3,5-Bis(arylidene)-4-piperidinones modified with bisphosphonate groups using a 1,2,3-triazole ring: synthesis and antitumor properties*

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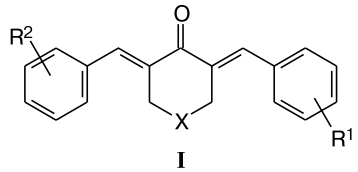
An approach to the synthesis of new conjugates of 3,5-bis(arylidene)-4-piperidone pharmacophore with bisphosphonate moiety using a 1,2,3-triazole ring as a linker has been developed. The approach is based on a Cu(I)-catalyzed reaction of tetraethyl (but-3-yne-1,1-diyl)bisphosphonate with an alkyl azide containing a 3,5-bis(arylidene)-4-piperidone moiety. *In vitro* evaluation of antitumor activity of new conjugates **7a—d** against human cancer cell lines HCT116 and MCF7 and human embryonic fibroblasts (HEF) has revealed that only compounds bearing strong electron-withdrawing substituents (cyano and nitro groups) in the aromatic rings possess moderate antitumor properties with the IC_{50} values ranging from 5 to 7.5 μmol L^{-1}.

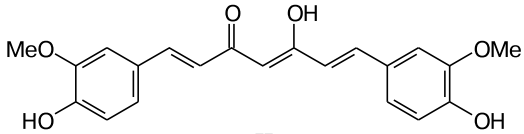
Key words: 3,5-bis(arylidene)-4-piperidinones, bisphosphonates, aminobisphosphonates, 1,2,3-triazoles, antitumor activity.

3,5-Bis(arylidene)-4-piperidinones belong to a wide class of cross-conjugated dienones **I** and contain a 1,5-diaryl-3-oxo-1,4-pentadienyl fragment responsible for their antitumor properties.[1] From the structural point of view, 3,5-bis(arylidene)-4-piperidinones can be considered as synthetic analogues of the natural compound curcumin **II**, which also exhibits antitumor activity.[2,3] Despite the mechanism of the anticancer activity of 3,5-bis(arylidene)-4-piperidinones is not yet clear, it is believed that they are capable of reacting with the intracellular thiols, leaving the nitrogen-containing nucleophiles, such as nucleic acids, intact. This can be a reason that these compounds have no mutagenic properties.[1] Thus, it was shown recently[4] that the vinyl bonds of bis(arylidene)piperidinones can form a covalent bond with the sulfhydryl group of cysteine-88 of the ubiquitine receptor RPN13, which leads to the accumulation of polyubiquitinated proteins in the cancer cells and, in the end, to their death.

The antitumor properties of bis(arylidene) compounds **I** can be controlled by the variation of aromatic substituents



I



II

X = $(CH_2)_n$, NH, NR^3

in their structure. However, especially wide possibilities for structural modifications and, therefore, for varying properties of such compounds are open in the case of 3,5-bis(arylidene)-4-piperidinones (X = NH), since the presence of a nitrogen atom in the heterocyclic fragment allows one to introduce various R^3 groups in the molecule. These groups possess biological activity themselves, improve bioavailability and solubility of compounds, and are capable of additional interactions with a corresponding receptor. Organic amides,[5] sulfonamides,[6] nitroxides,[7] as well as phosphorus acid amides[8] belong to 3,5-bis(aryl-

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idene)-4-piperidinone derivatives modified by such groups at the piperidinone nitrogen atom.

The use of phosphorus-containing fragments as such modifying groups is especially promising. In particular, a known approach to the modification of medicines is the synthesis of their phosphorylated derivatives (prodrugs). For example, the antitumor agents Ifosfamide and Cyclophosphamide[9] are such prodrugs, wherein the addition of oxazaphosphorinane ring to the alkylating pharmacophore allows one to considerably decrease the high toxicity of the agent. Phosphorylation was used to increase the solubility of such antitumor agents, as combretastatin[10] and 2-phenylquinolinon-4-one derivatives.[11] As to 3,5-bis-(arylidene)-4-piperidinone, it was shown that, in contrast to nonphosphorylated NH-compounds, the corresponding amides of phosphoric acids are also active against resistent tumors.[8] A special direction of studies is the conjugation of pharmaceutical agents and biologically active compounds (Gemcitabin,[12] Methotrexate,[13] Doxorubicin,[14] and nucleoside antimetabolites[15]) with a bisphosphonate moiety. These conjugates can be used for the targeted delievery of the pharmacophore to the bone tissue due to the high affinity of bisphosphonates to it.

Earlier,[16] we also have demonstrated that the addition of organophosphorus groups at the piperidinone nitrogen atom of 3,5-bis(arylidene)-4-piperidinones allows one in a number of cases to increase antitumor activity of these compounds. In particular, phosphoric acid amides based on 3,5-bis(3-pyridinylmethylidene)-4-piperidinones exhibit high antitumor activity, including that against carcinoma KB-8-5, which is distinguished by multiple drug resistance because of the protein Pgp170 hyperexpression. Strong cytotoxicity against a number of human tumors was found for 3,5-bis(arylidene)-4-piperidinones modified with bisphosphonate fragments, in which the aromatic rings have electron-withdrawing substituents.[17] In the latter case, such compounds can be considered as aminobisphosphonates, containing an additional cytotoxic bis(arylidene)piperidinone pharmacophore. It is neccesary to note that the ability of aminobisphosphonates of the last generation to suppress the bone resorbtion (including the cases of bone metastases) is tens of thousands of times higher than the antiresorbtive activity of nitrogen-free bisphosphonates of the first generation, that is explained by the different mechanisms of action of these two types of bisphosphonates.[18] Therefore, combining 3,5-bis(arylidene)-4-piperidinone and bisphosphonate fragments in one molecule seems to be an important direction of studies in order to develop new anticancer agents. The above-mentioned phosphoric amides and aminobisphosphonates have the advantage of considerably better solubility in aqueous media as compared to nonphosphorylated starting NH-3,5-bis(arylidene)-4-piperidinones.

