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Biologically active sulfur-containing polyamides as promising anticancer materials

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ABSTRACT

Thiazol-based molecules have practically infinite biological implementation. Today, there are many medical applications for compounds containing the thiazole moiety owing to their presence in most clinically applied anticancer drugs, such as dasatinib, dabrafenib, ixabepilone, patellamide A and epothilone. In this study, the polycondensation, of a new group of thiazole-containing polyamides with the formulas PA_{1-4} was carried out by the interaction of 2-aminothiazole diphenyl sulfide and variable diacid chlorides in dimethyl formamide in the presence of potassium carbonate anhydrous as a catalyst. Fourier transform-infrared spectroscopy (FTIR) was initially used to figure out the PA_{1-4} structures, which were further characterized using solubility, gel permeation chromatography (GPC), X-ray diffraction analyses (XRD) and scanning electron microscopy (SEM). The solubility results revealed that the presence of heteroaromatic thiazole ring units and sulfur content in the polyamides main chain, made the solubility easier as it increases the chain packing distance. From the values of average molecular weight, it was clear that all synthesized polyamides have almost the same chain length which ranged from 37,561.80 to 39,827.66. Moreover, the thermogravimetric analysis (TGA) confirm that PA_{1-4} were thermally stable even at high temperatures especially the polyamides which were synthesized from aromatic diacid chlorides. Furthermore, the newly synthesized polyamides were investigated for their antimicrobial properties against different species of Gram-positive and Gram-negative bacteria and also against different fungi. The results revealed that compound PA_2 showed the highest antibacterial activity. Also, their inhibitory activity against breast carcinoma cells (MCF-7 cell line) and colon carcinoma cells (HCT cell line) was evaluated. It was clear that there was an enhancement in the anticancer activity for the synthesized polyamides owing to the presence of the thiazole moiety as well as sulfur linkage. According to the results of the 50% inhibitory concentration (IC50), the synthesized polymers were found to be more active against the MCF-7 cell line than the HCT cell line.

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1. Introduction

Polyamides are an essential category of polymers that have an amide bond (NH-C=O) along the polymer chain. They are produced by the reaction of diamine monomers with diacid chlorides, and hydrochloric acid is the byproduct [1]. Polyamides are known as high-performance materials in the fields of industry, electronics, and aerospace applications, referring to their amazing chemical, thermal, and mechanical resistance [1] [2–4]. Nevertheless, one of the disadvantages of polyamides is that they usually present limited solubility in most organic solvents, making them difficult or expensive to utilize in many applications. Although polyamides are thermally stable, researchers have attempted to improve their solubility and processability through the inserting of various moieties in the backbone skeleton of the polymers or the integration of side chain bulky groups into the polymer structure [3,5]. Sulfur-containing polymers have attracted the attention of researchers due to their interesting properties. Rezania J. et al. reported that some novel sulfur-containing polyamides based on thiazole rings exhibit high-performance materials, soluble polymers, and mild thermal stability [3]. Also, thienothiophene units along the polymer backbone will achieve the goal with electrochemical and optical properties that can be used in photovoltaic applications [4]. In addition,

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the synthesis of a polyamide-based dithiophenylidene cyclohexanone moiety was reported by Hussein MA. These new polyamides were further used as candidates for healthcare and environmental fields [1].

Amide-containing heterocycles are reported as a class of compounds displaying extensive biological activities that consist of a large number of natural and synthetic products and are the main building blocks for the manufacture of bioactive compounds in pharmaceutical drug design and the agrochemical industry [6–8]. Thiazoles are an adaptable heterocycle present in several drugs that are used in the cure of cancer [9]. Xiao X. X. et al. discussed the synthesis of novel benzothiazole derivatives that displayed potent anticancer activity against HCT-116, MCF-7, U87 MG, and A549 cell lines [10]. Thiazole-containing compounds also show various pharmacological actions, including antimicrobial, anti-inflammatory, anticonvulsant, and antidiabetic activity [11–13]. It was reported that thiazole-containing polyamide derivatives show fire-retarding properties, electronic conductivity, chemical resistance, high thermal performance, high mechanical characters, photo-curing characters, conductivity, and biological activity [3,14]. Consequently, the current survey highlights a wide view of the preparation and biological actions of materials having a thiazole moiety [15].

In addition to the properties mentioned above, polyamides can also exhibit various antimicrobial activities. For example, Hammed H.A.M. Hassan et al. synthesized new polyamides containing aromatic rings that showed remarkable antibacterial activities against a gram-positive bacterium, S. pneumoniae, and a gram-negative bacterium, P. aeruginosa [16]. So, polymeric antimicrobial agents have become a subject of intense research owing to their promising advantages over monomeric forms [17,18]. In view of all the properties mentioned and owing to the promising activity of this class of sulfur-containing polyamides based on the thiazole ring, this encourages us to synthesize and biologically evaluate the anticancer efficiency of a series of novel polyamides containing the thiazole moiety.

2. Experimental method

2.1. Measurements

Both monomers' melting temperatures were measured with the use of a digital image processing-powered automated melting point device. A Perkin-Elmer infrared spectrophotometer was used to get the Fourier transform infrared spectra (FT-IR). All spectra were collected between 600 and 4000 cm^{-1} in wavenumber. The ^{1}H NMR and ^{13}C NMR spectra, obtained with $CDCl_3$ and DMSO-d_6, respectively, were recorded on a Bruker Advance 850 MHz spectrometer. The produced polymers solubility characteristics were estimated under the same conditions with numerous solvents: dimethylformamide (DMF), dimethyl sulfoxide (DMSO), benzene (C_6H_6), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), acetone, formic acid and concentrated sulfuric acid. The molecular weights were evaluated by gel permeation chromatography (GPC) on an Agilent-GPC. G-1362A was the refractive index detector with 100-104-105 A◦. For this experiment, polystyrene was used as a standard, and THF was used to elute the columns at a flow rate of 1 mL min^{-1}. Flow rate = 2,000 mL min^{-1}, injection volume = 100,00 L, and sample concentration = 1.000 g L^{-1} were the operating parameters for the GPC apparatus. Ni-filtered Cu K radiation at 40 kV voltages and 40 mA current across a 2 range of 5° to 80° in increments of 0.02° and a sampling speed of 4.0000 deg/min was used by the Rigaku Ultima IV X-ray diffractometer to estimate X-ray diffraction patterns.

