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Synthesis, antimicrobial and antimutagenic effects of novel polymeric-Schiff bases including indol

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ABSTRACT

Herein, the synthesis and characterization of three new polymeric-Schiff bases including indol (L_1, L_2, L_3) were reported. The antibacterial and antifungal activity of all compounds were investigated by the well-diffusion method against some selected microorganisms as potential antimicrobial agents. In addition, the anti-genotoxic properties of these polymeric-Schiff bases were examined against sodium azide in human lymphocyte cells by micronuclei (MN) and sister chromatid exchange (SCE) tests.

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1. Introduction

Schiff base polymers having azomethine have received increasing attention because of their useful properties such as conductivity, catalytic activity, thermal and chemical stability, luminescence and magnetism properties [1–4]. Polymer-bonded Schiff bases also have electrochemical, mechanical and enzymatic properties and have the potential to be used in sensors [5,6]. Immobilization of enzymes onto these type polymeric supports are improved the performance of storage stability and reusability [7,8]. The increase in resistance to antimicrobials attracts the attention of medical chemists as the new antimicrobial materials due to the pharmacological activities, antioxidant and antimicrobial properties of the polymeric-Schiff bases [9–11].

Recently, studies on mutagenic agents have been increased due of there has been an increase in mutation-related disease [12]. Therefore the discovery of new antimutagens has been became important. Mutagenic substances cause permanent base changes in genetic material (DNA) [13]. Antimutagen is a biological term for the compound that eliminates mutation process. The antimutagens are remarkable due to prospects of their practical use for the prevention of negative effects of induced mutagens in human, the main of which are highly associated with hereditary diseases and cancer [14]. The antimutagenic effect is that mutation can be prevented on genes or is the inactivation of the mutagenic agent. One of the mutagenic substances is sodium azide (NaN_3). It is widely used in industry, agriculture and medicine but it is a highly toxic substance [15–17]. If sodium azide find in the intracellular milieu, azide ions bind Fe^{3+} in hemoglobin and inhibit the respiratory chain of metabolism [18].

Indoles are an important class of organic heterocyclic compounds. Indole derivatives have antioxidant, anticancer, antibacterial, antifungal, anti-inflammatory, antiviral properties, anticonvulsant and antihypertensive activity [19,20]. They have also good thermal stability, high redox activity and selectivity [21]. Novel potential drug candidates are usually screened for their possible toxicity and mutagenic, antimutagenic and biological activities in many systems [22].

In this research, we report the synthesis and characterization of

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three novel polymeric Schiff bases containing indol. We also investigate the antimicrobial activities and inhibitory effects of all compounds against some pathogenic bacteria and yeast. To determine the antimutagenic effect, human peripheral lymphocytes were co-treated with sodium azide, a known mutagen, and polymeric-Schiff bases, and the resulting frequencies of SCEs and MNs were calculated.

2. Experimental

2.1. Materials and physical measurements

All chemicals were purchased from Sigma-Aldrich or Merck and used without further purification. Elemental analyses were performed using a Leco CHNS-932 analyser. Infrared spectra were recorded on a PerkinElmer 100 FT-IR spectrometer at 4000-400 cm^{-1} by KBr method. GPC measurements were obtained on a Tosoh EcoSEC HLC-8320 gel permeation chromatography. TGA measurements were made in PerkinElmer thermal analyser between 10 °C and 910 °C (in N_2; rate, 10 °C/min).

2.2. General procedure for synthesis of polymeric-Schiff bases including indol (L_1, L_2, L_3)

The polymeric-Schiff base L_1 (or L_2 or L_3) was prepared by reacting of (aminomethyl) polystyrene (1 g, 4,0 mmol/g -NH_2 loaded, 1% cross-linked) in hot dimethylformamide (DMF) (20 mL) and indole-3-carboxaldehyde (or 2-methylindole-3-carboxaldehyde or 2-phenylindole-3-carboxaldehyde) in DMF (15 mL), as shown in Fig. 1. Aldehyde solution was added to amine solution dropwise while stirring through 30 min. After 4 h of refluxing at 70 °C, the mixture was cooled to the room temperature and purification by acetone. The mixture was cooled to the room temperature and poured into acetone. The resulting clear colour solid was filtered, dried and kept in a desiccator over anhydrous $CaCl_2$.

