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RESEARCH ARTICLE

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Synthesis, antimicrobial and anticancer activities of Tetronic 1107 Schiff bases

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Abstract

As a result of the serious issues connected to the bacterial infections, there is an imperious need to improve strong and ecofriendly antimicrobial polymers to overcome the limitations of conventional antimicrobial agents. In this trend, poloxamines (Tetronics) which are X-shaped poly(ethylene oxide)–poly(propylene oxide) diblocks linked to a focal ethylenediamine group; were successfully modified to produce Tetronic Schiff base for enhancing the biological activities of Tetronic 1107. Modification of tetronic 1107 (T1107) was proceeded throughout chloroacetylation of T1107 followed by amination using *p*-phenylenediamine then the latter was treated with different aldehydes to yield Tetronic Schiff bases. Characterization of Tetronic Schiff bases was carried out by ^{1}H-NMR, Fourier-transform infrared spectroscopy, X-ray diffraction, elemental analysis and thermogravimetric analysis (TGA) analyses. The antimicrobial activities of four tested compounds coded (EK1, EK2, EK3, and EK4) were quantified using Microtiter-assay methods. The obtained data revealed potential antimicrobial activities for tested compounds against all tested microbes with priority against *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*. Sample coded EK4 exhibited the most effective treatment against *P. aeruginosa*, *Candida albicans*, *S. aureus* and *E. Coli* with minimal inhibitory concentration values of 6, 16, 12.5, and 1.5 μM, respectively. Furthermore, the safety results confirmed that EK4 and EK1 were the safest treatment with IC_{50} values of 76.01 and 62.67 μM, respectively. In addition, all tested compounds showed significant anticancer effects against MDA-MB-231cell line, while EK3 was effective treatment against A549 cell line with IC_{50} values of 39.63 μM. Meanwhile, both EK2 and EK4 showed the highest selectivity index (SI) values against MDA-MB-231 cell line with values 2.5 and 3.07, respectively. Interestingly, EK4 showed the maximum SI values on A549 and *Hep-G2* cell lines with values 1.62 and 1.52, respectively.

KEYWORDS
antimicrobial materials and anticancer materials, poloxamines, Schiff base, Tetronic 1107

1 | INTRODUCTION

Contagious diseases resulting from pathogenic microorganisms are a main problem in various biomedical areas including healthcare products, hygienic applications, food packaging and storage. Also, despite significant progress in understanding the mechanism of the cancer, antimicrobial diseases, the development of appropriate anticancer and antimicrobial agents for them.[1–5] Meanwhile, this is an urgent need for new and more selective anticancer and antimicrobial agents.[6] To get rid of these problems, new species of polymers that can display antimicrobial activity with various other functionalities are of prodigious value.[7]

Recently, researchers have localized on novel polymeric materials which have antimicrobial action.[8-14] The synthesis of polymers Schiff base improved the physicochemical features of the end products, such as thermo-stability, and synthetic variety. Schiff bases revealed varied biological activities, including antifungal, antiproliferative, antibacterial, anti-inflammatory, antimalarial, antiviral, antitumor, anti-COVID-19, and antipyretic properties.[15-20] The biological activities of various polymers containing Schiff base moiety were recorded, for example Chitosan,[21-23] cellulose,[24,25] and acrylic acid derivatives.[26,27] Tetronics are amphiphilic, synthetic polyethers composed of polyethylene oxide and polypropylene oxide connected to ethylenediamine central.[28] Tetronics are broadly used in various applications such as anti-foaming and wetting agents, thickeners, dispersants, and emulsifiers for diverse industrial drives.[29,30] Tetronics are regularly useful in biomedical domains such as genetic immunization, drug delivery, and membrane biochemistry.[31-36] Despite of this numerous and potential pharmaceutical applications, there are presently no studies reporting the antibacterial activity of tetronic derivatives. Whereas, slight modifications of Tetronic surface have been recently reported. Sosnik et al. modified Tetronic-methacrylate hydrogels with positively charged groups with the aim of improving cell attachment.[37] Composite hydrogel scaffolds of Tetronic 1107-acrylate and mix of collagen and hyaluronic acid were prepared and used for tissue engineering applications.[38] Liu et al.[39] and Chakrabarti et al.[40] studied the aggregation attitudes of Tetronic 1107 in different solvents. Tetronics were modified with allyl iodide to produce N-allylated T1107 to progress their versatility as drug nanocarriers.[35]

Regarding the exclusive structure of tetronics and its modification, there is a deficiency in chemical modification of the hydroxyl end groups in the literature.

In the current study, Tetronic 1107 was reacted with chloroacetyl chloride followed by modification with *p*-phenylendiamine which finally reacted with different aldehydes yielding Tetronic Schiff bases; which have never been reported. Tested four compounds were bio-evaluated in terms of their antimicrobial activity, selective index, cytotoxicity and anticancer activity.

2 | EXPERIMENTAL PART

2.1 | Materials

Tetronic 1107 (Mwt.: 15 kDa, HLB: 18–23, PEO = 60, PPO = 20) was obtained from BASF corporation and it was used without additional purification. Chloroacetyl chloride was purchased from El- Gomhouria chemicals company, Egypt and was utilized as received. Pyridine and diethyl ether were supplied from El-Nasr pharmaceutical chemicals, Egypt. Pyridine was dried with solid KOH followed by fractional distillation. *p*-phenylenediamine (PDA) was purchased from Acros, chemicals, USA. *p*-Chlorobenzaldehyde, *p*-hydroxybenzaldehyde and *p*-dimethyl aminobenzaldehyde was obtained from Sigma-Aldrich, USA and were used without crystallization. Absolute ethanol was purchased from Merck-Schuchardt, Hohenbrunn, Germany.

