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Ministry of Higher Education and Scientific
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College of Science
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# Synthesis and pharmacological activities of celecoxib derivatives

Research submitted by

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A research submitted to the Council of the College of Science, Department of Chemistry, University of Misan, as part of the requirements for obtaining a Bachelor's degree in the Department of Chemistry.

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بسم الله الرحمن الرحيم

﴿ يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ﴾

صدق الله العلي العظيم

سورة المجادلة الآية (11)

## SUPERVISOR CERTIFICATION

I certify that the preparation of this project entitled (**Synthesis and pharmacological activities of celecoxib derivatives**) was prepared by (**Khatam Moh. Abdul Hussein and Zahraa Rahim Faisal**); under my supervision at the chemistry science department, University of Misan in partial fulfillment of the requirements for the degree of B.Sc. in chemistry science.

Signature:

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## EXAMINATION COMM1IEE CERTIFICATION

We certify that we have read this project entitled (**Synthesis and pharmacological activities of celecoxib derivatives**), and as an examinirnt committee examined (he students (**Khatam Moh. Abdul Hussein and Zahraa Rahim Faisal**)) in its contents and in our opinion, it meets the standards of the B.Sc. in chemistry science

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**(Member)**

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**Head of chemistry department**

# Dedication

To the Creator of the soul and the pen, the Maker of the atom and the breath, and the Creator of everything from nothingness (to Allah)
To the one who conveyed the message and fulfilled the trust...and advised the nation...to the Prophet of Mercy and the Light of the Worlds, to the pure masters and his bond of piety...the people of the house of prophecy

To the desire of my heart and the one closest to me from my soul, hidden from sight and hidden in the eye of insight, to the Greatest Remnant of God...the Master of the Age and Time (may Allah hasten his reappearance)

To the one who taught me that the world is a struggle...and its weapon is knowledge and understanding, and to the one who did not withhold anything from me, to the one who strove for my comfort and success, to the greatest and most honorable man in the universe...my dear father

To that beloved with the pure heart, to the one whom the Most Merciful has advised me.  Praise and gratitude to those who worked and suffered for me, to those whose prayers are the secret to my success... My beloved mother

To those with whom I share my moments... To those who rejoice in my success as if it was their own...
Brothers and friends, with all my love, I dedicate this humble effort to you.

# Acknowledgment

Praise be to God so much that praise reaches its end, and prayers and peace be upon the most honorable of creation, Muhammad, may God bless him and his family and grant them peace.

Based on the principle that he who does not thank people does not thank God, I offer my sincere thanks and appreciation to the supervisor (Assnt. Lec. Ahmed Jaafar Al-Musawi), for his guidance and directives that he never withholds from us.

I also extend my thanks and gratitude to every hand that accompanied us to this work, whether from near or far, and thanks are also extended to our guardians, who have stayed up late to provide us with all the appropriate conditions to accomplish this work.

I also do not forget to thank all those who have offered us a helping hand and to all the colleagues and professors from whom we learned and from whom we learned a lot.

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# Abstract

The project includes a presentation of previous research on derivatives of the drug celecoxib, which is one of the drugs classified as non-steroidal anti-inflammatory drugs (NSAIDs). It also aims to identify the pharmaceutical activities of the derivatives prepared for this drug, while mentioning the mechanism of action of the drug in the human body and its side effects. Through the study, it was found that many researchers have been able to prepare a number of new derivatives with higher pharmaceutical activity than the initial treatment (celecoxib) with fewer side effects.

# CHAPTER ONE

# INTRODUCTION

# Chapter one: Introduction

## 1.1. Heterocyclic compounds

Heterocyclic compounds are organic compounds that contain rings composed of carbon atoms along with other non-carbon atoms, such as nitrogen, oxygen, or sulfur …etc. [1]. These compounds have diverse chemical and physical properties that make them of great importance in areas such as pharmaceuticals, pesticides, and industrial chemicals [2]. These compounds are divided into several types according to the number of atoms in the ring and the type of heteroatoms present in it, the most prominent of which are: Pyrazole.

### 1.1.1. Pyrazole

Pyrazole is an organic compound consisting of an unsaturated five-membered aromatic ring containing three carbon atoms and two adjacent nitrogen atoms. Compounds containing the pyrazole structure are known as pyrazoles. Pyrazoles satisfy the Hückel rule due to the presence of a lone pair of electrons that contributes to resonance [3].

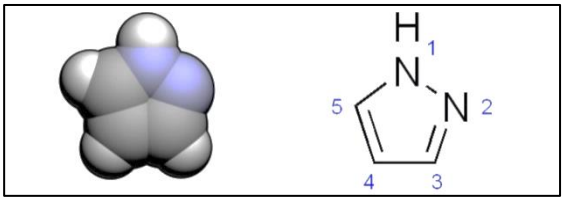



Fig. (1.1): Structure of pyrazole

Pyrazole and its derivatives are considered a pharmacologically important active scaffold that possesses almost all types of pharmacological activities. The presence of this nucleus in pharmacological agents of diverse therapeutic categories such as celecoxib, a potent anti-inflammatory, the antipsychotic CDPPB, the anti-obesity drug rimonabant, difenamizole, an analgesic, betazole, a $H_2$-receptor agonist and the antidepressant agent fezolamide have proved the pharmacological potential of the pyrazole moiety. Owing to this diversity in the biological field, this nucleus has attracted the attention of many researchers to study its skeleton chemically and biologically [4], [5].

