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Molecular Recognition *via* Base-pairing and Phosphate Chelation. Ditopic and Tritopic Sapphyrin-based Receptors for the Recognition and Transport of Nucleotide Monophosphates.

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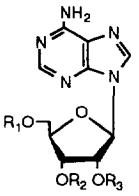
Abstract: Cytosine- (**8, 9**) and guanosine- (**10, 11**) substituted sapphyrin derivatives were prepared and tested as possible carriers for nucleotide monophosphate transport using a bulk liquid membrane model system at neutral pH. For each type of substituted sapphyrin, transport selectivity for the complementary nucleotide monophosphate was found. A high intrinsic preference for the 2'-, as opposed to 3'- or 5'-, isomer was also observed in the specific case of guanosine monophosphate transport effected by the cytosine-bearing carrier **8b**. Values from direct affinity constant determinations are used to rationalize these results.

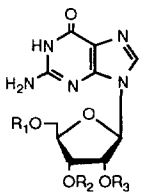
INTRODUCTION

Nucleotide monophosphates are of ubiquitous importance in biology. They play critical roles in processes as diverse as signal processing, feed-back inhibition, energy transduction, and gene replication.[1] The well-known purine- and pyrimidine-derived systems, adenosine-5'-monophosphate (5'-AMP, **1a**), guanosine-5'-monophosphate (5'-GMP, **2a**), cytosine-5'-monophosphate (5'-CMP, **3a**), uridine-5'-monophosphate (5'-UMP, **4a**), and thymidine-5'-monophosphate (5'-TMP, **5a**), for instance, are key constituents of DNA and RNA and thus essential to both genetic information storage and cellular replication. These same systems, and related cyclic derivatives, also play a critical role in energy transmutation and enzymatic regulation. Additionally, recently discovered analogues of these prototypical nucleotides, such

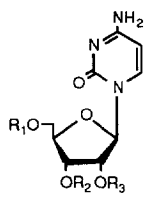
as Ara-AMP (**6**) and Xylo-GMP (**7**) have been found to be effective antiviral agents, active against a wide range of disorders including in certain instances herpes simplex and AIDS.[2]



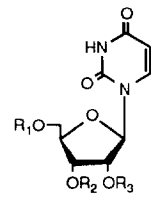
1a. $R_1 = HPO_3^-$; $R_2 = R_3 = H$
1b. $R_1 = R_3 = H$; $R_2 = HPO_3^-$
1c. $R_1 = R_2 = H$; $R_3 = HPO_3^-$



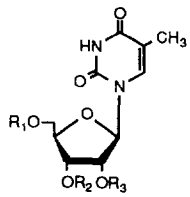
2a. $R_1 = HPO_3^-$; $R_2 = R_3 = H$
2b. $R_1 = R_3 = H$; $R_2 = HPO_3^-$
2c. $R_1 = R_2 = H$; $R_3 = HPO_3^-$



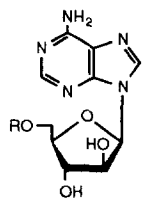
3a. $R_1 = HPO_3^-$; $R_2 = R_3 = H$
3b. $R_1 = R_3 = H$; $R_2 = HPO_3^-$
3c. $R_1 = R_2 = H$; $R_3 = HPO_3^-$



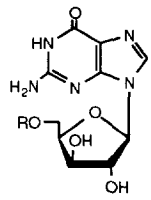
4a. $R_1 = HPO_3^-$; $R_2 = R_3 = H$
4b. $R_1 = R_3 = H$; $R_2 = HPO_3^-$
4c. $R_1 = R_2 = H$; $R_3 = HPO_3^-$



5a. $R_1 = HPO_3^-$; $R_2 = R_3 = H$
5b. $R_1 = R_3 = H$; $R_2 = HPO_3^-$
5c. $R_1 = R_2 = H$; $R_3 = HPO_3^-$

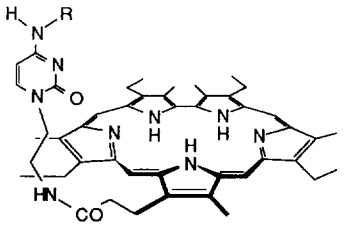


6. $R = PO_3^{2-}$

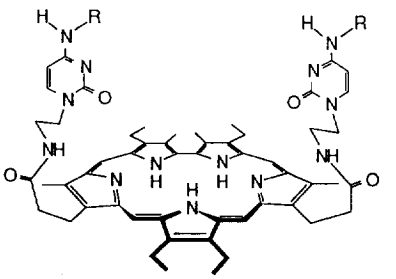


7. $R = PO_3^{2-}$

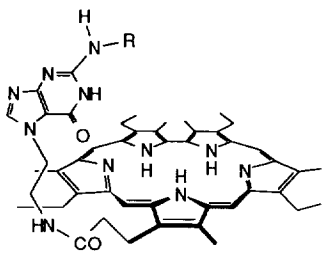
Given the above, it is not surprising that tremendous interest has attended to the problem of nucleotide monophosphate recognition and transport.[3] Nonetheless, in spite of this interest and in spite of a considerable body of work devoted to the more generalized problem of phosphate anion recognition and binding,[4-8] few viable systems exist that are capable of complexing these types of nucleotides under conditions of neutral pH and/or facilitating their transport through hydrophobic membranes of various descriptions.[9] Recently, however, we communicated the synthesis of **8b** and **9b**, systems that act as effective receptors and carriers[10] for 5'-GMP, and now, in this paper wish to report the synthesis and cytosine-5'-monophosphate binding properties of several "Watson-Crick analogues" of these earlier systems, namely receptors **10b** and **11b**.[11] We also wish to disclose the seemingly-surprising finding that systems such as **8b** display intrinsic selectivity within a given nucleotide monophosphate manifold, enhancing the through-membrane transport of the 2'-, as opposed to 3'- or 5'-, monophosphate species.