2.2 | Instrumental characterization

Fourier-transform infrared spectroscopy (FT-IR) spectral data were registered on a Perkin–Elmer 1430 ratio (Massachusetts, US). The samples were scanned against a blank pellet background of KBr within the wavelength range of 400–4000 cm^{-1} at Faculty of science, Tanta university, Egypt.

^1H NMR spectra were characterized using a Varian Mercury 300 spectrometer (California, USA). DMSO-d_6 and $CDCl_3$ were used as solvent at Faculty of Science, Kafr-Elsheikh University, Egypt.

Elemental microanalysis was preceded using Elemental Analyzer Model 1106, Carlo Erba Strumentazione, (Milan, Italy) at Microanalytical Center-Cairo University, Cairo, Egypt.

X-ray diffraction (XRD) was obtained with (Panalytical EMPYREAN, England) with CuK (=1.540 Å). The XRD patterns were measured at ambient temperature using GNR, APD 2000 PRO step scans X-ray diffractometer, Cu-K radiation (generator setting of 40 kV and 30 mA), scanning range of 2θ 5°–60° with a scanning step of 0.02θ at Nanotechnology Research Center, The British University in Egypt, Cairo, Egypt.

TGA and Differential thermogravimetric (DTG) were performed using a (Perkin Elmer TGA 4000 Thermogravimetric analyzer); samples of 5–10 mg was located into alumina crucibles and scanned (from 50 to 800°C) with rate 30°C/min surrounded by N_2 with a flow rate of 20 ml/min at Faculty of science, Tanta University.

Rotary evaporator, IKA RV 10 V digital rotary evaporator, 115 VAC, Germany.

Vacuum oven was supplied from BINDER Model VD 53, Germany.

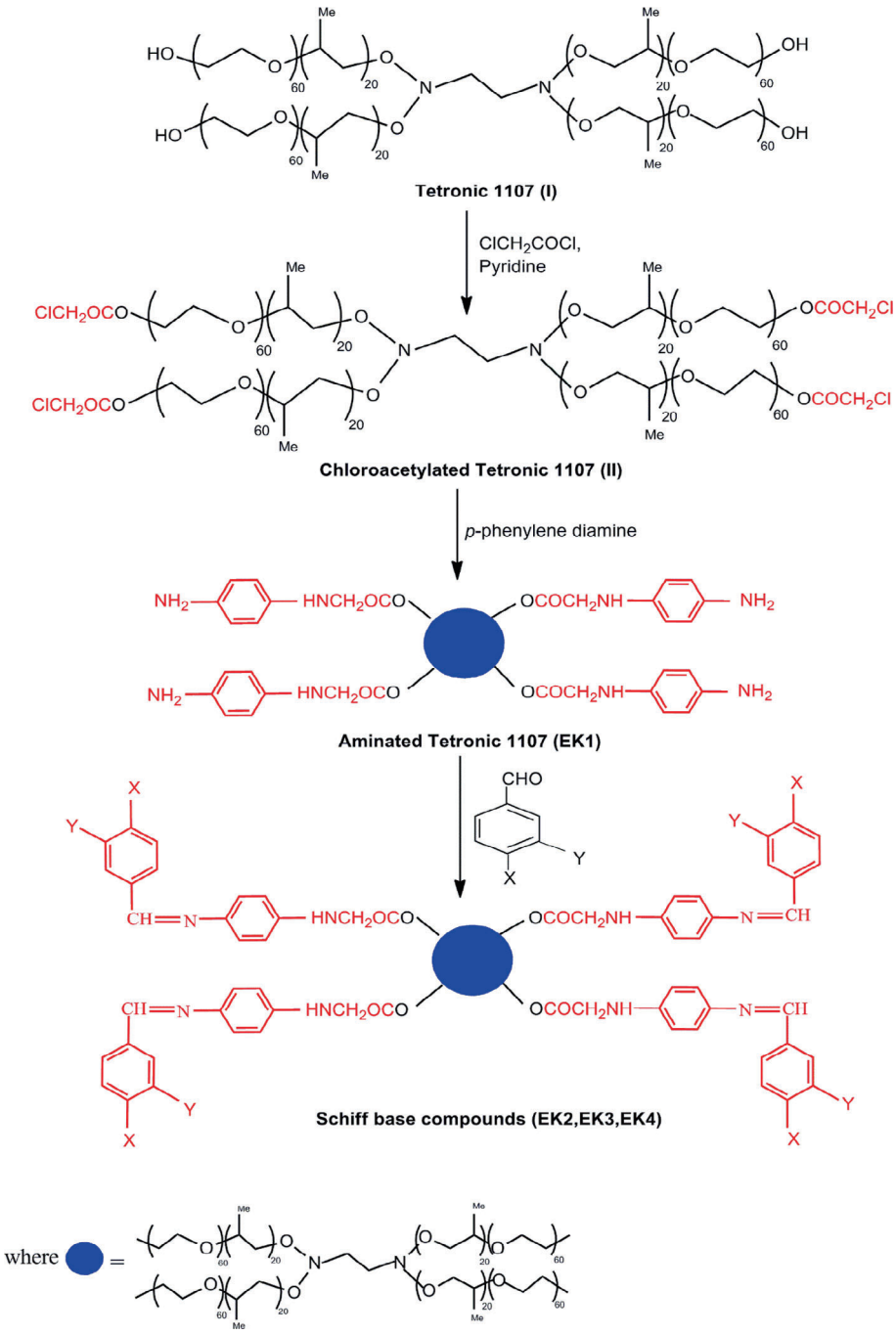
2.3 | Chloroacetylation of Tetronic 1107 (II)

They were carried out as reported previously in our work.[42] Briefly, chloroacetyl chloride (19 ml, 240 mmol) was added dropwise to the cold mixture of Tetronic 1107 (I) (10 g, 20 mmol) and pyridine (19 ml, 240 mmol) in dry ethanol with persistent stirring. Then, the reaction mixture was proceeded for 2 days. The precipitate was washed with diethyl ether after ethanol evaporation, then was dried under vacuum oven for 10 h (Scheme 1).

