Nucleophilic Aromatic Substitution on Pentafluorophenyl-substituted Dipyrranes and Tetrapyrroles as a Route to Multifunctionalized Chromophores for a Potential Application in Photodynamic Therapy

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Abstract: The application of porphyrinoids in biomedical fields like photodynamic therapy (PDT) requires the introduction of functional groups to adjust their solubility in the biological environment and to allow a coupling to other active moieties or carrier systems. A valuable motif in this regard is the pentafluorophenyl (PFP)-substituent, as the PFP-group easily undergoes a regiospecific nucleophilic replacement (S_NAr) of the *para*-fluorine atom by a number of nucleophiles. Here, it is shown that - alternatively to an amino-substitution on the final porphyrinoid or BODIPY - the precursor 5-(PFP)-dipyrrane can be modified with amines (or alcohols). These dipyrranes were transformed into amino-substituted BODIPYs. Condensation of these dipyrranes with aldehydes gives access to *trans*- A_2B_2 -porphyrins and $-A_2B$ -corroles. Using pentafluorobenzaldehyde another *para*-fluorine atom can be introduced enabling the synthesis of multifunctionalized tetrapyrroles. Furthermore, alkoxy- and amino-substituted dipyrranes were applied to the synthesis of A_3B_3 -hexaphyrins. With this approach polar porphyrins can be prepared, which exhibit *in vitro* PDT activity against several tumor cell lines.

Introduction

Tetrapyrroles play an important role in various biological systems and in industrial applications.^[1] In contrast to the naturally occurring β -substituted systems (e.g., heme and chlorophyll), synthetic tetrapyrroles are often substituted at the meso-position.^[2] Depending on the substituents and the central metal ion they are applied in diverse fields such as catalysis,^[3] solar technology,^[1a,b,4] material sciences,^[5] and (photo)medicine.^[3c,6] For all of these applications compounds with a specific substitution pattern are desirable. For a use in, e.g., photodynamic therapy (PDT), amphiphilic compounds combining hydrophilic and hydrophobic substituents are necessary to ensure membrane affinity.^[7] Established procedures for the synthesis of porphyrins and corroles are available. However, these condensation reactions employing smaller building blocks (aldehydes, pyrroles, dipyrranes) to construct the macrocycle are not particularly high-yielding. Conversely, there is a continuous interest in methods that either allow an easy post-functionalization of an existing macrocycle or that use precursors which enable different functional groups to be introduced.^[8] An approach that has proven to be particularly useful for a post-functionalization of porphyrinoids is the pentafluorophenyl (PFP) substitution.^[9] The PFP group readily undergoes a regiospecific nucleophilic replacement (S_NAr) of the *para*-fluorine atom^[9e] by a diverse set of nucleophiles and is suitable for a post-modification of porphyrin^[9a-c,10] or corrole macrocycles.^[11] Various nucleophilic substitution reactions at the *para*-position of meso-PFP substituents of porphyrins or corroles with alcohols,^[9a,c,10b,12] amines,^[9a,c,10b,11,13] and thiols^[9a,c,10b,13a,b,14] are known. However, apart from this post-functionalization of a PFP-substituted macrocycle a functionalization of the precursors (aldehydes, dipyrranes) is especially attractive as this allows the specific synthesis of, e.g., *trans*- A_2B_2 -porphyrins or *trans*- A_2B -corroles, carrying two different substituents in a defined arrangement. In the literature some examples for the nucleophilic substitution of pentafluorobenzaldehyde are given^[9f,15] and recently, the first nucleophilic substitution with alcohols on PFP-dipyrrane and their subsequent use in the synthesis of porphyrins and corroles has been described.^[16] With the intention to further expand this approach here the nucleophilic substitution of amines on PFP-dipyrrane and the suitability of such functionalized dipyrranes for porphyrinoid synthesis is investigated. Thereby, the focus lies on the synthesis of porphyrinoids carrying different functional groups for biomedical applications like PDT, i.e. polar groups (hydroxyl,

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amino) which increase the solubility of the highly lipophilic macrocycle in the biological environment and groups that enable a coupling to other active moieties or carrier systems (azido, alkynyl, alkenyl).^[6]