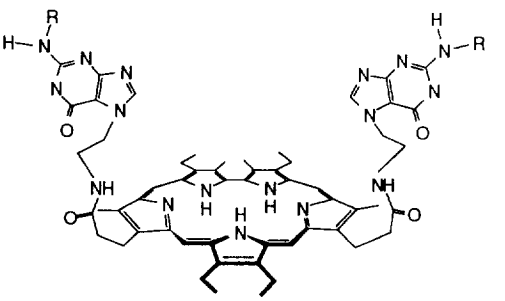
8a. R = Tr
8b. R = H



9a. R = Tr
9b. R = H



10a. R = Bz
10b. R = H



11a. R = Bz
11b. R = H

DESIGN CONSIDERATIONS

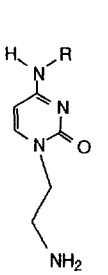
In early work[12] we found the diprotonated form of sapphyrin acts as a very efficient but nonselective carrier for the transport of nucleotide monophosphates at pH < 4. Unfortunately, however, no transport using this macrocycle was observed at physiological pH. On the other hand, in subsequent work various organic solubilized nucleosides were found by us to be good carriers for their corresponding phosphate-free Watson-Crick complements.[13] Taken together these results provided us with a hint as to how to develop carrier systems for the transport of biologically and pharmacologically important nucleotide monophosphates at neutral pH: We needed to combine both binding motifs into one molecule and, accordingly, sought to prepare the nucleic acid base ("nucleobase") substituted sapphyrins, **8** and **9**. The resulting systems, to our delight, proved to be highly selective carriers for the through-model-membrane transport of guanosine-5'-monophosphate at or near neutral pH.

Although considered to be encouraging in the extreme, these earlier results left undefined to a certain extent the critical question of whether the observed cytosine carrier-for-guanosine

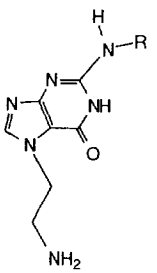
substrate selectivity was the result of specific Watson-Crick base pairing interactions or the combination of other, less obvious factors. In this work we address this concern. Specifically, we report the synthesis and through-model-membrane transport capabilities of the guanine-bearing sapphyrins **10b** and **11b** that, based on our earlier findings with **8b** and **9b**, would be predicted to be highly selective carriers for cytosine-containing substrates such as cytosine-5'-monophosphate near neutral pH.

SYNTHESIS

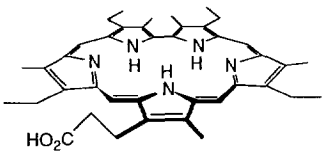
The synthesis of the nucleobase substituted sapphyrins **8-11** is given in detail in the experimental section and is summarized as follows. First, protected derivatives of aminoethylcytosine **12** and aminoethylguanosine **13** were prepared[14] and then, secondly, coupled with activated forms of "sapphyrin acid" (**14**) or "sapphyrin bisacid" (**15**). Activation of these latter acids was achieved through the use of acid chlorides or *via* the use of carbodiimide or carbonyldiimidazole. In all cases, good yields of nucleobase functionalized sapphyrin derivative were obtained following deprotection. Here, the trityl and benzoyl protecting groups were removed using TFA and ammonia (saturated solution in dichloromethane-methanol at 25 °C), respectively.



12a. R = Tr
12b. R = H



13a. R = Bz
13b. R = H



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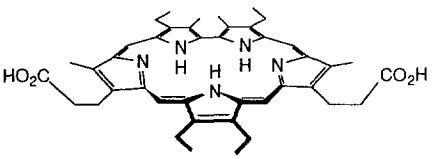

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TRANSPORT STUDIES

Transport experiments were performed using a dichloromethane model membrane as described elsewhere.[13] The results are summarized in Tables I and II (cytosine-bearing carriers **8b** and **9b**) and Table III (guanine-containing carriers **10b** and **11b**). Control experiments were performed using 2,3,7,8,12,13,17,18-octaethylporphyrin and 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin as putative carriers. In nearly all cases, little in the way of

detectable transport was observed at neutral pH in the absence of a carrier or when these latter control systems were used (k_T values of $< 10^{-12}$ were recorded). In the special case of 5'-TMP, however, high through-transport rates were observed even in the absence of a carrier. This particular nucleotide has, therefore, been excluded from this study.

Table I. Initial Nucleotide-5'-monophosphate Transport Rates for the Mono- and Ditopic Cytosine-containing Carriers 8b and 9b.

Carrier[a]	Aq. I (pH)[b]	Aq. II	k_T CMP[c] (10^{-8} mol / cm^2·h)	k_T GMP[d]	k_T AMP	k_G/k_A	k_G/k_C
8b	6.15	H_2O	0.0118	1.2015	0.157	7.66	101.7
8b	6.70	H_2O	0.0067	0.2873	0.033	8.87	42.9
8b	7.05	H_2O	0.00005	0.0011	0.0001	9.49	20.1
8b	6.15	10 mM NaOH	0.0541	1.4230	0.521	2.73	26.3
8b	6.70	10 mM NaOH	0.0301	1.2284	0.282	4.36	40.8
8b	7.05	10 mM NaOH	0.0164	0.7081	0.0738	9.60	43.3
8b	6.15	H_2O	0.0162	0.1006	0.0729	1.38	6.2
9b	7.05	10 mM NaOH	0.0049	0.1149	0.0362	3.18	23.7
none	6.15[e]	H_2O	$< 10^{-5}$	$< 10^{-5}$	$< 10^{-5}$	k_TTMP = 0.0134	
sapph.[f]	7.0	H_2O	$< 10^{-5}$	$< 10^{-5}$	0.00002		
sapph.[f]		10 mM NaOH	$< 10^{-5}$	$< 10^{-5}$	0.0004		

[a]0.1 mM in dichloromethane

[b]The source phase, Aq I, contained initially a 1:1:1 ratio of 5'-AMP, 5'-CMP and 5'-GMP at a 10 mM conc. and at the indicated pH.

[c]Transport experiments were performed in a manner similar to those reported in ref.13. Initial transport rates were calculated from the linear region of concentration vs time curve. Estimated errors < 5 %. Values are average of three measurements.

[d]Competitive transport of 5'-GMP and 2'-deoxy-5'-GMP showed $k_{rel} = 1.188$ ($k_T = 0.286 \times 10^{-8}$ mol/cm^2·h and 0.241×10^{-8} mol/cm^2·h for 5'-GMP and 2'-deoxy-5'-GMP, respectively).

[e]Contained 1:1:1:1 5'-AMP, 5'-CMP, 5'-GMP, 5'-TMP at 10 mM conc. and the indicated pH.

[f]Blank experiment using 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin.