2.4 | Amination of chloroacetylated Tetronic 1107 (aminated T1107) (EK1)

The hot ethanolic solution of *p*-phenylenediamine (13 g, 120 mmol) and chloroacetylated Tetronic 1107 (5 g, 6 mmol) were mixed. Then,

SCHEME 1 Schiff base formation of Tetronic 1107.



Polymer code	Aldehyde	X	Y
EK2	*p*-dimethylamino benzaldehyde	$(CH_3)_2N$	H
EK3	*p*-hydroxybenzaldehyde	OH	H
EK4	*p*-chlorobenzaldehyde	Cl	H

the procured mixture was refluxed for 4 days with uninterrupted stirring. The product was crystallized from ethanol and finally dried under vacuum for 48 h (Scheme 1).

2.5 | Synthesis of Tetronic Schiff bases (EK2, 3 and 4)

To an ethanolic solution of different aldehydes (*p*-dimethyl aminobenzaldehyde, *p*-hydroxy benzaldehyde and *p*-chlorobenzaldehyde) (8 mmol), aminated T1107 (EK1) (1 mmol) and five drops of glacial acetic acid were added. The reaction was proceeding at room temperature for 48 h, and then was heated to the ethanol boiling point for 10 h. The product was collected and washed with ethanol to remove the unwanted species, then was vacuum dried (Scheme 1).

2.6 | Microbial strains and cell lines

Bacterial strains of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus mutans* and the fungal strain *Candida albicans* were provided by Genetic Engineering and Biotechnology Research Institute (GEBRI), (SRTA-City), Egypt. *WISH cell* line (human amnion-derived normal epithelial cells), *MDA-MB-231* cell line (human, mammary gland/breast adenocarcinoma), *Caco-2* cell line (human colorectal adenocarcinoma, epithelial cells), *A549 cell* line (human lung adenocarcinoma, epithelial cells) cell lines and *HepG-2* (liver hepatocellular carcinoma) were purchased from the American Type Culture Collection (ATCC), Manassas, Virginia, USA.

2.7 | Biological activities

2.7.1 | Antimicrobial activities

The antimicrobial activity of EK1, EK2, EK3, and EK4 samples was tested against different multiple drug resistant microbes using different concentrations (500–15 μM). An aliquot of 100.0 μl of each sample concentration was mixed with an equal volume of each microbial dilution (about 10^6 CFU/ml) and inoculated into 96 well plate. Furthermore, 100.0 μl of LB media was incubated with 100.0 μl of microbial growth to establish the negative control group. After that, the prepared plates were incubated overnight at 37°C then, the microbial turbidity was measured within the automated ELIZA microplate reader (Binder Bioteck E LX 800) at 620 nm.

The microbial inhibition percentages after treatments were counted using the given equation:

$$\text{Inhibition percentage} = (A - A1/A0) \times 100, \quad (1)$$

where, *A*: the absorbance of the treatment group, *A*1: the absorbance of the blank, and *A*0: the absorbance of the control group.

The lowest concentration of the tested samples which resulted in the microbial growth inhibition was calculated and stated as the minimal inhibitory concentration (MIC).

2.7.2 | Safety assay

Safety assay was carried out by using MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) kit to quantify the exact treatment concentration which does not induce a toxic effect on the non-cancerous cell line (*WISH cells*). An aliquot of 100.0 μl of 6×10^4 cell/ml cells was seeded in each well of 96-well plates, the seeded plates were incubated for 24 h at 37°C in humidified 5.0% CO_2 or till semi-confluency. After incubation, 100.0 μl of different treatment concentrations (500–15 μM) medium was replaced with the exhausted old. The prepared plates were incubated at the previous growth conditions for another 24 h. After incubation, cellular viability was measured using an MTS assay kit (Promega) according to the instructions of its manual.

In vitro anticancer activities

The anticancer activity of the tested samples against A549, *Caco-2* and *HepG2* and *MDA-MB*-231 cell lines was studied using the MTS assay protocol as described previously.

Selectivity index

Cancer cell selectivity index of EK1, EK2, EK3 and EK4 samples was estimated as reported by Koch et al.,[43] with a minor modification as given equation:

$$\text{SI} = \text{IC}_{50}\text{nc}/\text{IC}_{50}\text{cc}, \quad (2)$$

where, IC_{50}nc refers to the value of IC_{50} of the tested compounds on normal cells, while IC_{50}cc refers to the IC_{50} of the tested compound on cancer cell line.

3 | RESULTS AND DISCUSSION

3.1 | Chloroacetylation of Tetronic 1107

The FT-IR spectrum of Tetronic 1107 (I) displays characteristic absorption peaks at ν 3446, 2904, 1109 cm^{-1} for ν (O–H), ν (C–H), and ν (C–O–C), respectively. All the characteristic absorption bands of T1107 (I) were also observed on the chloroacetylated Tetronic 1107 (II) spectrum in addition to the presence of new peaks at ν 753 cm^{-1} assigned to ν (CH_2Cl) and 1740 cm^{-1} assigned to ν (C═O) which confirm the chloroacetylation of terminal hydroxyl groups as shown in (Figure 1). Similar results were observed by Kenawy et al. for chloroacetylation of polyvinyl alcohol.[44]

