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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, structural and thermal characterizations, dielectric properties and in vitro cytotoxic activities of new 2,2,4,4-tetra(4′-oxy-substituted-chalcone)-6,6-diphenylcyclotriphosphazene derivatives

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Abstract In this study, we aimed to investigate the relationship between the cytotoxic and dielectric properties of newly synthesized 2,2,4,4-tetra(4′-oxy-substituted-chalcone)-6,6-diphenylcyclotriphosphazene derivatives **(3–10)**. Firstly, 2,2,4,4-tetrachloro-6,6-diphenyl cyclotriphosphazene **(2)** was obtained through Friedel Crafts alkylation in the presence of hexachlorocyclotriphosphazene, benzene and triethylamine and anhydrous $AlCl_3$. The compounds **3–10** were synthesized from the reaction of the hydroxychalcone compounds **(1a–h)** with **2** in the presence of K_2CO_3 and within the acetone solvent for the first time and their dielectric constant, dielectric loss factor and ac conductivity of compounds **3–10** were examined through the impedance analyzer as a function of frequency. The in vitro cytotoxic activities of compounds **3–10** in five different concentrations (1, 5, 25, 50, and 100 μM) were analyzed by colorimetric MTT assay which is based on reduction of MTT salt by mitochondria of alive cells over the human ovarian cancer (A2780) and human prostate cancer (PC-3 and LNCaP) cell lines. The $LogIC_{50}$ values of **3–10** were calculated by using a Graphpad prism 6 programs on a computer. The obtained results suggests that the compounds have a powerful cytotoxic activity (especially A2780, $p < 0.05$).

Keywords Chalcone-cyclotriphosphazene · Cancer cell lines · Dielectric property · Cytotoxic activity · Dielectric constant

Introduction

Cyclophosphazenes are versatile inorganic ring systems owing to the great stability of the phosphorus-nitrogen backbone and the ability to undergo substitution of side groups with retention of the ring structure (Gleria and De Jaeger 2004). The phosphazene compounds included in the group of phosphorus-nitrogen compounds are also termed as phosphonitrilic and hydroazophosphorane (Allcock 1972; Gleria and De Jaeger 2004). The phosphazene derivatives synthesized as the result of phosphazene reactions are generally formed as the result of the replacement of the chlorines existing on the phosphorus atom by an appropriate reagent (Allen 1992). The obtained derivatives are formed with the bonding of a nitrogen group (as $-NH_2$/NR) (Allcock et al. 1998; Tumer et al. 2013; Başterzi et al. 2015), an oxygen group $R(Ar)O^-$ (Benson et al. 2013; Koran et al. 2014; Reynes et al. 2016), a sulfur group $R(Ar)S^-$ (Ma et al. 2002), or through the direct bonding of alkyl/aryl groups with the phosphazene (Neilson et al. 1987; Uslu et al. 2013). Due to the reactivity of P-Cl bond within the structures of phosphazene compounds, the type of the organic or inorganic groups bonded as a side-group alter the physical, biological, and chemical properties of these compounds. The cyclo or poly phosphazene derivatives containing organic, inorganic or organometallic side-groups have many potential

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applications such as dielectric (Koran et al. 2016), liquid crystalline (Bao et al. 2010), chemosensor (Şenkuytu et al. 2015), littium-ion batteries (Xia et al. 2015), fire-retardant material (Jiang et al. 2014; Zhao et al. 2016), optic material (Rojo et al. 2000), antibacterial, and antitumor properties (Brandt et al. 2001; Siwy et al. 2006; Ozay et al. 2010; Görgülü et al. 2015; Akbaş et al. 2016).

On the other hand, the chalcone compounds, which are also referred to as 1,3-Diaryl-2-propen-1-ones, are natural and synthetic compounds and members of flavonoid family. Chalcone groups are the compounds in which two aromatic rings are bonded with one another through the three carbon α,β-unsaturated carbonyl group. Such compounds having a ketovinyl group have been among the natural compounds that have gained importance in recent years due to their various biological activities (Patil et al. 2009; Baggio et al. 2016). Furthermore, the fact that they are found densely in edible plants has increased the importance of these compounds in cancer researches (Bahekar et al. 2016; I-Monica et al. 2016). It has been found in the literature that chalcones show anti-cancer (Rao et al. 2004; Kitawat et al. 2013; Jayashree et al. 2016), anti-inflammatory (Herencıa et al. 1998), anti-HIV activity (Wu et al. 2003), antihyperglycemic activity (Damazio et al. 2010), antifungal activities (Boeck et al. 2005) as well as antioxidant (El-Sayed and Gaber 2015) and antituberculosis effects (Lin et al. 2002). Apart from the biological effects of chalcone and its derivatives, they are also used as UV-absorption filters in optic materials (Mager et al. 1997), in food industry and holographic recording technologies (Fayed and Awad 2004).

In the literature, there is no performed study as to the synthesis of 2,2,4,4-tetra(4′-oxy-substituted-chalcone)-6,6-diphenylcyclotriphosphazene derivatives and their cytotoxic and dielectric properties. For this reason, new phosphazene compounds carrying phenyl and chalcone rings were designed and synthesized. The structures of these compounds were characterized through spectroscopic methods. The dielectric properties of cyclotriphosphazene compounds, as the function of frequency, were identified by using the impedance analyzer device. Finally, the in vitro cytotoxic activities of chalcone-phosphazene compounds were determined through MTT assay method by using A2780, PC-3, and LNCaP cell lines. The compounds were determined to have showed a powerful cytotoxic activities effect against A2780 cancer cell in particular.

