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Article

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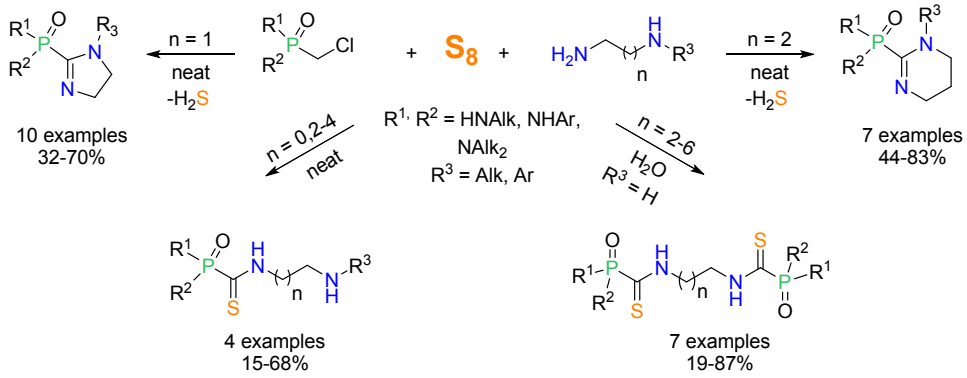
Flexible Synthesis of Phosphoryl-Substituted Imidazolines, Tetrahydropyrimidines and Thioamides by Sulfur-Mediated Processes

Mikhail Kozlov, Alexander Komkov, Timofey Losev, Alexey Tyurin, Andrey Dmitrenok, Igor Zavarzin, Yulia Volkova*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russia, *yavolkova@gmail.com*



ABSTRACT: The solvent-free sulfur-mediated reactions of phosphinic chlorides with alkyl diamines were developed for the practical synthesis of unknown phosphoryl-substituted 4,5-dihydro-1*H*-imidazoles, 1,4,5,6-tetrahydropyrimidines and thioamides. Their good tolerance to functional groups, broad substrate scope and easy scalability were shown. The chemoselective preparation of a variety of phosphoryl-substituted bis(thioamides) was accomplished *via* the adjustment of a solvent.

Introduction

Organophosphorus compounds are of great interest due to their wide occurrence in numerous natural products, various biologically active compounds, fine chemicals, metal ligands and materials.[1] In particular, imidazolines, tetrahydropyrimidines and thioamides with phosphoryl substituents are lead compounds for neuroprotective,[2] anti-inflammatory[3] and anticancer[4] agents (Figure 1). Phosphoryl-substituted imidazolines are used in the design of *N*-heterocyclic carbenes (NHC) complexes.[5] Tetrahydropyrimidines bearing a phosphoryl group are highly promising ligands for transition metal complexes.[6] Phosphoryl thioamides have found broad application as ligands for metal cations,[7] polymerization initiators,[8] hybrid materials building blocks [9] and multifunctional reagents.[10] In recent years organophosphorus compounds have gained significant attention in organic synthesis, but convenient and valuable synthetic approaches for their preparation are still required.[11] Masson et al. reported the synthesis of 2-phosphoryl-substituted imidazoline derivatives by cyclocondensation of phosphonodithioformates with diamines.[12] To the best of our knowledge, 2-phosphoryl-substituted tetrahydropyrimidines have not been reported previously. Synthetic approaches to phosphoryl thioamides *via* Pudovik-type[13] and Arbuzov-type reactions[14] are based on commercially unavailable, toxic and foul-smelling reagents. Hence, a facile flexible synthetic method particularly suitable for the preparation of a diversity of organophosphorus derivatives still needs to be developed.

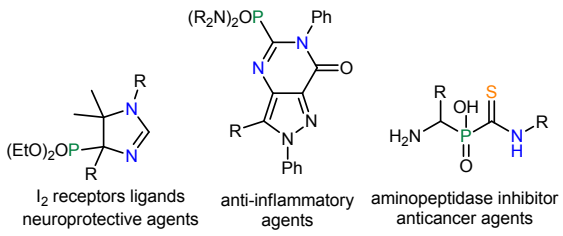
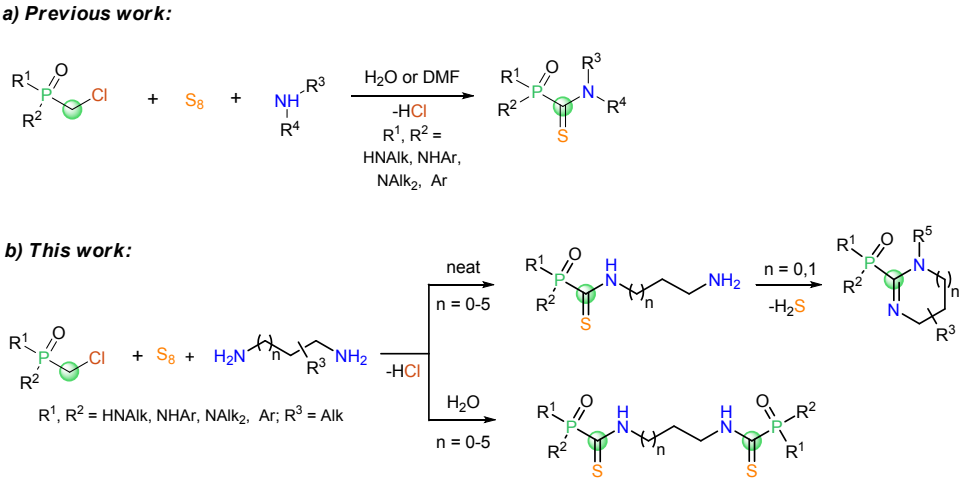


Figure 1. Biologically active organophosphorus compounds.

At the same time, sulfur mediated organic reactions are advantageous because of capacity to provide a range of structurally diverse products with good functional group tolerance.[15] A series

of reports published in the last decade demonstrate the utility of elemental sulfur in reactions with amines for the synthesis of imidazoles,[16] benzo[d]imidazoles,[17] imidazo[1,5-a]pyridines[18] and pyrazoles.[19] Recently, our group has disclosed the Willgerodt-type[20] reaction of phosphinic chlorides with sulfur and amines as a highly efficient approach to phosphoryl thioamides (Scheme 1a).[21] Herein, we propose that using alkyl diamines in the reaction with phosphinic chlorides and sulfur is an efficient tool for the construction of 2-phosphoryl-substituted 2-imidazolines and 1,4,5,6-tetrahydropyrimidines (Scheme 1b). Additionally, we discovered the switching of the reaction pathway to bis(thioamides) mediated by solvent effects.

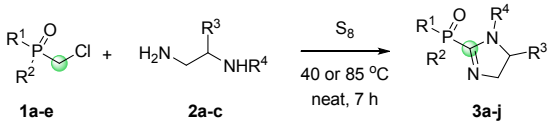
Scheme 1. Sulfur-mediated reaction of phosphinic chlorides with amines in the synthesis of phosphoryl thioamides and phosphoryl-substituted *N*-heterocycles.



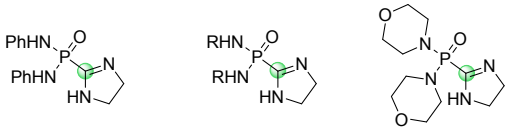
Results and Discussion

Initially, we studied the reaction of phosphinic chlorides **1** with 1,2-ethylenediamine derivatives **2** in the presence of sulfur (Table 1). A brief optimization identified mild conditions providing a reliable route to desired substituted imidazolines **3** (see Supporting Information). We were pleased to find that heating of mixtures of compounds **1a–f** with sulfur in ethylenediamine derivatives **2a–c** to 40–85 °C resulted in the formation of desired imidazolines **3a–j** in 32–70% yields. We also tested *N,N*-dimethylformamide, 1,4-dioxane and water as solvents. However the reactions were found to be fully inefficient.

Table 1. Synthesis of imidazolines **3**[a,b]



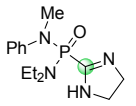
1a-e **2a-c** **3a-j**



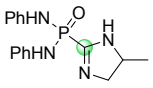
3a, 44% (**A**)

3b, R = Bu, 65% (**A**)
3c, R = ^{t}Bu, 43% (**B**)

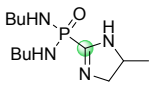
3d, 68% (**A**)
scale-up 1.6 g



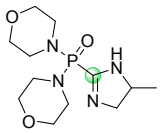
3e, 64% (**B**)



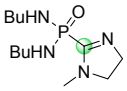
3f, 32% (**A**)



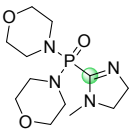
3g, 70% (**A**)



3h, 55% (**A**)



3i, 48% (**A**)



3j, 47% (**A**)

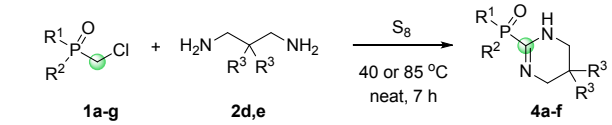
[a] *Reaction conditions*: sulfur (0.22 g, 7.0 mmol), phosphinic chloride **1** (1.4 mmol), diamine **2** (20 mmol) at 40 °C (**A**) or 85 °C (**B**) over 7 h. [b] Yields after column chromatography.

A variety of substituents at phosphorus were tolerated, and the use of ethylenediamine **2a** afforded compounds **3a**–**e** bearing symmetrical and asymmetrical phosphonic acid diamide substituents. Moreover, the reaction with 2-methyl-substituted ethylenediamine **2b** gave 5-methyl-4,5-dihydroimidazoles **3f**–**h** in 32–70% yields. *N*-methylethylenediamine **2c** successfully reacted with phosphinic chlorides **1b,c** to afford *N*-substituted imidazolines **3i** and **3j** in 48% and 47%, respectively. It's important to stress, that (chloromethyl)phosphonates, represented by formula $(RO)_2POCH_2Cl$ (R = OPh, OEt), under the optimized conditions did not give target imidazolines due to side processes of transamidation at the phosphinic center.

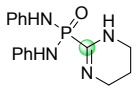
To explore the efficiency of this method, a gram-scale experiment was conducted. The proposed method can easily be scaled-up without loss in yield. Thus, the treatment of (chloromethyl)phosphonic acid bis(morpholide) **1d** (2.0 g, 7.0 mmol) with ethylenediamine **2a** (6.5 mL, 98 mmol, 14 equiv) and sulfur on heating to 40 °C for 7 h gave imidazoline **3d** in 79% yield (1.6 g).

