

The Production and Estimation of Diclofenac Amide Prodrug

Ali Taha Metaib¹, Manar Serhan Ahmed², Ghanem Shaker Al-Jebouri³, Ahmad AB Yosef⁴, Nibrass Taher Abdal⁵

^{1,2,3}Department of Pharmaceutical Chemistry/College of Pharmacy/Al-Farahidi University/ Baghdad/Iraq

^{4,5}Department of Pharmaceutics/College of Pharmacy/Al-Farahidi University/ Baghdad/Iraq

Email: alitaha198282@gmail.com

Abstract

Prodrug technique is used to remedy some troubles and enhance the interest of medication. Diclofenac is classified as non-steroidal and anti-inflammatory drug (NSAIDs) which used as anti-inflammatory and analgesic however it has many side effects causing gastro-intestinal ulcer, gastro-esophageal reflux disease (GERD). Prodrug of diclofenac is synthesized by using coupling of amine with diclofenac and ester derivatives of amino acids production in the presence of HCl in dichloromethane. These newly synthesized prodrugs lower a number of the gastrointestinal adverse effects through covering the free carboxylic acid group to improve the bioavailability through reduction the hydrolysis by the effect of GIT enzymes. The prodrug is estimated for solubility and analyzed by using FTIR spectroscopy and nuclear magnetic resonance.

Keywords: Prodrug, Coupling, Diclofenac, Bioavailability, Amines and Solubility.

1. INTRODUCTION

Albert has first brought the term of "Prodrug". Biotransformation of the prodrug into the pharmacologically active agent after absorption is the principle of this process [1]. Prodrugs technique is crucial way to improve the activity and solubility of a given drug to be used in the treatment of a particular disorder [2]. This technique enhances drug selectivity through increasing the solubility at the target site [3].

Basically prodrug represents the bioconversion of inactive compound into an active pharmacological which mostly controlled by the liver and tissue enzymes under a process known as biotransformation [4].

Diclofenac reduces the effects of pain and fever mediators that are responsible for the inflammation; through the inhibition of prostaglandin synthesis via blocking of cyclooxygenase (COX 1 and COX 2) enzymes to reduce the inflammation [5].

Diclofenac has been used in the treatment of chronic osteoarthritis sprains, mild strains, bruises and various type of traumas; although it has many side effects same as other NSAIDs which limits their used in the presence of gastrointestinal diseases and hypertension when formulated as sodium salt [6].

Diclofenac is one of the phenylacetic acid derivatives which interpret the anti-inflammatory mechanism of NSAIDs in the treatment of acute and chronic inflammation that induces by the effect of various pain mediators in the body; through blocking the production of pain hormones [7].

Address for correspondence: Ali Taha Metaib

Department of Pharmaceutical Chemistry/College of Pharmacy/Al-Farahidi

University/ Baghdad/Iraq

Email: alitaha198282@gmail.com

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How to cite this article: Ali Taha Metaib, Manar Serhan Ahmed, Ghanem Shaker Al-Jebouri, Ahmad AB Yosef, Nibrass Taher Abdal, The Production and Estimation of Diclofenac Amide Prodrug, J PHARM NEGATIVE RESULTS 2022;13: 761-765.

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10.47750/pnr.2022.13.03.114

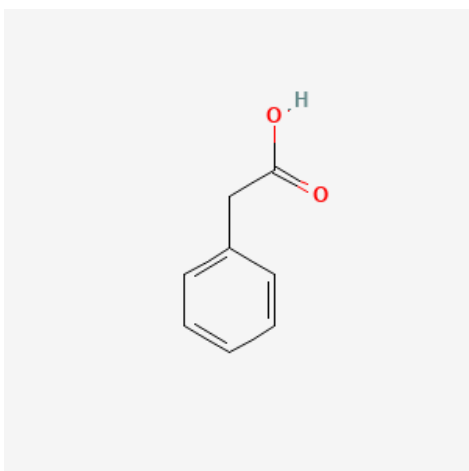


Figure 1: Phenylacetic acid structure

Diclofenac is approved by FDA in 1988 and named as Voltaren that produced by Novartis drug manufacturing company [8]

Phenylacetic acid structure is shown in figure 1; where the addition of chlorine groups on ortho-position of the phenyl moiety may enhance the potency of the drug and when loaded with misoprostol to reduce the GIT effects [9]. So the main goal of diclofenac prodrug is to modify the chemical structure to decrease the adverse effects and improve the activity [10].