Results and discussion

Chemistry

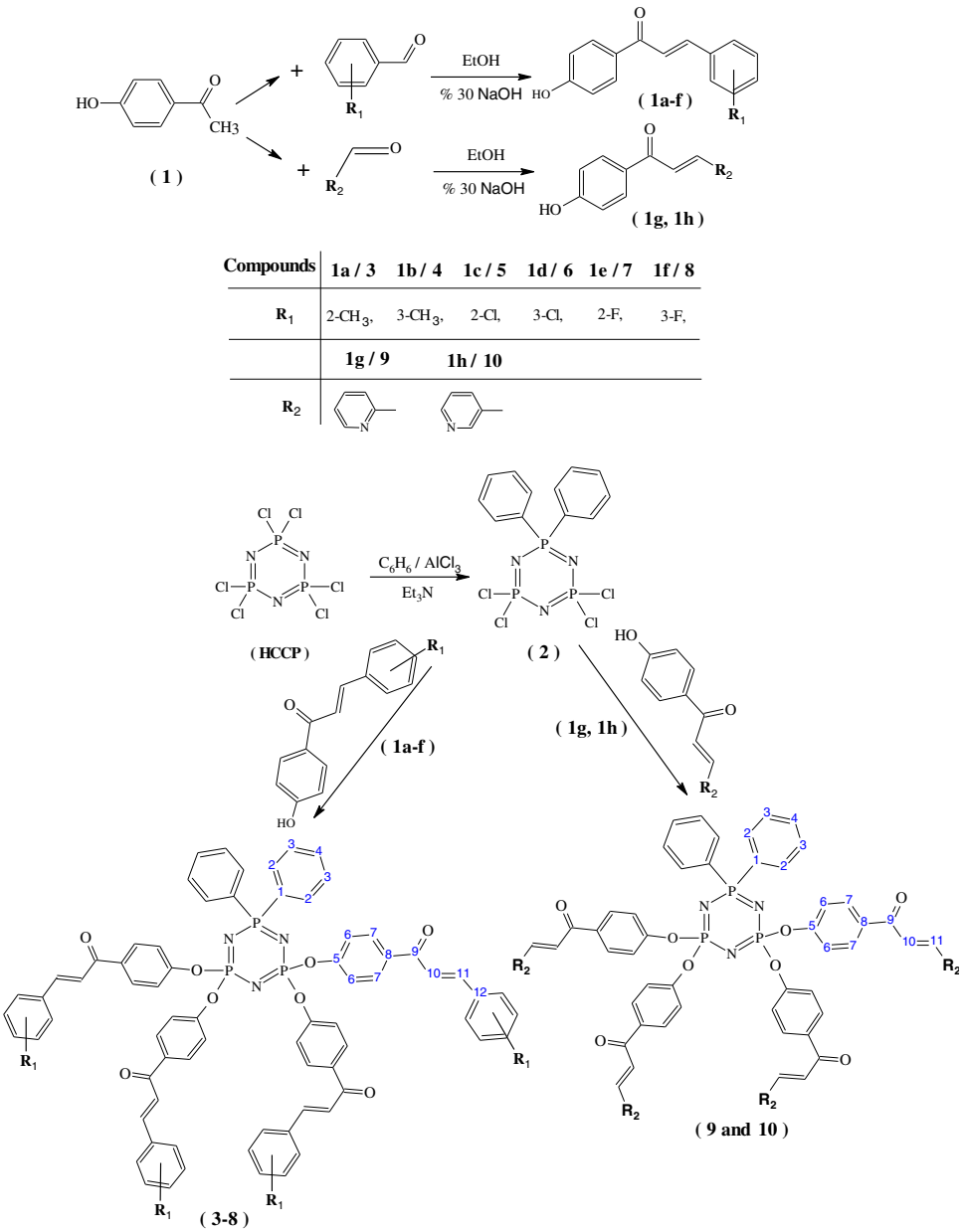
2,2,4,4-Tetrachloro-6,6-diphenylcyclotriphosphazene **(2)** compound was obtained through Friedel Crafts alkylation in the presence of hexachlorocyclotriphosphazene (trimer, HCCP), benzene and triethylamine and anhydrous $AlCl_3$ (McBee et al. 1965). In the second stage, the substituted hydroxychalcone compounds bearing different side groups at ortho or para positions **(1a–h)** were synthesized in accordance with Claisen–Schmidt Condensation protocol (Funiss et al. 2004; Modzelewska et al. 2006). 2,2,4,4-tetra(4′-oxy-substituted-chalcone)-6,6-diphenylcyclotriphosphazene **(3–10)** were synthesized for the first time from the interactions of 2,2,4,4-tetrachloro-6,6-diphenylcyclotriphosphazene **(2)** with 4.1 equiv. of 4′-hydroxy-substituted-chalcone analogs **(1a–h)** in the excess of potassium carbonate and within the acetone solvent. Reactions of cyclotriphosphazene compounds followed with thin layer chromatography and ^{31}P-nuclear magnetic resonance (NMR) spectroscopy. The general synthesis presentations for compounds are shown in Scheme 1.

The structures of **1a-h** were confirmed through Fourier transform infrared spectroscopy (FT-IR), ^{1}H and ^{13}C NMR spectroscopy methods. The structures of compounds **2–10** were identified through FT-IR, MS, ^{1}H, ^{13}C-APT and ^{31}P-NMR spectroscopy methods. When matrix assisted laser desorption ionization-time of flight mass spectrometry spectrums of compounds are examined, it is seen that they are almost the same as the molecular weights calculated theoretically. The molecular ion peaks of **3–10** have been given in the experimental section. For example, the molecular ion peak of compound **7** was displayed at 1255.32 (Supplementary data, Figure S2).

The melting points of **3–10** were determined through differential scanning calorimetry (DSC) thermograms (Supplementary data, Figure S1 (A)). The thermal stability of the compounds as well as the temperatures at which they begin to get degraded was determined through thermogravimetric analysis (TGA) analysis (Supplementary data, Figure S1 (B)). More than 50% of the structures of compounds do not get degraded at the temperatures reaching up to 500 °C. At the temperatures reaching up to 900 °C, however, almost all the compounds get degraded (Table 1). In the light of these results, the synthesized compounds are also seen to be thermally stable.

When FT-IR spectra of **3–10** were examined, the -OH stretching vibration in the structure of **1a–h** was not displayed. The –P=N stretching vibrations in the FT-IR spectrum of compound **2** were observed at 1172 and 1221 cm^{-1}. However, the –P=N stretching vibrations in the phosphazene compounds were observed to have shifted towards 1174 and 1206 cm^{-1}. The P-O-Ph stretching vibrations in the structure of phosphazenes were observed between 928 and 934 cm^{-1}. In addition, the PCl_2 bands are disappeared. When the FT-IR spectra of the chalcone-cyclotriphosphazene compounds **(3–10)** were examined, the carbonyl stretching vibrations (–C=O) were observed at

Scheme 1 Chemical structure and synthetic pathway of compounds **1a–h** and **2–10**



1661, 1659, 1662, 1662, 1663, 1662, 1661, and 1663 cm^{-1}, respectively.

^{31}P NMR spectra of **3–10** observe the expected AB_2 spin system. As expected, there are one double and triple including two peaks at ^{31}P NMR spectra of **2–10**. In ^{31}P-NMR spectrum of compound **2,** the doublet peaks belonging to two equivalent phosphorus was observed at 18.18 ppm, while the triplet peaks belonging to single phosphorus were observed at 20.40 ppm. When the chalcone compounds linked to the phosphazene ring, the doublet and singlet peaks belonging to two equivalent phosphorus and single phosphorus were shifted towards the range of 6.68–7.10 ppm and 22.10–22.14 ppm, respectively. The phosphorus peaks of compound **2** were unobserved at ^{31}P-NMR spectra of **3–10**. For example, the ^{31}P-NMR spectrum of compound **2** and **7** was given in Figure S3 (Supplementary data).

When ^{1}H-NMR spectra of **3–10** were examined, The –OH protons observed at 10.43 and 10.54 ppm in the ^{1}H-NMR spectra of **1a-h** were not observed at NMR spectra of **3–10**. The ratio of the protons integral height in the ^{1}H-NMR spectra of **3–10** supports the proposed structures. The locations of the primary, secondary and tertiary carbon peaks was determined by using ^{13}C-attached proton test (APT) NMR technique and the carbon peaks also support ^{1}H-NMR and the structure. The results are given in detail in

Table 1 TGA, dielectric results (at 1 kHz and at 25 °C) and $LogIC_{50}$ values for compounds **3–10**

TGA results	Chalcone substituted cyclotriphosphazene compounds							
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**
T_i/°C[a]	300	294	268	294	281	294	253	294
$T_{50\%}$/°C[b]	605	630	673	630	659	630	714	730
Residue (%)at 900 °C	0	0	4.7	0	2	1.9	2	2
Dielectric results	The dielectric constant (ε'), dielectric loss (ε'') and ac conductivity (σ) values of **3–10** in the frequency of 1 kHz and at 25 °C							
ε'	2.99	4.35	3.54	3.81	2.49	4.57	3.99	4.90
ε''	0.072	0.049	0.043	0.051	0.048	0.081	0.074	0.109
σ (10^{-9}, S/cm)	0.091	2.68	2.56	2.33	1.53	2.81	2.45	3.0
$LogIC_{50}$ values	$LogIC_{50}$ values (μM) of compounds **3–10** against a panel of three cancer cell lines. $LogIC_{50}$ is the half maximal effective concentration of drug that reduces cell growth by 50%.							
A2780	2.37	1.89	1.14	1.25	1.08	2.38	2.16	1.73
PC-3	2.76	2.30	1.70	2.09	2.35	2.39	2.31	2.35
LNCaP	2.55	2.31	1.84	2.05	1.90	2.35	2.25	2.11

[a] Initial decomposition temperature

[b] Decomposition temperature at 50% mass loss

the experimental section. For example, the ^{1}H and ^{13}C-APT NMR spectra of compound **7** were given in Figs. S4 and S5, respectively (Supplementary data).