The ^{1}H-NMR spectrum of the chloroacetylated Tetronic 1107 (II) showed a characteristic band at δ 4.08 ppm, which attributed to

protons of chloroacetate group. There are also bands at δ 1.12 ppm and δ 3. 27–3.85 ppm, which belong to protons of T1107 (I).[45]

3.2 | Amination of chloroacetylated T1107 (aminated T1107) (EK1)

The FTIR spectrum of aminated T1107 (EK1) showed peaks at ν 3399, 3321 cm^{-1} attributed to the new amino group (NH_2), strong band at ν 829 cm^{-1} for (C—H aromatic) and peaks at ν 1510, 1571 cm^{-1} for (C═C aromatic) as shown in (Figure 1).[28,46]

^{1}H-NMR spectrum of aminated T1107 (EK1) was confirmed by the appearance of the resonance signals at δ 3.3 ppm (NH_2), δ 6.5–7.3 ppm, which belong to aromatic protons, δ 3.27–3.62 ppm (CH_2) and δ 1.12–1.13 ppm (CH_3) in the main chain.

3.3 | Synthesis of Schiff base of T1107 (EK2, 3 and 4)

The FT-IR spectral data of Schiff base polymers (EK2–4) show strong band at ν 1581–1603 cm^{-1} due to ν (C═N) which confirm formation of Schiff base (Figure 2). The FT-IR spectrum of polymer EK4 displays a strong band at ν 709 cm^{-1} due to ν C-Cl group of *p*-chlorobenzaldehyde. The results are represented concisely in (Table 1).

The ^{1}H-NMR spectra of Schiff base polymers (EK3, EK4) were characterized by the appearance of peak at δ 8.5 ppm (CH═N) which confirms the formation of Schiff base of Tetronic 1107.

Polymers (EK3, EK4) show bands at δ 1.2 ppm, due to CH_3 protons, at δ 3.8, 3.5 ppm, respectively, due to CH_2 protons, at δ 6.7–7.9 ppm due to aromatic protons and δ 10.67 ppm due to OH proton in polymer EK3. The same results were reported by Kenawy et al. for poly(hydroxystyrene-co-methylmethacrylate) Schiff bases.[28] Tetronic and its Schiff bases were also depicted by elemental analyses which are consistent with the theoretical (calculated) values as shown in Table 2.

The TGA and DTG curves of T1107 (I) and modified T1107 (EK1-4) were shown in Figures 3 and 4, respectively. The 5 and 50% weight loss temperature ($T_{-5\ w\%}$, $T_{-50\ wt\%}$) and the total weight loss of polymers were listed in Table 3. The maximum rate of decomposition temperature (T_{peak}, first derivative peak temperature) was also measured. TGA pattern of pure T1107 (I) was analogous to aminated T1107 (II) and Schiff base (EK4) which shows a single step of degradation. While, thermograms of both Schiff bases (EK2) and (EK3) show three steps of degradation phases. Pure T1107 (I) shows the maximum weight loss at 403°C (from DTG curve) losing 75% of its weight and this is consistent with previous reports related the decomposition of T1107 polymer.[47] The total weight loss at 800°C for polymer (EK3) was 71%, which is considered the most stable among the modified polymers. This implies that, introducing *p*-hydroxybenzaldehyde moiety on the side chain of Tetronic increased its thermal stability. The thermal stability of pure Tetronic (I) and polymer (EK2) are almost the same (97% as a total loss) as shown in Table 3.

XRD patterns of Tetronic 1107 and their derivatives are displayed in Figure 5. Pure Tetronic 1107 (I) shows two characteristic patters at angle $2\theta = 19.2, 23.5°$ as previously reported,[48] while aminated Tetronic 1107 (EK1) shows a series of sharp lines in the regions of 17.3° < 2Θ >43°, which depicts that the aminated Tetronic has high crystallinity and long range ordering. Notably, XRD patterns of Tetronic Schiff bases (EK2, 3 and 4) also reveal multiple peaks, which are an indication to the crystallization is occurred obviously. Polymer (EK2) shows several patters in the regions of 2θ 6.7° to 28.2°, polymer (EK4) at 2θ 14° to 48° and polymer (EK3) at 2θ 11.09° to 33.6°, respectively. The peaks of neat Tetronic are still observed in the Schiff base spectra, however relatively with low intensity. From the presented patterns, it is noticed that, there is no broadening of peaks due to amorphous components as shown in Figure 5. The inter-planar distance was determined using Bragg's law,[49] as recorded in Table 4.

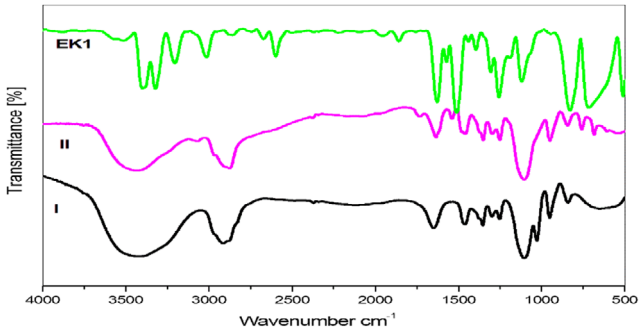


FIGURE 1 Fourier-transform infrared spectroscopy spectra of Tetronic 1107 (I), chloroacetylated Tetronic 1107 (II) aminated Tetronic 1107 (EK1).

