Synthesis and characterization of novel anti-inflammatory poly(spiro thiazolidinone)

Mona Ahmed Abdel-Rahmana, Essam Mostafa Husseina,b and Mahmoud Ali Husseinac

aPolymer Chemistry lab., Faculty of Science, Chemistry Department, Assiut University, Assiut, Egypt; bFaculty of Applied Science, Chemistry Department, Umm Al-Qura University, Makkah, Saudi Arabia; cFaculty of Science, Chemistry Department, King Abdulaziz University, Jeddah, Saudi Arabia

ABSTRACT
A new series of spirothiazolidinone polymers has been accomplished by solution polycondensation of 4,12-dioxa-1,9-dithiadispiro[4.2.4.2]tetradecane-3,11-dione (3) with different aliphatic and aromatic diamines. A model compound 4 was prepared by the reaction of spiro-monomer 3 with benzyl amine and was characterized by elemental and spectral analyses. These polymers were characterized by elemental and spectral analyses. The thermal properties of these polymers were investigated by thermogravimetric analysis and differential thermal analysis measurements. The morphological properties of selected polymers 5c and 5e were tested using scanning electron microscope to study their surface morphology. The molar masses of polymers 5a, 5b, and 5d were determined by gel permeation chromatography. In addition, the anti-inflammatory activities were studied for these spiro-polymers in comparison with the model compound by determination in vivo using acute carrageenan-induced paw edema in rats.

1. Introduction
In recent years, there has been an increasing interest in the preparation of new polymers with fungicidal, anti-inflammatory, antibacterial, and antiviral activities. Among these ones, spiro-polymers were investigated with respect to their properties such as thermal stability,[1] optical and electrical response,[2] antibacterial and antiviral activities,[3] and the biological/pharmacological activity.[4] In addition, spiroheterocyclic units are involved in the structure of many pharmacologically important synthetic and naturally occurring compounds like spiobrassinin. Spiro compounds provide many exciting medical applications such as antimicrobial, anti-inflammatory, antileukemic, and anticonvulsant activities.[5–7]

On the other hand, thiazolidinone compounds are very attractive target for combinatorial collection synthesis owing to their structure activity relationship [8] and its application in medicinal chemistry such as antioxidant, antibacterial, antifungal, antiviral, diuretic, antituberculosic, antihistaminic, anticancer, and anti-inflammatory.[9–11] Thiazolidinone derivatives have been shown to have high activity in vitro against mycobacterium tuberculosis and as drugs to treat HIV and cancer.[11–13] The combination of nitrogen or sulfur atoms in five- or six-membered heterocyclic ring caused diverse biological effects,[14–24] this increase the importance of thiazolidinone as a class of N and S including heterocyclic compounds, which are broadly used as key building blocks in the field of pharmaceutical agents and drugs.[25]

According to our best of knowledge, there are no reported examples in the literature for such spirothiazolidinone polymers or polyspiro macromolecules. Polymers containing spirothiazolidinone system have emerged as a new interesting type of polymeric materials. The impetus for the improvement of these materials is based on the premise that polymers containing spirothiazolidinone system are expected to possess properties significantly different from those of conventional organic polymers. The present work is aimed to synthesize a new series of spirothiazolidinone polymers using solution polycondensation method. The polymerization process has been carried out by the interaction of 4,12-dioxa-1,9-dithiadispiro[4.2.4.2]tetradecane-3,11-dione with different aliphatic and aromatic diamines. Prior the polymerization

CONTACT Mona Ahmed Abdel-Rahman mona.ali1@aun.edu.eg
Supplemental data for this article can be accessed here.
© 2016 Informa UK Limited, trading as Taylor & Francis Group
the new monomer has been synthesized and new model compound as well. Various characterization techniques for the new polymers have been tested and investigated in details as different identification tools in order to specify the major behavior for such synthesized polymers. Furthermore, the morphological properties and the anti-inflammatory activities have been studied.

2. Experimental part

2.1. Materials

All polymers and monomer are new; details of the synthesis and characterization of these compounds are given in the experimental part. 1,4-Cyclohexanediione (Sigma-Aldrich, 98%) mercaptoacetic acid (Sigma-Aldrich, 97%), p-toluenesulfonic acid (TCI), dry toluene (Acros Organics, 99.5%), decane-1,10-diamine (Merck, 96%), dodecane-1,12-diamine (Merck, 98%), p-phenylenediamine (Merck, 98%), and 4,4′-diaminodiphenyl sulfone (Sigma-Aldrich, 97%). Other reagents and solvents were purchased and used as received unless otherwise listed. All reactions were achieved under nitrogen atmosphere.

2.2. Instrumentation

Fourier transform infrared spectrophotometer (FT-IR) spectra were recorded on Nicolet 6700 – Thermo Fisher Scientific, using the KBr pellet technique, Assiut university, Egypt. 1H- and 13C-NMR spectra were recorded on GNM-LA 400-MHz NMR and on Bruker AV500 (1H: 500 MHz) spectrometers at room temperature in DMSO or CDCl 3, and chemical shifts are reported at δ values (ppm) relative to Me4Si. Mass spectra were measured on a JEOL JMS-600 spectrometer. Elemental analyses (C, H, N, and S) were done on a low-dose technique.[26] The molecular weights of selected examples from the newly synthesized poly(spiro thiazolidinodione) were determined using gel permeation chromatography (GPC; Agilent Technologies, Germany). This was a G-1362A with 100–104–105 Å. Altrastyragel columns connected in series. DMF was used as the eluent with a flow rate of 1 mL/min. Universal calibration was done using commercially available linear PMMA (poly methyl methacrylate) standards. The GPC measurements were carried out under these conditions: flow rate = 2000 ml/min, injection volume = 100,000 IL, and sample concentration = 1000 g/L.

