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Syntheses of Hexaminomonoferrocenylspiro(N/O)cyclotetraphosphazenes: Spectral Properties and Antituberculosis Activities

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ABSTRACT

In this study, 3-(N-ferrocenylmethylamino)-1-propanol, $FcCH_2N(CH_2)_3OH$, is prepared by the reduction of Schiff base with $NaBH_4$, which is obtained from the condensation reaction of ferrocenecarboxaldehyde and 3-amino-1-propanol in methanol. Reaction of octachlorocyclotetraphosphazene (OCCP, tetramer, $N_4P_4Cl_8$, 1) and bidentate ligand (L), sodium 3-(N-ferrocenylmethylamino)-1-propanoxide, give hexachloromonoferrocenylspiro (2). Fully substituted mono-ferrocenylhexaamino(N/O) spirocyclotetraphosphazenes (2a and 2b) have been synthesized by the reaction of 2 with excesses of propylamine and butylamine, respectively. The structures of 2a and 2b were determined using elemental analysis, mass spectrometry (ESI-MS), FTIR, ^{1}H, ^{13}C and ^{31}P NMR data. In addition, antituberculosis activity studies of 2a and 2b against *Mycobacterium Tuberculosis* H37Rv reference strain were performed.

Keywords: Monoferrocenyl(N/O)spirocyclotetraphosphazenes, Spectroscopy, Antituberculosis activity.

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Introduction

Cyclophosphazenes are an inorganic ring system consisting of a skeleton (N=PX2)n (n = 3, 4, 5…) linked by sequential binding of N and P atoms and two inorganic-organic and/or organometallic side groups (X) covalently bonded to each P atom [1,2]. Hexachlorocyclotriphosphazene (HCCP, trimer, N3P3Cl6) and octachlorocyclotetraphosphazene (OCCP, tetramer, N4P4Cl8, 1) are the renowned starting reagents [3]. Both starting reagents have been widely used in the preparation of trimeric and tetrameric phosphazenes substituted with a lot of mono- and multifunctional heterocyclic reagents 4-6]. However, since the number of Cl atoms is higher in tetrameric phosphazene than in trimeric phosphazene, the number of geometrical and optical isomers that can be formed is also higher as expected. Thus, the products formed from the reactions of the tetramer are more difficult to separate. However, although the product variety is more interesting, the studies on the tetramer are very limited [7,8].

In phosphazenes, geometrical (nongeminal, cis/trans and geminal) and chiral isomers are formed depending on the number of replacements of Cl atoms with nucleophiles and the reaction conditions [9]. Moreover, the reaction of unsymmetrical bidentate ligands, such as sodium 3-amino-1-propanoxide and N-methyl-1,3 diaminopropane, with HCCP resulted in the formation of monospiro-, dispiro-, and trispirocyclotriphosphazenes [10, 11]. It was noticed that monospiro product was created stereoselectively in THF from the reaction of sodium 3-(N-ferrocenylmethylamino)-1-propanoxide (L) with an equimolar amount of HCCP [12].

In addition, it is stated in the literature that many cyclophosphazene derivatives can be used as biologically active materials [13], ionic liquids [14, 15], fluorescent indicators [16], lubricants [17], and organic light-emitting diodes (OLEDs) [18]. Moreover, some ferrocene compounds are of interest in various applications such as photoluminescent systems [19], drug release systems responsive to redox stimuli [20], electron-transfer mediators [21], organometallic catalysts [22]. Moreover, the antituberculosis and anticancer activities of ferrocene derivatives have been investigated against some reference strains and cancer cells [23, 24]. In addition, in recent years, there are studies in which trimeric and tetrameric phosphazenes containing ferrocenyl groups were obtained and their biological activities were investigated [25, 26].

In the last two decades, partially/fully substituted cyclophosphazene derivatives have received great attention for their potential as antituberculosis, antimicrobial and anticancer agents [27]. Ferrocenylcyclophosphazenes show antituberculous activity against Mycobacterium tuberculosis H37Rv [28].

In the present study, hexachloro(N/O) spirocyclotetraphosphazene containing monoferrocenyl pendant arm (2) was resynthesized as the starting compound [29,30]. In dry THF, the reaction of 2 with excess propyl and butylamine gave the hexaamino(N/O)spirocyclotetraphosphazene derivatives (2a and 2b) (Figure 1). These compounds were also synthesized to study their bioactivity.

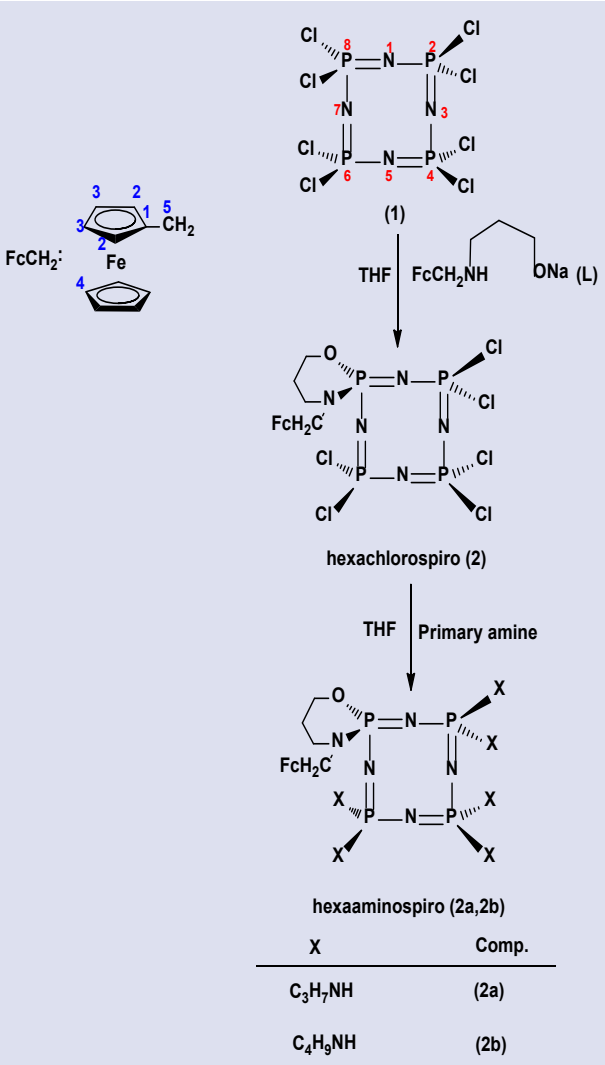


Figure 1. Synthesis of hexaaminomonoferrocenyl spiro(N/O)cyclotetraphosphazenes.