TRANSPORT RESULTS. DITOPIC RECEPTORS 8b AND 10b

The ditopic receptors, **8b** and **10b**, were designed to allow for specific base-pairing interactions as well as for more general phosphate binding recognition. Thus it was considered likely that these systems would act as highly specific carriers for the appropriate Watson-Crick nucleotide monophosphate complements. As detailed in Tables I and III (giving results for the cytosine- and guanine-substituted systems, respectively), this indeed proved to be the case. Specifically, the cytosine-bearing system **8b** acts as a highly effective carrier for the through-membrane transport of guanosine-5'-monophosphate (but not 5'-CMP or 5'-AMP), whereas **10b** serves to enhance the transport of cytosine-5'-monophosphate (but not 5'-GMP or 5'-AMP). Further, as expected, the control systems **8a** and **10a** proved completely ineffectual as carriers.

Table II. Initial Rates of GMP Isomer Transport for Carriers 8b and 9b.

Carrier[a]	Aq. I (pH)[b]	Aq. II	k_T 5'-GMP[c,d]	k_T 3'-GMP	k_T 2'-GMP	$k_{2'G}/k_{5'G}$
			(10^{-8} mol / cm^2·h)			
8b	6.70	H_2O	0.079	0.105	0.767	9.70
8b	6.70	1 mM NaOH	0.313	0.564	2.989	9.55
8b	7.00	H_2O	0.054	0.0760	0.597	11.06
8b	7.20	H_2O	$< 10^{-3}$	$< 10^{-3}$	0.421	
8b	7.35	H_2O	$< 10^{-3}$	$< 10^{-3}$	0.352	
8b	7.50	H_2O	$< 10^{-3}$	$< 10^{-3}$	0.183	
9b	6.70	1 mM NaOH	0.0312	0.0389	0.104	3.33
none	7.0	H_2O	$< 10^{-5}$	$< 10^{-5}$	$< 10^{-5}$	
sapph.[e]	7.0	H_2O	$< 10^{-5}$	$< 10^{-5}$	0.00002	

[a] 0.1 mM in dichloromethane.

[b] Aq. I contained initially a 1:1:1 ratio of 5'-GMP, 3'-GMP and 2'-GMP at a 10 mM conc. and at the indicated pH.

[c] Transport experiments were performed as indicated in footnote c of Table I.

[d] Competitive transport of 5'-GMP and 2'-deoxy-5'-GMP showed $k_{rel} = 1.175$ ($k_T = 0.286 \times 10^{-8}$ mol/cm^2·h and $0.244\ 10^{-8}$ mol/cm^2·h for 5'-GMP and 2'-deoxy-5'-GMP, respectively).

[f] Blank experiment using 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin.

For both ditopic carriers, **8b** and **10b**, going from pH 6.5 to physiological pH leads to a dramatic drop off in rate. This is because sapphyrin exists at neutral pH as a monoprotonated, singly charged entity, whereas nucleotide monophosphates are primarily dianionic at this pH.[15] As a consequence, the neutral form of the monoprotonated carrier - monobasic nucleotide monophosphate complex is no longer a dominant equilibrium species. Thus, the rate of its transport (and that of the starting mono- *or* dibasic nucleotide monophosphate) is necessarily reduced.

TRANSPORT RESULTS. TRITOPIC RECEPTORS 9b AND 11b

The tritopic receptors **9b** and **11b** were designed with the intention of allowing for the formation of complexation-derived "triple helix like" C-G-C and G-C-G motifs. In other words, the predicative idea here was that a central bound nucleobase subunit (i.e. guanine, G, in the case of **9b**) would be the beneficiary of two different kinds of hydrogen bonding interactions (from C *and* C in the case of **9b**), involving, e.g., both Watson-Crick and Hoogsteen recognition patterns. To the extent this thinking proved correct, it was expected that the stability of the nucleotide phosphate-receptor complex would be enhanced and the rate of through-membrane transport augmented. It was also expected that a higher level of substrate selectivity might be observed.

Table III. Initial Nucleotide-5'-monophosphate Transport Rates for the Mono- and Ditopic Guanine-bearing Carriers 10b and 11b.

Carrier[a]	Aq. I (pH)[b]	Aq. II	k_T 5'-CMP[c,d]	k_T 5'-GMP	k_T 5'-AMP	k_T 5'-(2'-deoxy)CMP
			(10^{-8} mol / cm^2·h)			
10b	6.70	H_2O	0.129	0.0144	0.041	0.101
10b	6.70	1 mM NaOH	0.541	0.0590	0.172	0.424
10b	6.80	H_2O	0.097			0.064
11b	6.70	1 mM NaOH	0.147	0.0084	0.014	

[a] 0.05 mM in dichloromethane

[b] Aq I contained initially a 1:1:1 ratio of 5'-GMP, 5'-AMP and 5'-CMP at a 10 mM conc. and at the indicated pH.

[c] Transport experiments were performed as detailed in footnote c of Table I.

[d] High selectivity was observed for the transport of 2'-CMP relative to the 3' and 5' isomers of this same species. However, the degree of this selectivity could not be quantified using our standard[13] HPLC analysis since overlapping peaks are observed for 2'- and 3'-CMP.

In spite of the above thinking, it was found (Table I) that the doubly functionalized cytosine derivative **9b** was both less efficient and less selective than its monofunctionalized analogue **8b** (Table I), perhaps as the result of internal C-C dimerization or an inability to protonate one of the cytosine subunits (as would be required for Hoogsteen binding) under the reaction conditions. On the other hand, highly selective transport was observed using the bis-guanosine substituted sapphyrin **11b** (k_{CMP}/k_{AMP} ratios of 3.15 and 10.5 were recorded for **10b** and **11b**, respectively), leading us to suggest that, at least in this particular instance, this design consideration is not necessarily devoid of merit (Table III). Still, even in this case, the absolute rates of carrier-induced, through-membrane transport were found to be larger for the monosubstituted system **10b** than for its doubly functionalized analogue **11b**.

TRANSPORT RESULTS. REGIOCHEMISTRY

For all carriers, transport of the 2'-XMP species was observed to be mediated selectively, relative to that of the corresponding 3'- and 5'-XMP regioisomers. This effect was specifically quantified in the case of carrier **8b** (Table II). Here, it was found that the 2' isomer of GMP was routinely transported at rates that were roughly 10 times higher than those observed for the through-CH_2Cl_2 transport of its 5' substituted congener.

Table IV. Associations Constants (Methanol, RT) for Complexes Formed between Nucleotide Monophosphates, XMP^-, and the Monoprotonated Form of Cytosine-sapphyrin (8b).