The TGA thermal performance of the new polyamides was displayed using a DTG-60 H thermal analyzer. The tests were achieved by placing the samples on a Platinum Macro Pan with a heating rate of 10◦C/min within the temperature range of 30–800◦C under a nitrogen atmosphere.

The surface morphology character of the novel polyamides was determined by field emission scanning electron microscopy (FESEM) (Jeol JSM-7600F) using the Quanta, FEI instrument.

2.2. Reagents and solvents

Diphenylsulfide, chloroacetyl chloride from (Merck) and used as received. Anhydrous aluminum chloride from (Sigma-Aldrich). Anhydrous potassium carbonate, anhydrous sodium acetate, sodium hydrogen carbonate, and thiourea were obtained (Fluka). Dry dimethyl formamide (DMF) was received from (Fisher Chemical) and dried by molecular sieves 5Å. Dry carbon disulfide was received from (Merck), and dried by molecular sieves 5Å. Various diacid chlorides, including both aliphatic & aromatic types (adipoyl chloride, sebacoyl chloride, terephthaloyl chloride, and isophthaloyl chloride) from Sigma-Aldrich, 97%, were also used without any purification. Absolute methanol and ethanol are 99% (Fisher Chemical). Both acetone and concentrated hydrochloric acid were from BDH. All stated chemicals (solvents and reagents) were utilized exactly as they were

purchased, with no extra purification because all were of high purity (99–97%).

2.3. Synthesis of monomers and polymers

2.3.1. Synthesis of 4-bis-chloroacetyl-diphenylsulfide (M1)

Chloroacetyl chloride, 1.59 ml (0.002 moles), was dissolved in 50 ml of dry carbon disulfide and poured into 1.6 ml (0.001 moles) of diphenyl sulfide. The mixture was then cooled over an ice bath and anhydrous aluminum chloride 5.34 g (0.004 moles) was added drop-wise with continuous stirring for 5 h. At the end of the reaction time, all the carbon disulfide was evaporated, and then 60 ml cold hydrochloric acid was poured into the residue. The resulting product was then filtered, washed with distilled water, and re-crystallized to obtain an orange precipitate with a melting point: 101–103 °C [19].

The FT-IR data of this monomer showed absorption bands at 1580 cm^{-1} for (C=C) and at 1676 cm^{-1} for (C=O) of the chloroacetyl group (Figure S1).^{1}H NMR spectra (850 MHz, CDCl3, δ) = 7.4–7.9 (m, 8 H of aromatic), 4.6 (s, 4 H of CH_2 chloroacetyl) (Figure S2). 13C NMR (850 MHz, CDCl3, δ) = 190.24, 141.98, 132.99, 130.82, 45.76 (Figure S3).

2.3.2. Synthesis of 4-bis-2-aminothiazole-diphenylsulfide (M2)

In a 250 ml round flask attached to a condenser, a mixture of 1 g (0.003 moles) M1 and 0.47 g (0.006 mol) thiourea was dissolved in 20 ml absolute ethanol and refluxed with stirring for 6 h. Then, a 25 ml of cold sodium acetate solution (20%; 100 ml) was added to the mixture. The precipitated material was then collected, filtered, and recrystallized by ethanol to give yellowish crystals with a melting point: 240 °C [20].

The FT-IR data of this monomer give rise to a band at 1615 cm^{-1} attributed to C=N stretching vibration of the thiazole ring and also two bands were observed at 3311–3123 cm^{-1} corresponding to the primary amine group (Figure S4). ^{1}H NMR spectra (850 MHz, DMSO-d_6, δ) = 7.7–7.3 (m, 8 H of aromatic and 2-CH-S) and at 6.9 (s, 4 H, NH_2) (Figure S5). 13C NMR (850 MHz, DMSO-d_6, δ) = 168.77, 149.44, 134.43, 133,79, 131.28, 127 (Figure S6).

2.3.3. Synthesis of polyamides PA_{1-4} derivatives

2.3.3.1. Polymerization general process.. A solution of 0.004 moles of M2 dissolved in 15 ml dry DMF was added in a dry 250 ml three-necked round-bottom flask attached to a condenser inside a system saturated with dry N_2 inlet/outlet. 0.5 g of anhydrous potassium carbonate was added to the solution as a catalyst. Then 0.004 moles of several aromatic and aliphatic diacid chlorides dissolved in 15 ml of dry DMF, were added to the mixture in a small portion with vigorous stirring for 10–12 h. at room temperature. The reaction mixture was then cooled in an ice bath to obtain yellowish-brown precipitates (PA_1, PA_2, PA_3, and PA_4). The products were collected by filtration, washed with diluted $NaHCO_3$ (5%, 100 ml), then with distilled water, ethanol, and acetone to eliminate all unreacted monomers and biproducts. PA_1, (83% yield – yellowish powder), PA_2, (85% yield – yellowish powder), PA_3, (88% yield – brown powder), and PA_4 (82% yield – brown powder) were obtained. Finally, the obtained polymers were dried at 70 °C in reduced pressure (1 mmHg) for two days [21]. The FT-IR spectra for all synthesized polyamides displayed typical absorption bands in the range of 3120–3124 cm^{-1} attributed to the NH stretching mode. In addition to other typical absorption bands in the range of 1610 – 1620 cm^{-1} corresponding to stretching vibrations of the C=O group.

2.4. Antimicrobial screening

Each bacterial strain's cell suspension was made from 48-hour-old cultures cultivated on nutrient agar in sterilized water [22,23]. On a 9-centimeter-diameter Petri plate, 1 mL of cell suspension was added, and then 15 mL of NA was added. The inoculum was mixed by gently shaking the dish. Both the tested polymer solution and ampicillin solution (0.1 and 0.05 mg/mL in DMSO) were impregnated onto sterile 5-mm filter paper discs (Whatman). Additional discs were impregnated with the solvent and utilized as a control (DMSO). After drying for 1 hour, the impregnated discs were put in the middle of each plate. The seeded plates were incubated for 24–48 hours at 30 ± 3 °C. The triplicate sets' inhibition zone radii (millimeters) were measured, and the findings are shown later in (Table 4).

