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Preparation and Characterization of a New Polymer for Mesalazine and Study of its Biological Activity against Colon Cancer

Fatimah Abdul Razzak Mageed[*1]; Zena T Omran[*2]; Shatha Abd Al-Jabbar[*3]

*Department of Biology, College of Education for Pure Science, University of Karbala, Karbala, Iraq

1) fatima.a@uokerbala.edu.iq
2) Zina.t@uokerbala.edu.iq
3) shatha.a@s.uokerbala.edu.iq

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Abstract: This work produced new homogenous and heterogeneous polymers with medical qualities to expand the controlled drug, as well as new drug-substituted monomers. The following three lines were included in this work: Preparation is the first stage (compound1) via reaction of furan-2,5-dione with 4-aminobenzoic acid, then compound (1) was reacted with amino drug such as (mesalazine) compound(2) monomer. Second line: The homogeneous polymer (compound 3) was produced by employing MEKP as an initiator in the polymerase reaction of the monomer's (compound 2) free radicals under nitrogen. Third line: Using MEKP as an initiator, The Polymerase Reaction of The Free Radicals of the monomer (compound2) with the acrylic acid under nitrogen was used to introduce the heterogeneous polymer (compound 3).Compound 2's monomer is described using FT-IR. Studies were conducted on the characteristics of biological activity. It was determined whether medication loading (compounds 3 and 4) had an anti-proliferating impact on the colon cancer cell lines. Compounds 3 and 4 may be a suitable and promising approach for creating an efficient drug delivery system for therapeutic use against colon malignancies, according to cytotoxicity assessments.
Keywords: furan-2,5-dione, mesalazine, biological activity, colon cancer, FTIR.

1. Introduction

A drug's therapeutic efficacy is limited by a number of issues, including poor solubility, low stability, a short half-life, and non-specific toxicity. Biopharmaceuticals including proteins, peptides, and nucleic acids are frequently constrained by their quick excretion from the body and poor stability. Those outside the polymer synthesis sector have limited access to drug delivery materials and techniques. Enhancing pharmacokinetics and therapeutics to facilitate drug distribution to the appropriate location is the goal of successful drug delivery. In the pharmaceutical sector, drug polymer techniques like encapsulation, compression, spraying, and immersing have been used with polymers as bioactive agents [1].

1.1 The Polymers of drugs

Over the past 20 years, functional polymers have gained attention in the medical field. Applications for polymers as biomaterials include tissue engineering, dentistry, medical device components, and artificial organs. Prior to being used as carriers for the sustained and selective administration of small molecules or macromolecular (such as proteins, genetic materials, etc.) medicinal agents, polymers with pharmacological properties that are beneficial as therapeutic agents can be employed [2].synthetic polymers containing Biological products components can Also be

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advantageous and appealing. The creation of systems that can dispense medications for extended periods of time at regulated rates has drawn more attention [3].

Certain features focused on the production of bioactive polymeric materials, in which a medication forms a covalent bond with a polymer. For instance, an acetal function group was used to bind chloromphenicol to a methacrylic, and the copolymer was subsequently produced by heteropolymerization with 2-hydroxyl methacrylate [4].When a medicine is restricted to a polymer; its activity may be prolonged. Achieving a delivery profile that would result in a high blood level of the drug for an extended length of time was the goal of several polymeric drug systems. When using conventional Tablets or injections, the Drugs stage in the Blood are following the profile depicted shows figure (1-1).Following each Drug administration, the drug stages climbs before falling until the subsequent administration.

Long-term administration is the goal of controlled drug delivery systems, and the medication's blood stage maintains a consistent profile between the planned maximum and minimum, as seen in Figure (1-2) [5], for a prolonged duration.