One of the approaches most frequently used for the modification of biologically active compounds by various pharmacologically and/or biologically active fragments is based on the so called "click" methodology, which is exampified by a copper(I)-catalyzed 1,3-dipolar cycloaddition of azides to the terminal alkynes (the Huisgen reaction, CuAAC).[19] In the Cu(I)-catalyzed version, this reaction regioselectively gives 1,4-disubstituted 1,2,3-triazoles under mild conditions and in good yields, that makes this transformation especially convenient for the conjugation of several biologically active fragments in one molecule. Despite the 1,2,3-triazole ring is not encountered with in natural compounds, synthetic molecules containing this fragment exhibit various types of biological activity: anticancer, antituberculotic, antibacterial, antifungal, as well as possess inhibiting activity against HIV.[19]

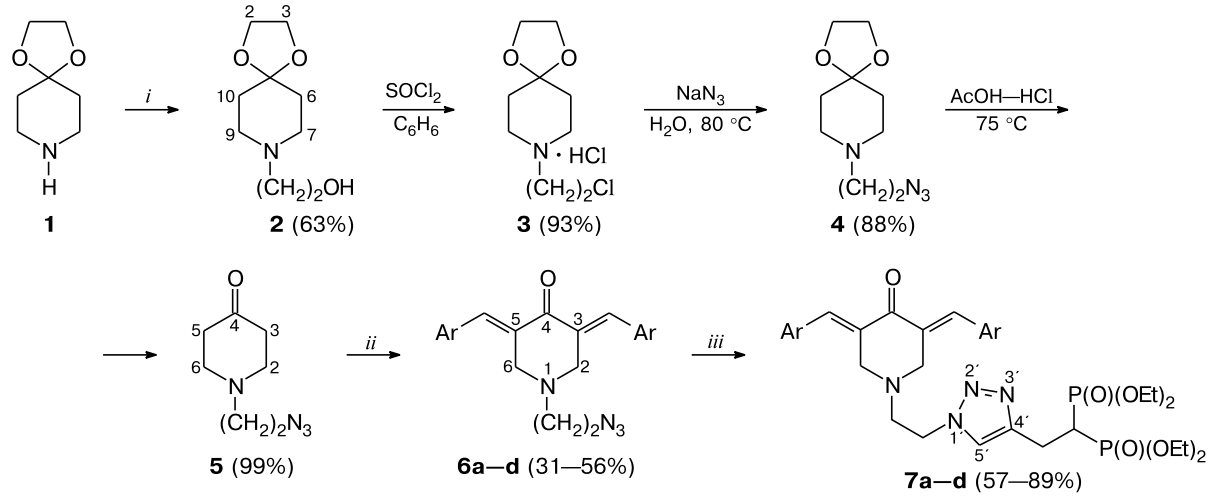
Taking into account the favorable characteristics of the Huisgen copper(I) catalyzed 1,3-dipolar cycloaddition, as well as a high antitumor activity of aminobisphosphonates with a bis(arylidene)piperidinone fragment, in the present work we studied a possibility of conjugation of 3,5-bis(arylidene)-4-piperidinone pharmacophore with a bisphosphonate moiety using a 1,2,3-triazole ring as a linker between the piperidinone and the bisphosphonate fragments and carried out the *in vitro* evaluation of antitumor properties of synthesized 3,5-bis(arylidene)-4-piperidinone bisphosphonates.

Results and Discussion

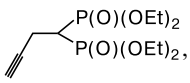
A sequence of the reactions for the synthesis of 3,5-bis-(arylidene)-4-piperidinones **7a—d**, modified with a bisphosphonate fragment attached to the piperidinone nitrogen atom through a 1,2,3-triazole ring is given in Scheme 1.

In the first step, the alkylation of commercially available 4-piperidinone ethylene ketal (**1**) with 2-chloroethanol gave alcohol **2** (see Ref. 20), which was converted to the corresponding chloride **3** in high yield. Azide **4** was synthesized by the reaction of compound **3** with sodium azide in aqueous solution at 80 °C similarly to the procedure suggested in the work.[21] The dioxolane protection in azide **4** was removed in a mixture of glacial acetic and 37% aqueous hydrochloric acid to obtain the corresponding piperidinone **5** in virtually quantitative yield. The synthesis of 3,5-bis(arylidene)-4-piperidinones **6a—d** containing the azido group was carried out in the presence of the system $LiClO_4$—Et_2NH according to the published procedure.[22] In the work,[22] this system was used for the synthesis of NH-3,5-bis(arylidene)-4-piperidinones, giving the target compounds in high yields. In our case, the yields were 31—56%, that can be explained by the side processes, which take place between the azido group and the vinyl bond of the α,β-keto unsaturated fragment present in the structures of piperidinones **6a—d** (a possibility of such reactions is described in Ref. 23). In the final stage, the CuAAC reaction of azides **6a—d** with tetraethyl (but-3-yne-1,1-diyl)bisphosphonate was carried out in aque-

Scheme 1



Ar = 4-NCC_6H_4 (**a**), 4-$O_2NC_6H_4$ (**b**), 3-Py (**c**), 4-$Me_2NC_6H_4$ (**d**)

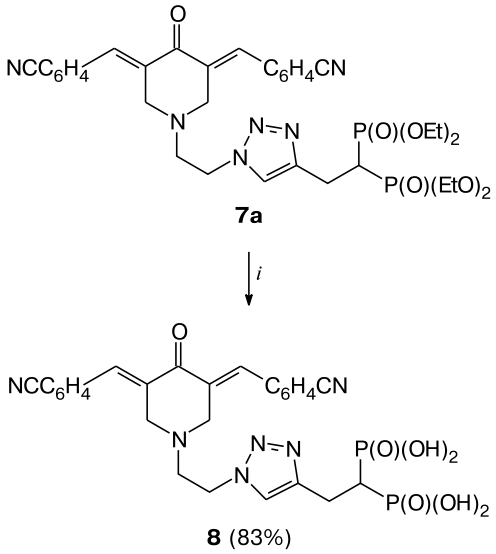
i. $Cl(CH_2)_2OH$, K_2CO_3, NaI, MeCN. *ii*. ArCHO, $LiClO_4$, Et_2NH. *iii*.  , Cu^I, DMF—H_2O.

ous dimethylformamide to provide a proper solubility of the starting reagents. The Cu(I)-containing catalyst was generated by the reduction of $CuSO_4$ with sodium ascorbate. The target products **7a—d** did not require additional purification and were isolated in good yields in the analytically pure form.

For evaluation of antitumor activity of free bisphosphonic acids containing the 3,5-bis(arylidene)-4-piperidinone fragment, ester **7a** was treated with bromotrimethylsilane according to the procedure[24] to obtain the corresponding acid **8** (Scheme 2) as an illustrative example.

