**T.R.N.C**

**NEAR EAST UNIVERSITY**

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# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES OF 2(3H)-BENZOXAZOLONE DERIVATIVE

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**Asst. Prof. Dr. Yusuf Mülazim**

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My first and foremost thanks goes to the one and only Almighty ALLAH (S.W.T) for his countless blessings and skills which enabled me to conduct this purposefully research work.

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I could not be standing in the position where I am right now without support of my father S.M.H Jamal Rizvi and family who increased my confidence to stay firm and accomplished the field of study.

## ABSTRACT

2(3H)-Benzoxazolone derivatives are known to show its diverse pharmacological behavior which depend on the position and type of substitient. The current study focuses on the synthesis and cytotoxic evaluation of 2(3H)-benzoxazolone derivative with classical Mannich reaction. The synthesized compound have piperazine ring in third position of the core structure. The compound was characterized by $^{1}H$ NMR and FTIR spectroscopy, the synthesized compound was found to be promising cytotoxic agent against MCF 7 Cell line. The different concentration of these molecule were incubated for 24 hrs and 48 hrs. The following concentration (5, 10, 20, 50 & 100 µg/ml) results depict the potential of synthesized compound against cancer cell lines, at 10 µg/ml showed better result among the other concentrations.



**Key words** : 5 Chloro 2(3H)- Benzoxazolone , Mannich reaction, Cytotoxicity, MTT assay.

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## LIST OF ABBREVIATION

| | |
|---|---|
| COX | Cyclo-oxygnase |
| BOA | 2(3H) Benzoxazolone |
| FT IR | Fourier Transform Infrared |
| $^{1}$H NMR | Proton Nuclear Magnetic Resonance |
| TLC | Thin Layer Choromatography |
| UV | Ultra Voilet |
| DMF | Dimethyleformamide |
| MR | Mannich Reaction |
| HIV | Human Immune Virus |
| WHO | World Health Organization |
| DNA | Deoxyribonucleic Acid |
| HPV | Human Papilloma Virus |
| EBV | Epstein Barr Virus |
| KSHV | Kesposis Sarcoma-associated Horpes Virus |
| CNS | Central Nervous System |

## 1. INTRODUCTION

2(3H)-Benzoxazolone is a simple biological molecule however it has vital contribution in the field of medicinal chemistry due to vast range of activity. It has distinct place in this field, the structure of 2(3H)-benzoxazolone is quite similar with nucleic bases. The cyclic ring of 2(3H)-benzoxazolone is isosters of natural occurring nucleotide i.e adenine and guanine and show the manifold activity such as Antimicrobial, anti-inflammatory or analgesic, antifungal, anticancer activity etc. [1]

2(3H)-Benzoxazolone with substitution of cyclic amine has cytotoxic effect in different cancer cell line. Research result showed dose dependent inhibition of cancer cell proliferation (IC50 values are less than 100µM). According to the result these compound are highly effective on human breast cancer (MCF-7) and lungs cancer cell (A549) than cervical cancer (HeLa) and colon cancer (SW-480) cells.[2]

The aim of this research is to synthesize the 5 Chloro 2(3H)- Benzoxazolone derivative through the substitution of 1-(2-fluorophenyl) piperazine on 3$^{rd}$ position of the core structure through Mannich reaction. The compound were characterized by Fourier Transform Infrared (FTIR) and Proton Nuclear Magnetic Resonance ($^{1}$H NMR) spectroscopy. The purity was also determine using by TLC and melting point. MTT assay were employed to measure cytotoxicity and cell growth for 24hrs and 48hrs incubation in different concentration of molecule (5, 10, 20, 50 and 100µg/ml).

## 2.LITERATURE REVIEW

### 2.1 CANCER

Cancer is abnormal growth of cells in anywhere of body, these abnormal cell called as cancer cell, malignant cells or tumor cells. These cells multiplied out of control and form a cluster which is called tumor. Most cancers turn to tumors, but not all tumors are cancerous. Cancer cells start growing by getting nutrition from the healthy cell and affect them too. These cell continue to grow and spread by the process called metastasis or by direct extension. These cell move via lymphatic vessels or blood vessels to the different tissues of the body and start making tumors by uncontrolled growth of abnormal cell. [3]

According to WHO report of 2018 this is the second leading cause of death globally. About 9.6 million people died in the year of 2018 due to suffering of different type of cancer colorectal, lungs, stomach, liver are the most common in men while breast, lung, colorectal, cervix and thyroid are the most common in women. Approximately 22% of death caused by cancer is leading by the use of tobacco. [4]