Materials and Methods

Apparatus

Nucleophilic substitution reactions were made under the Ar atmosphere. Necessary solvents were dried before use and purified by appropriate methods lit. $N_4P_4Cl_8$ (Otsuka Chemical Co. Ltd., crystallized from n-hexane), ferrocenecarboxaldehyde, (Aldrich), 3-amino-1-propanol, propylamine and butylamine (Merck) were procured. All the reactions were followed by TLC on Merck DC Alufolien Kiesegel 60 F254 plates in suitable solvents. Column chromatography was performed with Merck Kiesegel 60 (230-400 micronized ATSM) silica gel. The melting points of mono-ferrocenyl(N/O)cyclotetraphosphazenes were determined with a Gallenkamp instrument using a capillary tube. Micronalyses were performed with the Leco CHNS-932 instrument. FTIR spectra were recorded on KBr discs on a Jasco FTIR-430 spectrometer and reported in cm^{-1} units. Electron spray ionization-mass spectra (ESI-MS) were taken with a Waters 2695 Alliance Micromass ZQ spectrometer. The ^1H and ^{13}C NMR spectra of the phosphazenes were recorded on the Varian Mercury FT-NMR (400 MHz) spectrometer operating at 400.13 MHz and 100.62 MHz, respectively, and the ^{31}P NMR spectra were recorded on the Bruker Avance III HD (600 MHz) spectrometer operating at 242.94 MHz.

Synthesis of Phosphazenes

Synthesis of compound 2

The starting compound, hexachloro(N/O)spirocyclo tetraphosphazene (2), was synthesized from the reaction of OCCP (1) and equimolar amount of sodium L according to previous studies [29, 30].

Synthesis of Compound 2a

A propylamine solution (0.80 mL, 9.75 mmol) in dry THF (50 mL) was slowly added into a stirred solution of triethylamine (0.63 mL, 4.52 mmol) and 2 0.50 g, 0.75 mmol) in dry THF (100 mL) at room temperature. The mixture was refluxed for over 90 h. After the solvent was evaporated, the product was purified using column chromatography [THF-toluene (2:3)], and then it was purified by hexane: ethyl acetate (3:1) preparative thin-layer chromatography. Afterwards, the product was crystallized from *n*-hexane. Yield: (0.37 g, 62%). mp: 148 °C. Compound 2a: Anal. Calcd. for $C_{32}H_{65}ON_{11}P_4Fe.2C_7H_8O$: C, 47.88; H, 8.14; N, 15.35. Found: C, 48.38; H, 8.50; N, 15.20. ESI-MS (Ir %, Ir designates the fragment abundance percentage): *m/z* 801 ($[M2H]^+$, 100). FTIR (KBr, cm^{-1}): ν 2928, 2869 (C-H aliph.), 1265 (asymm.), 1113 (symm.) (P=N). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 4.23 (m, 2H, H_2), 4.16 (d, 2H, $^3J_{PH}$=13.2, $^3J_{HH}$=5.6 Hz, O-C*H*$_2$), 4.10 (bp, 5H, H_4), 4.06 (m, 2H, H_3), 3.92 (d, 2H, $^3J_{PH}$=7.6 Hz, H_5), 2.98 (m, 2H, Fc-CH$_2$-N-C*H*$_2$), 2.83 (m, 12H, P-NH-C*H*$_2$), 2.38 (bp, 6H, P-N*H*), 1.63 (m, 2H, O-CH$_2$-C*H*$_2$), 1.49 (m, 12H, P-NH-CH$_2$-C*H*$_2$), 0.91 ve 0.89 (t, 18H, $^3J_{HH}$=6.8 ve $^3J_{HH}$=7.6 Hz, CH$_2$-C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 85.27 (d, $^3J_{PC}$=10.8 Hz, C_1), 69.82 (s, C_2), 68.41 (s, C_4), 67.69 (s, C_3), 66.41 (d, $^2J_{PC}$=5.3 Hz, O-CH$_2$), 53.42 (s, P-NH-CH$_2$- *C*H$_2$), 47.36 (s, C_5), 45.56 (s, Fc-CH$_2$-N-CH$_2$), 42.96 ve 42.90 (s, P-NH-*C*H$_2$), 25.72 (s, O-CH$_2$-CH$_2$), 11.70 ve 11.64 (s, CH$_2$-*C*H$_3$). ^{31}P NMR (242.94 MHz, H_3PO_4 (85%), ppm): δ 3.32 (t, $^2J_{AC}$: 41.3 Hz, P_A, OPN), 6.01 (t, $^2J_{BC}$: 26.7 Hz, P_B, NPN), 5.80 (t, P_C, PNN).

