

T.R.N.C
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

SYNTHESIS AND CHARACTERIZATION OF
BENZYLPIPERIDINE SUBSTITUTED BENZOXAZOLONES

JASAM F. TAUFEG ALHUSNY

PHARMACEUTICAL CHEMISTRY
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Advisor

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Nicosia, 2016

The Directorate of Health science institute

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DEDICATION

I dedicate this research work to my beloved parent, late FARAJ TAUFEG ALHUSNY and late AMINA MUSBAH SULEIMAN and also for my great uncle, KHALIL TAUFEG ALHUSNY and my uncle's wife NAJMIA ABDULRAHIM and all those who have lost their life due to ISIS massacres. May their gentle soul rest in perfect peace and Jannatul fir'daus be their final abode.

To my angel... internist doctor (MARWA).

ABSTRACT

2(3H)-benzoxazolone and its derivatives are very important in the field of pharmacy being that they possess potential regulatory on therapeutic properties.

Two different mannich bases were synthesized in this study by using classic Mannich Reaction by three different reaction conditions. (Room temperature, Reflux and Microwave heating techniques). The reactions were monitored by TLC and melting point determination, while the chemical structures of compounds were determined by FT-IR and ¹H-NMR analysis.

Keywords: 2(3H)-benzoxazolone, 5-chloro-2-(3H)-benzoxazolone, Microwave assisted organic synthesis, Mannich reaction.

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LIST OF ABBREVIATION

NSAIDs: Non-steroidal anti-inflammatory drugs

COX: Cyclooxygenase

THF: Tetrahydrofuran

DMF: N, N-dimethylformamide

PPA: Polyphosphoric Acid

TEA: Triethanolamine

FT-IR: Fourier Transfer Infra-Red

^1H -NMR: Proton Nuclear Magnetic Resonance

TLC: Thin Layer Chromatography

1. INTRODUCTION

2(3H)-benzoxazolone nucleus is regarded as important scaffolds in the designed synthesis of various organic molecules. The high versatility of this nucleus has allowed a wide variety of chemical modifications to different positions of the molecule [1].

There have been various researches by various scientists, geared towards the production of a new analgesic and anti-inflammatory drugs with little or no side effects.

Many 2(3H)-benzoxazolones have been described in therapeutic as processing a variety of pharmacological activities in this regard, numerous derivatives of 2(3H)-Benzoxazolone such as 5-chloro-2(3H)-benzoxazolone (chloroxazone), have been synthesized and tested for various activities such as analgesics, antifungal, antibacterial, cardiotoxic, antimicrobial and anti-inflammatory activities [2-3].

Scientist further reported that chlorinated 2(3H)-benzoxazolone compounds have valuable analgesic and fungicidal properties and are therefore suitable for the protection of organic materials from attack by fungi and from damage due to rot [4].

In this research study one 3-substituted-5-chloro-2(3H)-benzoxazolone and one 3-substituted-2(3H)-benzoxazolone were synthesized by the substitution of 4-benzylpiperidine on heteroatomic nitrogen position 3 through Mannich reaction under three different conditions (room temperature, reflux, and microwave heating technique) [5].

In this present work in addition to reflux, two different mannich bases were synthesized at room temperature, and also microwave in order to compare the yields and as well as the purity. These two compounds were characterized by Fourier Transform Infra-Red (FT-IR), Proton Nuclear Magnetic Resonance ($^1\text{H-NMR}$). The purity was determined by melting point and thin layer chromatography (TLC).

2. LITERATURE REVIEW

2.1. Analgesics

The term analgesics encompasses a class of drugs that are designed to relieve pain without causing the loss of consciousness [6].

There are two main groups of analgesics in the market; Narcotic (Opioid) Analgesic and Non-steroidal Anti-inflammatory Drugs (NSAIDs).

2.1.1. Narcotics (Opioid) Analgesics

Narcotic analgesics are potent analgesics used for relief of severe pain. These analgesics are derived from opium alkaloids. Many alkaloids are isolated from opium, but few of them are used clinically (morphine, codeine, and papaverine). Synthetic narcotic drugs, such as methadone, may also be used for pain relief [7].

Narcotic pain medications work by dissociating the patient from the pain. Although the pain is still present the sensation of the pain is changed by the narcotic. All narcotics carry the risk of addiction, and if taken for a long time, may result in withdrawal symptoms such as sweating and anxiety when discontinued [8].

Narcotic analgesics may be classified into four major categories: Namely,

- i. Natural alkaloids of opium.
- ii. Synthetic derivatives of morphine.
- iii. Synthetic agents which resemble the morphine structure.
- iv. Narcotic antagonists.

2.1.1.1. Natural Alkaloids of Opium

Morphine was first extracted from opium in a pure form in the early nineteenth century. Morphine and codeine are contained in opium from the poppy seed (*Papaver Somniferum*). Opium contains over 20 compounds but only morphine (10%) and codeine (0.5%) are of any importance. Morphine is extracted from the opium and isolated in a relatively pure form. Since codeine is in such low concentration, it is synthesized from

morphine by an ether-type methylation of an alcohol group (Figure 2.1). Codeine has only a fraction of the potency compared to morphine. It is used with aspirin and as a cough suppressant [9].

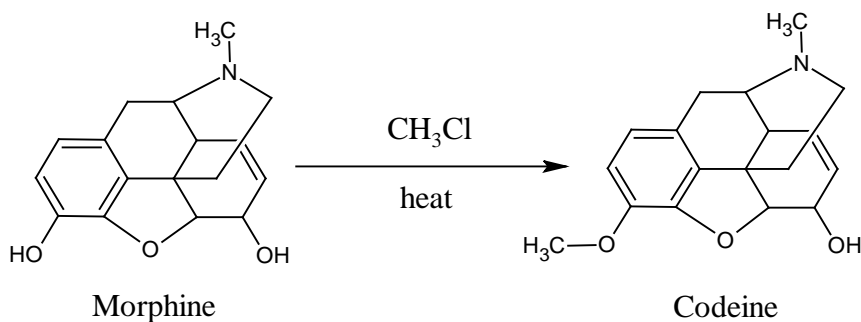


Figure 2.1. Methylation of morphine to codeine

2.1.1.2. Synthetic Derivatives of Morphine

The most common derivative of morphine is heroin. Heroin is synthesized by esterification of the two hydroxyl groups of morphine with acetic anhydride (Figure 2.2). Heroin was first isolated from morphine in 1874 and was originally used as a nonaddictive cure for morphine addiction [10].

This was later found to be incorrect and in the 1900s heroin abuse and addiction became common. It is now classified as a class A drug and possession or trading it results in heavy penalties in most countries [11].

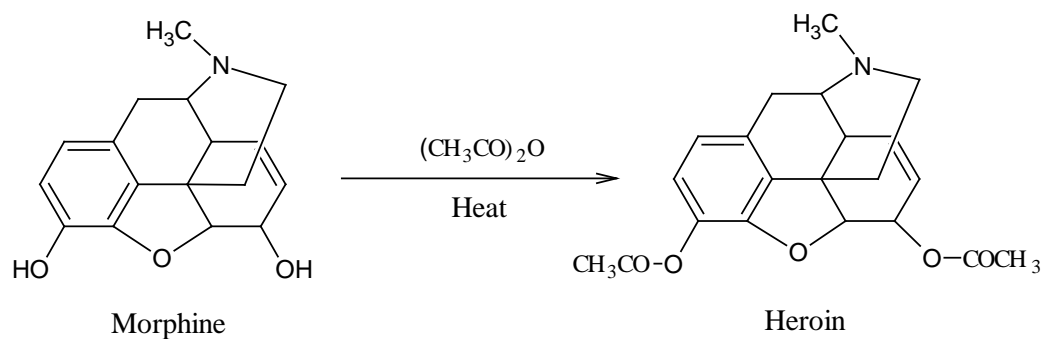


Figure 2.2. Esterification of morphine to heroin

Replacing the hydrogen-bonding -OH groups with -OCOCH₃ makes heroin much less soluble in water than morphine, but more soluble in non-polar solvents, like oils and fats. As a result, heroin is much more potent than morphine, but its effect does not last as the acetyl groups are removed once the molecule absorbed and undergo metabolism via hydrolysis [12].

2.1.1.3. Synthetic Agents Which Resemble The Morphine Structure

Examples of synthetic agents which resemble morphine include meperidine and methadone.

Meperidine is the most common substitute for morphine which acts on the central nervous system (CNS) to relieve pain. Meperidine was the first synthetic opioid synthesized in 1932 by the chemist Otto Eislib [13].

Methadone on the other hand was originally synthesized by the German pharmaceutical company Axis during the second world war. It was first marketed as 'Dolophine' (to honor Adolph Hitler) and was used as an analgesic for the treatment of severe pain. It is still occasionally used for pain relief, although it is more widely used now as a substitute drug for people addicted to heroin [14]. The structures of meperidine and methadone are shown in (Figure 2.3).

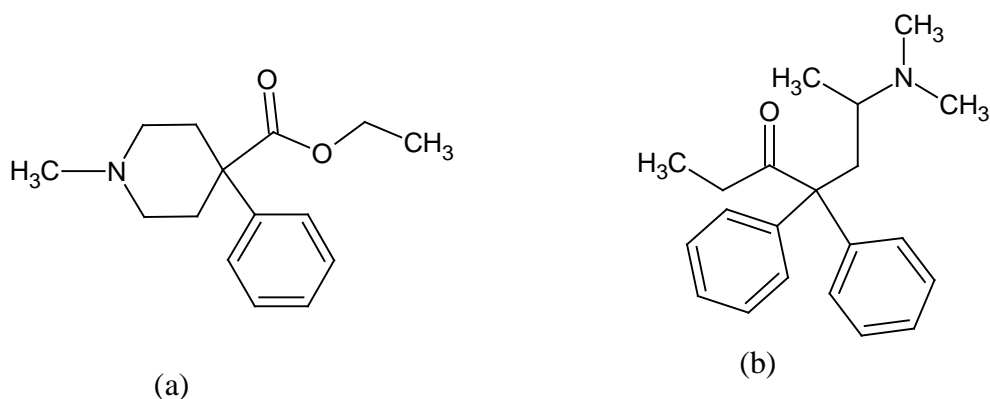


Figure 2.3. Structures of (a) meperidine and (b) methadone

2.1.1.4. Narcotic Antagonist

Examples of narcotic antagonist include naloxone and naltrexone.

Naloxone is used in emergency conditions to counter the effect of opioid (morphine and codeine) overdose while naltrexone on the other hand is used primarily in the management of alcohol dependence and opioid dependence [15]. The structures of naloxone and naltrexone are shown in (Figure 2.4).

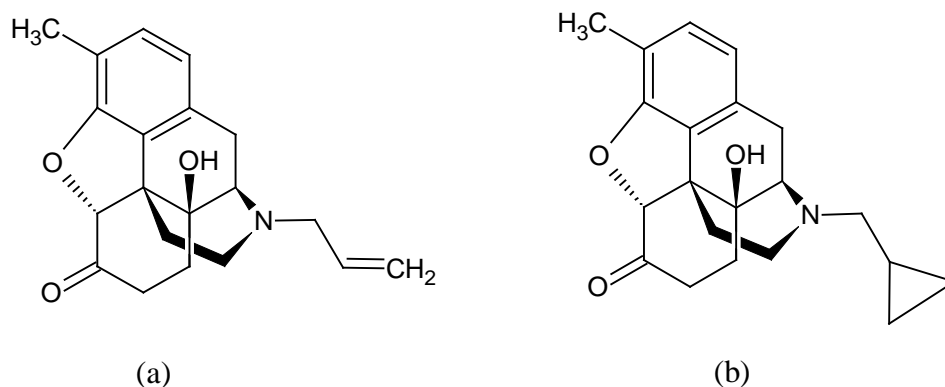


Figure 2.4. Structures of (a) naloxone and (b) naltrexone

2.1.2. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are a group of drugs that relieve pain, reduce a high temperature (fever). NSAIDs are used to treat a good number of conditions such as headaches, painful periods, toothache, sprains and strains infections (common cold or the flu) inflammation of the joints (arthritis) and other tissues [16].

This group possesses a common mode of action which is to block prostaglandin biosynthesis by inhibiting cyclooxygenase enzyme [17].

Inhibition of this enzyme centrally produces the analgesic and antipyretic effect of this group.

The inhibition of this enzyme peripherally produces its anti-inflammatory effect [18].

2.1.2.1. Development of cyclooxygenase (COX) inhibitors

COX is an enzyme that is responsible for the formation of prostanoids. The three main groups of prostanoids (prostaglandins, prostacyclins, and thromboxanes) are the key parts in the development of inflammation. However, this is not the only action of the different forms of COX, which are involved in many normal cellular processes [19].

In the 1990s, researchers discovered that two different COX enzymes existed, now known as COX-1 and COX-2 (Figure 2.6). Cyclooxygenase-1 (COX-1) is known to be present in most tissues. In the gastrointestinal tract, COX-1 is constitutive and makes prostaglandins (PGs) that maintain the normal lining of the stomach and also protect the stomach and kidney from damage. The enzyme is also involved in kidney and platelet function. Cyclooxygenase-2 (COX-2) is constitutively expressed in the brain, in the kidney, in bone, and probably in the female reproductive system. COX-2 is primarily present at sites of inflammation, induced by inflammatory stimuli, such as cytokines, and produces PGs that contribute to the pain and swelling of inflammation [20].

When arachidonic acid is converted to prostaglandin by COX enzymes; the sensation of pain starts, therefore, NSAIDs inhibit the synthesis of prostaglandin through the inhibition of COX enzymes. However the first generation of COX inhibitor was non-selective, it inhibited all COX-isoenzymes and due to this non-selective inhibition, the side effects started to appear [21].

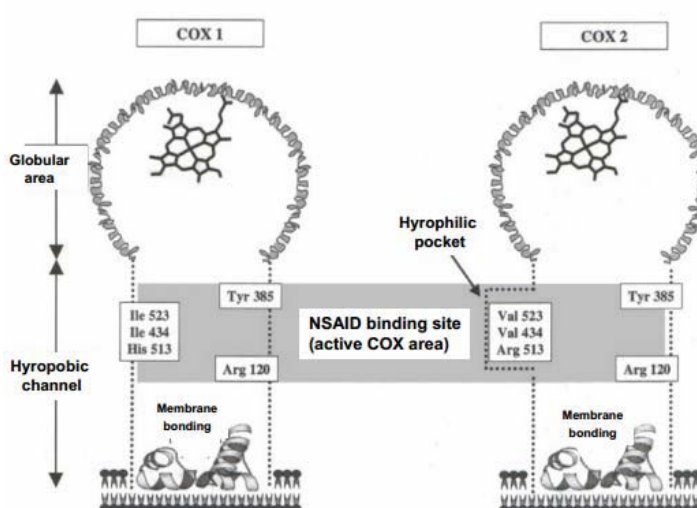


Figure 2.5. Structure of COX-1 and COX-2 Enzymes .

For COX-1 isoform, isoleucine 523 closes the hydrophobic binding pocket located laterally. In COX-2 isoform, there is a more accessible pocket. There is also a wider channel opening in COX-2 as compared to COX-1 due to narrowing of the phenyl sulphonamide interaction between arginine 120 and tyrosine 355 [22]. (Figure 2.6) shows the structures of COX-1 and COX-2 enzymes.

Upon development of COX-1 and COX-2, scientists develop the second generation of COX inhibitors which was selective to COX-2, by this way they the therapeutic activity of this group was improved and their side effect was also decreased [23].

2.1.2.2. Classification of Non-Steroidal Anti inflammatory Drugs

Classification of NSAIDs can be based on their chemical structures or their mechanism of action [24].

In terms of mechanism of action they are classified into two main groups;

- 1- Non selective cyclooxygenase (COX) inhibitors.
- 2- selective cyclooxygenase (COX-2) inhibitors.

