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SYNTHESIS AND HEMATOPOIESIS-STIMULATING ACTIVITY OF NEW IMIDAZOLYL-CONTAINING PHOSPHONATE INCLUSION COMPLEXES

Abstract: A series of novel imidazole-containing α-aminophosponate derivatives were synthesized based on 1-(3-aminopropyl)imidazole using the absolute benzene under the one-pot, three-component Kabachnik–Fields reaction. The hematopoiesis-stimulating activity was evaluated for the compounds 7βCD-12βCD. The structure of the obtained compounds was confirmed using nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR), and elemental analysis. All tested compounds were β-cyclodextrin inclusion complexes of dialkyl(3-(1*H*-imidazol-1-yl)propylamino)(fluoro- and trifluoromethylphenyl) methyl)phosphonates to enhance aqueous solubility, improve bioavailability, and modulate the pharmacokinetic profile of the phosphonates. Among the tested derivatives, compounds 7βCD, 8βCD, 10βCD, and 11βCD exhibited low hematopoiesis-stimulating activity, whereas 9βCD and 12βCD demonstrated a moderate stimulatory effect on leukopoiesis. Biological evalution in a cyclophosphamide-induced pancytopenia model revealed that several complexes exhibit hematopoietic properties. Notably, 9βCD and 12βCD moderately stimulated leukopoiesis at a level comparable to methyluracil, significantly restoring the total leukocyte and lymphocyte counts and normalizing the Harkavy index. Despite their positive effects on leukopoiesis, compounds 9βCD and 12βCD showed limited influence on erythropoiesis and thrombopoiesis. In contrast, other derivatives (7βCD, 8βCD, 11βCD) did not exhibit stimulatory activity and, in some cases, even suppressed hematopoietic parameters. Taken together, these findings indicate that complexes of β-cyclodextrin with imidazole-containing α-aminophosphonates – particularly the complex of dimethyl(((3-(1*H*-imidazol-1-yl)propyl)amino)(4-fluorophenyl)methyl)phosphonate with β-cyclodextrin (9βCD) and complex of dimethyl ((3-(1*H*-imidazol-1-yl)propylamino)(4-(trifluoromethylphenyl)-methyl) phosphonate with β-cyclodextrin (12βCD) – represent promising scaffolds for the development of novel modulators of hematopoiesis. The observed biological activity may be associated with the presence of electron-withdrawing substituents (fluoro- and trifluoromethyl groups) and the imidazole fragment, which can contribute to intermolecular interactions with biological targets and participate in hydrogen bonding, facilitating binding to enzyme active sites, while the phosphonate moiety provides enhanced metabolic stability. Overall, these holdings suggest the potential of certain phosphonate derivatives, particularly 9βCD and 12βCD, as possible candidates for the further development of immunomodulating agents.

Keywords: hematopoiesis-stimulating activity; phosphonate derivatives; β-cyclodextrin inclusion complexes of dialkyl ((3-(1*H*-imidazol-1-yl)propylamino) (fluoro- and trifluoromethylphenyl)methyl)phosphonate.

Introduction

The need for effective and safe immunomodulatory and leukopoiesis-stimulating agents remains one of the pressing challenges in modern pharmaceutical science. Disorders of hematopoiesis – whether caused by autoimmune diseases, chemotherapy, infections, or toxic exposures – often require pharmacological correction (El-Badry et al., 2025; Gholami et al., 2023; Regina et al., 2025; Strzelec et al., 2023; Zhang et al., 2025). The most common conditions associated with the acquired form of leukopoiesis deficiency, requir-

ing mandatory treatment for systemic infections, include: sepsis, purulent meningitis, etc.; chronic bronchitis with frequent relapses, concomitant with ENT conditions (purulent sinusitis, otitis media, lymphadenitis) resistant to standard treatments and with a history of pneumonia; recurrent pneumonia and bronchopleuropneumonia; bronchiectasis; chronic bacterial infections of the skin and subcutaneous tissue (pyoderma, furunculosis, abscesses, phlegmon, septic granuloma, recurrent paraproctitis in adults); chronic mycoses of the skin and mucous membranes, candidiasis, parasitic infections; recurrent aphthous stomatitis, concomitant with an increased incidence of acute viral respiratory infections. Recurrent herpesvirus infections of various sites; gastrointestinal conditions with chronic diarrhea of unknown etiology, intestinal dysbiosis; lymphadenopathy, recurrent lymphadenitis. Persistent low-grade fever and fever of unclear origin. However, the therapeutic options currently available to clinicians are limited (Bahrami et al., 2020; Cabañero-Navalon et al., 2024; Gubernatorova et al., 2021; Zaman & Toth, 2013).

Existing leukocytosis-inducing drugs include small molecules such as levamisole and high-molecular immunomodulators such as polyoxidonium (Gago et al., 2025; Ikeda et al., 2025; Tavakol et al., 2022; Wang et al., 2014). Despite their established clinical use, these agents possess significant limitations: a narrow activity spectrum, variable efficacy, adverse side effects, and limited applicability in long-term therapy. Therefore, the search for new low-toxicity compounds capable of safely stimulating hematopoiesis remains highly relevant.

Phosphonate derivatives represent a promising class of small molecules with significant immunotropic potential. Their unique chemical structure ensures high metabolic stability, resistance to enzymatic degradation, and strong binding interactions (Groaz & De Jonghe, 2021; Krečmerová et al., 2022). These features allow phosphonates to exhibit a wide range of biological activities, including anti-inflammatory, antitumor, and immunomodulatory effects. Structural modification of the phosphonate scaffold provides opportunities for targeted regulation of immune responses and the design of compounds with improved pharmacological profiles.

In aim of the present study to synthesize the dialkyl ((3-(1*H*-imidazol-1-yl)propylamino)(fluoro- and trifluoromethylphenyl)methyl)phosphonates and their inclusion complexes with β-cyclodextrin and evaluate their potential as myelostimulators to activation of hematopoiesis.

