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# A New Three-Component Pathway to the Production of Chlorin Ketazines. Optimized Functionalization Method of $13^1$-Keto Group of Pheophorbides

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*Attempts have been made recently by our research group to functionalize and modify the $13^1$-ketone group of phorbine derivatives via intermediate formation of the corresponding hydrazones. However, such an approach had a number of disadvantages, which were successfully eliminated in this work. We have synthesized various ketazines of methyl pyropheophorbide a (and its derivatives) via a three-component nucleophilic addition reaction. The in situ formed benzaldehyde hydrazones reacted at moderate temperatures with the carbonyl group at the $13^1$-position, which led to reproducible yields of previously unavailable products.*

**Keywords:** Chlorins, tetrapyrrole compounds, azines, ketazines, $13^1$-keto group modification.

# Новый трехкомпонентный подход к созданию хлориновых кетазинов. Оптимизированный метод функционализации $13^1$-кето группы феофорбидов

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*Ранее в нашей научной группе были предприняты попытки функционализации и модификации $13^1$-кетонной группы форбиновых производных через промежуточное образование соответствующих гидразонов. Однако, данный подход имел ряд недостатков, которые были успешно устранены в рамках настоящей работы. Нами были синтезированы различные кетазины метилового эфира пирофеофорбида а (и его производных) через трех-компонентную реакцию нуклеофильного присоединения. In situ образованные гидразоны бензальдегидов при умеренной температуре реагировали с карбонильной группой в $13^1$-положении, что приводило к воспроизводимым выходам ранее недоступных продуктов.*

**Ключевые слова:** Хлорины, тетрапиррольные соединения, азины, кетазины, модификация $13^1$-кето группы.

## Introduction

At present, tetrapyrrole compounds, and natural chlorins in particular, are widely used for various applications.[1] In most cases, chlorins and porphyrins with new unique photophysical and optical properties are required for these purposes. This is often achieved by chemical modification of the tetrapyrrole frame or its peripheral substituents. Due to the unique electron system of natural chlorins (Figure 1), their absorption spectra have an intense $Q_y$ absorption band, the position of which in the electronic absorption spectrum strongly depends on the nature of the substituents located along the *y* axis of the macrocycle. For example, it is well known that the introduction of electron-donor or electron-withdrawing substituents into the pyrrole rings A and C, as well as the

exocycle E, leads to a significant bathochromic shift of the $Q_y$ band.[2-4] Therefore, methyl pyropheophorbide *a* is a very promising starting material, since the presence of a reactive functional groups (vinyl and carbonyl) at the 3 and $13^1$ positions, allows one to easily introduce substituents of various nature and influence the properties of the whole molecule.

The formyl group at $3^1$ position of methyl pyropheophorbide *d*, and carbonyl keto group at $13^1$ position of all phorbine derivatives is a great opportunity to create azine and ketazine derivatives.[5-7] The introduction of substituents through the formation of an azine bridge can increase the antimicrobial, antibacterial, and antiproliferative activity of chlorine derivatives, which is also important for the development of effective photosensitizers.[8-10] Such activity of both symmetrical and unsymmetrical azines (aldazines and ketazines) has been demonstrated and used in various pharmacological studies.[11]

## Experimental

### *General*

Reactions were carried out under argon atmosphere, using commercially available reagents that were purchased and used as soon as received. Starting methyl pheophorbide *a* was obtained from commercial sources (spirulina). Heating reaction vessels was performed with oil bath. Column chromatography was performed using 40–63 μm silica gel, preparative thin layer chromatography (TLC) was performed using glass plates coated with 5–40 μm silica gel (5 mm thick). Reactions control was provided by TLC using aluminum-backed Silica Gel 60 F254 precoated plates. $^1$H and $^{13}$C NMR spectra were recorded with a Bruker Avance III 600 MHz spectrometer at 30 °C in $CDCl_3$. Chemical shifts are reported relative to signals of residual protons of solvents ($CDCl_3$–7.26 ppm). Mass spectra were recorded with UltrafleXtreme mass spectrometer (Bruker Daltonics) in a positive-ion mode using reflection mode with 20 kV voltage without matrix. Electronic absorption spectra were recorded with U-2900 (Hitachi) spectrophotometer in quartz rectangular cells of 10 mm path length at concentration $10^{-5}$ M in $CH_2Cl_2$.