Studies on the synthesis and biological activity of pyrazole derivatives developed by many scientists around the globe are reported nowadays, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties [6].

This heterocycles can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities (Fig. 1.2) [7].

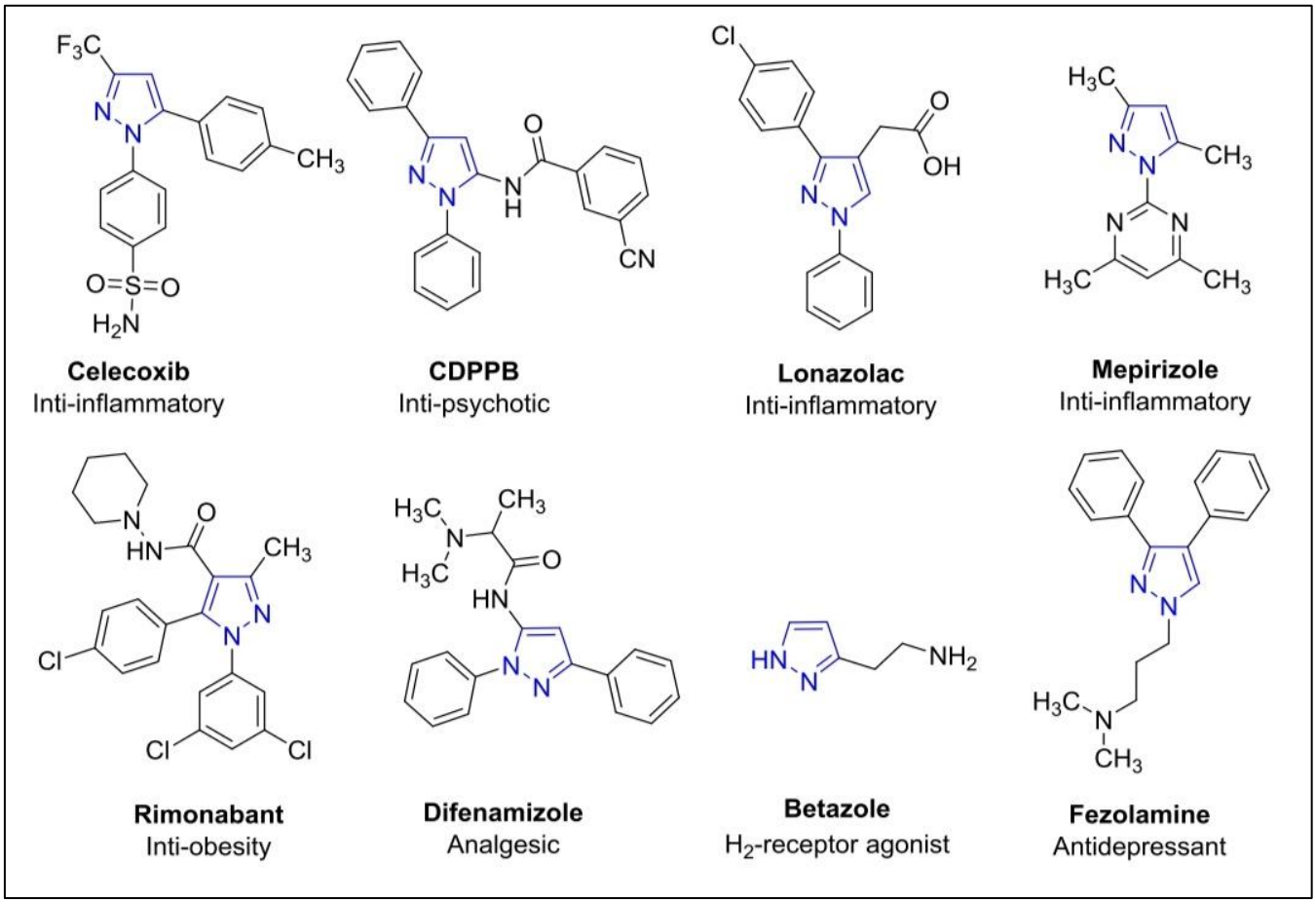



Fig. (1.2): Pharmaceutical drugs containing pyrazole unit

## 1.2. Non-steroidal anti-inflammatory drugs (NSAID's)

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of medications that are widely used to relieve pain, reduce inflammation, and reduce fever. These drugs primarily affect prostaglandins, which are chemicals in the body that contribute to inflammation and pain. NSAIDs are used to treat a wide range of conditions such as arthritis, back pain, headaches, colds, and sports injuries, as well as to relieve symptoms caused by inflammatory diseases such as inflammatory bowel disease [8].

### 1.2.1. Mechanism of NSAIDs Action:

NSAIDs work by inhibiting enzymes called COX. These enzymes play a major role in the production of prostaglandins, which are involved in the process of inflammation and causing pain. There are two types of enzymes: COX-1: It mainly works in normal physiological functions such as protecting the stomach lining and stimulating blood flow to the kidneys. COX-2: It is produced in response to inflammation and during injury or in response to pain-causing substances. Accordingly, NSAIDs are divided into two types:

1. Non-selective (inhibits both COX-1 and COX-2) such as ibuprofen and aspirin.
2. Selective for COX-2 (such as celecoxib) which targets only COX-2 to reduce side effects associated with COX-1 [9].