Materials and methods

All used chemicals (analytical grade) were purchased from Sigma Chemical Co. (Sigma-Aldrich Chemie Gmbh, Steinheim, Germany) and were used without further purification. These chemicals are as follows: benzene (C_6H_6≥98%), 1-(3-aminopropyl)imidazole ($C_6H_{11}N_3$≥97%), 2-fluorobenzaldehyde (FC_6H_4CHO≥97%), 3-fluorobenzaldehyde (FC_6H_4CHO≥97%), 4-fluorobenzaldehyde (FC_6H_4CHO≥97%), 2-(trifluoromethyl)benzaldehyde ($CF_3C_6H_4CHO$≥98%), 3-(trifluoromethyl)benzaldehyde ($CF_3C_6H_4CHO$≥98%), 4-(trifluoromethyl)benzaldehyde ($CF_3C_6H_4CHO$≥98%).

The course of the reaction and the purity of the compounds was monitored using TLC (by Al_2O_3, II degrees). Infrared spectra were recorded using a Nicolet 5700 spectrometer (Thermo Fisher Scientific, USA) on tablets containing potassium bromide that were sealed between potassium bromide plates. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra of the chemicals under study, dissolved in deuterated chloroform or dimethyl sulfoxide, were recorded using a JEOL JNM-ECA400 NMR spectrometer (JEOL Ltd, Japan) operating at 400 megahertz (MHz) for hydrogen nuclei. Tetramethylsilane (TMS) was used as an internal standard.

*Synthesis dimethyl (((3-(1H-imidazol-1-yl)propyl)amino)(2-fluorophenyl)methyl)-phosphonate (**1**).* A three-neck conical flask with a flat bottom and equipped with a Dean-Stark trap and reflux condenser was filled with 2.1 mL (0.018 mol of 1-(3-aminopropyl)imidazole and 185 mL of absolute benzene. Then 1.9 mL (0.018 mol) of 2-fluorobenzaldehyde and 1.7 mL (0.018 mol) of dimethyl phosphite were added successively. The reaction mixture is boiled with constant stirring for 63 h. After the reaction had completed, the solvent was removed and the resulting oily liquid was washed several times with hot hexane. This process yielded 3.71 grams of the desired product, dimethyl (((3-(1*H*-imidazol-1-yl)propyl) amino)(2-fluorophenyl)methyl)phosphonate, in the form of colorless crystals. Yield 3.71 g (62 %), R_f = 0.14 (hexane:chloroform – 1:3), Tm = 83-86 ^{0}C. $C_{15}H_{21}FN_3O_3P$, calculated, %: C 52.78; H 6.20; F 5.57; N 12.31; O 14.06; P 9.07. $C_{15}H_{21}FN_3O_3P$, found, %: C 52.76; H 6.17; F 5.59; N 12.34; P 9.05. IR spectra, cm^{-1}: 1044 (C-N); 1211 (P=O); 1044 (C-F). ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.19 (2H, m, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.08-3.10, 3.85 (4H, t, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.63 (6H, s, $POCH_3$), 4.72 (s, 1H, CH), 6.92-7.45 (3H, m, J = 3.40, 1.86, 1.15 Hz,

CH_{im}), 7.12-7.63 (4H, d, J = 7.84, 7.41, 1.52 Hz, J = 8.35, 1.52, 0.55 Hz, CH_{benz}). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 26.55 ($NCH_2CH_2CH_2N$), 47.22-47.37 ($NCH_2CH_2CH_2N$), 53.51 ($POCH_3$), 58.37 (CH), 116.11-162.13 (CH_{benz}), 120.45-136.33 (CH_{im}).

*Synthesis of diethyl (((3-(1H-imidazol-1-yl)propyl)amino)(3-fluorophenyl)methyl)-phosphonate (**2**)* is carried out in a similar way. Yield 3.85 g (58 %), R_f = 0.19 (hexane:chloroform – 1:3), Tm = 40-43 ^{0}C. $C_{17}H_{25}FN_3O_3P$, calculated, %: C 55.28; H 6.82; F 5.14; N 11.38; O 12.99; P 8.39. $C_{17}H_{25}FN_3O_3P$, found, %: C 55.26; H 6.80; F 5.11, N 11.36; P 8.42. IR spectra, cm^{-1}: 1039 (C-N); 1238 (P=O); 1039 (C-F). ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.15 (6H, t, J = 7.02, 7.00 Hz, $POCH_2CH_3$), 2.19 (2H, m, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.08-3.10, 3.85 (4H, t, 2.67 Hz, $NCH_2CH_2CH_2N$), 3.90-3.97 (6H, q, J = 7.02 Hz, $POCH_2CH_3$), 4.46 (1H, s, CH), 6.92-7.45 (3H, m, J = 3.40, 1.87 Hz, J = 3.40, 1.87 Hz, CH_{im}), 6.72-7.31 (4H, s, J = 8.09, 1.57, 1.25 Hz, J = 8.03, 1.25, 1.22 Hz, CH_{benz}). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 16.45 ($POCH_2CH_3$), 26.55 ($NCH_2CH_2CH_2N$), 47.22-47.37 ($NCH_2CH_2CH_2N$), 60.59 (CH), 63.10 ($POCH_2CH_3$), 115.32-163.99 (CH_{benz}), 120.45-136.33 (CH_{im}).

*Synthesis of dimethyl (((3-(1H-imidazol-1-yl) propyl)amino)(4-fluorophenyl)methyl)-phosphonate (**3**)* is carried out in a similar way. Yield 2.25 g (38 %), R_f = 0.27 (hexane:chloroform – 1:3), n_D^{20}=1,526. $C_{15}H_{21}FN_3O_3P$, calculated, %: C 52.78; H 6.20; F 5.57; N 12.31; O 14.06; P 9.07. $C_{15}H_{21}FN_3O_3P$, found, %: C 52.81; H 6.18; F 5.55; N 12.34; P 9.10. IR spectra, cm^{-1}: 1054 (C-N); 1220 (P=O); 1054 (C-F). ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.19 (2H, m, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.08-3.10, 3.85 (4H, t, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.63 (s, 6H, $POCH_3$), 4.47 (s, 1H, CH), 6.92-7.45 (3H, m, J = 3.40, 1.86 Hz, J = 3.40, 1.15 Hz, CH_{im}), 7.19-7.34 (4H, s, J = 8.40, 1.18, 0.55 Hz, J = 8.40, 1.18, 0.55 Hz, CH_{benz}). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 26.55 ($NCH_2CH_2CH_2N$), 47.22-47.37 ($NCH_2CH_2CH_2N$), 53.51 ($POCH_3$), 60.70 (CH), 115.48-163.81 (CH_{benz}), 120.45-136.33 (CH_{im}).