The chemical modification of NSAIDs is performed through a reaction between carboxyl group and amine to form an amide prodrug; which hydrolyzed by the presence of amidase enzyme in GIT to cleave the compound into the active drug and bulky group to exert the anti-inflammatory action [11]. The alteration in the binding site of carboxyl group on the cell may have direct impact on reducing the unwanted adverse effects on the mucosal layer of the stomach [12].

The application of prodrug technique is widely used nowadays in pharmaceutical chemistry and biopharmaceutical area; due to improving drug efficacy, targeting and bioavailability; in addition to limit the adverse effects that associated with conventional NSAIDs dosage form [13].

The drug chemical modification is applied for various drug groups through the formation of ester, amide and chemical complex to carry the original drug to the target site and increased the stability throughout the GIT portion [14]. The

production of prodrug is to maintain the active drug in a unionized form to facilitate the permeation via cell membrane to improve absorption and reach blood circulation to face the hydrolytic enzyme at the site of action and cleaved into the active form to exert its action according to purpose of treatment [15].

2. Materials and Methods

The hydrous solvents and other reagents are purchased from Riedel De-Haen (Germany), Bdh - Sigma-Aldrich (Germany), diclofenac is gifted from Al-Forat Drug Company and commercial Voltfast powder is supplied by Al-Noor medical store.

2.1 Diclofenac Sodium Conversion into Free Form

Before the perpetration of the diclofenac amide prodrug; diclofenac should be extracted from voltaren powder through adding 10mL of ethanol to the diclofenac potassium with continuous stirring for 10-minute; followed by addition of diluted HCL. Filtration is necessary to collect the extract that washed with 50mL DW to remove the impurities and dry at room temperature [16].

2.2 Synthesis of 4-(2-(2-((2,6-Dichlorophenyl) Amino) Phenyl) Acetamido Benzoic Acid (a1)

Taking 500mg (1.69 mmol) of diclofenac to be added to 8.5mL (5mL/mmol) of dichloromethane in ice bath to prevent the volatility of active ingredient and mix with 0.23gm (1.67 mmol) of para-amino benzoic acid in a beaker that placed in ice bath at 0 °C for 5-minute.

At the same temperature 3mL of dichloromethane is added to the mixture with continuous stirring for 10-minute. The mixture is removed from the ice bath and placed on magnetic stirrer for 8-hour at room temperature to ensure consistency. The reaction is stopped by adding 10mL DW and analyzed through using TLC solvent system ethyl acetate-hexane of ratio (1:1) and the extract is collected from the organic layer by using separator funnel.

The extract in ethyl acetate layer is washed with 20mL of saturated aqueous NaCl solution (brine); finally the drying is performed over anhydrous Na₂SO₄ and concentrated in vacuum to obtain the product as shown in figure 2 which illustrates the synthesise of the final product. The synthesis is performed triplicate (n=3) [17].

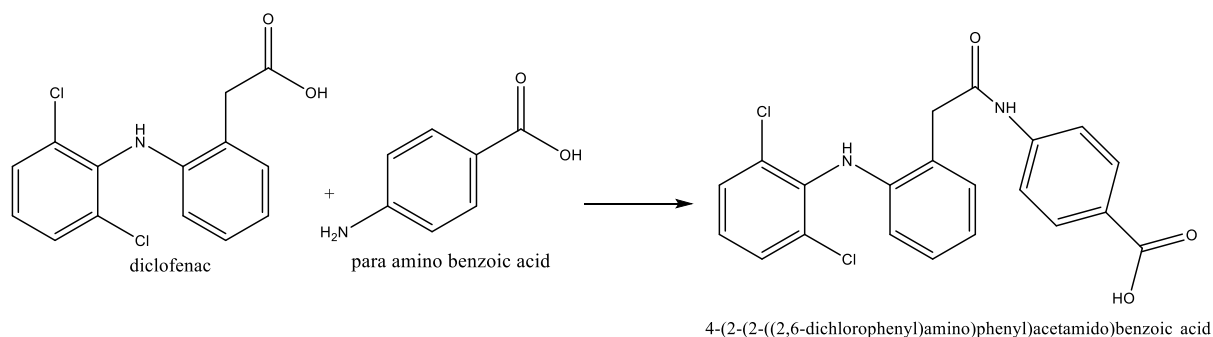


Figure 2: Synthesis pathway of 4-(2-(2-((2,6-dichlorophenyl) amino) phenyl) acetamido) benzoic acid (a1).

2.3 Synthesis of N-(2-Aminophenyl)-2-(2-((2,6-Dichlorophenyl) Amino) Phenyl)Acetamide (b1)

Taking 500mg (1.69 mmol) of diclofenac to be added to 8.5mL (5mL/mmol) of dichloromethane in ice bath to prevent the volatility of active ingredient and mix with 0.23gm (1.67 mmol) of para-amino phenol in a beaker that placed in ice bath at 0 °C for 5-minute.