### 1.2.2. Examples of NSAIDs: [10]

**Ibuprofen:** widely used to relieve mild to moderate pain and reduce fever.

**Aspirin:** used to reduce pain as well as to prevent cardiovascular disease.

**Naproxen:** used to relieve pain resulting from inflammation.

**Diclofenac:** mainly used to treat acute and chronic inflammation.

### 1.2.3. Side effects of NSAIDs drugs:

Despite the effectiveness of NSAIDs, their use may be associated with a number of side effects, including: Digestive problems such as ulcers or bleeding in the stomach, damage to the kidneys with long-term use, increase in blood pressure, which may put the heart and blood vessels at risk. Skin allergies or problems NSAIDs are among the most widely used drugs in modern medicine, but they must be used with caution and under medical supervision to reduce the risks associated with them. [11]

## 1.3. Structure of celecoxib:

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain and inflammation. The celecoxib molecule consists of a chemical structure that includes many functional groups [12].

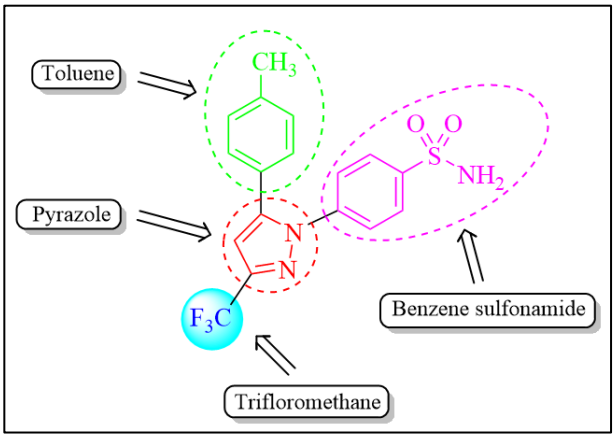



Fig. (1.3): Structure of celecoxib

### 1.3.1. Molecular structure of celecoxib: [12]

The chemical structure of celecoxib is as follows:

Chemical formula: $C_{17}H_{14}F_3N_3O_2S$

Components of the celecoxib molecule:

a) Benzene ring ($C_6H_5$): A benzene group is one of the basic organic compounds in the structure.

b) Fluorine (F): The molecule contains three fluorine atoms, which helps in improving the solubility and resistance properties.

c) Sulfonamide group ($SO_2NH$): It is a sulfonamide group that participates in the therapeutic properties and helps in the pharmacological effects.

d) Azo group ( −N=N− t is formed by resonance, it's contributes to the stability of the chemical structure.

e) Nitrogen (N): It is included in other sites of the structure to form chemical bonds.

### 1.3.2. Effect of celecoxib Molecule:

Celecoxib works by inhibiting the enzyme COX-2 (cyclooxygenase-2), which plays a role in the production of prostaglandins, which are compounds that lead to inflammation and pain. By inhibiting this enzyme, celecoxib reduces the feeling of pain and inflammation.

## 1.4. Physical and chemical properties of celecoxib:

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that belongs to the class of selective COX-2 inhibitors, which has fewer gastrointestinal side effects than conventional COX-1 inhibitors. The following is a detailed explanation of the chemical and physical properties of this drug:

### 1.4.1. Chemical Properties: [12]

Molecular Structure and mass of celecoxib drug:

A. **Molecular Formula**: $C_{17}H_{14}F_3N_3O_2S$

B. **Celecoxib contains** a central pyrazole nucleus linked to benzene rings; one of these rings is linked to a methyl group, and the other to a sulfonamide group.

C. **Molecular mass**: Estimated at approximately 381.4 g/mol.

D. **Functional Groups:**

   i. Sulfonamide group: contributes to the pharmacological activity and is characterized by its stability under storage conditions.

   ii. Trifluoromethyl group ($CF_3$): increases the hydrophobicity (hydrophobicity) and helps improve the lipid distribution of the drug.

   iii. Pyrazole nucleus: is the structural basis that distinguishes celecoxib from other anti-inflammatory drugs; it contributes to the selectivity towards the COX-2 enzyme.

E. **Chemical stability**: Celecoxib has good stability under normal conditions; it is not easily oxidized when stored in dry, dark conditions.

F. **Chemical reactions:** Generally, it does not react with most compounds under normal conditions, but may decompose or change under very strong acidic or basic conditions.

### 1.4.2. Physical Properties: [13]

A. **Physical Form**: It is available in the form of a white crystalline powder, which contributes to its easy conversion into tablets or capsules for medicinal use.

B. **Melting Point**: It ranges from about 160 to 165 degrees Celsius, which is an indicator of the regularity of the crystalline structure of the drug.

C. **Solubility**: In Water: Celecoxib has low solubility in water, which is due to the nature of its fatty groups (such as the $CF_3$ group) that increase its hydrophobic nature. In Organic Solvents: It shows better solubility in solvents such as DMSO and DMF, which are sometimes used in chemical and pharmaceutical analysis studies.

D. **Kinetic and Physiological Properties**: Logarithmic Distribution Constant (log P): It is estimated at about 3.5; it is an indicator of the average ability of the substance to move between the aqueous environment and the fatty environment. This property contributes to the absorption of the drug from the digestive system and its distribution in the tissues.

E. **Crystal structure**: The crystal structure was studied using X-ray diffraction techniques, and studies have shown the presence of a specific crystalline arrangement that affects the solubility and physical stability of the drug.

F. **Physical stability**: Celecoxib is stable at normal temperatures and under recommended storage conditions (dry and dark place). However, it may be affected if exposed to high temperatures or intense light for long periods.