According to the NMR spectroscopy data, the 1,5-diaryl-3-oxo-1,4-pentadienyl fragment in 3,5-bis(arylidene)-4-piperidinones **6a—d** and **7a—d** has the *E*,*E*-configuration of the vinyl bonds. The ^{31}P NMR spectra of bisphosphonates **7a—d** exhibit the only singlet signal at δ 22.4 attributable to the bisphosphonate fragment. In the ^{13}C NMR spectra, the signal corresponding to the carbon atom of the P—C—P fragment is found as a triplet at δ 36.5 with the spin-spin coupling constant $^1J_{P,C} = 133$ Hz. The proton at this carbon atom is found in the ^1H NMR spectra as a triplet of triplets at δ 2.9 with the spin-spin coupling constants $^3J_{H,H} = 6.4$ and $^2J_{P,H} = 23.4$ Hz. In the ^1H NMR spectra, the only triazole proton is observed as a singlet at δ 7.45, whereas its carbon atom C(5′) is represented by the signal at δ 122.8 in the ^{13}C NMR spectrum. In turn, the C(4′) carbon atom of the triazole ring bonded to the bisphosphonate moiety is found in the ^{13}C NMR spectrum as a triplet at δ 145 with the spin-spin coupling constant $^3J_{P,C} = 8.3$ Hz. The IR spectra of compounds **6a—d** contain an absorption band characteristic of the azido group at 2098—2109 cm^{-1}. The IR spectra of

Scheme 2



i. 1) Me_3SiBr, $CHCl_3$; 2) MeOH, H_2O.

compounds **7a—d** exhibit strong absorption bands of the P=O and P—O groups (1250 and 1025 cm^{-1}, respectively).

Antitumor activity. The antitumor activity of compounds **7a—d** and **8** was evaluated *in vitro* using the MTT-method[25] (MTT is 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) against the human tumor cell lines: bowel cancer HCT116 and breast cancer MCF7, as well as against normal human embryonic fibroblasts HEF. The results of these studies are given in Table 1 as the

Table 1. Cytotoxic activity of compounds **7a—d** and **8** against human tumor cell lines HCT116 and MCF7 and normal fibroblasts HEF

Compound	IC_{50}/μmol L^{-1}		
	HCT116	MCF7	HEF
7a	7.5±0.5	5.0±0.4	6.0±0.4
7b	7.5±0.6	7.0±0.5	5.0±0.3
7c	—	> 20	—
7d	—	> 20	—
8	—	> 50	—
Doxorubicin	1.6±0.3	0.3±0.1	2.1±0.4

corresponding IC_{50} values (the concentration of compound, which causes inhibition of the cell growth by 50%). The antitumor agent Doxorubicin was used as a comparison standard.

As it is seen from the data in Table 1, compounds **7a**,**b**, which contain electron-withdrawing CN and NO_2 substituents in the aromatic rings, exhibit moderate activity against the cell lines under studies with the IC_{50} ranging from 5 to 7.5 μmol L^{-1}. This level of antitumor activity is typical of the most 3,5-bis(arylidene)-4-piperidinones with electron-withdrawing groups in the aromatic fragments, with the most active compounds having the IC_{50} values within the range of 1—3 μmol L^{-1} (see Ref. 26). Therefore, it can be concluded that the introduction of a 1,2,3-triazole ring in the structure of 3,5-bis(arylidene)-4-piperidinones does not lead to considerable decrease of their cytotoxicity. The two other representatives of the series under study do not possess cytotoxic activity. Compound **7d** with the electron-releasing Me_2N groups is inactive, like a majority of the earlier studied 3,5-bis(arylidene)-4-piperidinones with dimethylamino groups in the aromatic rings.[26] Earlier,[16] for pyridine derivative **7c** we already observed a strong dependence of antitumor activity of 3,5-bis(3-pyridinylmethylidene)-4-piperidinones on the nature of phosphorus-containing group at the piperidinone nitrogen atom. As a rule, compounds, in which the phosphorus atom is bonded directly to the piperidinone fragment, possess more pronounced antitumor properties than compounds, where the phosphorus-containing fragment and the piperidinone nitrogen atom are separated by a linker. It is also neccesary to note that bisphosphonic acid **8** does not exhibit cytotoxic properties, unlike the corresponding bisphosphonate **7a**, that can be explained by its inability to penetrate the cell membrane.

To sum up, the results obtained indicate that the modification of 3,5-bis(arylidene)-4-piperidinones possessing antitumor properties by pharmacophore groups using a copper(I)-catalyzed Huisgen reaction, which leads to the formation of the 1,2,3-triazole ring as a linker, is a rather efficient approach to the preparation of new cytostatics. In order to search for more active cytostatic agents, our further studies can include variation of pharmacophore groups in the acetylene molecule, which is involved in the cycloaddition reaction with azides containing a 3,5-bis-(arylidene)-4-piperidinone fragment.

Experimental

NMR spectra were recorded on a Bruker AMX-400 spectrometer (400.13 (^{1}H), 161.97 (^{31}P), and 100.61 (^{13}C) MHz), using signals of residual protons of deuterated solvent ($CDCl_3$) as a reference (^{1}H, ^{13}C) and H_3PO_4 (^{31}P) as an external standard. ^{13}C NMR spectra were recorded in the JMODECHO mode (the signals of carbon atoms with even and odd number of protons have the opposite polarity). Melting points were measured on an EZ Melt apparatus (Stanford research systems, USA). Thin-layer chromatography was carried out on Merck silica gel 60 F_{254} plates (visualization under UV light). IR spectra were recorded in KBr pellets on a Magna-IR750 (Nicolet) Fourier-transform spectrometer, resolution 2 cm^{-1}, 128 scans. 2-Chloroethanol, 1,4-dioxa-8-azaspiro[4.5]decane, nicotine aldehyde, 4-nitro-, 4-dimethylamino-, 4-cyanobenzaldehyde, and lithium perchlorate (Acros) were used without additional purification. Before use, acetonitrile was distilled over P_2O_5, benzene over Na. Tetraethyl (but-3-yne-1,1-diyl)bisphosphonate was obtained according to the known procedure.[27]

