

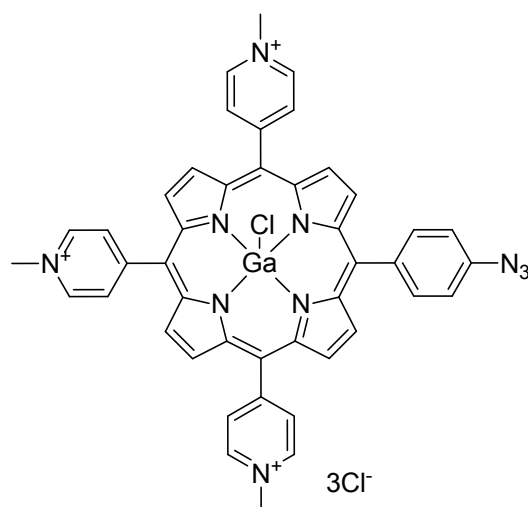
PET/PDT Theranostics: Synthesis and Biological Evaluation of a Peptide-Targeted Gallium Porphyrin

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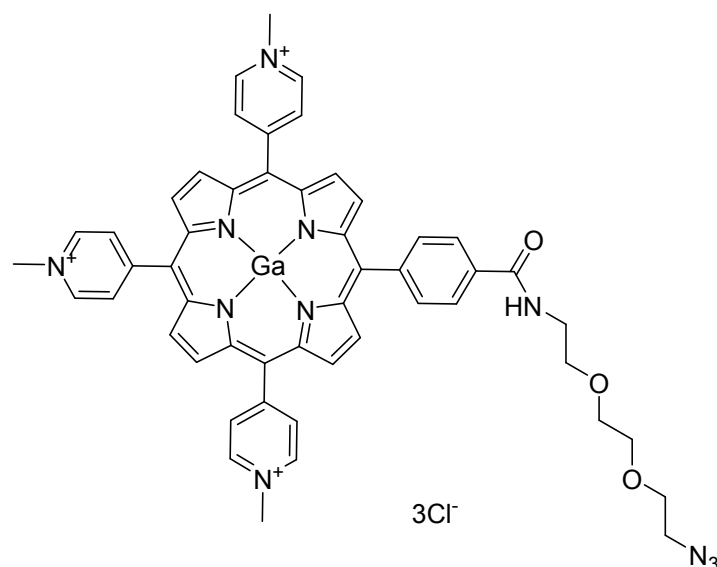
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5-[4-Azidophenyl]-10,15,20-tri-(*N*-methyl-4-pyridinium)porphyrinato gallium (III) trichloride **3**



