Advanced Mesalazine - Conjugated Polymeric Architecture for Colon Cancer Targeted Therapy: Synthesis, Characterization, and Biological Evaluation.

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Abstract

Background: Colorectal cancer remains one of the leading causes of cancer-related mortality worldwide, creating a continuous need for advanced drug delivery systems capable of improving therapeutic efficiency and controlled drug release. Polymeric drug conjugates have attracted considerable attention due to their ability to enhance drug stability, prolong release, and reduce side effects. In this study, novel mesalazine-based polymeric systems were developed and evaluated for their anticancer activity against colorectal cancer cells.

Objective: This study aimed to synthesize novel mesalazine-containing monomers and prepare homogeneous and heterogeneous polymeric drug delivery systems with enhanced controlled-release properties and improved anticancer efficacy against colorectal cancer cell lines.

Methods: Compound (1) was synthesized through the condensation reaction of 4-aminobenzoic acid with furan-2,5-dione to produce a functional intermediate. The intermediate was then conjugated with mesalazine to obtain the active monomer (compound 2), which was characterized using FT-IR spectroscopy. Subsequently, compound (2) underwent free radical polymerization under a nitrogen atmosphere using Ethyl Methyl Ketone Peroxide (EMKP) as an initiator to produce the homogeneous polymer (compound 3). A heterogeneous copolymeric system (compound 4) was also synthesized by copolymerization of compound (2) with acrylic acid under similar conditions. The cytotoxic activities of the synthesized compounds were evaluated against colon cancer cell lines.

Results: The synthesized polymeric systems demonstrated enhanced anticancer activity compared with the free drug form. Both homogeneous and heterogeneous polymers exhibited higher inhibitory effects on colon cancer cell growth, indicating improved therapeutic efficiency and more effective controlled drug release behavior.

Conclusion: The prepared mesalazine-based polymeric drug conjugates showed promising potential as controlled and targeted drug delivery systems for colorectal cancer treatment. The enhanced cytotoxic activity of the polymeric formulations suggests their suitability for future pharmaceutical and biomedical applications

Keywords: Mesalazine; Colon cancer; Polymer-drug conjugate; Targeted drug delivery; Free radical polymerization; Biocompatible polymers; FTIR; Cytotoxicity.

1. Introduction

Colorectal cancer remains among the leading causes of cancer-related deaths worldwide, despite significant advancements in diagnostic and treatment methods in recent years. Traditional chemotherapy still faces several challenges, most notably its high toxicity to healthy tissues, limited selectivity in targeting cancer cells, and the limited delivery and accumulation of drugs within the tumor, which negatively impacts treatment efficacy. For this reason, recent research has focused on developing intelligent drug delivery systems that can control drug release and target the tumor site more precisely. In this context, polymer-based drug delivery systems have garnered significant attention due to their modifiable properties, high biocompatibility, and their role in enhancing drug stability and regulating release mechanisms. These systems can also be designed to increase drug concentration in infected tissues while minimizing side effects in healthy tissues, thereby enhancing therapeutic efficacy. Among these systems, polymer-drug conjugates are promising approaches, relying on the chemical linkage of the drug to the polymer chain to achieve a gradual and sustained release of the active ingredient.

Mesalazine (5-aminosalicylic acid) is a well-known anti-inflammatory drug primarily used to treat inflammatory bowel diseases. Recent research has also shown its potential to have anti-cancer effects against colorectal cancer cells. However, its therapeutic application faces some limitations, such as its rapid biodegradability and poor selectivity in reaching diseased tissues, which reduces its clinical efficacy. Therefore, linking mesalazine to polymer carriers has emerged as an effective way to improve drug stability and enhance its therapeutic performance.

In this study, novel mesalazine-containing monomers were designed and synthesized, followed by polymerization to produce homopolymer and heteropolymer systems. These systems aimed to increase drug loading efficiency, regulate drug release in a controlled manner, and enhance their bioavailability against colon cancer cells (Dunn & Ottenbrite, 1991).