## 1.5. Impact of these properties on pharmacological activity: [14]

i. **Selectivity:** The specific chemical structure of celecoxib (particularly the presence of the pyrazole nucleus and the sulfonamide group) contributes to its selectivity for the COX-2 enzyme, which reduces the risks associated with COX-1 inhibition, such as gastrointestinal side effects.

ii. **Biodistribution**: Physical properties such as log P value and limited solubility in water help the drug to be adequately distributed in the body and reach the inflammatory tissues.

iii. **Stability**: Chemical and physical stability ensures that the drug's effectiveness is maintained during storage until it reaches the patient.

## 1.6. Pharmacological activity of celecoxib

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) belonging to the class of selective COX-2 inhibitors.

### 1.6.1. Mechanism of celecoxib action:

It inhibits the COX-2 enzyme responsible for the production of prostaglandins that cause inflammation, pain, and swelling. It differs from traditional NSAIDs (such as ibuprofen) in that it does not inhibit COX-1 to the same degree, making it less irritating to the stomach and reducing the risk of stomach ulcers and gastrointestinal bleeding.

#### 1.6.1.1. Biological Mechanism:

1- COX-2 Inhibition: Celecoxib works primarily by inhibiting the enzyme cyclooxygenase 2 (COX-2). This enzyme is involved in the production of chemicals known as prostaglandins, which are responsible for causing pain and inflammation. COX-2 is primarily produced in tissues that are injured or inflamed.

The prostaglandins produced by COX-2 are responsible for promoting inflammation, pain, and swelling.

2- COX-2 Selectivity: Celecoxib is more selective in inhibiting COX-2 than COX-1 (which is involved in vital functions such as protecting the gastric mucosa and regulating kidney function). This means that celecoxib reduces side effects that may affect the stomach and kidneys compared to some other medications, such as traditional nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2.

3- Reducing inflammation and pain: By reducing the production of prostaglandins, celecoxib reduces pain and swelling associated with inflammation. [14]

### 1.6.2. Medical Uses [15]

a) Treatment of osteoarthritis
b) Treatment of rheumatoid arthritis
c) Relief from menstrual pain (dysmenorrhea)
d) Management of acute pain following surgery or injury
e) Used in some cases to prevent tumors associated with familial adenomatous polyposis (FAP)

### 1.6.3. Possible Side Effects:

a) Digestive disturbances such as nausea, diarrhea, or stomach pain
b) Headache and dizziness
c) Slight increase in blood pressure
d) Increased risk of cardiovascular problems such as heart attacks and strokes with long-term use

### 1.6.4. Contraindications:

a) Allergy to the drug or other NSAIDs
b) History of heart disease or stroke
c) Active peptic ulcer or gastrointestinal bleeding
d) Severe liver or kidney disease

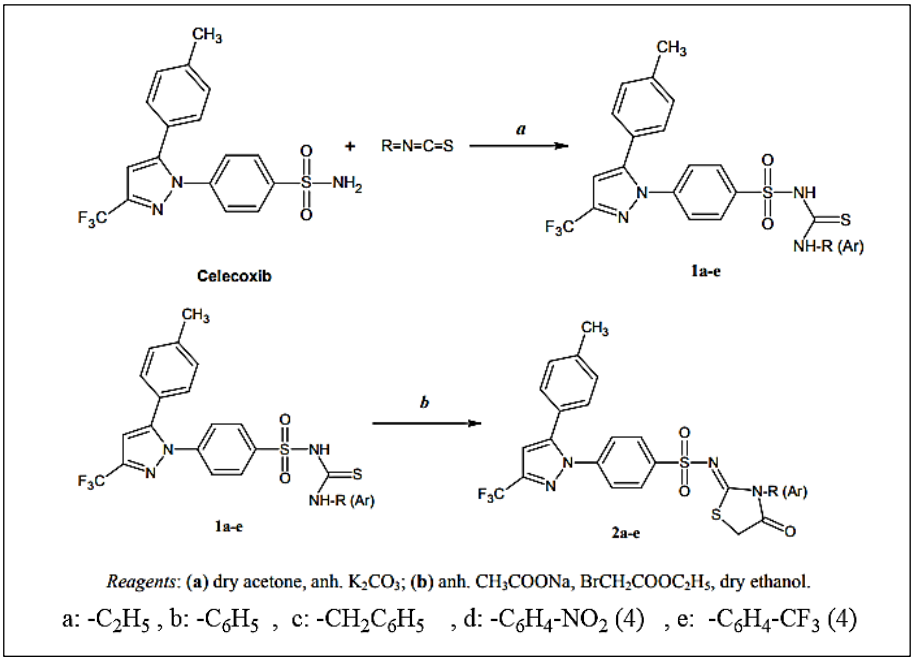
# Aim of the work

To review previous research on derivatives of the celecoxib drug, which is a drug from the group of anti-inflammatory steroid drugs, and to know the pharmaceutical activities of these prepared derivatives and to conduct a comprehensive analysis of these researches.

