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The Synthesis of Functionalized Dimethylphosphinoyl Cyclopropanes and Cyclobutanes

Abstract

A simple preparative approach to a series of functionalized dimethylphosphinoyl-containing cyclopropanes and cyclobutanes has been developed; it is based on cyclocondensation of dimethylphosphinoyl acetonitrile with 1,2- and 1,3-dibromoalkanes. Synthetic procedures for obtaining nitriles, amines and carboxylic acids containing in their structure small saturated cyclic rings of cyclopropane or cyclobutane and a dimethylphosphine oxide fragment, which are popular in drug design, have been developed.

Keywords: dimethylphosphine oxides; cyclopropane; cyclobutane; amines; carboxylic acids

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Синтез функціоналізованих диметилфосфіноіл циклопропанів і циклобутанів

Анотація

Розроблено зручний препаративний підхід до ряду функціоналізованих диметилфосфіноїлвмісних циклопропанів і циклобутанів, основою якого є циклоконденсація диметилфосфіноїлацетонітрилу з 1,2- та 1,3-дібромоеалканами. Розроблено синтетичні процедури для одержання нітрילів, амінів і карбонових кислот, які поєднують у своїй структурі популярні в drug-дизайні малі насичені циклічні системи циклопропану або циклобутану і диметилфосфіноксидний фрагмент.

Ключові слова: диметилфосфіноксиди; циклопропан; циклобутан; аміни; карбонові кислоти

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■ Introduction

The introduction of small saturated rigid carbocycles, specifically, cyclopropane (CyPr) and cyclobutane (CyBu), into the structure of biologically active compounds is an effective tool for improving their physicochemical and ADME (absorption, distribution, metabolism, excretion) properties [1]. The cyclopropyl group is present in more than 40 FDA-approved drugs used in the treatment of cancer, viral and bacterial infections, diabetes, CNS disorders, cardiovascular and

musculoskeletal system diseases, etc. (**Figure**, compounds **A–F**) [2]. The unique properties of the cyclopropane ring (coplanarity of carbon atoms, increased *p*-character of the C-C bonds and increased energy of the C-H bonds, high ring strain) enhance the resistance of molecules to metabolic degradation *in vivo*, lead to a decrease in their lipophilicity and conformational lability, and allow to apply cyclopropyl as an isostere of an olefin bond, as well as *i*Pr, Ph, and *tert*-Bu groups [3–7].

In turn, replacing the aliphatic part of the molecule with 1,2- or 1,3-disubstituted cyclobutane

ring allows to increase their conformational rigidity, prevents an undesirable *cis/trans*-isomerization and, as a result, leads to improved binding with the biological target (**Figure**, compounds **G–H**). Additionally, cyclobutane can act as a bioisoster of *gem*-dimethyl and aryl groups [1, 8]. Thus, the development of synthetic approaches to compounds that contain a mono-/polysubstituted cyclopropyl or cyclobutyl nucleus is definitely an important task of medicinal chemistry.

On the other hand, after the approval of the anticancer drug brigatinib (**Figure**, compound **I**) in 2017 [9, 10], which bears a dimethylphosphine oxide function, there is a growing interest in compounds modified by the $\text{Me}_2\text{P}(\text{O})$ moiety. Unlike phosphates and phosphonates, which are more usual in drug design [11], phosphine oxides represent a new and promising chapter of phosphorus-containing pharmaceuticals. It is due to the nature of the dimethylphosphine oxide group, which

provides better metabolic stability and bioavailability of the respective compounds as, unlike phosphoric acid derivatives, it does not undergo ionization at physiological pH. Moreover, dimethylphosphine oxides, usually, demonstrate high water solubility and the ability to form hydrogen bonds, which facilitates the transportation of the substances in the body, as well as their interaction with a target protein [12]. Taking into account that modern criteria for the design of pharmaceuticals favor molecules with an increased level of saturation (Fsp^3), [13–15] the development of new methods for obtaining saturated aliphatic dimethylphosphine oxides is an urgent task.