### *Synthesis*

*Obtaining of anhydrous hydrazine*. The procedure included a double distillation of hydrazine monohydrate with NaOH in an argon flow. 1 step: 200 ml of hydrazine monohydrate was distilled with 150 g. of NaOH under argon atmosphere. 2 step: the second time hydrazine was distilled with 25 g. of NaOH under argon atmosphere.

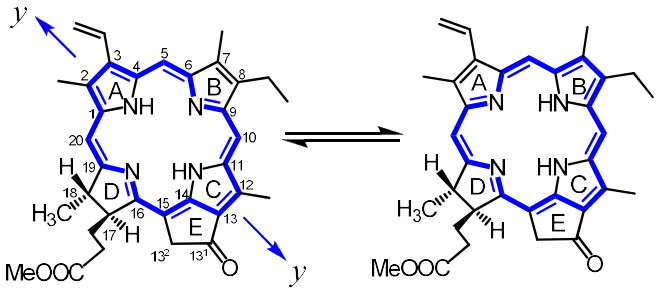



**Figure 1.** 20 π electron tetrapyrrole system of which 18 electrons are in any one localized pathway.

*Synthesis of methyl pyropheophorbide a, methyl pyropheophorbide d* and *methyl (E)-$3^2$-bromopyropheophorbide a* was carried out using known methods.[12,13] The synthesis of hydrazone **5** is also known and it was obtained following the corresponding procedure.[14]

*General procedure for the formation of unsymmetrical chlorin azines (**7**, **9a**, **9b**).* Trifluoroacetic acid (3 equiv.) was added to a solution of **1** (20 mg, 0.036 mmol, 1 equiv.) or **8** (20 mg, 0.032 mmol, 1 equiv.) in $CH_2Cl_2$ (3 mL). A mixture of dry hydrazine (1 equiv.) and aromatic aldehyde (1 equiv.) in methanol was added to the chlorin solution every 12 hours for 72 hours (6 times) at 30 °C (total amount of hydrazine and benzaldehyde added was 6 equivalents each). After the final addition, the reaction mixture was stirred for 12 hours at 30 °C until the reaction was complete. The reaction mixture was poured to a water solution of 0.01M $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined extracts were washed with water, dried over $Na_2SO_4$, and evaporated *in vacuo* to dryness. To remove excessive symmetrical azine benzaldehydes formed in the reaction, preliminary purification was carried out using thin-layer chromatography in ethanol (The required product was «at the start»). A subsequent purification was also carried out using thin layer chromatography in a $CH_2Cl_2$/EtOH system (100:2). The products were crystallized from $CH_2Cl_2$/hexane to afford **7**, **9a** and **9b**.

*Methyl mesopyropheophorbide a hydrazone (**2**)*. A methanol solution of dry hydrazine (18 μL, 0.562 mmol) and TFA (14 μL, 0.182 mmol) were added to a solution of methyl pyropheophorbide *a* (100 mg, 0.182 mmol) in $CH_2Cl_2$ (15 mL). The reaction was stirred for 96 h at 40 °C. The progress was monitored by TLC. The reaction mixture was poured to a water solution of 0.01M $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined extracts were washed with water, dried over $Na_2SO_4$, and evaporated *in vacuo* to dryness. The residue was redisolved in $CH_2Cl_2$ and purified by preparative thin-layer chromatography in a $CH_2Cl_2$/EtOH system (100:1). The product was crystallized from $CH_2Cl_2$/hexane to afford **2** (71 mg, 69%). *m/z* (SALDI) found: 564.4, 565.4, 566.4; calcd. for $C_{34}H_{40}N_6O_2$: 564.32 $[M]^+$, $C_{33}{}^{13}CH_{40}N_6O_2$: 565.32 $[M]^+$, $C_{32}{}^{13}C_2H_{40}N_6O_2$: 566.33 $[M]^+$. UV-Vis ($CH_2Cl_2$) $\lambda_{max}$ ($A_{rel}$) nm: 403 (1.00), 504 (0.18), 555 (0.06), 608 (0.10), 661 (0.75). $^1$H NMR ($CDCl_3$) $\delta_H$ ppm: 9.65 (1H, s, 10-H), 9.65 (1H, s, 5-H), 8.80 (1H, s, 20-H), 5.44 (1H, d, $J$ = 17.9 Hz, $13^2$-$CH_2{}^a$), 5.30 (1H, d, $J$ = 17.9 Hz, $13^2$-$CH_2{}^b$), 4.66 (1H, dq, $J$ = 7.4 Hz, $J$ = 1.7 Hz, 18-H), 4.48 (1H, m, 17-H), 4.01 (2H, q, $J$ = 7.8 Hz, $3^1$-$CH_2$), 3.85 (2H, q, $J$ = 7.8 Hz, $8^1$-$CH_2$), 3.71 (3H, s, $12^1$-$CH_3$), 3.63 (3H, s, $17^4$-$CH_3$), 3.46 (3H, s, $2^1$-$CH_3$), 3.43 (3H, s, $7^1$-$CH_3$), 2.79 (1H, m, $17^1$-$CH_2{}^a$), 2.63 (1H, m, $17^2$-$CH_2{}^a$), 2.40 (1H, m, $17^1$-$CH_2{}^b$), 2.26 (1H, m, $17^2$-$CH_2{}^b$), 1.88 (3H, d, $J$ = 7.4 Hz, $18^1$-$CH_3$), 1.83 (3H, t, $J$ = 7.8 Hz, $3^2$-$CH_3$), 1.80 (3H, t, $J$ = 7.8 Hz, $8^2$-$CH_3$), 0.16 and –2.83 (2H, each bs, NH×2). $^{13}$C NMR ($CDCl_3$) $\delta_C$ ppm: 173.8, 168.1, 160.7, 151.3, 150.7, 150.1, 144.8, 143.6, 140.6, 139.9, 139.6, 135.7, 134.7, 133.7, 129.1, 124.5, 105.0, 100.9, 97.1, 92.4, 52.7, 51.6, 49.6, 37.2, 30.8, 29.5, 23.7, 19.7, 19.6, 17.7, 17.3, 12.2, 11.5, 11.1.