# CHAPTER TWO

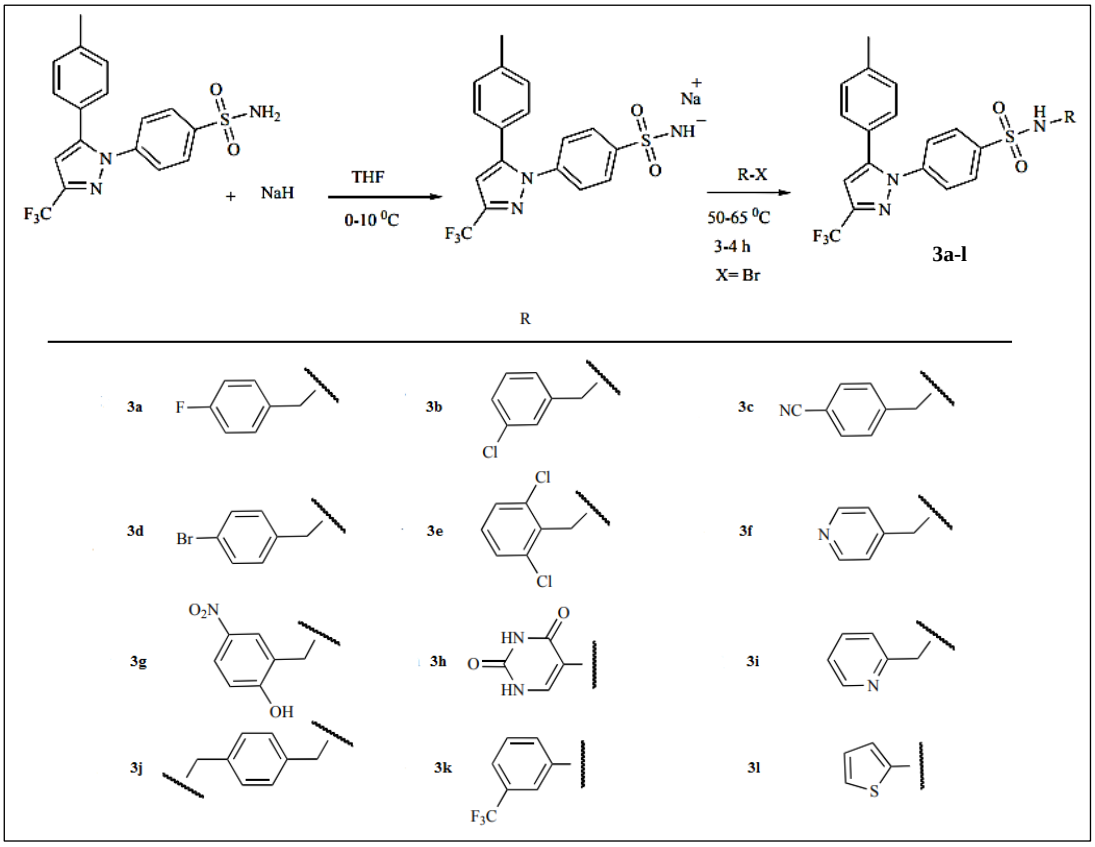
# SYNTHESIS OF CELECOXIB DERIVATIVES

Ş. Güniz Küçükgüzel et al. [16], synthesis A series of novel *N*-(3-substituted aryl/alkyl-4-oxo-1,3-thiazolidin-2-ylidene)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzene-sulfonamides **2a–e**, by the addition of ethyl α-bromoacetate and anhydrous sodium acetate in dry ethanol to *N*-(substituted aryl/alkylcarbamothioyl)-4-[5-(4-methylphenyl)-3- (trifluoromethyl) -1*H*-pyrazol-1-yl]benzene sulfonamides **1a–e**, which were synthesized by the reaction of alkyl/aryl isothiocyanates with celecoxib. The structures of the isolatedproducts were determined by spectral methods and their anti-inflammatory, analgesic, antioxidant, anticancer and anti-HCV NS5B RNA-dependent RNA polymerase (RdRp) activities evaluated. The compounds were also tested for gastric toxicity and selected compound 1a was screened for its anticancer activity against 60 human tumor cell lines. These investigations revealed that compound **1a** exhibited anti-inflammatory and analgesic activities and further did not cause tissue damage in liver, kidney, colon and brain compared to untreated controls or celecoxib. Compounds **1c** and **1d** displayed modest inhibition of HCV NS5B RdRp activity. *N*-(ethylcarbamothioyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzene-sulfonamide (**1a**) may have the potential to be developed into a therapeutic agent (Scheme 2.1).