However, only a few examples of the synthesis of saturated building blocks with the $\text{Me}_2\text{P}(\text{O})$ function are currently known, and the vast majority of them have a heterocyclic (oxirane, azetidine, pyrrolidine, or piperidine) core [16–18]. Moreover, despite the high relevance of the presence of a cyclopropyl or cyclobutyl fragment

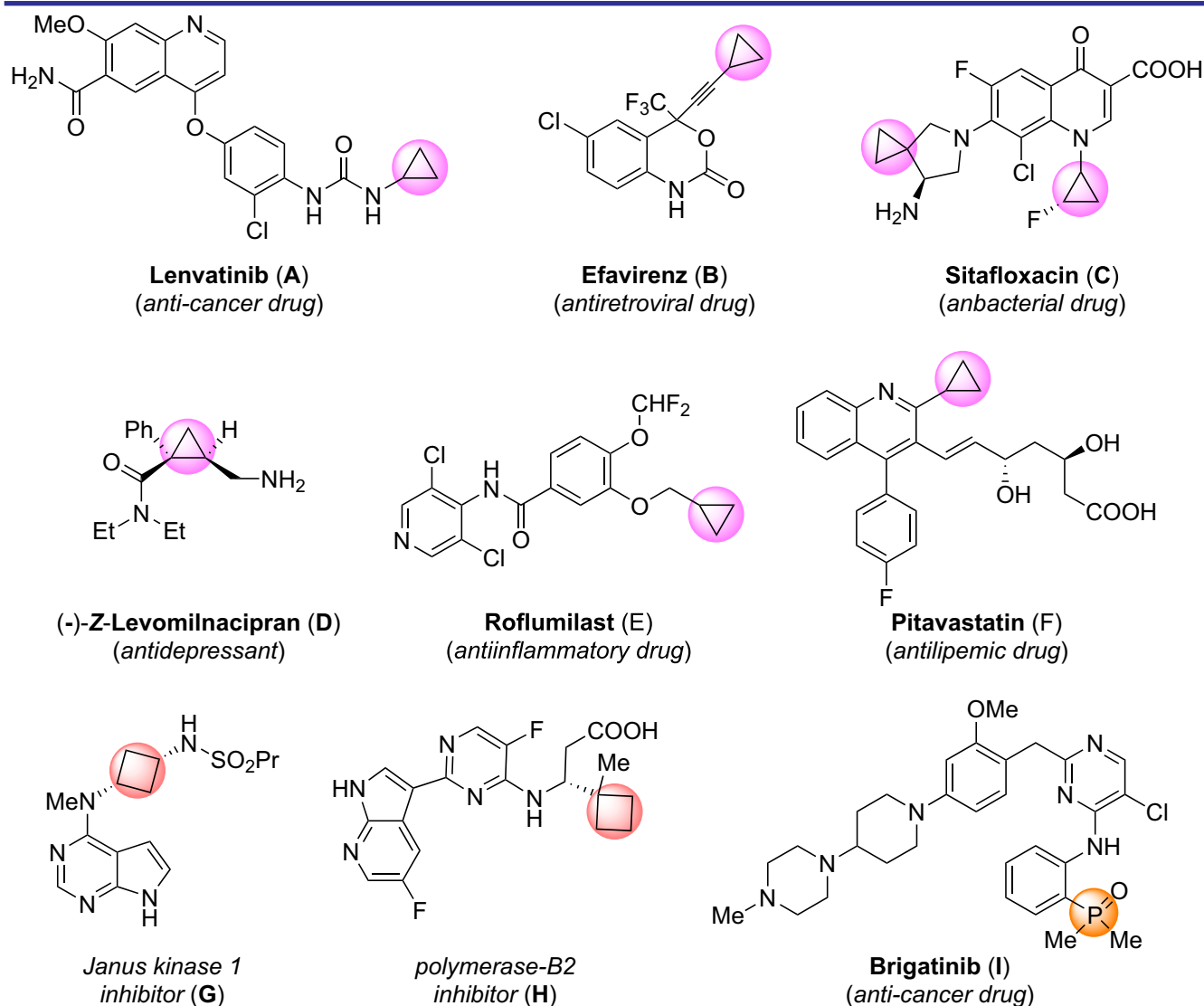


Figure. Approved drugs and drug candidates that contain a cyclopropyl-, cyclobutyl- or dimethylphosphine oxide moiety

in a molecule for drug discovery, any synthetic approaches to dimethylphosphinoyl derivatives of cyclopropane or cyclobutane were unknown. Therefore, this work aims to fill this gap and is devoted to the synthesis of dimethylphosphinoyl-containing cyclopropanes and cyclobutanes, bearing functional groups that can be used as building blocks for synthetic and medicinal chemistry.