8-(2-Hydroxyethyl)-1,4-dioxa-8-azaspiro[4,5]decane (2). A mixture of 1,4-dioxa-8-azaspiro[4,5]decane (20.0 g, 0.14 mol), 2-chloroethanol (11.26 g, 0.14 mol), NaI (2.7 g, 0.018 mol), and K_2CO_3 (25.7 g, 0.186 mol) was refluxed in MeCN (140 mL) with stirring for 20 h. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. The inorganic salts were filtered off and washed with CH_2Cl_2 on the filter. The organic phase was concentrated to dryness at reduced pressure, the residue was mixed with CH_2Cl_2. A mixture obtained was washed with water, the organic phase was separated, dried with Na_2SO_4, filtered through a paper filter, and concentrated at reduced pressure to obtain light yellow liquid. The product was distilled at reduced pressure (104—108 °C at ~0.5 Torr) to obtain a pure compound as a colorless clear dense liquid (17.8 g, 63%). ^{1}H NMR, δ: 1.67 (t, 4 H, C(6)H_2, C(10)H_2, $^3J_{H,H}$ = 5.6 Hz); 2.47—2.56 (two t, 6 H, C(7)H_2, C(9)H_2 and NC$\underline{H}_2$CH_2OH); 3.08 (br.s, 1 H, OH); 3.54 (t, 2 H, NCH_2C$\underline{H}_2$OH, $^3J_{H,H}$ = 5.4 Hz); 3.88 (s, 4 H, OCH_2CH_2O). ^{13}C NMR, δ: 34.88 (C(6), C(10)); 51.24 (C(7), C(9)); 58.18 (N$\underline{C}$H$_2$CH$_2$OH); 59.05 (NCH$_2\underline{C}$H$_2$OH); 64.27 (OCH$_2$CH$_2$O); 107.13 (O—C—O).

8-(2-Chloroethyl)-1,4-dioxa-8-azaspiro[4,5]decane hydrochloride (3). A solution of $SOCl_2$ (6.50 g, 0.0546 mol) in C_6H_6 (20 mL) was added slowly dropwise to a vigorously stirred solution of 8-(2-hydroxyethyl)-1,4-dioxa-8-azaspiro[4,5]decane (7.86 g, 0.042 mol) in C_6H_6 (70 mL) in such a way that only a slight heating of the reaction mixture was observed. Then, the reaction mixture was refluxed for 1.5 h with stirring. The volatile components were removed at reduced pressure to obtain an analytically pure product as a white powder (9.50 g, 93%), which softens at ~155 °C and melts at 186—188 °C with decomposition. Found (%): C, 44.67; H, 7.04; N, 5.75; Cl, 29.12. $C_9H_{17}Cl_2NO_2$. Calculated (%): C, 44.64; H, 7.08; N, 5.78; Cl, 29.28. ^{1}H NMR, δ: 1.97—2.06 (m, 4 H, C(6)H_2, C(10)H_2); 3.15—3.29 (m, 2 H, C(7)H_2); 3.55 (t, 2 H, NC$\underline{H}_2$CH$_2$Cl, $^3J_{H,H}$ = 6.0 Hz); 3.59—3.69 (m, 2 H, C(9)H_2); 3.89 (t, 2 H, NCH$_2$C$\underline{H}_2$Cl, $^3J_{H,H}$ = 6.0 Hz);

4.00 (s, 4 H, OCH_2CH_2O). ^{13}C NMR, δ: 31.34 (C(6), C(10)); 37.55 (CH_2Cl); 51.12 (C(7), C(9)); 56.94 (NCH_2CH_2Cl); 64.76 and 64.91 (OCH_2CH_2O); 104.15 (O—C—O).

8-(2-Azidoethyl)-1,4-dioxa-8-azaspiro[4,5]decane (4). A mixture of 8-(2-chloroethyl)-1,4-dioxa-8-azaspiro[4,5]decane hydrochloride (6.15 g, 0.0254 mol) and sodium azide (5.0 g, 0.077 mol) in water (30 mL) was heated at 77 °C (the bath temperature) with stirring for 19 h. Then, the reaction solution was cooled to room temperature and filtered, a solution of NaOH (1.04 g, 0.026 mol) in water (10 mL) was added to the filtrate. The reaction mixture was extracted with Et_2O (~150 mL), the organic phase was separated, dried with Na_2SO_4, filtered, and concentrated at reduced pressure to obtain the target product as a light yellow liquid (4.77 g, 88%), which was used in the following step without additional purification. Found (%): C, 50.99; H, 7.46; N, 26.64. $C_9H_{16}N_4O_2$. Calculated (%): C, 50.93; H, 7.60; N, 26.40. ^1H NMR, δ: 1.71 (t, 4 H, C(6)H_2, C(10)H_2, $^3J_{H,H}$ = = 6.0 Hz); 2.54 (t, 4 H, C(7)H_2, C(9)H_2, $^3J_{H,H}$ = 6.0 Hz); 2.57 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 6.0 Hz); 3.29 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 6.0 Hz); 3.90 (s, 4 H, OCH_2CH_2O). ^{13}C NMR, δ: 34.79 (C(6), C(10)); 48.62 (CH_2N_3); 51.46 (C(7), C(9)); 56.81 ($NCH_2CH_2N_3$); 64.27 (OCH_2CH_2O); 107.12 (O—C—O).

1-(2-Azidoethyl)piperidin-4-one (5). A stirring mixture of 8-(2-azidoethyl)-1,4-dioxa-8-azaspiro[4,5]decane (4.7 g, 0.022 mol), glacial acetic acid (22 mL), and 37% aqueous HCl (28 mL) was heated at 70 °C (the bath temperature) for 35 h. The volatile components were removed at reduced pressure, the residue was dissolved in water (15 mL), an aq. solution of $NaHCO_3$ (1.85 g, 50 mL) was added to reach pH ≈ 8. The aqueous phase was extracted with CH_2Cl_2. The organic phase was separated, dried with Na_2SO_4, and filtered. The solvent was evaporated on a rotary evaporator to obtain the target compound as a clear light yellow liquid (3.70 g, 99%). Found (%): C, 50.27; H, 7.11; N, 33.19. $C_7H_{12}N_4O$. Calculated (%): C, 49.99; H, 7.19; N, 33.31. ^1H NMR, δ: 2.45 (t, 4 H, C(3)H_2, C(5)H_2, $^3J_{H,H}$ = 6.1 Hz); 2.71 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.8 Hz); 2.80 (t, 4 H, C(2)H_2, C(6)H_2, $^3J_{H,H}$ = 6.1 Hz); 3.36 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = = 5.8 Hz). ^{13}C NMR, δ: 40.76 (C(3), C(5)); 48.22 (CH_2N_3); 52.66 (C(2), C(6)); 55.77 ($NCH_2CH_2N_3$); 208.15 (C=O).