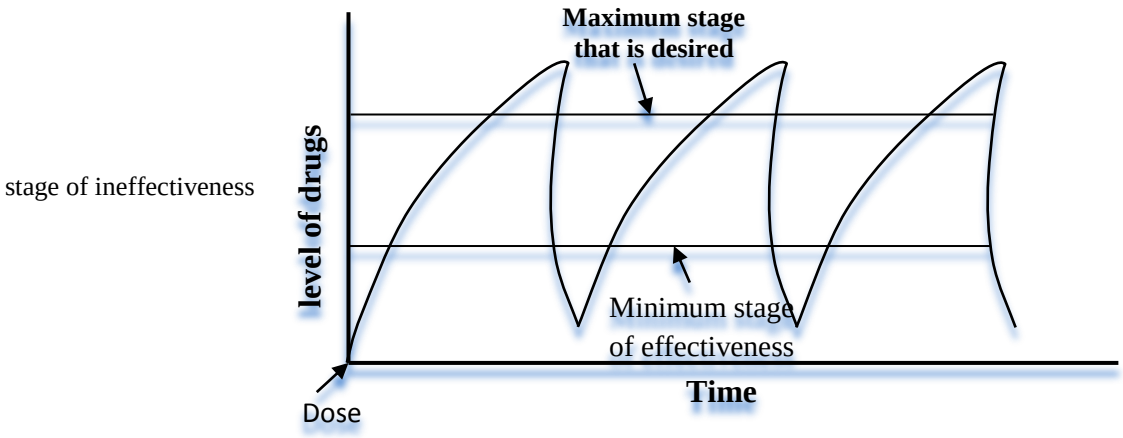

Fig.(1-1): blood drug level using conventional dosages

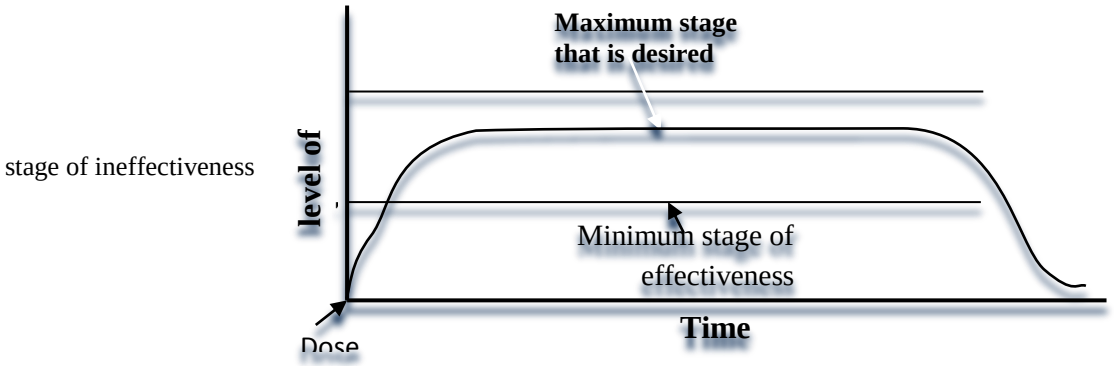

Fig. (1-2): Blood drug levels with regulated dosages.

macromolecular pro-Drugs with polymers serving as carrier molecules, tailored drug delivery at certain areas to reduce toxicity and improve selectivity for specific anticancer agents, and sustained drug delivery [6,7].The field of polymeric drug delivery systems, including commercial devices, has seen significant developments. It is crucial that

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the agent's Blood level stays between a minimal value, where the medicine loses its effectiveness, and a maximum value, which could indicate a toxic level [8].

1.2 The idea of in favor of drugs

Albert [9] the first was to propose the idea of favor of drugs strategy to boost drug effectiveness. He defined pro-drugs as chemical compounds that are pharmacologically inactive and that can be utilized to temporarily change the physicochemical characteristics of medications in order to make them more useful or less toxic. Consequently, a pro-drug is a drug derivative that, either enzymatically or without, undergoes biotransformation within the body prior to demonstrating its therapeutic action. When the Derivative is arriving at the action site, The favor of drugs is changed back into The Original Drug, and The release is derivative group is quickly removed without producing any negative side effects (Figure 1.4)[10].