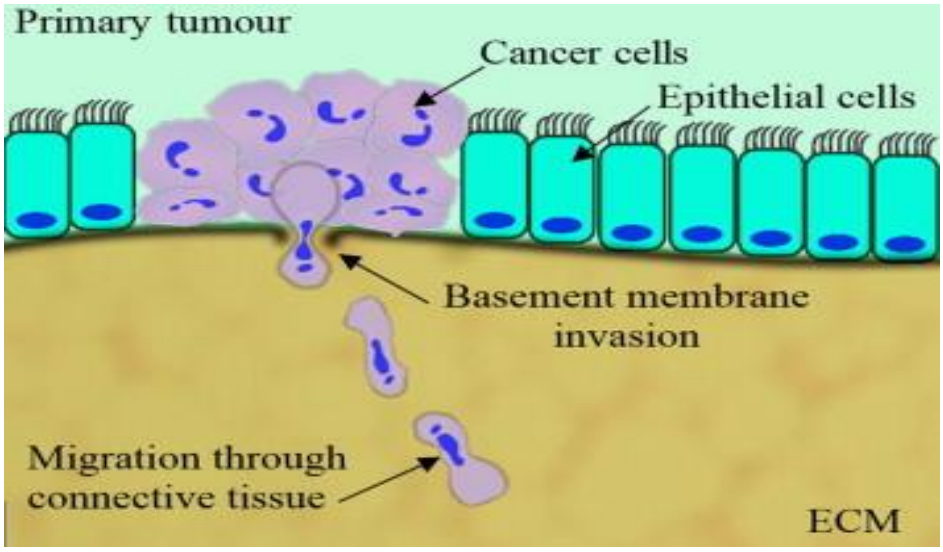



**Figure 2.1:** Malignant cell invasion

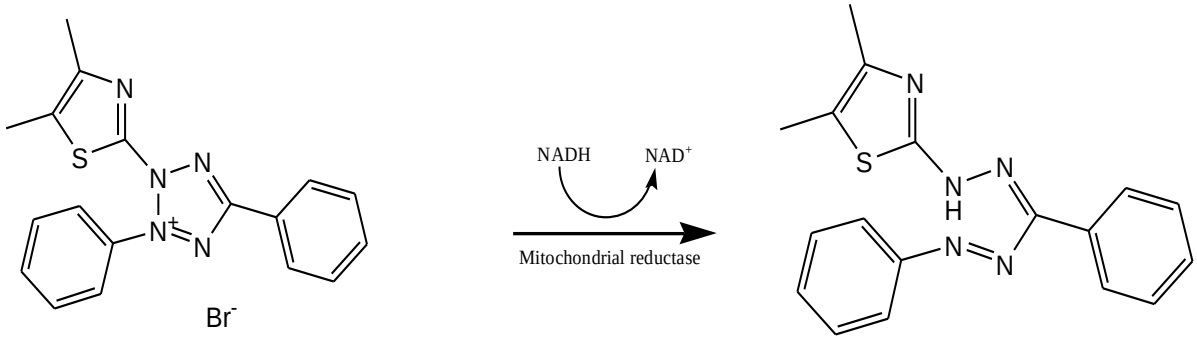
Cancer is rapid and death causing in this world but still the researches in difficult to find the actual and initial cause of the cancer. As per reported researches the following are cause and trigger agent of cancer chemical or toxic compound: Benzene, asbestos, nickel, cadmium, vinyl chloride, benzidine, N nitrosamine, tobacco and cigarette smoke (contain more than 66 known potential carcinogenic chemical and toxins) [5]

### 2.1.1 Cell Culture

The cell culture technique, which is simple, rapid, reproducible and relatively inexpensive, has been widely employed in recent years as an alternative to animal studies in the testing of toxic chemicals. They are based on cell viability, by measuring staining with MTT or neutral red and on cell proliferation, by measuring cell number, protein DNA or stained-dye absorbance 96-Well microtitre plates and a microplate reader have been introduced to these methods. We have also been using the cell culture technique to screen injection drugs. In the present study we used a crystal violet staining (CVS) method with 96-well microtitre plates to measure the cytotoxic effect of chemicals, and compared the results with cell counts and colony formation counts. In addition, we investigated the cytotoxicity of intramuscular injection drugs as a practical application of the method.[6]

### 2.1.2 MTT Assay

MTT assay is broadly used to evaluate the cell viability and proliferation of mammalian cell, it's a Colorimeteric, nonradioactive, fast and economical way. MTT assay used to test the cytotoxicity of some selected plant's methanolic extracts. The yellow tetrazolium MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) is reduced by metabolically active cell, the generation of reducing equivalent like NADH and NADPH by the action of dehydrogenase enzyme and form intercellular purple formazan which can be soluble and measure it by spectrophotometrically. The absorbance result show the rate of proliferation i.e absorbance less than control cell shows the lower reduction in the rate of cell proliferation while the higher absorbance shows increase in cell proliferation. Probably morphological changes may cause the cell death.[7]




(3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) (MTT)

(3-(4,5-dimethylthiazolyl-2)-2,5-diphenyl Formazan (Formazan)

**Figure 2.2:** Reaction of MTT dye.

Metabolic active viable cell have ability to convert MTT into violet blue coloured formazan with maximum absorbance about 570 nm. The dead cells are unable to convert MTT to Formazan hence this color formation is good and acceptable way to mark the viable cell. The insoluble precipitates formed in the cell also near the cell surface and in the culture medium by the result of conversion MTT to formazan. Different method is used to dissolve the fomazan product, stabilized the color, avoid to evaporation and reduce interference by phenol red and other culture medium component.[8] Variety of solution used to solubilized the formazan product like acidified isopropanol, DMSO, dimethylformamide, SDS and the combination of detergent sodium dodecyl in dilute hydrochloric acid.[9]

## 2.2 2(3H)-BENZOXAZOLONE

The 2(3H)-benzoxazolone is bicyclic ring system consisting of phenyl ring fused with carbamate. Light brown in color with molecular formula $C_7H_5NO_2$ and having molecular weight 135.12 g $mol^{-1}$. Due to distinct structural feature has a lot of crucial effect. One end of the compound is lipophilic and other one is hydrophilic and containing two hydrogen bonding accepting site and one hydrogen bonding donating site. The other face of compound is high dipole moment (4.47debye), a discrete partition coefficient (log P = 0.97) and pKa value of 8.7 [10]