2.3. Monomer synthesis

2.3.1. 4,12-dioxa-1,9-dithiadispiro[4.2.4.2]tetradecane-3,11-dione (3)

A mixture of 1,4-cyclohexanediione (1) (11.2 g, 100 mmol), mercaptoacetic acid (13.9 ml, 200 mmol), and p-toluenesulfonic acid (PTSA) (1.0 g, 5.8 mmol) was dissolved in 200 ml of dry toluene. The reaction mixture was stirred in oil bath at 115 °C and gently refluxed for 4 h, the liberated water was removed during reflux by water separator. After cooling, the solvent was removed under vacuum, and the oily residue was left at room temperature for 24 h, to get a solid product. Purification by recrystallization from toluene as off-white crystals yield: 50%; m.p.: 230–232 °C. C10H12O4S2: Calcd. C, 46.14; H, 4.65; S, 24.63. Found: C, 46.02; H, 4.71; S, 24.53. FT-IR (KBr): 1701 (C=O), 1657 (C–S); 1H-NMR: δ = 1.91–2.00 (m, 8H, 4CH 2), 3.40 (s, 4H, 2CH 2 benzylic). MS: m/z (%) 440.93 (M + 2), 66.4%. Mass spectra were measured on a JEOl JMS-600 analyzer and Shimadzu DTg 60. All measurements were carried out under these conditions: flow rate = 2000 ml/min, injection volume = 100,000 IL, and sample concentration = 1000 g/L.

2.4. Model compound synthesis

2.4.1. 4,12-dibenzyl-4,12-diaza-1,9-thiazolidinodione[4.2.4.2]tetradecane-3,11-dione (4)

A mixture of 3 (1.30 g, 5 mmol) in absolute ethanol (25 mL) and benzyl amine (1.07 g, 10 mmol). The reaction mixture was stirred in water bath at 80 °C and gently refluxed for 2 h. During reflux a solid product was separated out, then filtered off and dried. Purification by recrystallization from dioxane as white crystals yield: 65%; m.p.:174–175 °C. C24H26N2O2S2: Calcd. C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 65.60; H, 6.05; N, 6.32; S, 14.62. FT-IR (KBr): 1650 (N–C=O), 758 and 703 (5 adj Ar–H), 693 (C–S). 1H-NMR (DMSO-d6): δ = 1.89–1.95 (m, 8H, 4CH 2), 3.21 (s, 4H, 2CH 2 in thiazolidinodione ring), 4.00 (s, 4H, 2CH 2 benzyl), 7.20–7.48 (m, 10H, Ar–H). 13C-NMR (DMSO-d6): δ: 143.50, 128.43, 128.65, 128.70, 128.82, 128.91, 129.17, 137.31, 143.50, 61.13, 64.43, 127.26, 127.38, 127.74, 128.23, 128,38, 128.43, 128,65, 128.70, 128.82, 128.91, 129,17, 137.31, 172.17. MS: m/z (%) 440.93 (M + 2), 66.4%.
2.5. Polymers syntheses

2.5.1. General procedure for poly(spiro thiazolidinones)

2.5.1.1. General procedures. In a three-necked flask equipped with a condenser, dry nitrogen inlet, outlet, and dropping funnel, a mixture of (2 mmol) spiro monomer 3 suspended in 30 mL of absolute ethanol, piperidine as a basic catalyst was added in a dropwise manner over a period of 10 min. Solutions of different aliphatic and aromatic diamines (2 mmol) in 15 mL of absolute ethanol were added in a dropwise manner at 25 °C during stirring over a period of 20 min. After completing the addition, the stirring was continued for 12–15 h at about 80 °C; during the reaction time, the viscosity of the reaction mixture increased rapidly, and the polymer began to precipitate in the early stages of the reaction. A solid polymer separated out during reflux; then washed with hot methanol and dried under reduced pressure (1 mm/Hg) at 80 °C for 48 h. Using this general procedure, the following poly(spiro thiazolidinone) 5a–5e were obtained.

2.5.1.2. Poly(spiro thiazolidinone) 5a. The titled polymer was prepared according to the previous general procedure of polymerization from compound 3 (0.520 g, 2 mmol) in absolute ethanol (30 mL) with p-phenylenediamine (0.237 g, 2.2 mmol) in absolute ethanol (15 mL), and few drops of piperidine for 14 h. Black solid; yield: 58%. Anal. Calcd for C_{16}H_{16}N_{2}O_{2}S_{2}: C, 57.81; H, 4.85; N, 8.43; S, 19.29; Found: C, 57.21; H, 4.93; N, 8.51; S, 19.29. FT-IR (KBr, cm⁻¹): 3327 (CH aromatic), 2939 (CH aliphatic), 1640 (N–C=O), 822 (2 adj Ar–H), 685 (C–S).