1.1. Drugs polymers

Functional polymers have drawn interest in the medical field within the last 20 years. Polymers are used for example Biomaterials in skin Engineering, dentistry, artificial organs, and health stratagem components. Polymers with Pharmacological characteristics They advantageous as relaxing managers can be recycled as transporters for a long-term besides targeted organization of unimportant bits or Macromolecular(such as genomic materials, proteins, etc.) pharmaceutical managers (Duncan & Vicent, 2013). Biological product components in synthetic polymers can also be beneficial and appealing. More focus has been placed on developing devices that can distribute drugs at controlled rates for prolonged periods of time (Vogelstein & Kinzler, 2004).

The creation`s polymeric materials of bioactive, in which Drug establishes a link`s covalent with Apolymer, was one of the features. Example , chloramphenicol was bound to acrylicmeth using an function group Acetal, and the copolymer was then created by heteropolymerization using 2-hydroxyl methacrylate (Ghasemiyeh & Mohammadi-Samani, 2021), Large-molecule drug delivery systems (Nyamweya, 2021), where polymers act as the drug carriers, are used to control the release of the drug for a longer period and to target specific locations within the body. This helps reduce toxicity and increase the precision of targeting certain cancer treatments (De Smedt et al., 2000; Niculescu & Grumezescu, 2021) . Polymer-based drug delivery systems have seen significant development, and some have reached commercial use. It is essential to maintain the drug concentration in the blood at an appropriate level; it should not fall to a point where its effectiveness

is diminished, nor should it rise to a level that could cause harm or toxicity to the patient (Upadhya et al., 2021).

1.2. Idea for using the medicine

Albert was the major to recommend the knowledge of improving the properties of drugs to increase their therapeutic efficacy (Shariatinia, 2021). He described pro-drugs as compounds that are pharmacologically inactive when administered, but are designed to temporarily modify some of the physicochemical properties of the drug, thus helping to reduce its side effects or enhance its therapeutic benefit. After entering the body, these compounds are converted into the active drug form through biological processes that may be enzymatic or non-enzymatic. When the drug reaches its site of action, the original drug is released and the associated group is speedily uninvolved without causing harmful lateral effects Figure (3) (Kiran et al., 2021) .

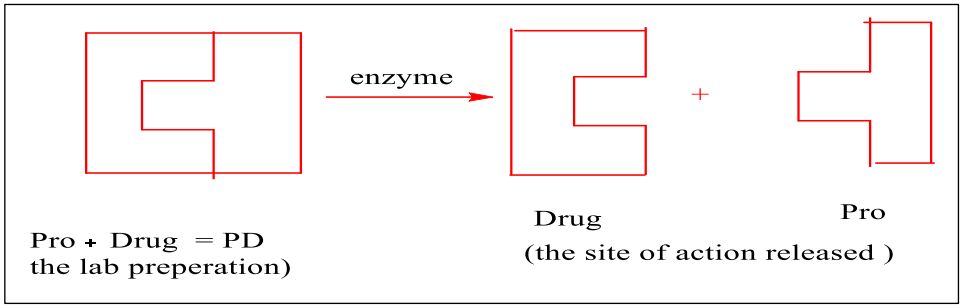


Figure 1. The prodrug (PD) is converted by enzymes at its site of action into the active pharmaceutical form (D).

1.3. The Development of Polymers in Medicine

The use of polymers dates back to ancient civilizations and has been crucial to the development of medicine. The word "polymer" means "many parts," referring to big molecules made up of many repeating units known as mers (Saleh et al., 2022). Based on their characteristics and uses, polymers have been divided into numerous groups over the ages (Saleh et al., 2022). With uses ranging from tissue engineering and regenerative medicine to drug delivery systems, they are now essential to contemporary medicine. Polymers have been used in medicine for more than 4,000 years. Their usage in sutures and wound closure was recorded in ancient papyrus scrolls from 4000 B.C., demonstrating an early understanding`s medicinal applications (Govindarasu et al., 2022; Perecin et al., 2022). The primary uses of Apolymers proved that scientists recognized their significant benefits early on, such as their mechanical strength and biocompatibility—properties still highly sought after in modern medical applications. Medicine has witnessed significant advancements since humans began using metals to treat bone injuries around 2000 BC. These uses have evolved over time to form a crucial foundation in modern orthopedic surgery and medicine. Metal implants and prosthetic limbs have contributed to improved joint replacement techniques, helping many patients regain mobility and improve their quality of life (Vallejos et al., 2022).