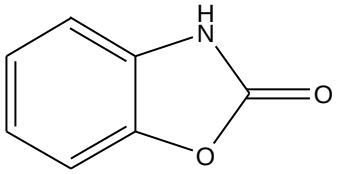


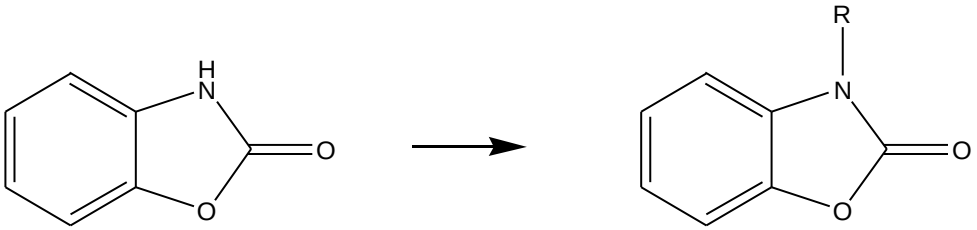

**Figure 2.3:** Structure of 2(3H)-benzoxazolone

### 2.2.1 Chemical Reactivity

#### 2.2.1.1. N Substitution

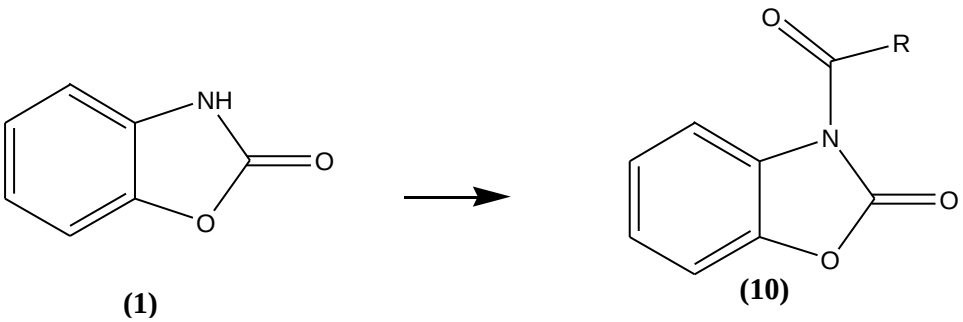
N-alkylation of **(1)** proceeds under base-catalyzed conditions to give derivatives of type **(9),** while N-acylation is submitted to generalized acid-base catalysis to give derivatives of type **(10).** [11]

**Acylation**




**(1)** **(9)**

**Alkylation**




**(1)** **(10)**

**Figure 2.4:** Schematic representation of alkylation and acylation on 2(3H)-benzoxazolone**.**

### 2.2.1.2. Aromatic ring electrophilic substitution

Aromatic electrophilic substitution is governed by the overwhelming preference for the 6-position which is observed not only for the straightforward halogenation, nitration, sulfonation and chlorosulfonation reactions, but also for the more troublesome Friedel-Craft acylation. Indeed, in the particular case of the friedel-craft reaction, due to the electron-rich character of Benzoxazolone(BOA), the heterocycle is extensively complexed by the Lewis acid present in the reaction medium, acts as electrophilic attack of acylium ions. To overcome this problem, the reaction can be run using either a less reactive electrophilic species (polyphosphoric acid) or preferably the $AICI_3$ DMF complex II to give 6-acyl derivatives of type **(11)**. As a most fruitful alternative, N-acyl derivatives can be rearranged at high temperature in a fries like reaction promoted by $AICI_3$ to 6-acyl derivatives. [12]

Reaction:

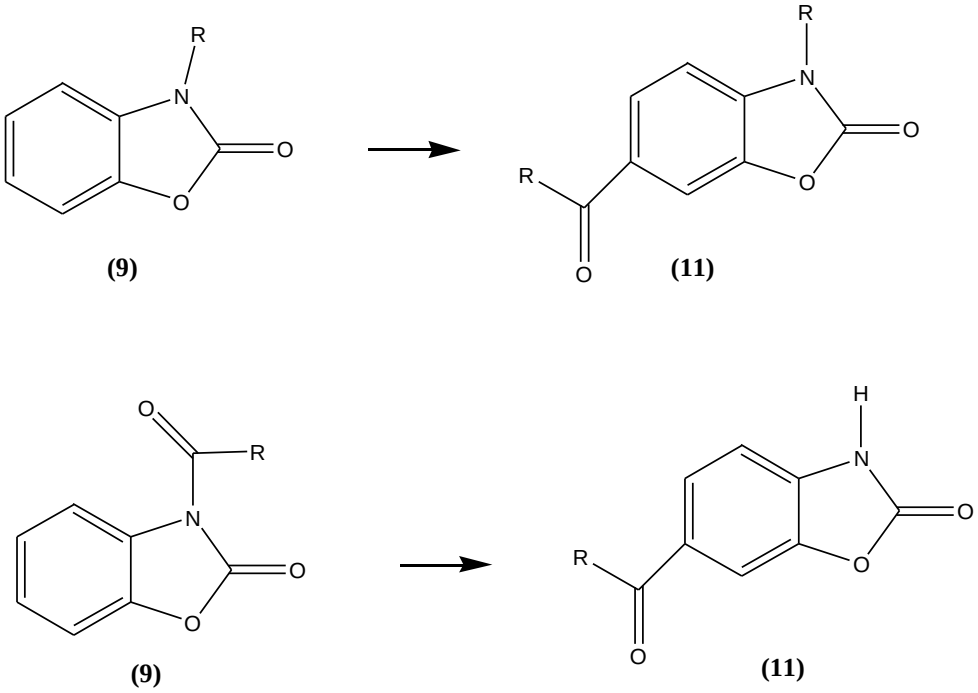



**Figure 2.5:** Electrophilic aromatic substitution reaction on 2(3H)-benzoxazolone.

### 2.2.1.3 Ring Opening Reaction

BOA derivatives are fairly stable in acid medium, they are quickly hydrolyzed in basic medium, leading to ring opening products such as 2- aminophenols. These 2-aminophenols can be acylated in position 4 . Subsequent ring closure leads to the otherwise inaccessible 5-acyl-BOA derivatives. Ring expansion of BOA derivatives to 2(3H)-benzoxazinones can be effected via the same 2-aminophenols reaction. [13]