2.5.1.3. Poly(spiro thiazolidinone) 5b. The titled polymer was prepared according to the previous general procedure of polymerization from compound 3 (0.520 g, 2 mmol) in absolute ethanol (30 mL) with 4,4’-diaminodiphenyl ether (0.440 g, 2.2 mmol) in absolute ethanol (15 mL), and few drops of piperidine for 12 h. Black solid; yield: 68%. Anal. Calcd for C_{22}H_{20}N_{2}O_{2}S_{2}: C, 60.57; H, 8.13; N, 7.06; S, 16.17; Found: C, 60.41; H, 8.18; N, 6.86; S, 16.23. FT-IR (KBr, cm⁻¹): 2940 (CH aliphatic), 1647 (N=C=O), 695 (C–S).

2.5.1.4. Poly(spiro thiazolidinone) 5c. The titled polymer was prepared according to the previous general procedure of polymerization from compound 3 (0.520 g, 2 mmol) in absolute ethanol (30 mL) with 4,4’-diaminodiphenyl sulfone (0.545 g, 2.2 mmol) in absolute ethanol (15 mL), and few drops of piperidine for 12 h. Off-white solid; yield: 63%. Anal. Calcd for C_{22}H_{20}N_{2}O_{2}S_{3}: C, 55.91; H, 4.27; N, 5.93; S, 20.35; Found: C, 55.69; H, 4.40; N, 5.88; S, 20.42. FT-IR (KBr, cm⁻¹): 2922 (CH aliphatic), 1644 (N=C=O), 1374 and 1138 (S=O sulfone), 815 (2 adj Ar–H), 685 (C–S).

2.5.1.5. Poly(spiro thiazolidinone) 5d. The titled polymer was prepared according to the previous general procedure of polymerization from compound 3 (0.520 g, 2 mmol) in absolute ethanol (30 mL) with 1,10-dianimodecan (0.378 g, 2.2 mmol) in absolute ethanol (15 mL), and few drops of piperidine for 14 h. Yellowish orange solid; yield: 78%. Anal. Calcd for C_{22}H_{36}N_{2}O_{2}S_{2}: C, 60.57; H, 8.13; N, 7.06; S, 16.17; Found: C, 60.41; H, 8.18; N, 6.86; S, 16.23. FT-IR (KBr, cm⁻¹): 2925 (CH aliphatic), 1647 (N=C=O), 695 (C–S).

2.5.1.6. Poly(spiro thiazolidinone) 5e. The titled polymer was prepared according to the previous general procedure of polymerization from compound 3 (0.520 g, 2 mmol) in absolute ethanol (30 mL) with 1,12-dianimododecan (0.440 g, 2.2 mmol) in absolute ethanol (15 mL), and few drops of piperidine for 14 h. Pale gray solid; yield: 73%. Anal. Calcd for C_{22}H_{36}N_{2}O_{2}S_{2}: C, 60.57; H, 8.13; N, 7.06; S, 16.17; Found: C, 60.41; H, 8.18; N, 6.54; S, 15.18. FT-IR (KBr, cm⁻¹): 2925 (CH aliphatic), 1632 (N=C=O), 685 (C–S).

2.6. Pharmacological evaluation

Adult male albino rats (120–150 g) (n = 24) were purchased from animal house in the Faculty of Medicine, Assiut University. The animals were kept under controlled conditions and fed with normal mouse chow and water ad libitum. All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethics Committee, Assiut University. Methods of statistical analysis were done according to Armitage et al. [27].

2.7. Anti-inflammatory activity screening

The anti-inflammatory activity screening of six newly prepared compounds 4, 5a–e was evaluated in vivo by applying the acute carrageenan-induced paw oedema standard method in rats using indomethacin as reference drug.[28] The test is established on the pedal inflammation in rat paws made by sub-plantar injection of 0.2-mL carrageenan (0.2%) suspension (5% sodium carboxymethylcellulose (NaCMC)) into the right hind paw of the rats. Male adult albino rats (120–150 g) were divided into eight groups, each of three animals. The thickness of rat paw was measured by a Vernier caliper (SMIEC (Shanghai Machinery
2.8. Determination of acute toxicity (LD$_{50}$)

The median lethal doses (LD$_{50}$) of the tested compounds 5a–e were determined in mice. A group of male adult albino mice of five animals (25–30 g) was injected (i.p.) at a certain grade. The percentage of mortality was determined 72 h after injection. Computation of LD$_{50}$ was processed by a graphical method.[29]

3. Results and discussion

3.1. Monomers syntheses

A new spiro-monomer namely 4,12-dioxa-1,9-dithiadispiro[4.2.4.2]tetradecane-3,11-dione (3) was synthesized in a good yield by the reaction of a mixture of 1,4-cyclohexanedione (1), mercaptoacetic acid and $p$-toluenesulfonic acid as described in Scheme 1. The structure of this monomer was established on the base of elemental analysis and spectral data. The FT-IR spectrum displayed characteristic absorption bands at 1701, 671 cm$^{-1}$ due to (C=O) and (C–S), respectively. This monomer gave fully assignable $^1$H NMR spectra. It showed the molecular ion peak in the mass spectrum.