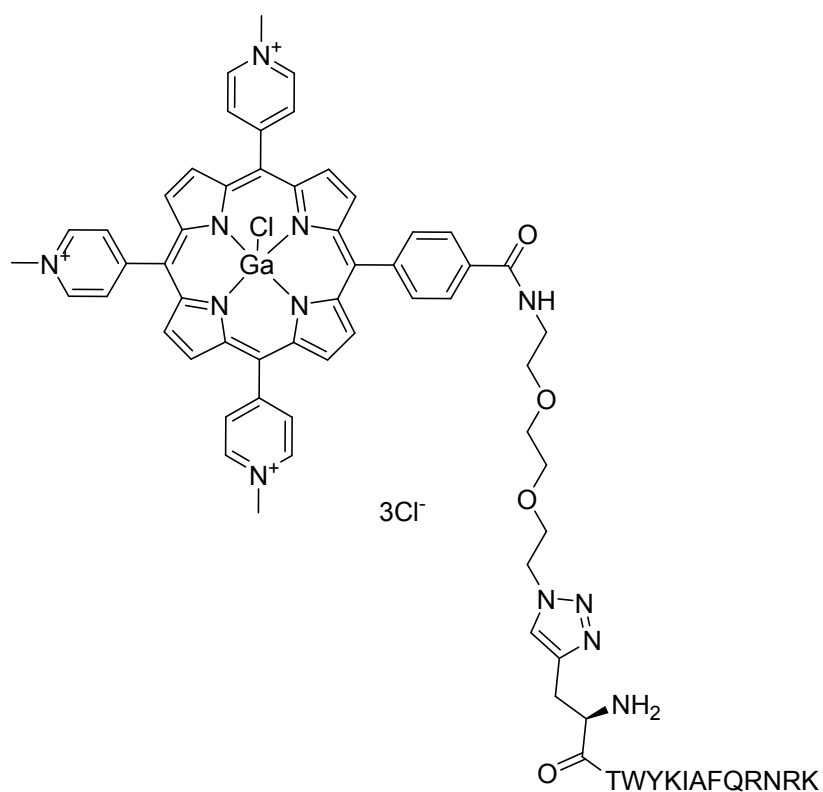
To a microwave tube was added porphyrin **1** (10 mg, 0.012 mmol) and water (5 ml). Gallium (III) chloride (10 mg, 0.06 mmol) was added and the mixture heated to 110°C (100W, MW) for 5 minutes. The mixture was neutralised with saturated sodium bicarbonate, and ammonium hexafluorophosphate added. The precipitated product was collected by filtration and redissolved in acetone. Tetrabutylammonium chloride was added and the precipitated product was collected by filtration. The product was precipitated from diethyl ether over methanol to yield the product as a red-purple solid (10 mg, 91%). UV-Vis (H₂O): λ_{\max} (log ϵ) 426 (5.51), 556, 597. ¹H-NMR (400 MHz, D₂O): δ 4.65 (under water peak, s, 9H, N-CH₃), 7.44 (s, 2H, 5-m-Ph), 8.17 (s, 2H, 5-o-Ph), 8.84 (s, 6H, 10,15,20-o-Py), 8.97-9.34 (m, 14H, 10,15,20-m-Py, β H). ¹³C-NMR (100.5 MHz, D₂O): δ 48.2 (C-CH₃), 114.1, 114.9, 117.7, 131.7, 132.4, 132.6, 133.0 (β -C), 134.5, 136.0, 143.9 (β -C), 146.2, 146.6, 149.1, 157.9. MS: (ESI) m/z 402 (100[M - 3Cl]²⁺), HRMS: calcd. for C₄₄H₃₂ClGa₁₀ [M - 3Cl]²⁺: 402.0872 observed 402.0881.

5-[4-2-(2-(2-Azidoethoxy)ethoxy)ethanaminocarbonyl]phenyl]-10,15,20-tris(1-methylpyridinium-4-yl)porphyrinato gallium (III) trichloride 4



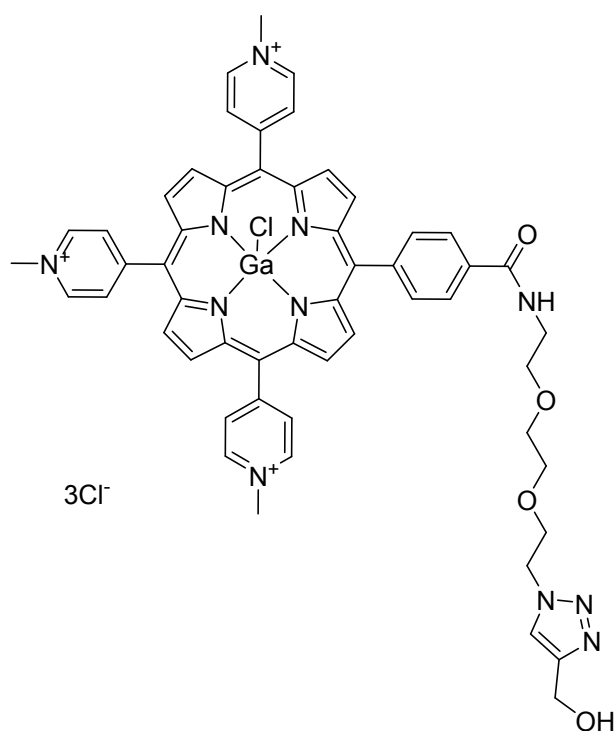
To a microwave tube was added porphyrin **2** (12 mg, 0.012 mmol) and water (5 ml). Gallium (III) chloride (10 mg, 0.06 mmol) was added and the mixture heated to 110°C (100W, MW) for 5 minutes. The mixture was neutralised with saturated sodium bicarbonate, and ammonium hexafluorophosphate added. The precipitated product was collected by filtration and redissolved in acetone. Tetrabutylammonium chloride was added and the precipitated product was collected by filtration. The product was precipitated from diethyl ether over methanol to yield the product as a red-purple solid (12 mg, 93%). UV-Vis: (H₂O) λ_{\max} (log ϵ): 430 (5.24), 559, 601. ¹H-NMR (400 MHz, DMSO-d₆): δ 3.40-3.45 (m, 2H, CH₂N₃), 3.71-3.87 (m, 10H, OCH₂), 4.84 (s, 9H, N-CH₃), 8.33-8.44 (m, 4H, 5-o,m-Ar), 8.97-9.07 (m, 6H, 10,15,20-o-Ar), 9.32-9.50 (m, 14H, 10,15,20-m-Ar and β -H). ¹³C-NMR: (100.5 MHz, DMSO-d₆) δ : 50.6 (CH₃), 69.4, 70.0, 70.2, 70.3, 126.0, 132.1, 132.8 (β -C), 133.0, 134.4, 144.4 (β -C), 146.8, 147.1, 149.0, 157.6. MS: (ESI) m/z 481 (100[M - 2Cl-H]²⁺), HRMS: calcd. for C₅₁H₄₅ClGaO₃N₁₀ [M - 2Cl-H]²⁺: 481.6320 observed 481.6313.