*Synthesis of dimethyl (((3-(1H-imidazol-1-yl) propyl)amino)(2-(trifluoromethyl)phenyl)methyl) phosphonate (**4**)* is carried out in a similar way. Yield 4.93 g (79 %), R_f = 0.32 (hexane:chloroform – 1:3), n_D^{20}=1,520. $C_{16}H_{21}F_3N_3O_3P$, calculated, %: C 49.11; H 5.41; F 14.56; N 10.74; P 7.92. $C_{16}H_{21}F_3N_3O_3P$, found, %: C 49.12; H 5.39; F 14.54, N 10.72; P 7.89. IR spectra, cm^{-1}: 1035 (C-N); 1166 (P=O); 1314 (C-F). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.19 (2H, m, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.08-3.10, 3.85 (4H, t, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.63 (6H, s, $POCH_3$), 4.13 (1H, s, CH), 6.92-7.45 (3H, m, J = 3.40, 1.87 Hz, J = 3.40, 1.15 Hz, CH_{im}), 7.47-7.93 (4H, s, J = 7.91, 7.39, 1.93 Hz, J = 7.59, 7.39, 1.60 Hz, CH_{benz}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 26.55 ($NCH_2CH_2CH_2N$), 47.22-47.37 ($NCH_2CH_2CH_2N$), 53.51 ($POCH_3$), 58.51 (CH), 125.98-132.77 (CH_{benz}), 120.45-136.33 (CH_{im}).

*Synthesis of dimethyl (((3-(1H-imidazol-1-yl) propyl)amino)(3-(trifluoromethyl)phenyl)methyl) phosphonate (**5**)* is carried out in a similar way. Yield 5.1 g (82%), R_f = 0.27 (hexane:chloroform – 1:3), n_D^{20}=1,517. $C_{16}H_{21}F_3N_3O_3P$, calculated, %: C 49.11; H 5.41; F 14.56; N 10.74; P 7.92. $C_{16}H_{21}F_3N_3O_3P$, found, %: C 49.07; H 5.43; F 14.58; N 10.77; P 7.95. IR spectra, cm^{-1}: 1030 (C-N); 1166 (P=O); 1329 (C-F). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.19 (2H, m, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.08-3.10, 3.85 (4H, t, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.63 (6H, s, $POCH_3$), 4.40 (1H, s, CH), 6.92-7.45 (3H, m, J = 3.40, 1.87 Hz, J = 3.40, 1.15 Hz, CH_{im}), 7.05-8.05 (4H, s, J = 7.71, 7.56, 0.45 Hz, J = 7.56, 1.52, 1.23 Hz, CH_{benz}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 26.55 ($NCH_2CH_2CH_2N$), 47.22-47.37 ($NCH_2CH_2CH_2N$), 53.51 ($POCH_3$), 62.25 (CH), 126.04-131.62 (CH_{benz}), 120.45-136.33 (CH_{im}).

*Synthesis of dimethyl (((3-(1H-imidazol-1-yl) propyl)amino)(4-(trifluoromethyl)phenyl)methyl) phosphonate (**6**)* is carried out in a similar way. Yield 5.68 g (91 %), R_f = 0.30 (hexane:chloroform – 1:3), n_D^{20}=1,517. $C_{16}H_{21}F_3N_3O_3P$, calculated, %: C 49.11; H 5.41; F 14.56; N 10.74; P 7.92. $C_{16}H_{21}F_3N_3O_3P$, found, %: C 49.08; H 5.40; F 14.59; N 10.76; P 7.90. IR spectra, cm^{-1}: 1038 (C-N); 1161 (P=O); 1314 (C-F). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.19 (2H, m, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.08-3.10, 3.85 (4H, t, J = 2.67 Hz, $NCH_2CH_2CH_2N$), 3.63 (6H, s, $POCH_3$), 4.47 (1H, s, CH), 6.92-7.45 (3H, m, J = 3.40, 1.87 Hz, J = 3.40, 1.15 Hz, CH_{im}), 7.61-7.72 (4H, s, J = 8.49, 1.92, 0.48 Hz, CH_{benz}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 26.55 ($NCH_2CH_2CH_2N$), 47.22-47.37 ($NCH_2CH_2CH_2N$), 53.51 ($POCH_3$), 60.70 (CH), 126.75-140.49 (CH_{benz}), 120.45-136.33 (CH_{im}).

*The complex of dimethyl (((3-(1H-imidazol-1-yl) propyl)amino)(2-fluorophenyl)methyl)-phosphonate with β-cyclodextrin (**7βCD**)*. Hot solutions of 0.4 g (0.001 mol) of dimethyl (((3-(1*H*-imidazol-1-yl)propyl)amino) (2-fluorophenyl) methyl) phosphonate (1) were mixed in 25 mL of ethyl alcohol and 1.13 g (0.001 mol) of β-cyclodextrin in 40 mL of distilled water. The mixture was placed in a drying chamber, and ethanol and water were evaporated at a temperature of 50-55 ^{0}C. Dimethyl (((3-(1*H*-imidazol-1-yl) propyl)amino) (2-fluorophenyl) methyl)phosphonate and β-cyclodextrin inclusion complex were obtained as a white powder. Yield 2.23 g (91 %).

$C_{57}H_{91}FN_3O_{38}P$, calculated, %: C 46.36; H 6.17; F 1.29; N 2.85; P 2.09. $C_{57}H_{91}FN_3O_{38}P$, found, %: C 46.39; H 6.19; F 1.32; N 2.87; P 2.06.

*The complex of diethyl (((3-(1H-imidazol-1-yl) propyl)amino)(3-fluorophenyl)methyl)-phosphonate with β-cyclodextrin (***8βCD***)* is carried out in a similar way. Yield 1.74 g (86 %). $C_{59}H_{95}FN_3O_{38}P$, calculated, %: C 47.09; H 6.32; F 1.26; N 2.79; P 2.06. $C_{59}H_{95}FN_3O_{38}P$, found, %: C 47.12; H 6.27; F 1.29; N 2.77; P 2.09.