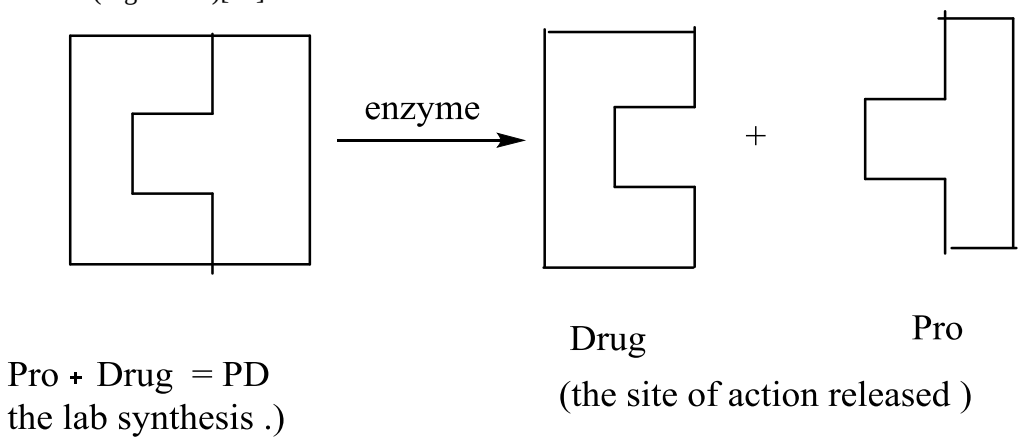

Figure (1-4) shows how an inactive pro-drug (PD) can be chemically or enzymatically changed into at the site of action, an active medication (D)

1.3 Polymer and Their Evolution in Medicine

Polymers have played a significant role in the evolution of medicine, with their utilization dating back to ancient civilizations. The term "polymer" signifies "many parts," denoting large molecules composed of numerous repeating units called mers [11]. Over the centuries, polymers have been classified into various categories based on their properties and applications [11]. Today, they are indispensable in modern medicine, with applications ranging from drug delivery systems to tissue engineering and regenerative medicine. The ancient roots of polymers in medicine extend over four millennia. Ancient papyrus papers from 4000 B.C. documented their use in sutures and wound closure, showcasing an early recognition of their medical applications [12,13]. This early utilization of polymers demonstrated the understanding of their beneficial properties, such as their mechanical strength and compatibility with biological systems. These properties continue to be highly valued in medical applications today. Around 2000 B.C., early practitioners explored the use of metals for bone repair, marking a significant milestone in medical history. The use of metals in medical applications continued to evolve over time and remains an important aspect of modern orthopedics. Metal implants and prostheses have revolutionized the field of joint replacement surgery, allowing patients to regain mobility and improve their quality of life .[14], goose quills were later employed for vascular repair, demonstrating the innovative spirit of medical pioneers. The use of natural polymers, such as quills, showed promise for restoring the functionality of blood vessels. However, it was not until the 1800s that metals played a crucial role in bone reconstruction. The development of metal plates, screws, and nails provided stability and support to fractured bones, facilitating the healing process. Meanwhile, western medicine was not officially brought to Nigeria until the 1860s, when Roman Catholic missionaries founded the Sacred Heart Hospital in Abeokuta, which also significantly contributed to the country's supply of contemporary medical facilities [15]. The 1930s saw the advent of synthetic polymers, coinciding with the growth of the plastic industry and presenting novel possibilities in medical applications [16]. The development of synthetic polymers opened up a whole new realm

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of biomaterials with tailored properties for specific medical needs. These polymers could be precisely engineered to have the desired mechanical, chemical, and biological characteristics, making them versatile for various applications in medicine.