Later, goose`s feathers used to repair blood vessels, reflecting the medical innovation of those early periods. Some natural materials, such as feathers and natural polymers, also demonstrated the ability to help restore blood vessel function. By the beginning of the 19th century, metals had become

a key component in fracture treatment, following the expansion of plates`s metallic, screws besides bolts that delivered support in addition stability to skeletons during healing.

Spaghetti western medication publicly entered Nigeria in 1860, following the establishment of the Sacred Heart Hospital in Abeokuta by Catholic missionaries. This event joked a major character in introducing modern health services towards country (Shan et al., 2022),In the 1930s, the expansion of the plastics industry led to the emergence of synthetic polymers, which opened up vast possibilities for their use in the medical field (Hiran et al., 2007a). These materials facilitated the development of new types of biomaterials with specific properties suited to various therapeutic applications. Their physical, chemical, and biological properties can be designed and controlled to suit diverse medical uses.

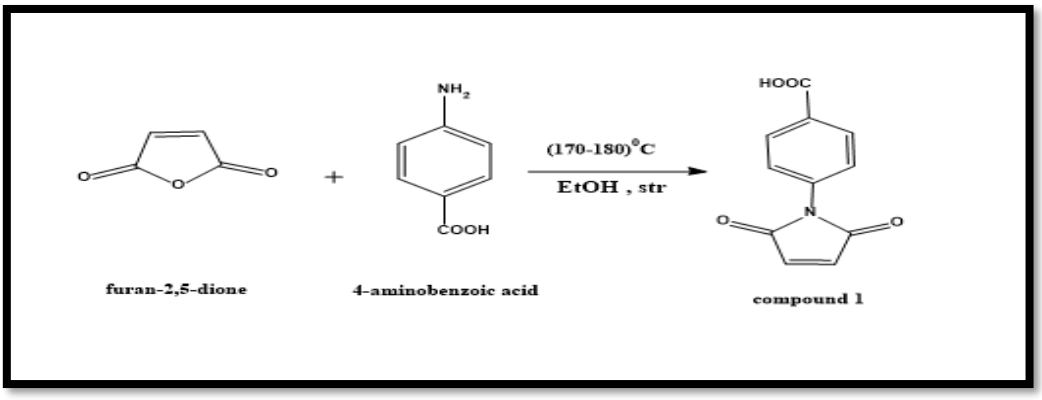
2. Part of the experiment

2.1. Chemicals and Methods

Mesalazine's (aminobenzoic acid-5) content was 99.5% (Fluka), and the Bruker FTIR spectra were captured at (500-4000) cm-1. The FT-IR instrument works by passing infrared radiation through or onto the sample (monomer, polymer). The chemical bonds absorb specific wavelengths depending on their nature. In practice and in the laboratory, the instrument is first switched on and the background reading is recorded. The sample is then placed on an ATR crystal. The scan is then performed within the 4000–4000 cm^{-1} range, and the signal is converted by Fourier transform into a spectrum that reveals absorption peaks. This spectrum is used to identify the functional groups in the prepared monomers and polymers. The positions and intensity of the peaks indicate the presence of bonds such as O–H, C=O, C–H, and others, which helps in determining the chemical structure of the resulting compounds. (Smith, B. C. 2011)

2.2. compound (1) preparation (Paliwal et al., 2007)