Moreover, the transformation was extended to the 1,3-propylenediamine (**2d)** (Table 2). Diverse phosphinic chlorides **1a**–**e** bearing aniline substituents, *n*-butylamine, *tert*-butylamine, morpholine and diethylamine substituents were well tolerated under the reaction conditions to give the tetrahydropyrimidines **4a**–**e** in 44% to 83% yields. Starting from (chloromethyl)phosphonic acid *N*-methyl-*N*-phenylazepane amide (**2g**), product **4f** bearing an asymmetric phosphonic acid diamide moiety was obtained in 68% yield. Besides, 2,2-dimethylpropane-1,3-diamine (**2e)** can also be employed to prepare 3,3-dimethyl-substituted tetrahydropyrimidine **4g** in 57% yield (Table 2).

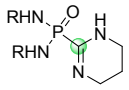
Table 2. Synthesis of tetrahydropyrimidines **4**[a,b]



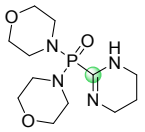
1a-g **2d,e** **4a-f**



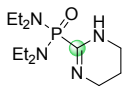
4a, 83% (**A**)



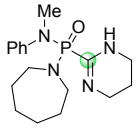
4b, R = *n*-Bu, 44% (**A**)
4c, R = *tert*-Bu, 78% (**B**)



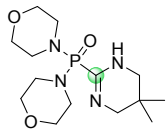
4d, 68% (**A**)



4e, 65% (**B**)



4f, 68% (**B**)

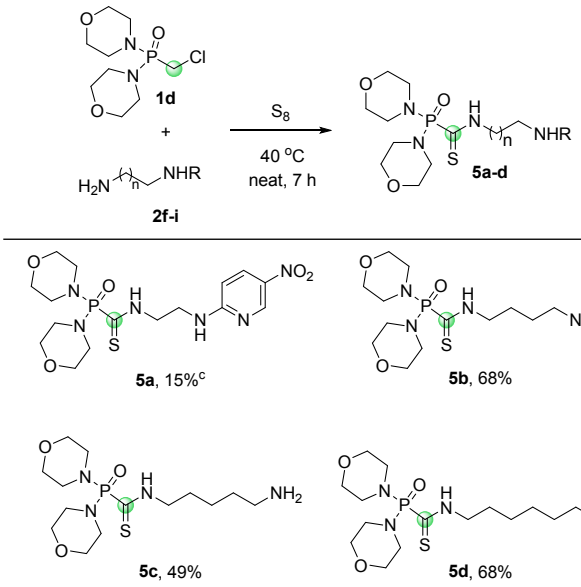


4g, 57% (**A**)

[a] *Reaction conditions*: sulfur (0.22 g, 7.0 mmol), phosphinic chloride **1** (1.4 mmol), diamine **2** (20 mmol) at 40 °C (**A**) or 85 °C (**B**) over 7 h. [b] Yields after column chromatography.

The subsequent elongation of diamine **2** alkyl chains, as well as the installation of electron-withdrawing substituents decreasing *NH*-group reactivity, resulted in the formation of linear products — phosphoryl thioamides **5** (Table 3). The reaction of (5-nitropyridin-2-yl)ethane-1,2-diamine (**2f**) with phosphinic chloride **1d** afforded product **5a** in 15% yield. 1,4-Butanediamine (**2g**), 1,5-pentanediamine (**2h**) and 1,6-hexanediamine (**2i**) reacted smoothly to form thioamides **5b-d** in 68%, 49% and 68% yields, respectively.

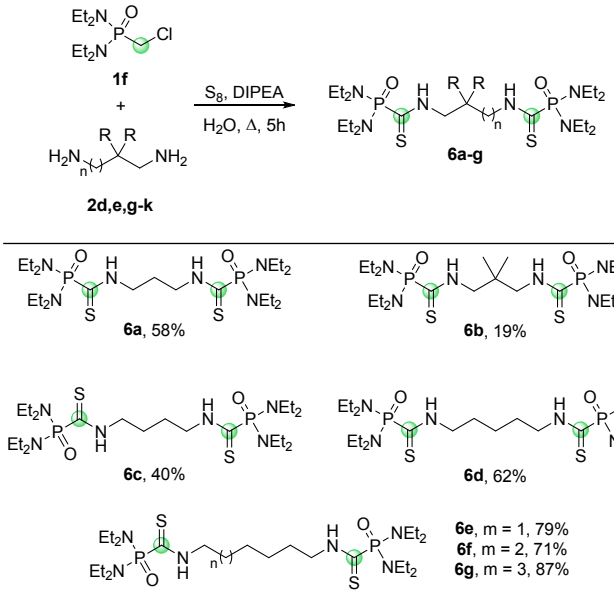
Table 3. Synthesis of phosphoryl thioamides **5**[a,b]



[a] *Reaction conditions*: sulfur (0.22 g, 7.0 mmol), phosphinic chloride **1d** (375 mg,1.4 mmol), diamine **2** (20 mmol), at 40 °C over 7 h. [b] Yields after column chromatography. [c] The reaction was performed with Et_3N in DMF at 45 °C over 5 h.

Surprisingly, it was found that in the presence of water reaction of phosphinic chlorides **1** with diamines **2** and elemental sulfur was accompanied by formation of bis(thioamides) **6** (Table 4). We assumed that water-organic two-phase system as media can provides a coacervate phase that is rich in phosphinic chloride **1** and diamine **2** aqueous-rich phase, hereby promotes bisthiophosphorylation of amine. Optimization of reaction conditions indicated that the maximum yields of compounds **6** were achieved at 1:1 ration of phosphinic chlorides **1** and diamines **2**. The principal result is the formation of bis(thioamides) **6** as the major products in all cases irrespective of the diamine alkyl chain length. Thus, various diamines with a C_3–C_8 alkyl chain reacted smoothly with (chloromethyl)phosphonic acid bisdiethyl amide (**2f**) to form compounds **6a**–**g** in 19–87% yields. Low yields of products **6b,c** are attributed to numerous side processes giving complex mixtures of products.

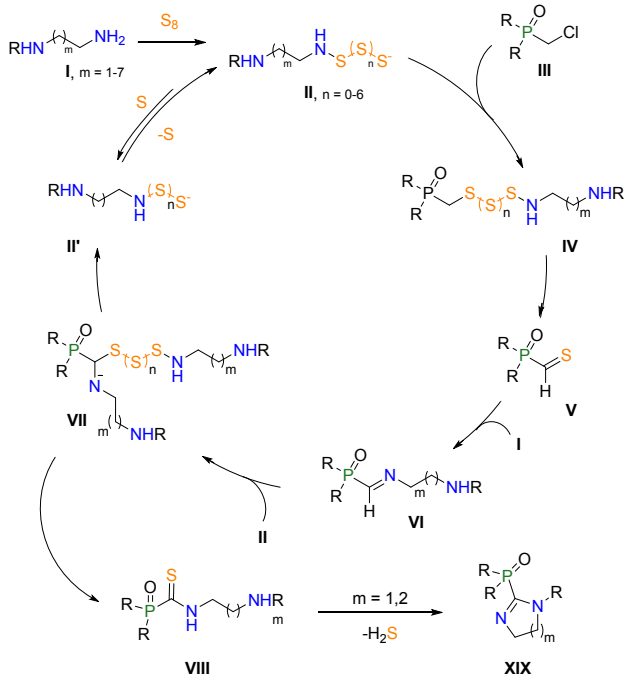
Table 4. Synthesis of bis(thioamides) **6**[a,b]



[a] *Reaction conditions*: sulfur (41 mg, 1.29 mmol), phosphinic chloride **1f** (100 mg, 0.43 mmol), diamine **2** (0.43 mmol), and DIPEA (224 μL, 1.29 mmol) in water (1 mL) under reflux over 5 h. [b] Yields after column chromatography.

The possible mechanism for the condensation of phosphinic chlorides with sulfur and alkyl diamines suggested by literature precedents[15,20] is shown in Scheme 2. The reaction is initiated by the nucleophilic ring opening of S_8 by amine **I**, leading to polysulfide **II**. Polysulfide **II** is highly nucleophilic and adds to the chloromethyl reaction center of phosphinic chloride **III** to provide polysulfide **IV**. The cleavage of intermediate **IV** S–S bond with amine along with proton abstraction results in thioaldehyde **V**. Following imination of the former gives **VI**, which undergoes addition with polysulfides **II**. Finally the elimination of polysulfide **II**' from intermediate **VII** affords thioamide **VIII**. The intramolecular ring closure of thioamides **VIII** with short alkyl chains (m = 1, 2) followed by hydrogen sulfide elimination provides cyclic products **XIX**. In water, compounds **VIII** with a terminal NH_2 group undergo subsequent thiophosphorylation to form bis(thioamides).

Scheme 2. Plausible mechanism.



In conclusion, we demonstrated the utility of the sulfur-mediated reaction of phosphinic chlorides with alkyl diamines for the easy access to a variety of phosphoryl-substituted products. A variety of 2-imidazoline, 1,4,5,6,-tetrahydropyrimidine and thioamide structures could be prepared from readily available materials under solvent-free conditions or in water. The new strategy significantly broadens the synthetic scope of organophosphorus compounds. Due to operational simplicity, these protocols may be useful in pharmacological research and the design of materials and ligands in metal complex catalysis.

■ EXPERIMENTAL SECTION

NMR spectra were acquired on Bruker Avance 600 and 300 spectrometers at room temperature; the chemical shifts δ were measured in ppm relative to the solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm, DMSO-d_6, δ = 2.50 ppm; ^{13}C: $CDCl_3$, δ = 77.00 ppm, DMSO-d_6, δ = 39.50 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double double doublet. The coupling constants (*J*) are in Hertz. High-resolution and accurate mass spectra were obtained on BrukermicrOTOF-QTM ESI-TOF (Electrospray Ionization/Time of Flight) and Thermo Scientific* LTQ Orbitrap mass spectrometers. Mass

spectra were recorded on a Finnigan Mat INCOS 50 Quadrupole Mass Spectrometer. Melting points (mp) are uncorrected and were measured on a Boetius capillary melting point apparatus. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254 aluminum supported plates); the visualization was accomplished with an UV lamp (365 nm) and using chemical staining with [$KMnO_4/H_2SO_4$]. Column chromatography was performed on silica gel 60 (230-400 mesh, Merck). Sulfur and all amines were commercially available and were used without additional purification. All reactions were carried out using freshly distilled and dry solvents. Phosphinic chlorides are readily available from chloromethylphosphonic dichloride by simple treatment with amines, alcohols and Grignard reagents.[22-24]

*Chloromethylphosphonic acid bisphenyl amide (**1a**)* was obtained according to literature protocol.[22] Pale yellow solid, m.p. 98 – 100 °C (m.p.$_{lit}$ 97 - 125 °C).[22] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.94 (d, J_{H-P} = 11.3 Hz, 2H, 2 × NH), 7.26 – 7.12 (m, 8H, 4 × CH + 4 × CH), 6.98 – 6.80 (m, 2H, 2 × CH), 3.88 (d, J_{H-P} = 8.0 Hz, 2H, CH_2Cl). ^{31}P NMR (121 MHz, DMSO-d_6): δ 10.74. MS (ESI) 280 $[M]^+$.