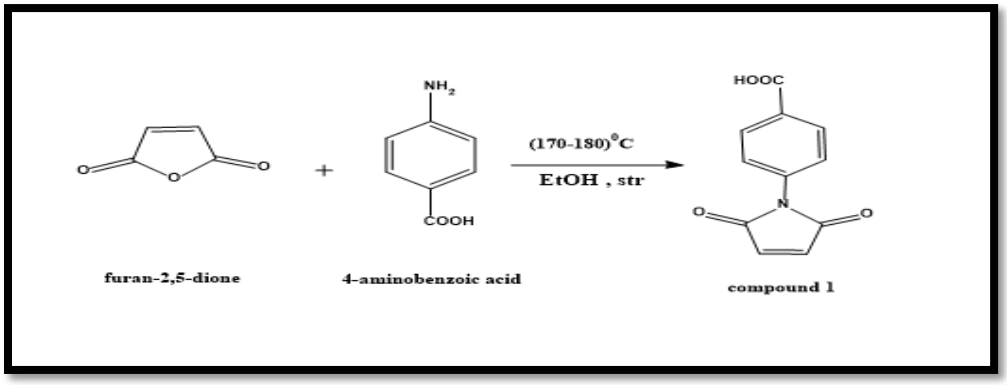
2. Experment Part

2-1- Chemical and Techniques:

A (5-aminobenzoic acid)(mesalazine) was 98.5% (Fluka) and the FTIR spectra was recorded on a Bruker at (500-4000)cm-1 .

2.2- Synthesis of the compound (1) [17]:

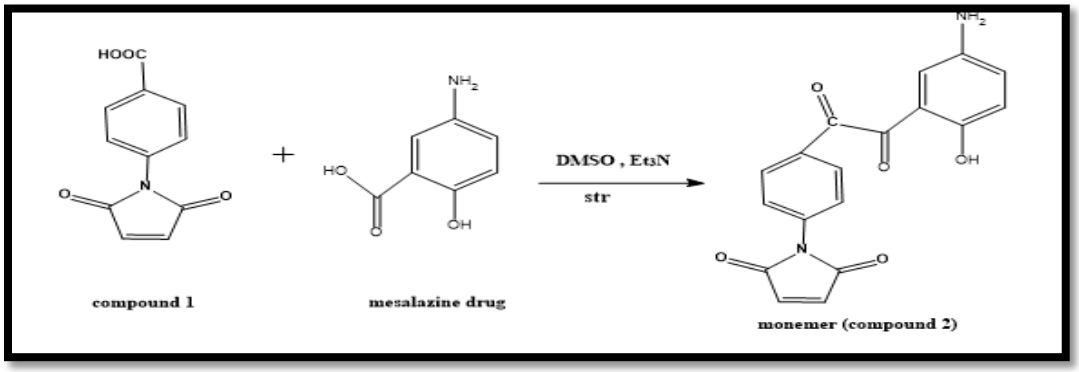
A 75 mL beaker containing approximately 0.6 g , 0.0035 mmol of 4-aminobenzoic Acid and 1.01 gm, 0.0022 mmol of furan-2,5-dione was heated with a glass stirrer in an oil bath at (170 -180 ^{o}C for 10 minutes until all of the materials fused to form a dark yellow liquid. The blend was then Allowed to Cool for 5.0 minutes before being re-crystallized by Ethan-ol. Equation (1)



Equation (1)

2.3 Synthesis Monomer compound (2) [17]:

Compound (1) (0.45 gm, 0.0021 mmole) and 20 ml of dimethylsulfoxide (DMSO) were added to a 150 ml beaker. Next, 4.2 gm, 0.035 mmole) of thionylchloride (SOCl2) was added, and the mixture was heated using a sensitive hot plate magnetic stirrer at 60 to 70 oC. After two hours, mesalazine (5-ABA) (0.581 gm, 0.0025 mmole) was added, And the blend was stirred at 30 ^{o}C for 30.0 minutes. After Cooling in an Ice Bath, the combinations were allowed to form a precipitate before being filtered and dried. Equation (2)



Equation (2)