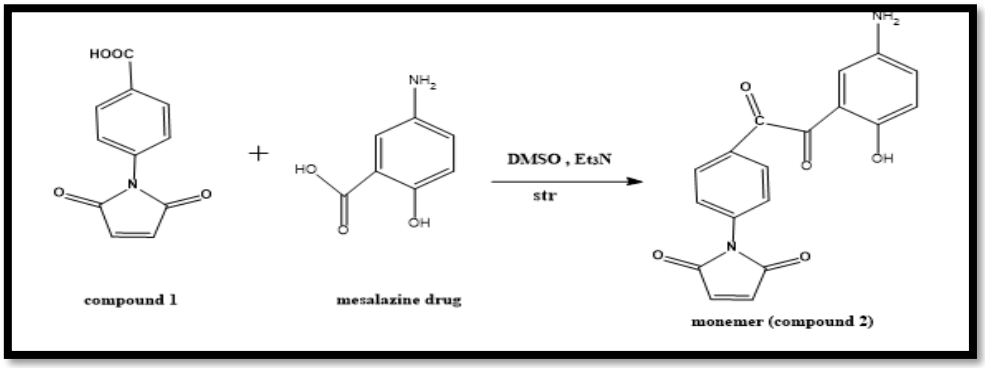
A glass stirrer was used to heat Nearly (0.65g) (0.0036mmol) of (4-ABA) Aminobenzoic acid-4 and (1.01g) (0.0022mmol) of 2,5-dione-Furan were placed in a 75 mL beaker and heated in the oil bath at(170–180)°C for 10min. pending A components were completely dissolved and a black creamy liquid was formed. Mixture stayed formerly permissible to cool for five minutes and subsequently recrystallized using ethanol (Scheme 1).



Scheme (1)

2.3. Monomer (2) preparation (Paliwal et al., 2007)

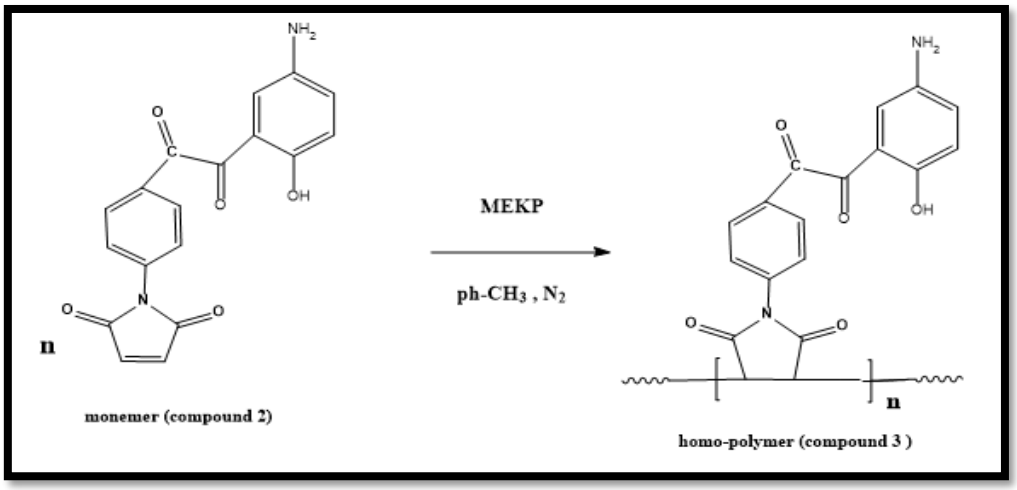
A 150 ml beaker was filled with Compound (1) (0.46gm, 0.0022mmole) besides 20ml of sulfoxidedimethyl (SODM). After adding 4.2gm (0.036 mmole) of thionyl chloride (SOCl2), the liquid was heated to 60 to 70 oC using a sensitive hot plate magnetic stirrer. (5-ABA) Mesalazine (0.582gm, 0.0026mmole) added after two hours, and the mixture was shaken for thirty minutes at 30 oC. The mixtures were allowed to precipitate after cooling in an ice bath, then they were filtered and dried. Scheme (2)



Scheme (2)

2.4. Preparation of homopolymer compounds (3) (Sulaiman et al., 2018)

A 50ml flask`s round with two open neck was filled with (0.22 g) (0.00049 mmole) of monomer`s (molecule2), 10ml Toluene, and two drops of methylethylketone peroxide (MEKP). After that, the flask was sealed tightly and heated to 90 degrees Celsius in a water bath. Next, one of the flask nozzles released the nitrogen gas. Following a two-hour reaction, the solvent evaporated, the precipitate was filtered, cleaned with ether, and dried in an oven heated to degree's 50 Celsius . Scheme (3).