*$13^1$-(4-Pyridine)hydrazono methyl mesopyropheophorbide a (**3**)*. Pyridine-4-carbaldehyde (25 μL, 0.256 mmol) was added to a solution of **2** (20 mg, 0.035 mmol) in $CH_2Cl_2$ (3 mL), and the mixture was stirred for 96 h at 30 °C. The reaction mixture was poured to water and extracted with $CH_2Cl_2$ several times. The combined organic layer was dried (using anhydrous $Ns_2SO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography in a $CH_2Cl_2$/EtOH system (100:1) and crystallized from $CH_2Cl_2$/hexane to afford **3** (12 mg, 52%). *m/z* (SALDI) found: 653.1, 654.1, 655.1; calcd. for $C_{40}H_{43}N_7O_2$: 653.34 $[M]^+$, $^{13}C^{12}C_{39}H_{43}N_7O_2$: 654.35 $[M]^+$, $^{13}C_2{}^{12}C_{38}H_{43}N_7O_2$: 655.35 $[M]^+$. UV-Vis ($CH_2Cl_2$) $\lambda_{max}$ ($A_{rel}$) nm: 415 (1.00), 508 (0.17), 538 (0.08), 615 (0.11), 671 (0.84). $^1$H NMR ($CDCl_3$) $\delta_H$ ppm: 9.59 (1H, s, 10-H), 9.44 (1H, s, 5-H), 8.82 (2H, m, ortho-H), 8.80 (1H, s, -N=CH- ), 8.65 (1H, s, 20-H), 7.91 (2H, m, meta-H), 5.80 (1H, d, $J$ = 19.8 Hz, $13^2$-$CH_2{}^a$), 5.67 (1H, d, $J$ = 19.8 Hz, $13^2$-$CH_2{}^b$), 4.58 (1H, m, 18-H), 4.46 (1H, m, 17-H),

3.93 (2H, q, $J$ = 7.8 Hz, $3^1$-$CH_2$), 3.78 (5H, m, 2-$CH_3$ and $8^1$-$CH_2$), 3.61 (3H, s, $17^2$-$CO_2CH_3$), 3.38 (3H, s, 12-$CH_3$), 3.35 (3H,s, 7-$CH_3$), 2.78 (1H, m, $17^1$-$CH_2^a$), 2.60 (1H, m, $17^2$-$CH_2^a$), 2.42 (1H, m, $17^1$-$CH_2^b$), 2.24 (1H, m, $17^2$-$CH_2^b$), 1.85 (3H, d, $J$ = 7,4 Hz, $18^1$-$CH_3$), 1.78 (6H, m, $3^2$-$CH_3$ and $8^2$-$CH_3$), 0.11 and –2.25 (2H, each bs, NH×2). $^{13}$C NMR ($CDCl_3$) $\delta_C$ ppm: 173.7, 170.0, 169.7, 160.4, 156.4, 153.3, 150.4, 150.3, 150.1, 146.2, 144.4, 142.6, 141.2, 141.0, 138.9, 135.7, 135.5, 131.8, 130.3, 127.2, 122.2, 106.6, 102.4, 96.4, 92.5, 52.0, 51.6, 49.9, 40.9, 30.8, 29.8, 29.7, 23.4, 19.6, 19.5, 17.6, 17.1, 12.6, 11.4, 11.0.