2.3. Detection of antimicrobial and antifungal activity

The antibacterial and antifungal activities of the polymeric-Schiff bases including indol (L_1, L_2, L_3) were studied by the well-diffusion method against *Bacillus cereus sp.*, *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermis* (ATCC 12228), *Micrococcus luteus (ATCC 93419), Listeria monocytogenes 4b* (ATCC 19115), *Salmonella typhi H* (NCTC 901.8394), *Brucella abortus (RSKK-03026), Escherichia coli (ATCC 1230), Klebsiella pneumonia (ATCC 27853), Proteus vulgaris* (RSKK 96026) and *Candida albicans* (Y-1200-NIH). In this screening, DMF was used as solvent control. It was found to have no antimicrobial activity against any of the tested organisms. All polymeric-Schiff bases were kept dry at room temperature and dissolved (3.5 μg/mL) in DMF. 1% (v/v) of a 24-h broth culture containing 106 CFU/mL was placed in sterile Petri dishes. Molten nutrient agar was studied for culturing the test bacteria and it was kept at ca. 45 °C. The molten agar was added into sterile petri dishes and was allowed to solidify. Then, holes of 6 mm diameter were punched carefully using a sterile cork borer and the test solutions were completely filled into each of the bores. As the last stage, the bacteria were incubated at 37 °C for 24 h. The mean value obtained for all the holes were used to calculate the zone of growth inhibition of samples. Bacterial cultures and yeast were tested for resistance to five antibiotics (produced by Oxoid Ltd., Basingstoke, UK): ampicillin (preventing the growth of gram-negative bacteria), nystatin (binding to sterols in the fungal cellular membrane, altering the permeability, and allowing leakage of the cellular contents), kanamycin (sensitive gram (−) and gram (+) are indicated for the treatment of infections that are sensitive to microorganisms), sulphamethoxazole (a bacteriostatic antibacterial agent that interferes with folic acid synthesis in susceptible bacteria), amoxicillin (it is a penicillin effective against gram (+) and gram (−) microorganisms and it is a broad spectrum antibiotic with bactericidal effect).

2.4. Detection of antimutagenic activity

The anti-genotoxic properties of the polymeric-Schiff bases including indol (L_1, L_2, L_3) were studied against sodium azide (NaN_3) in human lymphocyte cells by sister chromatid exchanges (SCE) and micronucleus (MN) assays.

Peripheral blood lymphocytes were taken from four (two men and two women) non-smoking healthy individuals. Lymphocyte cultures were set up by adding 0.5 mL of heparinized whole blood to RPMI-1640 chromosome medium supplemented with 15% heat