2.4.1. Antifungal screening

From 2- to 5-day-old cultures of the test fungi grown on potato dextrose agar or sabouraud agar medium (SDA), a spore suspension in sterile water was made [22,23]. The spore concentration at the end was 5×10^5 spores/mL. A sterile Petri plate 9 cm in diameter was filled with 15 mL of the growth media and injected with 1 mL of the spore suspension. To homogenize the inoculum, the plate was gently shaken. The antifungal activity of the polymers was determined using the standard agar disc diffusion method, as described below: The test polymer and dermatin solutions (0.1 or 0.05 mg/mL in DMSO) were impregnated onto sterile 5-mm filter paper discs (Whatman). In addition, control discs containing the solvent (DMSO) were employed. Once the impregnated

discs had dried for an hour, they were placed in the center of each plate. The plates were seeded, and then incubated for 5 days at 30 ± 3 °C. Measurements of the inhibition zone radii (in millimeters) were taken at regular intervals during the incubation period. Using duplicate sets, we were able to observe statistically significant differences between treatments (Table 4).

2.4.2. Bacterial cell culturing

The National Research Center in Cairo supplied *E. coli* O157:H7 for use as a model for assessing antibiotic activity. For the purpose of assessing antibacterial efficacy, bacterial cells were grown on nutritional agar (Sigma-Aldrich -70,148) supplemented with 1 g/L beef extract, 5 g/L peptones, 2 g/L yeast extract, 2 g/L sodium chloride, and 15 g/L agar in distilled water. Nutrient agar media plates were made, sterilized, and chilled. These plates were used to swab bacterial cultures after they had hardened.

2.4.3. Antibacterial assessment

Polymers PA_{1-4} were synthesized, and their antibacterial capabilities were tested using a colony-forming unit (CFU) count assay [24]. About 0.1 g/mL of samples were placed in each test tube containing 9 mL of liquid medium (Nutrient Broth). Then, a tube containing 9 ml of liquid medium was incubated at 35 °C for 24 hours after 1 ml of *E. coli* O157:H7 was added to the tube. Samples were serially diluted and then plated on nutrient agar. The number of colonies was determined by collecting samples at two different times (12 h and 24 h) and counting the results using a colony counter. There were three separate runs of the experiment, and the average findings are reported in (Table 5).

2.5. Anti-cancer activity

Skehan et al. used an in vitro experiment to determine the cellular toxicity of polymer samples [25]. All of the tested samples were subjected to multidose tests on the breast cancer cell line (MCF-7) and the colon carcinoma cell line (HCT). All tested samples were utilized at various concentrations (0.0, 5.0, 10.0, 20.0, 30.0, 40.0 and 50 g/ml). 100 l of minimal essential medium (MEM) was dispensed in 96-well flat bottomed plates, and cells were plated in the 96-multiwell plate (10^4 cell/well) for 24 hours prior to treatment with the compounds to enable cell adhesion to the plate wall. The products were then applied to the wells in triplicate for each individual dosage, and the monolayer cells were cultured over the chemicals for 48 hours at 37°C and in a 5% CO_2 environment. In this case, Sulfo-Rhodamine-B staining was performed after the cells had been fixed, washed, and allowed to adhere for 48 hours. The surplus stain was removed with acetic acid, and the attached stain was restored using Tris-EDTA buffer. To identify the IC_{50}, a survival curve was constructed for each tumor cell line and plotted against the proportion of cells that survived in response to the concentration of the drug.

3. Result and discussion

Polyamide polymers have been used in various fields of application. This encouraged us to synthesize four new series of polyamide derivatives possessing thiazole rings and sulfur linkages in the polymer backbone using the polycondensation method. Common characterization techniques helped to reveal the structures of the new polyamides.

3.1. Synthesis of monomers

First, the monomer 4-bis-chloroacetyl-diphenylsulfide (M1) was synthesized through the reaction of chloroacetyl chloride with diphenyl sulfide in dry carbon disulfide throughout the using of the most interesting F.C. catalyst (anhydrous aluminum chloride). The monomer 4-bis-2-aminothiazole diphenyl sulfide (M2) was then prepared by refluxing a mixture of M1 and thiourea in absolute ethanol for 6 h., in which sodium acetate was added to the mixture after completion of the reaction (Figure 1). The melting points for the synthesized monomers have been measured and the result was in agreement with the literature one [19,20]. The chemical structures of two monomers were elucidated by various spectral analysis including FT-IR, ^{1}H and ^{13}C NMR, that confirmed the proposed structures as presented in the experimental section.

3.2. Polymer synthesis

A novel series of polyamides containing thiazole moiety and sulfur content PA_{1-4} have been synthesized using the polycondensation procedure via the interaction between M2 and different diacid chlorides from both types (aromatic & aliphatic) in DMF as presented in (Figure 2). The synthesis of polyamide polymers generally achieved through the condensation of various aliphatic and aromatic diamines with diacid chlorides particularly in DMF, NMP or N,N′-DMAc which are classified in general as polar solvents [15,26].

The chemical structures of these new polymers were established by FT-IR analysis as presented in the experimental section and as illustrated in (Figure 3).