Synthesis of compounds 6a—d (general procedure). Azide **5** (5.3 mmol) and the corresponding aldehyde (10.6 mmol) were mixed in a flask, followed by addition of diethylamine (0.78 g, 10.7 mmol) and lithium perchlorate (0.56 g, 5.3 mmol). The reaction mixture was stirred at room temperature until it became dense and allowed to stand for 16 h at room temperature. Then, the mixture was diluted with water and CH_2Cl_2. The organic solution was separated, dried with Na_2SO_4, and filtered. The solvent was evaporated on a rotary evaporator to obtain a crude product as yellow (compounds **6a—c**) or red (compound **6d**) solid compounds, which were purified by column chromatography and, if neccesary, by subsequent recrystallization (reprecipitation) (purification conditions for each compound are given below).

1-(2-Azidoethyl)-3,5-bis(4-cyanobenzylidene)-4-piperidinone (6a). Purification by column chromatography (gradient elution from $CHCl_3$ to $CHCl_3$—EtOH (100 : 1)). The yield was 52%, m.p. 180—182 °C (decomp.). Found (%): C, 69.96; H, 4.41; N, 21.40. $C_{23}H_{18}N_6O$. Calculated (%): C, 70.04; H, 4.60; N, 21.31. IR (KBr), ν/cm^{-1}: 3076, 3061, 3042, 3023, 2950, 2924, 2854, 2806, 2745, 2230 (CN), 2101 (N_3), 1673, 1613, 1586, 1505, 1459, 1414, 1386, 1352, 1327, 1308, 1288, 1271, 1222, 1191, 1171, 1156, 1121, 1066, 1015, 985, 958, 940, 880, 834, 777, 652, 633, 621, 559, 490, 457. ^1H NMR, δ: 2.76 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.9 Hz); 3.29 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.9 Hz); 3.89 (s, 4 H, C(2)H_2, C(6)H_2); 7.46 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.2 Hz); 7.72 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.2 Hz); 7.79 (s, 2 H, =CH—C_{Ar}). ^{13}C NMR, δ: 48.73 (CH_2N_3); 54.39 (C(2), C(6)); 55.29 ($CH_2CH_2N_3$); 112.53 (C_{Ar}—CN); 118.22 (C≡N); 130.46 ($C_{Ar}H$); 132.28 ($C_{Ar}H$); 134.78 (C_{Ar}—CH=); 135.03 (C_{Ar}—CH=); 139.17 (C_{Ar}—CH=C); 185.96 (C=O).

1-(2-Azidoethyl)-3,5-bis(4-nitrobenzylidene)-4-piperidinone (6b). Purification by column chromatography (gradient elution from $CHCl_3$ to $CHCl_3$—EtOH (100 : 0.5)) with subsequent reprecipitation by a slow diffusion of pentane into the solution of **6b** in acetone. The yield was 33%, m.p. 165 °C (decomp.). Found (%): C, 58.09; H, 4.21; N, 19.44. $C_{21}H_{18}N_6O_5$. Calculated (%): C, 58.06; H, 4.18; N, 19.35. IR (KBr), ν/cm^{-1}: 3101, 3065, 2928, 2841, 2748, 2109 (N_3), 1670, 1615, 1599, 1579, 1517 (NO_2), 1493, 1450, 1412, 1344 (NO_2), 1305, 1280, 1261, 1216, 1190, 1153, 1110, 1062, 1013, 991, 941, 884, 858, 848, 811, 757, 714, 687, 599, 500, 444. ^1H NMR, δ: 2.78 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.8 Hz); 3.30 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.8 Hz); 3.91 (s, 4 H, C(2)H_2, C(6)H_2); 7.53 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.7 Hz); 7.83 (s, 2 H, =CH—C_{Ar}); 8.28 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.7 Hz). ^{13}C NMR, δ: 48.67 (CH_2N_3); 54.39 (C(2), C(6)); 55.33 ($CH_2CH_2N_3$); 123.78 ($C_{Ar}H$); 130.71 ($C_{Ar}H$); 134.62 (C_{Ar}—CH=); 135.16 (C_{Ar}—CH=); 141.03 (C_{Ar}—CH=C); 147.55 (C_{Ar}—NO_2); 185.87 (C=O).

1-(2-Azidoethyl)-3,5-bis[(pyridin-3-yl)methylidene]-4-piperidinone (6c). Purification by column chromatography (gradient elution from $CHCl_3$ to $CHCl_3$—EtOH (100 : 5)). The yield was 31%, m.p. 114—118 °C (decomp.). Found (%): C, 65.85; H, 5.05; N, 24.38. $C_{19}H_{18}N_6O$. Calculated (%): C, 65.88; H, 5.24; N, 24.26. IR (KBr), ν/cm^{-1}: 3082, 3046, 2933, 2885, 2820, 2752, 2102 (N_3), 1674, 1617, 1588, 1580, 1560, 1478, 1458, 1413, 1340, 1327, 1305, 1275, 1244, 1208, 1198, 1179, 1156, 1133, 1107, 1061, 1020, 988, 982, 959, 882, 824, 813, 770, 704, 636, 618, 556, 547, 509. ^1H NMR, δ: 2.76 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.9 Hz); 3.28 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 5.8 Hz); 3.90 (s, 4 H, C(2)H_2, C(6)H_2); 7.35 (dd, 2 H, PyH, $^3J_{H,H}$ = 4.8 Hz, $^3J_{H,H}$ = 7.9 Hz); 7.67 (d, 2 H, PyH, $^3J_{H,H}$ = 8.0 Hz); 7.77 (s, 2 H, =CH—C_{Ar}); 8.58 (dd, 2 H, PyH, $^3J_{H,H}$ = 4.9 Hz, $^4J_{H,H}$ = 1.6 Hz); 8.63 (d, 2 H, PyH, $^4J_{H,H}$ = 2.1 Hz). ^{13}C NMR, δ: 48.46 (CH_2N_3); 54.29 (C(2), C(6)); 55.22 ($CH_2CH_2N_3$); 123.30 ($C_{Py}H$); 130.58 (=CH—C_{Py}); 133.26 (C=CH—C_{Py}); 134.08 (C=CH—C_{Py}); 136.86 ($C_{Py}H$); 149.61 ($C_{Py}H$); 150.73 ($C_{Py}H$); 185.71 (C=O).