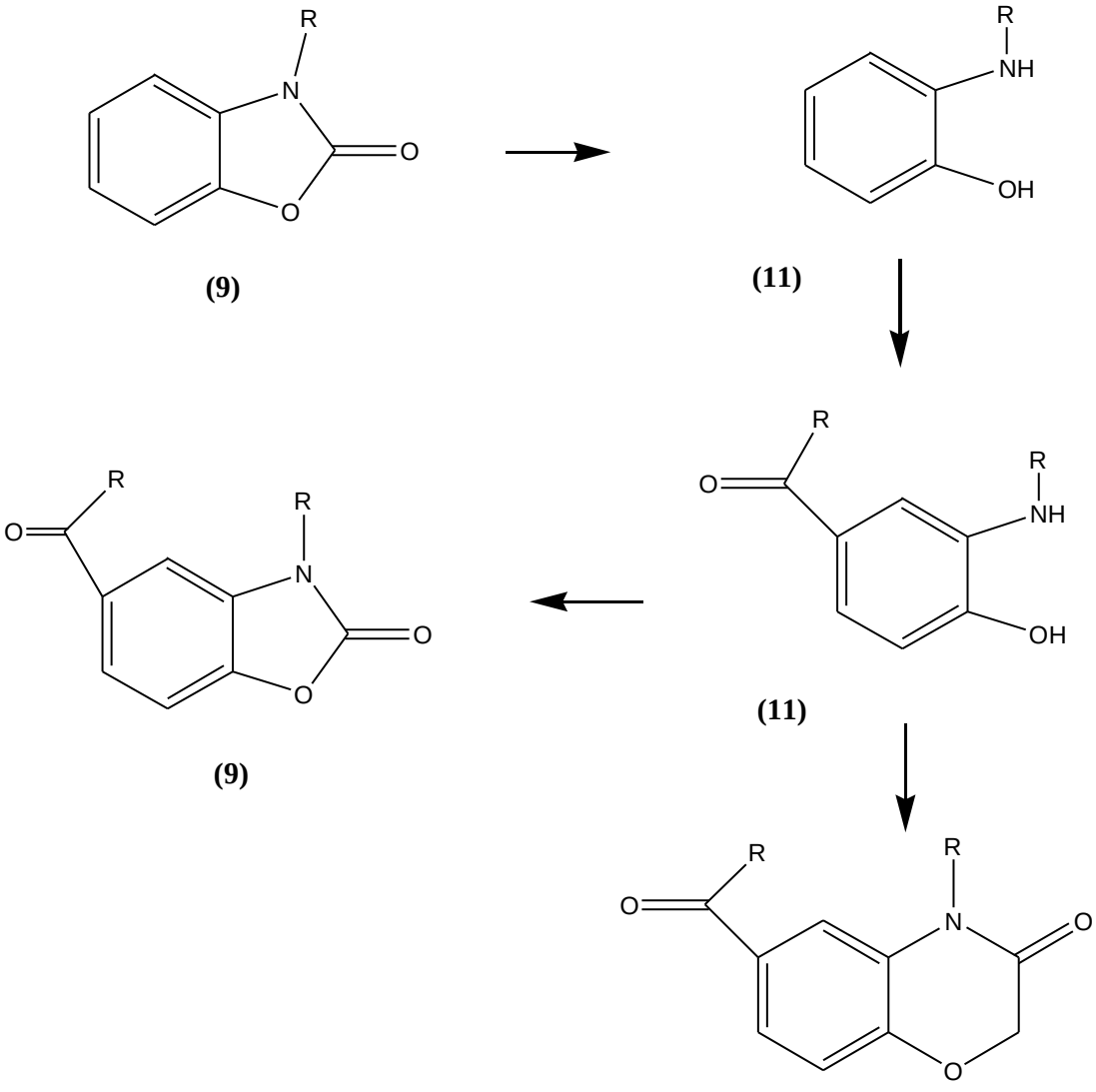



**Figure 2.6:** Ring expansion analogues of 2(3H)-benzoxazolone.

### 2.2.3 Synthesis of 2(3H)-Benzoxazolone and its derivative

(l) 2-Benzoxazolinones, substituted at position-5, were prepared from corresponding 4-substituted 2-aminophenol either by fusion with urea or reaction with 18 phosgene.[14]

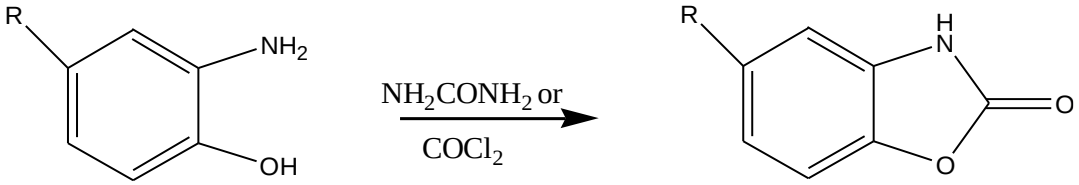



**Figure 2.7:** Synthetic scheme of benzoxazolone.

(2) Perumal *et. al* synthesized 2(3H)-benzoxazoIone derivatives by the reaction between salicylic acid, ammonium azide and vilsmeier complex.[15]

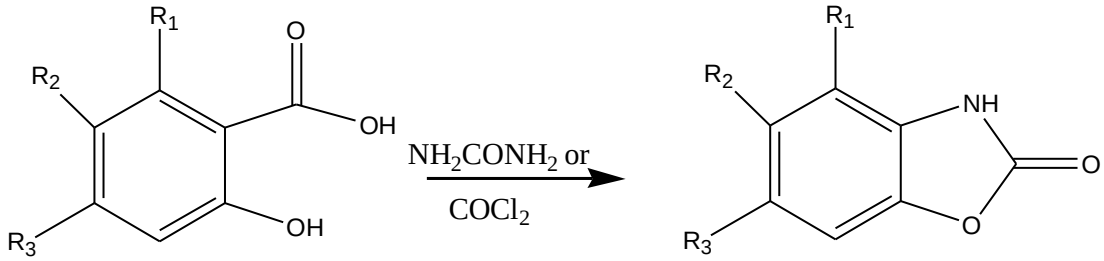



**Figure 2.8:** Synthesis of benzoxazolone by urea analogues.

### 2.2.4 Biological activity of 2(3H)-Benzoxazolone

L.Srikanth *et al*.[16] synthesized benzoxazole derivatives which have 1,3,4-thiadiazole and 1,3,4-oxadiazole nucleus and evaluate them for antibacterial activity.[16] The compound showed various zone of inhibition at 100 µg/ml against five fungi. The maximum zone of inhibition among the compounds screened was noted against *R. oyrzea, A. flavus and C. albicans,* at the concentration of 100 µg/ml. [16]

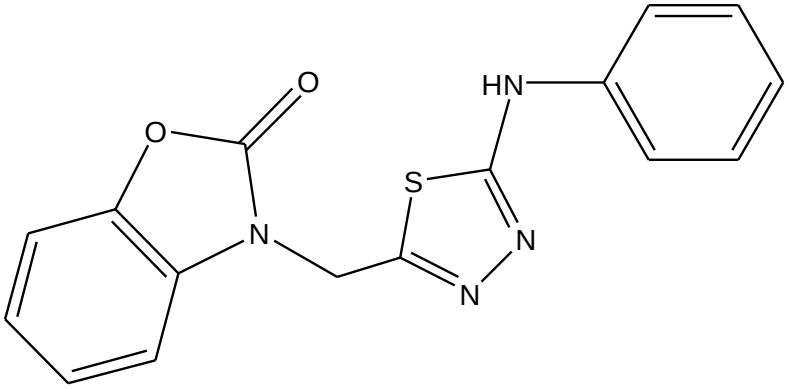



**Fig 2.9** : Antibacterial analogue of Benzoxazolone

Sultan Baytas *et al*.[17] synthesized a series of (*E*) -3-(3-(2,3-dihydro-3-methyl-2-oxo-3*H* -benzoxazole-6-yl)-1-phenyl-1*H* - pyrazole-4-yl) acrylamides exhibited dual anti-inflammatory and antiplatelet activity with selective COX-2 inhibition.[17]