Nucleotide Monophosphate[a] (XMP^-)	K_a (M^{-1})[b,c]	K_{XMP} / K_{CMP} (K_{rel})
5'-AMP^-	1,660	1.9
5'-CMP^-	880	1
5'-GMP^-	8,140	9.3
2'-GMP^-	22,000	25.0

[a] $XMP^-{\cdot}Et_3NH^+$ salts were prepared in water from the corresponding free acid by treating with 1 molar eqv. of triethylamine, evaporating off the water and redissolving the dry salt in MeOH.

[b] Methanol solvent, ambient temperature.

[c] Data reduction was accomplished using standard[16] Benesi-Hildebrand curve fitting of the changes in the optical absorbance observed upon addition of the XMP^- substrate; λ_{max} = 443 nm for **8b** and 449 nm for the complexes, with an isobestic point at 445 nm being observed; error in $K_a \leq 10\%$.

While the origins of this isomer-specific XMP^- transport selectivity remain recondite, they can, perhaps, be traced back to simple differences in relative binding affinities: Whereas carrier **8b**, as its monoprotonated derivative, has an association constant, K_a, for the binding of 2'-GMP in methanol at room temperature that is on the order of 2×10^4 M^{-1}, this same species binds 5'-GMP with a K_a of 8×10^3 M^{-1} (Table VI). Further, as shown schematically by Figures 1 and 2, molecular modeling studies (HyperChem™) indicate that 5'-GMP must adopt a less stable *syn* conformation when bound to **8b**, whereas 2'-GMP is easily accommodated by this receptor in its more stable *anti* orientation. Thus, the seemingly surprising preference for 2'-GMP observed for this carrier could simply be a reflection of structure-correlated binding differences; this is a possibility that is currently being explored *via* appropriate further experiments.

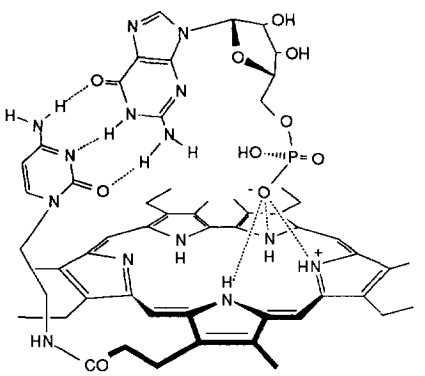

Figure 1. Proposed Structure for the Complex Formed Between the Monoprotonated Form of Receptor **8b** and Monobasic 5'-GMP.

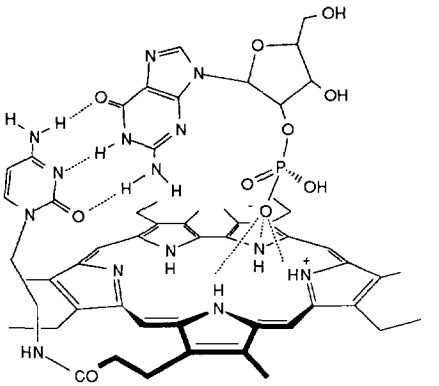

Figure 2. Proposed Structure for the Complex Formed Between the Monoprotonated Form of Receptor **8b** and Monobasic 2'-GMP.

CONCLUSION

As reported in this paper, certain nucleobase-substituted sapphyrin derivatives can act as efficient systems for the specific through-CH_2Cl_2 transport of nucleotide monophosphates at neutral pH. These findings, along with the fact that within the manifold of nucleotide 5'-, 3'-, and 2'-monophosphates, high selectivity for the 2' isomers is observed, leads us to suggest that this basic sapphyrin- and nucleobase-derived approach could be used to generate specific receptors for known antiviral agents that are suitable for use *in vivo*. Currently we are testing this possibility using analogues of **8-11** in various cell-based protocols.

ACKNOWLEDGMENT

This work was supported by NIH grant AI 33577 and funds from Pharmacylics, Inc.

EXPERIMENTAL

General Methods. Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were freshly distilled prior to use. Proton and ^{13}C NMR spectra were recorded on GE QE-300 (300 MHz) and GN-500 (500 MHz) spectrometers. Mass spectrometric measurements (FAB and CI) were made using either VG-ZAB or Finnigan MAT TSQ 70 instruments. UV-Vis spectra were recorded on a Beckman DU 640 spectrometer.

3,8,17,22-Tetraethyl-12-(carboxyethyl)-2,7,13,18,23-pentamethylsapphyrin (14).

Part a: Preparation of 3,8,17,22-tetraethyl-12-(methoxycarbonylethyl)-2,7,13,18,23-pentamethylsapphyrin. In accord with the general optimized procedure for the production of substituted sapphyrins,[17,18] 4,4′-diethyl-5,5′-diformyl-3,3′-dimethyl-2,2′-bipyrole (272 mg, 1.0 mmol) and 2,5-bis(5-carboxy-3-ethyl-4-methyl-pyrrol-2-ylmethyl)-3-methoxycarbonylethyl-4-methylpyrrole (523 mg, 1.0 mmol) were condensed to give this desired sapphyrin product in 75.4% yield (0.490 g). ^1H NMR (300 MHz, $CDCl_3$): δ = -4.78 (1H, s, NH), -4.76 (1H, s, NH), -4.32 (1H, s, NH), -4.13 (2H, s, NH), 2.35-2.43 (12H, m, $CH_2C\underline{H}_3$), 3.85 (2H, t, $CH_2C\underline{H}_2CO_2CH_3$), 3.99 (3H, s, CH_3), 4.29 (6H, s, CH_3), 4.38 (6H, s, CH_3), 4.44 (3H, s, CH_3), 4.67-4.74 (8H, m, $C\underline{H}_2CH_3$), 5.22 (2H, t, $C\underline{H}_2CH_2CO_2CH_3$), 11.82 (1H, s, meso-H), 11.85 (1H, s, meso-H), 11.88 (2H, s, meso-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 13.1, 15.9, 17.8, 17.9, 21.0, 23.0, 37.1, 52.1, 91.5, 92.0, 98.3, 98.4, 126.9, 127.0, 129.5, 129.6, 130.2, 132.7, 132.8, 134.7, 135.3, 135.5, 136.6, 136.7, 137.7, 139.1, 141.5, 141.7, 173.3. HRMS: Calcd. for $C_{41}H_{49}N_5O_2$: 643.3886; found: 643.3887.