*Chloromethylphosphonic acid bisbutyl amide (**1b**)*[21] was obtained according to literature protocol.[23] Pale yellow solid, m.p. 39 - 41 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.22 (dt, J_{H-P} = 11.5 Hz, J_{H-H} = 6.6 Hz, 2H, 2 × NH), 3.50 (d, J_{H-P} = 8.3 Hz, 2H, CH_2Cl), 2.86 – 2.67 (m, 4H, 2 × CH_2), 1.46 – 1.34 (m, 4H, 2 × CH_2), 1.33 – 1.20 (m, 4H, 2 × CH_2), 0.86 (t, J = 7.1 Hz, 6H, 2 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 39.9 (CH_2), 37.4 (d, $^1J_{C-P}$ = 118.4 Hz, CH_2Cl), 34.4 (d, $^3J_{C-P}$ = 5.4 Hz, CH_2), 19.9 (CH_2), 14.2 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.19.

*Chloromethylphosphonic acid bis(tert-butyl) amide (**1c**)*[21] was obtained according to literature protocol.[23] Pale yellow solid, m.p. 96 – 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.46 (d, J_{H-P} = 9.0 Hz, 2H, CH_2Cl), 2.90 (br. s, 2H, 2 × NH), 1.35 (s, 18H, 6 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 51.4 (d, $^2J_{C-P}$ = 40.6 Hz, 2 x C), 39.6 (d, $^1J_{C-P}$ = 117.9 Hz, CH_2Cl), 31.80 (d, $^3J_{C-P}$ = 4.1 Hz, 6 x CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 17.27.

*Chloromethylphosphonic acid bismorpholine amide (**1d**)*[21] was obtained according to literature protocol.[23] Pale yellow solid, m.p. 103 - 105 °C (m.p.$_{lit}$ 89-91 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 – 3.57 (m, 10H, 4 × CH_2 + CH_2), 3.29 – 3.12 (m, 8H, 2 × CH_2). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 67.1 (d, $^{3}J_{C\text{-}P}$ = 5.1 Hz, 4 × CH_2), 44.5 (4 × CH_2), 34.4 (d, $^{1}J_{C\text{-}P}$ = 123.7 Hz, CH_2Cl). ^{31}P NMR (121 MHz, $CDCl_3$): δ 23.79.

*Chloromethylphosphonic acid N-methyl-N-phenyl ethyl amide (**1e**)*[21] was obtained according to literature protocol.[22] Pale yellow solid, m.p. 58 – 60 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.29 (m, 4H, Ph), 7.25 – 7.17 (m, 1H, Ph), 3.50 (d, $J_{H\text{-}P}$ = 7.9 Hz, 2H, CH_2Cl), 3.34 – 3.02 (m, 7H, 2 × CH_2 + CH_3), 1.09 (t, J = 7.1 Hz, 6H, 2 × CH_3). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 144.6 (d, $^{2}J_{C\text{-}P}$ = 3.8 Hz, C), 129.4 (2 × CH), 126.7 (d, $^{3}J_{C\text{-}P}$ = 4.1 Hz, 2 × CH), 126.0 (CH), 39.0 (d, $^{2}J_{C\text{-}P}$ = 3.9 Hz, 2 × CH_2), 37.7 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz, CH_3), 36.2 (d, $^{1}J_{C\text{-}P}$ = 127.0 Hz, CH_2Cl), 13.8 (d, $^{3}J_{C\text{-}P}$ = 1.5 Hz, 2 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.04.

*Chloromethylphosphonic acid bisdiethyl amide (**1f**)*[21] was obtained according to literature protocol.[23] Colorless viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (d, $J_{H\text{-}P}$ = 8.2 Hz, 2H, CH_2Cl), 3.11-3.19 (m, 8H, 4 × CH_2), 1.14 (t, J = 7.1 Hz, 12H, 4 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 27.98. MS (EI) 240 $[M]^+$.

*Chloromethylphosphonic acid N-methyl-N-phenyl azepaneamide (**1g**)* was obtained according to literature protocol.[24] Whitre solid, m.p. 97 – 99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H, Ph), 7.26 – 7.17 (m, 1H, Ph), 3.65 – 3.58 (m, 1H, CH_2Cl), 3.58 – 3.51 (m, 1H, CH_2Cl), 3.28 – 3.16 (m, 4H, CH_2), 3.13 (d, $J_{H\text{-}P}$ = 9.1 Hz, 3H, CH_3), 1.77 – 1.51 (m, 8H, 4 × CH_2). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 144.8 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz, C), 129.3 (2 × CH), 126.3 (d, $^{3}J_{C\text{-}P}$ = 4.1 Hz, 2 × CH), 125.8 (CH), 47.5 (d, $^{2}J_{C\text{-}P}$ = 3.2 Hz, 2 × CH_2), 37.7 (d, $^{2}J_{C\text{-}P}$ = 3.6 Hz, CH_3), 35.8 (d, $^{1}J_{C\text{-}P}$ = 127.0 Hz, CH_2Cl), 30.1 (d, $^{3}J_{C\text{-}P}$ = 4.4 Hz, 2 × CH_2), 26.9 (2 × CH_2). ^{31}P NMR (121 MHz, $CDCl_3$): δ 24.74. HRMS (ESI) for $C_{14}H_{23}ClN_2OP$ ($[M+H]^+$): calcd 301.1231, found 301.1238.

General method for the synthesis of compounds 3,4, and 5. A mixture of diamine **2** (20 mmol, 14 equiv) and elemental sulfur (0.22 g, 7.0 mmol, 5 equiv) was stirred for 30 min at r.t. Phosphinic chloride **1** (1.4 mmol, 1 equv) was added and resulting mixture was additionally stirred for 7 h at 40 °C (procedure **A**) or at 85 °C (procedure **B**) in an oil bath until the complete conversion of phosphinic chloride (TLC monitoring). The resulted mixture was cooled to r.t. and viscous oil was extracted with $CHCl_3$ (3 ×10 mL, for reactions with **1b-g**) or MeOH (3 × 15 mL, for reaction with **1a**). Combined organic fraction was concentrated under reduced pressure and product was isolated by column chromatography (eluent $CHCl_3$ → $CHCl_3$:MeOH, 60:1 for **3b-j**, **4b-f**, **5**; $CHCl_3$: MeOH, 2:1 for **3a**, **4a**).

*(4,5-Dihydro-1H-imidazol-2-yl)di(phenylamino)phosphine oxide (**3a**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as pale yellow solid (186 mg, 44%), m.p. 218 - 219 °C, R_f = 0.24 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.59 (s, 4H, 2 × CH_2), 6.85 – 6.87 (m, 2H, 2 × CH), 7.14 – 7.17 (m, 8H, 8 × CH), 8.32 (br. s, 2H, 2 × NH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 49.5 (2 × CH_2), 118.6 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, 4 × CH), 121.5 (2 × CH), 129.3 (4 × CH), 141.1 (2 × C), 164.0 (d, $^1J_{C\text{-}P}$ = 185.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ -4.44. HRMS (ESI) for $C_{15}H_{18}N_4OP$ ($[M+H]^+$): calcd 301.1213, found 301.1203. IR (KBr): 3238, 2939, 2881, 1602, 1558, 1499, 1411, 1292, 1222, 1032, 948, 750, 691, 544, 503 cm^{-1}.

*(4,5-Dihydro-1H-imidazol-2-yl)di(n-butylamino)phosphine oxide (**3b**).* The general procedure **A** was followed. Purification by column chromatography afforded product as pale yellow solid (237 mg, 65%), m.p. 132 - 133 °C, R_f = 0.21 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, $J_{H\text{-}H}$ = 8.0 Hz, 6H, 2 × CH_3), 1.22 – 1.31 (m, 4H, 2 × CH_2), 1.35 – 1.42 (m, 4H, 2 × CH_2), 2.71 – 2.79 (m, 4H, 2 × CH_2), 3.44 (s, 4H, 2 × CH_2), 4.20 – 4.26 (m, 2H, 2 × NH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 14.2 (2 × CH_3), 19.9 (2 × CH_2), 34.5 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, 2 × CH_2), 39.7 (d, $^2J_{C\text{-}P}$ = 8.0 Hz, 2 × CH_2), 50.3 (2 ×

CH_2), 165.4 (d, $^1J_{C-P}$ = 181.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 8.45. HRMS (ESI) for $C_{11}H_{26}N_4OP$ ($[M+H]^+$): calcd 261.1839, found 261.1831. IR (KBr): 3268, 3070, 2957, 2929, 2861, 1568, 1467, 1378, 1291, 1192, 1119, 1098, 1039, 977, 952, 920, 869, 796, 677, 543 cm^{-1}.

*(4,5-Dihydro-1H-imidazol-2-yl)di(tert-butylamino)phosphine oxide (**3c**).* The general procedure **B** was followed. Purification by column chromatography afforded product as pale yellow solid (156 mg, 43%), m.p. 225 - 227 °C, R_f = 0.32 ($CHCl_3$: MeOH, 5:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (s, 18H, 6 × CH_3), 3.48 (s, 4H, 2 × CH_2), 3.95 (d, J_{H-P} = 8.0 Hz, 2H, 2 × NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 32.0 (d, $^3J_{C-P}$ = 4.0 Hz, 6 × CH_3), 50.6 (2 × CH_2), 51.1 (2 × C), 157.5 (d, $^1J_{C-P}$ = 196.4 Hz, C), signal of NH group was not observed. ^{31}P NMR (121 MHz, DMSO-d_6): δ 2.30. HRMS (ESI) for $C_{11}H_{26}N_4OP$ ($[M+H]^+$): calcd 261.1839, found 261.1846. IR (KBr): 3425, 3229, 2971, 2871, 1570, 1552, 1475, 1390, 1365, 1286, 1249, 1224, 1210, 1184, 1020, 974, 949, 850, 564 cm^{-1}.