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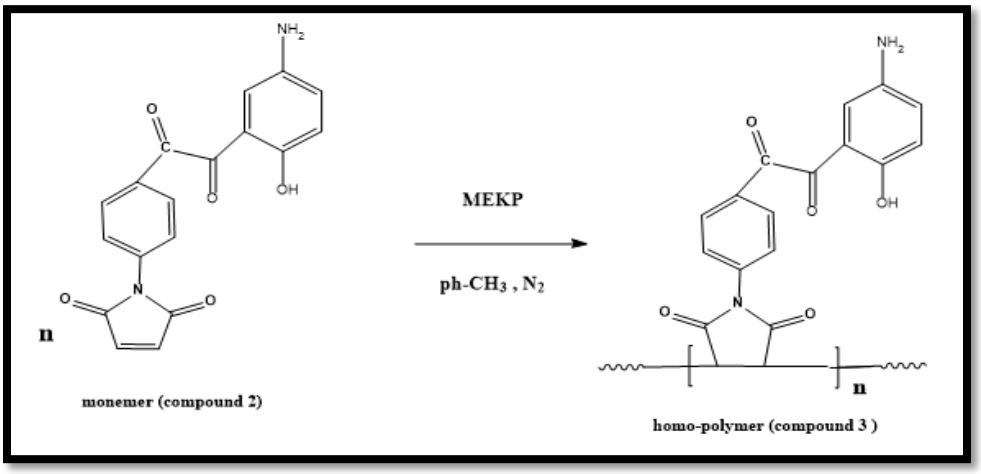
2.4 . Homo-polymer compound synthesis (3) [18]:

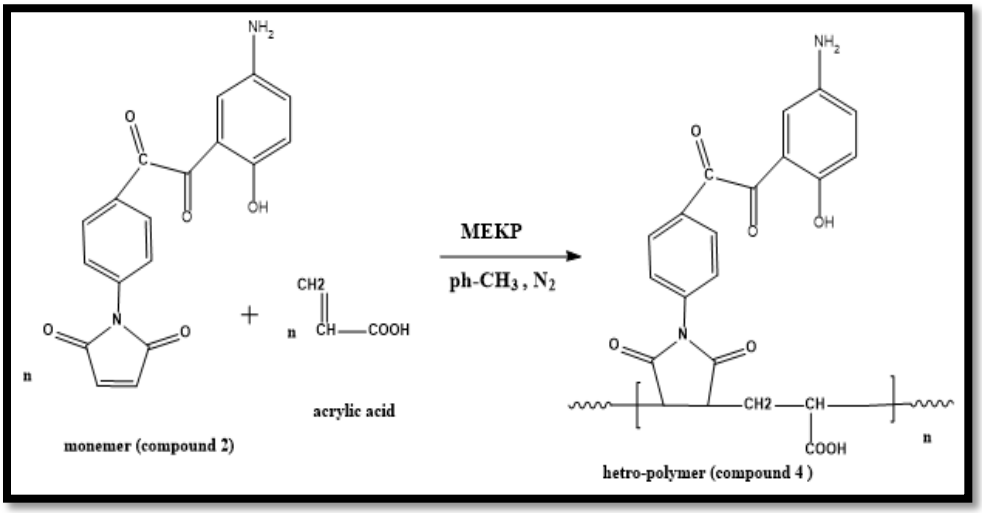
Two drops of methylethylketone peroxide (MEKP) were added to A 50 ml Round-Bottom Flask with Two necks, 0.21 g (0.00048 mMole) of Monomer (compound 2), and 10 ml of Toluene. The flask was Then tightly sealed and placed in a water bath at 90 ^{o}C. The Nitrogen Gas was then enacted from One of The Flask nozzles. After two hours of the reaction, the solvent was Evaporated, the Precipitate was been Filtering and washing with Ether, and it was dried in Oven set at 50.0 degrees Celsius. equation (3).