Results and Discussion

Synthesis

Dipyrromethanes or dipyrroles are well-known precursors for porphyrinoid synthesis,^[17] employed, e.g., for preparing porphyrins, expanded porphyrins, corroles or reduced porphyrin systems like chlorins, calixphyrins or calixpyrroles (porphyrinogens).^[8a,17f,g,18] Meso- or 5-substituted dipyrroles are simply accessible by the condensation of an excess of pyrrole and the desired aldehyde though other efficient synthetic protocols have also been reported.^[8a,17a,b,e,g,19] The stability of meso-substituted dipyrroles depends on their substitution pattern with electron-withdrawing substituents stabilizing the dipyrrole toward “scrambling” (acid-catalyzed recombination of the dipyrrole) or decomposition.^[17f,20] 5-(Pentafluorophenyl)-dipyrrole (**1**) combines this higher stability compared to simple meso-phenyl- or alkyl-substituted derivatives with a high susceptibility to nucleophilic substitution.^[16] Recently, the nucleophilic substitution with alcohols on PFP-dipyrrole has been described; as for other PFP substitutions a high regioselectivity for the *para*-position was observed. Amine-substitution has also been used to modify PFP-substituted porphyrins with polar substituents in order to increase their PDT activity.^[13d] Hence we were interested in investigating the suitability of S_NAr with amines on PFP-dipyrrole. Therefore, PFP-dipyrrole **1**^[21] was synthesized and reacted with several amines (Table 1). The reactions were performed in DMSO as an aprotic polar solvent which also in the literature has been employed for nucleophilic substitution with amines on PFP-substituted compounds.^[11,13a,18e] In nearly all cases the corresponding amino-substituted dipyrrole was obtained in high yield; the functional groups introduced in this way comprised allyl, propargyl, azido,^[22] hydroxyl and amino. The somewhat lower yield for the azido-substituted compound **2d** is a compromise between full consumption of the starting material and partial decomposition due to higher temperature and longer reaction times. For 1,4-dibutylamine (Table 1, entry 6) only a partial conversion could be achieved. However, in order to avoid side reactions only short reaction times were chosen. As for the alkoxy-substituted dipyrroles^[16] the reaction proceeded regioselectively at the *para*-position of the PFP-moiety which can be seen from the disappearance of the *para*-fluorine signal in the ¹⁹F NMR spectra of the dipyrroles. With the amino-functionalized precursors at hand their suitability for the synthesis of porphyrinoids and BODIPYs was evaluated.

Table 1. Synthesis of amino-substituted dipyrroles **2a-f**.

Entry	R	Time	Product	Yield (%)
1		24 h, 30 eq.	2a	91
2		72 h, 50 eq.	2b	92
3		72 h, 50 eq.	2c	94
4		72 h, 10 eq.	2d	42
5		20 h, 50 eq.	2e	98
6		6 h, 50 eq.	2f	14 ^[a]

^[a] 50% of the starting material **1** was recovered.

Apart from tetrapyrroles their smaller siblings, the BODIPYs, have recently found increased attention for possible applications in PDT.^[23] Moreover, they are well-established as fluorescence labels for diverse biochemical applications.^[24] Employing the well-known three-step-one-pot sequence^[25] we tested with four selected examples whether the amino-functionalized dipyrroles can be used for the synthesis of the corresponding amino-substituted BODIPYs (Scheme 1). With the exception of 2-hydroxyethylamino-substituted BODIPY **3d** (Scheme 1), all functionalized BODIPYs were obtained in yields typical for the BODIPY synthesis sequence showing that such amino-substituted dipyrromethanes provide a straightforward access to amino-substituted BODIPYs.

Scheme 1. Conversion of amino-substituted dipyrroles to BODIPYs.

In principle, such amino-substituted BODIPYs may alternatively be obtained by the direct reaction of BODIPY **4** with amines. To test this route, the parent PFP-substituted BODIPY **4** was synthesized according to a recently published procedure.^[16] In the literature the nucleophilic substitution of the *para*-fluorine atom in PFP-substituted BODIPYs has been carried out on core-substituted BODIPYs in DMF at room temperature to obtain in some cases a quantitative yield.^[26] Hence, BODIPY **4** was dissolved in DMF, *n*-butylamine (8 eq.) was added, and the mixture was stirred for one hour at room temperature. After work-up and purification by column chromatography two products were isolated. Besides the desired substitution in the *para*-position of the PFP-ring, an additional substitution in the *alpha*-position of the BODIPY core was observed (Compound **5a/b**). In fact, no exclusive *para*-substitution product could be detected, either *alpha*- or a combined *alpha*- and *para*-substitution occurred (for details see Supporting Information). Variation of the reaction conditions (time, temperature or solvent, see Scheme 2) had no effect on this outcome. The *alpha*-substitution on the BODIPY core – known as oxidative nucleophilic substitution of hydrogen (ONSH) – has first been described by Dehaen and co-workers, who used it for preparing functionalized BODIPYs.^[27]

Scheme 2. Reaction of BODIPY **4** with *n*-butylamine.