■ Results and discussion

Previously, we developed a preparative method for the synthesis of dimethylphosphinoyl acetonitrile (**1**) based on the interaction of chloroacetonitrile with (trimethylsilyl)dimethylphosphinite generated *in situ* from dimethylphosphine oxide and trimethylsilyl chloride in the presence of the Hunig's base (**Scheme 1**) [16]. This approach allows obtaining phosphine oxide derived acetonitrile **1** with a high yield (65%) in multi-gram quantities (>50 g).

Dimethylphosphinoyl acetonitrile (**1**) contains a methylene component activated by two strong electron-withdrawing groups, which alkylation with 1,2- and 1,3-dibromoalkanes allows the formation of cyclopropyl and cyclobutyl rings, respectively. Indeed, the cyclocondensation of nitrile **1** with 1,2-dibromoethane and 1,3-dibromopropane occurs chemoselectively in the presence of sodium hydride (THF, 65 °C) leading to the formation of C-phosphinoyl-containing nitriles of cyclopropanoic (**2**) or cyclobutanoic (**3**) acids (**Scheme 2**).

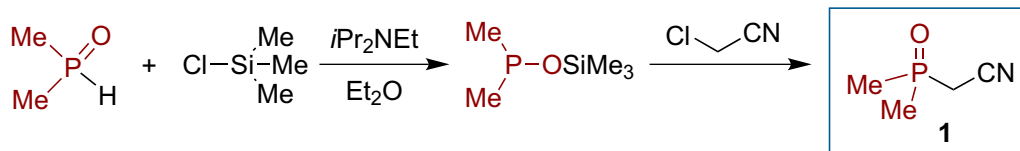
The high aqueous solubility of dimethylphosphine oxides is a greatly desired feature for improved drug bioavailability, but it frequently complicates isolation of these compounds and leads to a significant decrease in reaction yields. Considering this we could not use the standard

procedure, when isolating compounds **2** and **3**, and remove inorganic impurities from the reaction mixture by treating it with water. Instead, the inorganic precipitate was carefully (in order to prevent ignition of the remaining sodium hydride) filtered off, and the resulting solution was evaporated. The crude residue was recrystallized from MTBE to give pure nitriles **2** and **3** as low-melting hygroscopic crystals that could be stored for a long period in an anhydrous atmosphere.

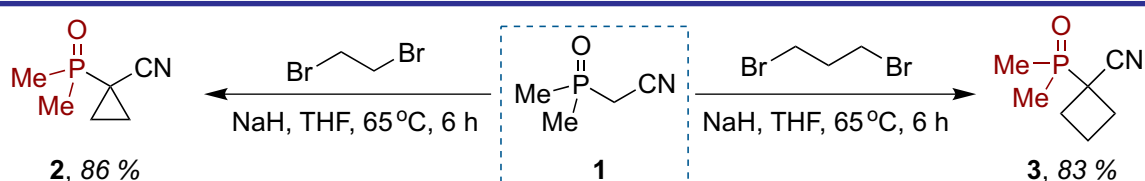
An interesting spectral characteristic of dimethylphosphinoyl cyanocyclopropane **2** is the shift of the doublet of the quaternary carbon atom in ^{13}C NMR spectrum, which is observed around 6.7 ppm. ($^1J_{\text{CP}} = 67$ Hz) compared to its CyBu-substituted analog **3**, for which the signal is located at 33.57 ppm. It is consistent with the previous data, which indicate a shift of the signals of cyclopropane ring carbon atoms, especially those bearing shielding substituents (CN, COOH), to a stronger field, due to the special nature of C-C bonds of the cyclopropane ring [19, 20].

The presence of the $\text{C}\equiv\text{N}$ group in cyclopropyl and cyclobutylphosphine oxides **2** and **3** allows using them as substrates for the synthesis of various classes of organic compounds, such as carboxylic acids, amides, amines, etc. Therefore, the next step of our study was to develop methods of reduction and hydrolysis of the nitrile function of nitriles **2**, **3** in order to obtain valuable dimethylphosphinoyl-substituted amines and acids as potential building blocks for drug discovery.