A- Non selective cyclooxygenase (COX-1) inhibitors

Non selective cyclooxygenase (COX-1) inhibitors are group of NSAIDs that are inhibit both types of cyclooxygenase (COX-1 and COX-2), cyclooxygenase (COX-1) consider as the protective prostaglandin in the gut and due to this non-selective inhibition the administration of this group of drug will be associated with high gastrointestinal lesion.

Examples of non selective cyclooxygenase (COX-1) inhibitors are shown in (Figure 2.5).

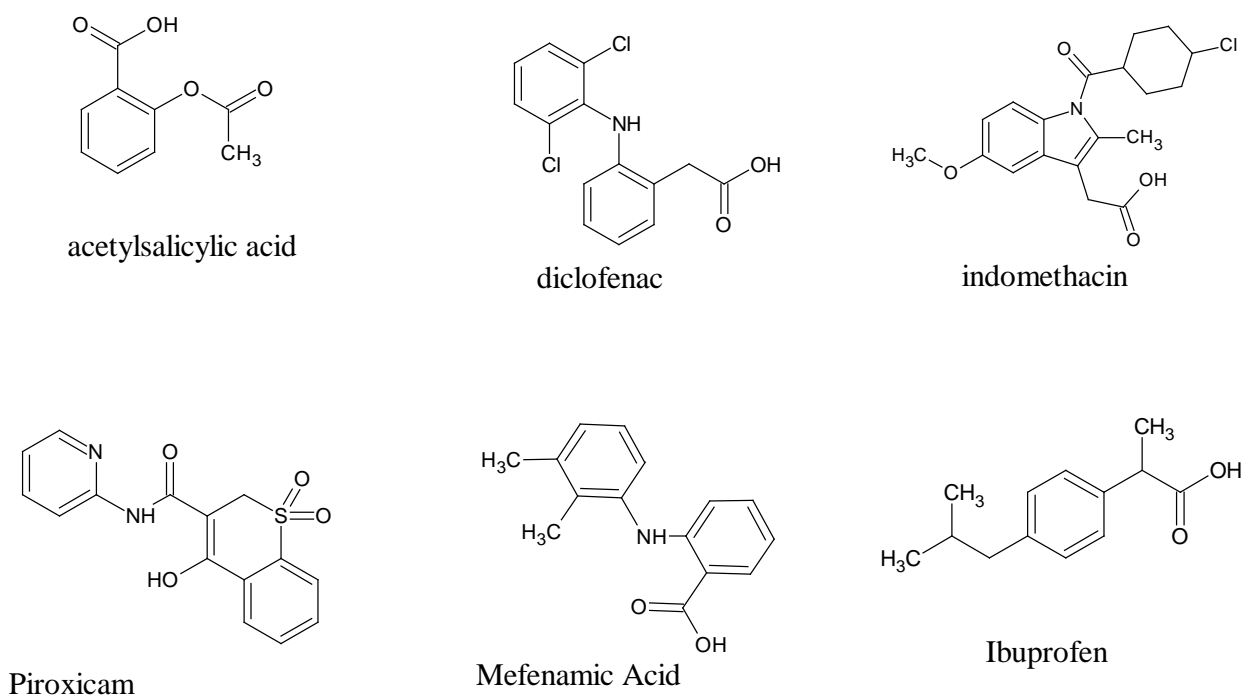


Figure 2.6. Structures of some examples of cyclooxygenase (COX) inhibitors

B- Selective COX-2 Inhibitors

Selective COX-2 inhibitors are a group of NSAIDs that directly targets cyclooxygenase-2. Since selective COX-2 inhibitors spare COX-1, they generally do not inhibit the synthesis of the protective prostaglandin in the gut. Hence, their anti-inflammatory effect is associated with less gastrointestinal adverse effects [25].

Selective blocking of the COX-2 enzyme and not the COX-1 enzyme makes COX-2 drugs uniquely different from traditional NSAIDs which usually block both COX-1 and COX-2 enzymes [26].

Examples of COX-2 selective inhibitors include; celecoxib, etoricoxib, and valdecoxib as shown in (Figure 2.7).

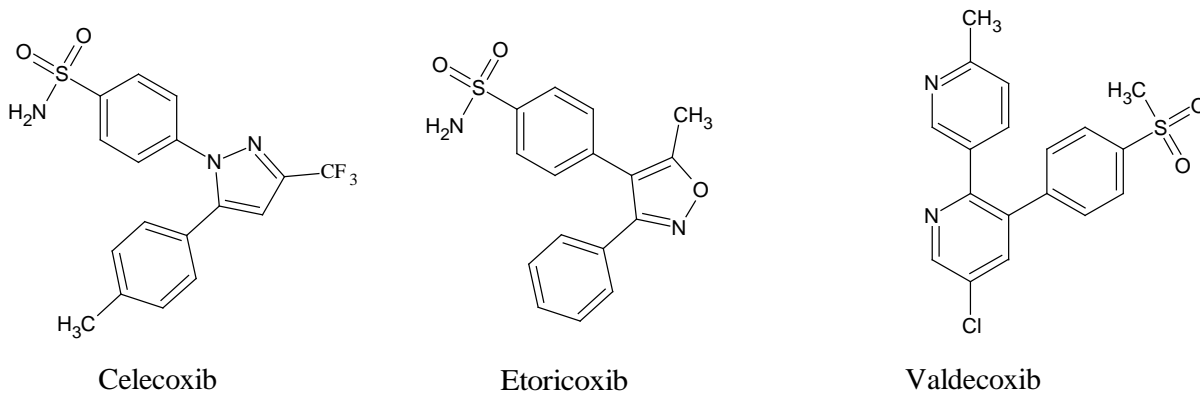


Figure 2.7. Examples of COX-2 selective inhibitors

2.2. 2(3H)-Benzoxazolone

The 2(3H)-benzoxazolone contains a phenyl ring fused to an oxazole ring, as indicated in the structure in (Figure 2.8). This important moiety has found practical application in a number of fields [27]. 2(3H)-benzoxazolone has received considerable attention during the last few decades as they are endowed with a variety of biological activities and has a wide range of therapeutic properties [28].

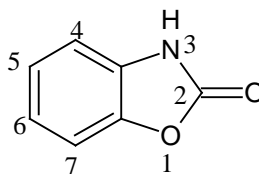


Figure 2.8. Structure and numbering of 2(3H)-benzoxazolone

After the pioneering discovery of the hypnotic properties of 2(3H)-benzoxazolone [29], the benzoxazolone ring has become an important building block in medicinal chemistry and has led to the discovery of a number of derivatives showing analgesic, anti-inflammatory, antiepileptic, anticholinergic, antibacterial, and antifungal effects [30]. In this respect, many benzoxazolone derivatives were prepared and 6-acyl- 2(3H)-benzoxazolones were reported to have significant analgesic activities constituting valuable starting materials for further medicinal developments [31].

2.2.1. Physical Properties of 2(3H)-Benzoxazolone

2(3H)-benzoxazolone has several important consequences to the medicinal chemist these include physiochemical properties such as,

- 2(3H)-benzoxazolone has a lipid loving edge and a water-loving edge with two hydrogen bonding accepting sites and a single hydrogen bonding donating site.
- High dipole moment (4.47 Debye) and a discrete partition coefficient ($\log P = 0.97$).
- 2(3H)-benzoxazolone is a weak acid in aqueous solution ($pK_a = 8.7$), somewhat comparable to pyrocatechol (a) ($pK_a = 9.2$), hence is often referred to as a pyrocatechol bioisostere.
- 2(3H)-benzoxazolone constitutes a scaffold of high versatility in organic synthesis, allowing for a wide variety of chemical modifications implying a good directionality in the implementation of the side-chains on a rigid platform;
- 2(3H)- benzoxazolone shares structural resemblance with phenylurethane (b) and coumarin (c) and per se is endowed with hypnotic, analgesic, and antipyretic properties of the former and bactericide properties of the latter [32].

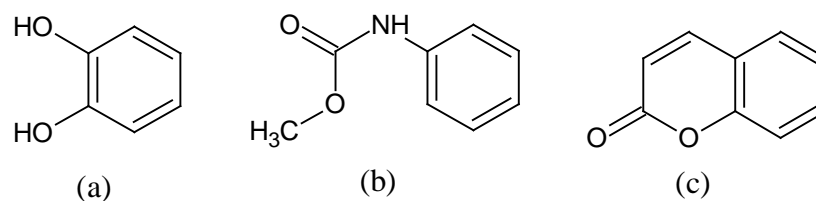


Figure 2.9. Structures of (a) pyrocatechol, (b) phenylurethane and (c) coumarin

2.2.2. Synthesis of 2(3H)-Benzoxazolone

2(3H)-benzoxazolone can be synthesized in many different ways. Nachman et al [33]. synthesized 2(3H)-benzoxazolones in excellent yields by refluxing 1,1'-carbonyldiimidazole and 2-aminophenol in dry tetrahydrofuran (THF) for four hours. The reaction is given in (Figure 2.10).

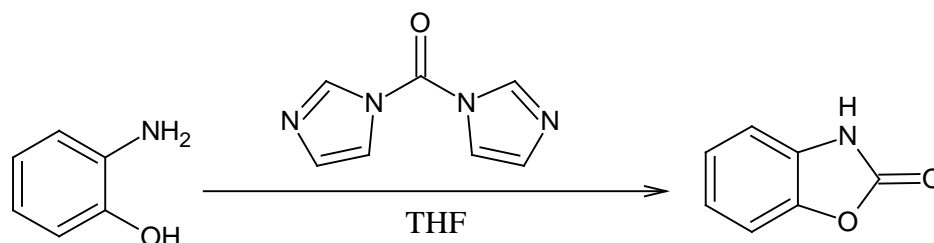


Figure 2.10. Synthesis of benzoxazol-2(3H)-ones from 2-aminophenol

Generally, 2(3H)-benzoxazolones substituted at position 5, are prepared from corresponding 4-substituted 2-aminophenol either by fusion with urea (Figure 2.11) or reaction with phosgene [34].

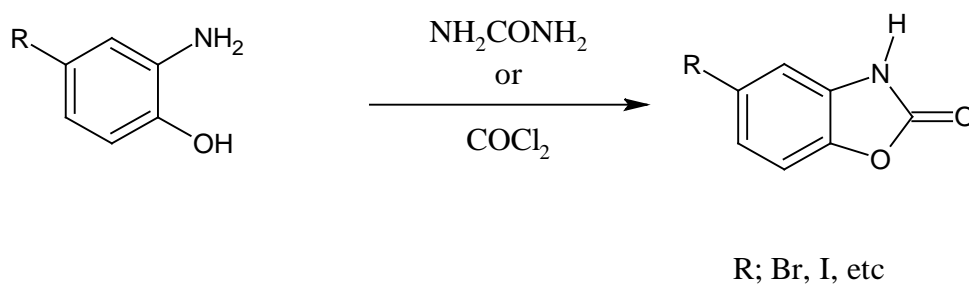


Figure 2.11. General synthesis of 5-substituted 2(3H)-benzoxazolones

Perumal et al also synthesized 2(3H)-benzoxazolone derivatives by the reaction between salicylic acid, ammonium azide and vilsmeier complex [35]. (Figure 2.12).

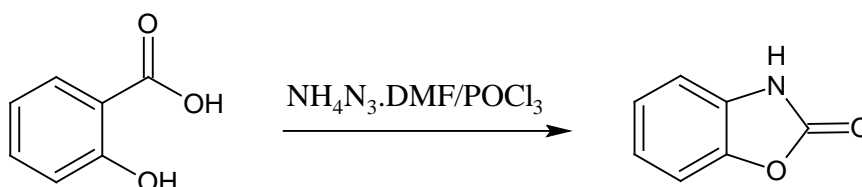


Figure 2.12. Synthesis of 2(3H)-benzoxazolone derivatives

Substitution of a chlorine atom at position 5 of 2(3H)-benzoxazolone gives 5-chloro-2(3H)-benzoxazolone which is well known for its muscle relaxant effect. In literature, 5-chloro-2(3H)-benzoxazolone was prepared by the reaction of 2-Amino-4-chlorophenol hydrochloride and urea in the presence of 60% sulfuric acid as shown in (Figure 2.13) [36].

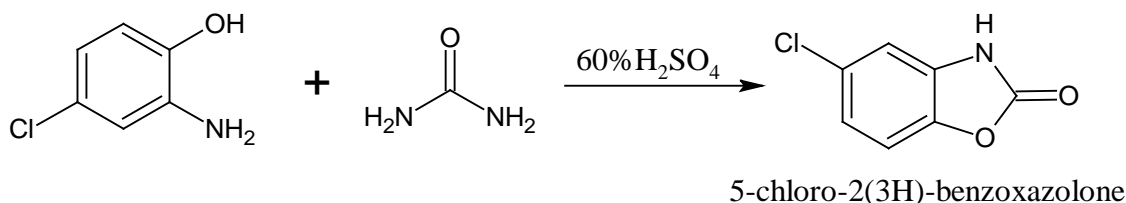


Figure 2.13. Synthesis of 5-chloro-2(3H)-benzoxazolone (Chlorzoxazone)

5-chloro-2(3H)-benzoxazolone can also be prepared by the reaction between salicylic acid, ammonium azide and vilsmeier complex [37]. (Figure 2.14) shows the synthesis reaction.



Figure 2.14. Synthesis of 5-chloro-2(3H)-benzoxazolone

2.2.3. Chemical Reactivity of 2(3H)-Benzoxazolone

2(3H)-Benzoxazolone heterocycles are considered ‘privileged scaffolds’ in the design of pharmacological probes. These heterocycles have, in fact, high versatility in chemical modifications, allowing changes to the characteristics side-chains on a rigid platform. Usually, functionalization of the nitrogen atom (3rd position) is of interest since the electronic characteristics of this atom can be important to the biological activity [38].

The enolizable character of the amide moiety allows several useful transformations at the third position of the heterocycle (Figure 2.15). They have received considerable attention from medicinal chemists, due to their capacity to mimic a phenol or a catechol moiety in a metabolically stable template [39].

The reactivity of 2(3H)-benzoxazolone permits to define three major types of reactions: N-substitution (either alkylation or acylation), electrophilic aromatic substitution and ring opening or expansion reactions [40].

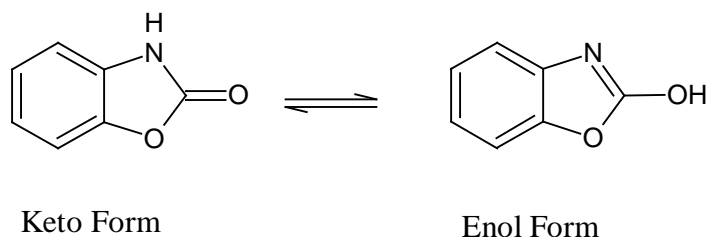


Figure 2.15. Tautomers of 2(3H)- benzoxazolone

A. N-substitution (either alkylation or acylation) Reactions

N-alkylation of 2(3H)-benzoxazolone proceeds under base-catalyzed conditions to give *N*-alkyl derivatives while *N*-acylation is carried out under acid-base catalysis to give *N*-acyl derivatives as shown in (Figure 2.16) [41].