These results underline that the amino-functionalized dipyrroles **2b-e** provide access to amino-substituted BODIPYs otherwise not easily accessible via direct amination.

For two of the amino-substituted BODIPYs (**3a** and **3d**) single crystals suitable for X-ray crystallography were obtained via liquid diffusion of CH₂Cl₂ and methanol. Compound **3a** solved with one molecule present in the asymmetric unit. The tilt angle of the BODIPY plane to that of the phenyl ring is 74.77(6)°. The unit cell features predominantly a head-to-head arrangement of molecules. This is aided by a hydrogen-fluorine interaction (H1...F24) of 2.399(1) Å between the BODIPY moieties (Figure 1).

Figure 1. Molecular structure of **3a** (thermal displacement 50%) and illustration of the close intermolecular packing. Hydrogens atoms and disordered positions are omitted for clarity.

Compound **3d** crystallized with one molecule in the asymmetric unit. The tilt angle of the BODIPY plane to that of the phenyl ring is 53.91(3)°. In the unit cell a head-to-tail overlap is exclusively observed with the BODIPY planes parallel to each other. This is aided by hydrogen bonds between N87-H87...O90 [2.097(17) Å], which join the two tails of a molecule together. These polymeric chains consist of dimers held together by F12-H90 interactions (Figure 2).

Figure 2. View of the molecular structure of **3d** in the crystal showing the formation of H...F bonded dimers.

Alkynyl-substituted BODIPYs like **3b** are suitable building blocks for further transformations, e.g., the copper(I)-catalyzed 1,3-dipolar cycloaddition ('click' chemistry).^[28] Therefore, in a follow-up reaction the propargylamino-substituted BODIPY **3b** was reacted with the bis(azido-propyl)-substituted corrole **6** (Scheme 3, see Supporting Information for synthesis details of **6**). Under standard conditions the corresponding corrole-BODIPY-heterotrimer **7** with flexible propyl-linkers was isolated in 41% yield. In the reaction copper(II) sulfate had to be used in excess because copper is complexed by the corrole during the reaction forming a diamagnetic copper complex which could be

characterized by standard NMR measurements.²⁹ For similar 'click' connections in the literature also the preceding complexation with copper has been described.^[29a] Conjugates like **7** have recently found attention as compounds for studying energy or electron transfer processes and as possible compounds for optoelectronic devices.³⁰

Scheme 3. Click-reaction of bis(3-azidopropyl)-substituted corrole **6** with alkynyl-substituted BODIPY **3b**.

The next step was the application of the dipyrroles in the synthesis of porphyrinoids. First, the synthesis of corroles was investigated starting with the amino-substituted dipyrroles (Table 2). As we were interested in connecting them to other molecular moieties, the alkynyl-substituted dipyrane **2c** was chosen as an example. Principally following Gryko's method of corrole synthesis^[17e] the amount of acid for the condensation step with the aldehyde was increased in this case due to the (expected) protonation of the amine. In the first example pentafluorobenzaldehyde (**8a**) was reacted with the alkynyl-substituted dipyrane **2c**. After purification the desired corrole **9a** was obtained in 10% yield (Table 2, entry 1). The possible by-product, the A₂B₂-porphyrin, was not detected in this case. Also with the other two aldehydes the corresponding A₂B corroles were obtained in acceptable yields. In the case of 3-acetoxybenzaldehyde, the A₂B₂-porphyrin was obtained as a by-product (Table 2, entry 2).

Table 2. Synthesis of amino-substituted corroles **9a-c** starting from pre-functionalized dipyrane **2c**.

Entry	R	Aldehyde	Product (Corrole)	Yield of A ₂ B-corrole (%)
1		8a	9a	10
2		8b	9b	18 ^[a]
3		8c	9c	10

^[a] The A₂B₂-porphyrin was isolated as a by product.