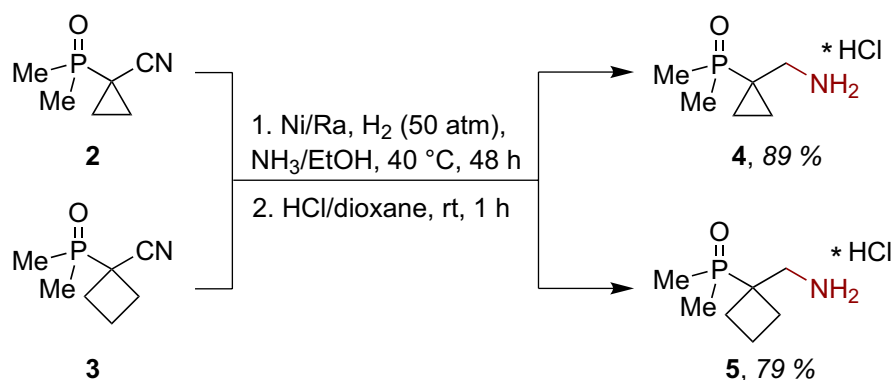
Thus, the reduction of the nitrile group of dimethylphosphine oxides **2** and **3** to the aminomethyl function was easily achieved by Ni-catalyzed hydrogenation in EtOH/ NH_3 solution resulting in the formation of dimethylphosphinoyl-substituted β -aminomethyl cyclopropane **4** and cyclobutane **5**



Scheme 1. The synthetic approach to dimethylphosphinoylacetonitrile reported previously [16]



Scheme 2. Dimethylphosphinoyl acetonitrile in the synthesis of dimethylphosphinoyl-substituted nitriles of cyclopropanoic and cyclobutanoic acids



Scheme 3. Reduction of the nitrile function of dimethylphosphinoyl cyanocyclopropane and cyclobutane

isolated as hydrochlorides with yields of 89% and 79%, respectively (**Scheme 3**).

The hydrolysis of the nitrile group of (CyPr) dimethylphosphine oxide **2** upon heating the substrate in the concentrated hydrochloric acid (90 °C, 6 hrs) was accompanied by the partial destruction of the cyclopropane cycle, and as a result, a complex mixture was formed. Instead, the hydrolysis of **2** with potassium hydroxide followed by careful acidification with an HCl/dioxane solution occurred selectively, and it allowed obtaining the target cyclopropylcarboxylic acid **6** isolated in an analytically pure state with the yield of 65% (**Scheme 4**).

In the case of (CyBu)dimethylphosphine oxide **3**, the hydrolysis with the concentrated hydrochloric acid proceeds chemoselectively and leads to a water-soluble cyclobutanecarboxylic acid **7**, isolated with the yield of 72%.

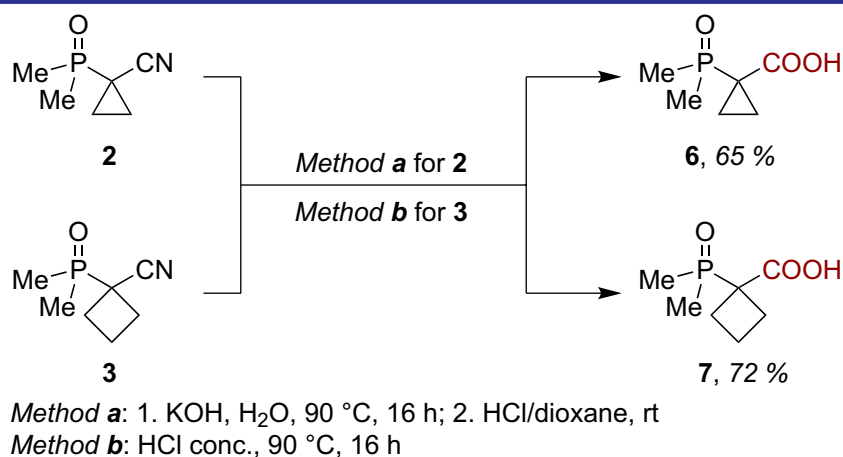
At the same time, dimethylphosphinoyl derivatives of cyclopropanoic and cyclobutanoic acids **6** and **7** can be involved in the Curtius reaction, which opens the way to geminal aminophosphine oxides. It has been found that the best results can be achieved when using diphenylphosphoryl azide (DPPA) in the presence of *tert*-butanol.