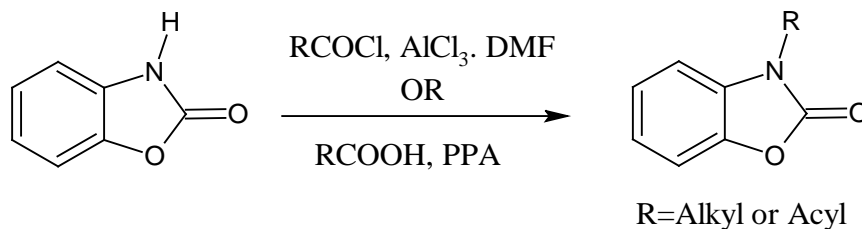


Figure 2.16. General synthesis of *N*-alkyl and *N*-acyl derivatives of 2-(3H) benzoxazolone

B. Aromatic Ring Electrophilic Substitution Reactions

Aromatic electrophilic substitution is governed by the overwhelming preference for the 6-position which is nitration, sulfonation, and chlorosulfonation reactions, but also for the more troublesome Friedel-Crafts acylation (Figure 2.17) [42]. Indeed, in the particular case of the Friedel-Crafts reaction, due to the electron-rich character of 2-(3H)-benzoxazolone, the heterocycle is extensively complexed (or protonated) by the Lewis acid present in the reaction medium, which acts as an electrophilic attack of acylium ions. To overcome this problem, the reaction can be run using either a less reactive electrophilic species (polyphosphoric acid, PPA, for example) [43], or preferably the $\text{AlCl}_3\cdot\text{DMF}$ complex [44], to give 6-acyl derivatives (Figure 2.17a). As a most fruitful alternative, *N*-acyl derivatives can be rearranged at high temperature (160°C) in a Fries-like reaction promoted by AlCl_3 , to 6-acyl derivatives as shown in (Figure 2.17b).

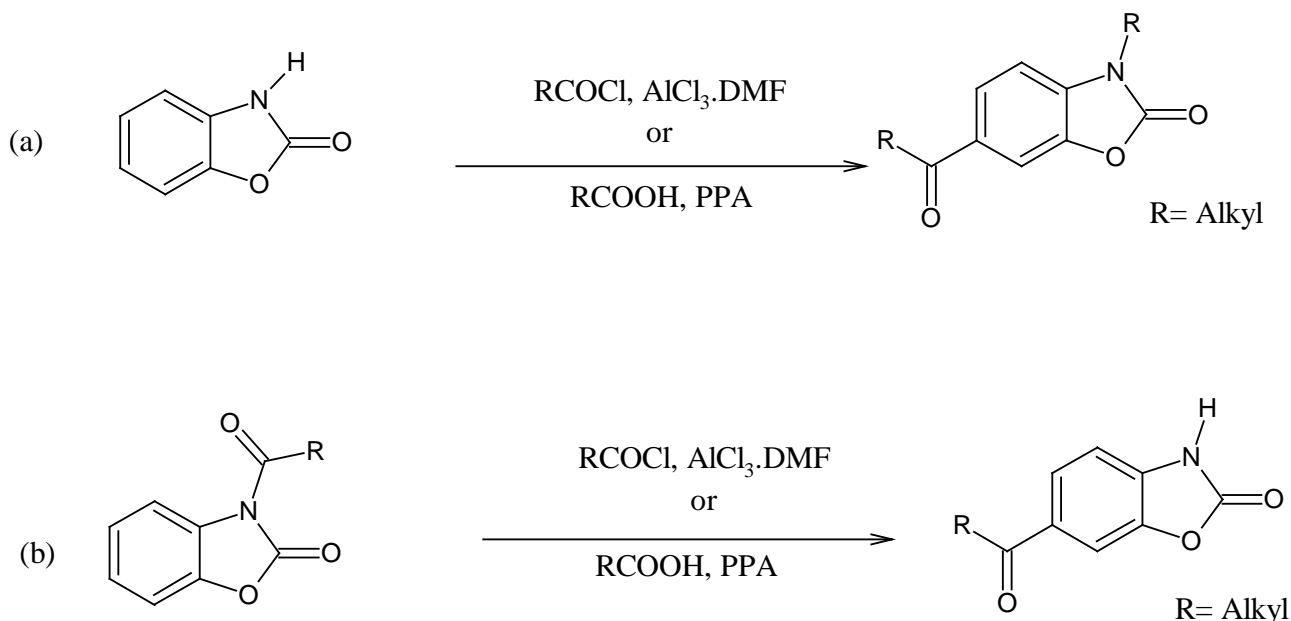


Figure 2.17. Aromatic ring substitution reaction (a). 2(3H)-benzoxazolone to 6-acyl derivative. (b). N-acyl benzoxazolone to 6-acyl derivative.

C. Ring Opening or Expansion Reactions

2(3H)-benzoxazolone derivatives are fairly stable in acid medium, they are quickly hydrolyzed in basic medium, leading to ring opening products such as 2-aminophenols (a) [45]. (Figure 2.18). These 2-aminophenols can be acylated in position 4 (b). Subsequent ring closure leads to the otherwise inaccessible 5-acyl-2(3H)-benzoxazolone derivatives (c). Ring expansion of 2(3H)-benzoxazolone derivatives to benzoxazinones (such as d) can be effected via the same 2-aminophenols as seen in (Figure 2.18).

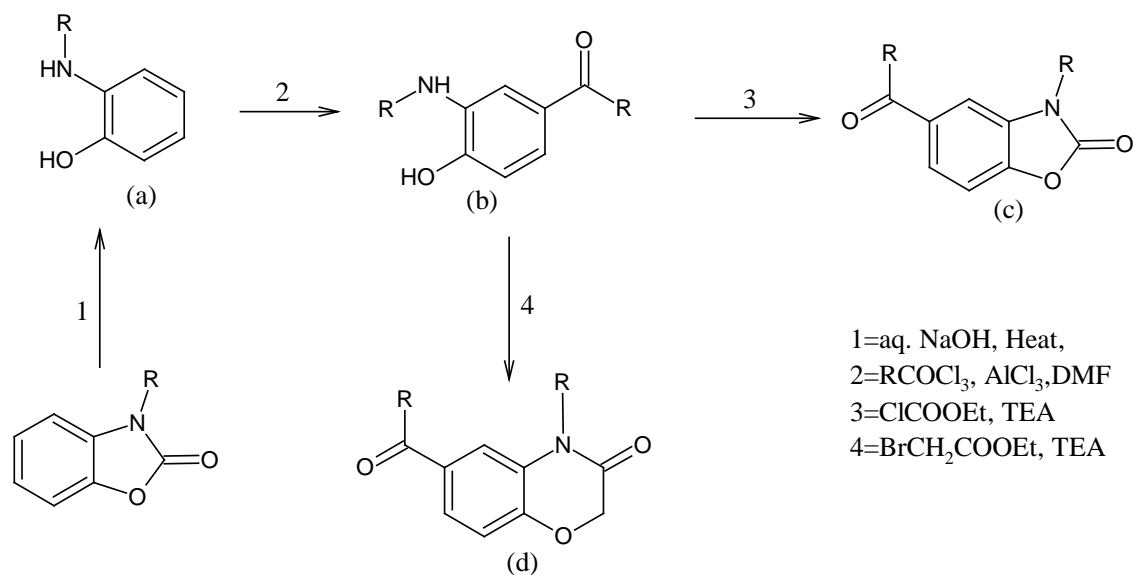


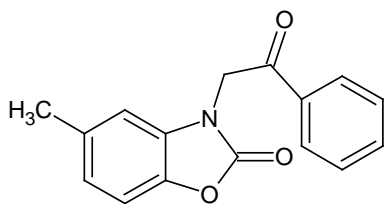
Figure 2.18. Ring opening and ring expansion reactions of 2(3H)-benzoxazolone

2.2.4. Therapeutic Applications of 2-(3H)-Benzoxazolones

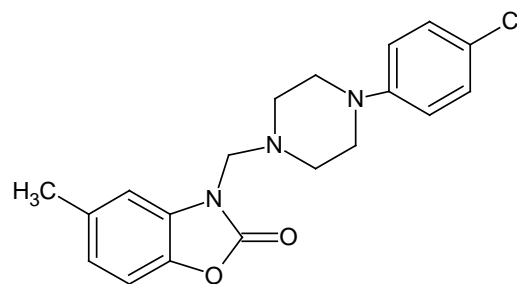
2(3H)-Benzoxazolone and its bioisosteres (e.g. 2(3H)-benzothiazolone, benzoxazinone etc.) have received considerable attention from the medicinal chemists owing to their capacity to mimic a phenol or catechol moiety in a metabolically stable template and assumed as a structure or template that when incorporated in a pharmacophore has a high degree of drug likeliness (privileged scaffold) in the design of pharmacological probes [46].

After the report made by Close and co-workers on the analgesic activities of 2(3H)-benzoxazolones, they have been structurally modified at the positions 3, 5 and 6 in order to screen for their antinociceptive properties [47].

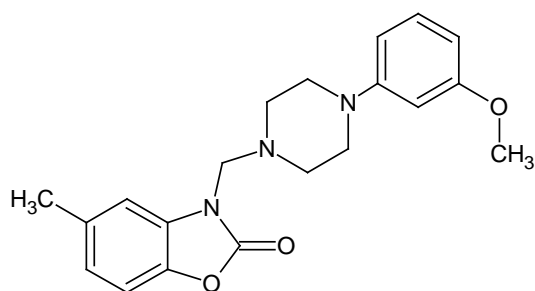
Some examples of therapeutically active benzoxazolinone derivatives [48]. shown in (Fig 2.19)



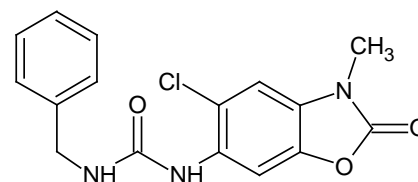
5-methyl-3-benzoylmethyl-benzoxazolinone-2-one



5-methyl-3-(4-chlorophenyl)pyprazinomethyl-2-benzoxazolinone



5-methyl-3-(4-(3-methoxy)phenyl)piperazinomethyl-2-benzoxazolinone



N-benzyl-N-(5-chloro-3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-yl)urea

Figure 2.19. Examples of some therapeutically active 2(3H)-benzoxazolones derivatives.

Glucan and co-worker synthesized 4-(5-chloro-2-(3H)benzoxazolone-3-yl) butanoic acid, its ethyl ester and amide are found as most potent antinociceptive and anti-inflammatory agent [49]. Examples of compound synthesized in this study shown in (Figure 2.20).

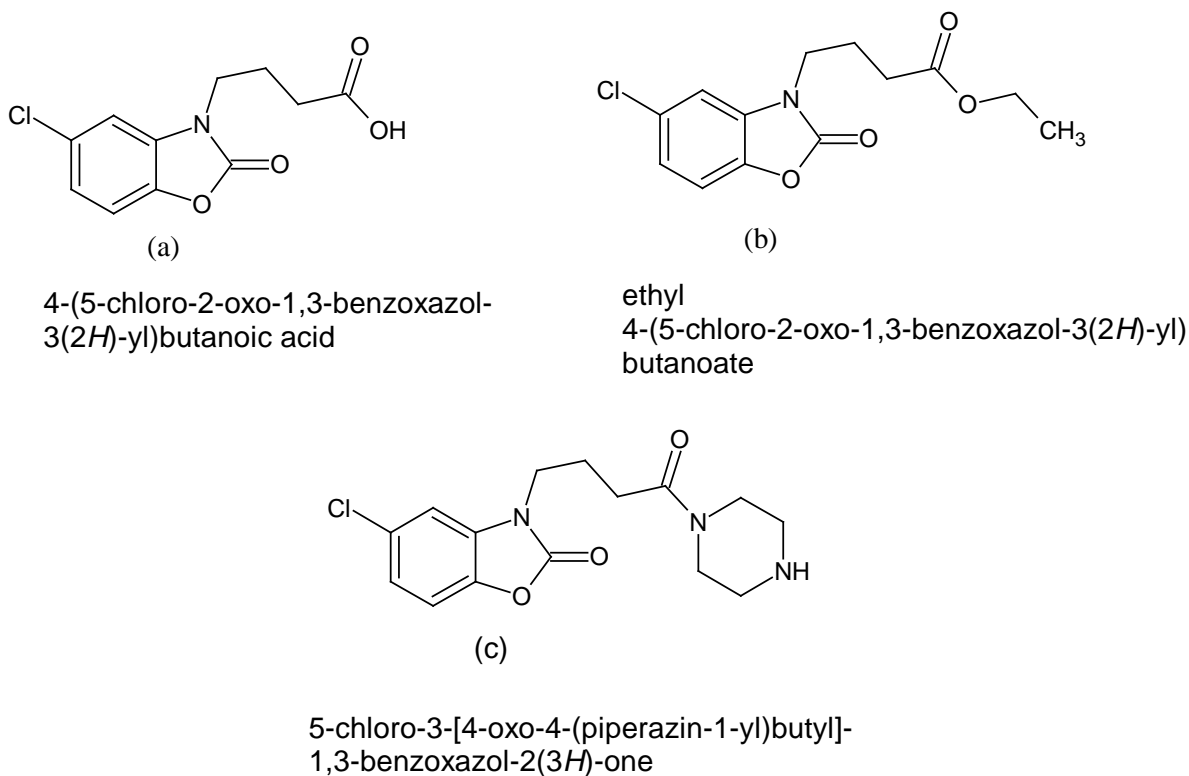
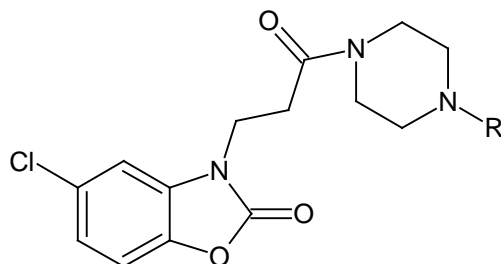


Figure 2.20 Examples of some most potent antinociceptive and anti-inflammatory derivatives of benzoxazolinone.

Later Onkol and co-workers synthesized (5-chloro-2-(3*H*)benzoxazolone-3-yl) propanamide derivatives as potent antinociceptive agent than the corresponding acetic acid derivatives [50].



R: phenyl, 2-methoxyphenyl, 3 or 4-chlorophenyl, 2-pyridyl

Figure 2.21. Example of (5-chloro-2(3*H*)benzoxazolone-3-yl) propanamide derivatives

Simple derivatives of 2(3*H*)-Benzoxazolone have been marketed, *e.g.* Benzolone, Paraflex, and Vinizene, (Figure 2.22) 6-Methoxy-2(3*H*)-benzoxazolone [51]. is a product

of natural origin found in corn and endowed with insecticide, antimicrobial, and antifungal properties. [52]. (Figure 2.22) gives the examples of 2(3H)-benzoxazolone drugs.

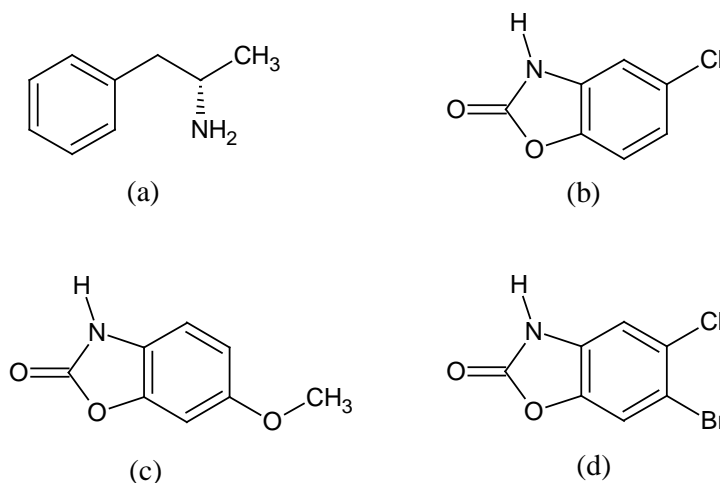


Figure 2.22. Structures of (a) benzolone, (b) paraflex, (c) 6-methoxy benzoxazolone, and (d) vinizine

In literature, it has been reported that 6-acyl-2-benzoxazolinone derivatives showed favorable analgesic activity on this basis, Calis and co-workers have reported that some derivatives of 2-benzoxazolinone, especially 3-substituted-6-acyl-2-benzoxazolinones, presented high analgesic activity in which the activity was found to be comparable to acetylsalicylic acid (Aspirin). Therefore, these findings led them to synthesize some new 3-methyl-6-amino ketone and amino alcohol-2-benzoxazolinone derivatives and screen them for their antinociceptive activity. Also it was found that all compounds are capable of inducing analgesia in animals [53]. (Figure 2.23) show some examples of synthesized compounds.