3.2. Synthesis of model compound

Before attempting polymerization, model compound 4 was prepared from the reaction of 1 mol of monomer 3 with 2 mol of benzyl amine in EtOH in presence of piperidine as described in Scheme 2. The structure of this model compound was confirmed by elemental and spectral analysis. The FT-IR spectrum showed a new characteristic absorption band at 1640 cm$^{-1}$ due to (N–C=O) stretching. Both $^1$H and $^{13}$C NMR spectra of model compound 4 (in DMSO) were in agreement with the suggested structure (see Figure 1). This model compound showed the molecular ion peak in the mass spectrum.
3.3. Polymerization and polymer characterization

Via solution polycondensation technique,[30] by the reaction of one mole of monomer 4 with one mole of diamine compounds in the presence of piperidine as basic catalyst, gives new spirothiozolidinone polymers 5a–e as described in Scheme 3. The structures of the resulting polymers were also established from elemental analyses and spectral data. Elemental analyses, FT-IR, 1H-NMR of these polymers are in agreement with the proposed structure of each polymer; the data are included in the experimental part. The FT-IR spectral data of all spirothiozolidinone polymers showed characteristic absorption band at 1632–1647 cm⁻¹ due to N–C=O, in addition to other characteristic absorption bands due to specific groups present in the various polymers. Also, the 1H-NMR spectra of spirothiozolidine polymers 5a and 5b (in DMSO) were in accordance with the proposed structures, as represented in the experimental part.

3.3.1. TGA study

The thermal behavior of spiro polymers 5a–e was evaluated by TGA in air with heating rate of 10 °C/min. The TGA, DTG, and DTA curves of one polymer: 5b is shown in Figure 2. TGA curves show a small weight loss in the range 0.5–4.5%, this is probably due to the residues of solvents which evaporate at lower temperatures (starting at 50 °C until 225 °C). The thermal parameters obtained from TGA and DTA curves are listed in Table 1. The initial decomposition (IDT) [31] corresponds to the temperature, at which the initial degradation may occur. IDT of these polymers (10% loss) is considered to be polymer decomposition temperature (PDT),[32,33] the predominant step of decomposition occurs in range 187–279 °C.

Poly(spiro thiozolidinone) 5a shows mass loss between 181.14 and 219.64 °C (–15.46%) in first region, then degradation step between 221.63 and 301.32 °C (–15.56%) which is overlapped with the previous region, between 303.31 and 457.11 °C (–24.08%) in third region, and sharp degradation step between 459.11 and 569.16 °C (–42.85%), also decomposes almost completely (residue at 600 °C is only 0.97%).

Poly(spiro thiozolidinone) 5b shows mass loss between 186.64 and 379.87 °C (–23.51%) in first region, between 380.67 and 506.57 °C (–27.14%), then sharp degradation step between 507.77 and 578.52 °C (–45.51%) in third region, also decomposes almost completely (residue at 600 °C is only 1.03%).

Poly(spiro thiozolidinone) 5c shows sharp degradation step between 191.08 and 277.75 °C (–24.40%) in first region, then mass loss between 279.67 and 423.86 °C (–23.97%), between 425.78 and 466.43 °C (–11.46%) in third region which is overlapped with the previous region, and the last degradation step between 468.35 and 568.21 °C (–37.87%),
DESIgNED MONOMERS AND POlyMERS

Figure 3), this can be a result of the merits of the core spiro-type structure.[34] The volume of the two rings joined to cyclohexane ring by two spiro carbons is much higher than the volume of cyclohexane ring only. The thermal stability of cyclohexan-1,4-dione is not high in comparison with the related spiro-polymers, it is completely thermal decomposed at 296 °C. Three major steps of degradation were found in all investigated polymers except 5a and 5c four degradation steps, the rate of degradation in the last step in all polymers is somewhat faster than the other steps. The first degradation step involves the scission of the spiro moiety and both the aliphatic and aromatic composition moieties in the polymer chains. The expected decomposition in the second step involved the cleavage of ether linkage or disulfide linkage in addition to random scission of the free linear chains.[35] The last step in degradation includes the degradation of the spiro moiety which has a high thermal stability as a result of high steric hindrances. [36]

Figure 2. TGA spectrum of spirothiozolidinone polymer 5b.

Table 1. Thermal parameters and results of spirothiozolidine polymers 5a–e.

| Polymer number | Temperature (°C) for various decomposition levels* | GPCb |           | Mw × 10^3 | Pw | PDI | Td (°C) |
|----------------|-------------------------------------------------|------|-----------|-------------|----|-----|---------|
| 5a             | 197 234 280 345 385 29.252 88 1.83 188           |      |           |             |    |     |         |
| 5b             | 279 340 403 441 484 16.484 39 5.13 132           |      |           |             |    |     |         |
| 5c             | 227 244 310 380 423 – – – 201                     |      |           |             |    |     |         |
| 5d             | 187 215 229 246 318 24.429 62 2.39 223           |      |           |             |    |     |         |
| 5e             | 219 242 321 396 432 – – – 215                     |      |           |             |    |     |         |

*The values were determined by TGA at heating rate of 10 °C min⁻¹.

**All GPC measurements were performed in DMF.

Weight average molecular weight.

PDI: average number of repeating units.

also decomposes almost completely (residue at 600 °C is only 0.94%).

