Synthesis of Tetraalkyl-bis(methoxycarbonylethyl) Amphiphilic Porphyrins

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Photodynamic Therapy (PDT)[1~3] is relatively new cancer treatment which is based on the administration of tumor-localizing photosensitizers and their subsequent activation by visible light to destroy cancer cells. Currently, Photofrin® is the only drug that has been approved in the United States and elsewhere for the treatment of various types of cancer by PDT. However, its mode of action is still not clear. According to one hypothesis[4,5] the uptake occurs by binding to low-density lipoprotein (LDL) receptors. Because tumor cells may show a higher LDL receptor activity than many normal cells, a specific Photofrin® enrichment in malignant tissue results.

In general, protein binding accounts for the transport of a very large portion of systemically injected porphyrins and their analogues. The affinity of serum albumin and serum lipoproteins for porphyrins indicates a potential role for these proteins as endogenous carriers for porphyrins in PDT.[6] It has been known that human serum albumin (HSA) binding affinity of various photosensitizers plays an important role in their biodistribution within the tumor stroma.[7,8]

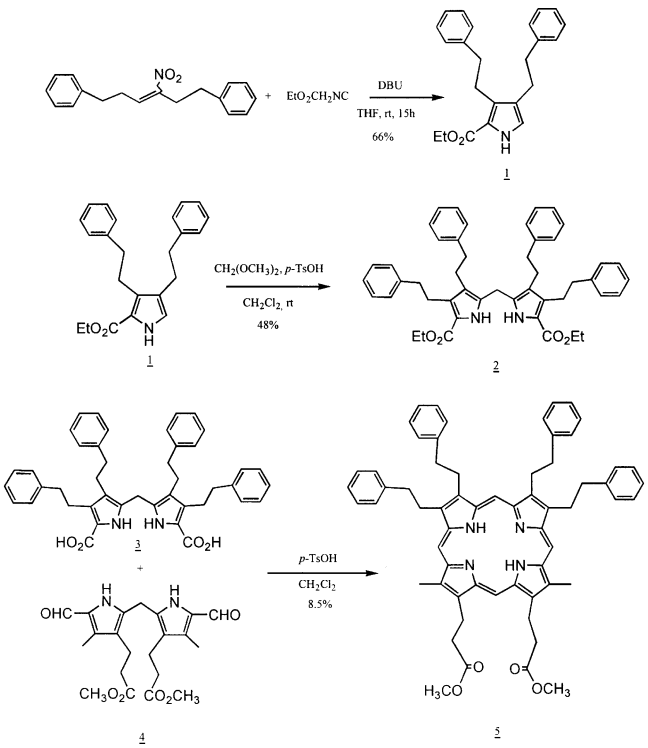
As a drug carrier, a protein may aid in the selective delivery of the porphyrin to a tumor region, and lipoproteins may facilitate drug access into the cell via receptor mechanisms. It has also been shown that the distribution of porphyrins among serum proteins is dependent upon their chemical structure. Studies on a series of alkyl ether analogues of pyropheophobide-a, a direct correlation of *in vivo* photosensitizing activity with the ability of the compound to bind to albumin site II was observed.[9]

Many compounds, especially amphiphilic drugs and some endogenous substance bind reversibly and with high affinity to HSA.[10] The formation of this complex affects the action of drugs.[11,12] For this reason, it is very important to find out general correlation between chemical structure and amphiphilicity. Our main objective was to determine the binding affinity of porphyrin analogues toward site II of HSA and LDL and determine if a correlation existed to their amphiphilicity, and a further correlation to their *in vivo* photosensitizing efficacy.

In the present study, we synthesized a series of amphiphilic porphyrin having alkyl chains on one side and acid chains on the other side. Symmetric lipophilic porphyrins[13~15] and symmetric hydrophilic porphyrins[16,17] were known, but synthesis of series of amphiphilic porphyrins have not been studied yet. These amphiphilic compounds will be then evaluated in terms of lipophilicity, HSA binding ability and their efficacy as a PDT.

For the preparation of desired amphiphilic porphyrins, dialkylpyrroles as lipophilic part and methoxycarbonylethylpyrrole as hydrophilic part were used. Dialkylpyrrole **1** was prepared by nitroalkene with ethyl isocyanoacetate in the presence of DBU as a base.[18,19] Reaction of dialkylpyrrole with dimethoxymethane gave the symmetric tetraalkyldipyrromethane **2**, which were converted into diacid by hydrolysis with 20% sodium hydroxide solution in THF. Diacid dipyrromethane **3** can be easily decarboxylated by catalytic amount of *p*-toluenesulfonic acid in dichloromethane to give α,α'-unsubstituted dipyrromethane.