*(4,5-Dihydro-1H-imidazol-2-yl)dimorpholinophosphine oxide (**3d**).* The general procedure **A** was followed. Purification by column chromatography afforded product as a pale yellow solid (275 mg, 68%), m.p. 144 - 145 °C, R_f = 0.33 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.00 – 3.05 (m, 8H, 4 × CH_2), 3.48 (s, 4H, 2 × CH_2), 3.52 (t, J_{H-P} = 4.0 Hz, 8H, 4 × CH_2), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 44.2 (4 × CH_2), 50.3 (2 × CH_2), 66.7 (d, $^2J_{C-P}$ = 5.0 Hz, 4 × CH_2), 162.3 (d, $^1J_{C-P}$ = 187.2 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 12.20. HRMS (ESI) for $C_{11}H_{22}N_4O_3P$ ($[M+H]^+$): calcd 289.1424, found 289.1424. IR (KBr): 3171, 2971, 2886, 2853, 1573, 1443, 1368, 1286, 1256, 1224, 1195, 1114, 1092, 758, 967, 917, 849, 734, 706, 598, 536, 479 cm^{-1}.

*(Methylphenylamino)(diethylamino)(4,5-dihydro-1H-imidazol-2-yl)phosphi-ne oxide (**3e**).* The general procedure **B** was followed. Purification by column chromatography afforded product as pale yellow oil (264 mg, 64%), R_f = 0.45 (CH_2Cl_2 : MeOH, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J_{H-H} = 7.1 Hz, 6H, 2 × CH_3), 3.25 – 3.00 (m, 7H, 2 × CH_2 + CH_3), 3.71 (s, 4H, 2 × CH_2),

7.19 – 7.05 (m, 1H, CH), 7.33 – 7.22 (m, 2H, 2 × CH), 7.46 – 7.36 (m, 2H, 2 × CH), signal of NH group was not observed. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 13.3 (d, $^3J_{C-P}$ = 2.2 Hz, 2 × CH_3), 37.6 (d, $^2J_{C-P}$ = 6.1 Hz, CH_3), 38.7 (d, $^2J_{C-P}$ = 4.5 Hz, 2 × CH_2), 48.9 (d, $^3J_{C-P}$ = 7.3 Hz, 2 × CH_2), 125.6 (CH), 126.0 (d, $^3J_{C-P}$ = 4.4 Hz, 2 × CH), 129.0 (2 × CH), 143.7 (d, $^2J_{C-P}$ = 3.9 Hz, C), 164.0 (d, $^1J_{C-P}$ = 178.3 Hz, C). ^{31}P NMR (121 MHz, $CDCl_3$): δ 11.08. HRMS (ESI) for $C_{14}H_{24}N_4OP$ ($[M+H]^+$): calcd 295.1682, found 295.1691.

*(5-Methyl-4,5-dihydro-1H-imidazol-2-yl)di(phenylamino)phosphine oxide (**3f**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as mixture of tautomers, pale yellow solid (229 mg, 52%), m.p. 192 - 193 °C, R_f = 0.25 ($CHCl_3$: MeOH, 10:1). ^1H NMR (300 MHz, DMSO-d_6): δ 1.06 (d, J_{H-H} = 4.0 Hz, 3H, CH_3), 3.18 (dd, J_{H-H} = 8.0, 12.0 Hz, 1H, CH_2), 3.72 (dd, J_{H-H} = 12.0 Hz, 1H, CH_2), 3.92 – 4.00 (m, 1H, CH), 6.80 – 6.88 (m, 2H, 2 × CH), 7.10 – 7.18 (m, 8H, 8 × CH), 8.04 (br. s, 2H, 2 × NH), signal of NH group was not observed. $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.7 (CH_3), 56.5 (CH), 57.5 (CH_2), 118.6 (d, $^3J_{C-P}$ = 4.0 Hz, 4 × CH), 121.4 (2 × CH), 129.2 (4 × CH), 141.1 (2 × C), 162.3 (d, $^1J_{C-P}$ = 186.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ -4.11. HRMS (ESI) for $C_{16}H_{20}N_4OP$ ($[M+H]^+$): calcd 315.1369, found 315.1369. IR (KBr): 3232, 1602, 1552, 1499, 1410, 1283, 1226, 1032, 944, 749, 690, 546, 503 cm^{-1}.

*(5-Methyl-4,5-dihydro-1H-imidazol-2-yl)di(n-butylamino)phosphine oxide (**3g**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as mixture of tautomers, pale yellow solid (270 mg, 70%), m.p. 91 - 92 °C, R_f = 0.21 ($CHCl_3$: MeOH, 10:1). ^1H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, J_{H-H} = 8.0 Hz, 6H, 2 × CH_3), 1.06 (d, J_{H-H} = 4.0 Hz, 3H, CH_3), 1.22 – 1.31 (m, 4H, 2 × CH_2), 1.35 – 1.42 (m, 4H, 2 × CH_2), 2.71 – 2.79 (m, 4H, 2 × CH_2), 3.05 (dd, J_{H-H} = 12.0 Hz, 1H, CH_2), 3.60 (dd, J = 12.0 Hz, 1H, CH_2), 3.78 – 3.87 (m, 1H, CH), 4.21 – 4.29 (m, 2H, 2 × NH), signal of NH group was not observed. $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 14.2 (2 × CH_3), 19.9 (2 × CH_2), 22.0 (CH_3), 34.1 (d, $^2J_{C-P}$ = 5.0 Hz, 2 ×

CH_2), 39.7 (2 × CH_2), 56.9 (CH), 58.0 (CH_2), 163.8 (d, $^1J_{C-P}$ = 180.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 8.26. HRMS (ESI) for $C_{12}H_{28}N_4OP$ ($[M+H]^+$): calcd 275.1995, found 275.1993. IR (KBr): 3202, 2957, 2931, 2870, 1567, 1450, 1225, 1167, 1130, 1099, 967, 912, 732, 582 cm^{-1}.

*(5-Methyl-4,5-dihydro-1H-imidazol-2-yl)dimorpholinophosphine oxide (**3h**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as mixture of tautomers, as pale yellow solid (232 mg, 55%), m.p. 94 - 95 °C, R_f = 0.47 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (d, J = 6.0 Hz, 3H, CH_3), 3.00 – 3.16 (m, 9H, 4 × CH_2), 3.53 (t, J_{H-P} = 5.0 Hz, 8H, 4 × CH_2), 3.59 – 3.61 (m, 1H, CH_2), 3.85 – 3.92 (m, 1H, CH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.9 (CH_3), 44.2 (4 × CH_2), 57.5 (CH_2 + CH), 66.7 (d, $^2J_{C-P}$ = 5.0 Hz, 4 × CH_2), 160.5 (d, $^1J_{C-P}$ = 187.2 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 12.03. HRMS (ESI) for $C_{12}H_{24}N_4O_3P$ ($[M+H]^+$): calcd 303.1581, found 303.1580. IR (KBr): 3259, 2963, 2917, 2854, 1568, 1453, 1371, 1299, 1259, 1226, 1188, 1138, 1112, 1090, 1022, 967, 916, 844, 733, 698, 610, 542, 477 cm^{-1}.

*(1-Methyl-4,5-dihydro-1H-imidazol-2-yl)di(n-butylamino)phosphine oxide (**3i**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as colorless oil (185 mg, 48%), R_f = 0.12 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, J_{H-H} = 8.0 Hz, 6H, 2 × CH_3), 1.22 – 1.30 (m, 4H, 2 × CH_2), 1.30 – 1.40 (m, 4H, 2 × CH_2), 2.72 – 2.78 (m, 4H, 2 × CH_2), 2.99 (s, 3H, CH_3), 3.27 (t, J_{H-H} = 12.0 Hz, 2H, CH_2), 3.60 (t, J_{H-H} = 12.0 Hz, 2H, CH_2), 4.50 – 4.58 (m, 2H, 2 × NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 14.2 (2 × CH_3), 19.9 (2 × CH_2), 33.9 (d, $^3J_{C-P}$ = 5.0 Hz, 2 × CH_2), 34.7 (CH_3), 39.5 (2 × CH_2), 52.8 (d, $^3J_{C-P}$ = 18.1 Hz, CH_2), 53.6 (d, $^3J_{C-P}$ = 5.0 Hz, CH_2), 165.0 (d, $^1J_{C-P}$ = 173.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 7.08. HRMS (ESI) for $C_{12}H_{28}N_4OP$ ($[M+H]^+$): calcd 275.1995, found 275.1993.

*(1-Methyl-4,5-dihydro-1H-imidazol-2-yl)dimorpholinophosphine oxide (**3j**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as colorless oil (200 mg, 47%), R_f = 0.18 ($CHCl_3$: MeOH, 20:1). ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.01 (s, 3H, CH_3), 3.01 – 3.06 (m, 8H, 4 × CH_2), 3.23 (t, J_{H-H} = 10.0 Hz, 2H, CH_2), 3.51 – 3.57 (m, 8H, 4 × CH_2), 3.68 (t, J_{H-H} = 10.0 Hz, 2H, CH_2). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 34.7 (CH_3), 44.2 (4 × CH_2), 52.7 (d, $^3J_{C-P}$ = 4.2 Hz, CH_2), 54.5 (d, $^3J_{C-P}$ = 20.0 Hz, CH_2), 66.8 (d, $^2J_{C-P}$ = 5.2 Hz, 4 × CH_2), 161.9 (d, $^1J_{C-P}$ = 184.1 Hz, C). ^{31}P NMR (243 MHz, DMSO-d_6): δ 12.41. HRMS (ESI) for $C_{12}H_{24}N_4O_3P$ ($[M+H]^+$): calcd 303.1581, found 303.1579.

*Di(phenylamino)(1,4,5,6-tetrahydropyrimidin-2-yl)phosphine oxide (**4a**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as pale yellow solid (366 mg, 83%), m.p. 193 – 195 °C, R_f = 0.30 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.60 – 1.67 (m, 2H, CH_2), 3.25 (t, J_{H-H} = 8.0 Hz, 4H, 2 × CH_2), 6.88 (t, J_{H-H} = 8.0 Hz, 2H, 2 × CH), 7.12 – 7.20 (m, 8H, 8 × CH), 8.20 (br. s, 2H, 2 × NH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 19.3 (CH_2), 40.8 (d, $^3J_{C-P}$ = 11.1 Hz, 2 × CH_2), 118.7 (d, $^3J_{C-P}$ = 7.0 Hz, 4 × CH), 121.6 (2 × CH), 129.4 (4 × CH), 141.0 (2 × C), 156.0 (d, $^1J_{C-P}$ = 185.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ -2.45. HRMS (ESI) for $C_{16}H_{20}N_4OP$ ($[M+H]^+$): calcd 315.1369, found 315.1374. IR (KBr): 3252, 3052, 2957, 2875, 1639, 1600, 1499, 1413, 1319, 1284, 1227, 1081, 1031, 938, 750, 691, 563, 486 cm^{-1}.