1-(2-Azidoethyl)-3,5-bis(4-dimethylaminobenzylidene)-4-piperidinone (6d). Purification by recrystallization from a mixture of toluene—hexane. The yield was 56%, m.p. 176—178 °C (decomp.). Found (%): C, 69.65; H, 7.14; N, 19.44. $C_{25}H_{30}N_6O$. Calculated (%): C, 69.74; H, 7.02; N, 19.52. IR (KBr), ν/cm^{-1}: 3093, 2910, 2881, 2810, 2100 (N_3), 1659, 1587, 1522, 1445, 1432, 1367, 1305, 1283, 1230, 1182, 1169, 1146, 1102, 1059, 992, 939, 913, 874, 813, 777, 657, 527, 512, 460. ^1H NMR, δ: 2.78 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 6.2 Hz); 3.02 (s, 12 H, NMe_2); 3.31 (t, 2 H, $NCH_2CH_2N_3$, $^3J_{H,H}$ = 6.2 Hz); 3.96 (s, 4 H, C(2)H_2, C(6)H_2); 6.71 (d, 4 H, C_6H_4, $^3J_{H,H}$= 8.8 Hz); 7.33 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.8 Hz); 7.80 (s, 2 H, =CH—C_{Ar}). ^{13}C NMR, δ: 39.85 (Me); 48.71 (CH_2N_3); 54.63 (C(2), C(6)); 54.84 ($CH_2CH_2N_3$); 111.46 ($C_{Ar}H$); 122.95 (C_{Ar}—CH=); 128.43 (C_{Ar}—CH=C); 132.33 ($C_{Ar}H$); 137.06 (C_{Ar}—CH=); 150.38 (C_{Ar}—NMe_2); 186.39 (C=O).

Synthesis of compounds 7a—d (general procedure). A mixture of azide **6** (0.7 mmol), tetraethyl (but-3-yne-1,1-diyl)bisphosphonate (0.7 mmol) and sodium ascorbate (0.1 g, 0.5 mmol) were suspended in DMF (5 mL) with subsequent addition of water (1 mL) and 0.5 *M* solution of $CuSO_4$ (0.075 mmol, 0.15 mL, 11 mol.%). The reaction mixture was stirred for 16 h at room temperature, then water (10 mL) and CH_2Cl_2 (50 mL) were added. The organic phase was separated, and sequentially washed with water several times, a saturated solution of NH_4Cl, and again with water. Then, the organic phase was dried with Na_2SO_4 and filtered, the solvent was evaporated on a rotary evaporator. The product obtained was triturated to a powder in a mixture of Et_2O—pentane.

Tetraethyl [2-{1-[2-{3,5-bis(4-cyanobenzylidene)-4-oxopiperidin-1-yl}ethyl]-1*H*-1,2,3-triazol-4-yl}ethane-1,1-diyl]bis(phosphonate) (7a). A yellow powder, the yield was 85%. M.p. > 79 °C (decomp.). Found (%): C, 57.71; H, 5.62; N, 11.55. $C_{35}H_{42}N_6O_7P_2$. Calculated (%): C, 58.33; H, 5.87; N, 11.66. IR (KBr), ν/cm^{-1}: 3141, 3094, 3040, 2982, 2933, 2908, 2826, 2760, 2227 (CN), 1674, 1617, 1604, 1584, 1504, 1443, 1418, 1392, 1368, 1318, 1251 (P=O), 1190, 1166, 1100, 1023 (P—O—C), 992, 973, 952, 873, 851, 837, 761, 561, 532, 457. ^{31}P NMR, δ: 22.28. ^{1}H NMR, δ: 1.21—1.28 (m, 12 H, $P(OCH_2C\underline{H}_3)_2$); 2.83 (tt, 1 H, $C\underline{H}[P(O)(OEt)_2]_2$, $^3J_{H,H}$ = 6.4 Hz, $^2J_{P,H}$ = 23.4 Hz); 3.02 (t, 2 H, $N(1)C\underline{H}_2CH_2N(1')$, $^3J_{H,H}$ = 6.4 Hz); 3.22 (td, 2 H, $C\underline{H}_2CH[P(O)(OEt)_2]_2$, $^3J_{P,H}$ = 16.3 Hz, $^3J_{H,H}$ = 6.4 Hz); 3.84 (br.s, 4 H, $C(2)H_2$, $C(6)H_2$); 4.01—4.16 (m, 8 H, $P(OC\underline{H}_2CH_3)_2$); 4.32 (t, 2 H, $N(1)CH_2C\underline{H}_2N(1')$, $^3J_{H,H}$ = 6.4 Hz); 7.43 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.2 Hz); 7.46 (s, 1 H, C(5′)H); 7.71 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.2 Hz); 7.76 (s, 2 H, =CH—C_{Ar}). ^{13}C NMR, δ: 16.20 (t, $P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 6.2 Hz); 21.95 (t, $\underline{C}H_2CH[P(O)(OEt)_2]_2$, $^2J_{P,C}$ = 4.4 Hz); 36.45 (t, $\underline{C}H[P(O)(OEt)_2]_2$, $^1J_{P,C}$ = 133 Hz); 47.74 ($N(1)CH_2\underline{C}H_2N(1')$); 54.36 (C(2), C(6)); 55.89 ($N(1)\underline{C}H_2CH_2N(1')$); 62.41 and 62.73 (both d, $P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 6.6 Hz); 112.58 ($\underline{C}_{Ar}$—CN); 118.17 (C≡N); 122.82 (C(5′)); 130.51 ($C_{Ar}H$); 132.33 ($C_{Ar}H$); 134.53 ($\underline{C}_{Ar}$—CH=); 135.07 (C_{Ar}—$\underline{C}$H=); 138.96 (C_{Ar}—CH=$\underline{C}$); 145.00 (t, C(4′), $^3J_{P,C}$ = 8.2); 185.96 (C=O).