The new polyamide derivatives were also characterized by different standard methods, including solubility

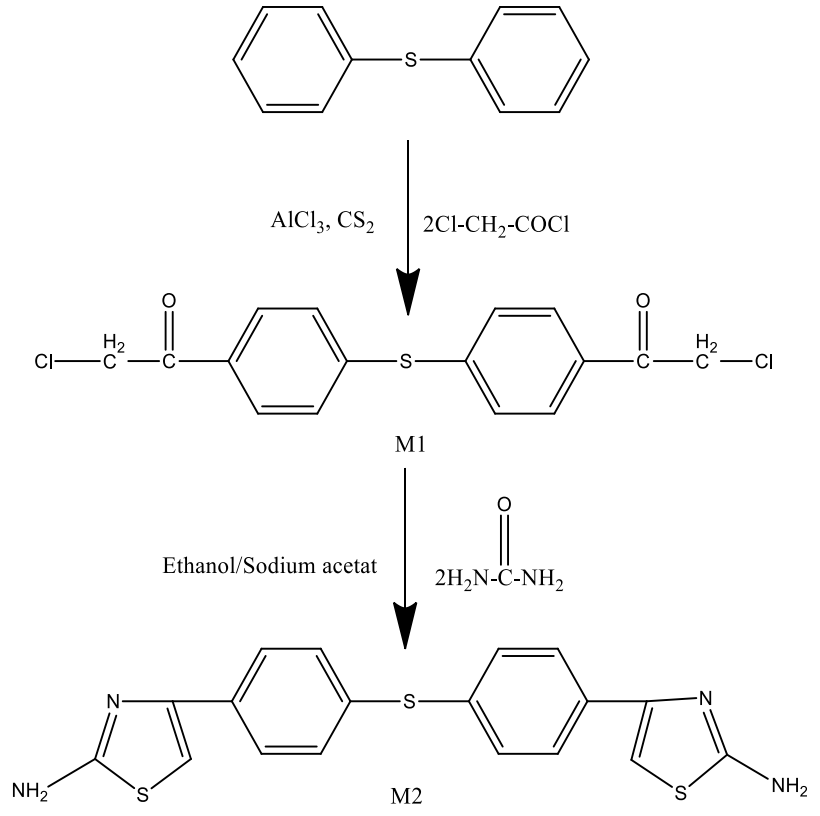

Figure 1. Synthesis of bis-4-chloroacetyl-diphenylsulfide M1 and 2-aminothiazolediphenylsulfide M2 monomers.

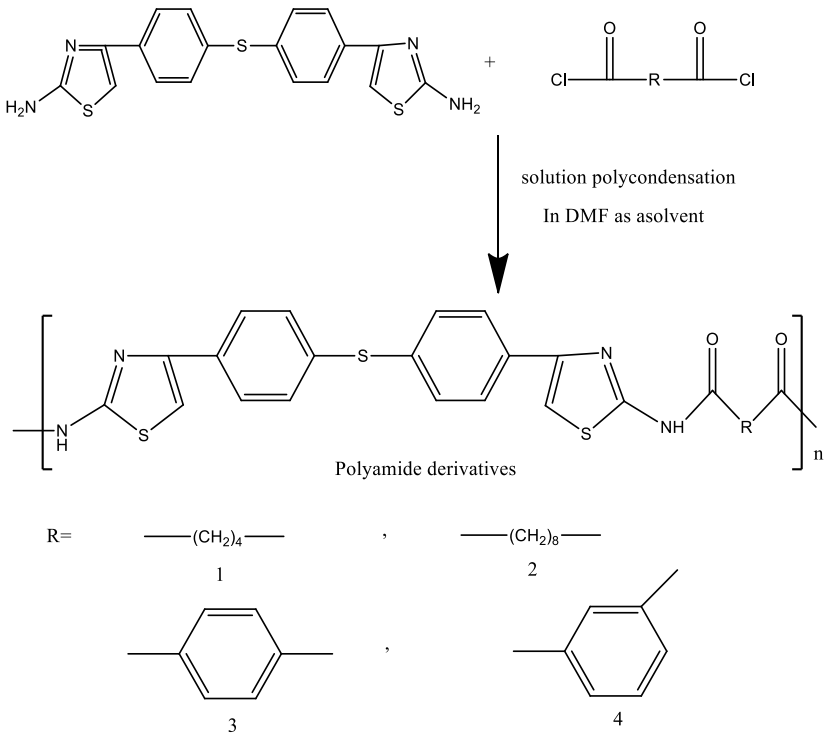

Figure 2. Synthesis of the polyamides PA_{1-4} derivatives.

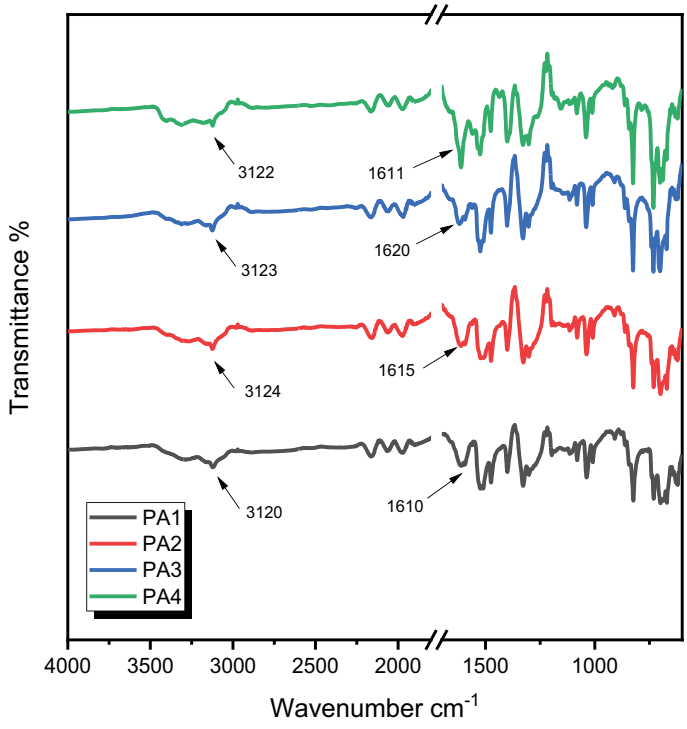

Figure 3. FTIR spectra of polyamide derivatives.

test, GPC molecular weight determinations, X-ray diffraction analysis, thermal analysis, as well as scanning electron microscopy.

3.3. Physical properties of the polymers

3.3.1. Solubility

Numerous selected organic solvents, including concentrated formic acid, concentrated sulfuric acid, acetone, benzene, chloroform, dichloromethane, dimethylformamide, dimethyl sulfoxide and tetrahydrofuran (THF), were employed to determine the room temperature solubility of the synthesized polyamide derivatives PA_1, PA_2, PA_3 and PA_4. All the polyamide derivatives solutions were prepared in the same conditions. The solubility behavior for the prepared polyamide derivatives in various organic solvents was displayed in (Table 1).