Synthesis of Compound 2b

The experimental procedure was similar to that of compound 2a, using 2 (0.50 g, 0.75 mmol), triethylamine (0.63 mL, 4.52 mmol) and butylamine (0.97 mL, 9.75 mmol). The mixture was refluxed for over 96 h. After the solvent was evaporated, the product was purified using column chromatography [THF-toluene (1:3)], and crystallized from *n*-hexane. Yield: (0.35 g, 53%). mp: 157 °C. Compound 2b: Anal. Calcd. for $C_{38}H_{77}ON_{11}P_4Fe.2C_7H_8$: C, 58.48; H, 8.77; N, 14.42.Found: C, 58.98; H, 8.99; N,13.92. ESI-MS (Ir %, Ir designates the fragment abundance percentage): *m/z* 885 ($[M+2H]^+$, 100). FTIR (KBr, cm^{-1}): ν 2926, 2859 (C-H aliph.), 1271 (asymm.), 1117 (symm.) (P=N). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 4.20 (m, 2H, H_2), 4.17 (d, 2H, $^3J_{PH}$=11.6, $^3J_{HH}$=4.0 Hz, O-C*H*$_2$), 4.11 (bp, 5H, H_4), 4.06 (m, 2H, H_3), 3.92 (d, 2H, $^3J_{PH}$=7.6 Hz, H_5), 3.01 (m, 2H, Fc-CH$_2$-N-C*H*$_2$), 2.85 (m, 12H, P-NH-C*H*$_2$), 2.68 (bp, 6H, P-N*H*), 1.61 (m, 2H, O-CH$_2$-C*H*$_2$),1.53 (m, 12H, P-NH-

CH_2-CH_2-CH_2) 1.47 (m, 12H, P-NH-CH_2-CH_2), 0.91 ve 0.89 (t, 18H, $^3J_{HH}$=7.2 ve $^3J_{HH}$=4.0 Hz, CH_2-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 83.88 (d, $^3J_{PC}$=11.2 Hz, C_1), 70.11 (s, C_2), 68.58 (s, C_4), 68.32 (s, C_3), 66.41 (d, $^2J_{PC}$=6.9 Hz, O-CH_2), 53.45 (s, P-NH-CH_2- CH_2), 47.42 (s, C_5), 45.60 (s, Fc-CH_2-N-CH_2), 41.41 ve 41.27 (s, P-NH-CH_2), 30.39 ve 30.29 (s, N-CH_2-CH_2), 29.40 (d, $^3J_{PC}$=3.0 Hz, O-CH_2-CH_2), 26.39 ve 26.37 (m, P-NH-CH_2-CH_2-CH_2) 13.84 ve 13.79 (s, CH_2-CH_3). ^{31}P NMR (242.94 MHz, H_3PO_4 (85%), ppm): δ 3.20 (t, $^2J_{AC}$: 41.2 Hz, P_A, OPN), 6.30 (t, $^2J_{BC}$: 36.4 Hz, P_B, NPN), 5.62 (t, P_C, PNN).

Evaluation of Antituberculous Activity

The antituberculosis activities of the hexaamino(N/O)spirocyclotetraphosphazenes (2a and 2b) were evaluated against the reference strain *Mycobacterium tuberculosis* H37Rv (ATCC 27294) using the "Agar proportion method" in agar-based Middlebrook 7H10 medium with respect to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). The final concentrations of each tetraphosphazene derivative in the medium were set at 5, 10, 20, 40 and 80 µg/mL, respectively. The rest of the experiments were carried out as stated in the literatüre [31].

Results and Discussion

Synthesis

It is known from previous studies that the replacement reaction of OCCP with an equimolar quantity of L yields two different types of products [29, 30]. These two products are mono-ferrocenyl-2-cis-4-dichloro-ansa- (2,4-ansa; yield 14%) and mono-ferrocenyl-spiro- (spiro; yield 35%) hexachlorocyclotetraphosphazene derivatives. In this study, monoferrocenylspiro-(2) with a higher yield was used as the starting reagent in this study. Compound 2 has six replaceable Cl atoms and is capable of substitution reactions with a wide variety of nucleophiles. In this study, hexapropylaminomonoferrocenylspiro(N/O) (2a) and hexabutylamino (2b) cyclotetraphosphazenes were obtained by reacting the spiro (2) (0.75 mmol) with excessive amounts of propylamine (9.75 mmol) and butylamine (9.75 mmol), respectively. Reactions during the formation of the spiro product are likely to proceed via the SN' (P) and/or SN^2 (P) reaction pathway (Fig. 2).

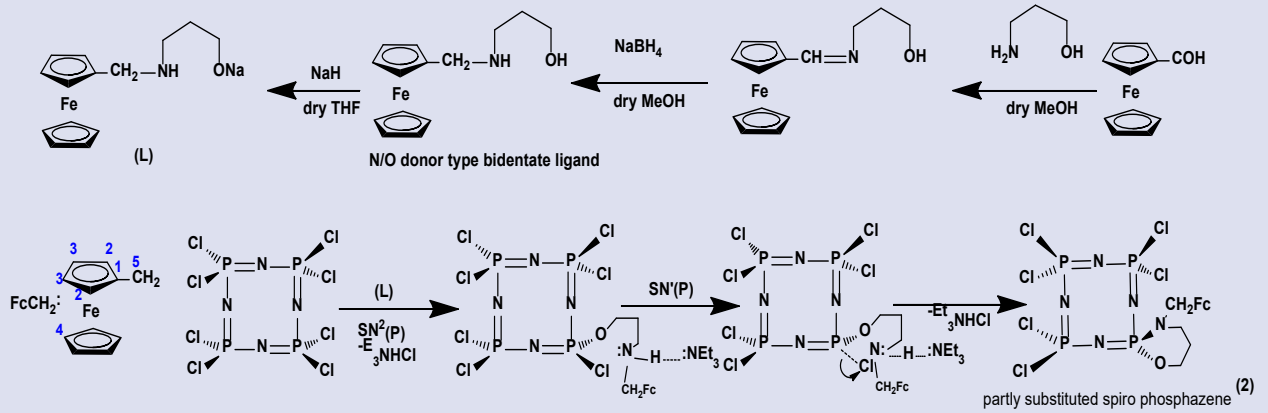


Figure 2. Proposed reaction mechanism of $N_4P_4Cl_8$ compound and sodium salt (**L**) of bidentate ligand with N/O donor atoms