Dielectric behaviors

The dielectric parameters (capacitance values (Cp), dielectric loss factor (DF), and conductivity (Gp)) of compounds **3–10** were measured by using with a Quad Tech 7600 precision LRC Meter impedance analyzer against increasing frequency (from 100 Hz to 20 kHz). And then the ε', ε'', and σ values for each compound were determined with Eqs. (1, 2, and 3). The dielectric constants, dielectric loss factors and AC conductivities of the compounds were compared with one another. All the results and comparisons are given in Fig. 1 and Table 1.

The dielectric properties of the cyclophosphazene compounds **(3–10)** were measured as a function of the frequency. The dielectric properties of compounds change with the frequency. The change in the dielectric properties of cyclotriphosphazenes is the result of electronic, ionic and molecular polarizability. These properties are associated with the physical and chemical structures of compounds. It is seen that the capacitance value and the dielectric constant decrease with the increasing frequency, while they remain constant at high frequencies. The reason for this can be thought to be the polarization effect. Polarization occurs since the effect of the dipoles increases as the frequency increases.

The change graphics along with the frequency, which pertain to the dielectric constant, dielectric loss factors and conductivity values of the compounds having $-CH_3$ (**3** and **4**), –Cl (**5** and **6**), and –F (**7** and **8**) groups in their ortho and meta position, is given in Fig. 1. Separately, the comparison related to compounds **9** and **10** having the pyridine ring instead of the phenyl ring is also given in the graphics. It was seen that the dielectric constant and dielectric loss values of the compounds had decreased along with the increasing frequency and remained unchanged after some point.

The dielectric constant of compound **5** having chlorine in its ortho position was found to be higher than that of compound **7** having fluorine. This is thought to be due to the fact that the –Cl atoms within the structure of compound **2** increase polarity; hence, the dipole moment increases. On the other hand, the dielectric constant in pyridine-substituted compounds **9** and **10** was found to be the highest (Fig. 1 (a)). Since the presence of a hetero-atom in the ring can increase polarization, this can be caused the situation mentioned above. Similar cases were also observed in dielectric loss and AC conductivity values (Fig. 1 (b) and (c)). The dielectric constant of compound **8**

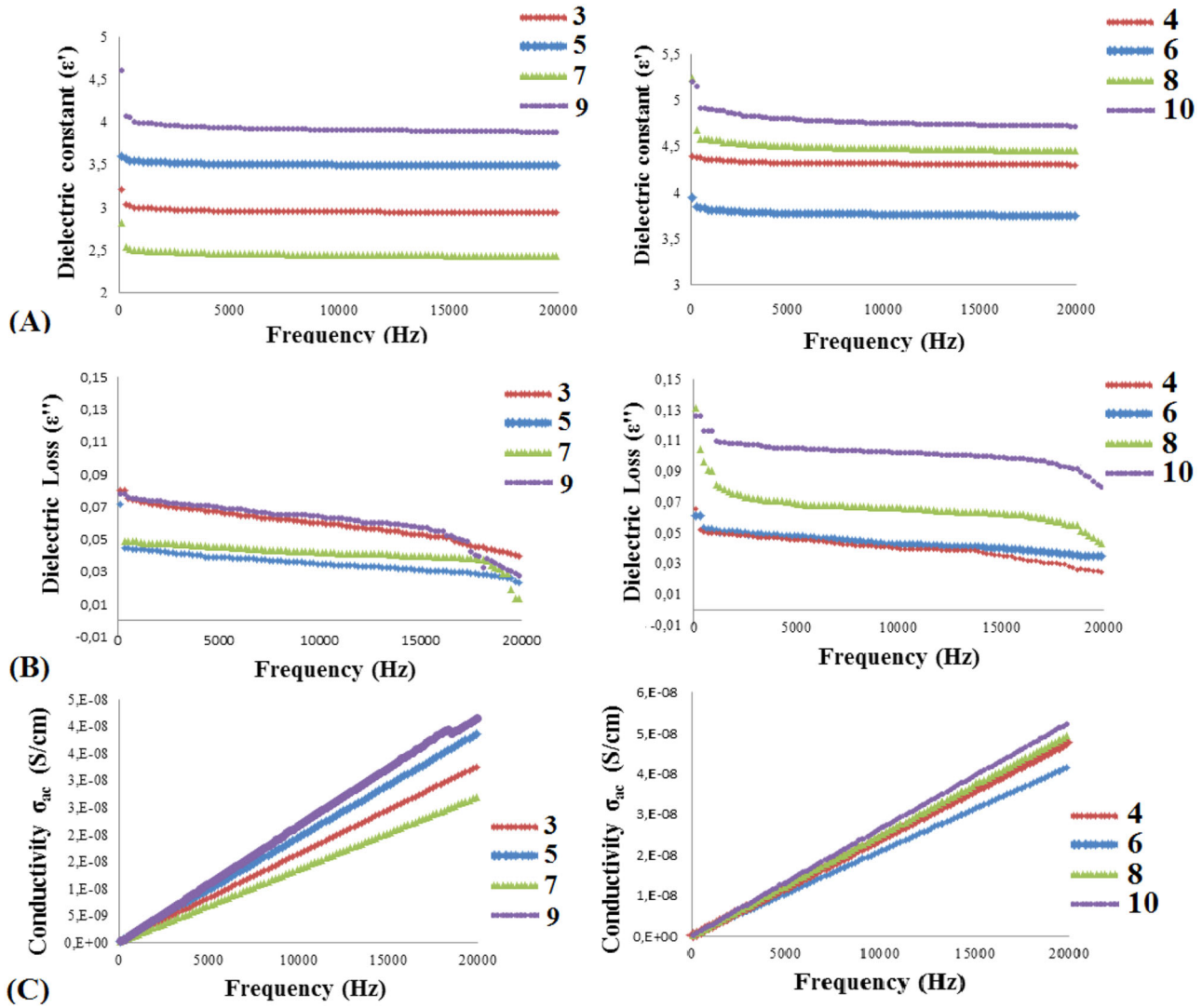


Fig. 1 Variation of dielectric parameters of compounds **3–10** against frequency; Dielectric constants **(a)**, Dielectric loss factors **(b)**, and AC Conductivity graphics **(c)**

having fluorine in its meta position proved to be higher than that of compound **6** having chlorine (Fig. 1 (a)).

The effect of the positions of R groups on the dielectric constants of the compounds is clearly understood through the graphic in Fig. 1. For instance, while the dielectric constant of the compound having fluorine group in its ortho position is lower than the dielectric constant of the compound having chlorine in its ortho position, this situation is the opposite in the meta position. This situation remained unchanged in the compounds carrying the pyridine ring. The highest dielectric constant was observed in pyridine-substituted compound **10**.

In vitro cytotoxic activities activity

In order to determine the effective dose of 2,2,4,4-tetra (substituted-chalcone)-6,6-diphenylcyclotriphosphazene **(3–10)** compounds on the androgen independent (negative) prostate cancer cell line (PC-3) and on the androgen dependent (positive) prostate cancer cell line (LNCaP) and also on the human ovarian cancer cell line (A2780), the % changes in the cell viability rates that were caused by 1, 5, 25, 50, and 100 μM concentrations of the substance for 24 h were determined through MTT assay. The $LogIC_{50}$ values of the compounds were given in Table 1. The comparisons of the compounds were made by considering the solvent control as the basis. According to the results of experiments, compounds **3–10** were quite effective on A2780 cancer cells. On the other hand, compounds **3–10** were observed to be effective on PC-3 and LNCaP cells in general.