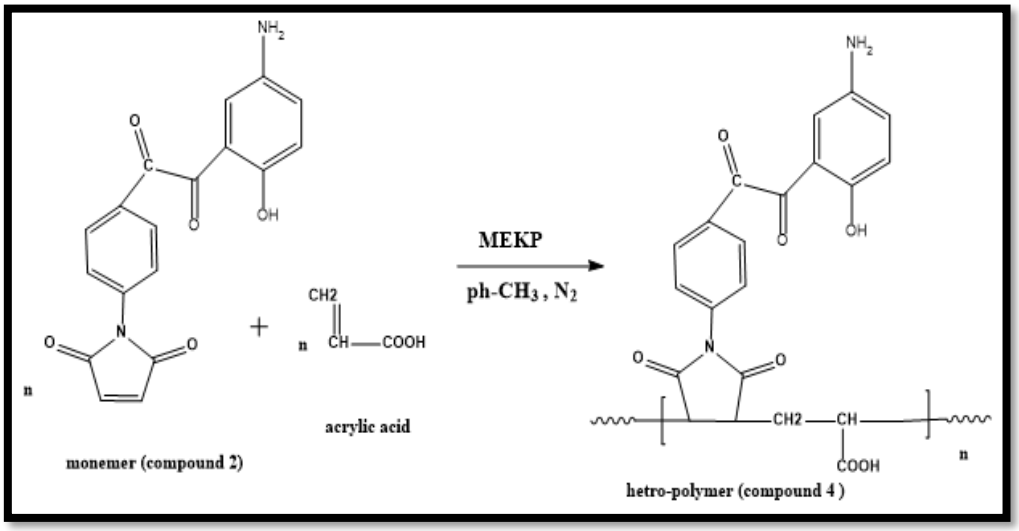


Scheme (3)

2.5. Preparation of heteropolymer compounds (4) (Sulaiman et al., 2018)

A 50ml flask`s round with two open neck was filled with Two Necks of (compound 2), (22gm, 0.00049 mmole), 10ml Toluene, then(0.032g) , (0.00044mmole of monomer(Acrylic Acid). The flask existed strongly wrapped and kept in Steam bath at 90ºC. After adding 2 to 3drops of

methylethylketone peroxide(MEKP), one from the flask nozzles was filled with nitrogen gas. The precipitate was filtered, cleaned with Ether,besides become dry in oven set at 50°C after the solvent evaporated during the two-hour reaction. Scheme (4).



Scheme (4)

2.6. Activity Biological (Al-Shammari et al., 2016; Mageed et al., 2025)

2.6.1. Maintenance of cell cultures

Colon cancer The cell lines were maintained Cubicles cultured in(RPMI-1640)medium improved with10% fetal bovine serum(FBS), with addition (100 units/ml) of penicillin and 100µg/ml of streptomycin. After a trypsin-EDTA pass-through, the cells were incubated at 37°C and re-cultured twice weekly when they reached approximately 80% confluence.

2.6.2. Cytotoxicity Test

A cytotoxicity test (MTT) was performed using 95-well plates to assess the cytotoxicity of the tested substances. Cubicles be present sown at density of (1×10^4) cells per well besides gestated for 24h. or until a nearly complete cell layer was formed, after which they wide-open to constituents under investigation.