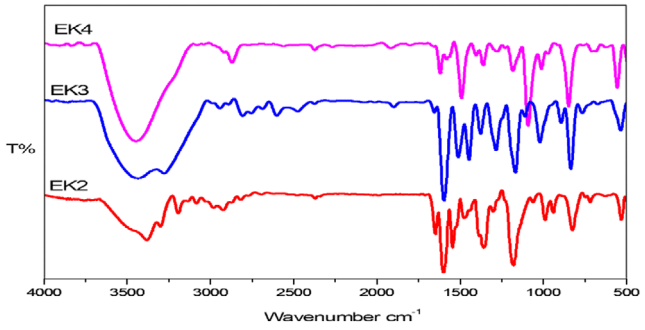


FIGURE 2 Fourier-transform infrared spectroscopy spectra of Schiff base of aminated Tetronic with *p*-dimethylamino benzaldehyde (EK2), *p*-hydroxybenzaldehyde (EK3) And *p*-chlorobenzaldehyde (EK4).

TABLE 1 Fourier-transform infrared spectroscopy analysis of Schiff base of Tetronic 1107 (EK2-4).

Polymer code	C—H (aliph)	CH═N	C—H (Ar)
EK2	2979,2818	1599	825
EK3	2942,2891	1603	834
EK4	2870	1581	846

3.4 | Antimicrobial assay

The antimicrobial assay was carried out against different multiple drug resistant strains using microplate assay method. The results indicate that, all tested compounds show remarked potentialities against all tested microbes with priority against *P. aeruginosa*, *E. coli* and *S. aureus* (Figure 6).

Furthermore, sample coded EK4 exhibits the most effective treatment against *p. aeruginosa*, *C. albicans*, *S. aureus* and *E. Coli* with MIC values of 6, 16, 12.5, and 1.5 μM, respectively. Furthermore, *Strep. mutans* shows the most resistant strain to treatments, however the sample coded EK1 treatment shows a moderate inhibitory effect against it with a MIC value of 18.5 μM (Figure 7).

3.5 | Safety assay and anticancer efficacy of treatments

The safety assay was accomplished using MTS assay to indicate the safety pattern of the tested four compounds against non-cancerous cell line (WISH). The obtained results indicated that, samples coded EK4 and EK1 were the safest treatment (Figure 8A), with IC_{50} = 76.01 and 62.67 μM, respectively. In addition, all treatments show activity against all tested cell lines with great inhibition potentialities against *MDA-MB-231* cell line (Figure 9A). EK3 treatment is the effective treatment against *A549* cell line (Figure 8B) with IC50 value of 39.63 μM followed by EK4 and EK1 with IC_{50} values of 46.88 and 50.4 μM, respectively (Figure 9A). Both *Caco-2* and *HepG-2* cell lines are the most resistant cell lines to treatments; while, EK1 and EK3 show noticeable effects against *Caco-2* and *HepG-2* cell lines, respectively, with IC_{50} values of 50.72 and 41.69, respectively (Figure 9A). As highlighted, *MDA-MB-231* cell line is the most sensitive cell line for the treatment and both EK2 and EK4 show the highest SI values of 2.5 and 3.07, respectively (Figure 9B). In addition, EK4 shows the maximum selectivity index (SI) values on A549 and Hep-G2 cell lines with values 1.62 and 1.52, respectively (Figure 9B).

3.6 | Mode of action test

It is notable that, the antimicrobial effect of Schiff base polymers was varied according to the aldehyde used and the tested microorganism. In previous studies, the quaternary ammonium salts inhibit bacterial activity within interacting with the cell

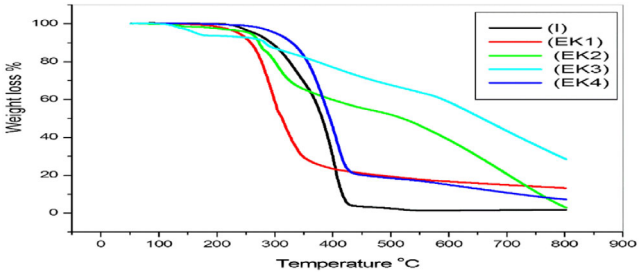


FIGURE 3 Thermogravimetric analysis of Tetronic 1107 (I), aminated Tetronic 1107 (EK1) and Schiff bases (EK2-EK3 and EK4).

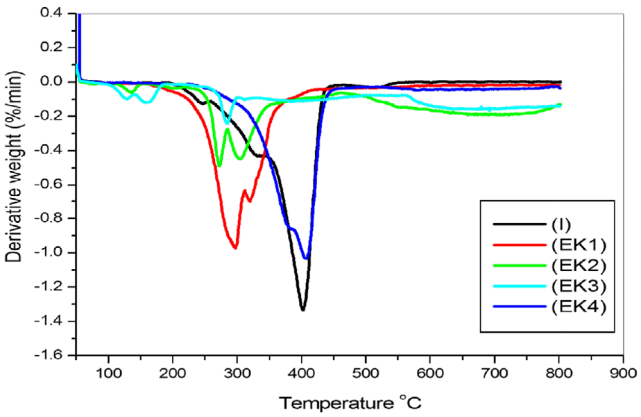


FIGURE 4 Differential thermogravimetric (DTG) curves of Tetronic and their derivatives.

TABLE 2 Elemental analysis of Tetronic 1107 and its modification.

	%C		%H		%Cl		%N	
Code	**Calculated**	**Found**	**Calculated**	**Found**	**Calculated**	**Found**	**Calculated**	**Found**
(I)	49.6	50.13	9.0	10.06	–	–	5.2	4.0
(II)	42.9	40.30	6.20	5.32	16.90	14.33	3.3	3.0
(EK1)	57.8	56.2	7.19	6.76	–	–	12.4	11.7
(EK2)	65.6	62.9	7.65	5.47	–	–	11.9	12.0
(EK3)	65.2	66.6	6.89	5.08	–	–	9.28	7.90
(EK4)	62.19	63.5	6.30	3.47	8.7	8.2	8.80	8.22

Polymer code	**Aldehyde**	**X**	**Y**
EK2	*p*-dimethylamino benzaldehyde	$(CH_3)_2N$	H
EK3	*p*-hydroxybenzaldehyde	OH	H
EK4	*p*-chlorobenzaldehyde	Cl	H

TABLE 3 Thermal analysis data of Tetronic and its modifications.