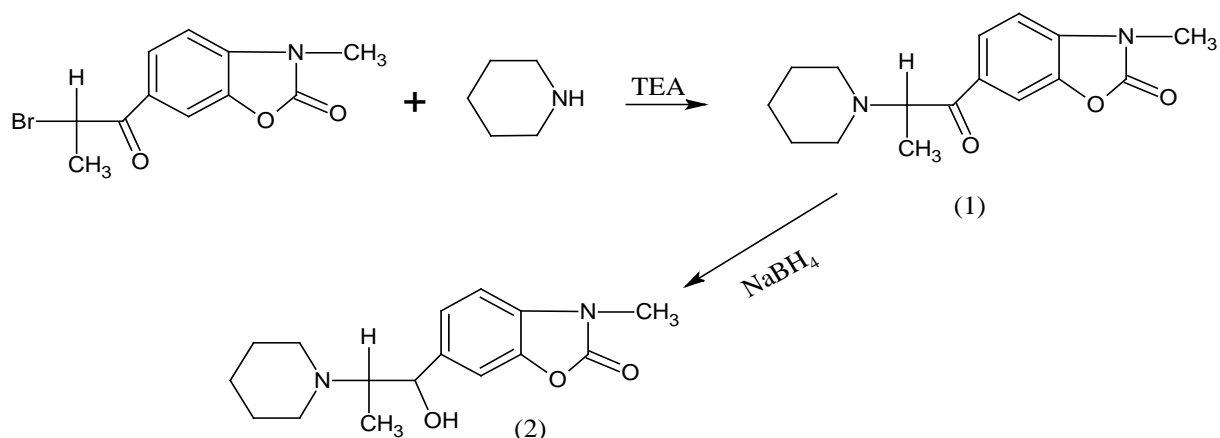


Figure 2.23. Synthesis of 3-methyl-6-(2-substituted aminopropanoyl)-2-benzoxazinone and 1-(3-methyl-2-benzoxazinone)-2-(substituted amino-1-yl) propanol derivatives.

Koksal and coworkers synthesized a series of new 6-acyl-3-alkyl-5-methyl-2(3H)-benzoxazolones starting from 5-methyl-2(3H)-benzoxazolone and evaluated their analgesic, anti-inflammatory and antioxidant activities. The invitro antioxidant capacity of the synthesized compounds was tested by nitric oxide scavenging assay. Most compounds showed anti-inflammatory activity. Among them, 3-[4-(4-florophenyl)piperazinomethyl]-6-(3-chlorobenzoyl)-5-methyl-2(3H)-benzoxazolone was found comparable with the reference drug indomethacin and showed the highest analgesic profile. Similar to anti-inflammatory results, 3-[4-(4-florophenyl)piperazinomethyl]-6-(3-chlorobenzoyl)-5-methyl-2(3H)-benzoxazolone, [6-(3-chlorobenzoyl)-5-methyl-2(3H)-benzoxazolone] also showed a comparable antioxidant activity with the reference drug ascorbic acid. [54]. (Figure 2.24) shows the structures of synthesized compounds.

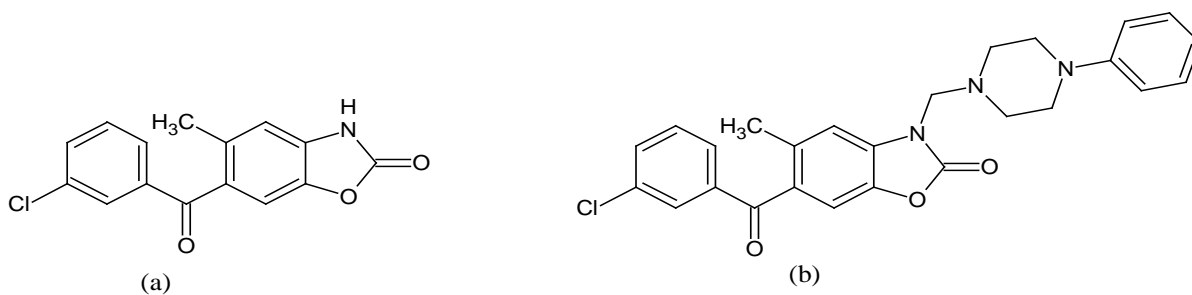


Figure 2.24. Structures of (a) 6-(3-chlorobenzoyl)-5-methyl-2(3H)-benzoxazolone and (b) 3-[4-(4-fluorophenyl)piperazinomethyl]-6-(3-chlorobenzoyl)-5-methyl-2(3H)-benzoxazolone,

GOKHAN et al [55]. synthesized a series of Mannich bases of 5-methyl-3-substituted piperazinomethyl-2-benzoxazolones in an attempt to find improved analgesic anti-inflammatory agents. One of the most interesting characteristics of these series of compounds was their basic nature, which differentiates them from the classical, acidic nonsteroidal anti-inflammatory agents. It was of interest, therefore, to study the analgesic anti-inflammatory properties of these compounds.

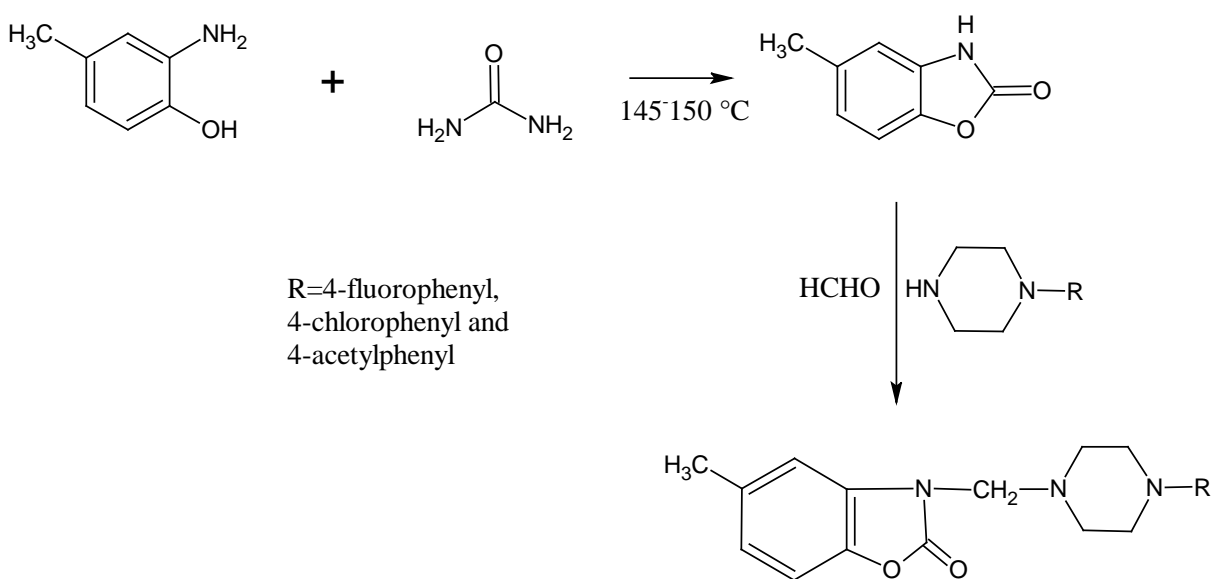


Figure 2.25. Synthesis of Mannich bases of 5-methyl-3-substituted piperazinomethyl-2-benzoxazolones

The synthesized compounds were then examined for their *in vivo* anti-inflammatory and analgesic activities in two different bioassays, namely, carrageenan-induced hind paw edema and p-benzoquinone-induced abdominal constriction tests in mice, respectively. In addition, the ulcerogenic effects of the compounds were determined. Among the derivatives tested the most promising results were obtained from the compounds bearing electron-withdrawing substituents at para position of the phenyl nucleus on the piperazine ring at the 3 position of benzoxazolone moiety (Figure 2.25). The analgesic activities of all compounds were said to be higher than their anti-inflammatory activities.

GOKHAN et al [56]. also synthesized eighteen new 3-[2-(2-/4-pyridyl)ethyl]benzoxazolone (benzothiazolinone) derivatives by reacting 2-/4-vinylpyridine and appropriate benzoxazolinones and benzothiazolinones. The analgesic activities of these compounds were investigated by modified Koster and hot-plate tests. Test results revealed that most of the compounds at 100 mg/kg dose levels have analgesic activity that can be comparable to that of acetylsalicylic acid. Compounds with bromo substituents on the phenyl ring in the (6th) position of the main ring seemed to show less activity than those with fluorinated ones. One of the compounds showed remarkably high activity in the hot-plate test, although it was inactive in the Koster test. Their results suggested that the 2-benzo(thia)oxazolinone ring may play a significant role in the management of pain.

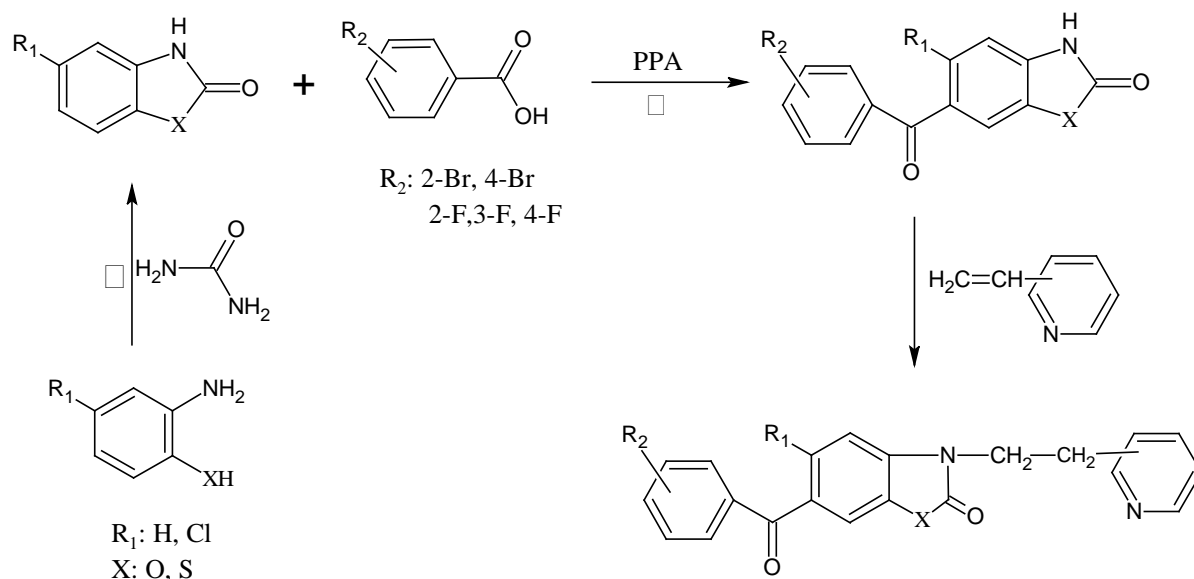


Figure 2.26. Synthesis of New Pyridylethylated Benzoxa(Thia)zolones

2.3. Mannich Reaction

The Mannich reaction may be defined as the condensation of ammonia, or a primary or a secondary amine, with formaldehyde and a compound containing a hydrogen atom of pronounced reactivity due to proximity to an electron withdrawing group.

Carl Mannich first recognized and developed the Mannich reaction in the early 20th century. The Mannich reaction is traditionally used to synthesize β -amino ketones and aldehydes for pharmaceuticals and natural products [57].

The reaction requires three different chemicals: a ketone, an amine, and an aldehyde, making it a 3-component reaction (Figure 2.27).

The original work by Mannich and coworkers was concerned primarily with aldehydes and ketones as the active hydrogen compounds but subsequent work has broadened the scope of the reaction to include carboxylic acids, esters, keto acids, acetylenes, nitroalkanes, nitrophenols, etc. The amine is usually employed as the hydrochloride, although in many cases the free amine can be used to a better advantage. The formaldehyde is used either as the 37% aqueous solution or as paraformaldehyde whenever an organic solvent is employed [58-61].

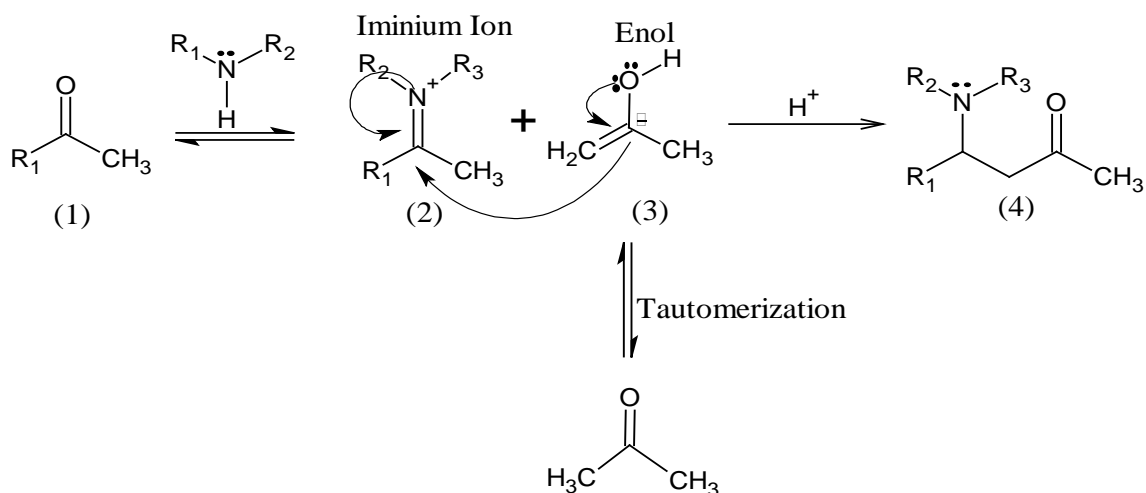


Figure 2.27. Mechanism for an acid catalyzed Mannich reaction from an aldehyde (1), an amine and a ketone, which reacts in the enol arrangement (3).

The 3-component reaction takes place in two steps, starting with a reaction between the aldehyde (1) and the amine. The nitrogen of the amine attacks the carbonyl of the aldehyde and undergoes an imine formation. This replacement of the oxygen with the nitrogen forms the iminium ion (2) and water. The equilibrium of this is a reversible reaction and is generally favored towards the imine form of the molecule. This preference is as a result of more basic nature of nitrogen over oxygen. Because nitrogen is more basic than oxygen, it is more likely to interact with the carbonyl than the oxygen with the formed imine [62].

The second step of the reaction occurs upon addition of the ketone. Ketones are naturally in equilibrium with a more reactive enol form through the process tautomerization (Figure 2.24). The resonance contributors of the enol form demonstrate why the form is less stable than the keto form (Figure 2.28). One resonance contributor of the enol form has a double bond with an alcohol as a substituent. The other resonance contributor to this form, however, can be represented by a protonated carbonyl and an unstable carbanion. The resonance hybrid of these two contributors has some carbanionic character at the β position, which allows this carbon to be a nucleophile and more

reactive. When the ketone is in its enol form (3), this carbanion acts as a strong nucleophile and it is this reactive species that attacks the positively charged iminium carbon in the Mannich reaction [63].

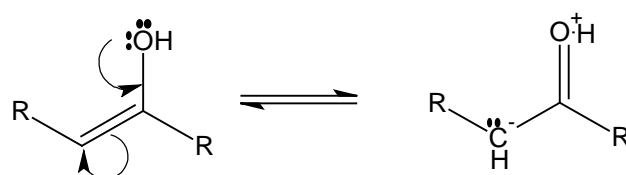


Figure 2.28. The resonance contributors of an enol.