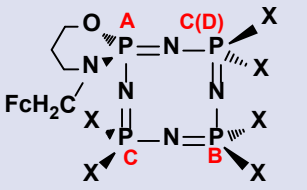
Triethylamine (4.52 mmol) was used to keep the acid formed as a result of the replacement reaction of the tetramer with aminolkoxide as the Et_3N.HCl salt. The intramolecular hydrogen bond occurred between the N–H hydrogen of the Pendant $FcCH_2$ arm and triethylamine plays a significant role in increasing the reaction yield. The yields of 2a and 2b were calculated as 62% and 53%, respectively. The structures of the products were characterized using elemental analysis, FTIR, ESI-MS, ^{1}H-, ^{13}C- and ^{31}P-NMR data. These findings are consistent with the structures of hexaaminomonoferrocenyl(N/O) spirocyclotetraphosphazenes. Analytical data and NMR results were presented in the "Experimental Part".

NMR and IR Spectroscopy

^{31}P NMR results of monoferrocenylspiro (N/O)cyclotetraphosphazenes were given in Table 1. The starting compound 2 has ABCD spin system due to four different phosphorus environments in the molecule, while the spin systems of 2a and 2b are are designated as ABC_2. The δP chemical shifts of 2a and 2b were found to be greater than the starting compound 2 (Table 1).

Electron spray ionization-mass spectra (ESI-MS) of 2a and 2b were given in Figure 3. The molar masses of the compounds were calculated based on ^{35}Cl and ^{56}Fe isotopes. The mass spectrum of 2a and 2b gave a protonated molecular $[M+2H]^+$ ion peak.

Table 1. ^{31}PNMR data of mono-ferrocenyl-(N/O)cyclotetraphosphazenes.

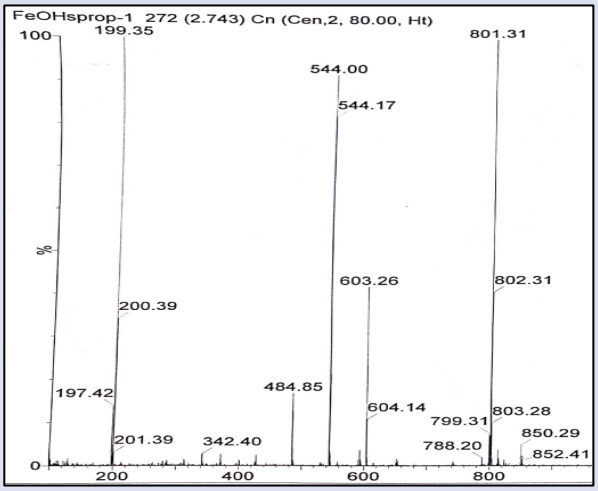


ABCC' (2); ABC_2 (2a and 2b)

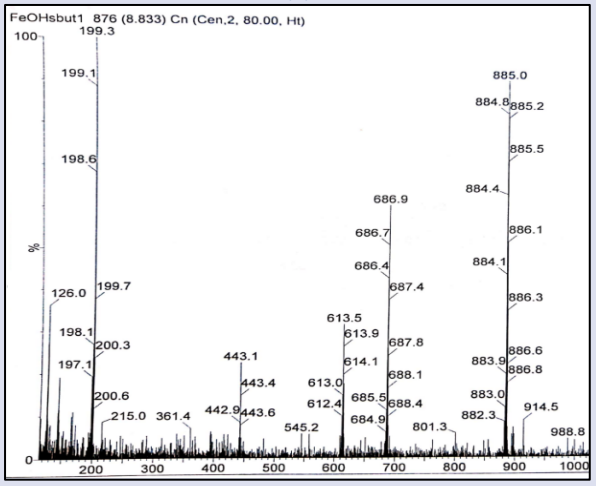
Fc= Ferrocenyl ; X= Cl, propylamine and butylamine

Compound	Spin System	OPN	δ(ppm) ClPCl	NPN	$^2J_{PP}$ (Hz)	
2*	ABCD	-5.89 (P_A)	-5.89 (PB) -7.44 (PC) -7.60 (PD)	-	$^2J_{AC}$: 38.9 $^2J_{AD}$: 41.3	$^2J_{BC}$: 26.7 $^2J_{BD}$: 29.2
2a	ABC_2	3.32 (P_A)	-	5.80 (P_C) 6.01 (P_B)	$^2J_{AC}$: 41.3	$^2J_{BC}$: 26.7
2b	ABC_2	3.20 (P_A)	-	5.62 (P_C) 6.30 (P_B)	$^2J_{AC}$:41.2	$^2J_{BC}$: 36.4

a^{31}P-NMR measurements were taken at 298 K in $CDCl_3$ solution at 242.93 MHz.
*^{31}P {^{1}H} NMR data are taken from the literature [31].



(a)



(b)

Figure 3. (*a*) Mass spectra of the compound hexapropylmonoferrocenylspiro (2a) and (*b*) hexabutylmonoferrocenylspiro (2b).

On the other hand, all δ chemical shifts, J coupling constants and abundance of signals are evaluated from the 13C and 1H NMR spectra of monoferrocenyl(N/O)cyclotetraphosphazenes. These values are given in the "Experimental Part". The signals of O-CH2 carbon of 2a and 2b are observed at 66.41 ppm and 2JPOC values are calculated as 5.3 and 6.9 Hz. Similarly, the 3JPOCC value for carbons O-CH2-CH2 was observed only for 2b (3JPOCC 3.0 Hz). In addition, the expected carbon (C1-C4) peaks from ferrocene rings were determined from the 13C spectra of 2a and 2b. These results were found to be in agreement with literature findings for ferrocenylcyclotetraphosphazenes[32]. The ipso-C1 carbons of Fc of 2a and 2b were observed at 83.88 and 85.27 ppm, respectively, and the average value of 3JPNCC was calculated as 11.0 Hz.