*Di(n-butylamino)(1,4,5,6-tetrahydropyrimidin-2-yl)phosphine oxide (**4b**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as pale yellow solid (169 mg, 44%), m.p. 86 - 87 °C, R_f = 0.12 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, J_{H-H} = 8.0 Hz, 6H, 2 × CH_3), 1.22 – 1.29 (m, 4H, 2 × CH_2), 1.33 – 1.40 (m, 4H, 2 × CH_2), 1.60 – 1.67 (m, 2H, CH_2), 2.68 – 2.76 (m, 4H, 2 × CH_2), 3.20 (t, J_{H-H} = 8.0 Hz, 4H, 2 × CH_2), 4.42 – 4.50 (m, 2H, 2 × NH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 14.2 (2 × CH_3), 20.0 (2 × CH_2), 20.2 (CH_2), 34.1 (d, $^2J_{C-P}$ = 5.0 Hz, 2 ×

CH_2), 39.6 (2 × CH_2), 41.1 (d, $^3J_{C\text{-}P}$ = 11.1 Hz, 2 × CH_2), 157.0 (d, $^1J_{C\text{-}P}$ = 183.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 10.51. HRMS (ESI) for $C_{12}H_{28}N_4OP$ ($[M+H]^+$): calcd 275.1995, found 275.1992. IR (KBr): 3298, 3228, 2958, 2932, 2872, 1637, 1602, 1506, 1465, 1443, 1362, 1316, 1206, 1162, 1098, 1038, 971, 858, 599, 518 cm^{-1}.

*Di(tert-butylamino)(1,4,5,6-tetrahydropyrimidin-2-yl)phosphine oxide (**4c**).* The general procedure **B** was followed. Purification by column chromatography afforded product as pale yellow solid (300 mg, 78%), m.p. 183 – 186 °C, R_f = 0.10 ($CHCl_3$: MeOH, 5:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.21 (s, 18H, 6 × CH_3), 1.55 – 1.62 (m, 2H, CH_2), 3.21 (t, $J_{H\text{-}H}$ = 6.0 Hz, 4H, 2 × CH_2), 3.95 (br. s, 2H, 2 × NH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 20.3 (CH_2), 31.9 (d, $^3J_{C\text{-}P}$ = 4.0 Hz, 6 × CH_3), 41.4 (d, $^3J_{C\text{-}P}$ = 11.1 Hz, 2 × CH_2), 50.9 (2 × C), 158.9 (d, $^1J_{C\text{-}P}$ = 191.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 4.78. HRMS (ESI) for $C_{12}H_{28}N_4OP$ ($[M+H]^+$): calcd 275.1995, found 275.2007. IR (KBr): 3423, 3229, 2969, 2931, 2870, 1603, 1440, 1389, 1364, 1314, 1251, 1229, 1191, 1024, 868 cm^{-1}.

*Dimorpholino(1,4,5,6-tetrahydropyrimidin-2-yl)phosphine oxide (**4d**).* The general procedure **A** was followed. Purification by column chromatography afforded product as pale yellow solid (288 mg, 68%), m.p. 143 – 144 °C, R_f = 0.25 ($CHCl_3$: MeOH, 5:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.58 – 1.64 (m, 2H, CH_2), 2.96 – 3.04 (m, 8H, 4 × CH_2), 3.23 (t, $J_{H\text{-}H}$ = 8.0 Hz, 4H, 2 × CH_2), 3.47 – 3.55 (m, 8H, 4 × CH_2), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_2), 41.4 (2 × CH_2), 44.0 (4 × CH_2), 66.4 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, 4 × CH_2), 152.4 (d, $^1J_{C\text{-}P}$ = 202.2 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 15.35. HRMS (ESI) for $C_{12}H_{24}N_4O_3P$ ($[M+H]^+$): calcd 303.1581, found 303.1572. IR (KBr): 3301, 2952, 2922, 2854, 2361, 2342, 1608, 1499, 1356, 1319, 1299, 1259, 1176, 1112, 1089, 962, 915, 846, 740, 700, 611, 554, 502 cm^{-1}.

*Di(diethylamino)(1,4,5,6-tetrahydropyrimidin-2-yl)phosphine oxide (**4e**).* The general procedure **B** was followed. Purification by column chromatography afforded product as colorless oil (246

mg, 65%), R_f = 0.31 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (t, J_{H-H} = 7.0 Hz, 12H, 4 × CH_3), 1.63 – 1.70 (m, 2H, CH_2), 2.96 – 3.05 (m, 8H, 4 × CH_2), 3.26 (t, J_{H-H} = 6.5 Hz, 4H, 2 × CH_2), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 14.0 (4 × CH_3), 19.6 (CH_2), 38.2 (d, $^2J_{C-P}$ = 4.0 Hz, 4 × CH_2), 41.2 (d, $^3J_{C-P}$ = 9.1 Hz, 2 × CH_2), 156.0 (d, $^1J_{C-P}$ = 185.1 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 16.99. HRMS (ESI) for $C_{12}H_{28}N_4OP$ ([M+H]$^+$): calcd 275.1995, found 275.2006.

*(Methylphenylamino)(azepano)(1,4,5,6-tetrahydropyrimidin-2-yl)phosphi-ne oxide (**4f**)*. The general procedure **B** was followed. Purification by column chromatography afforded product as pale yellow oil (318 mg, 68%), R_f = 0.31 (CH_2Cl_2 : MeOH, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 – 1.25 (m, 8H, 4 × CH_2), 1.98 – 1.81 (m, 2H, CH_2), 3.29 – 3.04 (m, 7H, 2 × CH_2 + CH_3), 3.50 (t, J_{H-P} = 5.5 Hz, 4H, 2 × CH_2), 7.18 (t, J_{H-H} = 7.6 Hz, 1H, CH), 7.30 (t, J_{H-H} = 7.6 Hz, 2H, 2 × CH), 7.58 (d, J_{H-P} = 7.6 Hz, 2H, 2 × CH), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.7 (CH_2), 26.4 (2 × CH_2), 29.4 (d, $^3J_{C-P}$ = 3.2 Hz, 2 × CH_2), 38.1 (d, $^2J_{C-P}$ = 5.8 Hz, 2 × CH_2), 39.5 (d, $^3J_{C-P}$ = 5.3 Hz, 2 × CH_2), 47.4 (d, $^2J_{C-P}$ = 3.3 Hz, CH_3), 127.5 – 126.5 (m, 4 × CH), 129.4 (CH), 142.4 (d, $^2J_{C-P}$ = 3.7 Hz, C), 158.3 (d, $^1J_{C-P}$ = 159.8 Hz, C). ^{31}P NMR (121 MHz, $CDCl_3$): δ 10.53. HRMS (ESI) for $C_{17}H_{28}N_4OP$ ([M+H]$^+$): calcd 335.1995, found 335.1986.

*(5,5-Dimethyl-1,4,5,6-tetrahydropyrimidin-2-yl)dimorpholinopho-sphine oxide (**4g**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as pale yellow solid (263 mg, 57%), m.p. 124 – 125 ^{o}C, R_f = 0.15 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (s, 6H, 2 × CH_3), 2.89 (s, 4H, 2 × CH_2), 3.00 – 3.05 (m, 8H, 4 × CH_2), 3.49 – 3.53 (m, 8H, 4 × CH_2), signal of NH group was not observed. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 25.3 (2 × CH_3), 25.9 (C), 44.4 (4 × CH_2), 53.7 (2× CH_2), 66.8 (d, $^2J_{C-P}$ = 5.0 Hz, 4 × CH_2), 151.7 (d, $^1J_{C-P}$ = 201.2 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 14.41. HRMS (ESI) for $C_{14}H_{28}N_4O_3P$ ([M+H]$^+$): calcd 331.1894, found 331.1887. IR (KBr): 3274, 2964, 2906, 2854,

1607, 1492, 1466, 1387, 1356, 1283, 1239, 1208, 1198, 1181, 1113, 1091, 967, 916, 844, 737, 308, 617, 507, 477, 453 cm^{-1}.

*1-(Dimorpholinophosphoryl)-N-(2-((5-nitropyridin-2-yl)amino)ethyl)methanethioamide (**5a**)*. A mixture of N^1-(5-nitropyridin-2-yl)ethane-1,2-diamine (0.17 g, 0.94 mmol, 1.5 equiv) and elemental sulfur (0.10 g, 3.13 mmol, 5 equiv) in DMF (2.0 mL) was stirred for 30 min at r.t. After triethylamine (0.40 mL, 2.88 mmol, 4.6 equiv) and 4,4'-chloromethylphosphonoyl-bis-morpholine (0.17 g, 0.63 mmol, 1 equiv) were added and resulting mixture was stirred for 5 h at 45 °C in an oil bath. Resulting mixture was concentrated under reduced pressure and residue was extracted with $CHCl_3$ (3 × 30 mL). Combined organic fraction was concentrated under reduced pressure and product was isolated by column chromatography (eluent $CHCl_3$ → $CHCl_3$:MeOH, 60:1) to get product as yellow solid (42 mg, 15%) with m.p. 180 – 181 °C, R_f = 0.60 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.92 – 3.08 (m, 8H, 4 × CH_2), 3.44 – 3.55 (m, 8H, 4 × CH_2), 3.68 – 3.78 (m, 2H, CH_2), 3.82 – 3.89 (m, 2H, CH_2), 6.56 (d, J_{H-H} = 8.0 Hz, 1H, CH), 8.12 (d, J_{H-H} = 8.0 Hz, 1H, CH), 8.22 (br. s, 1H, NH), 8.92 (s, 1H, CH), 10.71 (br. s, 1H, NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 39.0 (CH_2), 44.8 (4 × CH_2), 45.5 (CH_2), 66.5 (d, $^2J_{C-P}$ = 5.0 Hz, 4 × CH_2), 109.2 (CH), 132.3 (CH), 135.0 (C), 147.2 (CH), 161.1 (C), 196.5 (d, $^1J_{C-P}$ = 140.9 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 12.96. HRMS (ESI) for $C_{16}H_{26}N_6O_5PS$ ($[M+H]^+$): calcd 445.1418, found 445.1418. IR (KBr): 3295, 3244, 3187, 3116, 3083, 2962, 2914, 2849, 1612, 1585, 1545, 1500, 1478, 1332, 1293, 1255, 1186, 1113, 1090, 1006, 970, 911, 851, 733, 711, 660, 595, 514 cm^{-1}.