Thus, acids **6** and **7** react with DPPA in benzene or toluene at 90°C, the following treatment of the reaction mixture with *tert*-butyl alcohol leads to the formation of *N*-Boc aminophosphine oxides **8** and **9**. The following removal of the *tert*-butoxycarbonyl group was successfully achieved in mild conditions by the treatment with a HCl/dioxane solution, as a result the corresponding amines **10** and **11** were obtained as hydrochlorides with high yields (**Scheme 5**).

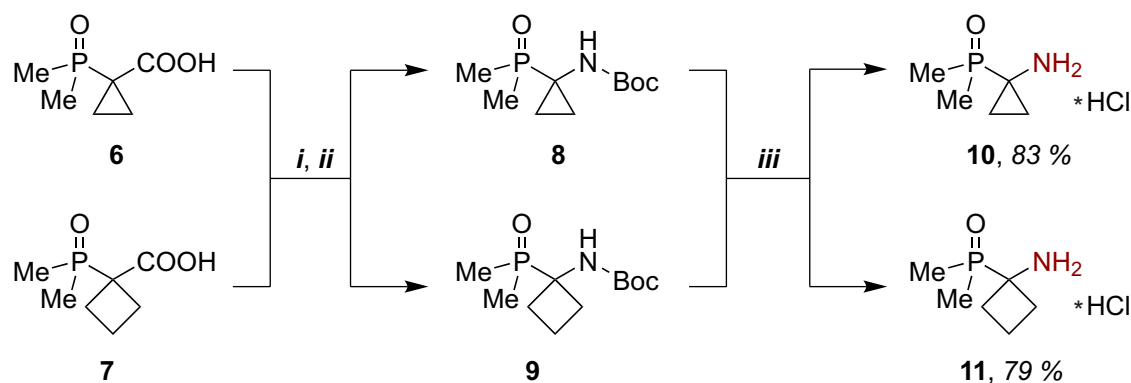
α - and β -Aminophosphine oxides **4**, **5** and **10**, **11** are promising substrates for the synthesis of biologically active compounds as they will allow the targeted introduction of both a dimethylphosphine oxide moiety and a saturated cyclopropane or cyclobutane framework into the structure of a molecule.

■ Conclusions

A preparative method for the synthesis of synthetically attractive dimethylphosphinoyl-substituted nitriles of cyclopropanoic and cyclobutanoic acids has been developed. Their potential in obtaining small saturated cyclic amines and carboxylic acids with a dimethylphosphine oxide



Scheme 4. The synthetic approach to dimethylphosphinoyl-containing cyclopropanoic and cyclobutanoic acids



i: DPPA, Et₃N, toluene, 90 °C, 2 h; *ii*: *t*BuOH, 90 °C, 3 h; *iii*: HCl/dioxane, rt, 2 h

Scheme 5. Dimethylphosphinoyl derivatives of cyclopropanoic and cyclobutanoic acids in the Curtius reaction

group that are interesting building blocks for medical chemistry and drug development has been shown.

Experimental part

NMR spectra were recorded on a Bruker Avance DRX 600 spectrometer (operating frequency 150.8 MHz for ¹³C); a Bruker Avance DRX 500 spectrometer (operating frequencies 499.9 MHz for ¹H, 125.7 MHz for ¹³C, 161.9 MHz for ³¹P); a Varian Unity Plus 400 instrument (operating frequencies 399.9 MHz for ¹H and 100.6 MHz for ¹³C); a Mercury Varian Unity Plus 300 instrument (operating frequencies 301.5 MHz for ¹H and 75.8 MHz for ¹³C). Chemical shifts were reported relative to internal TMS (¹H, ¹³C), and H₃PO₄ (³¹P) standards. Solvents were dried according to the standard procedures. Starting materials were purchased from Merck, Fluka, and Enamine Ltd. Melting points were uncorrected. The elemental analysis was carried out in the analytical laboratory of the Institute of Organic Chemistry, NAS of Ukraine.

The general procedure for the synthesis of compounds 2, 3

Nitrile 1 (10.0 g, 85.4 mmol) was added portionwise to a suspension of NaH (5.1 g, 213.5 mmol) in THF (100 mL) at 0–5 °C. The mixture was stirred at 20 °C for 1 h. Then the corresponding dibromoalkane (85.4 mmol) was added in one portion, and the mixture was refluxed for 5 h. After that it was cooled down to room temperature, the precipitate was filtered off, washed with CH₂Cl₂ (2×100 mL), the filtrate was concentrated *in vacuo*. The residue was recrystallized from MTBE (50 mL).