*The complex of dimethyl (((3-(1H-imidazol-1-yl) propyl)amino)(4-fluorophenyl)methyl)-phosphonate with β-cyclodextrin (***9βCD***)* is carried out in a similar way. Yield 4.32 g (98 %). $C_{57}H_{91}FN_3O_{38}P$, calculated, %: C 46.36; H 6.17; F 1.29; N 2.85; P 2.09. $C_{57}H_{91}FN_3O_{38}P$, found, %: C 46.33; H 6.21; F 1.31; N 2.84; P 2.07.

*The complex of dimethyl (((3-(1H-imidazol-1-yl)propyl)amino)(2-(trifluoromethyl)phenyl)) methyl)phosphonate with β-cyclodextrin (***10βCD***)* is carried out in a similar way. Yield 7.24 g (93 %). $C_{58}H_{91}F_3N_3O_{38}P$, calculated, %: C 45.63; H 5.97; F 3.74; N 2.75; P 2.03. $C_{58}H_{91}F_3N_3O_{38}P$, found, %: C 45.67; H 5.95; F 3.77; N 2.78; P 2.01.

*The complex of dimethyl (((3-(1H-imidazol-1-yl)propyl)amino)(3-(trifluoromethyl)phenyl)) methyl)phosphonate with β-cyclodextrin (***11βCD***)* is carried out in a similar way. Yield 7.2 g (92 %). $C_{58}H_{91}F_3N_3O_{38}P$, calculated, %: C 45.63; H 5.97; F 3.74; N 2.75; P 2.03. $C_{58}H_{91}F_3N_3O_{38}P$, found, %: C 45.66; H 5.99; F 3.76; N 2.72; P 2.06.

*The complex of dimethyl (((3-(1H-imidazol-1-yl)propyl)amino)(4-(trifluoromethyl)phenyl)) methyl)phosphonate with β-cyclodextrin (***12βCD***)* is carried out in a similar way. Yield 7.27 g (93 %). $C_{58}H_{91}F_3N_3O_{38}P$, calculated, %: C 45.63; H 5.97; F 3.74; N 2.75; P 2.03. $C_{58}H_{91}F_3N_3O_{38}P$, found, %: C 45.61; H 5.96; F 3.72; N 2.72; P 2.05.

Hematopoietic-stimulating activity. The experimental group included female white rats aged two and three months weighing 220-280 g, 24 individuals. The difference in groups compared to the initial body weight did not exceed 10%. The animals were obtained simultaneously from the same nursery, the biological clinic of the Faculty of biology and biotechnology of the Al–Farabi Kazakh National University. Before and during the experiment, control and experimental animals were kept under the same standard conditions, 6 individuals per cage. Animals were divided into the following groups: untreated (UT), placebo (PL), control (MU), experimental (6 groups). Eachgroup consisted of 6 rats. Hematopoiesis was inhibited by administration of the cytostatic cyclophosphamide (Baxter Oncology GmbH, Baxter Healthcare Corporation, Deerfield, IL 60015 USA, Made in Italy, Product of Germany). On days 1st, 3d and 5th of the experiment, animals in groups PL, MU and experimental groups received an intramuscular injection of 3% sodium cyclophosphamide solution at a dose of 30 mg/kg (solvent: isotonic sodium chloride solution). The average volume of the administered drug was 0.2-0.24 ml. Then, on the 6th, 7th and 8th days of the experiment, at 9:00 a.m., the newly synthesized compounds were injected into the animals of the experimental groups respectively (the compounds were dissolved in saline solution, administered intramuscularly at a dose of 10 mg/kg, in a volume of 0.2-0.25 ml (1% solution)), the control group (MU) animals were injected with 6-methyluracil (dissolved in saline solution, administered intramuscularly at a dose of 10 mg/kg, in a volume of 0.2-0.25 ml (1% solution)), animals of the placebo group (PL) were injected with a saline solution of 0.2-0.25 ml. Animals in the intact group did not receive any treatment.. In preclinical studies of newly synthesized compounds, an intermittent regimen of administration every other day is widely used, including a limited number of injections (for example, three doses), which reduces cumulative toxicity and provides a more accurate assessment of pharmacological activity in vivo (Liao et al., 2022).On the 15th day of the experiment (7 days after the last injection), at 9:00 AM animals were anesthetized under light anesthesia induced by intraperitoneal administration of ketamine/xylazine (91 mg/kg ketamine and 9.1 mg/kg xylazine), which corresponds to commonly used anesthetic regimens in rats (Wellington et al., 2013) blood was collected from the occipital sinuses of the rats into VF-052SDK hematology tubes (2 ml, Terumo Venosafe,Ukraine) containing 3.9 mg K2-EDTA The feed was removed from the feeders 12 hours before blood sampling. Blood analyses were performed using a MicroCC-20 Plus animal hematological analyzer (High Technology Inc, China). The device was configured to determine the following cell categories: WBC – total number of leukocytes ($\times 10^9$/L), LYM – absolute number of lymphocytes ($\times 10^9$/L); MON – absolute number of monocytes ($\times 10^9$/L); NEU – absolute number of neutrophils ($\times 10^9$/L); EO – absolute number of eosinophils ($\times 10^9$/L); BAS – absolute number of basophils ($\times 10^9$/L); LYM – comparative lymphocytic index (%); MON – comparative index of monocytes (%); NEU – comparative neutrophil index (%); EO – comparative index of eosinophils (%); BAS – comparative basophilic index (%), RBC – total value of erythrocytes (red blood cells) ($\times 10^{12}$/L); HGB – hemoglobin (g/L); HCT – hematocrit (%); MCV – average volume of erythrocytes

(fL); MCH – average hemoglobin content HGB/RBC (pg); MCHC – average concentration of hemoglobin in erythrocytes HGB/HCT (g/L); RDW-cv – relative width of red blood cell distribution by volume (coefficient of variation) (%); RDW-sd – relative width of red blood cell distribution by volume) (fL); PLT – total platelet volume ($\times 10^9$/L); PCT – thrombocrit volume (%); MPV – average platelet volume (fL). Blood smears were prepared for repeat cytological examination to determine the number of leukocytes. These smears were stained with Giemsa grade and counted under a Leica microscope (Wetzlar, Germany) (at 7x100 magnification), 100 cells were dipped into each sample. The relative number of each cell type was then converted to an absolute value.

Statistical data processing. The data obtained were processed by mathematical statistics methods using Microsoft Excel and the "Statistica 6.0" software. The data are presented as an average value (M) ± standard deviation (SD) (n=6 mice/group). We used one-way (single factor) ANOVA (analysis of variance) to determine a statistically significant difference, and the values were considered reliable at $p<0.05$ and $F>Fcrit$.