The Mannich reaction is extremely useful in organic synthesis but has several disadvantages. The reaction times are long (up to several days) and many side products are formed. Ketones with two reactive α -positions lead to bis_Mannich bases and regioselectivity of the reaction is difficult to control [64]. Intramolecular Mannich reactions, however, are very useful in natural product synthesis and are gateways to creating complex regio- and stereoselective molecules. (Figure 2.29) shows an example of an intramolecular Mannich reaction for synthesizing polysubstituted piperidines, where the amine and the enolizable ketone are functional on the same molecule, which subsequently reacts with the aldehyde [65,66].

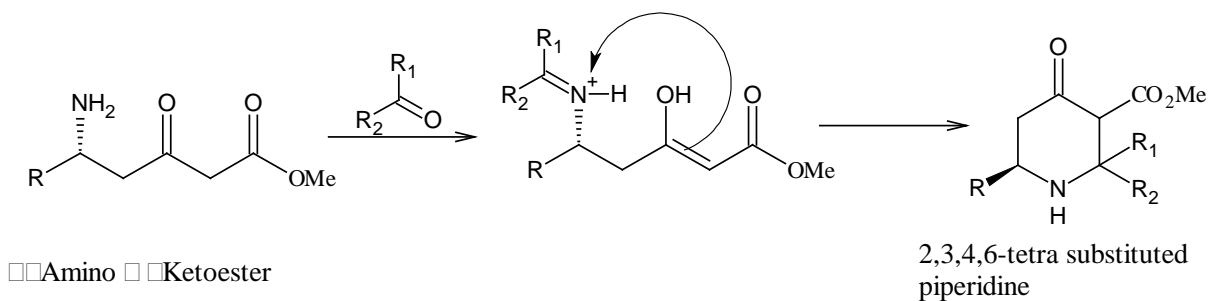


Figure 2.29. An example of an intramolecular Mannich reaction,
Synthesizing polysubstituted piperidines

2.3.1. Mannich Base

Mannich bases, beta-amino ketones carrying compounds, the end products of Mannich reaction [67].

Examples of clinically useful mannich bases which consist of the amino alkyl chain are cocaine, atropine, fluoxetine, as shown in (Figure 2.30).

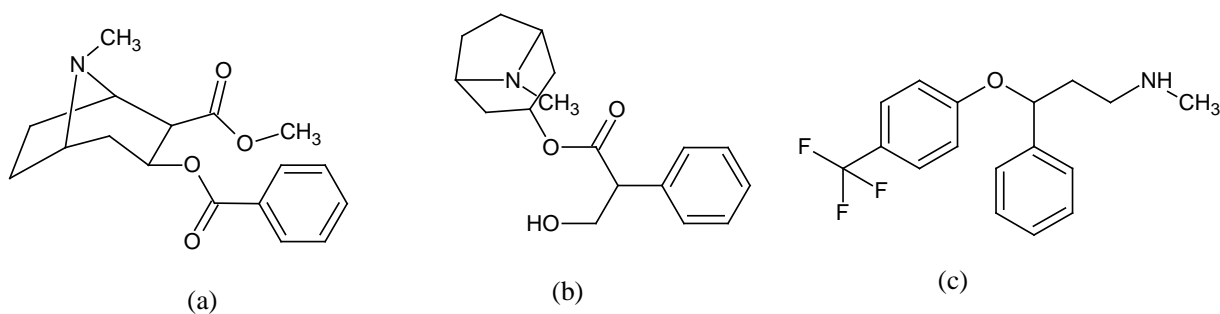


Figure 2.30. Structures of (a) cocaine, (b) atropine, and (c) fluoxetine

Mannich bases have provided an enormous number of applications. The versatility of Mannich bases is demonstrated by the large number of reactions these compounds can be subjected to. They are useful intermediates in synthetic chemistry for the preparation of a variety of new compounds [68].

2.3.2. Importance of Mannich of Base

- I. The basic functionality of the molecules renders them soluble in aqueous solvents upon protonation or alkylation. This property facilitates the pharmacological usage of the biologically active analogs.
- II. The amino function also provides a good synthetic tool for the transformation to numerous other compounds due to its reactivity.
- III. The reaction provides a good method for C-C bond formation. It essentially consists of the condensation of an aldehyde (mostly formaldehyde) and an amine with a substrate possessing acidic hydrogens [69].

2.4. Microwave Assisted Organic Synthesis (MAOS)

In recent years microwave assisted organic reaction has emerged as a new tool in organic synthesis. The technique offers simple, economic, clean, fast, and efficient method for the synthesis of a large number of organic molecules. Important advantage of this technology include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. MAOS technique is considered as an important approach toward green chemistry, because it is more environmentally friendly. This technology has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development [70].

Conventional method of organic synthesis could lead to longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses [71].

2.4.1. Microwave Frequency

Microwave heating refers the use of electromagnetic waves region from 0.01m to 1m wave length of certain frequency to generate heat in the material. These microwaves lie in the region of the electromagnetic spectrum between IR and radio wave, corresponding to frequency of 300GHz to 0.3GHz. (Figure 2.31) shows the electromagnetic spectrum [72].

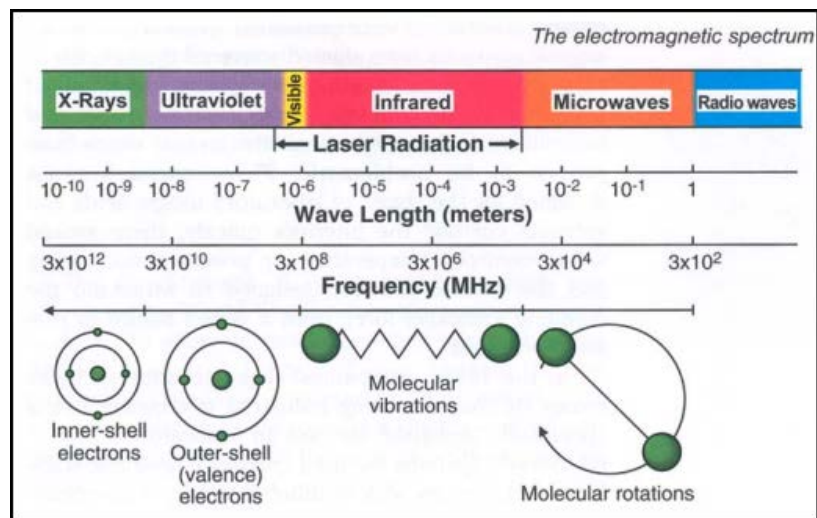


Figure 2.31. Electromagnetic spectrum

2.4.2. Principle of Microwave

The basic principle behind the heating in microwave oven is due to the interaction of charged particle of the reaction material with electro magnetic wavelength of particular frequency. The phenomena of producing heat by electromagnetic irradiation are either by collision or by conduction, some time by both. All the wave energy changes its polarity from positive to negative with each cycle of the wave. This cause rapid orientation and reorientation of molecule, which cause heating by collision. If the charge particles of material are free to travel through the material (e.g. electron in a sample of carbon), a current will be induced which will travel in phase with the field. If charge particles are bound within regions of the material, the electric field component will cause them to move until opposing force balancing the electric force [73].

2.4.3. Heating Mechanism

In microwave oven, material may be heated with use of high frequency electromagnetic waves. The heating arises from the interaction of electric field component of the wave with charge particle in the material. Two basic principal mechanisms involve in the heating of materials are dipolar polarization and conduction mechanism [74].

2.4.3.1. Dipolar Polarization

Dipolar polarisation is a process by which heat is generated in polar molecules. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. However, owing to inter-molecular forces, polar molecules experience inertia and are unable to follow the field. This results in the random motion of particles, and this random interaction generates heat. Dipolar polarisation can generate heat by either one or both the following mechanisms:

- Interaction between polar solvent molecules such as water, methanol and ethanol.
- Interaction between polar solute molecules such as ammonia and formic acid.

2.4.3.2. Conduction Mechanism

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor. The main limitation of this method is that it is not applicable for materials that have high conductivity, since such materials reflect most of the energy that falls on them [75]. (Figure 2.32) shows an illustration of mechanism of conduction and dipolar polarisation.

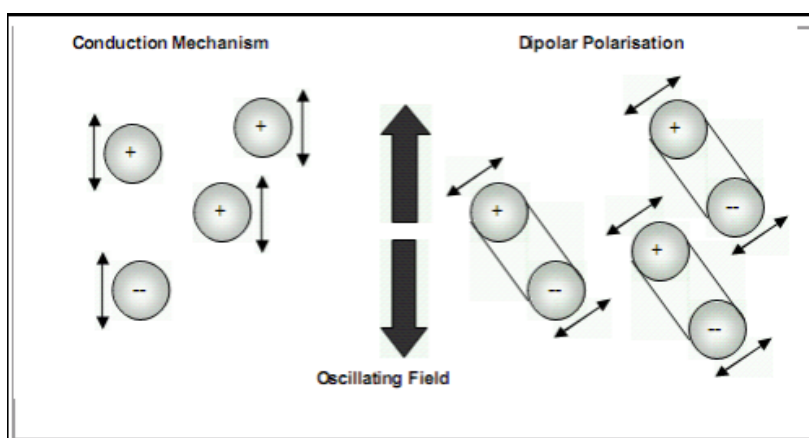


Figure 2.32. Mechanism of conduction and dipolar polarisation

2.4.4. Effects of Solvents

Every solvent and reagent absorb microwave energy differently. They each have a different degree of polarity within the molecule, and therefore, will be affected either more or less by the changing microwave field. A solvent that is more polar, for example, will have a stronger dipole to cause more rotational movement in an effort to align with the changing field. A compound that is less polar, however, will not be as disturbed by the changes of the field and, therefore, will not absorb as much microwave energy. The polarity of the solvent is not the only factor to determining the true absorbance of microwave energy, but it does provide a good frame of reference. Other factors such as, loss tangent (δ) and dielectric constant are also considered when choosing a suitable solvent for microwave synthesis. The ability of a substance to absorb microwave energy and convert it into heat is referred to as loss of tangent and is expressed in term of tangent value:

$$\tan\delta = \frac{\epsilon''}{\epsilon'} \dots\dots\dots (1)$$

where ϵ' is the dielectric constant (polarity) and ϵ'' is the dielectric loss factor.

The higher the tangent value the better is the solvent at absorbing microwave energy and thus better heat is generated. Table 2.1 below shows the loss tangent values of some pure common solvents at room temperature [76].

Table 2.1. Loss tangent values of some pure common solvents at room temperature.

Solvent	Dielectric constant (ϵ)	Loss of tangent($\tan\delta$) / 2.45 GHz
Ethylene glycol	38	1.17
Ethanol	24	0.94
Dimethyl sulfoxide	47	0.82
Methanol	33	0.66
Acetic acid	6.1	0.17
Dimethylformamide	37	0.16
Water	80	0.12
Chloroform	4.8	0.091
Acetonitrile	38	0.062
Ethyl acetate	6.0	0.059
Acetone	21	0.054
Tetrahydrofuran	7.6	0.047
Dichloromethane	9.1	0.047

2.4.5. Conventional vs Microwave Heating

Microwave heating is different from conventional heating in many respects. Table 2.2 below give the differences between microwave heating and conventional heating [77].

Table 2.2. Differences between microwave and conventional heating.

	Conventional	Microwave
1	Reaction mixture heating proceeds from a surface usually inside surface of reaction vessels	Reaction mixture heating proceeds directly inside mixture
2	The vessel should be in physical contact with surface source that is at a higher temperature source (e.g. mantle, oil bath, steam bath etc.)	No need of physical contact of reaction with the higher temperature source. While vessel is kept in microwave cavities.
3	Heating by thermal or electric source.	Heating by electromagnetic wave.
4	Heating mechanism involve conduction	Heating mechanism involve dielectric polarization and conduction
5	Transfer of energy occur from the wall, surface of vessel, to the mixture and eventually to reacting species	The core mixture is heated directly while surface (vessel wall) is source of loss of heat
6	In conventional heating, the highest temperature (for a open vessels) that can be achieved is limited by boiling point of particular mixture.	In microwave, the temperature of mixture can be raised more than its boiling point i.e. superheating take place
7	In the conventional heating all the compound in mixture are heated equally	In microwave, specific component can be heated specifically.

2.4.6. Application of microwave in organic synthesis in mannich Reaction

Microwave organic synthesis have a wide variety of applications in chemistry and other fields. The first microwave-assisted Mannich reaction (Figure 2.33) been synthesized and developed in the year 2000 [78].

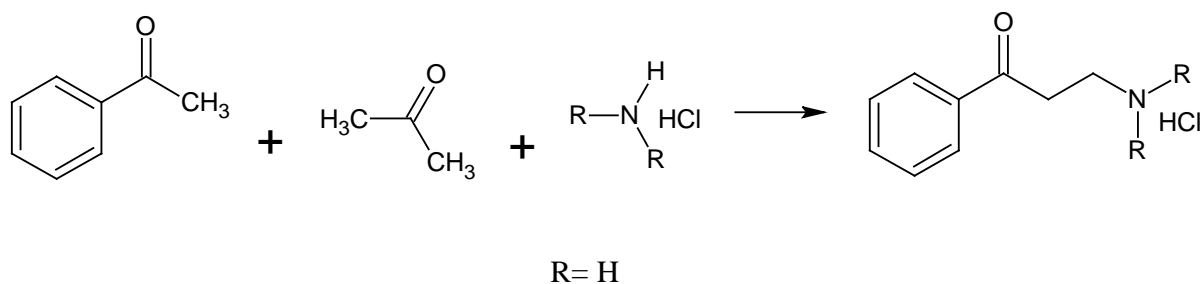


Figure 2.33. Microwave-assisted mannich reaction

Primary amines were readily obtained in 60 to 83 yield after 15 minutes of microwave irradiation under solvent free conditions when using ammonium chloride as the amine source. When substituted amine hydrochlorides were used, the reaction failed under solvent free conditions. However, when the same reaction was performed in ethanol, high yields were obtained (80-83%) in both cases, no traces of side product formation were obtained.

Recently, in 2014 piperazine derivatives of 5-chloro benzoxazolone synthesized at microwave condition: 150 W, 3 min, 65 °C, 100 W, 5 min, 65 °C the compound shown in (Figure 2.34) [79].

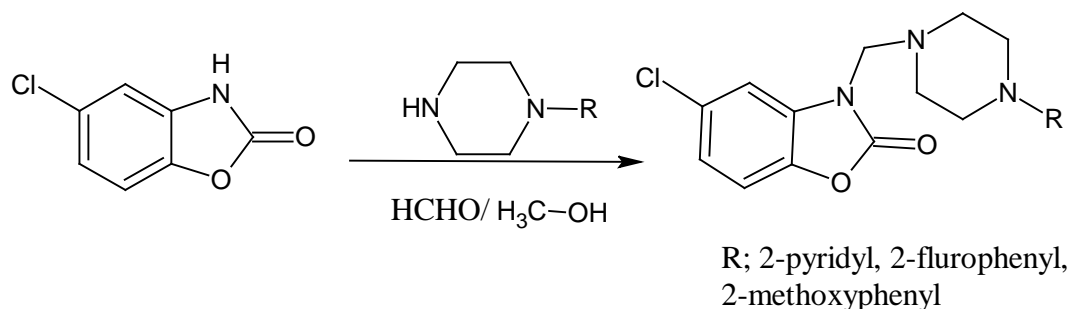


Figure 2.34. General microwave synthesis of 5-chloro-3-substituted benzoxazolone molecules

3. MATERIALS AND METHODS

3.1. Materials

The starting chemicals, 2-(3H)-benzoxazolone, 5-chloro-2-(3H)-benzoxazolone, benzyl piperidine, methanol and 37% formaldehyde solution used in this study were purchased from Sigma Aldrich Chemical Company and were used without any further purification or drying.