(1-Dimethylphosphinoyl)cyclopropane-1-carbonitrile (2)

A white crystalline solid. Yield – 10.5 g (86%). M. p. 76–78 °C. Anal. Calcd for C₆H₁₀NOP, %:

C 50.35, H 7.04, N 9.79. Found, %: C 50.28, H 7.09, N 9.89. ¹H NMR (399.9 MHz, CDCl₃), δ, ppm: 1.40–1.46 (2H, m, CH₂), 1.48–1.55 (2H, m, CH₂), 1.67 (6H, d, ²J_{HP} = 12.9 Hz, CH₃P). ¹³C NMR (125.7 MHz, CDCl₃), δ, ppm: 6.70 (d, ¹J_{CP} = 67 Hz, C_{CN}), 11.57 (d, ²J_{CP} = 8 Hz, CH₂), 14.84 (d, ¹J_{CP} = 70 Hz, CH₃P), 119.19 (d, ²J_{CP} = 4 Hz, C_{CN}). ³¹P NMR (161.9 MHz, CDCl₃), δ, ppm: 39.3.

(1-Dimethylphosphinoyl)cyclobutane-1-carbonitrile (3)

A yellowish crystalline solid. Yield – 11.2 g (83%). M. p. 67–68 °C. Anal. Calcd. for C₇H₁₂NOP, %: C 53.50, H 7.70, N 8.91. Found, %: C 53.35, H 7.79, N 8.99. ¹H NMR (399.9 MHz, CDCl₃), δ, ppm: 1.53 (6H, d, ²J_{HP} = 12.5 Hz, CH₃P), 2.09–2.20 (1H, m, CH₂), 2.26–2.37 (1H, m, CH₂), 2.42–2.51 (2H, m, CH₂), 2.72–2.83 (2H, m, CH₂). ¹³C NMR (125.7 MHz, CDCl₃), δ, ppm: 12.08 (d, ¹J_{CP} = 70 Hz, CH₃P), 17.56 (d, ³J_{CP} = 8 Hz, CH₂), 25.87 (d, ²J_{CP} = 4 Hz, CH₂), 33.57 (d, ¹J_{CP} = 67 Hz, C_{CN}), 120.80 (d, ²J_{CP} = 4 Hz, C_{CN}). ³¹P NMR (161.9 MHz, CDCl₃), δ, ppm: 42.9.

The general procedure for the synthesis of compounds 4, 5

A mixture of nitrile 2 or 3 (52.7 mmol) and Ni/Ra (0.5 g) in NH₃/EtOH (25 mL) was hydrogenated at 50 atm. and 40 °C for 48 h. The catalyst was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was dissolved in MTBE (100 mL) and triturated with HCl/dioxane solution (20 mL). The precipitate was collected by filtration, washed with acetone (20 mL) and dried *in vacuo*.

(1-(Aminomethyl)cyclopropyl)dimethylphosphine oxide hydrochloride (4)

Compound 4 was obtained from nitrile 2 (7.5 g, 52.7 mmol) as a white crystalline solid with the yield of 89% (8.6 g).

M. p. 234–235 °C. Anal. Calcd. for C₆H₁₅ClNOP, %: C 39.25, H 8.23, Cl 19.31, N 7.63.

Found, %: C 39.37, H 8.16, Cl 19.22, N 7.67. ^1H NMR (399.9 MHz, DMSO- d_6), δ , ppm: 0.94–1.02 (4H, m, CH_2), 1.46 (6H, d, $^2J_{\text{HP}} = 13.0$ Hz, CH_3P), 2.99–3.08 (2H, m, CH_2), 8.15 (3H, br. s, $\text{NH}_2\cdot\text{HCl}$). ^{13}C NMR (75.8 MHz, DMSO- d_6), δ , ppm: 9.62 (s, CH_2), 13.86 (d, $^1J_{\text{CP}} = 70$ Hz, CH_3P), 15.82 (d, $^1J_{\text{CP}} = 94$ Hz, CP(O)Me_2), 42.58 (d, $^2J_{\text{CP}} = 5$ Hz, CH_2NH_2). ^{31}P NMR (161.9 MHz, DMSO- d_6), δ , ppm: 50.6.