The successful transformation of the amino-substituted dipyrroles into corroles illustrates their capability of reacting in acid-catalyzed condensation reactions leading to tetrapyrroles. This is unexpected insofar as it might have been envisaged that the basic amino substituent, in contrast to the alkoxy-substituent,^[16] may interfere with the acid catalysis employed during porphyrinoid synthesis. Aminophenyl-substituted porphyrins are therefore usually obtained by reduction of the respective nitrophenyl-substituted porphyrins or by deprotection of acetamidophenyl-substituted porphyrins and not by direct condensation with pyrrole.^[31]

Dipyrroles are also regularly employed for the preparation of *trans*-A₂B₂-porphyrins.^[8a,17g] However, the use of meso-functionalized dipyrroles for condensation reactions to A₂B₂-porphyrins is limited especially for dipyrroles carrying sensitive functional groups.^[8a,17g,32,33] To examine scope and limitation of the reaction the conversion of several amino- and alkoxy-substituted dipyrroles into *trans*-A₂B₂-porphyrins was investigated (Table 3). The alkoxy-substituted dipyrroles **10a-c**

were synthesized according to literature procedures.^[16] Pentafluorobenzaldehyde **8a** was chosen as the second aldehyde as it has the advantage of introducing an additional PFP-substituent susceptible to subsequent S_NAr -reactions. As catalysts for these condensations, TFA and $BF_3 \cdot OEt_2$ are prominent.^[8a,34] For electron-deficient aldehydes, e.g., pentafluorobenzaldehyde, $BF_3 \cdot OEt_2$ is favored due to higher yields of porphyrin.^[35] Therefore, we decided to first employ this catalyst for the condensation.

Table 3. Condensation reaction of functionalized dipyrroles to *trans*- A_2B_2 -porphyrins (A = PFP substituent, B = R-tetrafluorophenyl substituent).

Entry	R	Acid catalyst	Product (A_2B_2)	A_2B_2 (%)	A_4 (%)	A_3B (%)	AB_3 (%)	B_4 (%)
1		$BF_3 \cdot OEt_2$	11a	6 ^[a]	-	-	18	2
2		TFA		8	-	<1	-	-
3		$BF_3 \cdot OEt_2$	11b	3 ^[a]	4	-	-	-
4		TFA		2	-	-	-	-
5		$BF_3 \cdot OEt_2$	11c	2	-	2	12	4
6		$BF_3 \cdot OEt_2$	11d	13	2	7	5	-
7		$BF_3 \cdot OEt_2$	11e	12	-	Traces	-	-

^[a] Mixture of isomers.

However, in particular for the two amino-substituted dipyrroles in addition to the desired A_2B_2 -porphyrins, other porphyrins were formed as by-products due to 'scrambling',^[36,37] for the dipyrroles **2b** and **10a** in amounts larger than the desired product (Table 3, entries 1 and 4). This observation is in accordance with a recent publication by Arunkumar and coworkers who also observed large amounts of scrambling products in the condensation reaction of 5-(4-cyanophenyl)-dipyrrole and **8a** with $BF_3 \cdot OEt_2$ as catalyst.^[38] Moreover, for product **11a** and **11b** the A_2B_2 -porphyrins were isolated as an inseparable mixture of the *cis*- and *trans*- A_2B_2 -porphyrin. Therefore, the reaction of amino-functionalized dipyrrole **2b,e** and aldehyde **8a** was repeated with TFA as the acid catalyst (Table 3, entry 2). This time a lower amount of scrambling products was observed with the desired *trans*- A_2B_2 -porphyrin being the main product. This does suggest that for the condensation of the amino-substituted dipyrroles under equilibrium conditions TFA is the preferable catalyst.

In the next step, selected *trans*- A_2B_2 porphyrins were subjected to a subsequent nucleophilic substitution of the two free *para*-fluorine atoms with alcohols and amines (Table 4). In all cases the tetrafunctionalized porphyrins carrying two different kinds of substituents in a specific arrangement could be obtained. In the reaction of different amines with porphyrin **11c** and **11d** – carrying allyloxy and propargyloxy substituents in the 5,15 positions, respectively – an unexpected side reaction was observed.