Equation (3)

2. 5 Hetero-polymer compound synthesis (4) [18]:

Two necks of monomer (compound 2), 0.21 gm, 0.00048 mmole, 10 mL of Toluene, and 0.031 g, 0.00043 mmole of Acrylic acid mono-mer were placed in a 50 ml Round-bottom Flask, sealed Strongly, and placed in a water Bath at 90 ^{o}C. two drops to three of methylEthylketone peroxide(MEKP) was been added, and The gas of Nitrogen was passed through one of the Flask nozzles. After two hours of the reaction, the solvent Evaporates, the Precipitate was been filtering and washed with Ether And it was Dried in an Oven set at 50.0 degrees Celsius. Equation (4).



Equation (4)

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2.6 Biological activity [19,20].

2.6.1 Cell culture maintenance

Cancer of the colon The cell lines were kept in RPMI-1640 supplemented with 100 units/ml of Penicillin, 100 µg/ml of streptomycin, and 10% fetal bovine. Trypsin-EDTA was used to passage the cells, which were then reseeded twice a week at 80.0% confluence and cultured at 37.0 °C.

2.6.2 Tests for Cytotoxicity

Using 95-well plates, The (MTT) Cell Viability experiment was been Performed to ascertain the cytotoxic effect of (x-substances). The seeding density of cell lines was 1×104 cells/well. Following a 24-hour period or the formation of a confluent monolayer, the cells were exposed to the tested substances. After 72 hours of Treatment, the Media was Removed, 28.0 µL of a 2.0 mg/mL (MTT) solution was been added, And the Cells were incubated for 2.5 hours at 37 °C to determine the cell viability. Following the removal of the MTT solution, 130 µl of DMSO (dimethyl Sulphoxide) was added to the wells to dissolve the crystals that remained, and the blend was then incubated for 15.0 minutes at 37.0 °C while being shaken. The assay was carried out in triplicate, and the absorbency was measured using a Microplate reader at the test wavelength of 492 nm. The following formula was used to determine the percentage of cytotoxicity, or the inhibition rate of cell growth:

Toxicology = N-O/N × 100

where N and O stand for the Optical densities of the test And control, Respectively.

2.6.3 Assay for DPPH radical scavenging and antioxidant activity

According to [21], stable DPPH radicals were used to test the antioxidant activity of (x-substance) with only modest modifications. Utilizing (X-substance), the scavenging activity was examined. the Sample was combined with 450.0 µl of DPPH Solution, And then 100% etha-nol was Added to bring the blend's volume up to one milliliter. As a positive control, ascorbic acid was used at a concentration of 10 µg/ml. For half an hour, the samples and Control are kept At Room temperature in The dark. At 517 nm, the absorbance was measured. Scavenging activity is calculated using the following formula:

$$Scavengingi\% = \frac{Absorbance\ ioficontrol - Abosrbanceiofisample}{Absorbance\ ioficontrol} \times i100\%$$

3. RESULTS AND DISCUSSION

3.1 FT- I.R Spectrum:

Figure (1), A FTI.R Spectrum of Compound (1) revealed the sense of an Absorption broad Band of O-H carboxylic acid at about (3500-3101) cm-1, as well as Absorption bands for C=C-H amide at (3100.45) and C=O carboxylic Acid at (1705.36) cm1, C-N-C at (1380.01) cm^{-1}, And C-O at (1175.01) cm^{-1} carboxylic acid.