At the same temperature 3mL of dichloromethane is added to the mixture with continuous stirring for 10-minute. The mixture is removed from the ice bath and placed on magnetic

stirrer for 8-hour at room temperature to ensure consistency. The reaction is stopped by adding 10mL DW and analyzed through using TLC solvent system ethyl acetate-hexane of ratio (1:1) and the extract is collected from the organic layer by using separator funnel.

The extract in ethyl acetate layer is washed with 20mL of saturated aqueous NaCl solution (brine); finally the drying is performed over anhydrous Na₂SO₄ and concentrated in vacuum to obtain the product as shown in figure 3 which illustrates the synthesise of the final product. The synthesis is performed triplicate (n=3) [18].

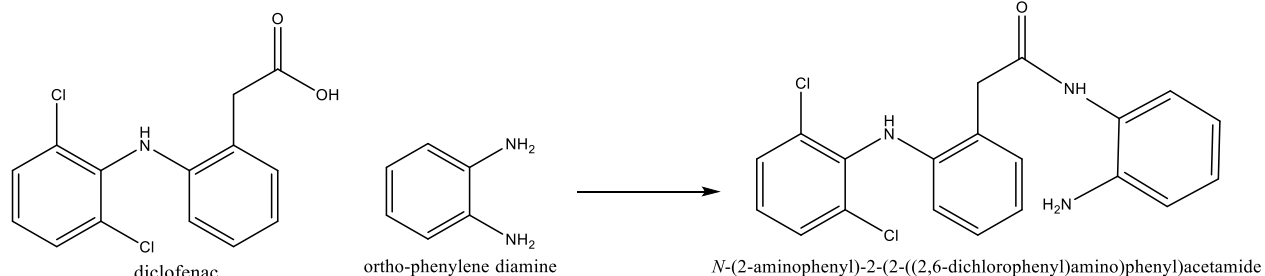


Figure 3: Synthesis pathway of N-(2-aminophenyl)-2-(2-((2,6-dichlorophenyl) amino) phenyl) acetamide (b1)

2.4 Synthesis of 2-(2-((2,6-Dichlorophenyl) Amino)Phenyl)-N-(2 Hydroxyphenyl)Acetamide (c1)

Taking 500mg (1.69 mmol) of diclofenac to be added to 8.5mL (5mL/mmol) of dichloromethane in ice bath to prevent the volatility of active ingredient and mix with 0.18gm (1.66 mmol) of ortho-amino phenol in a beaker that placed in ice bath at 0 °C for 5-minute.

At the same temperature 3mL of dichloromethane is added to the mixture with continuous stirring for 10-minute. The mixture is removed from the ice bath and placed on magnetic

stirrer for 8-hour at room temperature to ensure consistency. The reaction is stopped by adding 10mL DW and analyzed through using TLC solvent system ethyl acetate-hexane of ratio (1:1) and the extract is collected from the organic layer by using separator funnel.

The extract in ethyl acetate layer is washed with 20mL of saturated aqueous NaCl solution (brine); finally the drying is performed over anhydrous Na₂SO₄ and concentrated in vacuum to obtain the product as shown in figure 4 which illustrates the synthesise of the final product. The synthesis is performed triplicate (n=3) [19].

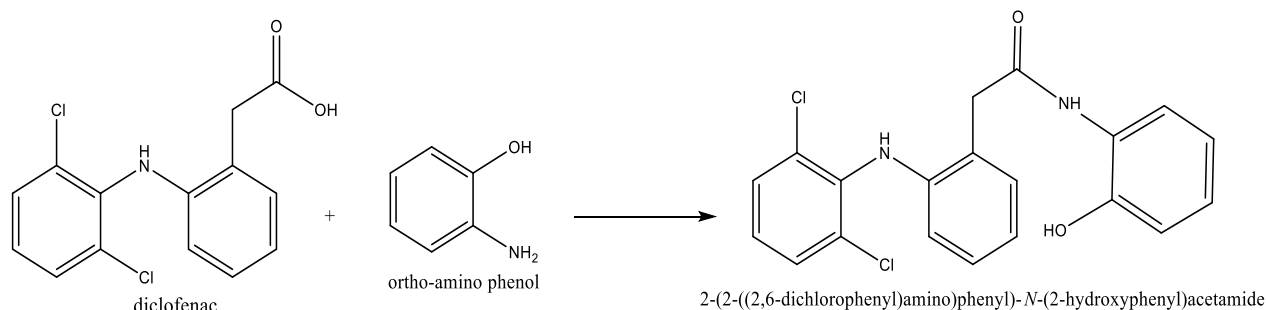


Figure 4: Synthesis pathway of 2-(2-((2,6-dichlorophenyl)amino) phenyl)-N-(2 hydroxyphenyl) acetamide (c1)

2.5 Determination of λ_{max} of Pure Diclofenac

λ_{max} is obtained by preparing 0.1/mL solution of diclofenac in 95% ethanol and scanned under Double Beam UV/VIS Spectroscopy Hinotek (China) to determine the maximum absorbance between 200-400nm [20].