3.2. Thin Layer Chromatography (TLC)

In TLC, the plate was made of silica gel/TLC-plates (DC-Alufolien-Kieselgel, Germany) and the solvents used were, benzene, ethyl acetate, hexane and methanol. Silica gel plates were detected under UV- Light (245nm).

Three different mobile phases were prepared with different solvents at different ratio as follows;

M-1: Benzene – Methanol (5:1)

M-2: Benzene – Methanol (9:1)

M-3: Ethylacetate – Hexane (1:2)

The solvent was poured into the chamber to a depth of just less than 0.5 cm, swirled gently, and allowed to stand while the TLC plate prepared.

TLC plates were cut horizontally into plates of about 6cm long by various widths and a line is drawn across the plate at 0.5 cm from the bottom of the plate and also about 0.5cm from the top with the aid of a pencil.

The starting materials and product were dissolved in chloroform and with the aid of a microcapillary spots were made on the TLC plate and the prepared plate was gently placed in the chamber. The plate was allowed to develop until the solvent front was reached to the previously drawn line about half a centimeter below the top of the plate and the plate was removed, then the plate allowed drying. The spots were viewed under UV light at 254 nm and Rf values calculated.

3.3. Melting Point Determination

Melting point of the compounds was recorded on the Mettler Toledo FP 900 Thermo System Digital melting point apparatus and the values are uncorrected.

3.4. Microwave

Microwave irradiation was carried out in a microwave reactor (MicroSYNTH, Milestone, Italy).

3.5. Spectroscopy

FT-IR Spectra: The FT-IR spectra of the compounds were recorded on a Perkin-Elmer Spectrum Bx¹¹ spectrophotometer with attenuated total reflection (ATR) (in wavenumbers) in cm^{-1} at Hecettepe University Science and Pharmacy Faculty, Department of chemistry.

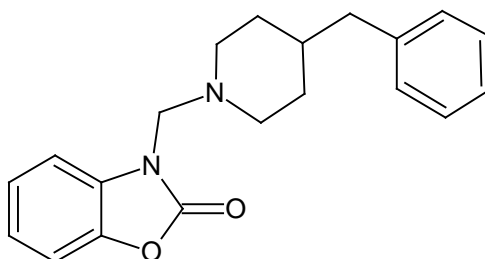
¹H-NMR Spectra: The ¹H-NMR spectra of the compounds were recorded on a Mercury Varian 400MHz NMR Spectrometer using deuterated chloroform (CDCl_3) as solvent at Boğaziçi University, Research and Development Laboratories. Chemical shifts were reported in parts per million (ppm).

3.6. Experimental.

Experimental procedures were taken from the literature [80].

3.6.1. Synthesis of Compound 1

3-[4-(benzylpiperidino)methyl]-2-benzoxazolone



Room Temperature (method A)

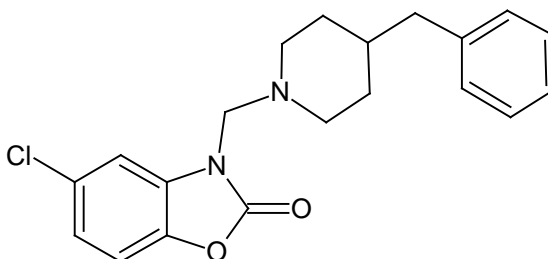
200 mg (0.00148mol) of 2(3H)-benzoxazolone was dissolved in 6mL of methanol followed by addition of 0.2 ml (0.00148 mol) of benzyl piperidine in 50 ml round bottom flask. Then 0.2 ml of 37% (w/v) formalin solution was mixed with 2 ml of methanol and poured into this reaction mixture. The reaction mixture was left at room temperature for 10 minute then filtered off, washed with methanol, dried and purified by crystallization using ethanol.

Reflux (method B)

200 mg (0.00148mol) of 2(3H)-benzoxazolone was dissolved in 6mL of methanol followed by addition of 0.2 ml (0.00148 mol) of benzyl piperidine in 50 ml round bottom flask. Then 0.2 ml of 37% (w/v) formalin solution was mixed with 2 ml of methanol and poured into this reaction mixture. The solution was refluxed in a water bath for one hour, the reaction mixture was then poured onto crushed ice and the resulting precipitate was filtered off, washed with methanol, dried and purified by crystallization using ethanol.

3.6.2. Synthesis of Compound 2

3-[4-(benzylpiperidino)methyl]- 5-chloro-2-benzoxazolone



Reflux (method B)

200 mg (0.00118mol) of 5-chloro-2(3H)-benzoxazolone was dissolved in 6mL of methanol followed by addition of 0.2 ml (0.00148 mol) of benzyl piperidine in 50 ml round bottom flask. Then 0.2 ml of 37% (w/v) formalin solution was mixed with 2 ml of methanol and poured into this reaction mixture. The solution was refluxed on a water bath for one hour. The reaction mixture was then poured onto crushed ice and the resulting precipitate was filtered off, washed with methanol, dried and purified by crystallization using ethanol.

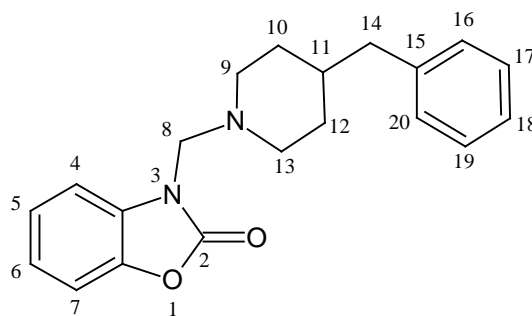
Microwave (method C)

200 mg (0.00118 mol) of 5-Chloro-2(3H)-benzoxazolone was dissolved in 6 ml of methanol followed by addition of 0.2 ml (0.00148 mol) of 4-benzyl piperidine in 50 ml round bottom flask. Then 0.2 ml of 37% (w/v) formalin solution was mixed with 2 ml of methanol and poured into this reaction mixture. A white precipitate immediately started to appear. The solution was placed in a microwave reactor and irradiated at 150 W for 3 minute to bring the temperature to 65 °C. Then, the power was lowered to 100 W and the temperature was kept at 65 °C for 5 minute. After cooling the mixture was poured into crushed ice upon which a precipitate was formed. The resulting precipitate was filtered off, washed with methanol, dried and purified by crystallization using ethanol.

4. RESULTS AND DISCUSSION

4.1. Results

Compound 1



3-[(4-benzylpiperidin-1-yl)methyl]-1,3-benzoxazol-2(3H)-one

The above compound was synthesized by two methods (method A and method B) mentioned in experimental part.

Room temperature

- _ White crystalline solid was obtained with a yield of 39.1% (186.7 mg) and melting point of 143.3 °C
- _ TLC in the M-1 and M-2 and M-3 mobile phase gave R_f values of 0.67 and 0.52 and 0.48 respectively.
- _ Fourier Transform Infra-Red (FT-IR) Spectroscopy (ν_{max}): FT-IR showed stretches at 2810-3030 cm^{-1} (C-H stretch), and 1782 cm^{-1} carbonyl group (C=O).
- _ Proton Nuclear Magnetic Resonance Spectroscopy (^1H NMR in CDCl_3 ; ppm): ^1H -NMR showed chemical shifts at 7.1-7.2 ppm (9H, m, Ar-H); 4.6 ppm (2H, s, H⁸); 2.5 ppm (2H, t, pip H⁹); 2.3 ppm (2H, q, pip H¹⁰); 1.5 ppm (1H, sep, pip H¹¹); 1.3 ppm (2H, q, pip H¹²); 1.7 ppm (2H, t, pip H¹³); 3 ppm (2H, d, H¹⁴).

Reflux

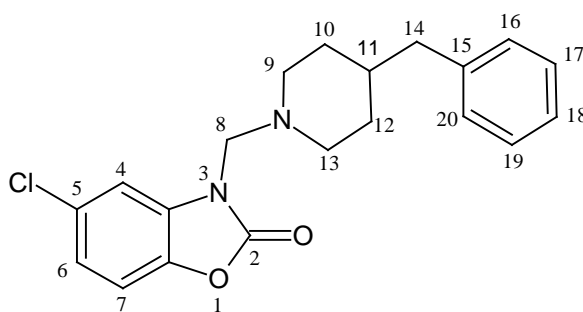
_ White crystalline solid was obtained with a yield of 47.2 % (225.1 mg) and melting point of 142.8 °C

_ TLC in the M-1 and M-2 and M-3 mobile phase gave R_f values of 0.63 and 0.49 and 0.43 respectively.

_ Fourier Transform Infra-Red (FT-IR) Spectroscopy (ν_{max}): FT-IR showed stretches at 2817-3030 cm^{-1} (C-H stretch), and 1760 cm^{-1} carbonyl group (C=O).

_ Proton Nuclear Magnetic Resonance Spectroscopy (^1H NMR in CDCl_3 ; ppm): ^1H -NMR showed chemical shifts at 7.1-7.2 ppm (9H, m, Ar-H); 4.6 ppm (2H, s, H^8); 2.5 ppm (2H, t, pip H^9); 2.3 ppm (2H, q, pip H^{10}); 1.5 ppm (1H, sep, pip H^{11}); 1.3 ppm (2H, q, pip H^{12}); 1.7 ppm (2H, t, pip H^{13}); 3 ppm (2H, d, H^{14}).

Compound 2



3-[(4-benzylpiperidin-1-yl)methyl]-5-chloro-1,3-benzoxazol-2(3H)-one

The above compound was synthesized by two methods (method B and method C) mentioned in experimental part.

Reflux

- _ White yellowish crystalline solid was obtained with a yield of 21.6 % (66.1 mg) and melting point of 101.9 °C
- _ TLC in the M-1 and M-2 and M-3 mobile phase gave R_f values of 0.74 and 0.68 and 0.71 respectively.
- _ Fourier Transform Infra-Red (FT-IR) Spectroscopy (ν_{max}): FT-IR showed stretches at 2790-3060 cm^{-1} (C-H stretch), and 1782 cm^{-1} carbonyl group (C=O).
- _ Proton Nuclear Magnetic Resonance Spectroscopy (^1H NMR in CDCl_3 ; ppm): ^1H -NMR showed chemical shifts at 7.1-7.2 ppm (8H, m, Ar-H); 4.6 ppm (2H, s, H^8); 2.5 ppm (2H, t, pip H^9); 2.3 ppm (2H, q, pip H^{10}); 1.5 ppm (1H, sep, pip H^{11}); 1.3 ppm (2H, q, pip H^{12}); 1.7 ppm (2H, t, pip H^{13}); 3 ppm (2H, d, H^{14}).

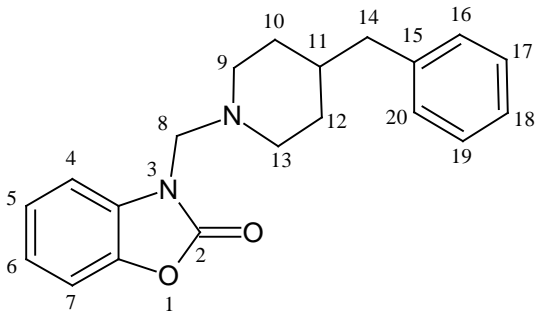
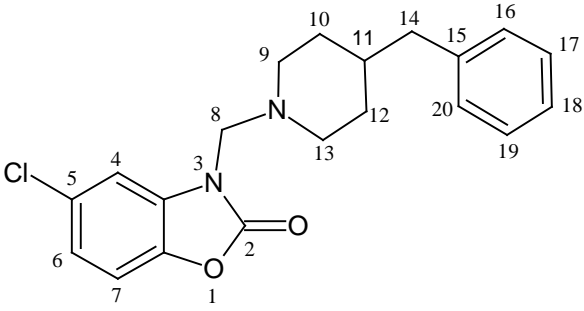
Microwave

- _ White yellowish crystalline solid was obtained with a yield of 11.7 % (47.3 mg) and melting point of 102.2 °C
- _ TLC in the M-1 and M-2 and M-3 mobile phase gave R_f values of 0.73 and 0.66 and 0.71 respectively.
- _ Proton Nuclear Magnetic Resonance Spectroscopy (^1H NMR in CDCl_3 ; ppm): ^1H -NMR showed chemical shifts at 7.1-7.2 ppm (8H, m, Ar-H); 4.6 ppm (2H, s, H^8); 2.5 ppm (2H, t, pip H^9); 2.3 ppm (2H, q, pip H^{10}); 1.5 ppm (1H, sep, pip H^{11}); 1.3 ppm (2H, q, pip H^{12}); 1.7 ppm (2H, t, pip H^{13}); 3 ppm (2H, d, H^{14}).

4.2. Discussion

In this study two benzylpiperidine-benzoxazolone compounds were synthesized by using Mannich reaction. Structures, numbering and names of compound 1 and 2, are given in table 4.1 below.

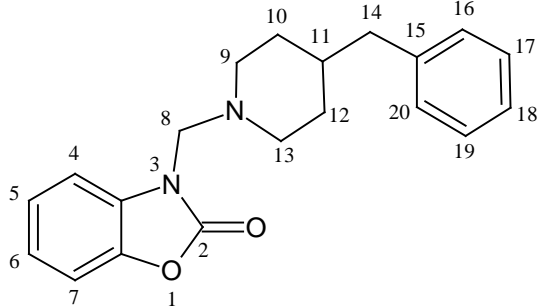
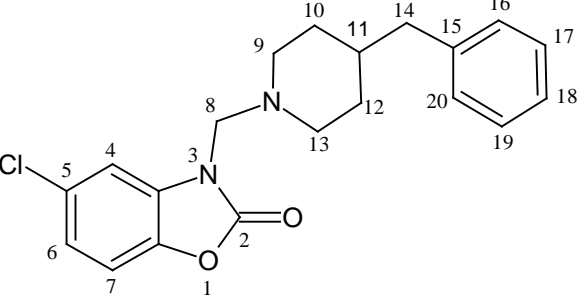
Table 4.1: The structures and chemical names of the synthesized compounds.

Chemical name	Structure
3-[(4-benzylpiperidin-1-yl)methyl]-1,3-benzoxazol-2(3H)-one	 <p style="text-align: center;">Compound 1</p>
3-[(4-benzylpiperidin-1-yl)methyl]-5-chloro-1,3-benzoxazol-2(3H)-one	 <p style="text-align: center;">Compound 2</p>

Both of the two synthesized compound have the same substitution on 3rd position of 2(3H)-benzoxazolone and 5-chloro-2(3H)-benzoxazolone ring. In this study, three different reaction conditions have been used for the synthesis of these compounds. Namely, room temperature, reflux and microwave condition reaction.

Table 4.2: shows the reaction condition, reaction time, melting point and the yield of compound 1 and 2.

Table 4.2: Comparison between the synthesized products.

Structure	Reaction condition	Reaction time	Melting point	yield
 <p style="text-align: center;">Compound 1</p>	Room temperature	10 minute	143.3 °C	39.1%
	Reflux	1 hour	142.8 °C	47.2%
 <p style="text-align: center;">Compound 2</p>	Ref lux	1 hour	101.9 °C	21.6 %
	Microwave	8 minute	102.2 °C	11.8%

The reaction for synthesis the target compound is carried out according to Mannich reaction conditions, in which 4-benzylpiperidine react with 2(3H)-benzoxazolone and 5-chloro-2-(3H)-benzoxazolone at 3-position, which is the reactive site for mannich reaction.

For synthesis of compound 1, (3-[(4-benzylpiperidin-1-yl)methyl]-1,3-benzoxazol-2(3H)-one) room temperature and reflux methods both form the product in moderate yields. Therefore microwave reaction condition was not obtained for this compound. On the other hand room temperature method did not produce compound 2, (3-[(4-benzylpiperidin-1-yl)methyl]-5-chloro-1,3-benzoxazol-2(3H)-one). While under reflux condition compound 2 was successfully prepared. In order to find another reaction condition for synthesis of compound 2, microwave assisted organic synthesis method was used, which gave the product in low yield. The reason could be due to the small amount of starting materials used in synthesis.