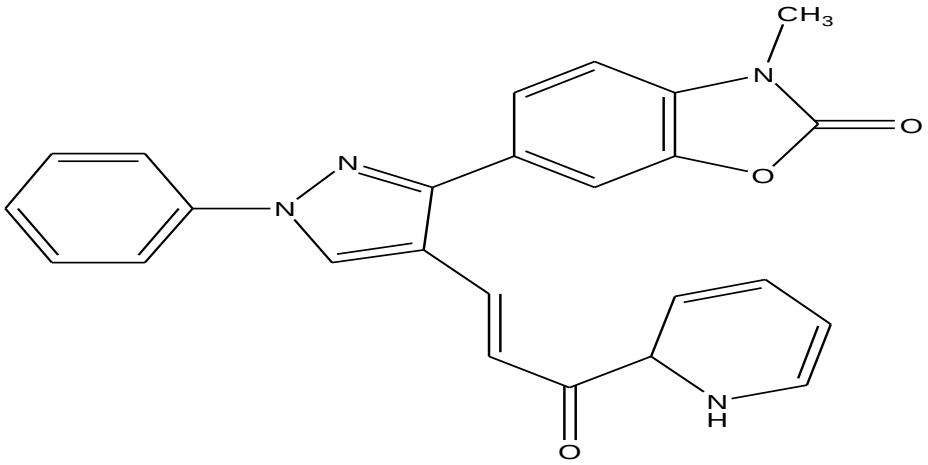



**Fig 2.10 :** Antiplatelates analogue of Benzoxazolone

Ivanova *et al*[18] synthesized Mannich bases of 6-(3-aryl-2-propenoyl)- 2(3H)-Benzoxazolones, figure 2.12. Mannich bases with chalcone core structure were showed cytotoxic effect against human pre-B-cell leukemia cell line BV-173 by using MTT dye reduction assay.[18]

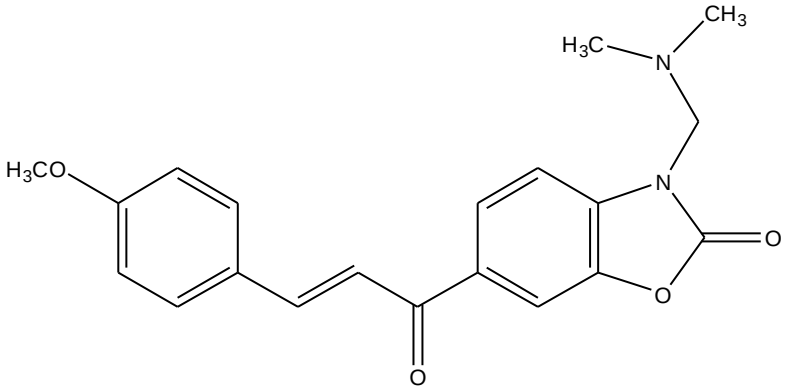



**Fig 2.11**: Anticancer Analogue of Benzoxazolone

Mulazim *et al*[19] synthesized the series of benzoxazolone derivative having potential of antinflamatory and analgesic activity. [19]

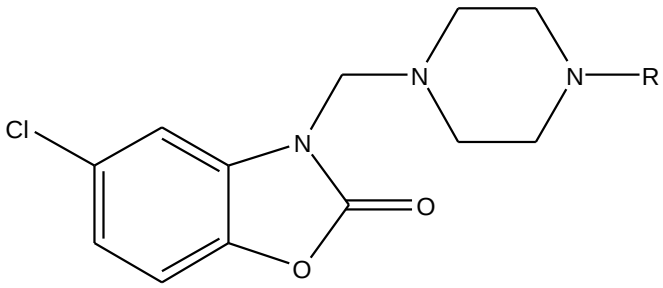



**Fig 2.12:** Antinflammatory and analgesic analogue of benzoxazolone

## 2.3 Chloroxazone

Chlorzoxazone is a 2(3H)-Benzoxazolone derivative. It is a bicyclic ring system made up of chlorophenyl fused to a carbamate. It is a white to off-white powder with the molecular formula $C_7H_4ClNO_2$, molecular weight (169.565 g $mol^{-1}$), octanol/$H_2O$ partition coefficient (log P = 1.6) and also have one H-bond donor and two H-bond acceptor sites having satisfied all the Lipinski's rule of five.25 5-chloro-2(3H)-Benzoxazolone structure is shown Fig 1.15

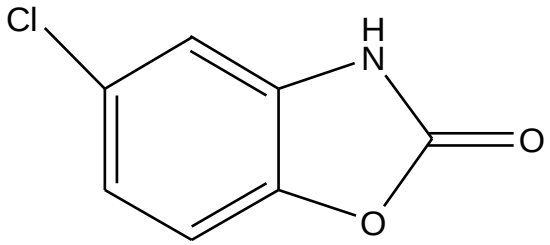



**Figure 2.13:** Structure of 5-chloro-2(3H)-Benzoxazolone.

## 2.4. Mannich reaction

Mannich reaction is a standout amongst the most crucial and essential,. Mannich reaction deals an extensive decent variety of chemical compounds and consequently, it has been seeing a constant development in the field of synthetic chemistry. The flood of writing on mannich reaction gives an exceptional proof for the assorted variety and utilizations reaction. [20] The mannich reaction what's more, its variations offer a powerful technique for the proportion of the aminocarbonyl and a few other derivatives. [21] Moreover, the traditional mannich reaction has restrictions, for example, absence of selectivity, focused aldol product, and so on. To conquer these constraints, recent variations of mannich reaction use to preformed imines, enolates, proper utilization of catalyst and conditions, and so on [22] various chiral auxillary and chiral catalyst are frequently utilized to do asymmetric mannich reaction. [23] Apart from this, essential nanocrystalline magnesium oxide, [24] recyclable copper nanoparticles, poly(amidoamine) catalyzed reactions and microwave-conditioned mannich reaction [25] have additionally been accounted for as of late. Hayashi et al. dissecured high weight lopsided Mannich-type reaction in solidified

water medium. [26] Cimarelli et al. detailed three part mannich reaction under perfect condition for the combination of diaminoalkylnaphthols. [27]

