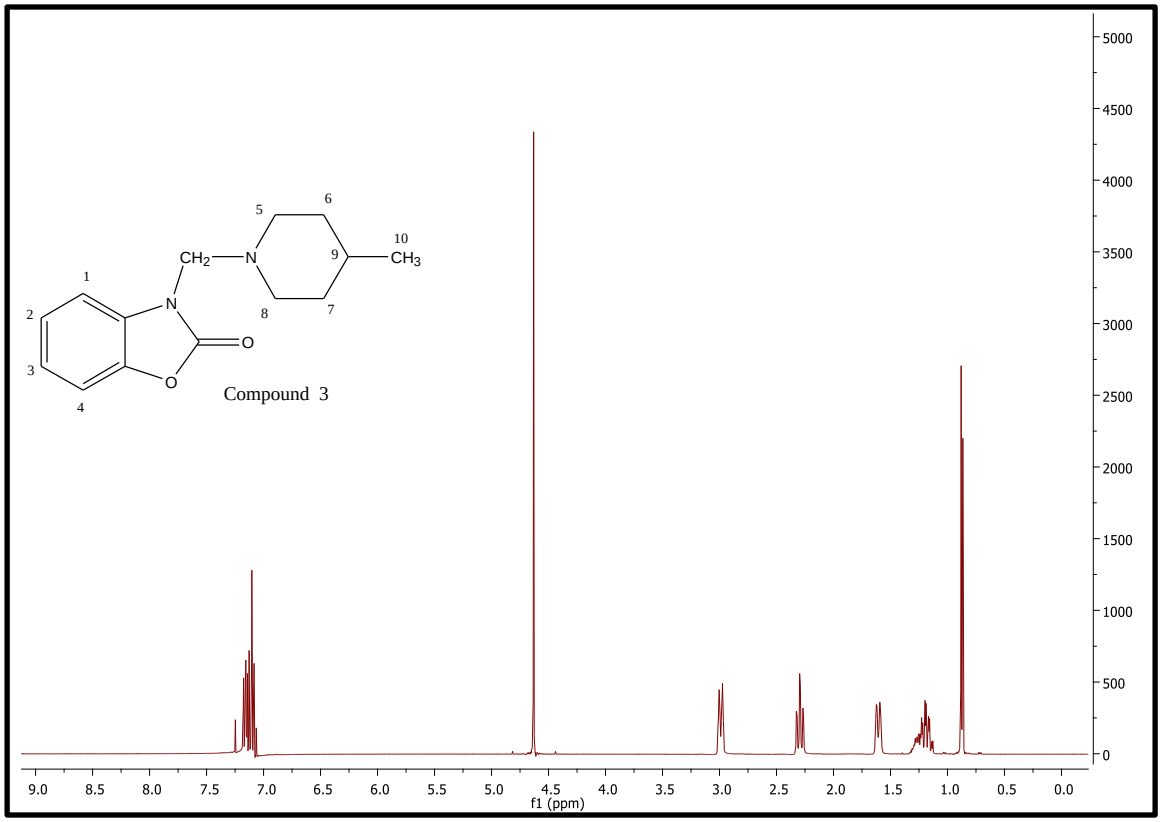


Figure 4.7: ^{1}H NMR spectrum of 3-[(4-methylpiperidin-1-yl)methyl]-2-benzoxazolinone.

5. CONCLUSION

This thesis focused on the confirmation of the 2(3H)-benzoxazolinone reactions at 3-position of the structure to prove the previously reported derivative obtained at that position. It provided a simple synthetic reaction condition (microwave assisted heating) so as to minimize the time taking for the synthesis of 2(3)-benzoxazolinone derivatives. Three 2(3H)-benzoxazolinone derivatives were synthesized by N-substitution (3-position), by reflux and microwave heating. The compounds were characterized with FT-IR and ^{1}H NMR spectroscopy. The microwave irradiation heating method was found simpler. It also decreased the reaction time from one hour to 8 mins with relatively high yield. Therefore, microwave assisted heating technique could be apply in synthesis of 2(3)-benzoxazolinone derivatives to investigate more of its biological activity.

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