*N-(4-Aminobutyl)-1-(dimorpholinophosphoryl)methane-thioamide (**5b**)*. The general procedure **A** was followed. Purification by column chromatography afforded product as viscous yellow oil (331 mg, 68%), R_f = 0.12 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30 – 1.37 (m, 2H, CH_2), 1.57 – 1.63 (m, 2H, CH_2), 2.53 (t, J_{H-H} = 8.0 Hz, 2H, CH_2), 2.98 – 3.12 (m, 8H, 4 × CH_2), 3.49 – 3.55 (m, 8H, 4 × CH_2), 3.61 (t, J_{H-H} = 8.0 Hz, 2H, CH_2), signals of NH and NH_2

groups were not observed. $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 24.8 (CH_2), 30.5 (CH_2), 41.3 (CH_2), 44.9 (4 × CH_2), 45.0 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, CH_2), 66.7 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, 4 × CH_2), 195.5 (d, $^{1}J_{C\text{-}P}$ = 143.9 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 13.15. HRMS (ESI) for $C_{13}H_{28}N_4O_3PS$ ($[M+H]^+$): calcd 351.1614, found 351.1606.

*N-(5-Aminopentyl)-1-(dimorpholinophosphoryl)methane-thioamide (**5c**).* The general procedure **A** was followed. Purification by column chromatography afforded product as viscous yellow oil (250 mg, 49%), R_f = 0.14 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.20 – 1.29 (m, 2H, CH_2), 1.30 – 1.37 (m, 2H, CH_2), 1.55 – 1.62 (m, 2H, CH_2), 2.52 (t, $J_{H\text{-}H}$ = 8.0 Hz, 2H, CH_2), 2.98 – 3.07 (m, 4H, 2 × CH_2), 3.07 – 3.12 (m, 4H, 2 × CH_2), 3.50 – 3.57 (m, 8H, 4 × CH_2), 3.62 (t, $J_{H\text{-}H}$ = 8.0 Hz, 2H, CH_2), signals of NH and NH_2 groups were not observed. $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6): δ 24.3 (CH_2), 27.0 (CH_2), 33.0 (CH_2), 39.7 (CH_2), 44.4 (4 × CH_2), 44.5 (d, $^{3}J_{C\text{-}P}$ = 15.0 Hz, CH_2), 66.7 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz, 4 × CH_2), 196.8 (d, $^{1}J_{C\text{-}P}$ = 135.0 Hz, C). ^{31}P NMR (243 MHz, DMSO-d_6): δ 13.01. HRMS (ESI) for $C_{14}H_{30}N_4O_3PS$ ($[M+H]^+$): calcd 365.1771, found 365.1769.

*N-(6-Aminohexyl)-1-(dimorpholinophosphoryl)me-thanethioamide (**5d**).* The general procedure **A** was followed. Purification by column chromatography afforded product as viscous yellow oil (359 mg, 68%), R_f = 0.19 ($CHCl_3$: MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.20 – 1.28 (m, 4H, 2 × CH_2), 1.28 – 1.37 (m, 2H, CH_2), 1.56 – 1.61 (m, 2H, CH_2), 2.52 (t, $J_{H\text{-}H}$ = 8.0 Hz, 2H, CH_2), 2.98 – 3.12 (m, 8H, 4 × CH_2), 3.49 – 3.58 (m, 8H, 4 × CH_2), 3.61 (t, $J_{H\text{-}H}$ = 8.0 Hz, 2H, CH_2), signals of NH and NH_2 groups were not observed. $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 26.5 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 33.1 (CH_2), 41.7 (CH_2), 44.3 (CH_2), 44.4 (4 × CH_2), 66.7 (d, $^{2}J_{C\text{-}P}$ = 4.0 Hz, 4 × CH_2), 195.8 (d, $^{1}J_{C\text{-}P}$ = 195.2 Hz, C). ^{31}P NMR (121 MHz, DMSO-d_6): δ 13.08. HRMS (ESI) for $C_{15}H_{32}N_4O_3PS$ ($[M+H]^+$): calcd 379.1927, found 379.1922.

General method for synthesis of compounds 6. Diamine **2** (0.43 mmol, 1.0 equiv) was added to the suspension of chloromethylphosphonic acid bisdiethyl amide **1** (100 mg, 0.43 mmol, 1.0

equiv), elemental sulfur (41 mg, 1.29 mmol, 3.0 equiv), and DIPEA (224 μL, 1.29 mmol, 3.0 equiv) in water (1 mL). The mixture was refluxed for 5 h in an oil bath until the complete conversion of phosphinic chloride (TLC monitoring). The resulted mixture was cooled to r.t., diluted with water (20 mL), carefully acidified with 2% HCl until pH 7 and extracted with CH_2Cl_2 (3 x 7 mL). Combined organic layers dried over Na_2SO_4, solvent was removed under reduced pressure and product was isolated by column chromatography.

N,N'-(Propane-1,3-diyl)bis(1-(bis(diethylamino)phos-phoryl)methanethioamide) ***(6a)***. The general procedure was followed using 31 mg (35 μL) of propane-1,3-diamine. Purification by column chromatography (eluent CH_2Cl_2 – MeOH, 1:0 → 50:1) afforded product as a yellow solid (65 mg, 58%), m.p. 151 – 153 °C, R_f = 0.19 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (br. s, 2H, 2 × NH), 3.84 – 3.70 (m, 4H, 2 × CH_2), 3.14 (dq, $J_{H\text{-}P}$ = 10.7 Hz, $J_{H\text{-}H}$ = 7.1 Hz, 16H, 8 × CH_2), 2.16 – 1.99 (m, 2H, CH_2), 1.10 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 199.7 (d, $^1J_{C\text{-}P}$ = 142.2 Hz, 2 × C), 42.2 (d, $^3J_{C\text{-}P}$ = 7.1 Hz, 2 × CH_2), 38.6 (d, $^2J_{C\text{-}P}$ = 3.9 Hz, 8 × CH_2), 26.2 (CH_2), 13.5 (d, $^3J_{C\text{-}P}$ = 2.9 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.03. HRMS (ESI) for $C_{21}H_{49}N_6O_2P_2S_2$ ($[M+H]^+$): calcd 543.2824, found 543.2828.

N,N'-(2,2-Dimethylpropane-1,3-diyl)bis(1-(bis(diethylamino)phosphoryl)methanethio-amide) ***(6b)***. The general procedure was followed using 42 mg (50 μL) of 2,2-dimethylpropane-1,3-diamine. Purification by column chromatography (eluent CH_2Cl_2 : MeOH, 1:0 → 75:1) afforded product as a yellow solid (23 mg, 19%), m.p. 158 – 160 °C, R_f = 0.31 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.86 (br. s, 2H, 2 × NH), 3.69 (d, $J_{H\text{-}P}$ = 6.0 Hz, 2H, 2 × CH_2), 3.16 (dq, $J_{H\text{-}P}$ = 17.2 Hz, $J_{H\text{-}H}$ = 7.6 Hz, 16H, 8 × CH_2), 1.11 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3), 1.09 (s, 6H, 2 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 200.5 (d, $^1J_{C\text{-}P}$ = 142.5 Hz, 2 × C), 51.4 (d, $^3J_{C\text{-}P}$ = 7.1 Hz, 2 × CH_2), 38.7 (d, $^2J_{C\text{-}P}$ = 4.1 Hz, 8 × CH_2), 38.2 (C), 23.8 (2 × CH_3),

13.5 (d, $^{3}J_{C\text{-}P}$ = 3.0 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.37. HRMS (ESI) for $C_{23}H_{53}N_6O_2P_2S_2$ ([M+H]$^+$): calcd 571.3141, found 571.3141.

N,N'-(Butane-1,4-diyl)bis(1-(bis(diethylamino)-phosphoryl)methanethioamide) ***(6c)***. The general procedure was followed using 37 mg (42 μL) of bytane-1,4-diamine. Purification by column chromatography (eluent CH_2Cl_2 : MeOH, 1:0 → 75:1) afforded product as a yellow solid (46 mg, 40%), m.p. 168 – 170 °C, R_f = 0.30 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.59 (br. s, 2H, 2 × NH), 3.77 – 3.64 (m, 4H, 2 × CH_2), 3.12 (dq, $J_{H\text{-}P}$ = 10.7 Hz, $J_{H\text{-}H}$ = 7.1 Hz, 16H, 8 × CH_2), 1.81 – 1.69 (m, 4H, 2 × CH_2), 1.09 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 199.2 (d, $^{1}J_{C\text{-}P}$ = 141.9 Hz, 2 × C), 44.4 (d, $^{3}J_{C\text{-}P}$ = 7.1 Hz, 2 × CH_2), 38.6 (d, $^{2}J_{C\text{-}P}$ = 4.1 Hz, 8 × CH_2), 29.7 (CH_2), 25.1 (CH_2), 13.4 (d, $^{3}J_{C\text{-}P}$ = 3.0 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.92. HRMS (ESI) for $C_{22}H_{51}N_6O_2P_2S_2$ ([M+H]$^+$): calcd 557.2982, found 557.2985.

N,N'-(Pentane-1,5-diyl)bis(1-(bis(diethylamino)-phosphoryl)methanethioamide) ***(6d)***. The general procedure was followed using 42 mg (49 μL) of pentane-1,5-diamine. Purification by column chromatography (eluent CH_2Cl_2 : MeOH, 1:0 → 75:1) afforded product as a yellow solid (74 mg, 62%), m.p. 96 – 98 °C, R_f = 0.23 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (br. s, 2H, 2 × NH), 3.74 – 3.60 (m, 4H, 2 × CH_2), 3.13 (dq, $J_{H\text{-}P}$ = 10.7 Hz, $J_{H\text{-}H}$ = 7.1 Hz, 16H, 8 × CH_2), 1.82 – 1.64 (m, 4H, 2 × CH_2), 1.54 – 1.36 (m, 2H, CH_2), 1.10 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 199.0 (d, $^{1}J_{C\text{-}P}$ = 141.7 Hz, 2 × C), 44.7 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz, 2 × CH_2), 38.6 (d, $^{2}J_{C\text{-}P}$ = 4.0 Hz, 8 × CH_2), 27.2 (2 × CH_2), 24.4 (CH_2), 13.4 (d, $^{3}J_{C\text{-}P}$ = 2.9 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.07. HRMS (ESI) for $C_{23}H_{53}N_6O_2P_2S_2$ ([M+H]$^+$): calcd 571.3156, found 571.3141.