The asymmetric mannich reaction assumes a fundamental job in enantioselective and diastereoselective C– C bond synthesis. In this, we present a delegate case of proline catalyzed profoundly enantioselective MR of ketones . [28] Similarly, proline and its related compounds catalyzes; multicomponent blend of 3-amino alkylated indoles by Mannich-type reaction, Mannich response of acetaldehyde, [29] readiness of azole Mannich adducts, [30] three segment domino responses, [31] enantioselective expansion of ketones to chalkogenazines, amalgamation of [1,4] thiazines, [32] hilter kilter Mannich response of cyclic ketones, and so on. Furthermore, different organocatalysed Mannich responses have likewise been accounted for.

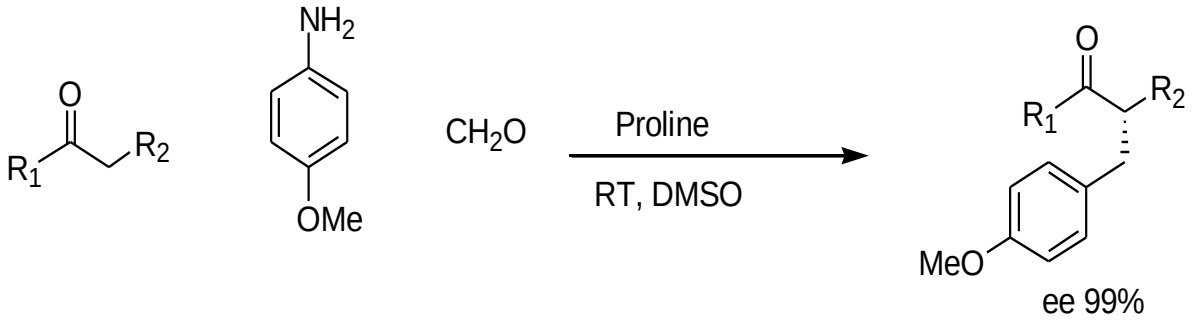



**Figure 2.14:** Proline based asymmetric mannich reaction.

The mannich reaction and its analogs are frequently utilized to get to different compounds, whose applications are going from bioactive skeletons to material science. A shown list of the bioactive compounds acquired by mannich reaction and the job of Mannich response in all out blend are exhibited in (fig 2.16). The amino carbonyl Mannich items are valuable in the development of β - peptides and β - lactams, which are available in a few bioactive atoms, for example, taxol (antitumour specialist), bestatine (immunological reaction modifier) and SCH48461 (hostile to cholesterol operator). [33] Tramadol B ,osnervan C and moban D are bioactive β - aminocarbonyl subordinates with pain relieving, antiparkinson and neuroleptic properties.

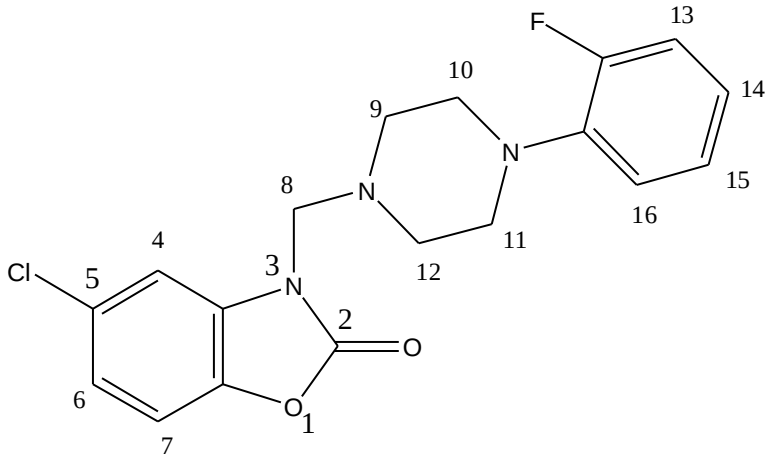
## 3. MATERIAL AND METHOD

### 3.1. Materials

5 Chloro 2(3H)-Benzaoxazolone , 1-(2-fluorophenyl) piperazine, Methanol and 37% (w/v) Formaline solution are used as a starting material were bought from Sigma Aldrich (Germany ) and they were used without any purification.

### 3.2. Synthesized Compound

**3-(2-fluorophenyl) piperazine 3-(5 chloro 2-(3H)Benzoxazolone.**




200mg(1.179mol) 5 chloro 2-(3H benzoxazolone is dissolved in 8 ml of methanol and 2 ml (1.179mol) of 1-(2-fluorophenyl) piperazine were added. In separate beaker take 2 ml of methanol and 0.2 ml of 37% formalin solution and pour into the reaction mixture then put into the reflux for 1 hour. Transfer all the mixture with continuous stirring into crushed ice and it was precipitated. The precipitated solid was separated by filtration using vacuum filteration method and allow them to cool and dry at room temperature. The reaction was monitored by TLC, melting point and final precipitated product was purified by recrystallization with cyclohexane.

### 3.3. Thin Layer chromatography Method

Thin Layer Chromatography (TLC) was performed on normal phase silica cards, TLC plate (DC-Alufplien-Kiesegel, Germany). Benzene and methanol are used as solvent in different composition in mobile phase. Product and starting material both dissolved in Chloroform. Benzene and Methanol (9 : 1 v/v ) was choose as solvent system for TLC analysis.

#### 3.3.1. Method

The mobile phase poured into the TLC chamber about 0.5c m depth and covered it from steel cap and leave it for few minute so it will saturate. In the meanwhile prepare plate. 6x3 cm plate was prepared having margin of 0.5cm margin drawn by pencil that is origin and have 2 spots.