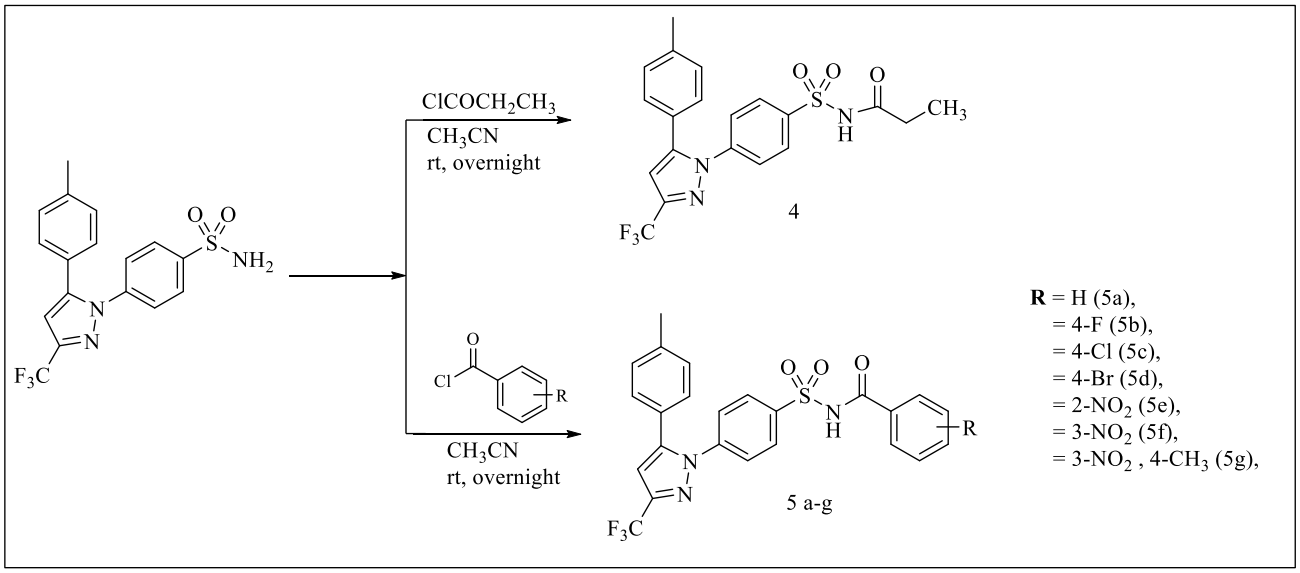

Scheme (2.1): Synthesis of celecoxib derivatives 1a–1e, 2a–2e.

Golla Madhava et al. [17], synthesis a series of *N*-substituted (aryl/heteroarylpyrazol-1-yl)benzenesulfonamide (Celecoxib) derivatives and characterized them using IR, NMR ($^{1}$H and $^{13}$C), mass and elemental analysis. Anti-inflammatory activity of the synthesized compounds was evaluated by in vitro initially using albumin denaturation and membrane stabilization methods, enzymatic activity against COX-2 enzyme using colorimetric assay and then in vivo by carrageenan induced paw edema and cotton pellet induced granuloma methods. The docking study was performed, additionally, to get the binding mode of the title compounds with the binding site of the COX-2 enzyme. Compound **3e** showed more potent COX-2 inhibit activity than that of parent drug, celecoxib (Scheme 2.2).



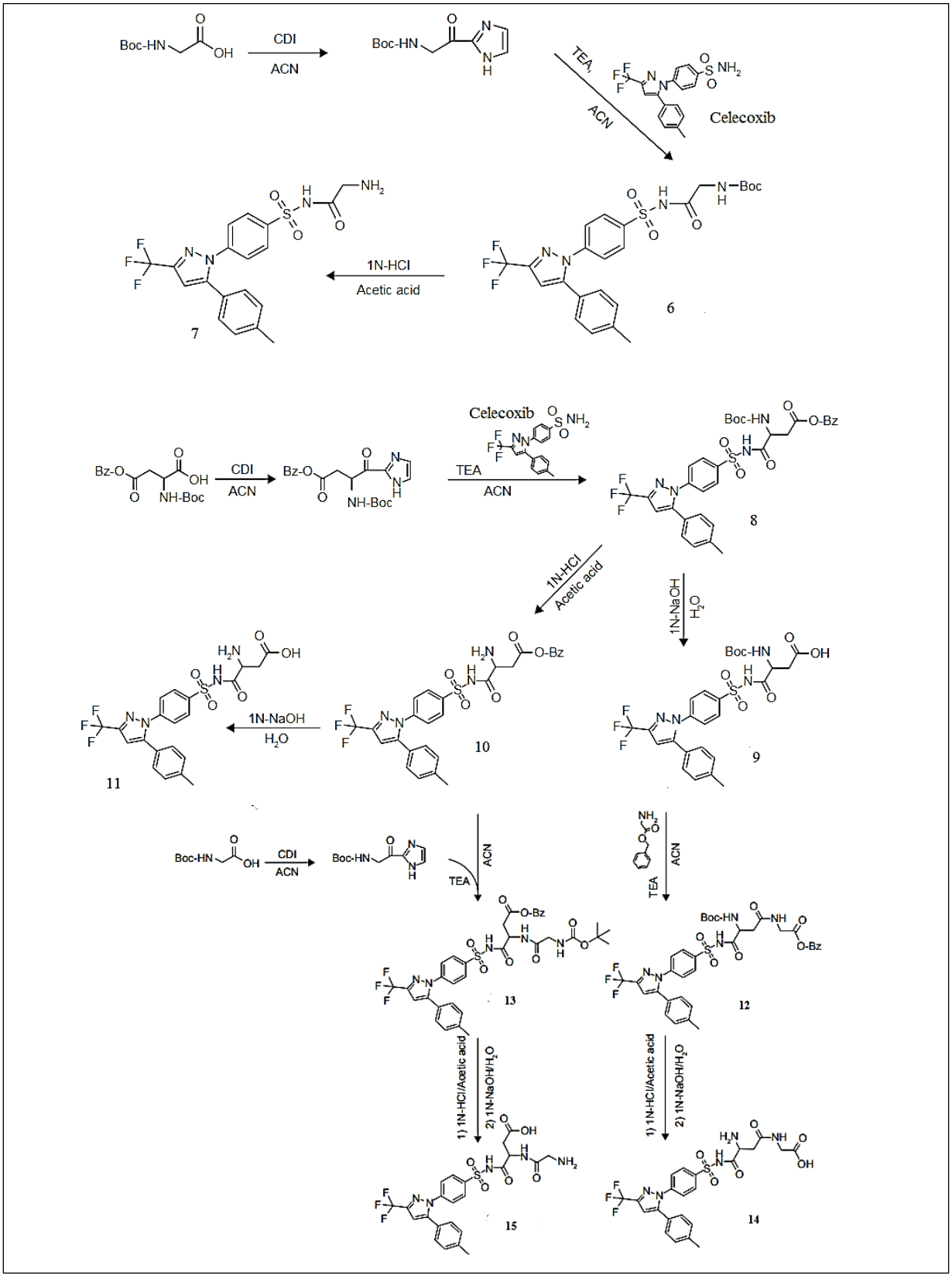

Scheme (2.2): Synthesis of *N*-substituted celecoxib derivatives 3(a-l).