Ethical considerations

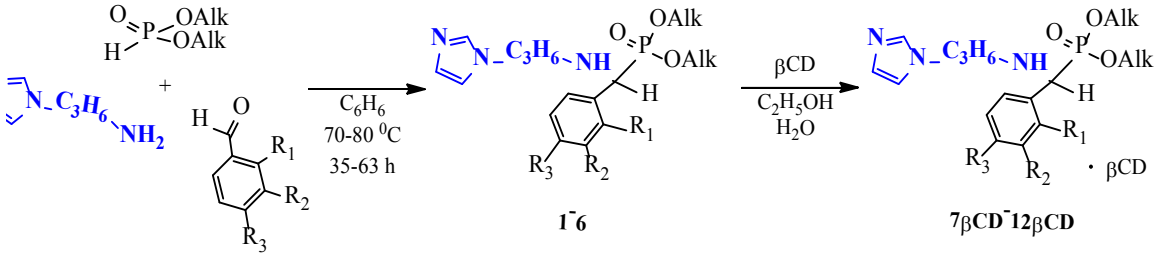
The study was conducted in accordance with the decree of the Minister of Health of the Republic of Kazakhstan No. KR DSM-181/2020 (November 04, 2020) and approved by the Local Ethics Commision of Asfendiyarov Kazakh National University (Protocol No.470, June 10, 2022) (Order of the Minister of Healthcare of the Republic of Kazakhstan, 2020).

Results and discussion

Synthesis of compounds. Based on initial research (Baktybayeva et al., 2026; Kaldybayeva et al., 2022), it has been demonstrated that the incorporation of an imidazole group into a system may provide beneficial biological effects. Additionally, ionic liquids containing an imidazole ring may have potential applications in the fields of agrochemistry and agriculture (Ten et al., 2020). The combination of two chemical compounds, phosphonates and imidazoles, has the potential to generate hybrid molecules that may exhibit positive effects. These effects include the promotion of the formation of new compounds with potential applications in the fields of medicine, agriculture, and corrosion inhibition (Kaldybayeva et al., 2020). The complexation of these compounds with medical polymers has been shown to increase their solubility (Seilkhanov et al., 2024). As a result, aminophosphonate derivatives have been developed based on 1-(3-aminopropyl) imidazole and novel complexes with β-cyclodextrin (βCD),

The reaction of 1-(3-aminopropyl)imidazole with *o-,m-,p*-fluorobenzaldehyde and *o-,m-,p*-(trifluoromethyl)benzaldehyde in the presence of dimethyl- and diethylphosphite under the conditions of the one-pot, three-component Kabachnik–Fields reaction in benzene at temperatures between 70 and 80°C, using a Dean–Stark trap for the removal of water from the reaction mixture by distillation of its azeotrope with benzene, resulted in the formation of α-aminophosphonate products with yields ranging from 58 to 91% (Figure 1, Table 1).

Figure 1
Synthesis of new systems with imidazole fragment



1, 7βCD Alk= CH_3; R_1=F, R_2 = R_3 = H
2, 8βCD Alk= C_2H_5; R_2=F, R_1 = R_3 = H
3, 9βCD Alk= CH_3; R_3=F, R_1 = R_2 = H
4, 10βCD Alk= CH_3; R_1=CF_3, R_2 = R_3 = H
5, 11βCD Alk= CH_3; R_2=CF_3, R_1= R_3= H
6, 12βCD Alk= CH_3; R_3=CF_3, R_1= R_2= H

Table 1
Physical and chemical characteristics of aminophosphonates 1-6

Compounds	Yield, %	R_f*	Calculated found, %		IR spectra, cm^{-1}					$t_{mel.}$ ^0C / n_D^{20} (liq.)*
			C	H	C=C	C-N	P=O	P-C	C-F	
1	62	0,14	52,78 / 52,76	6,20 / 6,17	1618	1044	1211	762	1044	83-86
2	58	0,19	55,28 / 55,26	6,82 / 6,80	1621	1039	1238	805	1039	40-43
3	38	0,27	52,78 / 52,81	6,20 / 6,18	1607	1054	1220	763	1054	1,526*
4	79	0,32	49,11 / 49,12	5,41 / 5,39	1578	1035	1166	770	1314	1,520*
5	82	0,27	49,11 / 49,07	5,41 / 5,43	1509	1030	1166	741	1329	1,517*
6	91	0,30	49,11 / 49,08	5,41 / 5,40	1558	1038	1161	773	1314	1,517*

The IR spectra of the α-aminophosphonate compounds **1-6** exhibit signals corresponding to the C-N bond at 1030–1054 cm^{-1}, the P=O bond at 1161–1238 cm^{-1} and the C-F bond at 1039–1054 and 1314–1329 cm^{-1} respectively. In the ^{13}C NMR spectrum, the carbon atoms of the propyl group (C-6–8) appear at 26.55 and 47.22–47.37 ppm. The carbon atoms belonging to the imidazole ring are resonated at 120.45–136.33 ppm, while the aromatic carbon atoms are observed at 115.32–163.99, and 125.98–140.49 ppm respectively. The tertiary carbon atom is located at 58.37–60.70 ppm, while the carbon atoms from the methoxy and ethoxy groups are recorded at 16.45 and 53.51–63.10 ppm respectively.

In the ^1H NMR spectra of compounds **1-6**, imidazole protons were observed as single-proton peaks at 6.92, 7.03, and 7.45 ppm. Aromatic protons from the phenyl ring were detected as single-proton doublets in a range between 6.72 and 8.05 ppm. Protons from the methylene group of the propyl group (H-6, H-7, and H-8) were observed as multiplets between 2.19 and 3.11 ppm. Proton H-10 appeared as a doublet between 4.13 and 4.72 ppm. Methoxy and ethoxy protons were detected at 1.15 ppm and 3.63 ppm, respectively.

The reaction products 1-6 were soluble only in organic solvents. Complexes 7βCD-12βCD with β-CD were obtained as solids and studied for myelostimulating activity, which includes stimulation of erythropoiesis, leukopoiesis and thrombocytopoiesis.