All the comparisons of compounds were made by considering the control group as the basis. When compounds containing $-CH_3$ **(3)**, –Cl **(5)**, and –F **(7)** in the ortho-position of the phenyl ring are examined in terms of

structure activity, compounds **5** and **7** were found to be quite effective on A2780 cells ($p < 0.05$, Fig. 2 (a)). Separately, it was observed that all the doses of compounds **5** and **7** had reduced the cancer cells. On the other hand, only 100 µM dose of compound **3** was determined to be effective. When it is the pyridine ring instead of the phenyl ring, they showed even a little cytotoxic effect on A2780 cell lines.

Compound **3** were not showed cytotoxic activity against PC-3 and LNCaP cell lines. Compound **5** were showed highest cytotoxic activity against PC-3 and LNCaP cell lines. Compounds **7** were found to be effective on LNCaP cell lines ($p < 0.05$, Fig. 2 (b)). When it is the pyridine ring instead of the phenyl ring, compound **9** showed even a little cytotoxic effect on PC-3 and LNCaP cell lines ($p < 0.05$). When examined in terms of structure activity, the electron-withdrawing group, –Cl and F, in the ortho position showed more effect than the electron releasing group ($–CH_3$), against A2780, PC-3, and LNCaP cell lines ($p < 0.05$, Fig. 2).

When compounds carrying $–CH_3$ **(4)**, –Cl **(6)**, and –F **(8)** in the meta-position of the phenyl ring are investigated in terms of structure activity, compounds **4** and **6** were found to be effective on A2780 cell lines ($p < 0.05$, Fig. 2 (a)). Separately, it was observed that all the doses of compounds **6** and 25, 50 and 100 µM doses of compounds **4** had reduced the cancer cells. Compounds **4**, **6**, **8,** and **10** were usually showed cytotoxic activity on PC-3 and LNCaP cell lines ($p < 0.05$, Fig. 2 (b) and (c)). Compound **6** bearing –Cl group in the meta-position showed more effect than other compounds against all cancer cell lines. When it is the pyridine ring instead of the phenyl ring, compound **10** showed cytotoxic effect on A2780 and LNCaP cell lines ($p < 0.05$, Fig. 2 (a) and (c)).

The cytotoxic effect of **5** and **6** compounds having Cl in their ortho- and meta-positions was examined according to the position of the chlorine atom. They showed a cytotoxic effect against three cancer cell lines in the cases in which –Cl atom was in the ortho or meta position ($p < 0.05$). However, it was determined that the cytotoxic effect in **5** compound having –Cl in its ortho position was found to be more effective than in **6** compound having –Cl in its meta position all the cancer cell lines (A2780, PC-3, and LNCaP).

The common results generally observed in three cancer cells are mentioned below:

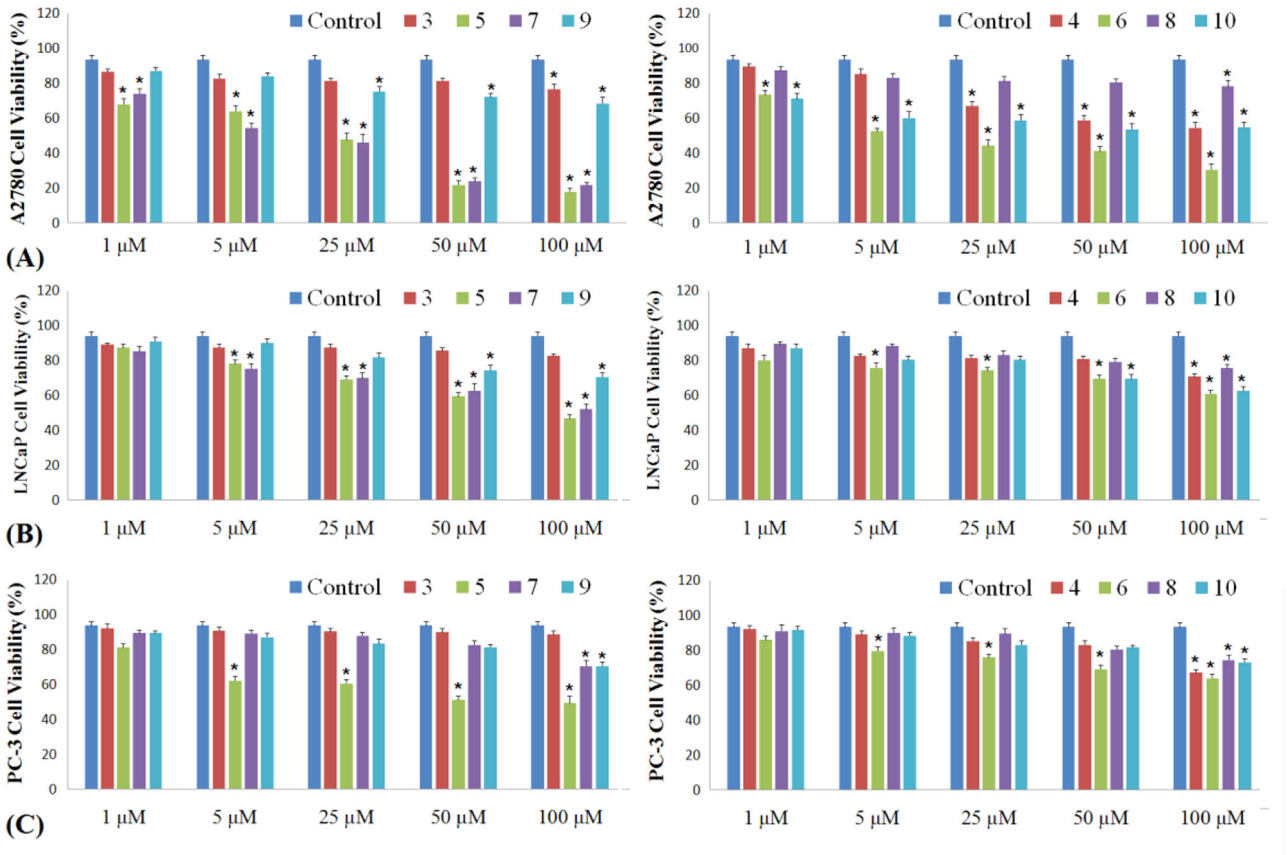


Fig. 2 The relative cell viability (%) of A2780 **(a)**, LNCaP **(b)**, and PC-3 **(c)** cells after a 24-h treatment with all the compounds **3–10**. The changes on the cell viability (%) caused by compounds **3–10** are compared with the control data. Each data point is an average of 10 viability (*$p < 0.05$)

The compounds containing chlorine at ortho and meta positions are effective on A2780, PC-3, and LNCaP cancer cells. The best cytotoxic effect in all of the three cell types was exhibited by chlorine-containing structures. The compound having methyl in its ortho position did not show any significant effect in the three cell types. However, the compound **4** having methyl in its meta position showed a better effect on especially A2780 cell lines. The compound having fluorine group in its ortho position showed better effect on all the cells when compared with its localization in meta position.

Conclusion

In conclusion, we successfully reported the synthesis of 2,2,4,4-tetra(4′-oxy-substituted-chalcone)-6,6-diphenylcyclotriphosphazene derivatives **(3–10).** The structures of compounds were identified by using spectroscopy and thermal analysis techniques (microanalysis, FT-IR, ^{31}P, ^{1}H, ^{13}C-APT NMR, MALDI-TOF MS, DSC, and TGA thermal analysis) and their the dielectric parameters (dielectric constant, dielectric loss and AC conductivity) of the compounds were determined through the impedance analyzer as a function of frequency.