Nabeela Kausar et al. [18], synthesis new compounds derived from celecoxib and study their activity as anti-inflammatory drug but none was found to be active. Subsequently a random biological screening was carried out. Interestingly many of them were found to be potent α-glucosidase inhibitors in vitro. Compound **5g** was the most potent inhibitor of α-glucosidase enzyme (Scheme 2.3).




Scheme (2.3): Synthesis new celecoxib derivatives (4 and 5a-g).

Sunyoung lee et al. [19], synthesis new glycine-bearing celecoxib derivatives and evaluated as a colon-specific mutual prodrug. The prepared compounds were found to have good efficacy (Scheme 2.4).




Scheme (2.4): Synthesis of glycine-bearing celecoxib derivatives

# CHAPTER THREE

# RESULTS AND DISCUSSION

# Chapter three: Results and discussion

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID), meaning it acts as a pain reliever, fever reducer, and anti-inflammatory. Because of its significant pharmacological activities, many researchers have conducted various studies on this drug, including attempts to find new derivatives with greater pharmacological activity than celecoxib. While most have demonstrated similar effects, no more effective compounds have been found. Researchers are therefore constantly working to find more effective compounds with fewer side effects. Celecoxib works by inhibiting the action of the enzyme cyclooxygenase-2 (COX-2), which is responsible for the release of chemicals that cause pain and inflammation. Since celecoxib only targets COX-2, it has less gastrointestinal effects than most other NSAIDs, which inhibit both COX-2 and COX-1, such as ibuprofen. Through the research mentioned in the second chapter of this research, we note that researchers are trying to find more effective compounds by adding different effective groups in order to find a compound that is inhibitorier to the COX-2 enzyme.

A review of the research conducted to prepare celecoxib derivatives reveals that researchers have relied on modifications to the amino group of the drug. These studies include the addition of a saturated heterocyclic ring containing nitrogen and sulfur atoms and a carbonyl group (compounds 2a-e). These derivatives were found to have pharmacological activity, but not very high compared to celecoxib. Of the prepared compounds, compound (1a) demonstrated anti-inflammatory and analgesic activity, and did not cause tissue damage to the liver, kidney, colon, or brain compared to the untreated control group or celecoxib. Compound (1c) showed slight inhibition of RdRp activity in HCV NS5B. It may be possible to develop N-(ethylcarbamothioyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene- sulfonamide (1a) into a therapeutic agent [16].

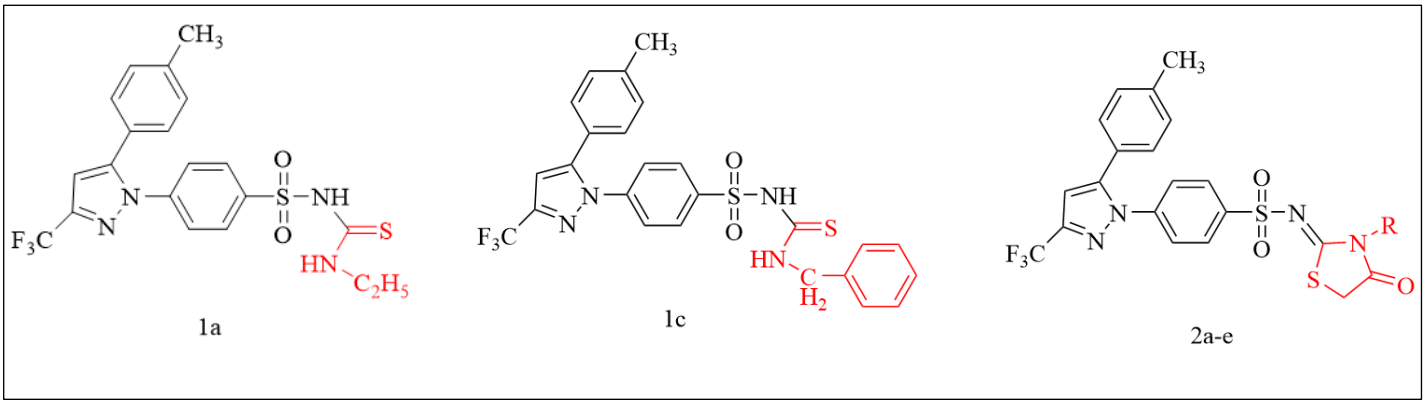



Fig. (3.1): Structures of compounds 1a,1c, and 2a-e

In compound (3e), adding the (2,6-dichlorobenzyl) group was found to increase the effectiveness of the compound in inhibiting the enzyme COX-2 higher than the effectiveness of the drug celecoxib, which indicates that the presence of this group increased the compound's binding to the enzyme COX-2 Which increases the effectiveness of the compound in inhibiting pain and inflammation [17].