Tetraethyl [2-{1-[2-{4-oxo-3,5-bis(4-nitrobenzylidene)piperidin-1-yl}ethyl]-1*H*-1,2,3-triazol-4-yl}ethane-1,1-diyl]bis(phosphonate) (7b). A yellow powder, the yield was 83%. M.p. > 118 °C (decomp.). Found (%): C, 52.04; H, 5.59; N, 11.28; P, 8.24. $C_{33}H_{42}N_6O_{11}P_2$. Calculated (%): C, 52.11; H, 5.57; N, 11.05; P, 8.14. IR (KBr), ν/cm^{-1}: 3123, 3075, 2984, 2934, 2906, 1677, 1616, 1601, 1519 (NO_2), 1346 (NO_2), 1307, 1253 (P=O), 1187, 1163, 1108, 1067, 1026 (P—O—C), 970, 938, 853, 811, 757, 714, 687, 657, 529. ^{31}P NMR, δ: 22.40. ^{1}H NMR, δ: 1.19—1.27 (both t, 12 H, $P(OCH_2C\underline{H}_3)_2$, $^3J_{H,H}$ = 7.0 Hz); 2.82 (tt, 1 H, $C\underline{H}[P(O)(OEt)_2]_2$, $^3J_{H,H}$ = 6.4 Hz, $^2J_{P,H}$ = 23.4 Hz); 3.04 (t, 2 H, $N(1)C\underline{H}_2CH_2N(1')$, $^3J_{H,H}$ = 6.5 Hz); 3.20 (td, 2 H, $C\underline{H}_2CH[P(O)(OEt)_2]_2$, $^3J_{P,H}$ = 16.3 Hz, $^3J_{H,H}$ = 6.4 Hz); 3.86 (br.s, 4 H, $C(2)H_2$, $C(6)H_2$); 4.00—4.15 (m, 8 H, $P(OC\underline{H}_2CH_3)_2$); 4.32 (t, 2 H, $N(1)CH_2C\underline{H}_2N(1')$, $^3J_{H,H}$ = 6.3 Hz); 7.46 (s, 1 H, C(5′)H); 7.50 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.7 Hz); 7.80 (s, 2 H, =CH—C_{Ar}); 8.27 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.7 Hz). ^{13}C NMR, δ: 16.39 (t, $P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 6.5 Hz); 22.10 (t, $\underline{C}H_2CH[P(O)(OEt)_2]_2$, $^2J_{P,C}$ = 4.2 Hz); 36.59 (t, $\underline{C}H[P(O)(OEt)_2]_2$, $^1J_{P,C}$ = = 133 Hz); 47.95 ($N(1)CH_2\underline{C}H_2N(1')$); 54.55 (C(2), C(6)); 56.06 ($N(1)\underline{C}H_2CH_2N(1')$); 62.61 and 62.95 (both d, $P(OCH_2CH_3)_2$, $^3J_{P,C}$ = 6.6 Hz); 123.04 (C(5′)); 124.03 ($C_{Ar}H$); 130.96 ($C_{Ar}H$); 134.92 (=$\underline{C}$H—C_{Ar}); 135.11 (=CH—$\underline{C}_{Ar}$); 141.01 (C_{Ar}—CH=$\underline{C}$); 145.18 (t, C(4′), $^3J_{P,C}$ = 8.1 Hz); 147.79 (C_{Ar}—NO_2); 185.88 (C=O).

Tetraethyl [2-{1-[2-{4-oxo-3,5-bis(3-pyridinylmethylidene)-piperidin-1-yl}ethyl]-1*H*-1,2,3-triazol-4-yl}ethane-1,1-diyl]-bis(phosphonate) (7c). A yellow powder, the yield was 57%. M.p. > 88 °C (decomp.). Found (%): C, 54.99; H, 6.34; N, 12.46; P, 9.27. $C_{31}H_{42}N_6O_7P_2$. Calculated (%): C, 55.35; H, 6.29; N, 12.49; P, 9.21. IR (KBr), ν/cm^{-1}: 3086, 3036, 2981, 2932, 2908, 2816, 2757, 1671, 1618, 1583, 1563, 1478, 1459, 1444, 1421, 1393, 1368, 1327, 1278, 1247 (P=O), 1198, 1183, 1165, 1101, 1047, 1024 (P—O—C), 991, 959, 874, 843, 829, 806, 776, 706, 621, 553, 532. ^{31}P NMR, δ: 22.47. ^{1}H NMR, δ: 1.19—1.26 (both t, 12 H, $P(OCH_2C\underline{H}_3)_2$, $^3J_{H,H}$ = 7.0 Hz); 2.88 (tt, 1 H, $C\underline{H}[P(O)(OEt)_2]_2$, $^3J_{H,H}$ = 6.4 Hz, $^2J_{P,H}$ = 23.4 Hz); 3.02 (t, 2 H, $N(1)C\underline{H}_2CH_2N(1')$, $^3J_{H,H}$ = 6.5 Hz); 3.21 (td, 2 H, $C\underline{H}_2CH[P(O)(OEt)_2]_2$, $^3J_{P,H}$ = 16.3 Hz, $^3J_{H,H}$ = 6.4 Hz); 3.87 (br.s, 4 H, $C(2)H_2$, $C(6)H_2$); 3.99—4.16 (m, 8 H, $P(OC\underline{H}_2CH_3)_2$); 4.32 (t, 2 H, $N(1)CH_2C\underline{H}_2N(1')$, $^3J_{H,H}$ = 6.3 Hz); 7.36 (dd, 2 H, PyH, $^3J_{H,H}$ = 4.9 Hz, $^3J_{H,H}$ = 7.9 Hz); 7.42 (s, 1 H, C(5′)H); 7.67 (d, 2 H, PyH, $^3J_{H,H}$ = 7.9 Hz); 7.77 (s, 2 H, =CH—C_{Ar}); 8.58 (dd, 2 H, PyH, $^3J_{H,H}$ = 4.9 Hz, $^4J_{H,H}$ = 1.4 Hz); 8.61 (s, 2 H, PyH). ^{13}C NMR, δ: 16.19 (t, $P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 5.3 Hz); 21.92 (t, $\underline{C}H_2CH[P(O)(OEt)_2]_2$, $^2J_{P,C}$ = 4.6 Hz); 36.39 (t, $\underline{C}H[P(O)(OEt)_2]_2$, $^1J_{P,C}$ = 133 Hz); 47.71 ($N(1)CH_2\underline{C}H_2N(1')$); 54.45 (C(2), C(6)); 55.96 ($N(1)\underline{C}H_2CH_2N(1')$); 62.36 and 62.66 (both d, $P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 6.6 Hz); 122.68 (C(5′)); 123.48 ($C_{Py}H$); 130.53 (=CH—$\underline{C}_{Py}$); 133.57 (C=$\underline{C}$H—C_{Py}); 133.89 ($\underline{C}$=CH—C_{Py}); 136.91 ($C_{Py}H$); 144.95 (t, C(4′), $^3J_{P,C}$ = 8.1 Hz); 149.88 ($C_{Py}H$); 150.93 ($C_{Py}H$); 185.60 (C=O).