After 72h. of management, the middle was disinterested and 28.0µL of 2.00mg/mL (MTT)solution was additional. The cubicles were then incubated at 37°C for 2.5 hours to measure their viability. Subsequently, 130 µL of dimethyl sulfoxide (DMSO) was added to dissolve the crystals formed after the MTT solution was removed,The samples were then mixed and incubated again at 37°C for 15 minutes. The measurement was then performed using a microplate reader at a wavelength of 492 nm, with triplicates,The cytotoxicity ratio, or the degree of cell growth inhibition, can be calculated using the following equation:

$$\text{Toxicity } \% = \frac{O-N}{N} \times 100$$

N = Optical density of the experimental sample (Test)

O = Optical density of the control group (Control)

2.6.3. Antioxidant Activity Assessment Using the DPPH Method

The antioxidant capacity of compound (X) was assessed using the DPPH stable free radical assay with minor modifications according to references (Al-Shammari et al., 2016; Mageed et al., 2025). The sample's ability to scavenge free radicals using substance (X) was measured.

The model was mixed with 450.0µL of (DPPH) solution, formerly absolute ethanol (100%) was added to bring the volume of the mixture to 1 mL. Ascorbic acid at a concentration of 10 µg/mL was used as a positive control.

The models were then incubated with the control solution at room temperature and away from light for 30 minutes. The absorbance was then measured at a wavelength of 517 nm.

The scavenging activity was calculated using the following equation.:

$$Scavenging\text{i}\% = \frac{Absorbance\ \text{io}ficontrol - Abosrbanceiofisample}{Absorbance\ \text{io}ficontrol} \times \text{i}100\%$$

3. Results and Discussion

3.1. FT-IR Spectrum

In addition to the absorption bands of C=C–$H_{(amide)}$ at (3100.451cm^{-1}), C=$O_{(carboxylic\ acid\ group)}$ at (1705.360 cm^{-1}), C–(N–C) at (1380.011)cm^{-1}, and(C–O)at(1175.011cm^{-1}), a broad absorption band is observed for the (O–H) group in the carboxylic acid within the range of 3500–3102 cm^{-1}. Figure 2 expression (FT-IR) spectrum for compound (1).

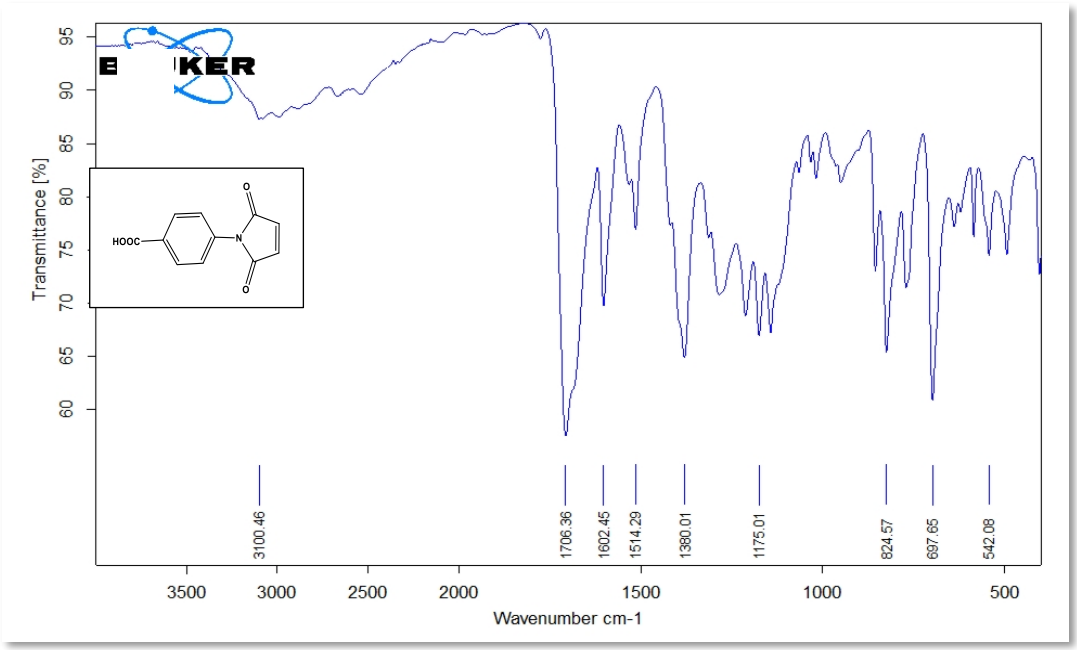


Figure 2. FT- I.R for Compound`s (1).