It is clear that the synthesized polyamides were utterly soluble in formic acid and concentrated sulfuric acid as a protonic solvent. In contrary, all derivatives displayed bad solubility behavior in benzene as non-polar solvents. In acetone, polyamides PA_{1-2} with aliphatic spacers were completely soluble, whereas polyamides PA_{3-4} with aromatic spacers are partially soluble. Moreover, all polymers were completely soluble in DMSO, DMF, THF. However, partially soluble in DCM, and chloroform as organic solvents. The presence of heteroaromatic thiazole ring units and sulfur content in the polyamides main chain made the solubility easier as it increases the chain packing distance; however, the inter-chain interactions like hydrogen bonding decrease [27].

3.3.2. GPC molecular weight determinations

The commonly utilized technique to examine the molecular weight is Gel Permeation Chromatography. The molecular weight values were conducted and calculated by using a computer program [28,29]. The values of the average number and weight average molecular weights, as well as polydispersity index (Mw, Mn, Pw and DPI) of polyamides were evaluated, and the results are illustrated in (Table 2).

From the values of average molecular weight (Mw), the results revealed that all cases (aliphatic and aromatic moieties) had almost the same chain length ranged from (37561.80 to 39,827.66) [29,30]. The synthesized polyamide PA3 provided the highest molecular weight, while PA1 had the lowest molecular weight.

3.3.3. Thermal properties

The thermal characteristics of sulfur-containing polyamide PA_{1-4} derivatives was evaluated by thermogravimetric analysis (TGA) under N_2 atmosphere and heating rate of 10 °C/min as seen in (Figure 4). Thermal stability

Table 1. Solubility characteristics of PA_1, PA_2, PA_3 and PA_4.

Sample	THF	DMF	Formic acid	$CHCl_3$	DCM	DMSO	Sulfuric acid	Benzene	Acetone
PA_1	+	+	+	+ –	+ –	+	+	–	+
PA_2	+	+	+	+ –	+ –	+	+	–	+
PA_3	+	+	+	+ –	+ –	+	+	–	+ –
PA_4	+	+	+	+ –	+ –	+	+	–	+ –

+ Soluble at room temperature.
+ – Partially soluble.
– Insoluble.

Table 2. The GPC results for PA_1, PA_2, PA_3 and PA_4.

		GPC results			
Sample	formula	[a]Mw	[b]Mn	[c]Pw	PDI
PA_1	$C_{24}H_{20}O_2S_3N_4$	37561.80	34002.78	~ 76	1.10
PA_2	$C_{28}H_{28}O_2S_3N_4$	38591.55	34458.24	~ 70	1.12
PA_3	$C_{26}H_{16}O_2S_3N_4$	39827.66	36090.80	~ 78	1.10
PA_4	$C_{26}H_{16}O_2S_3N_4$	38430.21	34985.01	~ 75	1.09

[a]Weight-average molecular weight.
[a]Number-average molecular weight.
[b]Average number of repeating units.

of the synthesized polymers was elaborated in the range 30–700 °C. The thermographs showed similar decomposition manner for all polyamide derivatives except PA4. The thermogravimetric curves displayed the loss of moisture accompanied solvents, with a weight loss in the range 1–5%. This weight loss observed from ambient temperature and to 268C for all derivatives except PA_4 at 213 °C. The values of T_{10}-T_{40} illustrated the temperatures of different weight losses at 10, 20, 30, and 40 %, as represented in (Table 3). The thermal degradation occurs in two successive decomposition steps. The first decomposition step starts at 316, 293, 264 °C and ends at 407, 372, 372 °C for PA_1, PA_2, and PA_3, respectively, while the second decomposition step starts 426 °C for all polyamides except PA_4 and ends at about 416 °C. On the other hand, only one polymer PA_4 displayed substantial separation between three degradation steps. The first decomposition step for this polyamides range from 230 °C to 330 °C while the second step starts at 416 °C and ends at 500 °C.

The latter step related to pyrolytic oxidation of carbon, carbon double bonds that separate from numerous bonds with the elimination of free shorter chains depend on the structure of these polymers and creation of char as end products [1,14]. The decomposition of this step occur more rapidly than the first one.

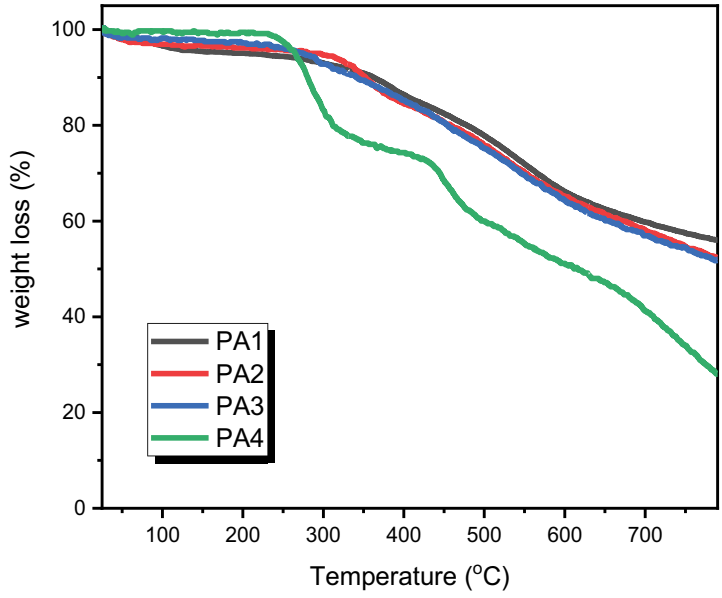

Figure 4. TGA curves of PA_1, PA_2, PA_3 and PA_4 in air-flow at a heating rate of 10 °C/min.

Table 3. Thermal properties of polyamide PA_1 - PA_4 derivatives.