The in vitro cytotoxic activities of compounds **3–10** in five different concentrations (1, 5, 25, 50, and 100 µM) were analyzed by colorimetric MTT assay which is based on reduction of MTT salt by mitochondria of alive cells over the human ovarian cancer (A2780) and human prostate cancer (PC-3 and LNCaP) cell lines. The $LogIC_{50}$ values of **3–10** were calculated by using a Graphpad prism 6 programs on a computer. The obtained results suggests that the compounds have cytotoxic activity (especially A2780, $p < 0.05$). All the doses of the compounds **5** and **7**, which are orto-substituted phosphazenes containing chloro and fluoro groups on the chalcone ring, are very effective. It can be said that cytotoxicity effects of **5** and **7** on A2780 cells are structure and dose-dependent. In the light of the obtained results, it was studied to be determined with this study that besides the importance of the organic side-group in cancer researches, the type of the substituents linked to this side-group and their ortho or meta position within the structure change the effect on activity to a considerable degree.

Materials and methods

Chemistry

Triethylamine, anhydrous $AlCl_3$, 2-Methylaldehyde, 3-methylbenzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzal deyde, 2-fluorobenzaldehyde, 3-fluorobenzaldehyde, 2-pyridinecarboxaldehyde, 3-pyridinecarboxaldehyde, benzene, ethanol, and acetone were supplied from Merck. Hexachlorocyclotriphosphazene (trimer, HCCP), potassium carbonate, sodium hydroxide (powder), chloroform-d and DMSO-d_6 for NMR analysis were supplied from Sigma-Aldrich.

Physical measurement

Elemental analysis, Mass spectra, FT-IR, and ^{1}H, ^{13}C and ^{31}P-NMR spectra were recorded on a LECO 932 CHNS-O apparatus, a Bruker Daltonics microflex mass spectrometer, a Perkin Elmer FT-IR spectrometer and a Bruker DPX-400 and, respectively. Thermal characterizations of the chalcone-phosphazene compounds were determined by DSC and TGA using a SHIMADZU DSC (10 °C min^{-1}) and a TGA-50 thermobalance (20 °C min^{-1}), respectively. Dielectric measurements against increases frequencies were detected by using a Quad Tech 7600 precision LRC Meter impedance analyzer.

*General reaction method for the synthesis of chalcones **(1a–h)***

4′-Hydroxy-substitutedchalcone compounds were synthesized and purified in accordance with Claisen–Schmidt Condensation protocol (Scheme 1) (Funiss et al. 2004; Modzelewska et al. 2006).

3 g (22.02 mmol) 4′-hydroxyacetophenone (**1**) was dissolved in 50 mL absolute ethyl alcohol and was added into 250 mL reaction flask. The reaction medium was set to 0 °C, after which 30% of NaOH solution was added into the reaction flask. After it was mixed for half an hour, 22.02 mmol of substituted aldehyde was added in drop by drop. The reagent was mixed at room temperature for 24 h. After the reaction was stopped, the reagent mixture was precipitated in acidic water. The solid matter that was precipitated was filtered and washed with plenty of water. Afterwards, the substance in question was dissolved once again in acetone, and after it was precipitated once again within the water containing sodium bisulphate, it was washed with plenty of water and was then dried up in a vacuum-oven. The obtained compounds were recrystallized in acetone-water mixture, and then compounds **1a–h** was obtained.

*Synthesis of 2,2,4,4-tetrachloro-6,6-diphenylcyclotriphosphazene **(2)***

2,2,4,4-tetrachloro-6,6-diphenyl*cyclotriphosphazene* compound **(2)** was obtained through Friedel Crafts alkylation protocol (Scheme 1) (McBee et al. 1965).

200 mL benzene was added into a three-necked reaction flask in argon atmosphere. 26.56 g (0.2 mol) anhydrous $AlCl_3$ and 7.91 g (0.078 mol) triethylamine was added onto it. The reaction was heated up and mixed at the boiling point of benzene for 30 min Following this process, 10 g (0.029 mol) HCCP was added into it gradually in solid form, and it became refluxed for 48 h. The reaction was stopped and left for cooling 48 h later. The solution was added into 200 mL HCl solution and mixed. Then, the mixture was put into the separating funnel, and the benzene extract was removed. 15 mL benzene was added into the aqueous solution three times, and the extraction was performed. Then, the benzene solutions were combined, and anhydrous $MgSO_4$ was added into this mixture, after which it was mixed and filtered. Then it was evaporated by means of a rotary evaporator until 15 mL of benzene solution was left in the reaction flask, and then hexane was added into the solution. The residue that had precipitated was filtered and separated. The solvent of the remaining was re-evaporated, and the solid matter that remained within the balloon was dissolved once again in 5–10 mL benzene, after which it was recrystallized. A white-colored solid crystal was obtained. Yield: 7.4 g (60%). M.p.: 93–96 °C. Anal. Calcd. For $C_{12}H_{10}N_3Cl_4P_3$: C, 33.44; H, 2.34; N, 9.75. Found: C, 33.48; H, 2.39; N, 9.82. MALDI-MS: *m/z* calc. 430.96. Found: 431.97 $[M+H]^+$. FT-IR (KBr, cm^{-1}) ν 3056 and 3069 (C–H aromatic), 1438, 1483, 1590 and 1610 (C=C), 1172 and 1221 (P=N). ^{31}P NMR (400 MHz, $CDCl_3$) $\delta =$ 16.18 (d, 2P, PB), 20.40 (t, 1P, PA). ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.52–7.55$ (2H, Ar-H^4), 7.58–7.60 (4H, Ar–H^3), 7.81–7.87 (4H, Ar–H^2). ^{13}C NMR (400 MHz, $CDCl_3$) $\delta = 131.95–133.31$ C^1 (P-C(Ar)), 128.73-128-87 C^2 (Ar-CH), 130.60–130.72 C^3 (Ar–CH), 132.56–132.59 C^4 (Ar–CH).

*General reaction method for the synthesis of 2,2,4,4-tetra (4′-oxy-substituted-chalcone)-6,6-diphenylcyclotriphosphazene compounds **(3–10)***

Synthesis and characterization of chalcone substituted cyclophosphazene compounds **(3–10)** were prepared along with a similar procedure. Therefore, detailed procedures for the synthesis and purification procedure were only given compound **3.**

50 mL of acetone was added into a three-necked reaction flask of 100 mL, and then 1 g (2.32 mmol) 2,2,4,4-tetrachloro-6,6-diphenylcyclotriphosphazene **(2)**, 3.32 g (13.92 mmol) 4′-hydroxy-2-methylchalcone **(1a)**, and 1.92 g (13.92 mmol) K_2CO_3 were added onto it in cold condition (0 °C) in argon atmosphere. After the reaction was mixed at room temperature for 30 min in argon atmosphere at 0 °C, it became refluxed for 12 h. After the reaction was stopped, the reaction mixture was filtered. The mixture was precipitated within 5% of 250 mL NaOH. The precipitated solid was filtered and washed with plenty of water until it reached pH~7, after which it was dried up. The dried solid was dissolved in chloroform, and n-hexane was precipitated once again, after which it was washed up with ethyl alcohol three times and was then dried up under the vacuum. The white solid matter (compound **3**) was obtained in pure form. Yield: 2.15 g (75%). M.p.: 142–143 °C. Anal. Calcd. For $C_{76}H_{62}N_3O_8P_3$: C, 73.72; H, 5.05; N, 3.39. Found: C, 73.76; H, 5.09; N, 3.31. MALDI-MS: *m/z* calc. 1238.24. Found: 1238.43. FT-IR (KBr, cm^{-1}) ν 3026 and 3058 (C–H aromatic), 2922 and 2957 (C–H Aliphatic), 1661 (C=O), 1503, 1576 and 1601 (C=C), 1182 and 1206 (P=N), 934 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) δ=7.05 (d, 2P, PB), 22.14 (t, 1P, PA). ^1H NMR (400 MHz, DMSO-d_6) $\delta =$ 2.38 (12H, s, H^{18}, –CH_3), 7.75 (4H, d, $J = 15.6$, H^{10}, –CH=), 7.22–7.46 (30H, m, $H^{3,4}$, H^6, $H^{14–17}$, Ar–H), 7.93–7.99 (8H, m, H^2, Ar–H and H^{11}, =CH–), 8.01–8.03 (8H, d, H^7, Ar–H).^{13}C NMR (400 MHz, DMSO-d_6) $\delta =$ 133.61 C^1 (P–C(Ar)), 128.80–128.93 C^2 (Ar–CH), 130.26–130.37 C^3 (Ar–CH), 130.96 C^4 (Ar–CH), 153.97 C^5 (Ar–C), 121.56 C^6 (Ar–CH), 131.26 C^7 (Ar–CH), 135.09 C^8 (Ar–C), 188.16 C^9 (C=O), 122.78 C^{10} (–CH=), 141.63 C^{11} (=CH–), 133.61 C^{12} (Ar–C), 138.56 C^{13} (Ar–C), 130.96 C^{14} (Ar–CH), 130.96 C^{15} (Ar–CH), 126.83 C^{16} (Ar–CH), 127.32 C^{17} (Ar–CH), 19.75 C^{18} (–CH_3).