3.2. Activity Biological

Colorectal cancer is a popular term used to describe malignant tumors in the large intestine and rectum. These cancers are regarded as a single disease despite their heterogeneity in molecular makeup and treatment.In the present investigation, we evaluated the degree to which drug-loading compounds (3) and (4) prevented colon cancer cell lines from proliferating. According to cytotoxicity evaluations, compounds (3) and (4)This strategy might be equitable and favorable option of developing an effective medicine delivery system in targeted relaxing applications against colon cancer. The results also showed that the IC50 value of compound (3) was significantly lower compared to both the activated apoptosis alleyway and the purified drugs (IC50 = 18.33). The results of the investigation suggest that compound (3) may have medical applications and offer a helpful chemotherapeutic formulation.

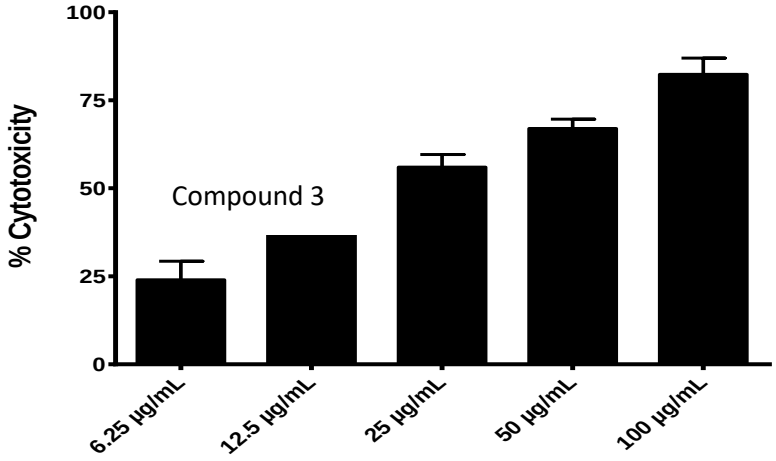


Figure 3. Compound (3) cytotoxic Colon Cancer Cells (IC50 is 18.33).

4. Conclusions

novel maleimide-based homo- and heteropolymers containing 4-aminobenzoic acid and acrylic acid units were successfully synthesized and characterized. FT-IR analysis confirmed the formation of the targeted structures through the appearance of characteristic functional group bands. The prepared polymers exhibited promising therapeutic properties, while compound (3) demonstrated significant antiproliferative activity against colon cancer cell lines. These findings suggest that the synthesized polymeric system may serve as a potential controlled drug delivery platform for future colon cancer treatment applications.

5. References

Al-Shammari, A. M., Salman, M. I., Saihood, Y. D., Yaseen, N. Y., Raed, K., Shaker, H. K., Ahmed, A., Khalid, A., & Duiach, A. (2016). In vitro synergistic enhancement of Newcastle Disease Virus to 5-fluorouracil cytotoxicity against tumor cells. *Biomedicines*, *4*(1), 3.

De Smedt, S. C., Demeester, J., & Hennink, W. E. (2000). Cationic polymer based gene delivery systems. *Pharmaceutical Research*, *17*(2), 113–126.

Duncan, R., & Vicent, M. J. (2013). Polymer therapeutics-prospects for 21st century: the end of the beginning. *Advanced Drug Delivery Reviews*, *65*(1), 60–70.

Dunn, R. L., & Ottenbrite, R. M. (1991). *Polymeric drugs and drug delivery systems*. ACS Publications.

Ghasemiyeh, P., & Mohammadi-Samani, S. (2021). Polymers blending as release modulating tool in drug delivery. *Frontiers in Materials*, *8*, 752813.