(1-(Aminomethyl)cyclobutyl)dimethylphosphine oxide hydrochloride (5)

Compound **5** was obtained from nitrile **3** (8.3 g, 52.7 mmol) as a white crystalline solid with the yield of 79% (8.2 g).

M. p. 215–218 °C. Anal. Calcd. for $\text{C}_7\text{H}_{17}\text{ClNOP}$, %: C 42.54, H 8.67, Cl 17.94, N 7.09. Found, %: C 42.47, H 8.61, Cl 17.92, N 7.17. ^1H NMR (399.9 MHz, DMSO- d_6), δ , ppm: 1.53 (6H, d, $^2J_{\text{HP}} = 13.1$ Hz, CH_3P), 1.79–1.90 (1H, m, CH_2), 1.99–2.32 (5H, m, CH_2), 3.27 (2H, d, $^3J_{\text{HP}} = 13.1$ Hz, CH_2), 8.18 (3H, br. s, $\text{NH}_2\cdot\text{HCl}$). ^{13}C NMR (100.6 MHz, D_2O), δ , ppm: 10.58 (d, $^1J_{\text{CP}} = 67$ Hz, CH_3P), 15.03 (d, $J_{\text{CP}} = 8$ Hz, CH_2), 23.90 (d, $J_{\text{CP}} = 2$ Hz, CH_2), 37.62 (d, $^1J_{\text{CP}} = 67$ Hz, CP(O)Me_2), 43.38 (d, $^2J_{\text{CP}} = 5$ Hz, CH_2NH_2). ^{31}P NMR (161.9 MHz, DMSO- d_6), δ , ppm: 54.9.

(1-Dimethylphosphinoyl)cyclopropane-1-carboxylic acid (6)

Nitrile **2** (10 g, 69.9 mmol) was added to a solution of KOH (3.3 g, 139.7 mmol) in H_2O (50 mL), and the mixture was heated at 90 °C for 16 h. Then it was concentrated *in vacuo*, and HCl/dioxane (10 mL) was added to the residue. The suspension was triturated with ethanol (20 mL), and the precipitate was filtered off. The filtrate was evaporated, and the residue was triturated with acetone (2×20 mL), the precipitate was collected by filtration to give **6** as a white crystalline solid.

Yield – 7.4 g (65%). M. p. >170 °C (decomp.). Anal. Calcd. for $\text{C}_6\text{H}_{11}\text{O}_3\text{P}$, %: C 44.45, H 6.84. Found, %: C 44.56, H 6.81. ^1H NMR (399.9 MHz, DMSO- d_6), δ , ppm: 1.24–1.26 (4H, m, CH_2), 1.55 (6H, d, $^2J_{\text{HP}} = 13.6$ Hz, CH_3P), 12.89 (1H, br. s, COOH). ^{13}C NMR (75.8 MHz, DMSO- d_6), δ , ppm: 12.52 (s, CH_2), 15.67 (d, $^1J_{\text{CP}} = 74$ Hz, CH_3P), 28.49 (br. s, CCOOH), 172.52 (s, COOH). ^{31}P NMR (161.9 MHz, DMSO- d_6), δ , ppm: 39.3.

(1-Dimethylphosphinoyl)cyclobutane-1-carboxylic acid (7)

A solution of nitrile **3** (10 g, 63.6 mmol) in conc. HCl aqueous solution (50 mL) was heated at 90 °C for 16 h. After that the mixture was cooled down to room temperature, it was concentrated to dryness *in vacuo* and triturated with acetone (100 mL). The precipitate was filtered off, the

filtrate was concentrated *in vacuo* to dryness. The residue was triturated with MeCN (50 mL), and the precipitate was collected by filtration to give acid **7** as a white crystalline solid.