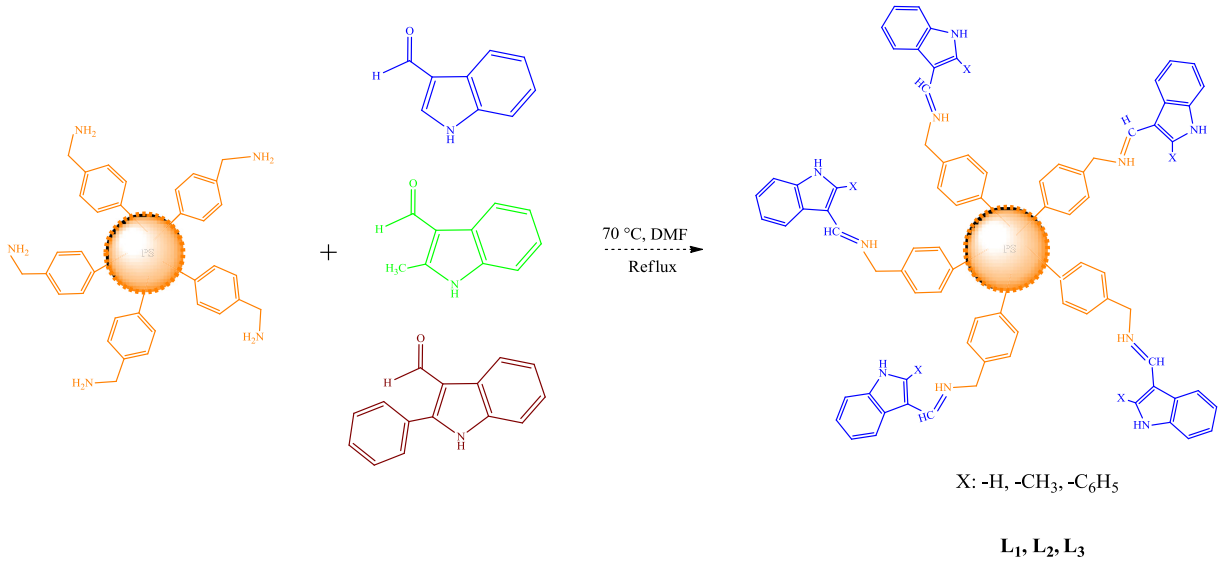


Fig. 1. Synthesis of polymeric-Schiff bases (L_1, L_2, L_3).

Table 1
Infrared vibrations, thermal data and physical properties of polymeric-Schiff bases (L_1, L_2, L_3).

Compound	Chemical formula Colour, M_w^a	(M_w, M_n), PDI	ν(CH)$_{arom.}$	ν(CH)$_{aliph.}$	ν(C=N)	ν(C=C)$_{arom.}$	T_i (°C)	$T_{1/2}$ (°C)	T_f (°C)	Residue mass at 900 °C (wt%)
L_1	$[(C_8H_8)_{10}(C_{18}H_{16}N)]$ Yellow, 1286	(1385, 1087), 1.27	3043	2909	1651	1585	268,12	450,13	871,43	15,25
L_2	$[(C_8H_8)_{10}(C_{19}H_{18}N_2)$ Yellow, 1314	(1329, 1201), 1.11	3014	2915	1614	1571	281,72	435,95	838,48	18,73
L_3	$[(C_8H_8)_6(C_{24}H_{20}N_2)]$ Yellow, 960	(970, 811), 1.20	3028	2929	1657	1586	271,85	453,46	901,26	22,53

*Determined by elemental analyses.

inactivated fetal calf serum, 100 IU/mL streptomycin, 100 IU/mL penicillin and 1% L-glutamine. Lymphocytes were stimulated to divide by 1% phytohaemagglutinin. The well-known mutagen NaN_3 (5 μM) was used as positive control.

The experiments were performed on eight groups for each compound as follows:

Group 1:Solvent control;
Group 2: 5 μM NaN_3;
Group 3: Compound 80 μg/mL;
Group 4: 5 μM NaN_3 + Compound (5 μg/mL);
Group 5: 5 μM NaN_3 + Compound (10 μg/mL);
Group 6: 5 μM NaN_3 + Compound (20 μg/mL);
Group 7: 5 μM NaN_3 + Compound (40 μg/mL);
Group 8: 5 μM NaN_3 + Compound (80 μg/mL);

For SCE demonstration, the cultures were incubated at 37 °C for 72 h, and 5-bromo 2-deoxyuridine at 8 mg/mL was added at the initiation of cultures. All cultures were kept in dark, and then, 0.1 mg/mL of colcemide was added 3 h before harvesting to arrest the cells at metaphase. The cultures were centrifuged at 1200 g for 10 min. The supernatants were used for enzyme analysis. Cells were harvested and treated for 28 min with hypotonic solution (0.075 M KCl) and fixed in a 1:3 mixture of acetic acid/methanol (v/v). Bromodeoxyuridine incorporated metaphase chromosomes were stained with fluorescence plus Giemsa technique as described previously [23]. In SCE study, by selecting 60 satisfactory metaphases, the results of SCE were recorded on the evaluation table. For each treatment condition, well-spread second division metaphases containing 42–46 chromosomes in each cell were scored, and the values obtained were calculated as SCEs per cell.