Samples code	$T_{-5wt\%}$ (°C)	$T_{-50wt\%}$ (°C)	T_{peak} (°C) (DTG)	%Total loss of mass
I	263	381	403	98
EK1	237	314	296,320	87
EK2	253	521	135,241,304	96.8
EK3	164	657	127,160,284	71
EK4	302	396	410	92.5

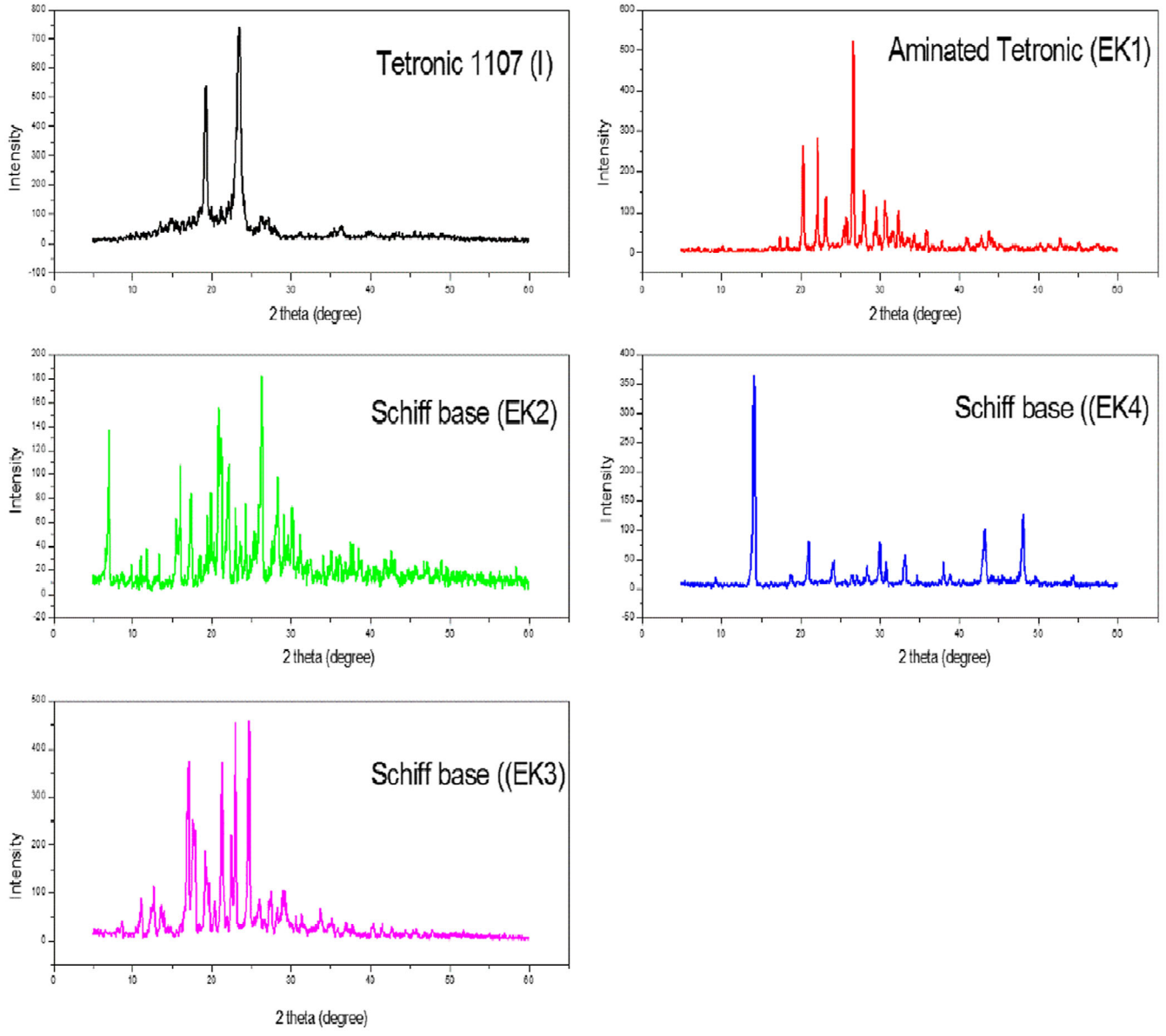


FIGURE 5 X-ray diffraction patterns of Tetronic 1107 (I), aminated Tetronic 1107 (EK1) and its Schiff base (EK2, EK3, and EK4).

membrane.[50–52] Thus, the inhibitory effect of tested polymers could be due to the influential charge density of the active sites. It is rational to visualize that the charge density of the aminated Tetronic with different aldehydes leads to improved absorption into the microbial cells. The cytoplasmic membranes contain numerous negatively charged species such as acidic phospholipids and some membrane proteins. Microbial activity of the biocides basically results from the disruption of the plasma membrane.

Therefore, it is rational to suppose that larger the amount of the bound biocide, the more stimulated is the disruption, and consequently leads to rising the inhibitory effect. Tetronic Schiff base bearing *p*-chlorobenzaldehye moiety (coded EK4) records the highest antimicrobial effect and this result is consistent with a previous report of Kenawy et al..[53]

TABLE 4 The d-spacing and 2θ of Tetronic 1107 and their derivatives.