One of the best confirmations that the Cl atoms of the spiro (2) derivative are replaced by amines is the observation of the carbon signals of the amino groups in the ^{13}C NMR spectra of 2a and 2b (Fig. 4).

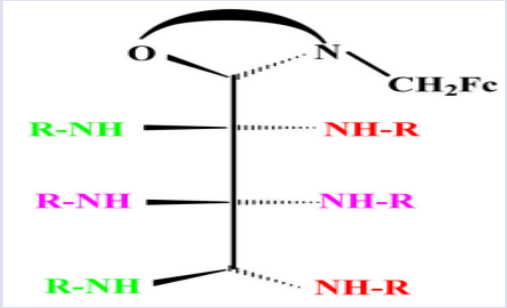


Figure 4. The stick diagram of hexaaminoferrocenyl(N/O)spirocyclotetraphosphazenes (2a and 2b)

From the integral ratios of the ^{1}H spectra of 2a and 2b compounds, it is determined that six alkylamino groups are bonded to the P2, P4 and P6 atoms. The average δ values of aliphatic OCH_2, O-CH_2-CH_2 and NCH_2 protons were calculated as 4.16, 1.61 and 2.98 ppm, respectively. In addition, the expected proton (H_2-H_4) peaks of ferrocene rings were observed in the ^{1}H NMR spectra of aminocyclotetraphosphazenes. The results are consistent with the literature findings for ferrocenylphosphazenes [31]. Fc-CH_2 (H_5) protons were determined as a doublet with an average value of 3.92 ppm, and the coupling constant ($^3J_{PH}$ =7.6 Hz) was calculated.

The characteristic FTIR frequencies of hexaminospiro(N/O)cyclotetraphosphazenes were also given in the "Experimental Part". The characteristic symmetric and asymmetric $\nu_{P=N}$ bands of P=N bonds belong to the P_4N_4 ring and appear at 1113-1117 cm^{-1} and 1265-1271 cm^{-1}, respectively [33, 34]. In addition, ν_{P-Cl} stretching frequencies of the starting compound spiro (2) were observed at 556 cm^{-1} (asymm.) and 488 cm^{-1} (sym.), while these peaks disappeared in completely amino substituted products (2a and 2b) [35, 36, 37].

Antituberculosis Activity against M.Tuberculosis H37Rv Reference Strain

Tuberculosis is an infectious disease caused by *Mycobacterium Tuberculosis* and is known to cause death in large numbers of people. Although the disease is controlled with various treatment methods, many patients die from this disease every year and it is among the top 10 causes of death worldwide [38].

In this study, antituberculosis activities of 2a and 2b against *M. tuberculosis* H37Rv (ATCC 27294) reference strain were tested using the “Agar proportional method” [39] to contribute to the treatment of tuberculosis (TB). *M. tuberculosis* H37RV strain was found to be susceptible to two compounds [2a (35 µg/mL) and 2b (70 µg/mL)]. The MIC value of compound 2a (35 µg/mL) was found to be much smaller and more effective than compound 2b (Table 2) (Figure 5.).However, the MIC value of 2 was reported as 80 µg/mL in the literature [29], which shows that the new compounds (2a and 2b) formed by binding to primary amines are more effective.

The MIC values of the drugs currently used against the reference strain of *M. tuberculosis* H37Rv are as follows; rifampicin (1.0 µg/mL), isoniazid (1.0 µg/mL), ethanebutol (10.0 µg/kg) and streptomycin (10 µg/mL). The MIC of 2a is closer to the MIC of streptomycin and ethanebutol. Therefore, it is thought that this compound can be used as a promising new drug in the treatment of TB at low doses.

As a result, it can be stated that the synthesized compounds contain elements such as chlorine, phosphorus and nitrogen in the body and when these compounds are decomposed, they will not harm living cells by transforming into ammonium and phosphate ions in the human body.

However, as a result of long-term use of first and second choice drugs used currently in the treatment of tuberculosis, many serious side effects are encountered in patients.