For MN analysis, the cultures were incubated at 37 °C for 72 h then Cytochalasin B was added 44 h after phytohaemagglutinin (PHA) stimulation to a final concentration of 3 g/mL. Twenty-eight hours later (after 72-h cultivation), the cells were harvested by centrifugation (1200r x 10 min). The supernatant was removed. The cells were harvested and treated for 20 min at 37 °C with hypotonic solution (0.05 M KCl), centrifuged for 10 min at 1200 r/min, and then fixed in a 1:3 mixture of glacial acetic acid/methanol (v/v). This fixative process was repeated three times. The cell pellet was then resuspended in 1 mL of fresh fixative, dropped onto a clean microscope slide, incubated at 37 °C or at room temperature overnight, and stained with Giemsa dye. Encoded slides were scored blind by two independent individuals. Only binucleated cells were scored for MN analysis. For each subject, at least 1000 binucleated cells were analyzed for the presence of MN [24]. For the MN scoring, the micronucleus criteria described by Countryman and Heddle were used: a diameter less than 1/3 of the main nucleus, non-refractility, not touching, and with the same colour as the nucleus or lighter [25].

3. Results and discussion

3.1. Characterization of polymeric-Schiff bases including indol (L_1, L_2, L_3)

The analytical data and some of physical properties of polymeric-Schiff bases including indol (L_1, L_2, L_3) are presented in Table 1. The weight average moleculer weight (*Mw*), the number average moleculer weight (*Mn*) and polydispersity index (PDI) were determined with gel permeation chromatography (GPC). Additionally, (*Mw*) was suggested from elemental analysis. The elemental analyzes can be considered compatible with the chemical formulas of the compounds.

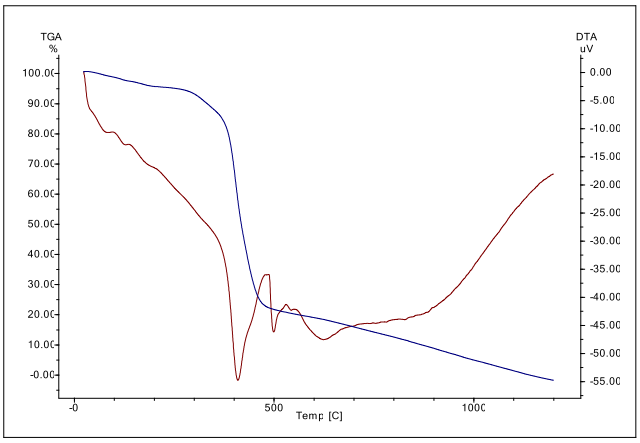
The characteristic IR spectra of polymeric-Schiff bases including indol are presented in Table 1. Imine bands were observed in the region 1614-1657 cm^{-1}. This observation indicate that the condensation of amine and carbonyl groups [26]. The νC = C bands of all polymeric-Schiff bases are observed in the ranges 1571-1586 cm^{-1} [27]. The ν(CH)aromatic and ν(CH)aliphatic bands were observed in the region 3014–3043 and 2909-2929 cm^{-1}, respectively.