Yield – 8.1 g (72%). M. p. 234–235 °C. Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{O}_3\text{P}$, %: C 47.73, H 7.44. Found, %: C 47.87, H 7.42. ^1H NMR (399.9 MHz, DMSO- d_6), δ , ppm: 1.39 (6H, d, $^2J_{\text{HP}} = 13.0$ Hz, CH_3P), 1.84–1.95 (2H, m, CH_2), 2.39–2.50 (4H, m, CH_2), 12.82 (1H, br. s, COOH). ^{13}C NMR (125.7 MHz, DMSO- d_6), δ , ppm: 12.65 (d, $^1J_{\text{CP}} = 68$ Hz, CH_3P), 16.19 (d, $^3J_{\text{CP}} = 7$ Hz, CH_2), 25.70 (d, $^2J_{\text{CP}} = 4$ Hz, CH_2), 48.25 (d, $^1J_{\text{CP}} = 58$ Hz, CCOOH), 174.48 (d, $^2J_{\text{CP}} = 3$ Hz, COOH). ^{31}P NMR (161.9 MHz, DMSO- d_6), δ , ppm: 43.9.

The general procedure for the synthesis of compounds 10 and 11

Diphenylphosphoryl azide (10 g, 36.7 mmol, 7.8 mL) was added to a solution of the corresponding acid **6/7** (34.9 mmol) and Et_3N (3.9 g, 38.5 mmol, 5.4 mL) in toluene (200 mL) at 90 °C. The resulting mixture was heated at this temperature until the gas release stopped, then *tert*-butanol (13 g, 175.0 mmol, 16 mL) was added in one portion, and the mixture was heated for additional 3 h. The solvent was evaporated, dioxane (50 mL) was added to the residue, followed by KOH (7 g, 175.0 mmol), and the suspension was stirred at room temperature for 2 h. The precipitate was filtered off, the filtrate was triturated with HCl/dioxane (10 mL) for 2 hrs. The precipitate was collected by filtration, washed with acetone (2×50 mL) and dried *in vacuo*.

(1-Aminocyclopropyl)dimethylphosphine oxide hydrochloride (10)

Compound **10** was obtained from acid **6** (5.0 g, 34.9 mmol) as a white crystalline solid.

Yield – 4.7 g (79%). M. p. >198 °C (decomp.). Anal. Calcd. for $\text{C}_6\text{H}_{15}\text{ClNOP}$, %: C 35.41, H 7.73, Cl 20.91, N 8.26. Found, %: C 35.57, H 7.78, Cl 20.83, N 8.31. ^1H NMR (399.9 MHz, DMSO- d_6), δ , ppm: 1.10–1.19 (2H, m, CH_2), 1.38 (2H, d, $^3J_{\text{HP}} = 12.9$ Hz, CH_2), 1.59 (6H, d, $^2J_{\text{HP}} = 13.3$ Hz, CH_3P), 8.97 (3H, br. s, $\text{NH}_2\cdot\text{HCl}$). ^{13}C NMR (75.8 MHz, D_2O), δ , ppm: 9.61 (s, CH_2), 13.33 (d, $^1J_{\text{CP}} = 72$ Hz, CH_3P), 30.18 (d, $^1J_{\text{CP}} = 104$ Hz, CP(O)Me_2). ^{31}P NMR (161.9 MHz, DMSO- d_6), δ , ppm: 40.1.

(1-Aminocyclobutyl)dimethylphosphine oxide hydrochloride (11)

Compound **11** was obtained from acid **7** (5.0 g, 34.9 mmol) as a white crystalline solid.

Yield – 5.3 g (83%). M. p. >193 °C (decomp.). Anal. Calcd. for $\text{C}_6\text{H}_{15}\text{ClNOP}$, %: C 39.25, H 8.23, Cl 19.31, N 7.63. Found, %: C 39.39, H 8.28, Cl

19.33, N 7.61. ^1H NMR (399.9 MHz, $\text{DMSO-}d_6$), δ , ppm: 1.59 (6H, d, $^2J_{\text{HP}} = 13.1$ Hz, CH_3P), 1.73–1.87 (1H, m, CH_2), 2.00–2.10 (1H, m, CH_2), 2.34–2.49 (4H, m, CH_2), 9.23 (3H, d, $^3J_{\text{HP}} = 7.1$ Hz, NH_2^*HCl). ^{13}C NMR (75.8 MHz, $\text{DMSO-}d_6$), δ , ppm: 12.08 (d, $^1J_{\text{CP}} = 68$ Hz, CH_3P), 14.35 (s, CH_2), 26.55 (s, CH_2), 53.16 (d, $^1J_{\text{CP}} = 70$ Hz, CNH_2). ^{31}P NMR (161.9 MHz, $\text{DMSO-}d_6$), δ , ppm: 45.5.

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