N,N'-(Hexane-1,6-diyl)bis(1-(bis(diethylamino)-phosphoryl)methanethioamide) ***(6e)***. The general procedure was followed using 48 mg of hexane-1,6-diamine. Purification by column chromatography (eluent CH_2Cl_2 : MeOH, 1:0 → 75:1) afforded product as a yellow solid (96

mg, 79%), m.p. 110 – 112 °C, R_f = 0.31 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (br. s, 2H, 2 × NH), 3.70 – 3.55 (m, 4H, 2 × CH_2), 3.10 (dq, $J_{H\text{-}P}$ = 10.8 Hz, $J_{H\text{-}H}$ = 7.1 Hz, 16H, 8 × CH_2), 1.73 – 1.56 (m, 4H, 2 × CH_2), 1.45 – 1.31 (m, 4H, 2 × CH_2), 1.07 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 198.8 (d, $^1J_{C\text{-}P}$ = 141.8 Hz, 2 × C), 44.8 (d, $^3J_{C\text{-}P}$ = 6.9 Hz, 2 × CH_2), 38.6 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, 8 × CH_2), 27.4 (2 × CH_2), 26.6 (2 × CH_2), 13.4 (d, $^3J_{C\text{-}P}$ = 2.9 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.04. HRMS (ESI) for $C_{24}H_{55}N_6O_2P_2S_2$ ($[M+H]^+$): calcd 585.3309, found 585.3298.

N,N'-(Heptane-1,7-diyl)bis(1-(bis(diethylamino)-phosphoryl)methanethioamide) ***(6f)***. The general procedure was followed using 56 mg of heptane-1,7-diamine. Purification by column chromatography (eluent CH_2Cl_2 : MeOH, 1:0 → 75:1) afforded product as a yellow solid (91 mg, 71%), m.p. 108 – 110 °C, R_f = 0.21 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (br. s, 2H, 2 × NH), 3.77 – 3.60 (m, 4H, 2 × CH_2), 3.16 (dq, $J_{H\text{-}P}$ = 10.7 Hz, $J_{H\text{-}H}$ = 7.1 Hz, 16H, 8 × CH_2), 1.75 – 1.64 (m, 4H, 2 × CH_2), 1.45 – 1.34 (m, 2H, CH_2), 1.42 – 1.35 (m, 4H, 2 × CH_2), 1.12 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 198.8 (d, $^1J_{C\text{-}P}$ = 141.7 Hz, 2 × C), 45.0 (d, $^3J_{C\text{-}P}$ = 6.9 Hz, 2 × CH_2), 38.6 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, 8 × CH_2), 28.8 (CH_2), 27.5 (2 × CH_2), 26.9 (2 × CH_2), 13.4 (d, $^3J_{C\text{-}P}$ = 2.9 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.13. HRMS (ESI) for $C_{25}H_{57}N_6O_2P_2S_2$ ($[M+H]^+$): calcd 599.3460, found 599.3454.

N,N'-(Octane-1,8-diyl)bis(1-(bis(diethyl-amino)phosphoryl)methanethioamide) ***(6g)***. The general procedure was followed using 56 mg of octane-1,8-diamine. Purification by column chromatography (eluent CH_2Cl_2 : MeOH, 1:0 → 75:1) afforded product as a yellow solid (111 mg, 87%), m.p. 115 – 117 °C, R_f = 0.31 (CH_2Cl_2 : MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (br. s, 2H, 2 × NH), 3.67 – 3.52 (m, 4H, 2 × CH_2), 3.07 (dq, $J_{H\text{-}P}$ = 10.8 Hz, $J_{H\text{-}H}$ = 7.1 Hz, 16H, 8 × CH_2), 1.69 – 1.53 (m, 4H, 2 × CH_2), 1.35 – 1.22 (m, 8H, 2 × CH_2 + 2 × CH_2), 1.04 (t, $J_{H\text{-}H}$ = 7.1 Hz, 24H, 8 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 198.6 (d, $^1J_{C\text{-}P}$ = 141.8 Hz, 2 × C), 44.9 (d, $^3J_{C\text{-}P}$ = 6.9 Hz, 2 × CH_2), 38.6 (d, $^2J_{C\text{-}P}$ = 3.9 Hz, 8 × CH_2), 29.0 (2 × CH_2), 27.5 (2 ×

CH_2), 26.9 (2 × CH_2), 13.4 (d, $^3J_{C-P}$ = 2.9 Hz, 8 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.02. HRMS (ESI) for $C_{26}H_{59}N_6O_2P_2S_2$ ($[M+H]^+$): calcd 613.3607, found 613.3611.

Scaled-up synthesis of (4,5-dihydro-1*H*-imidazol-2-yl)dimorpholinophosphine oxide (3d). A mixture of 1,2-ethylenediamine **2a** (6.5 mL, 98 mmol, 14 equiv) and elemental sulfur (1.1 g, 35.0 mmol, 5 equiv) was stirred for 30 min at r.t. Phosphinic chloride **1d** (2.0 g, 7.0 mmol, 1 equv) was added and resulting mixture was additionally stirred for 7 h at 40 °C in an oil bath until the complete conversion of phosphinic chloride (TLC monitoring). The resulted mixture was cooled to r.t. and viscous oil was extracted with MeOH (3 × 20 mL). Combined organic fraction was concentrated under reduced pressure and product was isolated by column chromatography (eluent $CHCl_3$: MeOH, 2:1) to get pale yellow solid (1.6 g, 79%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H,^{13}C, and ^{31}P NMR spectra for compounds **1,3-6** (PDF).

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yavolkova@gmail.com

ORCID

Igor V. Zavarzin 0000-0002-8194-5756

Yulia A. Volkova 0000-0001-8554-838X

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ **REFERENCES**

1. (a) Eto, M. *Organophosphorus Pesticides*. CRC press: 2018. (b) George, A.; Veis, A. Phosphorylated Proteins and Control Over Apatite Nucleation, Crystal Growth, and Inhibition. *Chem. Rev.* **2008**, *108*, 4670-4693. (c) Shengqian, M. *Elaboration and Applications of Metal-organic Frameworks*. World Scientific: 2018; Vol. 2. (d) Wendels, S.; Chavez, T.; Bonnet, M.; Salmeia, K. A.; Gaan, S. Recent Developments in Organophosphorus Flame Retardants Containing PC Bond and Their Applications. *Materials* **2017**, *10*, 784. (e) Walters, M. A. Metal Complexes in Reverse Micelles. *Novel Nanoscale Hybrid Materials*. John Wiley & Sons, Inc.: 2018, 301. (f) Leoncini, A.; Huskens, J.; Verboom, W. Ligands for *f*-Element Extraction Used in the Nuclear Fuel Cycle. *Chem. Soc. Rev.* **2017,** *46*, 7229-7273. (g) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine Organocatalysis. *Chem. Rev.* **2018,** *118*, 10049-10293.

2. Abás, S.; Erdozain, A. M.; Keller, B.; Rodríguez-Arévalo, S.; Callado, L. F.; García-Sevilla, J. A.; Escolano, C. Neuroprotective Effects of a Structurally New Family of High Affinity Imidazoline I_2 Receptor Ligands. *ACS Chem. Neur.* **2017**, *8*, 737-742.

3. (a) Abdou, W. M.; Barghash, R. F.; Bekheit, M. S. Carbodiimides – Key Mediators in the Synthesis of Novel Cytotoxic and Analgesic/Antiinflammatory Motifs Based on *α*-Amino-, Enaminophosphonates, and Azaphosphones. *RSC Adv.* **2013,** *3*, 1528-1540. (b) Abdou, W. M.; Barghash, R. F.; Bekheit, M. S. Carbodiimides in the Synthesis of Enamino- and *α*-Aminophosphonates as Peptidomimetics of Analgesic/Antiinflammatory and Anticancer Agents. *Arch. Pharm.* **2012,** *345*, 884-895.

4. (a) Grzywa, R.; Oleksyszyn, J.; Salvesen, G. S.; Drąg, M. Identification of Very Potent Inhibitor of Human Aminopeptidase N (CD13). *Bioorg. Med. Chem. Lett.* **2010,** *20*, 2497-2499. (b) Kočalka, P.; Rejman, D.; Vaněk, V.; Rinnová, M.; Tomečková, I.; Králíková, Š.; Petrová,

M.; Páv, O.; Pohl, R.; Buděšínský, M. Structural Diversity of Nucleoside Phosphonic Acids as a Key Factor in the Discovery of Potent Inhibitors of Rat T-Cell Lymphoma Thymidine Phosphorylase. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 862-865.

5. (a) Majhi, P. K.; Schnakenburg, G.; Streubel, R. From Bis(imidazole-2-thion-4-yl)phosphane to a Flexible P-bridged Bis(NHC) Ligand and its Silver Complex. *Dalt. Trans.* **2014,** *43*, 16673-16679. (b) Majhi, P. K.; Sauerbrey, S.; Leiendecker, A.; Schnakenburg, G.; Arduengo Iii, A. J.; Streubel, R. Synthesis and First Complexes of C 4/5 P-bifunctional Imidazole-2-thiones. *Dalt. Trans.* **2013,** *42*, 13126-13136.

6. (a) Wilkins, L. C.; Melen, R. L.; Platts, J. A.; Newman, P. D. Amidine Functionalized Phosphines: Tuneable Ligands for Transition Metals. *Dalt. Trans.* **2017,** *46*, 14234-14243. (b) Kariuki, B. M.; Newman, P. D. Asymmetric Cationic Phosphines: Synthesis, Coordination Chemistry, and Reactivity. *Inorg. Chem.* **2018,** *57*, 9554-9563.