	Temperatures for variable % of degradations (°C)[a]						
Sample	T_{10}	T_{20}	T_{30}	T_{40}	IDT[a] (°C)	PDT [b] (°C)	FDT [a] (°C)
PA_1	363	478	565	694	316.7	432.14	594.7
PA_2	352	459	551	673	293.1	190.12	594.7
PA_3	335	456	544	651	264.9	250.63	500
PA_4	280	312	443	499	230.4	224.69	500

[a]calculated from TGA.
[a]calculated from DTG.

The initial degradation temperature (IDT) is identified as the temperature at which degradation occurs31,32] [30]. The value of initial decomposition of the new polyamides occurs before T_{10} values, and the degradation step does not start before ~230 °C, this confirm that they were thermally stable even at high temperatures [1] according to the following order PA_1< PA_2< PA_3< PA_4. The final decomposition temperature (FDT) is the temperature at which any possible deterioration is virtually comprehensive [26,32,33]. The thermographs displayed the FDT for the aliphatic substituent polymers PA1 and PA_2 at about 594.7 °C and for aromatic substituent polymers PA_3 and PA_4 at approximately 500 °C. From the above data, it was concluded that the polyamides synthesized from aromatic diacid chlorides are more thermally stable than those created from aliphatic diacid chlorides [26,34].

3.3.4. X-ray diffraction analysis

Patterns of X-ray diffraction were investigated using an X-ray diffractometer of the RIGAKU ULTIMA IV model type (provided by Mannai Technical Services) throughout a temperature range of 5–80 degrees Celsius. The obtained data confirms the structure of the sulfur-containing polyamides PA_{1-4} as presented in (Figure 5).

The results revealed that all polymers are crystalline in nature; however, the degree of crystallinity differs owing to the polymer structure as measured by the connected aromatic or aliphatic spacers. In the diffraction spectrum, a few peaks are reasonable between crystalline and amorphous intervention. This indicates that there is a wide class of structures (C=O as a polar group as well as C=C bond levels), that cause some order between two approaching chains of the polymers [35]. Furthermore, the bulky heterocyclic rings throughout the main chain of the polyamides are possibly the primary reason of their crystallinity. PA_1

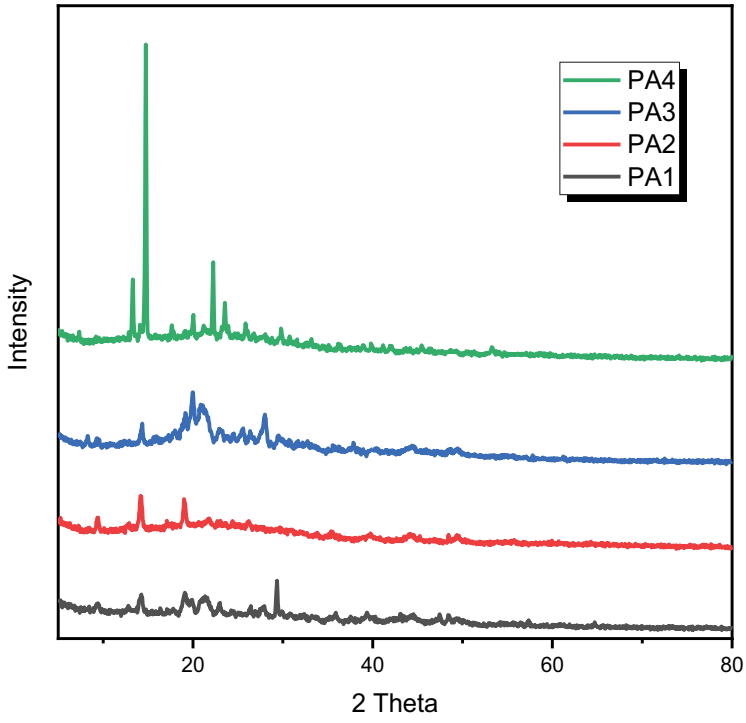

Figure 5. XRD of polyamides PA_{1-4} derivatives.

and PA_2 with aliphatic spacer offered crystalline structure owing to the methylene groups in the polymer chain, which increases their flexibility [36]. In contrast, the synthesized polyamides PA_3 and PA_4 containing aromatic spacer have a somewhat lower degree of crystallinity [21].

Some of the synthesized polyamides PA_1, PA_2, and PA_3 were studied by Field Emission Scanning Electron Microscope FE-SEM (Jeol JSM-7600F) using Quanta, FEI instrument in order to evaluate the morphological properties. The images illustrated that the three polymer surfaces are relatively analogous. The surface of PA_1 displayed that it involves of dust moistened with water (clay precise) in all higher and lower magnification. Alternatively, it shows wholly fussed cumulative spherical grains, which form a rock-like structure [14]. As illustrated in (Figure 6), with magnification X = 3000 and X = 30000.

3.4. Antimicrobial activities

The antibacterial properties of all synthesized polymers were evaluated against *Bacillus Cereus* and *S. aureus* as a Gram-positive bacteria and *E. coli* and *S. Marcescens* as some gram-negative bacteria. Also two species of fungi called *C. Albicans* and *A. flavus* were used for antifungal testing of the prepared polymers. All antimicrobial results have been illustrated in (Figure 7).