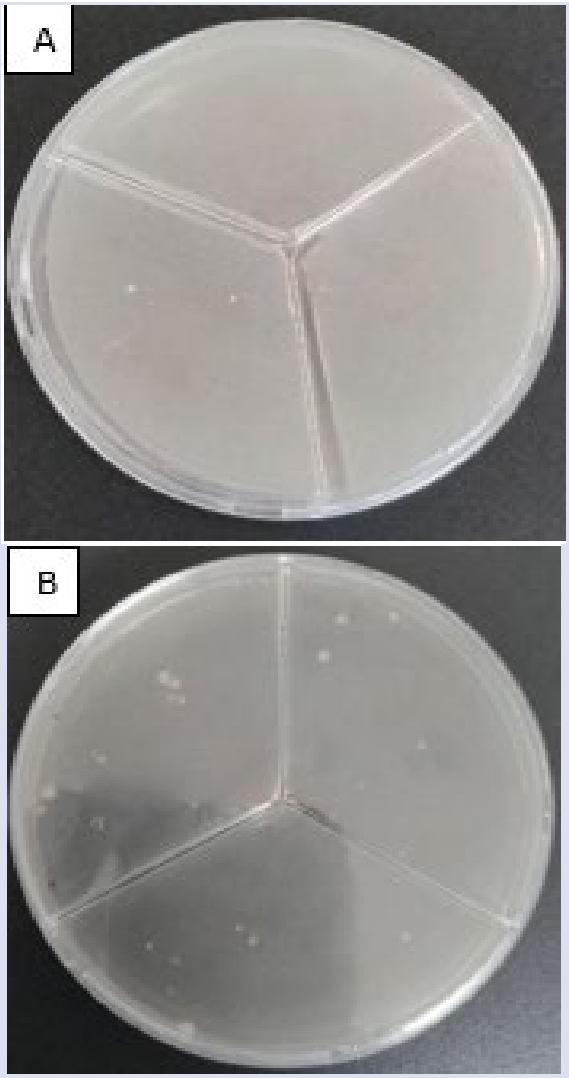


Figure 5. Anti-tuberculosis activity test of compound 2a against *M. tuberculosis* H37RV reference strain. Bacterial growth (control) was observed for compound 2a in the first 3-compartment petri dish (control, 40 and 35 µg/mL) in A.. B was reproduced in the second petri dish with 3 compartments (30, 25 and 20 µg/mL). In this case, the MIC of 2a is 35 µg/mL

Table 2. Effects of compounds (2a and 2b) in DMSO against *M. tuberculosis* H37Rv strain.

Comp.	Concentration (µg/mL)					MIC (µg/mL)
	80	40	20	10	5	
2a	S	S	R	R	R	35
2b	S	R	R	R	R	70

R: resistant, S: susceptible.

On the other hand, when the MIC values of the fully monoamine substituted monoferrocenylspiro cyclotetraphosphazene derivatives in the literature in antituberclosis activity studies against the reference strain *M. tuberculosis* H37RV were compared: it was seen that the most effective compounds were monoferrocenyl (N/N)spirocyclotetraphosphazene derivative pyrrolidine substitued derivatives (3 µg/mL) [26, 30, 31].

Table 3. MIC values of the compounds of fully substituted monoferrocenylspirocyclotetraphospahazenes.

Test organism	*M. tuberculosis* H37Rv
Compounds	**MIC (µg/mL)**
Monoamines-substituted monoferrocenyl (N/O)spirocyclotetraphosphazenes:	
Pyrrolidine-substituted [30]	65
Piperidine-substituted [30]	I
Morpholine-substituted [30]	70
DASD-substituted [30]	I
Hexylamine-substituted [31]	35
Benzylamine-substituted [31]	70
Monoamines-substituted monoferrocenyl (N/N)spirocyclotetraphosphazenes:	
Pyrrolidine-substituted (4a) [26]	3
Pyrrolidine-substituted (5a) [26]	3
Pyrrolidine-substituted (6a) [26]	3
Morpholine-substituted (4b) [26]	I
Morpholine-substituted (5b) [26]	I
Morpholine-substituted (6b) [26]	I
DASD-substituted (4c) [26]	I
DASD-substituted (5c) [26]	70
DASD-substituted (6c) [26]	I

I:Ineffective

Conclusion

In phosphorus-nitrogen chemistry, the replacement of Cl atoms in OCCP with various organic/inorganic mono- and bidentate ligands can enable the synthesis of organic-inorganic-based hybrid cyclotetraphosphazene derivatives or their composite materials and thus their application in various fields. For this purpose, in this article, organic-inorganic based hybrid cyclotetraphosphazenes; 2a and 2b were prepared. The structures of both tetraphosphazenes are elucidated using ESI-MS, FTIR and NMR data.

On the other hand, the antituberculosis activities of 2a and 2b were compared and it was observed that 2a with MIC value (35 µg/mL) had a more significant antituberculosis effect against M. tuberculosis H37Rv reference strain than 2b. Also, since the MIC of 2 is greater than the amino-substituted derivatives (2a and 2b), this indicated that the antituberculosis activity increased when Cl atoms were replaced by amine groups.

As a result of these findings, these phosphazenes may have the chance to be used as promising new antituberculosis agents in medicine in the future.

Acknowledgment

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Conflicts of Interest

The author declares that there is no conflict of interest.

References

[1] Chandrasekhar V., Chakraborty A., Phosphazenes, *Organophosphorus Chem.,* 49 (2020) 349-376.

[2] Stewart F. F., Phosphazenes, *Organophosphorus Chem*., 44 (2015) 397-430.

[3] Gleria M., Jaeger R. D., Phosphazenes:A Worldwide Insight. New York: Nova Science Publishers, (2004), 1047.

[4] Medjdoub L., Mohammed B., New method for nucleophilic substitution on hexachlorocyclotriphosphazene by allylamine using an algerian proton exchanged montmorillonite clay (Maghnite-H+) as a green solid catalyst, *Bull. Chem. React. Eng.&Catal.,* 11(2) (2016) 151-160.

[5] Elmas G., Syntheses and structural characterizations of 2-pyridyl(N/O)spirocyclotriphosphazene derivatives, *Phosphorus, Sulfur Silicon Relat. Elem.,* 194 (1-2) (2019) 13-24.

[6] Elmas G., Okumuş A., Kılıç Z., Çam M., Açık L., Hökelek T., Phosphorus-nitrogen compounds. Part 40. The syntheses of (4-fluorobenzyl) pendant armed cyclotetraphosphazene derivatives: spectroscopic, crystallographic and stereogenic properties, DNA interactions and antimicrobial activities, *Inorg. Chim. Acta*, 476 (2018) 110-122.

[7] Mutlu G., Elmas G., Kılıç Z., Hökelek T., Koç L. Y., Türk M., Açık L., Aydın B., Dal H., Phosphorus-nitrogen Compounds: Part 31. Syntheses, structural and stereogenic properties,

in vitro cytotoxic and antimicrobial activities, DNA interactions of novel bicyclotetraphosphazenes containing bulky side group, *Inorg. Chim. Acta,* 436 (2015) 69-81.