The general reaction used for the synthesis of the target compound is shown in (Figure 4.1).

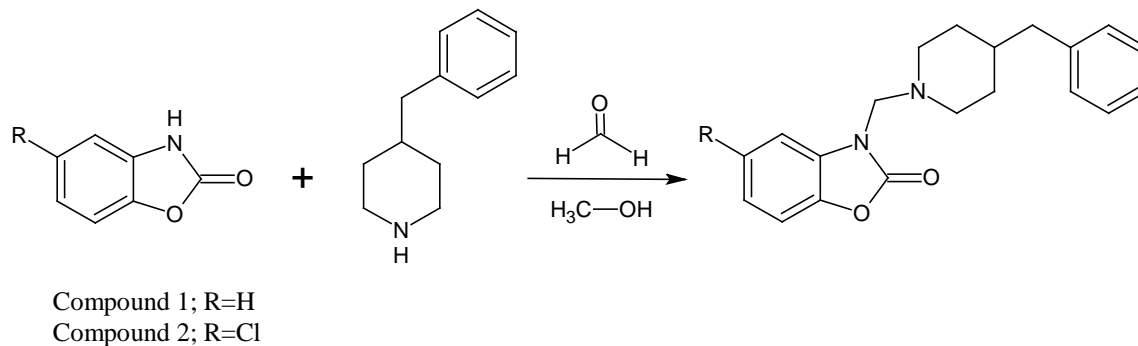


Figure 4.1. General reaction used for synthesis of target compound

The structures of the synthesized compound were confirmed by Fourier Transform Infra-Red (FT-IR) and Proton Nuclear Magnetic Resonance (^1H NMR) Spectroscopy.

The FT-IR spectra of the two synthesized compounds showed absence of (N-H) stretch which supposed to appear at $(3100-3550) \text{ cm}^{-1}$, which indicates that the substitution had taken place at 3-position as expected.

Also as expected, the strong (C=O) stretch band of 2(3H)-benzoxazolone and 5-chloro-2-(3H)-benzoxazolone derivatives are visible at $1745-1782 \text{ cm}^{-1}$ in all spectra.

The (C-H) stretch for the products also appear at 2792-3270 cm^{-1} as expected in all spectra.

FT-IR spectra of compound 1 and 2 made under different reaction conditions are given in Figure 4.2, 4.3 and 4.4, respectively.

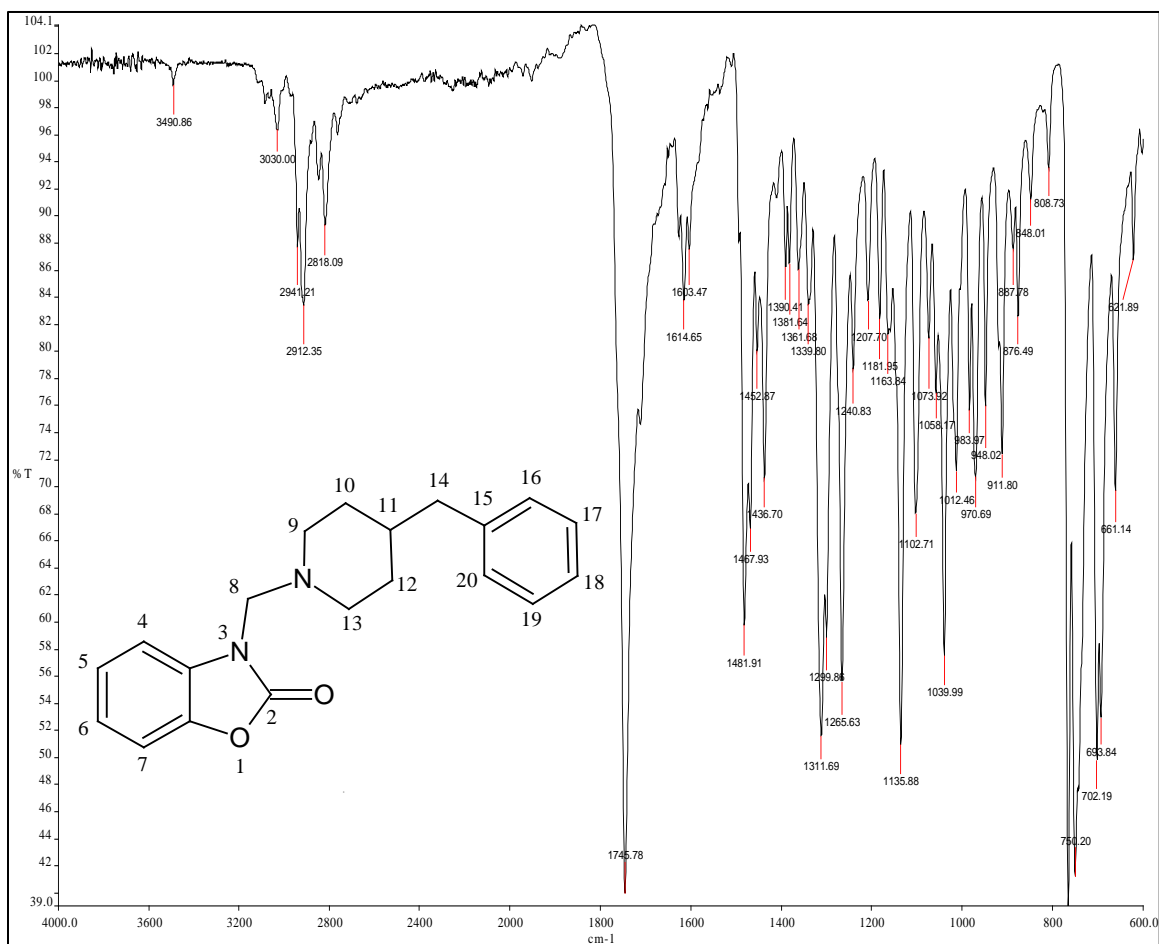


Figure 4.2: FT-IR spectrum of 3-[(4-benzylpiperidin-1-yl) methyl]-1,3-benzoxazol-2(3H)-one. (synthesized at room temperature)

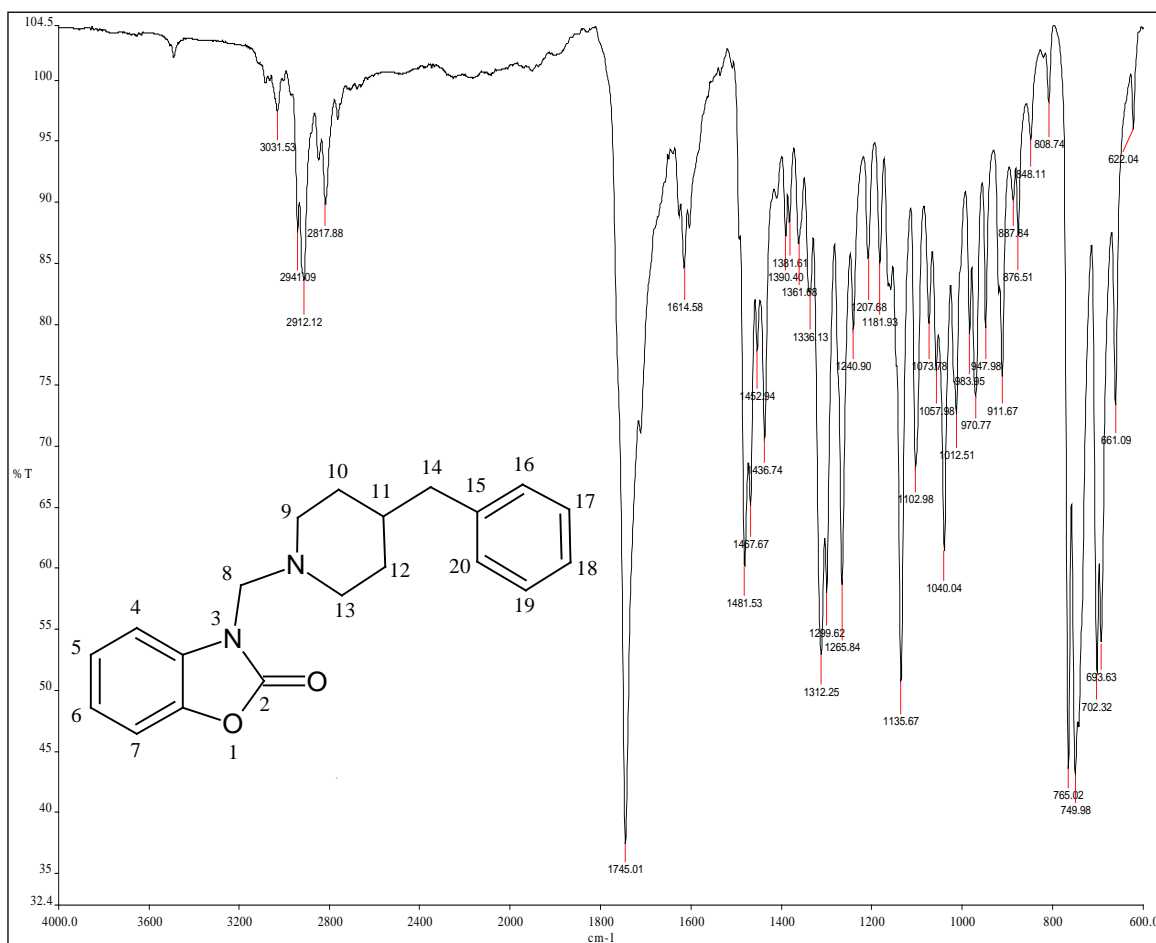


Figure 4.3: FT-IR spectrum of 3-[(4-benzylpiperidin-1-yl) methyl]-1,3-benzoxazol-2(3H)-one. (synthesized by reflux)

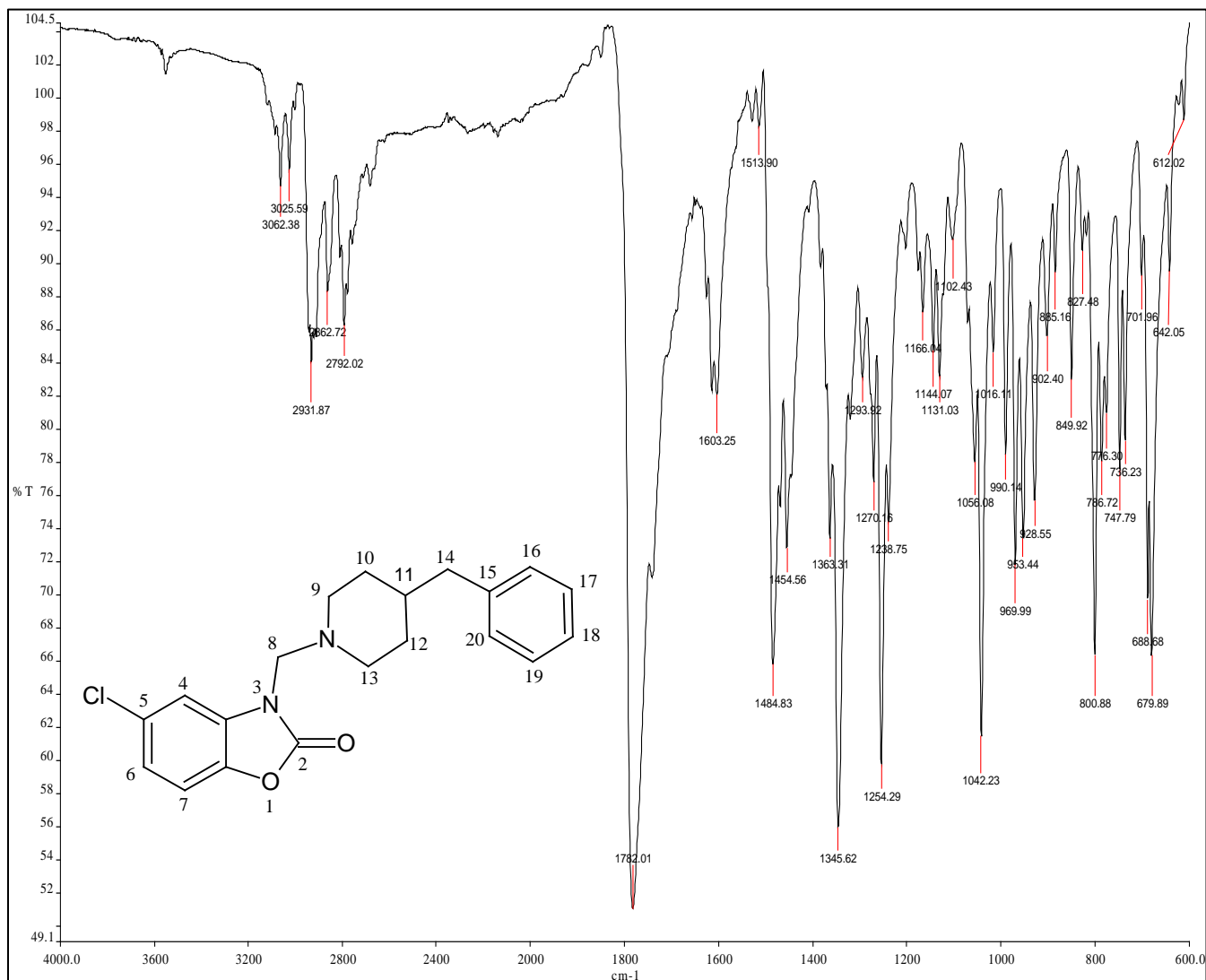


Figure 4.4: FT-IR spectrum of 3-[(4-benzylpiperidin-1-yl) methyl]-5-chloro-1,3-benzoxazol-2(3H)-one. (synthesized by reflux)

¹H-NMR spectra of the synthesized compounds shows peaks at expected chemical shifts. For compound 1, ¹H-NMR showed aromatic protons (¹H) chemical shifts at 7.1-7.2 ppm (9H, m, Ar-H); methylene (-CH₂-) chemical shift at 4.6 ppm which indicate the accuracy of the substitution at heteroatomic nitrogen at position-3, and piperidine chemical shifts at

(2H, s, H⁸); 2.5 ppm (2H, t, pip H⁹); 2.3 ppm (2H, q, pip H¹⁰); 1.5 ppm (1H, sep, pip H¹¹); 1.3 ppm (2H, q, pip H¹²); 1.7 ppm (2H, t, pip H¹³); 3 ppm (2H, d, H¹⁴).

The integral value also matches the number of protons (¹H) exactly.

For compound 2, ¹H-NMR showed chemical shifts at 7.2-7.4 ppm (8H, m, Ar-H); methylene (-CH₂-) chemical shift at 4.6 ppm which indicate the accuracy of the substitution at heteroatomic nitrogen at position-3, and piperidine chemical shifts at (2H, s, H⁸); 2.5 ppm (2H, t, pip H⁹); 2.3 ppm (2H, q, pip H¹⁰); 1.5 ppm (1H, sep, pip H¹¹); 1.3 ppm (2H, q, pip H¹²); 1.7 ppm (2H, t, pip H¹³); 3 ppm (2H, d, H¹⁴).

The integral value also matches the number of protons (¹H) exactly.

¹H-NMR spectra of compound 1 and 2 are given in figure 4.5, 4.6, 4.7 and 4.8, respectively.