Part b: Preparation of sapphyrin acid **14**. A ca. 1:1 v.v. mixture of trifloroacetic acid and conc. hydrochloric acid (10 ml for 100 mg of starting sapphyrin) was used to hydrolyze the ester. The reaction was run at 50 °C for 2 days after which time the desired sapphyrin acid product was obtained as its bis HCl adduct. After drying in vacuo, this protonated product was purified by column chromatography on silica gel (methanol 5% in dichloromethane, eluent). The yield of **14** was ca. 95%. ^1H NMR (300 MHz, $CDCl_3$): δ = –5.84 (2H, bs, NH), –5.35 (3H, bs, NH), 2.15 (6H, t, $C\underline{H}_3CH_2$), 2.26 (6H, t, $C\underline{H}_3CH_2$), 3.75 (2H, t, $CH_2C\underline{H}_2CO_2H$), 4.03 (H, s, CH_3), 4.15 (6H, s, CH_3), 4.23 (3H, s, CH_3), 4.41 (3H, s, CH_3), 4.53 (4H, q, $C\underline{H}_2CH_3$), 4.74 (4H, q, $C\underline{H}_2CH_3$), 5.12 (2H, m, $C\underline{H}_2CH_2CO_2H$), 11.42 (2H, s, meso-H), 11.55 (1H, s, meso-H), 11.58 (1H, s, meso-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 12.9, 14.3, 15.9, 17.7, 17.9, 20.6, 20.9, 22.8, 36.5, 36.7, 61.9, 91.6, 98.1, 120.7, 120.9, 125.4, 125.4, 127.3, 129.1, 129.2, 130.0, 132.7, 132.8, 134.8, 134.9, 135.2, 135.4, 135.6, 135.7, 136.1, 136.8, 136.9, 137.0, 137.7, 139.31, 141.4, 141.8, 141.8, 174.4. FAB MS, m/e (rel intensity): 631 (48, $[M+ 2H]^+$), 630 (100, $[M+H]^+$), 629 (52, M^+); HRMS: Calcd. for $C_{40}H_{48}N_5O_2$ $[M+H]^+$: 630.3808; found: 630.3798. Anal. calcd. for $C_{40}H_{47}N_5O_2$ (629.85): 76.28% C, 7.52% H, 11.12% N; found: 76.11% C, 7.54% H, 11.03% N.

3,8,17,22-Tetraethyl-12-[2-[1-[2-oxo-4-[(triphenylmethyl)amino]pyrimidinyl]ethyl]-aminocarbonylethyl]-2,7,13,18,23-pentamethylsapphyrin (8a).

Method A: The sapphyrin acid **14,** as prepared above (63 mg, 0.1mmol), was dissolved in 10 ml of dry dichloromethane under argon. Oxalylchloride (0.2 ml) was added followed by 0.03 ml of DMF. The reaction mixture was stirred at room temperature for 3 hours under argon and then evaporated to dryness in vacuo. The sapphyrin acid chloride so obtained was then redissolved in dry dichloromethane (20 ml) and added slowly under argon and at room temperature to a solution of 59.4 mg (0.15 mmol) of 1-(2-aminoethyl)-4-[(triphenylmethyl)-amino]-pyrimidin-2-one **12a**[14] containing 5 mg 4-dimethylaminopyridine and 0.4 ml of dry pyridine in 20 ml of dry dichloromethane. After the addition was complete (ca. 1 hour), the reaction mixture was stirred overnight. The reaction mixture was then washed in succesion with dilute hydrochlorid acid (3%, 20 ml), water (20 ml), saturated sodium bicarbonate (20 ml), and water (20 ml) once again. The organic phase was then dried over sodium sulfate and the solvent removed in vacuo. The desired product was isolated by column chromatography on silica gel using methanol, 2-5% in dichloromethane as the eluent. The yield of **8a** is 91.0 mg (ca. 90%).

Method B. The sapphyrin acid **14** described above (31.5 mg, 0.05 mmol) was dissolved in dry dichloromethane (20 ml). The resulting solution was then cooled to 0 °C and dicyclohexylcarbodiimide (41.27 mg, 0.2 mmol) and 1-hydroxybenzotriazole (5mg) added. The resulting solution was then stirred in an ice bath for 30 min. and the amino-functionalized cytosine, 1-(2-aminoethyl)-4-[(triphenylmethyl)amino]pyrimidin-2-one **12a**[14] (29.7 mg, 0.075 mmol) was added, followed by 0.1 ml of dry pyridine. The reaction mixture was then stirred, first for 0.5 h at 0 °C and then for 48 h at room temperature. Acetic acid (0.2 ml) was then added and the solution stirred a further 1 h at room temperature. Dicyclohexylurea was then filtered off and the reaction worked up as per method A. The yield obtained using this method was 42 mg (83.3%) ^{1}H NMR (300 MHz, $CDCl_3$): δ = -5.43 (2H, bs, NH), -4.67 (2H, bs, NH), 2.21 (12H, t, $CH_2C\underline{H}_3$), 3.23 (2H, t, $CONHC\underline{H}_2CH_2$), 3.75 (2H, t, $CH_2C\underline{H}_2CONH$), 3.85 (2H, t, $CONHCH_2C\underline{H}_2$), 4.07 (9H, s, CH_3), 4.18 (3H, s, CH_3), 4.30 (3H, s, CH_3), 4.50 (4H, m, $C\underline{H}_2CH_3$), 4.60 (4H, m, $C\underline{H}_2CH_3$), 4.98 (2H, m, $C\underline{H}_2CH_2CONH$), 5.50 (1H, d, C^5H), 6.80, (1H, bs, NH), 6.83 (1H, d, C^6H), 7.06-7.26 (15H, m, Tr H), 7.54 (1H, s, CONH), 11.55 (2H, s, meso-H), 11.56 (2H, s, meso-H). FAB MS, m/e (rel. intensity): 1008 (25, $[M+H]^+$), 1007 (58, M^+), 1006 (22, $[M-H]^+$), 765 (22, $[M-Tr]^+$). HRMS: Calcd. for $C_{65}H_{70}N_9O_2$ ($[M+H]^+$): 1008.5652; found: 1008.5654. Anal. calcd. for $C_{65}H_{69}N_9O_2$ (1008.33): 77.43% C, 6.90% H, 12.50% N; found: 77.24% C, 6.90% H, 12.34% N.