Govindarasu, M., Abirami, P., Alharthi, S. S., Thiruvengadam, M., Rajakumar, G., & Vaiyapuri, M. (2022). Synthesis, physicochemical characterization, and in vitro evaluation of biodegradable PLGA nanoparticles entrapped to folic acid for targeted delivery of kaempferitrin. *Biotechnology and Applied Biochemistry*, *69*(6), 2387–2398.

Hiran, B. L., Paliwal, S. N., Chaudhary, J., & Meena, S. (2007a). Preparation, polymerization and characterization of some new maleimides. *Journal-Indian Chemical Society*, *84*(4), 385.

Paliwal, S. N., Hiran, B. L., Chaudhary, J., & Meena, S. (2007b). Preparation, polymerization and characterization of some new maleimides. *Journal-Indian Chemical Society*, *84*(4), 385.

Kiran, P., Khan, A., Neekhra, S., Pallod, S., & Srivastava, R. (2021). Nanohybrids as protein-polymer conjugate multimodal therapeutics. *Frontiers in Medical Technology*, *3*, 676025.

Mageed, F. A. R., Mueen, A. A., Omran, Z. T., Heriz, M. H., Al-Jabbar, S. A., Al-Bahrani, H. A., & Kazemi, M. (2025). Sustainable Synthesis of 2, 4-Diarylquinoline Derivatives Using Recyclable BiFeO3 Nanocatalyst in Ionic Liquid. *Journal of Organometallic Chemistry*, 123792.

Niculescu, A.-G., & Grumezescu, A. M. (2021). Polymer-based nanosystems—A versatile delivery approach. *Materials*, *14*(22), 6812.

Nyamweya, N. N. (2021). Applications of polymer blends in drug delivery. *Future Journal of Pharmaceutical Sciences*, *7*(1), 18.

Perecin, C. J., Sponchioni, M., Auriemma, R., Cerize, N. N. P., Moscatelli, D., & Varanda, L. C. (2022). Magnetite nanoparticles coated with biodegradable zwitterionic polymers as multifunctional nanocomposites for drug delivery and cancer treatment. *ACS Applied Nano Materials*, *5*(11), 16706–16719.

Saleh, N., Elshaer, S., & Girgis, G. (2022). Biodegradable polymers-based nanoparticles to enhance the antifungal efficacy of fluconazole against Candida albicans. *Current Pharmaceutical Biotechnology*, *23*(5), 749–757.

Shan, P., Lu, Y., Lu, W., Yin, X., Liu, H., Li, D., Lian, X., Wang, W., Li, Z., & Li, Z. (2022). Biodegradable and light-responsive polymeric nanoparticles for environmentally safe herbicide delivery. *ACS Applied Materials & Interfaces*, *14*(38), 43759–43770.

Shariatinia, Z. (2021). Big family of nano-and microscale drug delivery systems ranging from inorganic materials to polymeric and stimuli-responsive carriers as well as drug-conjugates. *Journal of Drug Delivery Science and Technology*, *66*, 102790.

Smith, B. C. (2011). Fundamentals of Fourier Transform Infrared Spectroscopy (2nd ed.). Boca Raton, FL: CRC Press.

Sulaiman, G. M., Jabir, M. S., & Hameed, A. H. (2018). Nanoscale modification of chrysin for improved of therapeutic efficiency and cytotoxicity. *Artificial Cells, Nanomedicine, and Biotechnology*, *46*(sup1), 708–720.

Upadhya, R., Kosuri, S., Tamasi, M., Meyer, T. A., Atta, S., Webb, M. A., & Gormley, A. J. (2021). Automation and data-driven design of polymer therapeutics. *Advanced Drug Delivery Reviews*, *171*, 1–28.

Vallejos, S., Trigo-López, M., Arnaiz, A., Miguel, Á., Muñoz, A., Mendía, A., & García, J. M. (2022). From classical to advanced use of polymers in food and beverage applications. *Polymers*, *14*(22), 4954.

Vogelstein, B., & Kinzler, K. W. (2004). Cancer genes and the pathways they control. *Nature Medicine*, *10*(8), 789–799.