Thermal analysis results of polymeric-Schiff bases including indol presented in Table 1 and in Fig. 2. The TGA curve of L_1 exhibited one-step weight. The values of initial (T_i) and finally (T_f) decomposition temperature were 268,12 and 871,43 °C, respectively. L_2 exhibited one-step weight and the values of T_i and T_f were 281,72 and 838,48 °C, respectively. The TGA curve of L_3 also consists

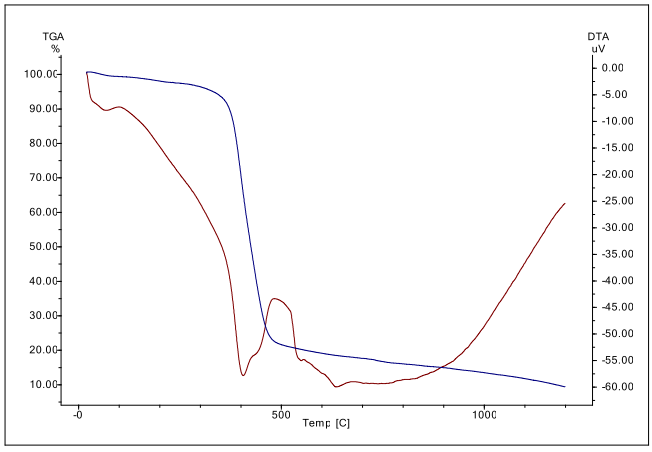
Table 2
Antimicrobial activities of polymeric-Schiff bases (L_1, L_2, L_3) (diameter of zone of inhibition (mm)).

Microorganisms	Compounds			Positive Control				
	L_1	**L_2**	**L_3**	K30	SXT25	AMP10	AMC30	NYS100
B.cereus sp.	25	19	25	–	–	–	–	–
S.aureus	15	18	22	25	24	30	30	–
S.epidermis sp.	20	18	23	–	–	–	–	–
M..luteus	–	–	–	–	–	–	–	–
L.monocytogenes 4b	20	27	23	–	–	–	–	–
S.typhi H	20	19	22	20	17	11	19	–
Br. abortus	–	–	–	–	–	–	–	–
E.coli	23	25	18	25	18	10	14	–
K.pneumoniae	–	–	–	–	–	–	–	–
P.vulgaris	20	25	22	–	–	–	–	–
C. albicans (Fungus)	30	26	30	–	–	–	–	20
DMF (solvent control)	–	–	–	–	–	–	–	–

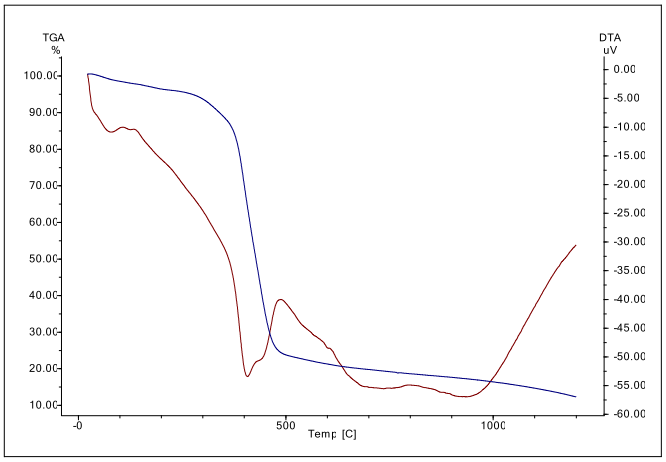
K30 Kanamycin 30 μg, SXT25 Sulfamethoxazol 25 μg, AMP10 Ampicillin 10 μg, AMC30 Amoxycillin 30 μg, NYS100 Nystatin 100 μg, (–; (positive control) not tried).



(a)



(b)



(c)

Fig. 2. TGA/DTA curves of polymeric-Schiff bases (L_1) (a), (L_2) (b), (L_3) (c).

of one decomposition step in the range of 271,85 and 901,26 °C. In the decomposition process of the polymeric-Schiff bases, the mass losses under 150 °C, can be evaluated as the absorbed volatile molecules and low molecular weight segments in polymer matrix [28]. Maximum mass loss of the compounds is at 900 °C. According to the high decomposition temperature values, it can be concluded that all compounds are thermally stable. The TGA curve of (L_1, L_2, L_3) exhibited residue mass of 15,25%, 18,73% and 22,53% at 900 °C, respectively. In the disintegration of the polymeric-Schiff bases, these values corresponded to the percent of residual solid in polymer matrix at final temperature.