Poly(spiro thiozolidinone) 5d shows sharp degradation step between 160.70 and 294.06 °C (–41.98%) in first region, then mass loss between 296.05 and 447.38 °C (–19.95%), between 449.37 and 592.63 °C (–32.60%) in third region, also decomposes almost completely (residue at 600 °C is only 0.20%).

Poly(spiro thiozolidinone) 5e shows sharp degradation step between 180.11 and 287.17 °C (–23.86%) in first region, then mass loss between 288.37 and 476.22 °C (–38.04%), between 479.00 and 588.93 °C (–35.23%) in third region, also decomposes almost completely (residue at 600 °C is only 0.93%).

The thermal stability of these spiro-polymers comparing with 1,4-cyclohexanediolone is relatively high. These spiro-polymers exhibit high decomposition temperatures (Td 10% weight loss) at 197, 279, 227, 187, and 219 °C, while the Td of 1,4-cyclohexanediolone is at 140 °C (see
solvent and the solution was analyzed by visual inspection. The results are shown in Table 2. All spiro-polymers are freely soluble in polar, aprotic solvents such as DMF and DMSO except 5c, e are partially soluble in DMF and 5e is partially soluble in DMF. All spiro-polymers 5a–e are clearly less soluble in moderate polar solvent THF and in protic solvents such as formic acid, while they are virtually insoluble in non-polar solvents such as benzene and CHCl₃ (chlorinated solvent).

Comparing between these spiro-polymers 5a–e, there are two types in this series, spiro-polymers with aromatic or aliphatic moieties in the back bone. Two factors affected the solubility of these spiro-polymers, the flexibility of the polymer chains and the packing distances between these chains. The presence of aliphatic moieties in the chain backbone increase the flexibility of these chains than that with the aromatic moieties. On the other hand, the presence of

Table 2. Room-temperature solubility characteristics of spirothiozolidine polymers 5a–e. (++: soluble according to visual inspection, +: partially soluble, –: insoluble).

| Polymer number | DMF | DMSO | THF | HCOOH | CHCl₃ | Benzene |
|----------------|-----|------|-----|-------|-------|---------|
| 5a             | ++  | ++   | +   | +     | –     | –       |
| 5b             | ++  | ++   | +   | +     | –     | –       |
| 5c             | +   | ++   | ++  | +     | –     | –       |
| 5d             | +   | +    | +   | +     | –     | –       |
| 5e             | +   | +    | +   | +     | –     | –       |

3.3.2. Solubility

The solubility of the new spirothiozolidine polymers 5a–e was tested using solvents including dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), chloroform (CHCl₃), benzene, tetrahydrofuran (THF), and formic acid. Fifty milligrams of the polymer were added to 1 mL of the chosen solvent and the solution was analyzed by visual inspection. The results are shown in Table 2. All spiro-polymers are freely soluble in polar, aprotic solvents such as DMF and DMSO except 5c, e are partially soluble in DMF and 5e is partially soluble in DMF. All spiro-polymers 5a–e are clearly less soluble in moderate polar solvent THF and in protic solvents such as formic acid, while they are virtually insoluble in non-polar solvents such as benzene and CHCl₃ (chlorinated solvent).

Comparing between these spiro-polymers 5a–e, there are two types in this series, spiro-polymers with aromatic or aliphatic moieties in the back bone. Two factors affected the solubility of these spiro-polymers, the flexibility of the polymer chains and the packing distances between these chains. The presence of aliphatic moieties in the chain backbone increase the flexibility of these chains than that with the aromatic moieties. On the other hand, the presence of

Table 3. Anti-inflammatory activity of model 4 and spirothiozolidine polymers 5a–e using acute carrageenan-induced paw oedema in rats.

| Compound | Mean swelling volume ± SEM* (% inhibition of oedema) | Potencyb |
|----------|----------------------------------------------------|----------|
|          | 0.5 h | 1 h   | 2 h  | 3 h  | 4 h  | 5 h  |         |
| Control  | 0.733 ± 0.028 (00.0) | 0.733 ± 0.028 (00.0) | 0.733 ± 0.028 (00.0) | 0.733 ± 0.028 (00.0) | 0.733 ± 0.028 (00.0) | 0.733 ± 0.028 (00.0) | –          |
| Indomethacin | 0.650 ± 0.050 (11.3) | 0.550 ± 0.050 (24.9) | 0.483 ± 0.028 (34.1) | 0.416 ± 0.028 (43.2) | 0.400 ± 0.000 (45.4) | 0.383 ± 0.028 (47.7) | 1.00        |
| 4        | 0.700 ± 0.000 (4.5) | 0.650 ± 0.050 (11.3) | 0.583 ± 0.028 (20.4) | 0.550 ± 0.050 (24.9) | 0.483 ± 0.028 (34.1) | 0.450 ± 0.050 (38.6) | 0.81        |
| 5a       | 0.700 ± 0.000 (4.5) | 0.633 ± 0.057 (13.6) | 0.516 ± 0.028 (29.6) | 0.466 ± 0.057 (36.4) | 0.433 ± 0.057 (40.9) | 0.400 ± 0.000 (45.4) | 0.95        |
| 5b       | 0.716 ± 0.028 (2.3) | 0.683 ± 0.028 (6.8) | 0.666 ± 0.028 (9.1) | 0.650 ± 0.050 (11.3) | 0.550 ± 0.050 (24.9) | 0.550 ± 0.050 (24.9) | 0.52        |
| 5c       | 0.700 ± 0.000 (4.5) | 0.683 ± 0.028 (6.8) | 0.583 ± 0.028 (20.4) | 0.550 ± 0.050 (24.9) | 0.516 ± 0.028 (29.6) | 0.500 ± 0.000 (31.7) | 0.66        |
| 5d       | 0.700 ± 0.000 (4.5) | 0.666 ± 0.057 (9.1) | 0.616 ± 0.028 (15.9) | 0.583 ± 0.028 (20.4) | 0.550 ± 0.050 (24.9) | 0.433 ± 0.057 (40.9) | 0.86        |
| 5e       | 0.683 ± 0.028 (6.8) | 0.650 ± 0.030 (11.3) | 0.583 ± 0.104 (29.6) | 0.533 ± 0.028 (27.2) | 0.500 ± 0.000 (31.7) | 0.466 ± 0.057 (36.4) | 0.76        |