Under the reaction conditions (base, high temperature, long reaction times) the propargyloxy and the allyloxy substituents were in part split off generating the respective *para*-hydroxy-substituted compound (see Supporting Information for details). For the propargyloxy substituent this side reaction may be rationalized by a base-promoted rearrangement leading to the corresponding alkoxyallene that decomposes under the reaction conditions;^[39] a similar conversion of the propenyl group is conceivable.

Table 4. Synthesis of multifunctionalized *trans*-A₂B₂-porphyrins **12a-i**.

Entry	R ¹	R ²	Conditions	Product	Yield (%)
1			THF, KOH rt, 4 d	12a	60
2			THF, KOH rt, 24 h	12b	35
3			DMSO, 80 °C, 4 h	12c	7
4			DMSO, 80 °C, 4 h	12d	11 ^[a]
5			DMSO 80 °C, 4 h	12e	21 ^[a]
6			DMSO 80 °C, 2 h	12f	63
7			DMSO 80 °C, 8 h	12g	31
8			DMSO 80 °C, 4 h	12h	30
9			DMSO 80 °C, 6 h	12i	57

^[a] Partial split off of the propargyloxy and the allyloxy substituent was observed. For further information see Supporting Information.

During the condensation reaction of the amino- and alkoxy-functionalized dipyrroles to *trans*-A₂B₂-porphyrins a considerable amount of the corresponding AB₃-porphyrins carrying one PFP group had been obtained (cf. Table 4, entries 1 and 4). Therefore, the possibility of mono-functionalization with alcohols and amines was explored with these compounds (Table 5, compounds **13a,b**). As expected, the reactions proceeded well and the desired tetra-functionalized AB₃-porphyrins could be obtained in all cases (Table 5, entries 1-5).

Table 5. Reaction of AB₃-porphyrins **13a,b** with nucleophiles leading to **14a-e**.

Entry	R ¹	R ²	Conditions	Product	Yield (%)
1			DMSO 80 °C, 4 h	14a	53
2			THF, KOH rt, 3 d	14b	63 ^[a]
3			THF, KOH rt, 4 d	14c	43 ^[b]
4			THF, KOH rt, 3 d	14d	34
5			THF, KOH rt, 4 d	14e	43

^[a] As a by-product the compound with R² = OH was isolated in 24% yield. ^[b] Starting material was recovered in 26% yield.

After successful synthesis of BODIPYs, corroles and porphyrins starting from amino- and alkoxy-substituted dipyrroles we were also interested in applying this concept to the synthesis of expanded porphyrin systems such as hexaphyrins as prominent examples of expanded porphyrins.^[18b,40] The meso-hexakis(pentafluorophenyl)-substituted [26]hexaphyrin was first reported by Cavaleiro *et al.*^[41] and later its chemistry and synthesis was investigated in detail by Osuka and co-workers.^[18c] Most work with hexaphyrins and other expanded porphyrin systems has been performed with compounds carrying only identical substituents.^[40a] Hexaphyrins involving different substituents are rare.^[18c,42,43] The synthetic scope of [26]hexaphyrin was at first limited to reactions of pyrrole with a few fluorinated aromatic aldehydes.^[44] In 2003, Osuka and co-workers published a synthesis starting from PFP-dipyrrole and various aldehydes, involving mostly alkyl- and alkoxy-substituted benzaldehydes.^[18c] The modification of hexaphyrins is also possible via S_NAr-reactions at the *para*-position of meso-PFP substituents using alcohols and amines as nucleophiles.^[9g,45,46] However, the direct introduction of functional groups via the dipyrrole precursors is a more attractive synthetic approach, specifically for the synthesis of unsymmetrically substituted hexaphyrins. Osuka *et al.* were the first to synthesize hexaphyrins with two different kinds of substituents in the meso-