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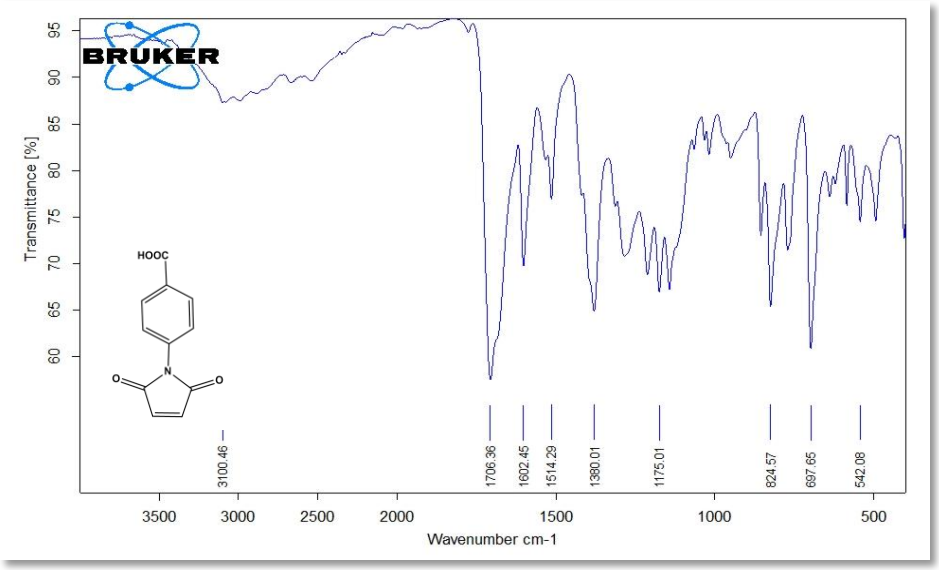

Fig. (1): FT- I.R spectrum of Compound (1)

3.2 Biological Activity

Malignant tumors in the rectum and large intestine are commonly referred to as colorectal cancer. Despite their molecular and therapeutic differences, these malignancies are treated as a single illness. In the current study; we assessed how well drug-loading compounds (3) and (4) inhibited the growth of colon cancer cell lines. Compounds (3) and (4) may be a suitable and promising approach for creating an efficient drug delivery system for therapeutic use against colon malignancies, according to cytotoxicity assessments.

Compound (3)'s IC50 value was substantially lower than that of pure medications and the triggered apoptotic cell death pathway (IC50=19.32). According to the study's findings, compound (3) may find utility in medicine and provide a useful chemotherapeutic formulation. Figure (2)

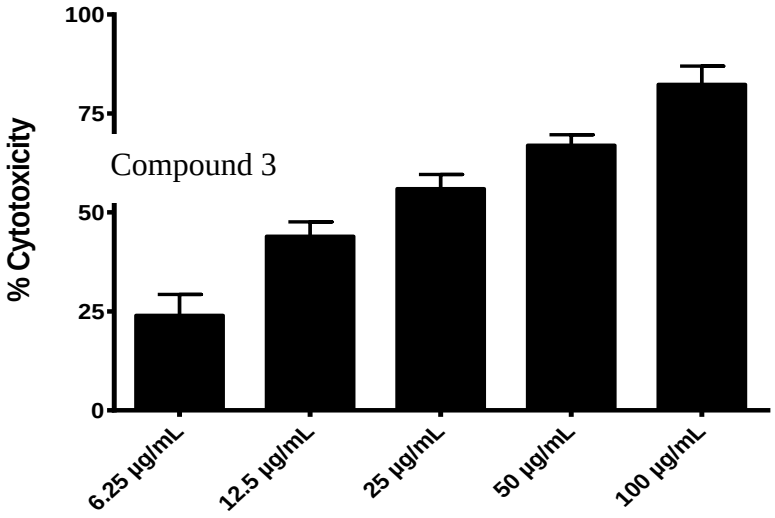

Figure 2: Compound (3)'s cytotoxic effect on colon cancer cells. IC50 is 19.32.

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4. CONCLUSIONS

New compound 4-Aminobenzoic acid was produced and described using molecules of Amino Drug Based on Maleimide. We produced by synthesizing and studied a New Homo polymer based on Maleimide and drug Chloride monomer that is Loaded with medicinal features To improve the controlled drug. In order to extend the controlled drug, New Hetero polymers based on Maleimide and drug chloride monomer with acrylic Acid were also created and described. These polymers were packed with medicinal qualities. Using the FT-IR approach, all of these synthesized monomers and polymers showed distinctive bands that demonstrated the production of the intended target molecules from the starting material. After assessing compound (3)'s anti-proliferating action on colon cancer cell lines, we came to the conclusion that it might be a suitable and promising approach for creating a drug delivery system that can be used in clinical settings to treat colon tumors.

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