3,8,17,22-Tetraethyl-12-[2-[1-(4-amino-2-oxopyrimidinyl)ethyl]aminocarbonylethyl]-2,7,13,18,23-pentamethylsapphyrin (8b). Compound **8a** (50.4 mg, 0.05 mmol) was dissolved in trifluoroacetic acid (5 ml) and the solution heated at reflux for 1 h. After allowing the solution to cool, the solvent was removed in vacuo. The residue was then redissolved in dichloromethane, filtered, and taken to dryness on a rotory evaporator. The crude product so obtained was purified by recrystallization from a dichloromethane-hexane (1:3, v.v.) mixture, or by column chromatography on silica gel using dichloromethane-methanol 9:1 v.v. as the eluent. Such purifications afforded compound **8b** as its bistrifluoroacetic acid adduct in ca. 75% yield

(37.3 mg). Prior to use in transport studies, this trifluoroacetate salt was dissolved in dichloromethane and washed with a 1 M solution of NaOH and H_2O. ^1H NMR (300MHz, $CDCl_3$): δ = -6.66 (1H, s, NH), -6.57 (1H, s, NH), -6.50 (1H, s, NH), -6.45 (1H, s, NH), -5.79 (1H, s, NH), 2.17 (12H, m, $C\underline{H}_3CH_2$), 3.27 (2H, t, $CONHC\underline{H}_2CH_2$), 3.75 (2H, t, $CONHCH_2C\underline{H}_2$), 3.98 (2H, t, $CH_2C\underline{H}_2CONH$), 4.11 (6H, s, CH_3), 4.20 (3H, s, CH_3), 4.23 (3H, s, CH_3), 4.25 (3H, s, CH_3), 4.54 (4H, q, $C\underline{H}_2CH_3$), 4.68 (4H, q, $C\underline{H}_2CH_3$), 5.12 (2H, t, $C\underline{H}_2CH_2CONH$), 5.50 (1H, d, J = 7.2, C^5H), 6.26 (2H, s, NH_2), 6.84 (1H, d, J = 7.2, C^6H), 7.47 (1H, s, CONH), 11.52 (1H, s, meso-H), 11.65 (1H, s, meso-H), 11.69 (1H, s, meso-H), 11.70 (1H, s, meso-H). ^{13}C NMR (125 MHz, $CDCl_3$, 10 % CD_3OD): δ = 12.52, 12.67, 12.86, 15.47, 15.83, 17.33, 17.51, 17.55, 17.57, 20.57, 20.68, 20.75, 22.55, 36.99, 37.74, 48.46, 91.50, 91.81, 91.87, 98.08, 98.22, 121.47, 126.37, 127.08, 127.82, 129.08, 129.92, 130.15, 130.20, 132.95, 132.98, 135.02, 135.25, 135.35, 135.61, 137.41, 138.51, 138.59, 140.49, 142.03, 142.10, 142.48, 147.08, 158.57, 173.65. FAB MS, m/e (rel. intensity): 768 (65, $[M+2H]^+$), 767 (78, $[M+H]^+$), 766 (100, M^+), 766 (45, $[M-H]^+$). HRMS: Calcd. for $C_{46}H_{56}N_9O_2$ ($[MH]^+$): 766.4556; found: 766.4535. Anal. calcd. for $C_{46}H_{55}N_9O_2$ (766.01): 72.13% C, 7.24% H, 16.46% N; found: 72.00% C, 7.24% H, 16.46% N.

3,12,13,22-Tetraethyl-8,17-bis[2-[1-[2-oxo-4-[(triphenylmethyl)amino]pyrimidinyl]-ethyl]aminocarbonylethyl]-2,7,18,23-tetramethylsapphyrin (9a). 3,12,13,22-Tetraethyl-8,17-bis(carboxyethyl)-2,7,18,23-tetramethylsapphyrin **15**[18] (34.5 mg, 0.05 mmol) was suspended in dry dichloromethane (20 ml). To the resulting solution, oxalylchloride (0.3 ml) and DMF (0.03 ml) were added under argon. The reaction mixture was stirred at room temparature for 3 hours and subsequently evaporated to dryness. The resulting sapphyrin bis acid chloride was dissolved in dry dichloromethane (15 ml) and slowly added to a solution of 1-(2-aminoethyl-4-[(triphenylmethyl)amino]-pyrimidin-2-one **12a**[14] (51.48 mg, 0.13 mmol) in dry dichloromethane (20 ml) containing both 4-dimethylaminopyridine (5 mg) and dry pyridine The reaction mixture was stirred under argon at room temperature for 12 hours, then washed with dilute hydrochloric acid (3%, 30 ml), water, saturated aqueous sodium bicarbonate, and water once again. After drying over sodium sulfate and evaporative removal of solvent, the product was isolated by column chromatography (silica gel; dichloromethane-methanol (1-10% gradient), eluent). The yield of **9a** is 65.0 mg (89.9%). ^1H NMR (300MHz, $CDCl_3$): δ -5.25 (2H, s, NH), -5.05 (2H, s, NH), 2.13 (12H, t, $C\underline{H}_3CH_2$), 3.30 (4H, t, $CONHC\underline{H}_2CH_2$), 3.73 (4H, t $CH_2C\underline{H}_2CONH$), 3.83 (4H, t, $CONHCH_2C\underline{H}_2$), 4.00 (6H, s, CH_3), 4.15 (3H, s, CH_3), 4.25 (3H, s, CH_3), 4.57 (4H, q, $C\underline{H}_2CH_3$), 4.75 (4H, q, $C\underline{H}_2CH_3$), 4.99 (4H, m, $C\underline{H}_2CH_2CONH$), 5.50 (2H, d, C^5H), 6.73 (2H, s, NH), 6.89 (2H, d, C^6H), 7.01-7.29 (30H, m, Tr H), 7.67 (2H, s, CONH), 11.43 (4H, bs, meso-H). FAB MS m/e (rel intensity): 1446 (58, M^+), 1447 (38, $[MH]^+$). HRMS: Calcd for $C_{92}H_{95}N_{13}O_4$: 1445.7645; found 1445.7658. Anal. calcd. for $C_{92}H_{95}N_{13}O_4$ (1446.86): 76.37% C, 6.62% H, 12.58% N; found: 76.12% C, 6.67% H, 12.39% N.