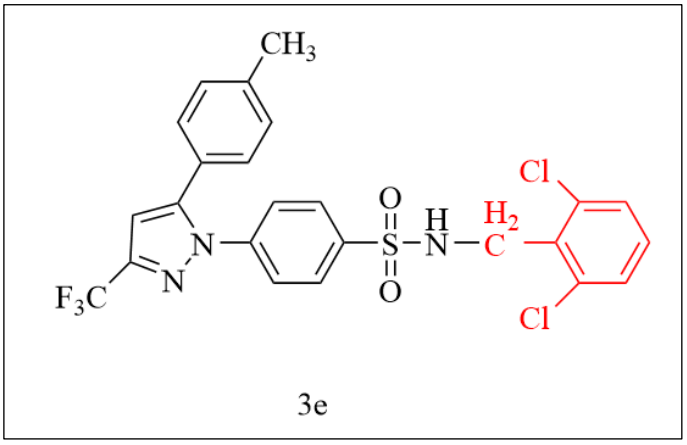



Fig. (3.2): Structure of compound 3e

Celecoxib derivatives do not only work as anti-inflammatory agents, as some derivatives were found not to have high efficacy as anti-inflammatory agents, but were found to have efficacy in another medical aspect, such as the compound (5g) which was found to have high efficacy as an inhibitor of the α-glucosidase enzyme [18]. It can therefore be developed and used as an oral antidiabetic drug for the treatment of type 2 diabetes, as α-glucosidase inhibitors work by blocking the digestion of carbohydrates (such as starch and table sugar). Carbohydrates are normally converted into simple sugars (monosaccharides) by alpha-glucosidase enzymes located in the cells lining the intestine, enabling the monosaccharides to be absorbed across the intestine. Thus, α-glucosidase inhibitors reduce the effect of dietary carbohydrates on blood sugar [20], [21].

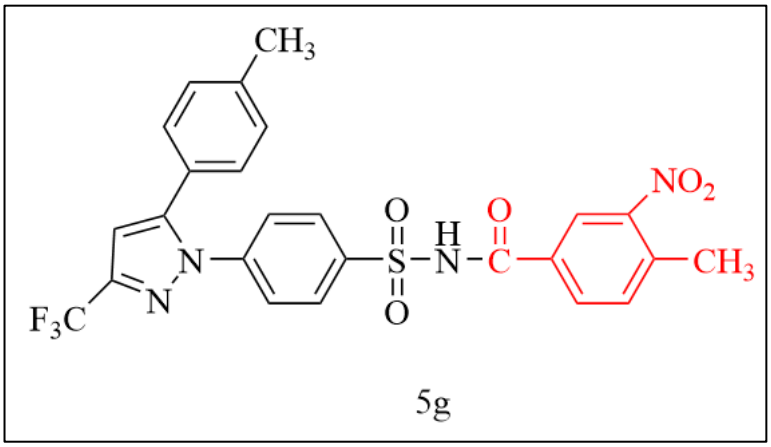
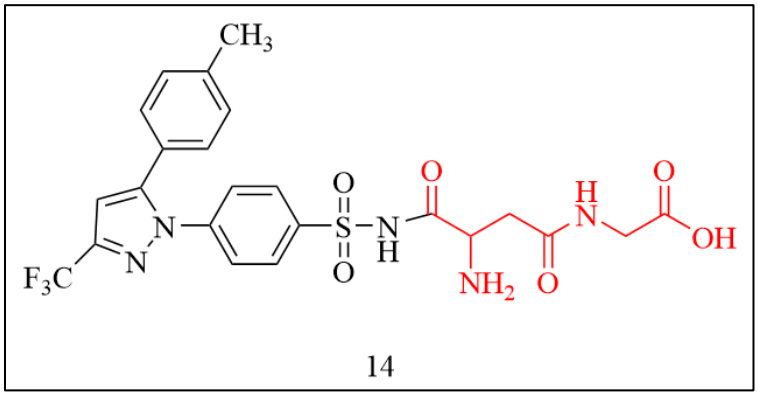



Fig. (3.3): Structure of compound 5g

Glycine-bearing celecoxib derivatives were prepared and evaluated as a colon-specific mutual prodrug, an anticolitic target. The compound (14) was found to be effective as is a potential colon-specific mutual prodrug [19].




14

Fig. (3.4): Structure of compound 14

# Conclusion

Through the research mentioned in the second chapter, which includes the preparation of new derivatives of the drug celecoxib and the study of their pharmaceutical and biological activities, it was found that many of these derivatives have provided good activities, but there are derivatives that have provided higher activities than the original drug (Celecoxib). These high activities are attributed to the presence of heterocyclic structures and the presence of nitrogen atoms, which increase the pharmaceutical activity of these derivatives. In addition, the substitution sites on the benzene ring attached to the new derivatives also play an important role in influencing this activity.

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| Abbreviations | |
|---|---|
| **ACN** | Acetonitrile |
| **BOC-** | Butoxycarbonyl |
| **CDI** | 1,1′-carbonyldiimidazole |
| **TEA** | Triethylamine |
| **r.t** | Room temperature |
| **RdRp** | RNA-dependent RNA polymerase |
| **HCV NS5B** | Hepatitis C virus nonstructural protein 5B |
| **COX-1** | Cyclooxygenase 1 |
| **COX-2** | Cyclooxygenase 2 |
| **DMSO** | Dimethyl sulfoxide |
| **DMF** | Dimethylformamide |