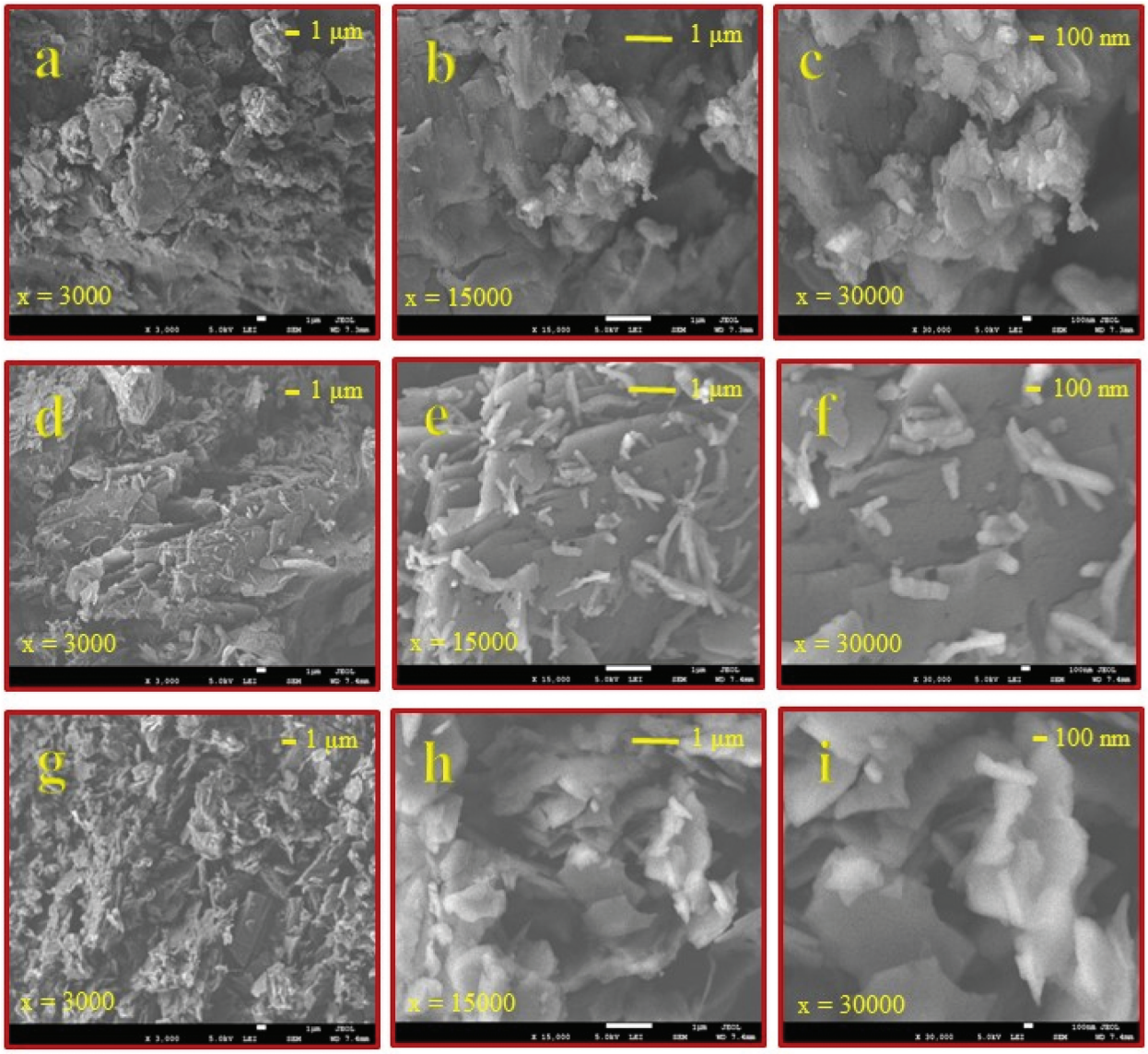

Figure 6. SEM images for PA1 (a-c), PA2 and e-f PA3 (g-i) at magnification x = 3000, 15000 & 30000 for each sample.

The inhibition area was introduced in mm and the antibacterial and antifungal activities were compared with the standard drugs *Chloramphenicol* and *Clotrimazole* respectively.

As shown in (Table 4), the tested compounds possessed variable antibacterial activity, in which the highest inhibitory effect against the selected bacteria was reported for compound PA_2. On the other hand, all synthesized polymers showed low antifungal activity against *C. Albicans* and *A. flavus*, with compound PA_4 that do not exhibit any activity against the selected fungi. Positive controls produced significant sized inhibition zones against the tested bacteria and fungi.

The results revealed that all tested compounds were found to be most effective against the gram-negative bacteria *E. coli* with *a* zone of inhibition ranging between 16 mm and 23 mm. On the basis of maximum inhibitory effect, the synthesized polymer PA2 show the highest activity against *E. coli* as shown in (Table 5).

3.5. Anticancer activities

The antitumor activities of prepared polymers were evaluated against breast carcinoma cells MCF-7, and colon carcinoma cells HCT according to Skehan *et al*. assay. The obtained results are displayed in (Figure 8) and (Table 6).