*2,2,4,4-Tetra(4′-oxy-3-methylchalcone)-6,6-diphenylcyclotriphosphazene **(4)***

For the synthesis of compound **4** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1b** (3.32 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 24 h. Yield: 2.35 g (82%). M.p.: 127–128 °C. Anal. Calcd. For $C_{76}H_{62}N_3O_8P_3$: C, 73.72; H, 5.05; N, 3.39. Found: C, 73.78; H, 5.11; N, 3.43. MALDI-MS: *m/z* calc. 1238.24. Found: 1238.32. FT-IR (KBr, cm^{-1}) ν 3029 and 3064 (C–H aromatic), 2864 and 2921 (C–H Aliphatic), 1659 (C=O), 1484, 1501, and 1595 (C=C), 1175 and 1203 (P=N), 933 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta =$ 6.82 (d, 2P, PB), 22.10 (t, 1P, PA). ^1H NMR (400 MHz, DMSO-d_6) $\delta = 3.40$ (12H, s, H^{18}, –CH_3), 7.24–7.45 (26H, m, $H^{3,4}$, H^6, H^{13}, H^{15}, H^{17}, Ar–H), 7.62–7.68 (12H, m, H^2, H^{16}, Ar–H, H^{10}, –CH=), 7.81–7.85 (4H, d, $J = 15.6$ Hz, H^{11}, =CH–), 8.02–8.04 (8H, d, $J = 8.4$ Hz, H^7, Ar–H).^{13}C NMR (400 MHz, DMSO-d_6) $\delta = 134.95$ C^1 (P–C(Ar)), 128.78–128.92 C^2 (Ar–CH), 130.24–130.35 C^3 (Ar–CH), 131.89 C^4 (Ar–CH), 153.98 C^5 (Ar–C), 121.48 C^6 (Ar–CH), 130.94 C^7 (Ar–CH), 135.94 C^8 (Ar–C), 188.22 C^9 (C=O), 121.88 C^{10} (–CH=), 144.78 C^{11} (=CH–), 138.63 C^{12} (Ar–C), 130.94 C^{13} (Ar–CH), 138.63 C^{14}

(Ar–C), 129.68 C^{15} (Ar–CH), 126.26 C^{16} (Ar–CH), 126.75 C^{17} (Ar–CH), 21.34 C^{18} ($–CH_3$).

*2,2,4,4-Tetra(4′-oxy-2-chlorochalcone)-6,6-diphenylcyclotriphosphazene **(5)***

For the synthesis of compound **5** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1c** (3.6 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 18 h. Yield: 2.63 g (86%). M.p.: 157–158 °C. Anal. Calcd. For $C_{72}H_{50}Cl_4N_3O_8P_3$: C, 65.52; H, 3.82; N, 3.18. Found: C, 65.59; H, 3.87; N, 3.24. MALDI-MS: *m/z* calc. 1319.92. Found: 1320.02. FT-IR (KBr, cm^{-1}) ν 3005 and 3063 (C–H aromatic), 2921 and 2952 (C–H Aliphatic), 1662 (C=O), 1469, 1501, and 1598 (C=C), 1178 and 1203 (P=N), 931 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta = 6.93$ (d, 2P, PB), 22.10 (t, 1P, PA). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.24–7.26$ (8H, d, $J = 8.8$ Hz, H^6, Ar–H), 7.34–7.37 (4H, H^3, Ar–H), 7.44–7.47 (14H, m, H^4, $H^{15–17}$, Ar–H), 7.56 (4H, d, $J = 15.6$ Hz, H^{10}, –CH=), 7.86–7.90 (4H, d, $J = 15.6$ Hz, H^{11}, =CH–), 7.98–8.04 (12H, m, H^2, H^7, Ar–H), 8.17–8.19 (4H, d, H^{14}, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) $\delta = 132.62$ C^1 (P–C(Ar)), 128.83–128.97 C^2 (Ar-CH), 130.26–130.37 C^3 (Ar–CH), 132.48 C^4 (Ar–CH), 154.14 C^5 (Ar–C), 121.49 C^6 (Ar–CH), 132.48 C^7 (Ar–CH), 134.89 C^8 (Ar–C), 187.96 C^9 (C=O), 124.67 C^{10} (–CH=), 139.14 C^{11} (=CH–), 132.62 C^{12} (Ar–C), 134.76 C^{13} (Ar–C), 131.10 C^{14} (Ar–CH), 129.01 C^{15} (Ar–CH), 130.46 C^{16} (Ar–CH), 128.08 C^{17} (Ar–CH).

*2,2,4,4-Tetra(4′-oxy-3-chlorochalcone)-6,6-diphenylcyclotriphosphazene **(6)***

For the synthesis of compound **6** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1d** (3.6 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 24 h. Yield: 1.98 g (65%). M.p.: 145–146 °C. Anal. Calcd. For $C_{72}H_{50}Cl_4N_3O_8P_3$: C, 65.52; H, 3.82; N, 3.18. Found: C, 66.01; H, 3.89; N, 3.27. MALDI-MS: *m/z* calc. 1319.92. Found: 1319.98. FT-IR (KBr, cm^{-1}) ν 3003 and 3059 (C–H aromatic), 2836 and 2967 (C–H Aliphatic), 1662 (C=O), 1503, 1580, and 1597 (C=C), 1179 and 1203 (P=N), 932 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta = 6.68$ (d, 2P, PB), 22.12 (t, 1P, PA). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.23–7.25$ (8H, d, $J = 8.4$ Hz, H^6, Ar–H), 7.34–7.37 (4H, H^3, Ar–H), 7.43–7.49 (14H, m, $H^{14–17}$, Ar–H), 7.64–7.68 (4H, d, $J = 15.6$ Hz, H^{10}, –CH=), 7.76–7.78 (4H, d, H^2, Ar–H), 7.91–7.95 (4H, d, $J = 15.6$ Hz, H^{11}, =CH–), 8.02–8.06 (12H, m, H^7, H^{13}, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) $\delta = 134.25$ C^1 (P–C(Ar)), 128.84–128.97 C^2 (Ar–CH), 130.24–130.35 C^3 (Ar–CH), 130.66 C^4 (Ar–CH), 154.12 C^5 (Ar–C), 121.42 C^6 (Ar–CH), 131.12 C^7 (Ar–CH), 134.25 C^8 (Ar–C), 188.02 C^9 (C=O), 123.55 C^{10} (–CH=), 142.86 C^{11} (=CH–), 137.28 C^{12} (Ar–C), 138.43 C^{13} (Ar–CH), 134.87 C^{14} (Ar–C), 128.36 C^{15} (Ar–CH), 131.12 C^{16} (Ar–CH), 131.12 C^{17} (Ar–CH).