*$13^1$-(4-Pyridine)hydrazono methyl pyropheophorbide a (7)*. The reaction yield was 12 mg (51%), following the general procedure for aldehyde-derived hydrazone formation. *m/z* (SALDI) found: 651.1, 652.1, 653.1; calcd. for $C_{40}H_{41}N_7O_2$: 651.33 $[M]^+$, $^{13}C^{12}C_{39}H_{41}N_7O_2$: 652.33 $[M]^+$, $^{13}C_2{}^{12}C_{38}H_{41}N_7O_2$: 653.33 $[M]^+$. UV-Vis ($CH_2Cl_2$) $\lambda_{max}$ ($A_{rel}$) nm: 416 (1.00), 513 (0.17), 542 (0.08), 623 (0.09), 681 (0.69). $^1$H NMR ($CDCl_3$) $\delta_H$ ppm: 9.62 (2H, m, 10-H and 5-H), 8.80 (2H, m, ortho-H), 8.79 (1H, s, -N=CH-), 8.74 (1H, s, 20-H), 8.12 (1H, dd, $J$ = 11.5 Hz, $J$ = 17.8 Hz, $3^1$-H), 7.91 (2H, m, meta-H), 6.34 (1H, d, $J$ = 17.8 Hz, $3^2$-$H^a$), 6.21 (1H, d, $J$ = 11.5 Hz, $3^2$-$H^b$), 5.79 (1H, d, $J$ = 19.7 Hz, $13^2$-$CH_2^a$), 5.68 (1H, d, $J$ = 19.7 Hz, $13^2$-$CH_2^b$), 4.60 (1H, m, 18-H), 4.47 (1H, m, 17-H), 3.80 (3H, s, 2-$CH_3$), 3.78 (2H, q, $J$ = 7.9 Hz, $8^1$-$CH_2$), 3.61 (3H, s, $17^2$-$CO_2CH_3$), 3.50 (3H, s, 12-$CH_3$), 3.34 (3H, s, 7-$CH_3$), 2.79 (1H, m, $17^1$-$CH_2^a$), 2.61 (1H, m, $17^2$-$CH_2^a$), 2.42 (1H, m, $17^1$-$CH_2^b$), 2.26 (1H, m, $17^2$-$CH_2^b$), 1.86 (3H, d, $J$ = 7,5 Hz, $18^1$-$CH_3$), 1.76 (3H, t, $J$ = 7.9 Hz, $8^2$-$CH_3$), 0.10 and -2.29 (2H, each bs, NH×2). $^{13}$C NMR ($CDCl_3$) $\delta_C$ ppm: 173.7, 169.6, 169.5, 160.9, 156.4, 153.3, 150.7, 150.5, 150.0, 146.3, 144.3, 142.7, 140.2, 139.5, 136.2, 135.3, 134.7, 132.2, 130.5, 129.6, 127.6, 122.2, 122.1, 106.8, 102.2, 97.7, 93.1, 52.2, 51.6, 49.8, 41.0, 30.8, 29.8, 29.7, 23.4, 19.6, 17.5, 12.6, 12.2, 11.4.