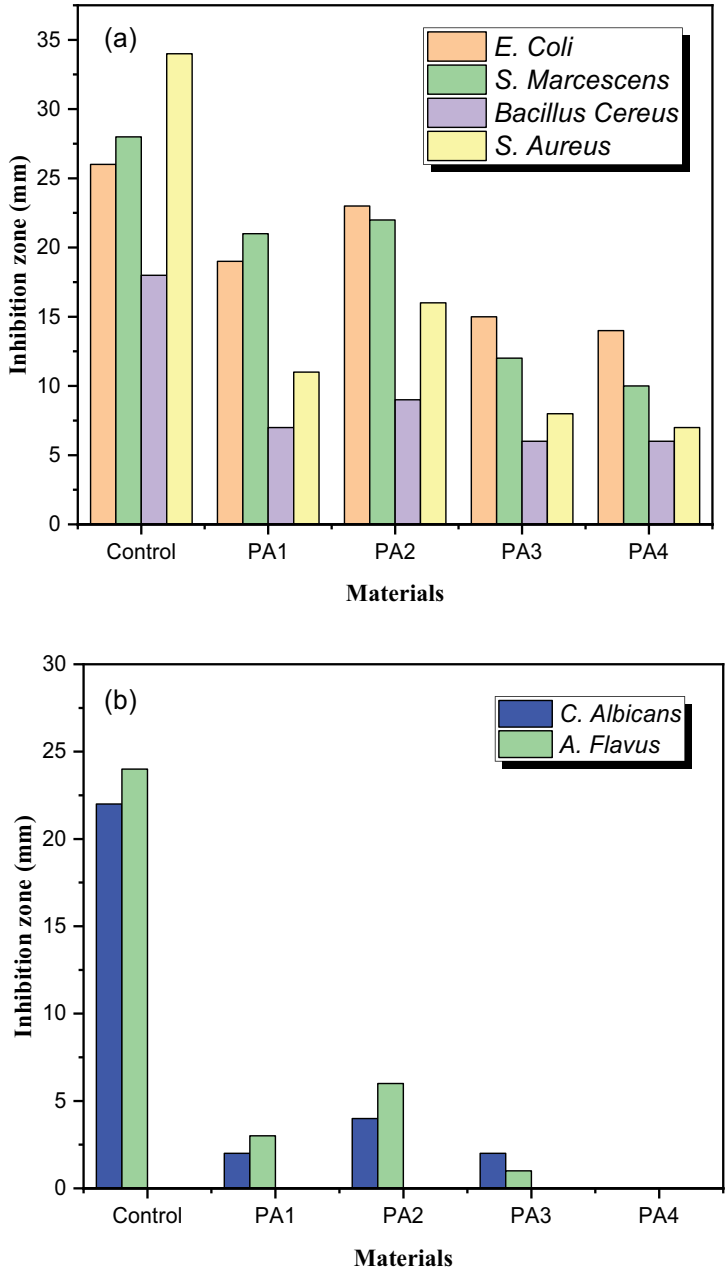

Figure 7. Antibacterial (a) and antifungal (b) diagrams for PA_{1-4} against the tested Gram (+) & Gram (-) bacteria and fungi.

Table 4. Antimicrobial screening of polyamide PA_1 - PA_4 derivatives against selected bacteria and fungi.

	Material Used/Inhibition zone (mm)				
Microorganism	Control	PA_1	PA_2	PA_3	PA_4
E. Coli	26	19	23	15	14
S. Marcescens	28	21	22	12	10
Bacillus Cereus	18	7	9	6	6
S. Aureus	34	11	16	8	7
C. Albicans	22	2	4	2	0
A. Flavus	24	3	6	1	0

* *Clotrimazole* and *Chloramphenicol* were used as control for antifungal and antibacterial activities respectively.

Table 5. Growth conditions and percent inhibition of E. coli in the presence of PA_{1-4}.

Material Used (Cfu/ml)	Incubation Time (h)		Reduction (%)	
	12 (h)	24 (h)	12 (h)	24 (h)
Control	70×10^6	93×10^6	0	0
PA_1	9×10^6	9×10^6	91	91
PA_2	5×10^6	5×10^6	95	95
PA_3	4×10^5	4×10^5	86	86
PA_4	8×10^5	8×10^5	82	82

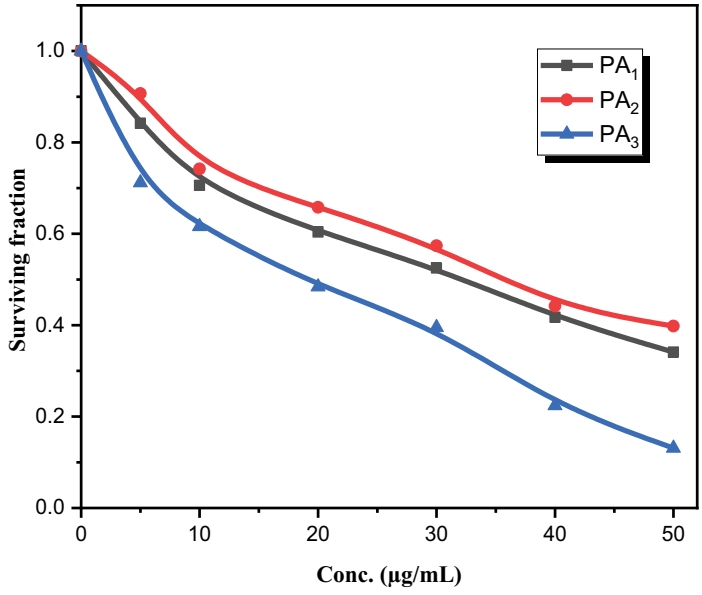

Figure 8. Inhibitory effects of PA_1, PA_2 and PA_3 on colon carcinoma cell lines in vitro.

Doxorubicin was regarded as the gold standard medication. Varying concentrations of the materials (50, 40, 30, 20, 10, 5, and 0 g/ml) were used to assess their inhibitory effect against the MCF-7 cell line and the HCT cell line, and cell viability (percent) was calculated using a colorimetric technique. Table 6 summarized the 50% inhibitory concentration (IC50) data for MCF-7 and HCT cell lines. In comparison with standard antitumor drug doxorubicin, we found that the new polyamides PA_1, PA_2 and PA_3 exhibited good cytotoxicity against the MCF-7 cell line, in the order $PA_3 > PA_1 > PA_2$ with IC50 values of 11.5, 21.52 and 25.40 µg/mL respectively, while the polyamide PA_4 showed no activity against the selected cell line. On the other hand, the synthesized polyamides displayed no activity against HCT

Table 6. Anticancer activity of the polyamides PA_{1-4} derivatives (IC_{50}) against two HCT and MCF7 cell lines.

	IC_{50} (µg/ml)	
Product code	HCT	MCF7
PA_1	ND	21.52
PA_2	8.11	25.40
PA_3	ND	11.5
PA_4	ND	ND
Doxorubicin	0.469	0.426

cell line, except the polyamide PA_2 which showed a significant cytotoxicity against HCT cell line with IC50 value of 8.11 µg/mL.

4. Conclusion

Four novel series of polyamides PA_{1-4} containing thiazole moieties and sulfur contents are produced via the common polycondensation polymerization reaction at RT condition. The polymerization was occurred by the interaction of 4-bis-2-aminothiazole diphenylsulfide with various diacid chlorides including both types (aliphatic & aromatic). The novel monomer and polymer structures were investigated by spectral common characterizations method, which give fully assignable spectra considering excepted structures besides their solubility. The new polyamides were examined by TGA, and XRD to study the thermal behaviors and crystallinity of the polymers, respectively. In addition, SEM measurement evaluates the morphological properties, which confirm that the surface of new polyamides forms a rock-like structure. The antimicrobial activity results showed that the newly synthesized polyamides possessed variable antibacterial activity. Also, the anticancer activity has been investigated which confirms that all synthesized polyamides showed good activity against MCF-7 cell line than HCT cell line except PA_4.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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