position.^[18c,42] We set out to synthesize unsymmetrical hexaphyrins starting from alkoxy- and amino-substituted dipyrroles and aldehyde **8a**. For this purpose the amino-substituted dipyrrole **2e** and the alkoxy-substituted dipyrroles **10b** and **15** were selected which were synthesized according to the literature.^[41] Following the method by Osuka *et al.*^[43] BF₃·OEt₂ was used as the catalyst. With the two alkoxy-substituted dipyrroles **10b** and **15** only the formation of the purple [26]hexaphyrins **16a** and **16b** was observed (Scheme 4). On the other hand, with the amino-substituted dipyrrole **2e** the blue [28]hexaphyrin **23** was isolated (Scheme 4). The outcome of two hexaphyrins with a different π -system is in accordance with observations in literature.^[9g,45,46] It has been described that the reaction of meso-hexakis(pentafluorophenyl)hexaphyrin with amines yielded the substituted [28]hexaphyrin, whereas the reaction with alcohols gave the expected substituted [26]hexaphyrin.^[9g,45,46] Interestingly, the [28]hexaphyrin **17** is obtained though the amino-substituent is already incorporated in the dipyrrole, suggesting that the simple presence of amino groups in the reaction accounts for the formation of the [28]hexaphyrin system. In the synthesis of hexaphyrins by-products such as porphyrin, *N*-fused pentaphyrin, heptaphyrin, octa- and nonaphyrin have often been isolated.^[39c,44] In the synthesis of **16a,b** and **17** in all cases a small amount of the respective *trans*-A₂B₂-porphyrin was isolated in 3-6% yield.

Scheme 4. Synthesis of [26]hexaphyrins **16a,b** and [28]hexaphyrin **17** starting from pre-functionalized dipyrroles and aldehydes **8a**.

The introduction of alternating *para*-substituted fluorophenyl moieties was verified by ^{19}F NMR spectroscopy in comparison to the ^{19}F NMR data of the basic meso-hexakis(pentafluorophenyl)-substituted [26]hexaphyrin.^[47] Characteristically, in the ^{19}F NMR spectrum two *para*-fluorine signals corresponding to only three fluorine atoms (of the PFP-moieties) can be detected, which ascertains the introduction of the pre-functionalized dipyrrole. Beside these two signals of the *para*-fluorine atoms, signals for the *ortho*- and *meta*-position, four signals each, are visible (Figure 3).

The alternating position of the two substituents can also be confirmed by the ^1H -NMR spectrum, which shows four sets of doublets, indicative of the symmetry (see Supporting Information).

The difference between [26]hexaphyrins and [28]hexaphyrins is clearly visible in the ^1H NMR spectra (see Supporting Information). In the ^1H NMR spectrum of [26]hexaphyrin **16a**, the inner NH protons appear as a broad signal at -2.06 ppm, the inner pyrrolic β -protons appear at -2.41 ppm and the outer pyrrolic β -protons appear as four sharp doublets at 9.09, 9.14, 9.42, and 9.45 ppm, respectively, corresponding to the $[4n + 2]$ Hückel aromaticity of the compound. In contrast, the [28]hexaphyrin **17** exhibits no signals at negative δ values (not shown, see Supporting information). This compound shows a signal for the inner pyrrolic β -protons at 2.56 ppm and the inner NH protons appear as a broad singlet at 4.48 ppm. The outer pyrrolic β -protons are observed as two sharp doublets at 7.69 and 7.91, respectively, and one multiplet at 7.81.

Figure 3. ^{19}F NMR spectrum (CDCl_3 , 376 MHz) of [26]hexaphyrin **16a**.

Absorption spectroscopy

All new compounds were fully characterized by NMR spectroscopy and mass spectrometry, additionally the absorption spectra of all new chromophores were measured. In summary, the synthesized compounds – BODIPYs, corroles, A_2B_2 - and A_3B -porphyrins, [26]hexaphyrins and the [28]hexaphyrin – exhibited absorption properties typical for the respective chromophore class, with the BODIPYs also exhibiting strong fluorescence at ~ 530 nm. The UV/Vis absorption of the compounds spans from ~ 380 to ~ 800 nm (Figure 4), with the most intensive absorption band ranging from ~ 410 nm for the porphyrins to ~ 600 nm for the [28]hexaphyrin. Within one group of chromophores (porphyrins, corroles, and BODIPYs, respectively) the different substituents also do not change absorption properties significantly, i.e. the exchange of the para-fluorine by alkoxy or amino moieties seems to have only a very limited effect on the chromophore compared to the basic PFP-substituted compounds. This limited effect has also been observed for porphyrins where more than one fluorine atom in the PFP moieties has been exchanged.^[48] It can mainly be attributed to the tilt angle of the substituted phenyl ring relative to the chromophore plane (cf. e.g. above the x-ray data of the BODIPYs) which lowers the electronic interaction.

Figure 4. Absorption spectra (normalized) of compounds **3b**, **9a**, **11d**, **16b** and **17**.