*2,2,4,4-Tetra(4′-oxy-2-fluorochalcone)-6,6-diphenylcyclotriphosphazene **(7)***

For the synthesis of compound **7** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1e** (3.37 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 24 h. Yield: 1.75 g (60%). M.p.: 147–148 °C. Anal. Calcd. For $C_{72}H_{50}Cl_4N_3O_8P_3$: C, 68.96; H, 4.02; N, 3.35. Found: C, 69.02; H, 4.09; N, 3.39. MALDI-MS: *m/z* calc. 1254.10. Found: 1255.32. FT-IR (KBr, cm^{-1}) ν 3064 (C–H aromatic), 2921 and 2952 (C-H Aliphatic), 1663 (C=O), 1504, 1578, and 1602 (C=C), 1180 and 1204 (P=N), 933 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta = 6.78$ (d, 2P, PB), 22.15 (t, 1P, PA). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.23–7.39$ (16H, m, H^6, H^{14}, H^{16}, Ar–H), 7.35–7.37 (4H, m, H^3, Ar–H), 7.43–7.52 (10H, m, H^4, H^{17}, Ar–H and H^{10}, –CH=), 7.76–7.88 (8H, m, H^2, Ar–H and H^{11}, =CH–), 7.98–8.0 (8H, d, $J = 8.8$ Hz, H^7, Ar–H), 8.04–8.06 (4H, t, H^{15}, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) $\delta = 133.15$ C^1 (P–C(Ar)), 128.82–128.95 C^2 (Ar–CH), 130.27–130.38 C^3 (Ar–CH), 132.25 C^4 (Ar–CH), 154.06 C^5 (Ar–C), 121.51 C^6 (Ar–CH), 131.0 C^7 (Ar–CH), 133.24 C^8 (Ar–C), 187.95 C^9 (C=O), 124.04 C^{10} (–CH=), 135.76 C^{11} (=CH–), 122.58 C^{12} (Ar–C), 160.15–162.65 C^{13} (Ar–C), 116.64 C^{14} (Ar–CH), 131.0 C^{15} (Ar–CH), 125.38 C^{16} (Ar–CH), 129.57 C^{17} (Ar–CH).

*2,2,4,4-Tetra(4′-oxy-3-fluorochalcone)-6,6-diphenylcyclotriphosphazene **(8)***

For the synthesis of compound **8** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1f** (3.37 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 30 h. Yield: 1.93 g (66%). M.p.: 169–170 °C. Anal. Calcd. For $C_{72}H_{50}Cl_4N_3O_8P_3$: C, 68.96; H, 4.02; N, 3.35. Found: C, 69.03; H, 4.11; N, 3.29. MALDI-MS: *m/z* calc. 1254.1. Found $[M+H]^+$: 1255.6. FT-IR (KBr, cm^{-1}) ν 3001 and 3060 (C–H aromatic), 2838 and 2969 (C–H Aliphatic), 1662 (C=O), 1504, 1581, and 1597 (C=C), 1179 and 1203 (P=N), 930 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta = 6.91$ (d, 2P, PB), 22.15 (t, 1P, PA). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.24–7.26$ (8H, d, $J = 8.8$ Hz, H^6, Ar–H), 7.28–7.37 (8H, m, H^3, H^{13}, Ar–H), 7.43–7.52 (10H, m, H^4, H^{15}, H^{16}, Ar–H), 7.64–7.71 (8H, m, H^{17}, Ar–H and H^{10}, -CH=), 7.79–7.81 (4H, d, H^2, Ar–H), 7.89–7.93 (4H, d, $J = 15.6$ Hz, H^{11}, =CH–), 8.04–8.06 (8H, d, $J = 8.8$ Hz, H^7, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) $\delta = 134.88$ C^1

(P–C(Ar)), 128.83–128.96 C^2 (Ar–CH), 130.23–130.34 C^3 (Ar–CH), 131.25–131.34 C^4 (Ar–CH), 154.11 C^5 (Ar–C), 121.45 C^6 (Ar–CH), 130.10 C^7 (Ar–CH), 137.54 C^8 (Ar–C), 188.05 C^9 (C=O), 123.45 C^{10} (–CH=), 143.13 C^{11} (=CH–), 137.62 C^{12} (Ar–C), 115–02–115.24 C^{13} (Ar–CH), 161.72–164.14 C^{14} (Ar–C), 117.71–117.92 C^{15} (Ar–CH), 130.10 C^{16} (Ar–CH), 126.10 C^{17} (Ar–CH).

2,2,4,4-Tetra(1-(4′-oxyphenyl)-3-(2-pyridine)-2-propene-1-one)-6,6-diphenylcyclotriphosphazene ***(9)***

For the synthesis of compound **9** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1g** (3.14 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 24 h. Yield: 1.76 g (64%). M.p.: 156–157 °C. Anal. Calcd. For $C_{68}H_{50}N_7O_8P_3$: C, 68.86; H, 4.25; N, 8.27. Found: C, 68.92; H, 4.30; N, 8.31. MALDI-MS: *m/z* calc. 1186.08. Found $[M+H]^+$: 1187.10. FT-IR (KBr, cm^{-1}) ν 3006 and 3065 (C–H aromatic), 2838 and 2930 (C–H Aliphatic), 1661 (C=O), 1503, 1579, and 1597 (C=C), 1177 and 1203 (P=N), 928 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta = 7.03$ (d, 2P, PB), 22.14 (t, 1P, PA). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.26$–7.28 (8H, d, $J = 8.8$ Hz, H^6, Ar–H), 7.34–7.35 (4H, H^3, Ar–H), 7.41–7.46 (10H, m, H^2, H^4, H^{14}, Ar–H), 7.65–7.69 (4H, d, $J = 15.6$ Hz, H^{10}, –CH=), 7.87–7.89 (8H, m, H^{15}, H^{16}, Ar–H), 7.95–7.97 (8H, d, $J = 8.8$ Hz, H^7, Ar–H), 8.03–8.07 (4H, d, $J = 15.6$ Hz, H^{11}, =CH–). ^{13}C NMR (400 MHz, DMSO-d_6) $\delta =$ 133.71–135.07 C^1 (P–C(Ar)), 128.81–128.94 C^2 (Ar–CH), 130.27–130.38 C^3 (Ar–CH), 132.24 C^4 (Ar–CH), 153.13 C^5 (Ar–C), 121.64 C^6 (Ar–CH), 130.95 C^7 (Ar–CH), 134.86 C^8 (Ar–C), 188.54 C^9 (C=O), 125.26 C^{10} (–CH=), 143.61 C^{11} (=CH–), 154.07 C^{12} (Ar–C), 150.51 C^{13} (Ar–CH), 130.95 C^{14} (Ar–C), 137.63 C^{15} (Ar–CH), 130.95 C^{16} (Ar–CH).