[8] Elmas G., Okumuş A., Sevinç P., Kılıç Z., Açık L., Atalan M., Türk M., Deniz G., Hökelek T., Phosphorus–nitrogen compounds. Part 37. Syntheses and structural characterizations, biological activities of mono and bis (4-fluorobenzyl) spirocyclotetraphosphazenes, *New J. Chem.,* 41 (13) (2017) 5818-5835.

[9] Chandrasekhar V., Thilagar P., Pandian B. M., Cyclophosphazene-based multi-site coordination ligands, *Coord. Chem. Rev.,* 251 (2007) 1045-1074.

[10] Okumuş A., Elmas G., Kılıç Z., Ramazanoğlu N., Açık L., Türk M., Akça G., The reactions of $N_3P_3Cl_6$ with monodentate and bidentate ligands: The syntheses and structural characterizations, In vitro antimicrobial activities and DNA interactions of 4-fluorobenzyl (N/O) spirocylotriphosphazenes, *Turk. J. Chem.,* 41 (2017) 525-547.

[11] Beşli S., Coles S. J., Davies D. B., Kılıç A., Shaw R. A., Bridged cyclophosphazenes resulting from deprotonation reactions bearing a P-NH group, *Dalton Trans.,* 40 (19) (2011) 5307-5315.

[12] Tümer Y., Asmafiliz N., Kılıç Z., Hökelek T., Açık L., Solak A. O., Yola M. L., Phosphorus–nitrogen compounds: part 30. Syntheses and structural investigations, antimicrobial and cytotoxic activities and DNA interactions of vanillinato-substituted NN or NO spirocyclic monoferrocenyl cyclotriphosphazenes, *J. Biol. Inorg. Chem.,* 20(8) (2015) 165-178.

[13] Xu L. C., Chen C., Zhu J., Tang M., Chen A., Allcock H. R., Siedlecki C. A., New cross-linkable poly[bis(octafluoropentoxy) phosphazene] biomaterials: Synthesis, surface characterization, bacterial adhesion, and plasma coagulation responses, *J. Biomed. Mater. Res.,* 108 (8) (2020) 3250-3260.

[14] Elmas G., Okumuş A., Kılıç Z., Çelik S. P., Açık L., The Spectroscopic and Thermal Properties, Antibacterial and Antifungal Activity and DNA Interactions of 4-(Fluorobenzyl)Spiro(N/O) Cyclotriphosphazenium Salts, *J. Turk. Chem. Soc. Sect. A: Chem.,* 4 (3) (2017) 993-1016.

[15] Jimenez J., Pintre I., Gascon E., Sanchez-Somolinos C., Alcala R., Cavero E., Serrano J. L., Oriol L., Photoresponsive Liquid-Crystalline Dendrimers Based on a Cyclotriphosphazene Core, *Macromol. Chem. Phys.,* 215 (2014) 1551-1562.

[16] Selberg S., Pagano T., Tshepelevitsh S., Haljasorg T., Vahur S., Luik J., Saame J., Leito I., Synthesis and photophysics of a series of lipophilic phosphazene-based fluorescent indicators*, J. Phys. Org. Chem.,* 32 (7) (2019) e3950.

[17] Wang X., Tan A. Y. X., Cho C. M., Ye Q., He C., Ji R., Xie H. Q., Tsai J. W. H., Xu J., Perfluoropolyether Boundary Lubricants Based on the Star Architecture, *Tribology Int.*, 9 (2015) 257–262.

[18] Mucur S. P., Canımkurbey B., Kavak P., Akbaş H., Karadağ A., Charge carrier performance of phosphazene-based ionic liquids doped hole transport layer in organic light-emitting diodes, *Appl. Phys. A,* 126 (12) (2020) 1-14.

[19] Singh S. K., Kumar V., Drew M. G. B., Singh N., Syntheses, crystal structures and photoluminescent properties of new heteroleptic Ni(II) and Pd(II) complexes of ferrocene functionalized dithiocarbamate-and dipyrromethene ligands, *Inorg. Chem. Commun*., 37 (2013) 151-154.

[20] Haibin G., Shengdong M., Guirong Q., Xiong L., Li Z., Yanfei Y., Didier A., Redox-stimuli-responsive drug delivery systems with supramolecular ferrocenyl-containing polymers for controlled release, *Coord. Chem. Rev.*, 364 (2018) 51-85.

[21] Lennox A. J. J., Nutting J. E., Stahl S. S., Selective electrochemical generation of benzylic radicals enabled by ferrocene-based electron-transfer mediators, *Chem. Sci.,* 9 (2018) 356-361.

[22] Singh R. K., Kukrety A., Saxena R. C., Chouhan A., Jain S. L., Ray S. S., Phosphazene-based novel organo-inorganic hybrid salt: synthesis, characterization and performance evaluation as multifunctional additive in polyol, *RSC Adv.*, 7 (2017)13390-13397.

[23] Elmas G., Okumuş A., Cemaloğlu R., Kılıç Z., Çelik S. P., Açık L., Tunalı B. Ç., Türk M., Çerçi N. A., Güzel R., Hökelek T., Phosphorus-Nitrogen Compounds. Part 38. Syntheses, characterizations, cytotoxic, antituberculosis and antimicrobial activities and DNA interactions of spirocyclotetraphosphazenes with bis-ferrocenyl pendant arms, *J. Organomet. Chem.,* 853 (2017) 93-106.

[24] Elmas G., Kılıç Z., Çoşut B., Keşan G., Açık L., Çam M., Tunalı B. Ç., Türk M., Hökelek T., Synthesis of Bis(2,2,3,3-tetrafluoro-1,4-butanedialkoxy)-2-trans-6-bis(4-fluorobenzyl)spiro cyclotetraphosphazene: Structural Characterization, Biological Activity and DFT Studies, *J. Chem. Crystallogr.,* 51 (2020) 235-250.