The starting materials and the product dissolve in appropriate solvent. By using micro capillary made spot accordingly and with the help of forceps put the TLC plate in to the TLC chamber without disturbing the chamber and close the lid. Allow the solvent to move to sufficient distance, then removed and put into dry paper and marked solvent front by using pencil. Leave it for drying after drying the plate. UV light at the wavelength 256nm used to see the retention of spots and calculated Rf value.

### 3.4. Melting Point

The melting point of product were determine by using Metler Toledo FP900 thermosystem digital melting point apparatus.

### 3.5. Spectroscopic Techniques

FTIR spectra: The FTIR spectra of the product were recorded from Perkin Elmer spectrum 100 spectrophotometer at Eastern Mediterranean University, department of chemistry, Famagusta, North Cyprus

$^{1}$H NMR Spectra: The Spectra of the compound were determine by Agilent Mercury 400 plus NMR.

# 4. Result and Discussion

## 4.1. Synthesis of 3 (2-fluorophenyl) piperazine 3-(5 chloro 2-(3H benzoxazolone)

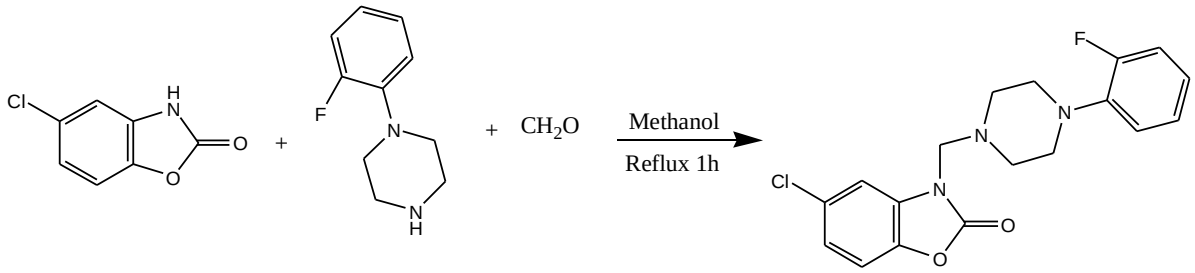



**Figure 4.1:** Schematic representation of the synthesis of 3 (2-flourphenyl piperazine 3-(5 chloro 2-(3H benzoxazolone).

- The synthesized compound 3 (2-fluorophenyl piperazine 3-(5 chloro 2-(3H benzoxazolone) was obtained as white crystalline powder having 62.17 % yield.
- TLC in the mobile phase (9:1 v/v) benzene and methanol gave Rf value 0.28.
- The synthesized was confirmed by FTIR spectroscopy and $^{1}$H NMR spectroscopy as depicted in (fig 2.2 and 2.3). The FTIR spectra show characteristic absorption around 2828.5 and 1650 $cm^{-1}$ was corresponds to CH stretch and carbonyl compound. There is no NH stretch was found it means that the compound was successfully synthesized.

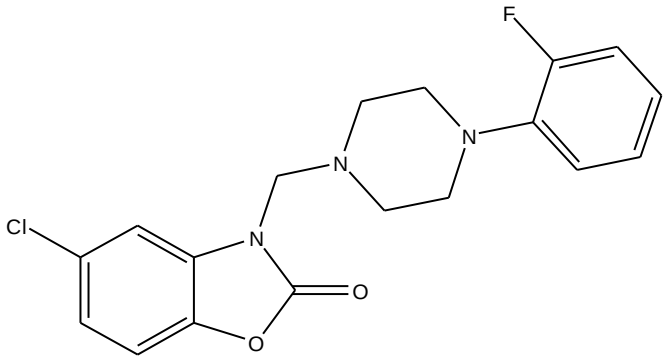



**Figure 4.2:** $^{1}$H NMR shifts of synthesized compound.

- $^{1}H$ NMR shows two triplets around 3.11 and 2.88 ppm corresponds to $CH_2$ groups in the piperidine ring.
- Aromatic signals at 7.26-7.12 ppm was corresponds to aromatic ring in benzoxazolone ring.
- Aromatic signals of fluorine containing ring was observed at 6.96-6.95 ppm confirms the successive synthesis of our desired compound.
- The singlet at 4.69 showing the bridge CH between core structure and piperazine indicating the desired product is formed.