*SEM. = Standard error mean and all showed at least significant difference at \( p < 0.05 \) in comparison with control group.

bPotency was expressed as percentage oedema inhibition of the tested compounds relative to percentage oedema inhibition of indomethacin ‘reference standard’ at 5 h effect.
3.3.4. Molecular weight determination

The molecular weights of selected examples from the newly synthesized poly(spiro thiazolidinone) 5a, 5b, and aromatic moieties like diphenyl ether, diphenyl sulfoxide, and benzene in the polymer backbone leads to increase chains packing distances and increasing inter-chain interaction such as hydrogen bonding, thereby increasing the solubility compared with the spiro-polymers which contain aliphatic moieties in the chain back bone.[30,37] Compared to other polyazomethines,[38] the introduction of spiro thiazolidinone systems did not improve the solubility of the resulting polymers significantly.

This is probably due to the structural characteristics of polyazomethines compared to those of other poly(spiro thiozolidine)s. In the case of poly(spiro thiozolidine)s (see Figure 4), the polymer main chain is twisted 90º periodically in each spiro point in every repeating unit owing to two aliphatic or aromatic moieties attached to different thiozolidine rings which are linked perpendicularly with cyclohexane ring by spiro carbon. Therefore, diamines which attached on the dispiro unit are extended in the same direction, resulting in a linear configuration of main chain. So, it was expected that the linear and rigid structure of dispiro unit could hardly enhance the solubility of resulting spirothiozolidine polymes,[1] this decrease the polarity of the polymer chains.

3.3.3. Morphology (SEM)

The morphology of selected examples of spiro-polymers 5c and 5e was examined by SEM using a low-dose technique.[26] Figure 5(a) (X = 5000) shows that spiro-polymers 5c has polymorph spongy structure the higher magnification (X = 1500) in Figure 5(b) shows rods with some coalescence structure. Figure 6(a) (X = 5000) shows that spiro-polymers 5e has polymorph caves structure. The higher magnification (X = 15,000) in Figure 6(b) shows flower structure.
and 5c have moderate activities with potency 0.52 and 0.66, respectively (see Figure 7). Structure–activity relationships based on the obtained results indicated that: model compound 4 showed noticeable activity (potency 0.81), so, dispirothiazolidinones have potent anti-inflammatory activity. The total pharmacological properties of the synthesized polymers are depending on the type of substituents attached to nitrogen atom in the thiazolidinone ring. The best observed anti-inflammatory property is that in which the nitrogen atom is bearing a phenyl group in 5a (potency 0.95). However, in the case of diphenyl ether and/or diphenyl sulfone the function was relatively decreased as in spiro-polymers 5b and 5c. The anti-inflammatory activity was relatively increased as the substituent is flexible aliphatic long chain (C10 and C12) with potency 0.86 and 0.76, respectively, as shown in spiro-polymers 5d and 5e.

3.3.5. Anti-inflammatory activity

Anti-inflammatory activity of the target compounds 4 and 5a–e (at a dose of 10 mg/kg body weight) were determined in vivo by the acute carrageenan-induced paw oedema standard. [24] The anti-inflammatory properties were recorded at successive time intervals 0.5, 1, 2, 3, 4, and 5 h and compared with that of indomethacin (at a dose of 10 mg/kg body weight) which was used as a reference standard. From the obtained results (Table 3) it has been noticed after 5 h, that all of the tested compounds exhibit considerable anti-inflammatory properties. Specially, the model compounds 4, as well as spiro-polymers 5a, 5d, and 5e which reveal remarkable activities with potency (percentage oedema inhibition of the tested compounds relative to percentage oedema inhibition of indomethacin) of 0.81, 0.95, 0.86, and 0.76, respectively. However, polymers 5b and 5c have moderate activities with potency 0.52 and 0.66, respectively (see Figure 7).

The total pharmacological properties of the synthesized polymers are depending on the type of substituents attached to nitrogen atom in the thiazolidinone ring. The best observed anti-inflammatory property is that in which the nitrogen atom is bearing a phenyl group in 5a (potency 0.95). However, in the case of diphenyl ether and/or diphenyl sulfone the function was relatively decreased as in spiro-polymers 5b and 5c. The anti-inflammatory activity was relatively increased as the substituent is flexible aliphatic long chain (C10 and C12) with potency 0.86 and 0.76, respectively, as shown in spiro-polymers 5d and 5e.