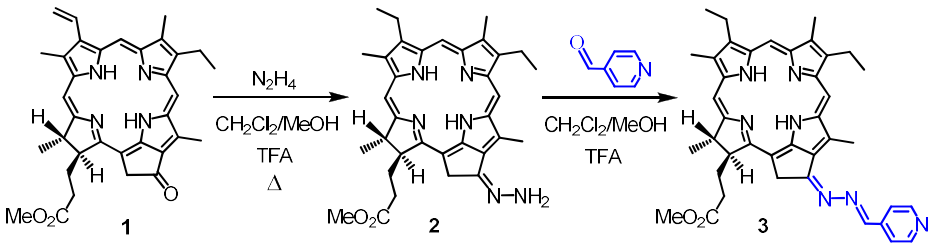
*$13^1$-(4-Pyridine)hydrazono methyl (E)-$3^2$-bromopyropheophorbide a (**9a**)*. The reaction yield was 11 mg (47%), following the general procedure for aldehyde-derived hydrazone formation. *m/z* (SALDI) found: 729.0, 730.0, 731.0, 732.0, 733.0; calcd. for $^{79}BrC_{40}H_{40}N_7O_2$: 729.24 $[M]^+$, $^{79}Br^{13}C^{12}C_{39}H_{40}N_7O_2$: 730.25 $[M]^+$, $^{81}BrC_{40}H_{40}N_7O_2$ and $^{79}Br^{13}C_2{}^{12}C_{38}H_{40}N_7O_2$:731.24 $[M]^+$, $^{81}Br^{13}C^{12}C_{39}H_{40}N_7O_2$: 732.24, $^{81}Br^{13}C_2{}^{12}C_{38}H_{40}N_7O_2$: 733.25. UV-Vis ($CH_2Cl_2$) $\lambda_{max}$ ($A_{rel}$) nm: 392 (1.00), 513 (0.15), 545 (0.17), 628 (0.07), 685 (0.51). $^1$H NMR ($CDCl_3$) $\delta_H$ ppm: 9.60 (1H, s, 10-H), 9.45 (1H, s, 5-H), 8.81 (2H, m, ortho-H), 8.78 (1H, s, -N=CH-), 8.74 (1H, s, 20-H), 8.45 (1H, d, $J$ = 14.1 Hz, $3^1$-H), 7.79 (2H, m, meta-H), 7.31 (1H, d, $J$ = 14.1 Hz, $3^2$-H), 5.76 (1H, d, $J$ = 19.6 Hz, $13^2$-$CH_2^a$), 5.65 (1H, d, $J$ = 19.6 Hz, $13^2$-$CH_2^b$), 4.61 (1H, m, 18-H), 4.47 (1H, m, 17-H), 3.77 (5H, m, 2-$CH_3$ and $8^1$-$CH_2$), 3.62 (3H, s, $17^2$-$CO_2CH_3$), 3.44 (3H, s, 12-$CH_3$), 3.32 (3H, s, 7-$CH_3$), 2.79 (1H, m, $17^1$-$CH_2^a$), 2.61 (1H, m, $17^2$-$CH_2^a$), 2.41 (1H, m, $17^1$-$CH_2^b$), 2.28 (1H, m, $17^2$-$CH_2^b$), 1.87 (3H, d, $J$ = 7,5 Hz, $18^1$-$CH_3$), 1.76 (3H, t, $J$ = 7.8 Hz, $8^2$-$CH_3$), 0.11 and –2.43 (2H, each bs, NH×2). $^{13}$C NMR ($CDCl_3$) $\delta_C$ ppm: 173.5, 169.3, 169.0, 161.3, 156.6, 152.9, 151.0, 150.2, 146.3, 144.3, 142.4, 139.9, 139.5, 136.3, 133.6, 132.7, 130.1, 127.9, 122.1, 111.7, 107.0, 102.0, 97.4, 93.3, 52.4, 51.5, 49.7, 40.9, 30.9, 29.8, 29.7, 23.4, 19.6, 17.4, 12.5, 12.4, 11.3.