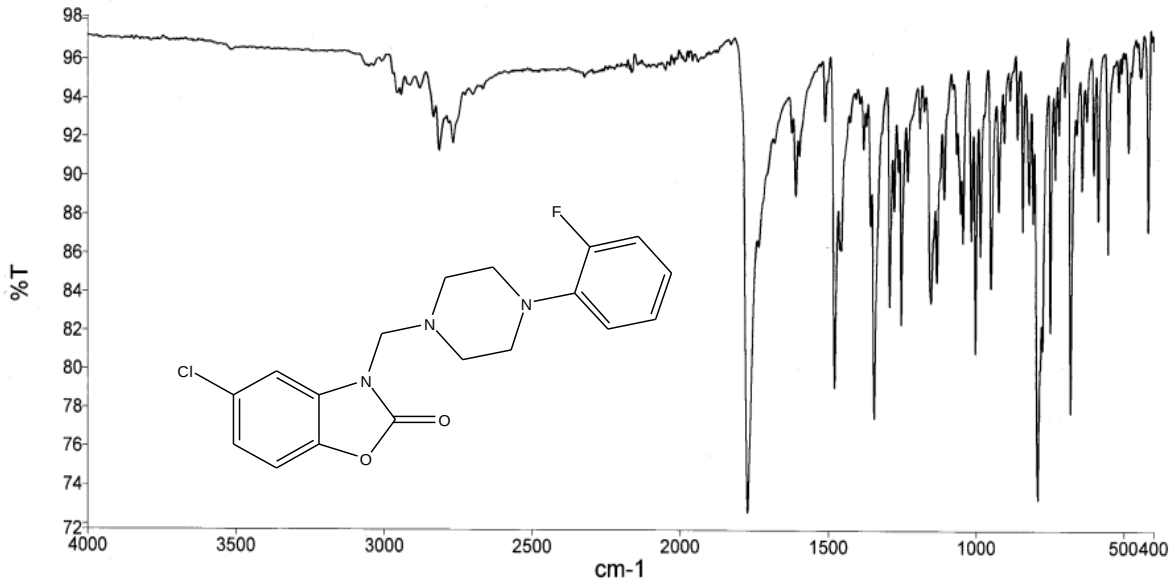



**Figure 4.3:** FTIR spectra of synthesized Compound.

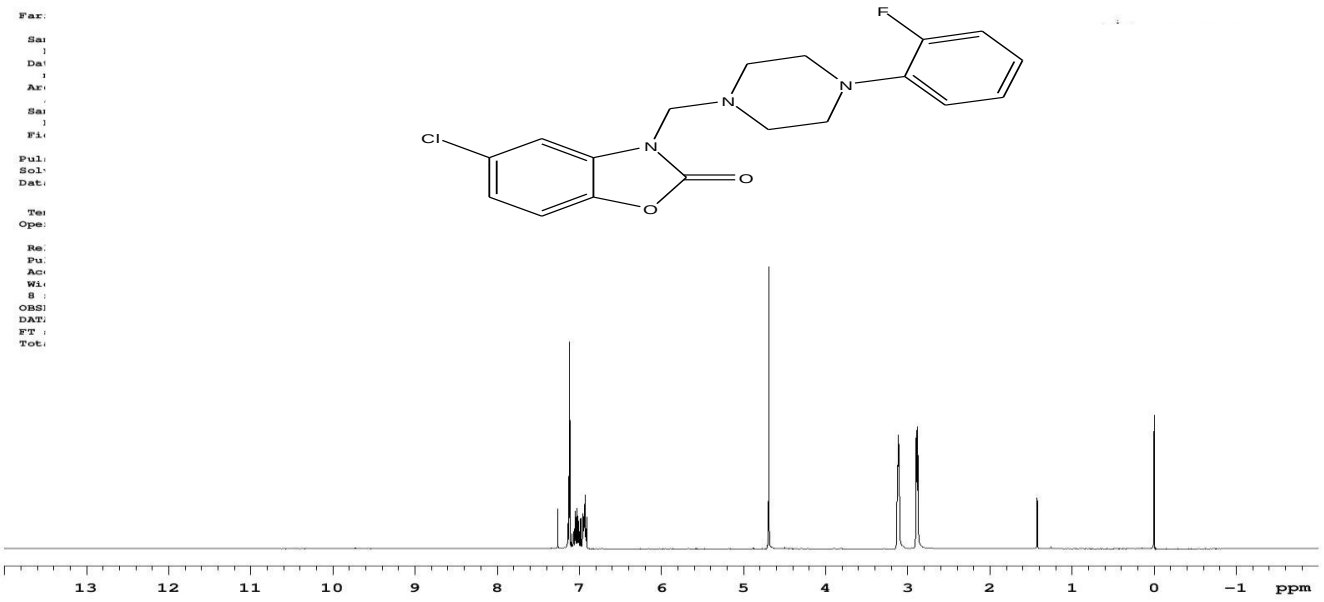



**Figure 4.4:** $^{1}$H NMR spectra of synthesized compound.

## 4.2. Cytotoxic Studies against MCF 7 cell lines

The synthesized compound was screened for its cytotoxic potential against MCF 7 cell lines MTT assay was used for that in order to check its cytotoxic potential. The synthesized compound shows moderate cytotoxic potential when incubated with MCF 7 cell lines in a concentration range of 5, 10, 20, 50 and 100 µM form 24 to 48 h respectively (fig 2.5). 10 µM shows the 50% inhibition.

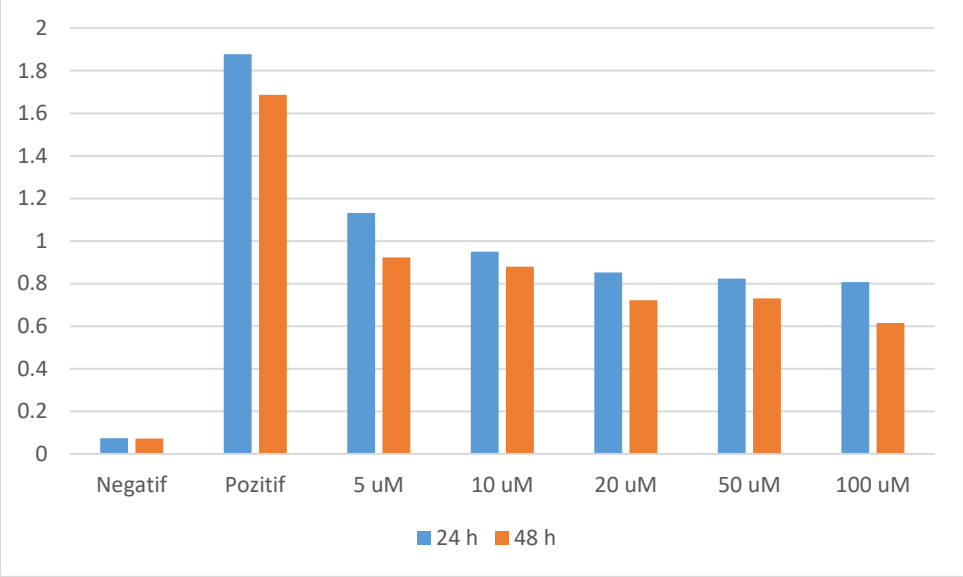



**Figure 4.5:** Cytotoxicity assay of synthesized compound at various concentrations for 48 hour incubation time on MCF-7 cell lines.

## 4.3. CONCLUSION

The compound 3-(2-fluorophenyl piperazine 3-(5 chloro 2-(3H benzoxazolone) was successfully synthesized and characterized via $^{1}$HNMR and FTIR spectroscopic techniques. The synthesized compound showed positive cytotoxic potential against MCF 7 cell lines in different concentration of the molecule which is (5, 10, 20, 50 & 100 µg/ml) among all of them the 10 µg is promising.

In the future, the result of the compound is promising, to continue with further studies to develop the better cytotoxic agent against MCF 7 cell line by changing halogen attached to the phenyl ring of piperazine.

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