3.3.5.1. Acute toxicity (LD50).

The median lethal doses (LD50) of all tested compounds 4 and 5a–e were determined in mice according to reported procedures. [28] The animals got injection of a certain grade. The results showed that the tested compounds 4 and 5a–e were nontoxic at doses up to 160 mg/kg.

4. Conclusion

In this research study, a new interesting series of thermally stable spirotiazolidine polymers 5a–e were synthesized via solution polycondensation reactions of new spiromonomer 3 with different aliphatic and aromatic diamines. All polymers were synthesized by convenient route and prepared in good yield. For investigation the characterization of the prepared polymers elemental and spectral analyses were used in addition to solubility measurement. In the thermal analysis, the polymer decomposition temperature of these new spiropolymers did not start before 187 °C, this is an indication of their
Acknowledgment

The authors are very thankful to the management of the Faculty of Science and Assiut University (Assiut – Egypt) for providing financial assistance and analytical instrumentation facility to carry out the research work.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Assiut University.

References

[1] Wen P, Kim Y, Chun H, et al. Syntheses and characterizations of cardo polyimides based on new spirobifluorene diamine monomer. Mater. Chem. Phys. 2013;139:923–930.

[2] Wenb Y, Shen Y, Wen S, et al. Synthesis and characterization of luminescent poly(ester-imide) derivatives constituted of alternating spirobifluorene moiety. J. Taiwan Inst. Chem. Eng. 2012;43:644–649.

[3] Arya K, Rawat DS, Dandia A, et al. Brensted acidic ionic liquids: green, efficient and reusable catalyst for synthesis of fluorinated spiro[indole-thiazinones/thiazolidinones] as antihistaminic agents. J. Fluorine Chem. 2012;137:117–122.

[4] Triolo C, Patane S, Mazzeo M, et al. Pure optical nanowriting on light-switchable spiropyrans/merocyanine thin film. Opt. Express. 2014;22:283–288.

[5] Behera RK, Behera AK, Pradham R, et al. Studies on spirophorocycles. Part 1. Installation of biologically active heterocyclic nucleic into spiro compounds derived from cyclohexanone and diphenyl thiobarbituric acid. Indian J. Chem., Sect. B. 2006;45:933–942.

[6] Hussein EM, Abdel-Monem MI. Regioselective synthesis and anti-inflammatory activity of novel dispiro[pyrazolidine-4,3′-pyrrolidine-2,3′-indoline]-2,3,5-triones. Arkivoc. 2011;10:85–98.

[7] Sinha NK, Asnani AJ, Dravyakar BR, et al. Synthesis and pharmacological evaluation of spiropinazolinones as anti-inflammatory and analgetic agents. Int. J. Adv. Res. 2013;1:445–450.

[8] Sharma MC, Sahu NK, Kohli DV, et al. Qsar, synthesis and biological activity studies of some thiazolidinones derivatives. Dig. J. Nanomater. Biostruct. 2009;4:223–232.

[9] Walmik P, Saundane AR. Synthesis of novel indolyl-thiazolidinone derivatives as antioxidant, antimicrobial and atitubercular agents. Der Pharma Chem. 2015;7:131–140.

[10] Ottana R, Maccari R, Barreca ML, et al. 5-Arylidene-2-imino-4-thiazolidinones: design and synthesis of novel anti-inflammatory agents. Bioorg. Med. Chem. 2005;13:4243–4252.

[11] Kucukguzel G, Kocatepe A, de Clercq E, et al. Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from difunisal hydrazide. Eur. J. Med. Chem. 2006;41:353–359.

[12] Chen H, Bai J, Jiao L, et al. Design, microwave-assisted synthesis and HIV-RT inhibitory activity of 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5(uns)ubstituted-pyrimidin-2-yl)thiazolidin-4-ones. Des. Monomers Polym. 2009;17:3980–3986.

[13] Bhatt JD, Nimavat KS, Vyas KB. Studies on novel thiazolidinone and their biological studies. J. Chem. Pharm. Res. 2013;5:327–331.

[14] Hammam AS, Abdel-Rahman M A, Hassan AA, et al. Synthesis and characterization of pyrrolo[2,3-f] indole-3,7-dicarbonitriles. Int. J. Adv. Med. 2013;1:11–17.

[15] Vishnu KT, Hardesh KM, Dharmendra BY, et al. Naphtho[2,3-b][1,4]-thiazine-5,10-diones and 3-substituted-1,4-dioxo-1,4-dihydrongaphthalen-2-yl-thioalkanoate derivatives: synthesis and biological evaluation as potential antibacterial and antifungal agents. Bioorg. Med. Chem. Lett. 2006;16:5883–5887.

[16] Gomez-Monterrey I, Santelli G, Campiglia P, et al. Synthesis and cytotoxic evaluation of novel spirohydantoin derivatives of the dihydrothieno[2,3-b]naphtho[2,3-c][1,4]-pyrazoles and their 2-imino-4-thiazolidinones: design and synthesis of biological and cytotoxic evaluation of novel spirohydantoin derivatives with CDC25 phosphatase inhibitory activity. Bioorg. Med. Chem. 2005;13:4871–4879.