Polymer	2θ degree angle	*d* value (Å)
T1107 (I)	19.2	4.6
	23.5	3.77
Aminated T1107 (EK1)	20.3	4.3
	22.1	4.01
	26.6	3.34
(EK2)	6.9	12.7
	20.8	4.25
	26.4	3.39
(EK3)	17	5.2
	21.3	4.17
	24.7	3.6
(EK4)	14.2	6.22
	43	2.09
	49.6	1.89

4 | CONCLUSIONS

The possibility of developing a novel Schiff base possessing high antibacterial and anti-cancer effect based on Tetronic for the first time in literature was achieved successfully. The current study verified the possible usage of aminated Tetronic 1107 (EK1) and its Schiff base of *p*-chlorobenzaldehyde (EK4) as antimicrobial agents against drug resistant microbial strains. Furthermore, both EK4 and EK1

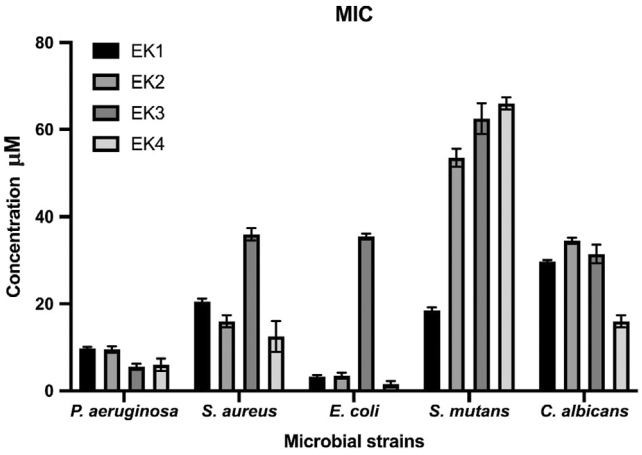


FIGURE 7 Minimal inhibitory concentration of four tested compounds versus *p. aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mutans*, and *Candida albicans*

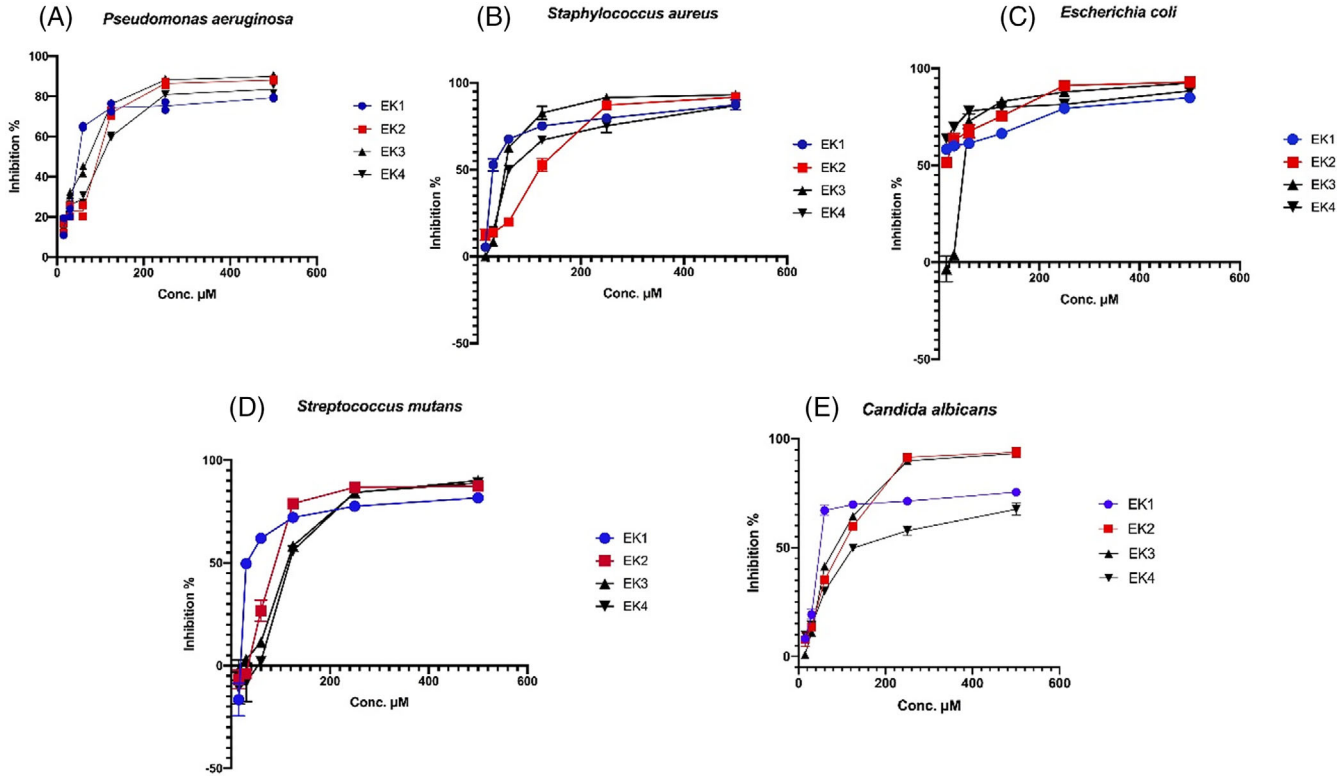


FIGURE 6 Antimicrobial effects of Tetronic 1107 against *Pseudomonas aeruginosa* (A), *Staphylococcus aureus* (B), *Escherichia coli* (C), *Streptococcus mutans* (D) and *Candida albicans* (E).