The molecular weights (*Mw*, *Mn*) and the molecular weight distribution (Mw/Mn) are given in Table 1. According to the gel permeation chromatography, polymeric-Schiff bases have a very narrow molecular weight distribution (PDI: 1.27, 1.11 and 1.20 for L_1, L_2 and L_3, respectively).

3.2. Antimicrobial activity

The antifungal and antimicrobial activities for polymeric-Schiff bases including indol (L_1, L_2, L_3) are presented in Table 2. The polymeric-Schiff bases were screened for antimicrobial activity against gram positive *Bacillus cereus sp.*, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Micrococcus luteus, Listeria monocytogenes 4b*, gram negative *Salmonella typhi H, Brucella abortus, Escherichia coli, Klebsiella pneumonia, Proteus vulgaris* and the fungus *Candida albicans* in DMF solvent control. All polymeric-Schiff bases are exhibited varying degree of inhibitory effects on the growth of different tested pathogenic strains. L_1 and L_3 are exhibited the highest antibacterial activity against *Bacillus cereus sp.* The bacteria is known as opportunist pathogens and is associated with food-borne illness [29]. L_2 is showed the highest activity against *Listeria monocytogenes 4b*. The pathogen is the causative agent of listeriosis which is the leading cause of death among foodborne bacterial pathogens [30]. Additionally, the antimicrobial activity of L_1, L_2 and L_3 was also compared with five commercial antibiotics. L_3 is showed higher antibacterial activity than K30 antibiotic, which is showed the highest activity for *S.typhi H.* It is known as enteric fever and is responsible for causing diseases typhoid fever in humans. K30 is also showed the highest activity for *E.coli.* L_2 is exhibited the same activity as this antibiotic. *E.coli.* Additionally, L_1, L_2 and L_3 are showed higher antifungal activity than NTYS100 antibiotic. This shows that all substances are effective against yeast. *C. albicans* is caused some infections for people and animals for antifungal activity [31]. The antibacterial screening results indicate that the polymeric-Schiff bases including indol (L_1, L_2, L_3) are more effective against gram positive bacteria.

3.3. Antimutagenic activity

The antimutagenic activities for polymeric-Schiff bases including indol (L_1, L_2, L_3) are presented in Table 3. The antigenotoxic effects of polymeric-Schiff bases were investigated against NaN_3 in human lymphocyte cells by MN and SCE tests. NaN_3 is a well-known genotoxic agents, widely affecting many organisms. The different concentrations (5, 10, 20 and 40 μg/mL) of L_1, L_2, L_3 were studied for reduced the toxic effect of NaN_3. Compared to control group with SCE and MN frequencies determined when NaN_3 is added to culture media, NaN_3 is determined to induce DNA damage. The SCE and MN frequencies are increased depending on NaN_3 and observed values are statistically significant ($p < 0.05$). A comparison is made between the polymeric-Schiff bases (L_1, L_2, L_3) and their concentrations in order to prevent NaN_3 increasing the SCE and MN frequencies. According to these screening results, it was determined that the polymeric-Schiff bases have no antimutagenic properties. L_3 has more effect at a concentration of μg/mL compared to L_1 and L_2. The antimutagenic effects of the compounds may be related to their antioxidant action or cofactor on the enzymatic activation system [32].

Table 3
The effects of polymeric-Schiff bases (L_1, L_2, L_3) and NaN_3 on SCE and MN.