Then 5,5'-diformyl-di(2-methoxycarbonylethyl)dipyrromethane **4** prepared by literature procedure[21] were condensed with dipyrromethane diacid in dichloromethane in the presence of *p*-toluenesulfonic acid followed by oxidation with DDQ to give the desired amphiphilic porphyrin **5**.[22]



Using the above reaction pathways, we have synthesized several derivatives of amphiphilic porphyrins such as 2,3,7,8-tetrapentyl-13,17-bis(methoxycarbonylethyl)-12,18-

dimethylporphyrin,[23] 2,3,7,8-tetrakis(1-cyclohexylmethyl)-13,17-bis(methoxycarbonylethyl)-12,18-dimethylporphyrin.[24] Now the HSA binding tests and distribution coefficients of those compounds are under investigation.

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20. Melting points are uncorrected and were measured on Electrothermal 9100. Mass spectra were obtained on a Shimadzu GC MS-QD 5050A mass spectrometer using a direct insertion probe (EI) and on a JEOL JMX-DX 303 spectrometer (FAB+). ^{1}H NMR spectra were obtained using a Varian EM360 spectrometer.
Compound **2**; Diethyl 3,3',4,4'-tetra(2-phenylethyl)-dipyrromethane-5,5'-dicarboxylate (yield; 48%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.28 (2H, NH, s), 7.32-7.06 (20H, m, aromatic), 4.28 (4H, q, -CH_2-), 3.24 (2H, s, -CH_2-), 3.00-2.78 (8H, m, -CH_2CH_2-), 2.58-2.74 (8H, m, -CH_2CH_2-) 1.34 (6H, t, -CH_3); Mass, m/e (rel intensity) 708 (M^+, 1.49%), 91 (100), mp 167-169.
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22. Compound **5**; 2,3,7,8-Tetra(2-phenylethyl)-13,17-bis(2-methoxycarbonyl ethyl)-12,18-dimethylporphyrin (yield; 8.5%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.04 (1H, s, -CH=), 9.94 (3H, s, -CH=), 7.19 (20H, s, aromatic), 4.38 (6H, t, -CH_2CH_2-), 4.14 (8H, t, -CH_2CH_2-), 3.60 (6H, s, -OCH_3), 3.55 (6H, s, -CH_3), 3.44 (8H, t, -OCH_2CH_2-), 3.23 (6H, t, -OCH_2CH_2-), -3.78 (2H, s, =NH). UV/Vis (CH_2Cl_2): λ=401, 499.2, 534.2, 567.6, 621.6, Ms (FAB) m/z 927 (M^+, 100%) mp: >300 °C.
23. 2,3,7,8-Tetrapentyl-13,17-bis(2-methoxycarbonylethyl)-12,18-dimethylporphyrin (Yield; 6.4%): 1H NMR ($CDCl_3$, 300 MHz) 10.07 (1H, s, -CH=), 10.06 (1H, s, -CH=), 9.96 (2H, s, -CH=), 4.38 (4H, t, -CH_2CH_2-), 3.63 (6H, s, -OCH_3), 3.50 (6H, S, -CH_3), 3.36 (6H, s, -CH_3), 2.68 (4H, t, -CH_2CH_2-), 2.42 (4H, t, -CH_2CH_2-), 1.68-1.18 (24H, m, -$CH_2CH_2CH_2$-), 0.96-0.82 (12H, m, -CH_3), -3.80 (2H, s, =NH). UV/Vis (CH_2Cl_2): =392, 499, 534, 568, 621. Ms (FAB) m/z 790 (M+) mp >300 °C.
24. 2,3,7,8-Tetrakis(1-cyclohexylmethyl)-13,17-bis(2-methoxycarbonylethyl)-12,18-dimethylporphyrin (Yield; 11.2%): 1H NMR ($CDCl_3$, 300 MHz) 10.06 (2H, s, -CH=), 9.88 (1H, s, -CH=), 9.82 (1H, s, -CH=), 4.38 (4H, t, -CH_2CH_2-) , 3.71 (6H, s, -OCH_3), 3.63 (8H, d, -OCH_2CH_2), 3.57 (6H, s, -CH_3), 3.26 (4H, t, -CH_2CH_2-), 1.69-1.23 (36H, m, cyclohexyl), 1.08-0.86 (8H, m, -CH_2-), -3.86 (2H, s, =NH). UV/Vis (CH_2Cl_2): =385, 498, 532, 567, 621, Ms (FAB) m/z 894 (M+) mp >300 °C.