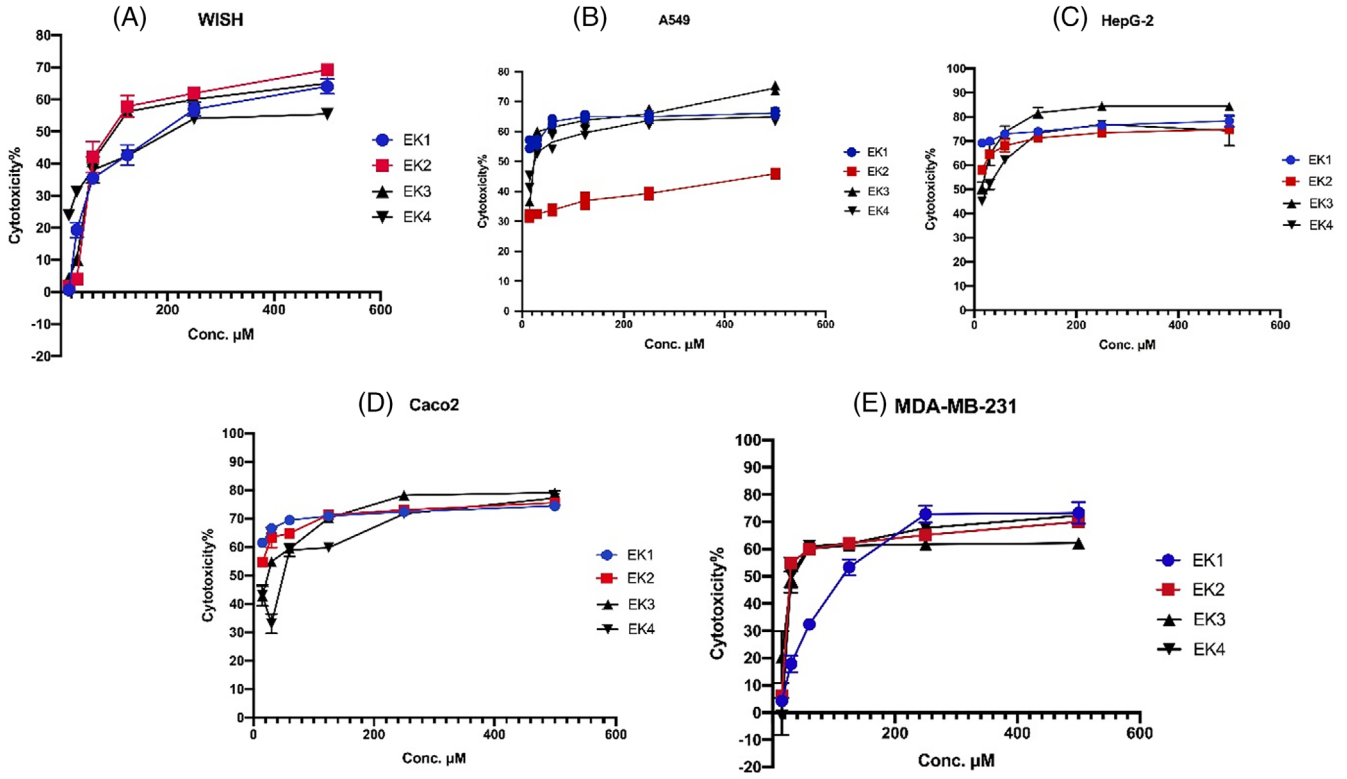


FIGURE 8 MTS safety assay and anticancer effects of tested four compounds were quantified on non-cancerous cell line (WISH) (A) for 24 h, on A549 (B), HepG-2 (C), Caco-2 (D), and MDA-MB-231 (E) cell lines

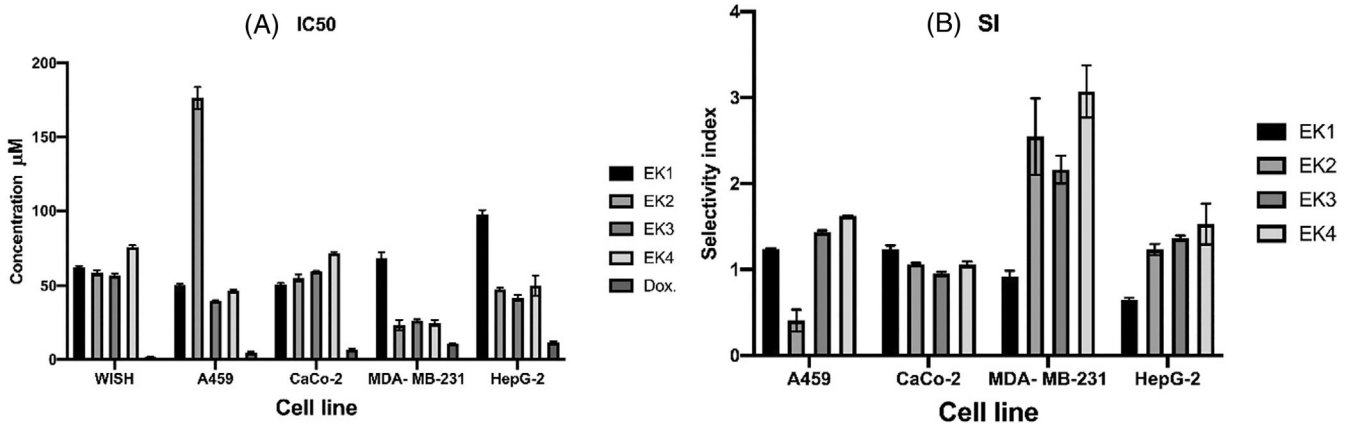


FIGURE 9 The calculated IC_{50} values on both non-cancerous and cancerous cell lines were quantified using GraphPad Prism 9 (A). In addition, the cancer cells selectivity index of the compounds was quantified comparing with non-cancerous cell line (B).

compounds showed acceptable nontoxic effects on normal and non-cancerous used cell lines. While, EK2 and EK4 showed great effects against the *MDA-MB-231* cell line, this could support their using as promising anticancer agent or in combination with chemotherapies and other specific pharmaceutical purposes.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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