2,2,4,4-Tetra(1-(4′-oxyphenyl)-3-(3-pyridine)-2-propene-1-one)-6,6-diphenylcyclotriphosphazene ***(10)***

For the synthesis of compound **10** was used the synthesis procedure in 3 and was prepared using **2** (1 g, 2.32 mmol), **1h** (3.16 g, 13.92 mmol) and K_2CO_3 (1.92 g, 13.92 mmol) for 30 h. Yield: 2.06 g (75%). M.p.: 188–189 °C. Anal. Calcd. For $C_{68}H_{50}N_7O_8P_3$: C, 68.86; H, 4.25; N, 8.27. Found: C, 68.93; H, 4.28; N, 8.33. MALDI-MS: *m/z* calc. 1186.08. Found $[M+H]^+$: 1187.11. FT-IR (KBr, cm^{-1}) ν 3036 and 3058 (C–H aromatic), 2930 and 2963 (C–H Aliphatic), 1663 (C=O), 1504, 1569, and 1604 (C=C), 1174 and 1200 (P=N), 934 (P-O-Ph). ^{31}P NMR (400 MHz, DMSO-d_6) $\delta = 6.92$ (d, 2P, PB), 22.16 (t, 1P, PA). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.24$–7.26 (8H, d, $J = 7.6$ Hz, H^6, Ar–H), 7.34–7.36 (6H, m, H^3, H^6, Ar–H), 7.47–7.50 (12H, m, H^2, H^{15}, H^{16}, Ar–H), 7.70–7.74 (4H, d, $J = 15.6$ Hz, H^{10}, –CH=), 7.97–8.01 (4H, d, $J = 15.6$ Hz, H^{11}, =CH–), 8.04–8.06 (8H, d, $J = 7.6$ Hz, H^7, Ar–H), 8.30–8.32 (4H, dd, H^{14}, Ar–H), 8.62 (4H, s, H^{13}, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) $\delta = 133.76$–135.58 C^1 (P–C(Ar)), 128.83–128.96 C^2 (Ar–CH), 130.25–130.36 C^3 (Ar–CH), 132.25 C^4 (Ar–CH), 153.14 C^5 (Ar–C), 121.47 C^6 (Ar–CH), 131.10 C^7 (Ar–CH), 134.82 C^8 (Ar–C), 187.95 C^9 (C=O), 123.92 C^{10} (–CH=), 141.15 C^{11} (=CH–), 130.86 C^{12} (Ar–C), 151.51 C^{13} (Ar–CH), 150.81 C^{14} (Ar–C), 124.36 C^{15} (Ar–CH), 135.58 C^{16} (Ar–CH).

Thermal behaviors of compounds 3–10

The melting points of the synthesized cyclotriphosphazene compounds were determined by heating them up at the heating rate of 20 °C min^{-1} until it reached 250 °C and by recording the DSC curves from DSC thermograms. The thermal degradation of compounds **3–10** were determined by heating them up at the heating rate of 10 °C min^{-1} until it reached 900 °C and then by recording the TGA curves. TGA measurements were carried out on approximately 5 mg samples at a heating rate of 10 °C min^{-1} under conditions of nitrogen flow (10 cm^3 min^{-1}). DSC and TGA curves of **3–10** were given in Figs. S1 (A) and (B), respectively. In general, the starting degradation temperatures of compounds is higher than 250 °C and 50% weight loss are generally higher than 500 °C. According to the results of TGA measurements, the temperatures at which degradation started on as well as the temperature ratings at which degradation proved to be 50%, and the residue percentages at 900 °C are given in Table 1.

Dielectric properties of compounds 3–10

Dielectric constant, loss factors, and electrical conductivity

To examine the dielectric behaviors of the synthesized cyclotriphosphazenes, compounds **3–10** were turned into tablets with the help of a disc under the pressure of 4 tons, and the disc thickness was measured, in addition to which the Cp,DF, and Gp values parameters were measured with the help of golden conductors. The measurements were performed at the range of 100 Hz–20 kHz. The dielectric constant, dielectric factors, and ac conductivity of **3–10** were calculated with the help of the following Eqs. (1), (2), and (3), respectively (Singh and Gupta 1998; Biryan and Demirelli 2016). As for the obtained compounds, the results of the dielectric constant (ε'), dielectric loss (ε''), and conductivity ($\log\sigma$) that were measured against the frequency are given in Fig. 1. In Table 1, the dielectric results at the

fixed frequency (1000 Hz) are shown.

$$\varepsilon' = C_p \frac{d}{A\varepsilon_0} \quad (1)$$

$$\varepsilon'' = \varepsilon' DF \quad (2)$$

$$\sigma = G_p \frac{d}{A} \quad (3)$$

where ε' is dielectric constant, σ is ac conductivity, ε_0 is the dielectric constant of vacuum (8.854×10^{-12}), d is the thickness (m) and A is effective area (m^2) of the sample, ε'' is dielectric loss factors and C is the capacitance (F) of test device.

In vitro assay for cytotoxic activities

The % changes in cell viability rates that were caused by 1, 5, 25, 50, and 100 µM concentrations specified for the synthesized compounds were determined against human ovarian cancer (A2780) and human prostate cancer (PC-3 and LNCaP) cell lines. The cytotoxic activities of the substituted-cyclotriphosphazene compounds was analyzed by MTT assay which is based on reduction of MTT salt by mitochondria of alive cells. This method is based on the principle that the MTT dye is capable of breaking down the tetrazolium ring. In this method, MTT is actively absorbed into the live cells, and the reaction is catalyzed by mitochondrial succinate dehydrogenase and is, then, reduced to blue-purple colored, water-insoluble formazan. The formation of formazan is only observed in the live cells in which active mitochondria are found, which is also accepted as the indicator of cell viability, and the value specified spectrophotometrically is associated with the number of living cells. 0.5 mg/mL of MTT study solution was prepared from out of the stock MTT solution prepared within sterile PBS, and it was added into the plaques with 96 wells. After keeping it waiting for 3 h in the incubator, the optical densities of the cells in the plaques were made to be read at 550 nm- wave lengths on the ELISA device (Synergy HT ABD). By having the control wells read, the average of the obtained absorbance values was taken, and this value was accepted as 100% live cell. The absorbance values obtained from the solvent (the group into which only dimethylsulfoxide (DMSO) was added) as well as agent-applied wells were proportioned to the control absorbance values, in addition to which the percentage (%) viability values were calculated (Mosamann et al. 1986; Singh and Singh 2002; Özen et al. 2016; Kucukbay et al. 2016). These experiments were carried out on different days by being repeated for at least 10 times, independent from each other.

The human prostate cancer cell series (PC-3 and LNCaP) and human ovarian cancer cell series (A2780) were used as the cell types. All the cells in 25 cm^2 culture flasks were fed within RPMI-1640 medium (that which was prepared by adding 10% FCS, 100 U/mL penicillin and 0.1 mg/mL streptomycin into it). The media of the cells kept in a humid atmosphere at 37 °C and in a carbon dioxide-incubator (5% CO_2) were changed twice a week. When the cells became confluent, they were extracted from the flasks by using trypsin-EDTA solution, after which they were transferred into the plaques with 96 wells and were used in the analyses of 3-(4,5-dimethylthiazol-2-yl)-diphenyltetrazolium bromide (MTT). The solutions of the substances in DMSO solvent were used in cell culture. Thus, in the comparison of the results obtained, the effects of the substances on DMSO were determined by performing a statistical analysis. The toxic effect of DMSO on the cell was determined, and it was seen that this was statistically insignificant in spite of its toxic effect. 1, 5, 25, 50, and 100 µM-concentrations pertaining to the tested compounds **(3–10)** as well as the solvent with the same amount (DMSO) were added into the wells where cells were put, and then it was left for incubation in CO_2 incubator (Panasonic/Japan) at 37 °C for 24 h. In the wake of the incubations, the viability rate of the cells was determined on a hemocytometer by using 0.4% tryphan blue (Singh and Singh 2002).

The compliance of the groups with the normal distribution was evaluated through Kolmogorov Smirnov test. In the comparison of the groups, on the other hand, one-way analysis of variance was used. The homogeneity of the variances was analyzed through Levene's test. It was observed after one-way analysis of variance that the variances were not homogeneous. For multiple comparisons, TAMHANE T2 test was used. The value $p < 0.05$ was accepted as statistically significant. The data were expressed in the form of mean ± standard error. The $LogIC_{50}$ values were calculated through a Graphpad prism 6 programs on a computer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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