[25] Asmafiliz N., Kılıç Z., Öztürk A., Hökelek T., Koç L. Y., Açık L., Kısa Ö., Albay A., Üstündağ Z., Solak A. O., Phosphorus−Nitrogen Compounds. 18. Syntheses, stereogenic properties, structural and electrochemical investigations, biological activities, and DNA interactions of new spirocyclic Mono- and bisferrocenylphosphazene derivatives, *Inorg. Chem.,* 48 (21) (2009) 10102-10116.

[26] Okumuş A., Elmas G., Cemaloğlu R., Aydın B., Binici A., Şimşek H., Açık L., Türk M., Güzel R., Kılıç Z., Hökelek T., Phosphorus-Nitrogen Compounds. Part 35. Syntheses, spectroscopic and electrochemical properties, antituberculosis, antimicrobial and cytotoxic activities of mono-ferrocenyl-spirocyclotetraphosphazenes, *New J. Chem.,* 40 (2016) 5588-5603.

[27] Elmas G., Okumuş A., Kılıç Z., Özbeden P., Açık L., Tunalı B. Ç., Türk M., Çerçi N. A., Hökelek T., Phosphorus-nitrogen compounds. Part 48. Syntheses of the phosphazenium salts containing 2-pyridyl pendant arm: Structural characterizations, thermal analysis, antimicrobial and cytotoxic activity studies, *Indian J. Chem. Sec. A,* 59A (2020) 533-550.

[28] Elmas G., Okumuş A., Koç L. Y., Soltanzade H., Kılıç Z., Hökelek T., Dal H., Açık L., Üstündağ Z., Dündar D., Yavuz M., Phosphorus-Nitrogen Compounds. Part 29. Syntheses, crystal structures, spectroscopic and stereogenic properties, electrochemical investigations, antituberculosis, antimicrobial and cytotoxic activities and DNA interactions of ansa-spiro-ansa cyclotetraphosphazenes, *Eur. J. Med. Chem.*, 87 (2014) 662-676.

[29] Okumus A., Elmas G., Kılıç Z., Binici A., Ramazanoğlu N., Açık L., Çoşut B., Hökelek T., Güzel R., Tunalı B. Ç., Türk M., Şimşek H., The comparative reactions of 2- cis -4-ansa and spiro cyclotetraphosphazenes with difunctional ligands: Structural and stereogenic properties, electrochemical, antimicrobial and cytotoxic activity studies, *App. Organomet Chem.,* e6150 (2021) 1-28.

[30] Binici A., Okumus A., Elmas G., Kılıç Z., Ramazanoğlu N., Açık L., Şimşek H., Tunalı B. Ç., Türk M., Güzel R., Hökelek T., Phosphorus-nitrogen compounds. Part 42. The comparative syntheses of 2-cis-4-ansa(N/O) and spiro(N/O) cyclotetraphosphazene derivatives: spectroscopic and crystallographic characterization, antituberculosis and cytotoxic activity studies, *New J. Chem.,* 43 (2019) 6856-6873.

[31] Binici A., Okumus A., Yakut M., Elmas G., Kılıç Z., Koyunoğlu D., Açık L., Şimşek H., Phosphorus-nitrogen compounds. Part 56. Comparative syntheses and spectral properties of multiheterocyclic 2-cis-4-ansa and spiro-ferrocenyl (N/O)cyclotetraphosphazenes: Antituberculosis and antimicrobial activity and DNA interaction studies, *Phosphorus, Sulfur Silicon Relat. Elem.,* (2021)

[32] Elmas G., Okumuş A., Hökelek T., Kılıç Z., Phosphorus-Nitrogen Compounds. Part 52. The reactions of octachlorocyclotetraphosphazene with sodium 3-(N-ferrocenylmethylamino)-1-propanoxide: investigations of spectroscopic, crystallographic and stereogenic properties, *Inorg. Chim. Acta*, 497 (11) (2019) 119106.

[33] Elmas G., The reactions of 2-trans-6-bis(4-fluorobenzyl)spirocyclotetraphosphazene with primary amines: spectroscopic and crystallographic characterizations, *Phosphorus Sulfur Silicon Relat. Elem.,* 192 (11) (2017) 1224-1232.

[34] Carriedo G. A., Alonso F. G., Gonzalez P. A., Menendez J. R., Infrared and Raman spectra of the phosphazene high polymer $[NP(O_2C_{12}H_8)]_n$, *J. Raman Spectrosc.*, 29 (1998) 327-330.

[35] Elmas G., Syntheses and spectroscopic investigations of 2-pyridyl(N/N)spirocyclotriphosphazenes, *J. Turk. Chem. Soc. Sect. A: Chem.,* 5(2) (2018) 621-634.

[36] Mutlu Ö. F., Binici A., Okumuş A., Elmas G., Cosut B., Kılıç Z., Hökelek T., Phosphorus-nitrogen Compounds. Part 54. Syntheses of Chiral Amino-4-fluorobenzyl-spiro(N/O)cyclotriphosphazenes: Structural and Stereogenic Properties, *New J. Chem.,* 45 (2021) 12178-12192.

[37] Binici A., Elmas G., Okumus A., Tayhan, S. E., Hökelek, T., Şeker, B. N., Açık, L., Kılıç Z., Phosphorus-nitrogen compounds. Part 58. Syntheses, structural characterizations and biological activities of 4-fluorobenzyl-spiro(N/O)cyclotriphosphazene derivatives, *J. Biomol. Struc.& Dyn.,* (2021).

[38] World Health organization, Tuberculosis. Key facts. Available at: https://www.who.int/news-room/fact-sheets/detail/tuberculosis. Retrieved October 14, 2021.

[39] Clinical and Laboratory Standards Institute, M24-A2, Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard-Second Edition, (2011).