Hematopoietic-stimulating activity. The intact group of animals had leukocyte, platelet, and red blood cell counts within normal limits for obviously healthy animals. The total erythrocytes count was $(7.5 \pm 0.9) \cdot 10^{12}$ /L of blood, with a hemoglobin level (140.70 ± 8.90) g/L. The average amount of hemoglobin in red blood cells was (350.60 ± 14.28) g/L of blood. Hematocrit value and mean corpuscular volume were (21.21 ± 7.79)% and (82.6 ± 0.23) fl, respectively, within the normal range.

Platelet counts. The total platelet count, mean platelet volume, and platelet crit were (660.0±12.2) $\cdot 10^9$/L of blood, (7.90±0.10) fl, and (0.44±0.01)%, respectively, which were also within normal limits.

Leukocyte count. The total leukocyte count was $(12.10\pm0.80) \cdot 10^9$/L of blood which was within the normal range. In the leukogram, the relative lymphocyte count, relative granulocyte count, and relative monocyte count were (63.72±1.1) %, (30.0±0.8) %, and (6.28±0.1)%, respectively. The normal absolute values of lymphocytes, granulocytes and monocytes were $(7.71\pm0.10) \cdot 10^9$/l of blood, $(3.63\pm0.01) \cdot 10^9$/l of blood, $(0.76\pm0.01) \cdot 10^9$/l of blood, respectively.

The introduction of the cytostatic cyclophosphamide resulted in a 2.0-2.6-fold decrease in all peripheral blood parameters. The red blood cell count decreased 1.52-fold to $(4.67\pm0.1) \cdot 10^{12}$ /L of blood, with a 1.54-fold decrease in the hemoglobin level to (96.60±10.00) g/L of blood. The average hemoglobin concentration in the red blood cell mass decreased insignificantly to (342.50±6.50) g/L of blood, the hematocrit and the average corpuscular volume decreased to (28.1±0.47)% and (50.00±11.30) fl, respectively. It is the erythrocytes that primarily make up the volume of formed elements of the blood, and the decrease in the hematocrit reflected a decrease in the volume

of erythrocytes to the volume of blood plasma. The platelet mass showed a significant decrease in the platelet count by 6.34 times to (70.50±23.33) · 10^9/L of blood. The average platelet volume and platelet crit decreased by 1.34 and 1.6 times to (5.28±2.00) fl and (0.05±0.03)%, respectively.

Significant changes in absolute and relative leukocyte counts were observed in placebo group. The total leukocyte count decreased by 5.10 times to (3,83±0,73) · 10^9/L of blood. A leftward shift in the leukogram occurred, with a decrease in agranulocyte leukocytes, specifically lymphocytes, and an increase in the relative granulocyte count. Absolute counts decreased more significantly than relative counts. The absolute lymphocyte count decreased to (2.22±0.90) · 10^9/L of blood, a 6.88-fold decrease, while the absolute granulocyte count decreased to (1.44±0.13) · 10^9/L of blood, a 5.85-fold decrease.

Thus, we observed a decrease in the proliferative activity of erythropoiesis, thrombocytopoiesis, and leukopoiesis in experimental groups.

Reduction of erythrocytes, leukocytes and platelets with cyclophosphamide in an experiment with mice due to its pronounced anti-cytotoxic and marrow-suppressive effects. Cyclophosphamide is widely used in preclinical studies as a standard model of induced myelosuppression and immunodeficiency in experimental animals (Sharata et al., 2026). Cyclophosphamide is a prodrug that is activated in the liver and produces cytotoxic metabolites, including the phosphoramide mustard. These compounds stimulate DNA alkylation and form interlinked networks within and between cells, thereby disrupting transcription and copying, as well as inducing cell cycle arrest and controlled cell death. Experimental studies in mice have shown that cyclophosphamide mainly affects rapidly growing bone marrow cells, thereby inhibiting hematopoiesis and changing the bone marrow microenvironment (Sun et al., 2025). This is accompanied by a significant decrease in the number of cells in the blood and the development of hemocytopenia, including anemia, leukemia and thrombocytopenia. Therefore, the use of cyclophosphamide in experimental models allows replicating cytotoxic stimulation by inhibiting the proliferation of hematopoietic cells, which makes it a suitable tool for studying the processes of hemotoxic action and evaluating potential protective or therapeutic agents (Gao et al., 2025).

Furthermore, against the background of erythropoiesis, thrombocytopoiesis, and leukopenia, experimental newly synthesized compounds were administered intramuscularly to stimulate erythropoiesis, thrombopoiesis, and leukopoiesis.

Next, against a background of pancytopenia, the test compounds of the βCD-complexes series were administered: 7βCD-12βCD. Among the compounds studied, 7βCD, 8βCD, and 11βCD not only showed a hematopoietic-stimulating effect, but even inhibited the hematopoietic system, as blood counts in these experimental groups were lower than in the placebo group. Therefore, 9βCD, 10βCD, and 12βCD exhibit hematopoietic activity comparable to that of methyluracil as the parent drug. 9βCD and 12βCD exhibited similar hematopoietic activity. Both compounds exhibited moderate leukopoiesis-stimulating activity without affecting the Harkavi index. The total leukocyte count in the 9βCD and 12βCD injection groups was (7.09÷7.40) · 10^9/L blood, which was slightly higher than the MU blood group count (5.20±0.80) · 10^9/L blood, but significantly exceeded the PL group count by 3.22 times (3.84±0.93) · 10^9/L blood. The Harkavi index reflects the body's recovery process after stress. During the experiment, it demonstrated rapid hematopoiesis recovery without disrupting the lymphocyte-to-granulocyte ratio. In rats, the relative lymphocyte count prevails over the relative neutrophil count. It is due to this ratio that the adaptive immune system of rodents is more reactive than that of other animal species. The relative lymphocyte index of the blood in the group with compounds 9βCD and 12βCD was (91.16÷91.27)%, significantly exceeding the values of the intact group of animals (63.72±1.10)%, being at the upper limit of the norm, which indicated a significant increase in lymphocyte values. The absolute indices of peripheral blood lymphocytes in the group receiving compounds 9βCD and 12βCD were also high and amounted to (6,73± 2,27)·10^9/l of blood, which exceeded the indices of the MU group (3,32± 0,04)·109/l of blood by 2.88 times ($p \leq 0.01$), the indices of the PL group (2.22±0.90) · 10^9/l of blood by 4.17 times, and the UT group (7.71±0.10)·10^9/l of blood by 1.20 times.