Gallium-peptide conjugate 5



To a stirred solution of gallium porphyrin **4** (2 mg, 2.0 μmol) in water (1 ml) was added THPTA (174 μg , 0.4 μmol), aminoguanidine bicarbonate (54 μg , 0.4 μmol), copper (II) sulfate pentahydrate (50 μg , 0.2 μmol) and sodium ascorbate (80 μg , 0.4 μmol) in water (0.2 ml). The dodecapeptide (2 mg, 1.7 μmol) in water (2 ml) was added and the mixture stirred at rt for 1 hour. The crude was purified on a column of Sephadex G-15, and lyophilised to remove water, to isolate the product as a pale green powder. R_f : 8.40 min. MS: (MALDI) m/z 2635.2 (100[M - 4Cl]⁺).

Control conjugate 6



To a microwave tube containing gallium porphyrin **4** (10 mg, 10.0 μmol) in water (6 ml) was added THPTA (174 μg , 0.4 μmol), aminoguanidine bicarbonate (54 μg , 0.4 μmol), and copper (II) sulfate pentahydrate (50 μg , 0.2 μmol) and sodium ascorbate (80 μg , 0.4 μmol) in water (0.2 ml). Propargyl alcohol (100 μl , MOL) in THF (1 ml) was added, and the mixture heated to 45°C for 1 hour (100 W, MW). The solvent was removed under reduced pressure and ammonium hexafluorophosphate added. The precipitated product was collected by filtration and redissolved in acetone. Tetrabutylammonium chloride was added and the precipitated product was collected by filtration. The product was precipitated from diethyl ether over methanol to yield the product as a red-purple solid (12 mg, 93%). UV-Vis: (H_2O) λ_{max} (log ϵ): 430 (5.22), 560, 601. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 3.55-3.73 (m, 10H, OCH_2), 3.85-3.91 (m, 2H, CH_2N_3), 4.52-4.58 (m, 4H, CH_2NH_2 and CH_2OH), 4.72 (s, 9H, N- CH_3), 8.01 (s, 1H, triazole H), 8.23-8.36 (m, 4H, 5-o,m-Ar), 8.85-9.05 (m, 14H, 10,15,20-o-Ar and β -H), 9.36-9.48 (m, 6H, 10,15,20-m-Ar). $^{13}\text{C-NMR}$: (100.5 MHz, DMSO-d_6) δ : 48.2 ($\underline{\text{C}}\text{H}_3$), 49.9 ($\underline{\text{C}}\text{H}_2$), 55.9, 65.5, 69.4, 69.6, 70.0, 70.1, 70.2, 75.4, 115.4, 116.1, 122.8, 123.6, 132.2, 132.7 (β -C), 134.6, 144.2 (β -C), 145.4, 148.2, 148.7, 148.9, 150.5, 159.0, 166.8 (C=O). MS: (ESI) m/z 334 ($100[\text{M} - 4\text{Cl} + \text{OH}]^{3+}$), HRMS: calcd. for $\text{C}_{54}\text{H}_{51}\text{GaO}_5\text{N}_{11}$ $[\text{M} - 4\text{Cl} + \text{OH}]^{3+}$: 334.1110 observed 334.1107.