Tetraethyl [2-{1-[2-{3,5-bis(4-dimethylaminobenzylidene)-4-oxopiperidin-1-yl}ethyl]-1*H*-1,2,3-triazol-4-yl}ethane-1,1-diyl]-bis(phosphonate) (7d). An orange powder, the yield was 89%. M.p. > 142 °C (decomp.). Found (%): C, 58.69; H, 7.31; N, 11.09; P, 8.16. $C_{37}H_{54}N_6O_7P_2$. Calculated (%): C, 58.72; H, 7.19; N, 11.10; P, 8.19. IR (KBr), ν/cm^{-1}: 3068, 2984, 2906, 2810, 1659, 1588, 1523, 1443, 1367, 1327, 1310, 1279, 1254 (P=O), 1231, 1181, 1166, 1130, 1100, 1045, 1022 (P—O—C), 989, 975, 821, 531, 515. ^{31}P NMR, δ: 22.55. ^{1}H NMR, δ: 1.21—1.25 (both t, 12 H, $P(OCH_2C\underline{H}_3)_2$, $^3J_{H,H}$ = 7.0 Hz); 2.88 (tt, 1 H, $C\underline{H}[P(O)(OEt)_2]_2$, $^3J_{H,H}$ = 6.4 Hz, $^2J_{P,H}$ = 23.4 Hz); 3.16 (m, 14 H, NMe_2 and $N(1)C\underline{H}_2CH_2N(1')$); 3.22 (td, 2 H, $C\underline{H}_2CH[P(O)(OEt)_2]_2$, $^3J_{P,H}$ = 16.3 Hz, $^3J_{H,H}$ = 6.4 Hz); 3.91 (s, 4 H, $C(2)H_2$, $C(6)H_2$); 4.02—4.13 (m, 8 H, $P(OC\underline{H}_2CH_3)_2$); 4.36 (t, 2 H, $N(1)CH_2C\underline{H}_2N(1')$, $^3J_{H,H}$ = 6.0 Hz); 6.70 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.7 Hz); 7.30 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 8.5 Hz); 7.45 (s, 1 H, C(5′)H); 7.78 (s, 2 H, =CH—C_{Ar}). ^{13}C NMR, δ: 16.19 ($P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 6.0 Hz); 21.92 (m, $\underline{C}H_2CH[P(O)(OEt)_2]_2$); 36.42 (t, $\underline{C}H[P(O)(OEt)_2]_2$, $^1J_{P,C}$ = 132 Hz); 39.97 (NMe_2); 47.81 ($N(1)CH_2\underline{C}H_2N(1')$); 54.91 (C(2), C(6)); 56.09 ($N(1)\underline{C}H_2CH_2N(1')$); 62.39 and 62.60 (both d, $P(OCH_2\underline{C}H_3)_2$, $^3J_{P,C}$ = 6.3 Hz); 111.61 ($C_{Ar}H$); 122.70 (C(5′)); 122.86 ($\underline{C}_{Ar}$—CH=); 128.22 (C_{Ar}—CH=$\underline{C}$); 132.43 ($C_{Ar}H$); 137.23 (C_{Ar}—$\underline{C}$H=); 144.76 (t, C(4′), $^3J_{P,C}$ = 8.5 Hz); 150.58 ($\underline{C}_{Ar}$—NMe_2); 186.28 (C=O).

2-{1-[2-{3,5-Bis(4-cyanobenzylidene)-4-oxopiperidin-1-yl}-ethyl]-1*H*-1,2,3-triazol-4-yl}ethylidenebisphosphonic acid (8). Bromotrimethylsilane (0.55 g, 3.6 mmol) was added to a stirred solution of bisphosphonate **7a** (0.3 mmol) in anhydrous chloroform (3 mL). The reaction solution was allowed to stand in a capped flask at room temperature in dark for 8 days. Then, the solution was concentrated to dryness at reduced pressure, the

residue was dissolved in MeOH (8 mL) and diluted with water (2 mL). The mixture was stirred at room temperature for ~0.5 h. A precipitate formed was filtered off, washed with water on the filter, dried first in air and then over P_2O_5 *in vacuo* to obtain the corresponding acid as a yellow powder. The yield was 83%, m.p. > 250 °C (decomp.). Found (%): C, 50.37; H, 4.20; N, 12.98. $C_{27}H_{26}N_6O_7P_2 \cdot 2H_2O$. Calculated (%): C, 50.32; H, 4.69; N, 13.04. ^{31}P NMR (DMSO-d_6), δ: 20.08. ^{1}H NMR (DMSO-d_6), δ: 2.35—2.50 (m, 1 H, C<u>H</u>[P(O)$(OH)_2]_2$); 3.00—3.20 (m, 4 H, N(1)C<u>H</u>$_2$CH$_2$N(1′) and C<u>H</u>$_2$CH[P(O)$(OEt)_2]_2$); 4.04 (br.s, 4 H, C(2)H_2, C(6)H_2); 4.49 (m, 2 H, N(1)CH$_2$C<u>H</u>$_2$N(1′)); 5.54 (br.s, OH); 7.68 (d, 4 H, C_6H_4, $^3J_{H,H}$ = 7.7 Hz); 7.71 (s, 2 H, =CH—C_{Ar}); 7.84 (s, 1 H, C(5′)H); 7.94 (d, 4 H, C_6H_4, $^3J_{H,H}$ = = 7.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 21.92 (br.s, <u>C</u>H$_2$CH-[P(O)$(OH)_2]_2$); 37.09 (t, <u>C</u>H[P(O)$(OH)_2]_2$ partially overlapped with the signal of DMSO); 46.64 (N(1)CH$_2$<u>C</u>H$_2$N(1′)); 53.60 (C(2), C(6)); 55.56 (N(1)<u>C</u>H$_2$CH$_2$N(1′)); 111.82 (<u>C</u>$_{Ar}$—CN); 118.92 (C≡N); 123.50 (C(5′)); 131.53 (C_{Ar}H); 132.83 (C_{Ar}H); 134.74 (<u>C</u>$_{Ar}$—CH=); 134.86 (C_{Ar}—<u>C</u>H=); 139.05 (C_{Ar}—CH=<u>C</u>); 145.81 (br.s, C(4′)); 185.83 (C=O).

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