Compound 9βCD did not exhibit erythropoiesis-stimulating activity. The total erythrocyte count was (4.61 ± 0.2) · 10^{12}/L of blood, lower than the UT group count (7.50 ± 0.9) · 10^{12}/L. Hemoglobin levels were also low (89.50 ± 4.2) g/L, close to placebo group and lower than those in the UT and MU groups. The mean hemoglobin concentration in erythrocyte mass, hematocrit, and mean corpuscular volume corresponded to those in the placebo group and were lower than those in the intact and control groups.

Table 2
Hemogram parameters of peripheral blood in experimental groups

	7βCD	8βCD	9βCD	10βCD	11βCD	12βCD	PL	MU	UT	P
	1	2	3	4	5	6	7	8	9	10
WBC, $\times 10^9$/L	2.43±0.1	3.29±0.1	7.40±1.2	5.33±0.91	2.66±0.18	7.09±3.06	3.83±0.73	5.20±0.80	12.10±0.80	P_{1-8}= 0.004 P_{1-9}= 0.01 P_{2-8}= 0.02 P_{2-9}= 0.03 P_{3-8}= 0.01 P_{3-9}= 0.01 P_{4-9}= 0.1 P_{5-8}= 0.003 P_{5-9}= 0.004
LYM, $\times 10^9$/L	1.88±1.0	3.16±0.5	6.78±0.9	3.47±0.38	1.67 ±0.08	6.73±2.27	2.22 ±0.90	3.32±0.04	7.71±0.10	P_{1-8}= 0.003 P_{1-9}= 0.02 P_{2-8}= 0.01 P_{2-9}= 0.02 P_{3-8}= 0.02 P_{3-9}= 0.03 P_{4-9}= 0.1 P_{5-8}= 0.002 P_{5-9}= 0.003
MON, $\times 10^9$/L	0.46±0.05	0.28±0.13	0.54±0.17	0.31±0.03	0.21± 0.01	0.19± 0.09	0.19 ±0.01	0.27± 0.00	0.76±0.01	P_{1-8}= 0.002 P_{1-9}= 0.02 P_{2-8}= 0.02 P_{2-9}= 0.03 P_{3-8}= 0.01 P_{3-9}= 0.02 P_{4-9}= 0.1 P_{5-8}= 0.003 P_{5-9}= 0.003
NEU, $\times 10^9$/L	0.09±0.01	0.11±0.01	0.09±0.02	1.54 ±0.00	0.76±0.01	0.15±0.01	1.44±0.13	1.70±0.04	3.63±0.01	P_{1-8}= 0.001 P_{1-9}= 0.01 P_{2-8}= 0.01 P_{2-9}= 0.03 P_{3-8}= 0.01 P_{3-9}= 0.02 P_{4-9}= 0.1 P_{5-8}= 0.001 P_{5-9}= 0.002

Continuation of the table

	7βCD	8βCD	9βCD	10βCD	11βCD	12βCD	PL	MU	UT	P
	1	2	3	4	5	6	7	8	9	10
LYM, %	72.05±4.2	88.16±4.5	91.27±9.9	65.67±1.18	63.07± 0.47	92.16± 2.07	57.60±1.65	62.04± 3.93	63.72±1.10	ND
MI, %	24.22±4.5	7.34±0.50	7.56±0.80	7.15± 2.43	7.84±1.12	2.40± 0.20	4.84± 5.30	5.28± 0.40	6.28 ±0.10	ND
NEU, %	3.78±0.50	4.67±0.30	1.33±0.01	26.73±3.83	29.10±0.65	4.99±2.05	37.56±9.30	32.68±1.60	30.00±0.80	P_{1-7}=0.04 P_{1-8}=0.02 P_{2-8}= 0.01 P_{2-9}= 0.02 P_{3-8}= 0.01 P_{3-9}= 0.02 P_{6-8}= 0.01 P_{6-9}= 0.03
RBC, × 10^{12}/L	1.81±0.10	2.88±0.10	4.61±0.20	6.29±0.42	5.29±0.43	5.14±0.01	4.67±0.10	5.69± 0.36	7.50±0.90	P_{1-8}= 0.003 P_{1-9}= 0.006 P_{2-8}= 0.01 P_{2-9}= 0.03
HGB, g/L	40.00±1.2	59.50±4.6	89.50±4.20	111.50± 4.33	94.00±10.67	89.00±2.67	96.60±10.00	106.0±12.20	140.70±8.90	P_{1-8}= 0.003 P_{1-9}= 0.005 P_{2-8}= 0.01 P_{2-9}= 0.002
MCHC, g/L	437.00±37.5	400.00±22.2	360.00±16.6	297.50±1.00	301.00±4.67	299.00±2.00	342.50±6.50	34.69±0.70	350.6±14.28	P_{1-7}=0.01 P_{3-8}= 0.01 P_{4-8}= 0.01 P_{4-9}= 0.01 P_{5-8}= 0.01 P_{5-9}= 0.01
MCH, pg	22.72±2.10	21.11±3.20	19.50±1.20	17.70± 0.50	17.70±0.53	17.30±0.47	17.00±0.30	52.50 ±1.50	27.30±5.27	P_{1-7}=0.03
MCV, fL	51.72±1.50	52.67±11.20	54.00±4.60	59.70 ±1.87	58.80± 0.87	57.95±1.17	50.00±11.30	18.45±0.55	82.60±0.23	P_{1-8}= 0.004 P_{2-8}= 0.02 P_{2-9}= 0.002 P_{3-8}= 0.01 P_{3-9}= 0.02 P_{4-8}= 0.005 P_{4-9}= 0.007 P_{5-8}= 0.001 P_{5-9}= 0.002 P_{6-8}= 0.002 P_{6-9}= 0.002