*$13^1$-(4-Bromobenzylidene)hydrazono methyl (E)-$3^2$-bromopyropheophorbide a (**9b**)*.The reaction yield was 12 mg (47%) following the general procedure for aldehyde-derived hydrazone formation. *m/z* (SALDI) found: 805.9, 806.9, 807.9, 808.9, 809.9, 810.9, 811.9; calcd. for $^{12}C_{41}H_{40}N_6O_2{}^{79}Br_2$: $[M]^+$, 806.16, $^{13}C^{12}C_{40}H_{40}N_6O_2{}^{79}Br_2$: $[M]^+$, 807.16; $^{12}C_{41}H_{40}N_6O_2{}^{79}Br^{81}Br$: $[M]^+$, 808.16; $^{13}C^{12}C_{40}H_{40}N_6O_2{}^{79}Br^{81}Br$: $[M]^+$, 809.16; $^{12}C_{41}H_{40}N_6O_2{}^{81}Br_2$: $[M]^+$, 810.16; $^{13}C^{12}C_{40}H_{40}N_6O_2{}^{81}Br_2$: $[M]^+$, 811.16, $^{13}C_2{}^{12}C_{39}H_{40}\ N_6O_2{}^{81}Br_2$: $[M]^+$, 812.16. UV-Vis ($CH_2Cl_2$) $\lambda_{max}$ ($A_{rel}$) nm: 429 (1.00), 516 (0.21), 546 (0.03), 629 (0.05), 683 (0.72). $^1$H NMR ($CDCl_3$) $\delta_H$ ppm: 9.66 (1H, s, 10-H), 9.54 (1H, s, 5-H), 8.83 (1H, s, $13^1$-N=CH-), 8.78 (1H, s, 20-H), 8.52 (1H, d, $J$ = 14.1 Hz, $3^1$-H), 7.94 (2H, d, $J$ = 8.2 Hz, $13^1$-meta-H × 2), 7.70 (2H, d, $J$ = 8.2 Hz, $13^1$-ortho-H × 2), 7.36 (1H, d, $J$ = 14.1 Hz, $3^2$-H), 5.78 (1H, d, $J$ = 19.7 Hz, $13^2$-$H^a$), 5.68 (1H, d, $J$ = 19.7 Hz, $13^2$-$H^b$), 4.62 (1H, m, 18-H), 4.50 (1H, m, 17-H), 3.81 (5H, m, 12-$CH_3$ and $8^1$-$CH_2$), 3.61 (3H, s, $17^2$-$CO_2CH_3$), 3.48 (3H, s, 2-$CH_3$), 3.37 (3H, s, 7-$CH_3$), 2.80 (1H, m, $17^1$-$H^a$), 2.60 (1H, m, $17^2$-$H^a$), 2.43 (1H, m, $17^1$-$H^b$), 2.28 (1H, m, $17^2$-$H^b$), 1.87 (3H, d, $J$ = 7.4 Hz, 18-$CH_3$), 1.78 (3H, t, $J$ = 7.7 Hz, $8^2$-$CH_3$), 0.11 and –2.47 (2H, each bs, NH × 2). $^{13}$C NMR ($CDCl_3$) $\delta_C$ ppm: 173.4, 168.9, 167.6, 161.4, 158.0, 152.7, 151.1, 146.3, 144.2, 140.2, 139.2, 139.1, 136.3, 134.2, 133.4, 132.6, 132.0, 130.2, 129.9, 129.8, 127.8, 125.1, 111.5, 107.2, 101.8, 97.5, 93.3, 52.5, 51.3, 49.7, 40.9, 30.9, 29.7, 29.6, 23.4, 19.6, 19.5, 17.4, 12.4, 12.3, 11.3.

## Results and Discussion

Modification of the most important 3 and 13 positions of chlorophyll *a* phorbine derivatives has always been one of the main scientific direction of our research group. In earlier works method was showed for selective halogenation of MePPB's vinyl group which was further used to increase the conjugation chain and, consequently, fine-tune the optical properties.[13,15]

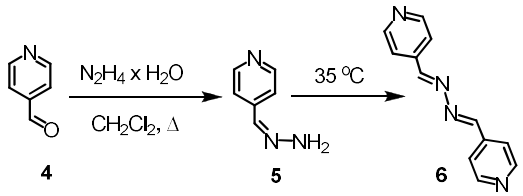
In addition, the possibility was demonstrated for synthesis of azine and ketazine derivatives of methyl pyropheophorbides *a*/*d*. However, the nucleophilic addition reaction of hydrazine with $13^1$-keto group proceeded much worse than the same reaction with formyl group. The reason for this was a low yields, long reaction time, poor reproducibility, hydrazone instability and its dimerization tendency.[5] In case of the nucleophilic addition reaction of hydrazine to carbonyl atom of the keto group there is another one significant problem: the use of aqueous hydrazine (with varying degrees of water content) leads to very low conversion due to reversible reaction character in the presence of water.




**Scheme 1.** Non-selective formation of hydrazone methyl pyro-pheophorbide *a* and its reaction with 4-pyridinecarboxaldehyde.