7. (a) Härling, S. M.; Görls, H.; Krieck, S.; Westerhausen, M. Potassium-Mediated Hydrophosphorylation of Heterocumulenes with Diarylphosphane Oxide and Sulfide. *Inorg. Chem.* **2016,** *55*, 10741-10750. (b) Albuerne, I. G.; Alvarez, M. A.; García, M. E.; García-Vivó, D.; Ruiz, M. A. Chemistry of CS 2-and SCNPh-adducts of the Pyramidal Phosphinidene-Bridged Complex [$Mo_2Cp(\mu–\kappa^1:\kappa^1, \eta^5\text{-}PC_5H_4)(CO)_2(\eta^6\text{-}HMes^*)(PMe_3)$]. *Dalt. Trans.* **2017,** *46*, 3510-3525. (c) Olafsson, S. N.; Bjornsson, R.; Helgason, Ö.; Jonsdottir, S.; Suman, S. G. Coordination Geometry Determination of Stannane Compounds with Phosphinoyldithioformate Ligands Using Multinuclear NMR, Sn Mössbauer and DFT methods. *J. Organomet. Chem.* **2016,** *825*, 125-138.

8. (a) Lebouc, F.; Dez, I.; Gulea, M.; Madec, P.-J.; Jaffres, P.-A. Synthesis of Phosphorus-Containing Chitosan Derivatives. *Phosphorus, sulfur, silicon* **2009,** *184*, 872-889. (b) Langer, M.; Mueller, J. O.; Goldmann, A. S.; Schacher, F. H.; Barner-Kowollik, C. *α,ω*-Reactive

Building Blocks Based on a Dual Functional RAFT Agent for Thermal and Light-Induced Ligation. *ACS Macro Lett.* **2016,** *5*, 597-601.

9. (a) Tischer, T.; Goldmann, A. S.; Linkert, K.; Trouillet, V.; Börner, H. G.; Barner-Kowollik, C. Modular Ligation of Thioamide Functional Peptides Onto Solid Cellulose Substrates. *Adv. Func. Mat.* **2012,** *22*, 3853-3864. (b) Schenzel, A. M.; Moszner, N.; Barner-Kowollik, C. Self-Reporting Dynamic Covalent Polycarbonate Networks. *Polymer Chem.* **2017,** *8*, 414-420.

10. (a) Guo, W.-S.; Dou, Q.; Hou, J.; Wen, L.-R.; Li, M. Synthesis of 6-Phosphorylated Phenanthridines by Mn(II)-Promoted Tandem Reactions of 2-Biaryl Isothiocyanates with Phosphine Oxides. *J. Org. Chem.* **2017,** *82*, 7015-7022. (b) Guo, W.-S.; Gong, H.; Zhang, Y.-A.; Wen, L.-R.; Li, M. Fast Construction of 1,3-Benzothiazepines by Direct Intramolecular Dehydrogenative C–S Bond Formation of Thioamides Under Metal-Free Conditions. *Org. lett.* **2018,** *20*, 6394-6397. (c) Folgueiras-Amador, A. A.; Qian, X. Y.; Xu, H. C.; Wirth, T. Catalyst- and Supporting-Electrolyte-Free Electrosynthesis of Benzothiazoles and Thiazolopyridines in Continuous Flow. *Chem. Eur. J. A* **2018,** *24*, 487-491.

11. (a) Timperley, C. *Best Synthetic Methods: Organophosphorus (V) Chemistry*. Newnes: 2014. (b) Quin, L. D., *A Guide to Organophosphorus Chemistry*. John Wiley & Sons: 2000. (c) Nie, S.-Z.; Davison, R. T.; Dong, V. M. Enantioselective Coupling of Dienes and Phosphine Oxides. *J. Am. Chem. Soc.* **2018**, 140, 48, 16450-16454. (d) Hey-Hawkins, E.; Wonneberger, P.; König, N.; Kraft, F. B.; Sárosi, M. B. Access to 1-Phospha-2-azanorbornenes by Phospha-Aza-Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2019**, *4*, 3208-3211. (e) Wen, L.-R.; Sun, Y.-X.; Zhang, J.-W.; Guo, W.-S.; Li, M. Catalyst- and Solvent-Free Bisphosphinylation of Isothiocyanates: A Practical Method for the Synthesis of Bisphosphinoylaminomethanes. *Green Chem.* **2018,** *20*, 125-129. (f) Nishiyama, Y.; Hazama, Y.; Yoshida, S.; Hosoya, T. Synthesis of

Unsymmetrical Tertiary Phosphine Oxides *via* Sequential Substitution Reaction of Phosphonic Acid Dithioesters with Grignard Reagents. *Org. Lett.* **2017**, *19*, 3899-3902.

12. Le Roy-Gourvennec, S.; Masson, S., The Amination of Phosphonodithioformates; a Preparation of New Functionalized Phosphonates. *Phosphorus, Sulfur, Silicon* **1994,** *89*, 119-132.

13. (a) Rao, D. S.; Madhava, G.; Rasheed, S.; Thahir Basha, S.; Lakshmi Devamma, M. N.; Naga Raju, C. $CeCl_3$. $7H_2O$-SiO_2 Catalyzed Ultrasonicated Solvent-Free Synthesis of Carbamoyl/Carbamothioyl Phosphonates and Antimicrobial Activity Evaluation. *Phosphorus, Sulfur, Silicon* **2015**, *190*, 574-584. (b) Kaboudin, B.; Zahedi, H. A Novel and Convenient Method for Synthesis of Carbamoyl and Thiocarbamoyl Phosphonates. *Heteroatom Chem.* **2009,** *20*, 250-253. (c) Renard, P. Y.; Schwebel, H.; Vayron, P.; Josien, L.; Valleix, A.; Mioskowski, C. Easy Access to Phosphonothioates. *Chem. Eur. J. A* **2002,** *8*, 2910-2916.

14. (a) Pudovik, A. N.; Khairullin, V. K.; Vasyanina, M. A. Synthesis of *N,N*-dialkylchlorothioformamides and Their Reactions with Phosphorous Acid Esters. *J. Gen. Chem. USSR* **1988**, *58*, 1328-1331. (b) Bruns, A.; Hiller, W.; Kunze, U. NMR Spectra and Crystal Structure of Diphenyl (thio) phosphoryl-*N,N*-dimethylthioformamide. *Z. Naturforsch., B: J. Chem. Sci.* **1984**, *39*, 14-19.

15. Nguyen, T. B. Recent Advances in Organic Reactions Involving Elemental Sulfur. *Adv. Synth. Catal.* **2017,** *359*, 1066-1130.

16. Chen, X.; Wang, Z.; Huang, H.; Deng,G. Elemental Sulfur-Promoted Aerobic Cyclization of Ketones and Aliphatic Amines for Synthesis of Tetrasubstituted Imidazoles. *Adv. Synth. Catal*. **2018**, *360*, 4017-4022.

17. (a) Nguyen, T. B.; Ermolenko, L. ; Dean, W. A. ; Al-Mourabit, A. Benzazoles from Aliphatic Amines and o-Amino/Mercaptan/Hydroxyanilines: Elemental Sulfur as a Highly Efficient and Traceless Oxidizing Agent. *Org. Lett.*, **2012**, *14*, 5948-5951. (b) Nguyen, T. B.;

Ermolenko, L.; Al-Mourabit, A. Iron Sulfide Catalyzed Redox/Condensation Cascade Reaction Between 2-Amino/Hydroxy Nitrobenzenes and Activated Methyl Groups: a Straightforward Atom Economical Approach to 2-Hetaryl-Benzimidazoles and –Benzoxazoles. *J. Am. Chem. Soc.* **2013**, *135*, 118-121. (c) Nguyen, T. B. ; Le Bescont, J. ; Ermolenko, L. ; Al-Mourabit, A. Cobalt- and Iron-Catalyzed Redox Condensation of o-Substituted Nitrobenzenes with Alkylamines: A Step- and Redox-Economical Synthesis of Diazaheterocycles. *Org. Lett*. **2013**, *15*, 6218-6221. (d) Gan, H. Iron/S_8-catalyzed Redox Condensation of o-Nitroarenes with Arylmethyl Chloride: Synthesis of Benzimidazoles and Benzothiazoles. *Asian J. Org. Chem*. **2016**, *5*, 1111-1114.

18. Sheng, J.; Liu, J.; Zhao, H.; Zheng, L.; Wei, X. Metal-Free Synthesis of Imidazo[1,5-a]pyridines *via* Elemental Sulfur Mediated Sequential Dual Oxidative Csp^3–H Amination. *Org. Biomol. Chem*. **2018**, *16*, 5570-5574.

19. (a) Vanjari, R.; Guntreddi, T.; Kumara, S.; Singh, K. N. Sulphur Promoted $C(sp^3)$–$C(sp^2)$ Cross Dehydrogenative Cyclisation of Acetophenone Hydrazones with Aldehydes: Efficient Synthesis of 3,4,5-Trisubstituted 1*H*-Pyrazoles. *Chem. Commun*. **2015**, *51*, 366-369. (b) Adib, M.; Ayashi, N.; Heidari, F.; Mirzaei, P. Reaction Between 4-Nitro-1,3-diarylbutan-1-ones and Ammonium Acetate in the Presence of Morpholine and Sulfur: An Efficient Synthesis of 2,4-Diarylpyrroles. *Synlett* **2016**, *27*, 1738-1742.

20. Priebbenow, D. L.; Bolm, C., Recent Advances in the Willgerodt–Kindler Reaction. *Chem. Soc. Rev.* **2013,** *42*, 7870-7880.

21. Kozlov, M.; Kozlov, A.; Komkov, A.; Lyssenko, K.; Zavarzin, I.; Volkova, Y. Synthesis of Phosphoryl Thioamides *via* Three-Component Reaction of Phosphinic Chlorides with Amines and Sulfur. *Adv. Synth. Catal.* **2019**, 361, 12, 2904-2915.

22. Collins, D. J.; Drygala, P. F.; Swan, J. M. Organophosphorus Compounds. XX. Approaches to the Synthesis of 2,3-Dihydro-1*H*-1,2-benzazaphospholes Involving CC and CP Ring Closure. *Aus.J. Chem.* **1984**, *37*, 1009-1021.

23. Tsvetkov, E. N.; Malevannaya, R. A.; Kabachnik, M. I. Synthesis of Some Chloromethyl Phosphorus Compounds. *J. Gen. Chem. USSR* (Engl. Transl.), **1969**, 39, 1490-1492, Zhurnal Obshchei Khimii, **1969**, *39*, 1520-1524. CAN 71:113054.

24. Sowa, S.; Stankevič, M.; Flis, A.; Pietrusiewicz, K. M. Reduction of Tertiary Phosphine Oxides by BH_3 Assisted by Neighboring Activating Groups. *Synthesis* **2018**, *50*, 2106-2118.