Continuation of the table

	7βCD	8βCD	9βCD	10βCD	11βCD	12βCD	PL	MU	UT	P
	1	2	3	4	5	6	7	8	9	10
RDW-CV, %	14.83±2.30	14.22±0.30	16.33±1.30	12.20±0.20	11.65±0.03	12.50± 0.80	12.25±0.30	17.2±0.20	12.40±0.17	$P_{1\text{-}9}$ = 0.01 $P_{2\text{-}9}$ = 0.002 $P_{3\text{-}9}$ = 0.02 $P_{4\text{-}8}$ =0.0001 $P_{4\text{-}9}$ = 0.008 $P_{5\text{-}8}$ = 0.001 $P_{5\text{-}9}$ = 0.003 $P_{6\text{-}8}$ = 0.004 $P_{6\text{-}9}$ = 0.002
RDW-SD, fL	27.83±7.50	28.28±6.20	29.11±2.10	25.20±0.60	23.45±0.43	24.50± 0.93	23.00±0.40	12.70±0.40	23.6±0.20	$P_{1\text{-}8}$ = 0.001 $P_{1\text{-}9}$ = 0.01 $P_{2\text{-}7}$ = 0.02 $P_{2\text{-}8}$ = 0.002 $P_{3\text{-}7}$ = 0.01 $P_{3\text{-}8}$ = 0.02 $P_{4\text{-}7}$ =0.0001 $P_{4\text{-}8}$ = 0.008 $P_{5\text{-}7}$ = 0.001 $P_{5\text{-}8}$ = 0.003 $P_{6\text{-}7}$ = 0.004 $P_{6\text{-}8}$ = 0.002
HCT, %	9.17±0.90	14.94±0.90	24.94±1.10	37.35±1.37	31.20±3.00	29.80± 0.60	28.10±0.84	28.10±0.47	21.21±2.79	$P_{1\text{-}8}$ = 0.01 $P_{1\text{-}9}$ = 0.02
PLT, × 10^9/L	174.50±5.50	189.1±13.20	397.0±18.90	503.0±50.00	362.0±62.00	309.5±21.33	70.50 ±7.33	518.25±19.9	670.0±14.20	ND
MPV, fL	6.44±0.50	7.72±0.80	7.72±0.10	6.10±0.40	5.70±0.01	6.20±0.20	5.28±2.00	6.63±0.30	7.90±0.10	ND
PDW, %	7.67±0.10	9.78±0.90	9.00±.0.01	14.40±2.47	10.90±0.07	11.40±0.20	7.10±0.00	12.25±0.57	11.40±0.43	ND
PCT, %	0.12±0.01	0.12±0.01	0.31±0.01	0.31± 0.05	0.21±0.04	0.19±0.04	0.05±0.04	0.31±0.25	0.44±0.01	ND
P-LCR, %	10.06±0.90	15.38±1.30	13.89±0.80	4.75±1.70	3.30±0.20	6.15±0.67	2.5±0.47	4.95± 0.46	2.1± 0.15	ND

Note: ND – not discussed (non-informative values)

The compound 9βCD showed moderate platelet-stimulating activity.The total trombocyte count was (397,0±18,9)·10^9/L of blood. This indicator was lower than the UT group (670,00 ±14,20)·10^9/L blood and the MU group (518.25 ± 19.90) ·10^9/L blood. The platelet crit, platelet distribution width, and mean platelet count in the blood were also low. Thus, compound 9βCD had low thrombopoiesis-stimulating activity.

Compound 12βCD slightly exceeded compound 9βCD in erythro- and thrombopoiesis-stimulating activity. The total erythrocyte count was (5.14 ± 0.01) · 10^{12}/L blood and was at the level of the MU group. The hemoglobin level was low (89.00 ± 2.67) g/L and was close to the blood values of animals of the PL group and inferior to the blood values of animals of the UT group and MU group. The values of the average concentration of hemoglobin in the erythrocyte mass, the hematocrit index, and the average volume of erythrocytes corresponded to the blood values of the animals in the PL group were lower than in the UT and MU groups. The level of platelet-stimulating activity of compound 12βCD was low. The total platelet index was (309.5 ± 48.33) ·10^9/l of blood. This indicator was lower than the value of the UT group (660.00 ± 12.20) ·10^9/l of blood and the MU group (518.25 ± 19.90) ·10^9/l of blood. The values of thrombocrit, platelet distribution width and average platelet index in the blood were also low. Thus, compound 12βCD had low thrombocytopoiesis-stimulating activity. The observed effects are likely due to the effects of the compound on redox homeostasis and cytokine-mediated signaling pathways that regulate hematopoietic cell proliferation and differentiation. In general, phosphonates are characterized by a range of biological activities, including antioxidant and immunomodulatory properties (Cui & Ju, 2025).

The obtained results indicate the presence of strong structural and functional dependence and confirm the possibility of directed synthesis of phosphate derivatives with selective influence on various foci of hematopoiesis (Krečmerová et al., 2022).

Conclusion

A series of α-aminophosphonate compounds were synthesized through a one-pot reaction involving 1-(3-aminopropyl)imidazole, fluoro- or trifluoromethyl-substituted benzaldehydes, and dialkyl phosphite under azeotropic drying conditions using benzene as the solvent. The target compounds were obtained with yields ranging from 58% to 91%. Spectroscopic analysis (IR, ^{1}H and ^{13}C NMR) confirmed the anticipated structures, revealing the presence of characteristic signals for C–N, P=O, and C–F groups, as well as for the imidazole, aromatic, alkoxy, and propyl moieties. The α-aminophosphonates were converted into β-cyclodextrin inclusion complexes (7βCD–12βCD) to improve solubility, enabling biological evaluation.

Biological testing demonstrated that several complexes exhibited hematopoiesis-stimulating properties in a cyclophosphamide-induced pancytopenia model. Among them, 9βCD and 12βCD showed the most promising activity, producing moderate stimulation of leukopoiesis comparable to methyluracil, with significant recovery of total leukocyte and lymphocyte counts and restoration of the Harkavi index. However, their effects on erythro- and thrombopoiesis were limited. Other derivatives (7βCD, 8βCD, 11βCD) did not exhibit stimulatory effects and further suppressed hematopoietic parameters.

Overall, the data indicate that β-cyclodextrin complexes of imidazole-containing α-amino phosphonates, particularly 9βCD and 12βCD, represent promising skeletons for the development of novel small-molecule hematopoietic system modulators.

Authors contributions

A.S. Sokolenko: Conceptualization, Methodology, Investigation, Writing – Original Draft;

A.B.Kaldybayeva: Data Curation, Formal Analysis, Visualization, Writing – Review & Editing;

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G. Deniz: Supervision, Funding Acquisition, Project Administration, Writing – Review & Editing;

V.K. Yu: Supervision, Funding Acquisition, Project Administration, Writing – Review & Editing.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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