Test Items	Concentrations	Range of SCE	SCE/Cell ± S.E.	MN numbers ±S.E.
Solvent control		2–7	6.04 ± 0.2^{a}	4.23 ± 0.71^{a}
NaN_3	5 μM	8–14	13.70 ± 0.22^{e}	9.34 ± 0.52^{e}
L_1	80 μg/mL	2–6	6.07 ± 0.18^{a}	4.42 ± 0.48^{b}
$NaN_3 + L_1$	5 μM + 5 μg/mL	7–13	13.50 ± 0.12^{e}	9.12 ± 0.40^{e}
$NaN_3 + L_1$	5 μM + 10 μg/mL	6–12	13.64 ± 0.17^{e}	9.04 ± 0.55^{e}
$NaN_3 + L_1$	5 μM + 20 μg/mL	5–12	13.30 ± 0.53^{e}	9.00 ± 0.73^{de}
$NaN_3 + L_1$	5 μM + 40 μg/mL	4–11	13.42 ± 0.81^{e}	8.92 ± 0.33^{d}
$NaN_3 + L_1$	5 μM + 80 μg/mL	3–8	13.26 ± 0.44^{e}	8.95 ± 0.35^{d}
L_2	80 μg/mL	2–6	6.10 ± 0.18^{a}	4.36 ± 0.48^{a}
$NaN_3 + L_2$	5 μM + 5 μg/mL	7–13	13.68 ± 0.17^{e}	9.20 ± 0.17^{e}
$NaN_3 + L_2$	5 μM + 10 μg/mL	6–13	13.46 ± 0.66^{e}	9.14 ± 0.64^{e}
$NaN_3 + L_2$	5 μM + 20 μg/mL	5–12	13.52 ± 0.76^{e}	9.09 ± 0.87^{e}
$NaN_3 + L_2$	5 μM + 40 μg/mL	4–10	13.54 ± 0.33^{e}	8.96 ± 0.28^{d}
$NaN_3 + L_2$	5 μM + 80 μg/mL	3–8	13.40 ± 0.35^{e}	8.90 ± 0.44^{d}
L_3	80 μg/mL	2–8	6.14 ± 0.11^{ab}	4.34 ± 0.48^{a}
$NaN_3 + L_3$	5 μM + 5 μg/mL	7–12	13.00 ± 0.73^{d}	9.06 ± 0.19^{e}
$NaN_3 + L_3$	5 μM + 10 μg/mL	6–12	12.84 ± 0.16^{de}	8.92 ± 0.54^{d}
$NaN_3 + L_3$	5 μM + 20 μg/mL	5–11	12.70 ± 0.64^{d}	8.90 ± 0.57^{d}
$NaN_3 + L_3$	5 μM + 40 μg/mL	4–9	12.74 ± 0.38^{d}	8.86 ± 0.45^{cd}
$NaN_3 + L_3$	5 μM + 80 μg/mL	3–7	12.68 ± 0.25^{cd}	8.94 ± 0.97^{d}

Sodium azide (NaN_3) was used as positive controls for human lymphocytes.
L_1: $[(C_8H_8)_{10}(C_{18}H_{16}N)]$; L_2: $[(C_8H_8)_{10}(C_{19}H_{18}N_2)]$; L_3: $[(C_8H_8)_6(C_{24}H_{20}N_2)]$.
[a, b, c, d, e, f] Statistically significant differences in the same column are indicated by the different superscripts ($\alpha = 0.05$).

4. Conclusions

In this work, novel polymeric-Schiff base including indol were synthesized by condensation method and were structurally identified using spectral analyses. The inhibitory activities of the polymeric-Schiff bases were investigated against the mutagenic effects of NaN_3. The protective roles of the compounds are related to their concentration. The antimicrobial activities of the compounds were also evaluated for antimicrobial activity against some pathogenic strains. All compounds were exhibited varying degree of inhibitory effects on the growth of different tested pathogenic strains. According to the antimicrobial results, it can be said that the polymeric-Schiff base including indol are pharmacologically active compounds and may be used in various biomedical applications as antimicrobial agents.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2019.06.042.

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