3,12,13,22-Tetraethyl-8,17-bis[2-[1-(4-amino-2-oxopyrimidinyl)ethyl]aminocarbonylethyl] -2,7,18,23-tetramethylsapphyrin (9b). The bis(trityl) sapphyrin derivative **9a** (72.3 mg, 0.05 mmol) was dissolved in trifluoroacetic acid (5 ml), heated to reflux, and held there for an additional 0.5 hour. After cooling, the remaining trifluoroacetic acid was evaporated off, and the desired product purified using column chromatography (silica gel; dichloromethane-methanol (17:3), eluent) and/or by crystalization from a mixture of dichloromethane-hexane-methanol (1:1:0.1). The yield of product **9b** obtained this way as its bis trifluoroacetic acid adduct is 47.0 mg (79.0%). Prior to use in transport studies, this trifluoroacetate salt was dissolved in dichloromethane and washed with a 1 M solution of NaOH in H_2O. ^1H NMR (300 MHz, $CDCl_3$): δ = -5.91 (1H, s, NH), -5.70 (2H, s, NH), -5.47 (2H, s, NH), 2.08 (6H, m, $C\underline{H}_3CH_2$), 2.13 (6H, m, $C\underline{H}_3CH_2$), 3.28 (4H, t, $CONHC\underline{H}_2CH_2$), 3.68 (4H, t, $CH_2C\underline{H}_2CONH$), 3.80 (4H, t, $CONHCH_2C\underline{H}_2$), 4.07 (3H, s, CH_3), 4.13 (3H, s, CH_3), 4.20 (3H, s, CH_3), 4.23 (3H, s, CH_3), 4.51 (4H, q, $C\underline{H}_2CH_3$), 4.68 (4H, q, $C\underline{H}_2CH_3$), 5.19 (4H, t, $C\underline{H}_2CH_2CONH$), 5.69 (2H, d, J = 7.20, C^5H), 6.35 (4H, bs, NH_2), 6.89 (2H, d, J = 7.20, C^6H), 7.50 (2H, s, CONH), 11.52 (1H, s, meso-H), 11.57 (1H, s, meso-H), 11.61 (1H, s, meso-H), 11.63 (1H, s, meso-H). ^{13}C NMR (125 MHz, $CDCl_3$ with 10% CD_3OD): δ = 12.88, 12.90, 12.98, 16.03, 17.55, 17.63, 17.70, 18.23, 18.29, 18.37, 18.43, 20.23, 20.55, 20.75, 20.89, 20.91, 20.96, 22.58, 29.59, 35.58, 37.69, 37.84, 37.91, 48.80, 48.98, 49.15, 49.32, 49.48, 49.66, 49.83, 97.79, 97.91, 97.94, 97.97, 122.99, 128.27, 129.62, 129.74, 129.84, 129.86, 129.91, 129.95, 130.06, 130.10, 130.15, 130.24, 130.32, 135.38, 135.43, 138.93, 139.53, 143.23, 144.23, 144.59, 172.66. FAB MS m/e (rel intensity) 962 (45, M^+), 963 (38, $[M+H]^+$). HRMS: Calcd for $C_{54}H_{67}N_{13}O_4$: 961.5439; found: 961.5448. Anal. calcd. for $C_{54}H_{67}N_{13}O_4$ (962.22): 67.41% C, 7.02% H, 18.92% N; found: 67.22% C, 7.08% H, 18.67% N.

3,8,17,22-Tetraethyl-12-[2-[7-(2-benzamido-6-oxopurinyl) ethyl]aminocarbonylethyl]-2,7,13,18,23-pentamethylsapphyrin (10a). The sapphyrin acid **14**, prepared as described above (63 mg, 0.1 mmol), was dissolved in 10 ml of dry DMF. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (103.2 mg, 0.5 mmol) and 1-hydroxybenzotriazole (5 mg) were added. The resulting solution was then stirred in an ice bath for 45 min. before the amino-functionalized guanosine derivative, 7-(2-aminoethyl)-2-benzamidopurin-6-one **13a**[14] (60 mg, 0.2 mmol) was added followed by 0.5 ml of dry pyridine. The reaction mixture was then stirred, first for 0.5 h at 0 °C, and then for 48 h at room temperature. Acetic acid (0.4 ml) was added and the solution stirred for a further 1 h at room temperature. After filtration, the solvent was evaporated off under high vaccum and the reaction mixture redissolved in dichloromethane (30 ml). It was then washed with dilute hydrochloric acid (3%, 15 ml), water (20 ml), aqueous sodium bicarbonate (10 ml), and then water (20 ml) once again. The organic phase was separated off and dried over sodium sulfate. After the solvent was removed in vaccuo, the desired product was purified by column chromatography (silica gel; dichloromethane-methanol (2-10%), eluent). The yield of **10a** is 81 mg (89.0%). ^1H NMR (300 MHz, $CDCl_3$, 10% CD_3OD): δ = 2.12 (12, t, $CH_2C\underline{H}_3$), 3.51 (2H, t, $CONHC\underline{H}_2CH_2$), 3.75 (2H, t, $CH_2C\underline{H}_2CONH$), 4.00 (6H, s, CH_3), 4.10 (3H, s, CH_3),

4.14 (3H, s, CH_3), 4.23 (3H, s, CH_3), 4.40 (4H, q, $C\underline{H}_2CH_3$), 4.45 (2H, t, $CONHCH_2C\underline{H}_2$), 4.65 (4H, m, $C\underline{H}_2CH_3$), 4.99 (2H, t, $C\underline{H}_2CH_2CONH$), 7.37-7.65 (5H, m, BzH), 7.74 (1H, s, C^8H), 11.55 (2H, s, meso-H), 11.65 (2H, s, meso-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.65, 12.83, 15.57, 17.70, 20.62, 20.72, 20.77, 23.41, 24.70, 30.87, 33.40, 38.62, 39.70, 45.72, 49.65, 70.02, 111.42, 122.80, 127.40, 128.50, 128.80, 129.11, 131.13, 134.32, 138.44, 141.32, 142.40, 143.53, 156.10, 157.51, 158.10, 167.73, 173.04. FAB MS, m/e (rel. intensity): 910 (78 $[M+H]^+$), 911 (41, $[M+2H]^+$). HRMS: calcd for $C_{54}H_{60}N_{11}O_3$ ($[M+H]^+$): 910.488060; found: 910.489765. Anal. calcd. for $C_{54}H_{59}N_{11}O_3$ (910.14): 71.26% C, 6.53% H, 16.93% N; found: 71.05% C, 6.44% H, 16.69% N.