[17] Seradj H, Cai W, Erasga NO, et al. Total synthesis of novel 6-substituted lavendamycin antitumor agents. Org. Lett. 2004;6:473–476.

[18] Brun MP, Braud E, Angotti D, et al. Design, synthesis, and biological evaluation of novel naphthoquinone derivatives with CDC25 phosphatase inhibitory activity. Bioorg. Med. Chem. 2005;13:4871–4879.

[19] Kim YS, Park SY, Lee HJ, et al. Synthesis and cytotoxicity of 6,11-dihydro-pyrido- and 6,11-dihydro-benzo[2,3-b]phenazine-6,11-dione derivatives. Bioorg. Med. Chem. 2003;11:1709–1714.

[20] dos Santos EVM, Carneiro JWD, Ferreira VF. Quantitative structure–activity relationship in aziridinyl-1,4-naphthoquinine antimalarias: study of theoretical correlations by the PM3 method. Bioorg. Med. Chem. 2004;12:87–93.

[21] Tandon VK, Yadav DB, Chaturvedi AK, et al. Synthesis of (1,4)-naphthoquinone-(3,2-c)-1H-pyrazoles and their (1,4)-naphthoquinone derivatives as antifungal, antibacterial, and anticancer agents. Bioorg. Med. Chem. Lett. 2005;15:3288–3291.

[22] Ryu CK, Shim JY, Chae MJ, et al. Synthesis and antifungal activity of 2/3-arylthio- and 2,3-bis(arylthio)-5-hydroxy-5-methoxy-1,4-naphthoquinones. Eur. J. Med. Chem. 2005;40:438–444.

[23] Ryu CK, Choi IH, Lee JY, et al. Synthesis of benzo[b]naphtho[2,3-d]thiophene-6,11-diones via palladium(I) acetate-mediated cyclization of 3-arylthio-1,4-naphthoquinone. Heterocycles. 2005;65:1205–1214.
[24] Tadeusz SJ. Thioamides as useful synthons in the synthesis of heterocycles. Chem. Rev. 2003;103:197–228.

[25] Abhinit M, Ghodke M, Pratima NA. Exploring potential of 4-thiazolidinone: a brief review. Int. J. Pharm. Pharm. Sci. 2009;1:47–64.

[26] Tager A. Physical chemistry of polymers. Moscow: Mir; 1972.

[27] Armitage P, Berry G, Matthews JNS. Statistical methods in medical research. Oxford: Blackwell Science; 2002.

[28] Winter CA, Risley EA, Nuss GN. Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. Exp. Biol. Med. 1962;111:544–547.

[29] Sztaircskaí F, Takacs IE, Pusztai F, et al. Antiulcer effect of the N-and O-β-D-glucopyranosides of 5-aminosalicylic acid. Arch. Pharm. 1999;332:321–326.

[30] Hsiao SH, Liou GS. A new class of aromatic poly(1,3,4-oxadiazole)s and poly(amide-1,3,4-oxadiazole)s containing (naphthalenedioxy)diphenylene groups. Polym. J. 2002;34:917–924.

[31] Mallakpour S, Zadehnazari A. Use of ionic green solvent for the synthesis of optically active aromatic polyamides containing a L-leucine moiety under microwave irradiation. Des. Monomers Polym. 2009;12:589–604.

[32] Abdel-Rahman MA, Hussein MA. Polyarylidene containing saturated silicon spacers in the polymers main chain. Des. Monomers Polym. 2013;16:377–388.

[33] Aly KI, Hammam AS, Radwan SM, et al. New unsaturated copolyesters based on diarylideneclycopentanone. Optimum conditions of synthesis, characterization and morphology. Int. J. Bas. Appl. Sci. 2011;11:15–45.

[34] Chu Z, Wang D, Zhang C, et al. Synthesis of spiro[fluorene-9,9′-xanthene] derivatives and their application as hole-transporting materials for organic light-emitting devices. Polym. J. 2012;162:614–620.

[35] Hussein MA, Abdel-Rahman MA, Geies AA. New heteroaromatic polyazomethines containing naphthyridine moieties: synthesis, characterization, and biological screening. J. Appl. Polym. Sci. 2012;126:2–12.

[36] Chylińska M, Kaczmarek H. Thermal degradation of biocidal organic N-halamines and N-halamine polymers. Thermochim. Acta. 2014;583:32–42.

[37] Tager A. Physical chemistry of polymers. Moscow: Mir; 1972.

[38] Armitage P, Berry G, Matthews JNS. Statistical methods in medical research. Oxford: Blackwell Science; 2002.

[25] Abhinit M, Ghodke M, Pratima NA. Exploring potential of 4-thiazolidinone: a brief review. Int. J. Pharm. Pharm. Sci. 2009;1:47–64.

[39] Hussain MA, Abdel-Rahman MA, Geies AA. New heteroaromatic polyazomethines containing naphthyridine moieties: synthesis, characterization, and biological screening. J. Appl. Polym. Sci. 2012;126:2–12.

[38] Abdel-Rahman MA, Hussein MA. Polyarylidene containing saturated silicon spacers in the polymers main chain. Des. Monomers Polym. 2013;16:377–388.