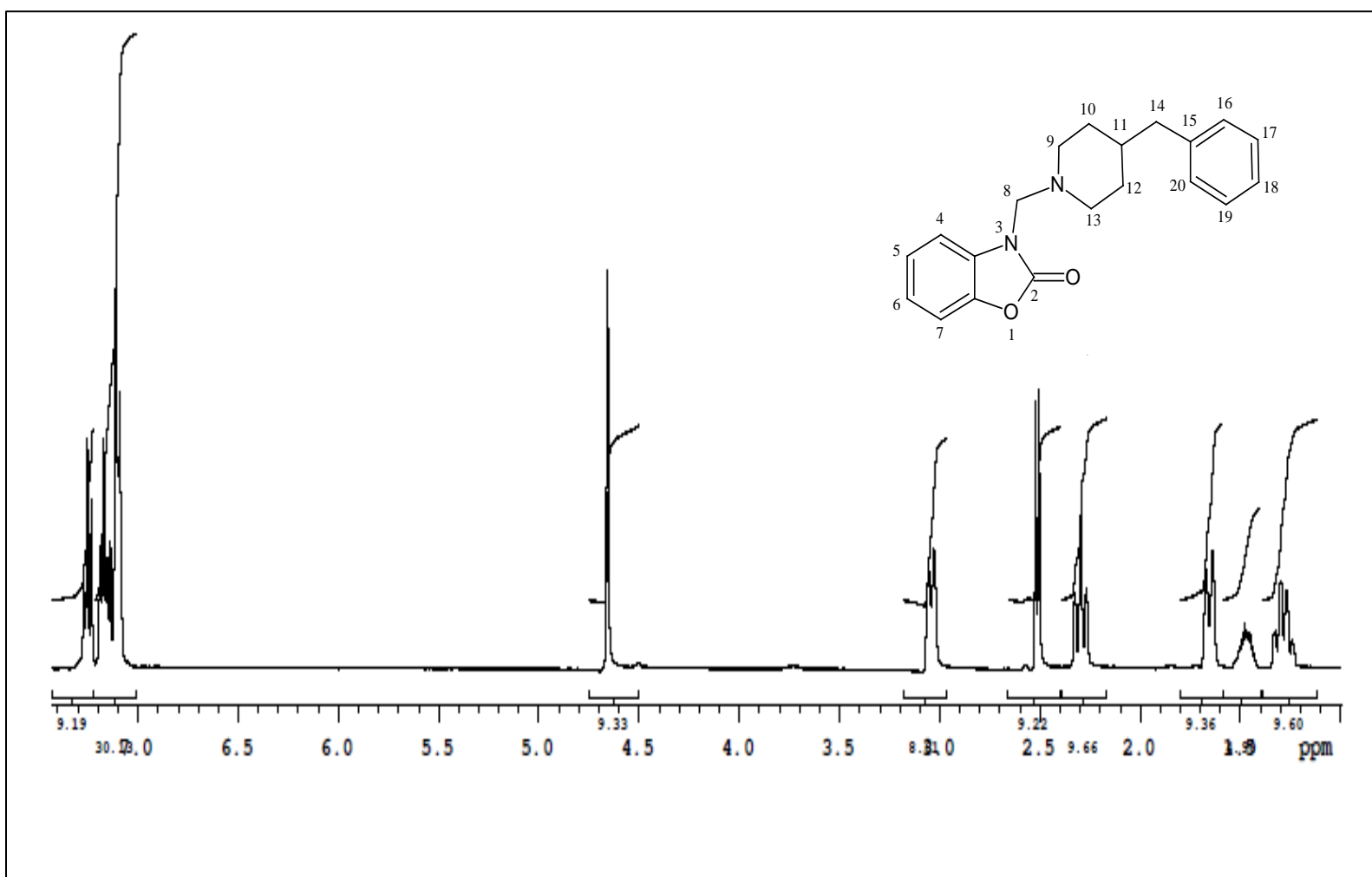


Figure 4.5: $^1\text{H-NMR}$ spectra of 3-[(4-benzylpiperidin-1-yl)methyl]-1,3-benzoxazol-2(3H)-one. (synthesized at room temperature)

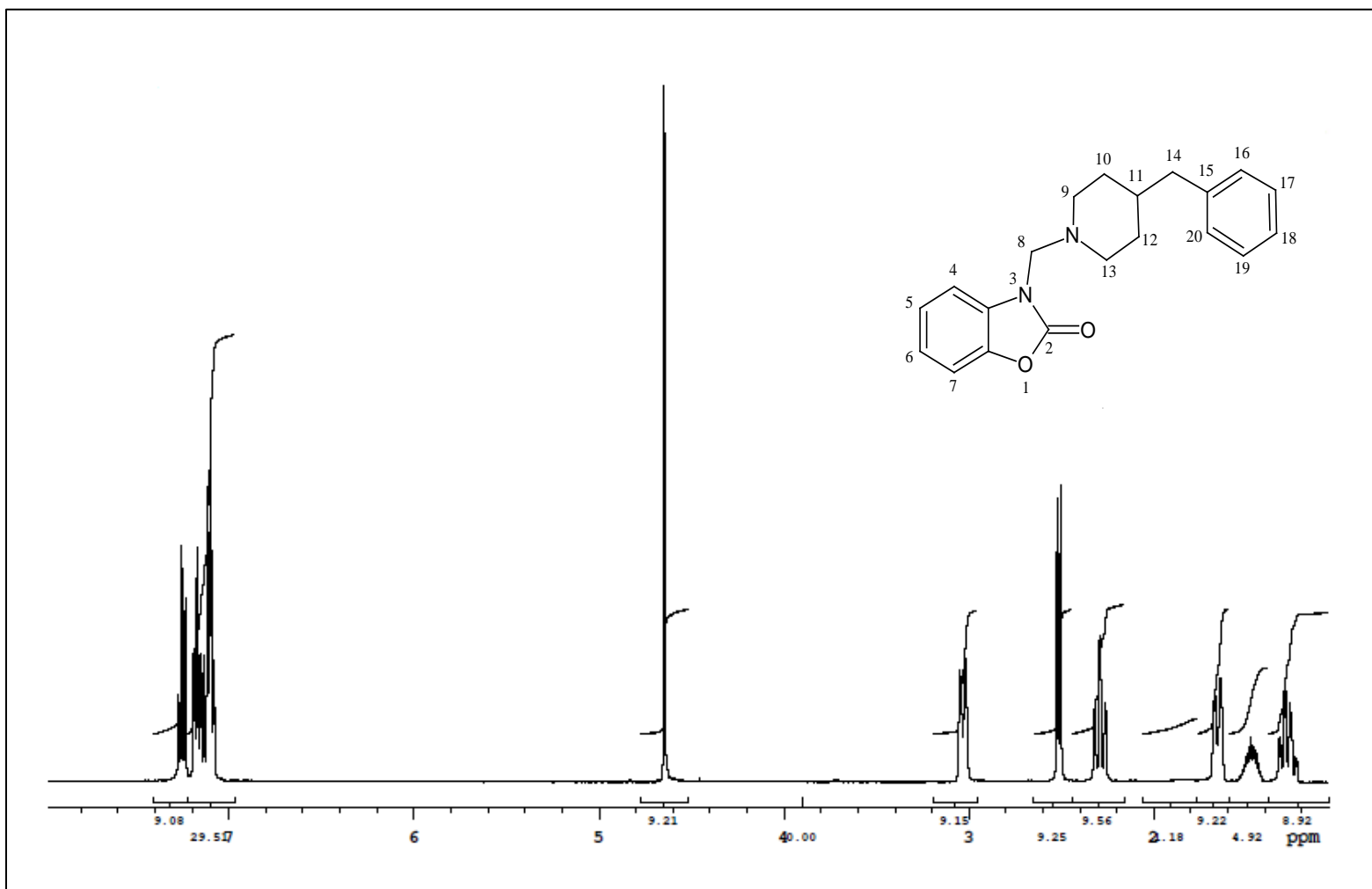


Figure 4.6: $^1\text{H-NMR}$ spectra of 3-[(4-benzylpiperidin-1-yl) methyl]-1,3-benzoxazol-2(3H)-one. (synthesized by reflux)

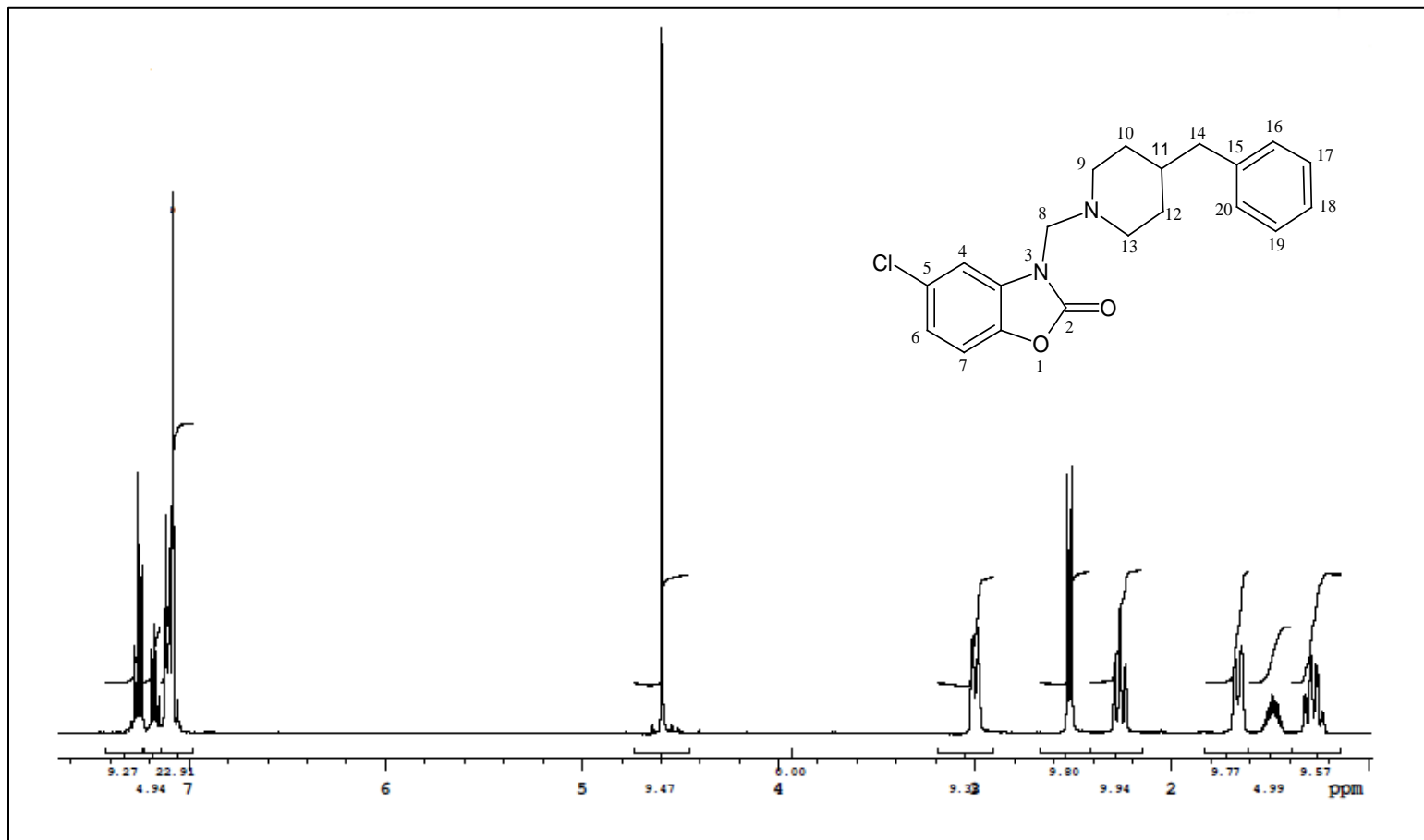


Figure 4.7: $^1\text{H-NMR}$ spectra of 3-[(4-benzylpiperidin-1-yl) methyl]-5-chloro-1,3-benzoxazol-2(3H)-one. (synthesized by reflux)

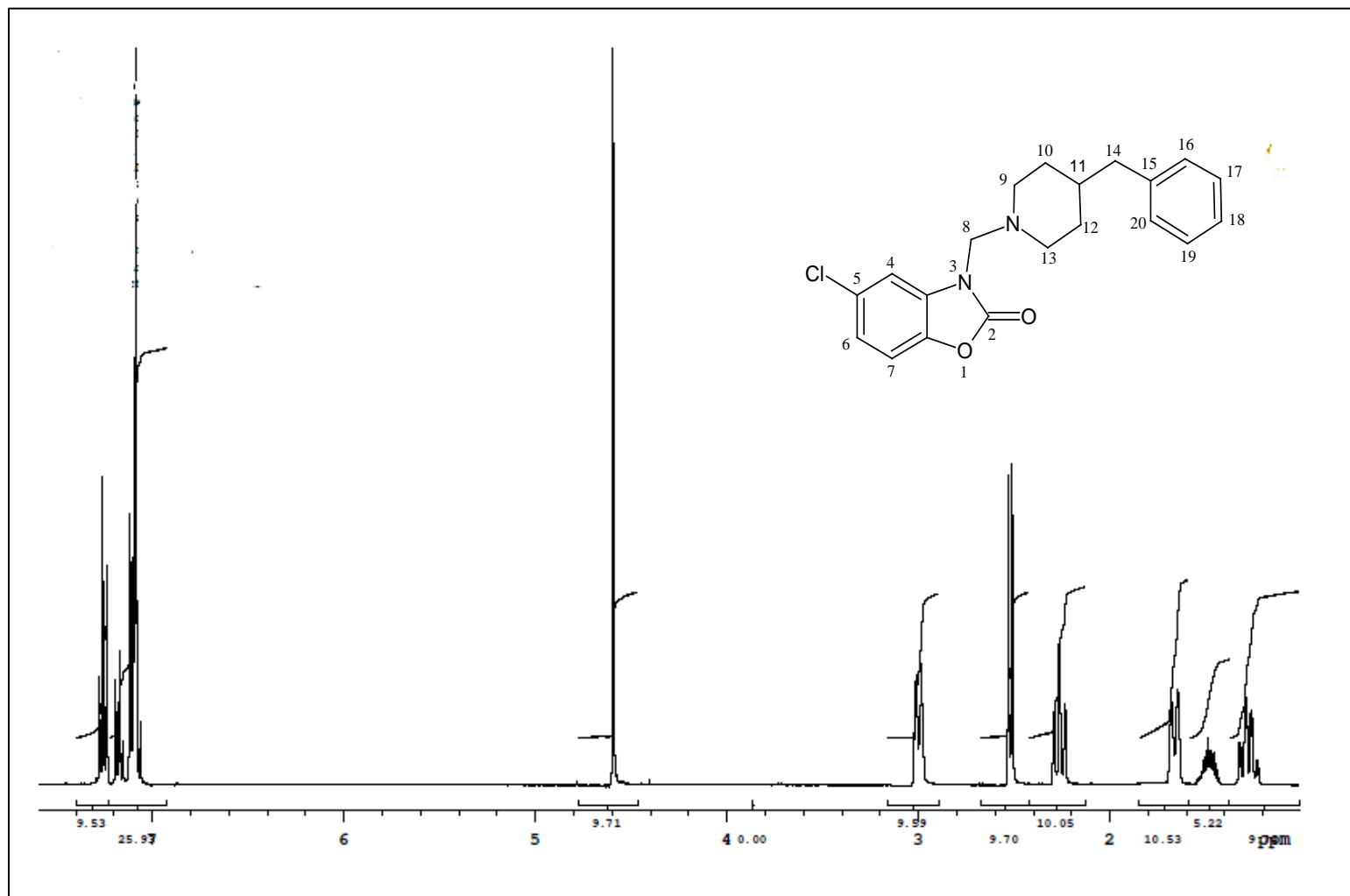


Figure 4.8: $^1\text{H-NMR}$ spectra of 3-[(4-benzylpiperidin-1-yl) methyl]-5-chloro-1,3-benzoxazol-2(3H)-one. (synthesized by microwave technique)

5. CONCLUSION

Two different mannich base of 2-(3H)benzoxazolone and 5-chloro-2-(3H)benzoxazolone derivatives were synthesized in this thesis using the classical mannich reaction by three different methods, room temperature, reflux, and microwave.

Since it is possible to do substitutions at different sites of benzoxazolone structure, its more easier to synthesize a lot of compound 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.

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