3,8,17,22-Tetraethyl-12-[2-[7-(2-amino-6-oxopurinyl)ethyl]aminocarbonylethyl]-2,7,13,18,23-pentamethylsapphyrin (10b). Compound **10a** (0.1 mmol) was dissolved in a mixture of dichloromethane-methanol 1:1, v.v. (20 ml). The resulting solution was cooled to 0 °C and saturated by bubbling with ammonia. for 20 min. The reaction was then stirred at room temperature for 24 hours. The solvent was evaporated off under vaccum and the product (**10b**) isolated by recrystallization (dichloromethane-toluene 1:1) or column chromatography (silica gel; dichloromethane-methanol (5-25%), eluent). The yield of **10b** is 78%. ^1H NMR (300 MHz, $CDCl_3$, 10% CD_3OD): δ = 2.11 (6, t, $CH_2C\underline{H}_3$), 2.13 (6, t, $CH_2C\underline{H}_3$), 3.53 (2H, t, $CONHC\underline{H}_2CH_2$), 3.80 (2H, t, $CH_2C\underline{H}_2CONH$), 4.10 (9H, s, CH_3), 4.12 (3H, s, CH_3), 4.20 (3H, s, CH_3), 4.38 (2H, t, $CONHCH_2C\underline{H}_2$), 4.53 (4H, q, $C\underline{H}_2CH_3$), 4 63 (4H, m, $C\underline{H}_2CH_3$), 5.00 (2H, t, $C\underline{H}_2CH_2CONH$), 7.91 (1H, s, C^8H), 11.43 (1H, s, meso-H), 11.57 (1H, s, meso-H), 11.62 (2H, s, meso-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.83, 12.87, 15.40, 16.61, 17.34, 18.24, 20.42, 20.62, 20.77, 23.41, 29.30, 29.40, 33.40, 70.00, 70.38, 109.42, 127.10, 132.23, 138.40, 143.32, 146.53, 156.10, 157.51, 167.73, 172.8, 173.04. FAB MS, m/e (rel. intensity): 806 (52, $[M+H]^+$), 807 (43, $[M+2H]^+$). HRMS: calcd. for $C_{47}H_{56}N_{11}O_2$ ($[M+H]^+$): 806.461846, found: 806.460637. Anal. calcd. for $C_{47}H_{55}N_{11}O_2$ (806.03): 70.04% C, 6.88% H, 19.12% N; found: 69.89% C, 6.94% H, 18.99% N.

3,12,13,22-Tetraethyl-8,17-bis[2-[7-(2-benzamido-6-oxopurinyl)ethyl]aminocarbonyl]-ethyl-2,7,18,23-tetramethylsapphyrin (11a). The sapphyrin bis acid **15** (69 mg, 0.1 mmol) was dissolved in dry dimethylformamide (20 ml) and reacted with 7-(2-aminoethyl)-2-benzamido-purin-6-one **13a**[14] (90 mg, 0.3 mmol) under conditions similar to those described for the preparation of derivative **10a**. The yield of **11a** was 110 mg (88.0%). The same result was obtained when the sapphyrin bis acid chloride described above was allowed to react with the same amino component in dry dichloromethane (89.0% yield). ^1H NMR (300 MHz, $CDCl_3$, 10% CD_3OD): δ = 1.95 (6H, m, $CH_2C\underline{H}_3$), 2.18 (6H, m, $CH_2C\underline{H}_3$), 3.55 (2H, t, $CONHC\underline{H}_2CH_2$), 3.95 (2H, t, $CH_2C\underline{H}_2CONH$), 4.07 (3H, s, CH_3), 4.11 (3H, s, CH_3), 4.21 (3H, s, CH_3), 4.23 (3H, s, CH_3), 4.48 (2H, t, $CONHCH_2C\underline{H}_2$), 4.52 (4H, q, $C\underline{H}_2CH_3$), 4.62 (4H, m, $C\underline{H}_2CH_3$), 5.10 (2H, t, $C\underline{H}_2CH_2CONH$), 7.34-7.65 (5H, m, Bz-H), 7.90 (1H, s, C^8H), 11.50 (1H, s, meso-H), 11.60 (1H, s, meso-H), 11.80 (2H, s, meso-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.95, 15.67, 17.60,

18.43, 20.72, 20.81, 22.80, 23.26, 33.90, 46.32, 48.36, 63.10, 92.08, 98.80, 110.02, 123.00, 127.14, 127.73, 128.34, 128.65, 128.85, 128.95, 129.91, 131.13, 133.20, 133.32, 138.64, 138.90, 142.62, 144.00, 148.31, 151.40, 168.51, 168.80, 172.93, 173.31. FAB MS, m/e (rel. intensity): 1248, (43, $[M]^+$), 1249 (48, $[M+H]^+$). HRMS: Calcd. for $C_{70}H_{74}N_{17}O_6$ ($[M+H]^+$): 1248.6007494; found: 1248.60054.

3,12,13,22-Tetramethyl-8,17-bis[2-[7-(2-amino-6-oxopurinyl)]ethyl]aminocarbonyl] -ethyl]-2,7,18,23-tetraethylsapphyrin (11b). Compound **11a** (0.1 mmol) was deprotected and purified in accord with the procedure used to obtain **10b.** The product **11b** was isolated in 68% yield. ^1H NMR (300 MHz, $CDCl_3$, 10% CD_3OD): δ = 2.09 (3H, t, $CH_2C\underline{H}_3$), 2.11 (3H, t, $CH_2C\underline{H}_3$), 2.21 (3H, t, $CH_2C\underline{H}_3$), 2.31 (3H, t, $CH_2C\underline{H}_3$), 3.49 (2H, t, $CONHC\underline{H}_2CH_2$), 3.85 (2H, t, $CH_2C\underline{H}_2CONH$), 3.97 (6H, s, CH_3), 4.02 (6H, s, CH_3), 4.27 (2H, t, $CONHCH_2C\underline{H}_2$), 4.32 (4H, q, $C\underline{H}_2CH_3$), 4.58 (4H, q, $C\underline{H}_2CH_3$), 5.05 (2H, t, $C\underline{H}_2CH_2CONH$), 7.78 (1H, s, C^8H), 11.60 (1H, s, meso-H), 11.78 (2H, s, meso-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.13, 16.23, 17.26, 20.27, 47.32, 77.73, 106.02, 126.51, 127.94, 132.90, 138.90, 142.62, 144.00, 148.31, 151.40, 168.80, 173.3. FAB MS, m/e (rel. intensity): 1040 (25, $[M]^+$), 1041 (47, $[M+H]^+$), 1042 (39, $[M+2H]^+$). HRMS: Calcd. for $C_{56}H_{66}N_{17}O_4$ ($[M+H]^+$): 1040.5483; found: 1040.5500. Anal. calcd. for $C_{56}H_{65}N_{17}O_4$ (1040.25): 64.66% C, 6.30% H, 22.89% N; found: 64.39% C, 6.34% H, 22.65% N.

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