2.6 Fourier Transform Infrared Spectroscopy Analysis

JASCO Fourier transform infrared spectroscopy (Japan) is used to obtain an Infra-Red spectroscopy absorption by the functional groups of the compounds; which collects data of high-resolution spectrum. The spectrometer is referred to Herschel series (FT-IR 4000-400cm-1) [21].

2.7 Nuclear Magnetic Resonance NMR Analysis

Borehole nuclear magnetic resonance (China); the physical behaviors of resonance transition of magnetic level energy is occurred when the atomic nuclei immersed in a magnetic field by applying an electromagnetic radiation at a particular frequency to detecting the absorption of signals [22].

3. Results and Discussion

3.1 Determination of λ_{max} of Pure Diclofenac

The maximum UV absorbance for the prepared solution is obtained at 242nm by using UV spectroscopy analysis.

3.2 Fourier Transform Infrared and Nuclear Magnetic Resonance Analysis

FTIR spectroscopy of 4-(2-(2-((2,6-dichlorophenyl)amino)phenyl) acetamido) benzoic acid (a1)

is detected at 3380cm-1 for NH group, 1624cm-1 for COOH group and for amide group at 1662cm-1.

The collected NMR data is recorded at 1H NMR 400MHz (CDCl3) as followed; 1H ArH (7.37), 1H ArH (7.85), 1H ArH (7.92), 1H ArH (7.22), 1H ArH (7.13), 1H ArH (7.17), 1H ArH (6.82), 2H ArH (8.24), 1H HN (5.95), 1H HN (12.11).

FTIR spectroscopy of N-(2-aminophenyl)-2-(2-((2,6-dichlorophenyl) amino) phenyl) acetamide (b1) is detected at 3321cm-1 for NH group, 3454cm-1 for OH group and for amide group at 1663cm-1.

The collected NMR data is recorded at 1H NMR 400MHz (CDCl3) as followed; 1H ArH(7.32), 1H ArH(7.95), 1H ArH(7.76), 1H, ArH(7.29), 1H ArH(7.19), 1H, ArH(7.12), 2H ArH(6.78), 1H HN amid(9.97), 1H, HN amine(9.47) and 2H HN amine (5.65).

FTIR spectroscopy of 2-(2-((2,6-dichlorophenyl) amino)phenyl)-N-(2-hydroxyphenyl) acetamide (c1) is detected at 3324cm-1 for NH group, 3454cm-1 for OH group and for amide group at 1663cm-1.

The collected NMR data is recorded at 1H NMR 400MHz (CDCl3) as followed;

1H ArH(7.39), 1H ArH(7.87), 1H ArH(7.68), 1H ArH(7.20), 1H ArH(7.09), 1H ArH(7.01), 2H ArH(3.78), 1H HN amid(10.12), 1H HN amine(9.22) and 1H OH(10.33). The recorded data regarding melting point and molecular weight is illustrated in table 1 for different amide groups of diclofenac prodrug and table 2 shows the solubility of the compounds in different solvents.

Table 1: The data of molecular weight and melting point of diclofenac prodrug

Name of the Compound	Molecular Formula	Molecular weight(gm)	Melting point(°C)
Diclofenac	C ₁₄ H ₁₁ O ₂ NaCl ₂	296	156-158
a1	C ₂₁ H ₁₆ Cl ₂ N ₂ O ₃	415.27	147-150
b1	C ₂₀ H ₁₇ Cl ₂ N ₃ O	386.28	78-80
c1	C ₂₀ H ₁₈ Cl ₂ N ₂ O	372.08	149-153

Table 2: The solubility of diclofenac prodrug in different solvents

Compounds name	Ethanol	Acetone	Chloroform	Water	Diethyl ether
a1	Soluble	Soluble	soluble	Insoluble	Soluble
b1	Soluble	Soluble	Soluble	Insoluble	Soluble
c1	soluble	Soluble	Soluble	insoluble	soluble

4. CONCLUSION

A successful synthesis of the prepared compounds is estimated for physical properties of melting point and molecular weight, FTIR spectroscopy and ¹H-NMR spectra are confirmed the characterization and identification of the synthesized compounds.

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