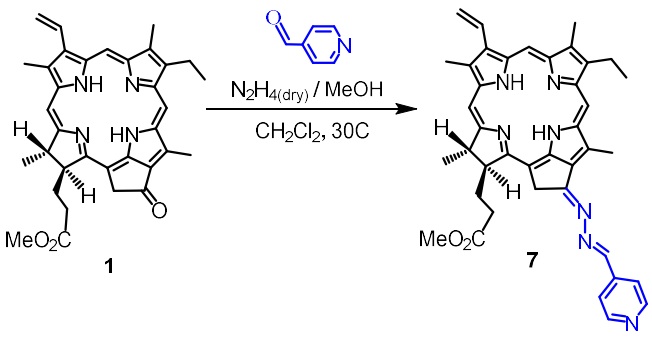
Therefore, an attempt was made to carry out this reaction using dry hydrazine, which was carefully dried and distilled under alkali and argon flow. These conditions in fact allowed one to significantly increase the reaction rate and the initial chlorin completely reacted. However, the stronger reducing power of anhydrous hydrazine also resulted in complete vinyl group reduction (the active agent for the reduction of alkenes being diimide) at 3-position of methyl pyropheophorbide *a*. Subsequent addition of 4-pyridinecarboxaldehyde resulted in the formation of compound **3** in 52 % yield (Scheme 1).

The non-selectivity of this method makes it not fascinating for further synthesis of chlorins with extended π system. In order to avoid reduction of the vinyl group, an attempt was made to search for a new synthetic approach. A theoretically possible alternative way involving the synthesis of hydrazones of various aromatic aldehydes, followed by their purification and use in the reaction with pyropheophorbide failed, since most of such hydrazones are also tend to easily dimerize to the corresponding non-reactive azines even at low temperature when trying to concentrate them in a vacuum evaporator.[16] Hydrazone **5**, formed as a result of the reaction of 4-pyridinecarbaldehyde **4** with hydrazine monohydrate, was sensitive to heating, and temperatures exceeding 30 degrees led to its rapid conversion to the azine structure **6** (Scheme 2).



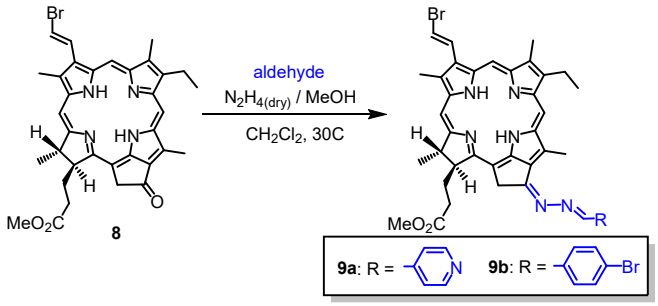

**Scheme 2.** Hydrazones dimerization process.

Taking into account all the factors described above, a three-component synthesis was proposed. The mixture of aldehyde **4** and dry hydrazine (1:1 eq.) in MeOH was added several times to a solution of methyl pyropheophorbide *a* in $CH_2Cl_2$ until the reaction was completed. Temperature was set to 30 °C to avoid dimerization of *in situ* generated aldehyde hydrazone. Due to the weak electrophilicity of the carbonyl carbon atom in the $13^1$-keto group, the reaction rate was low and the reaction time was 84 hours (Scheme 3).




**Scheme 3.** One-pot three-component synthesis of azine **7**.

Such a three-component approach can be used to synthesis of bifunctionalized derivatives **9a**/**9b** via the modification of previously obtained methyl (*E*)-$3^2$-bromopyropheophorbide *a* **8** (Scheme 4). As in the case of methyl pyropheophorbide, compound **8** reacted with hydrazones of various aromatic aldehydes to form unsymmetrical azines. As a result, in addition to the functional bromovinyl group (the use of which has been described in detail previously[13]) it becomes possible to more effectively use the carbonyl group at position $13^1$ to obtain more effective photosensitizers based on forbin derivatives. Such sequential functionalization of positions 3 and 13 opens up the possibility of creating multifunctional molecules with different properties that depend on the nature of the introduced substituents.




**Scheme 4.** Application of a new synthesis strategy on methyl (*E*)-$3^2$-bromopyropheophorbide *a*.

## Conclusions

In conclusion, a facile and efficient one-pot three-component method was developed for modification difficult to react keto group located in the exocycle E of methyl pyropheophorbide *a* and its derivatives. The use of this method enabled to obtain previously unavailable $13^1$-substituted chlorin derivatives. The approach proposed opens up a broad possibility for synthesis of biologically active conjugates based on natural chlorins. This will also allow one to introduce a numerous aromatic and unsaturated substituents along the y-axis of the macrocycle to form extended π-conjugated chlorin systems.

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