The nucleophilic substitution with amines (and alcohols) on PFP-substituted dipyranes thus allows an efficient synthesis of functionalized chromophores without affecting the basic absorption properties.

Cell testing

By combining the pre-functionalization with amines of the dipyrane precursor with the post-functionalization of the formed porphyrin, specifically substituted *trans*-A₂B₂-porphyrins could be prepared. Due to their polar substituents (OH and NH) in combination with the hydrophobic porphyrin skeleton these exhibit a 'medium' polarity which is also found in clinically applied photosensitizers such as Temoporfin^[49] or TOOKAD.^[50] Moreover, *trans*-A₂B₂-porphyrins carrying polar substituents have been reported to exhibit a high PDT activity.^[51] Hence, compounds **12e**, **12h**, **12i** and the bisamino-substituted precursor **11b** were selected for testing against four tumor cell lines (Figure 5a-d): Human epidermoid carcinoma cell lines A431 and A253, respectively, squamous carcinoma cell line CAL-27, and colorectal adenocarcinoma cell line HT29. In brief, cells were incubated for 24 h with a solution of either 0, 2 or 10 $\mu\text{mol/L}$ concentration of the photosensitizer and medium, then the medium was changed (to assure that only photosensitizer taken up by the cells contributes to the effect) and the cells were irradiated with light of 652 nm (corresponding to the longest wavelength absorption band of the porphyrins); after another incubation period (24 h) with medium the vitality of the cells was determined using the XTT-test (see experimental section for details).

As can be seen in Figure 5 none of the four compounds exhibited any significant dark toxicity at the concentrations investigated (Figure 5a-d, left side, DT = dark toxicity, i.e. toxicity in the absence of light). Regarding phototoxicity, the squamous carcinoma cell line CAL-27 seems to be especially sensitive to PDT, as a pronounced phototoxicity is observed for all four compounds at 10 $\mu\text{mol/L}$ and a lower phototoxic effect already a 2 $\mu\text{mol/L}$ for **11b**, **12h**, and **12i**. For the other three cell lines (A431, A253, HT29), apparently no phototoxicity is found at the lower concentration (2 $\mu\text{mol/L}$). With 10 $\mu\text{mol/L}$ of photosensitizer, all three tetrafunctionalized *trans*-A₂B₂-porphyrins (**12e**, **12h**, and **12i**) exhibit strong phototoxicity in the A431, A253, and HT29 cell line (comparing the cell viability at 10 $\mu\text{mol/L}$ of photosensitizer without and with light). The precursor **11b**, carrying two polar groups and two unfunctionalized PFP groups, however, shows no sign of phototoxicity in these three cell lines. As the concentrations for which a phototoxic effect is observed with **12e**, **12h**, and **12i** are still quite high, compared to clinically applied photosensitizers like Temoporfin,^[13d] further structure optimization will be necessary. However, these cell testing results suggest that the nucleophilic substitution with amines and alcohols on PFP-substituted compounds can be used to fine-tune the properties of porphyrins towards a higher amphiphilicity and membrane affinity.^[7,52] Currently, further substitution patterns on the porphyrins are investigated to increase this membrane affinity.

Figure 5a-d. Cell testing of compounds **11b**, **12e**, **12h**, and **12i** against A431, A253, CAL-27, and HT29 tumor cells (24 h incubation; DT: dark toxicity; laser: laser irradiation 652 nm 50 J/cm²).

Conclusions

In conclusion, we have developed a new and flexible access to amino-substituted porphyrinoids employing 4-amino-substituted tetrafluorophenyl-dipyrroles. It is shown that the dipyrromethane precursor, PFP-dipyrrole, readily reacts with amines affording the corresponding amino-substituted dipyrromethanes in high yields. These pre-functionalized dipyrromethanes were transformed into BODIPYs, carrying e.g. an alkyne moiety which was used in a subsequent copper(I)-catalyzed 1,3-dipolar cycloaddition to form a trimeric corrole-BODIPY conjugate. The amino-substituted dipyrroles were – in combination with a second aldehyde – also successfully employed in condensation reactions towards specifically substituted A₂B-corroles and *trans*-A₂B₂-porphyrins and even for the synthesis of novel A₃B₃-hexaphyrins. When combined with pentafluorobenzaldehyde additional reactive *para*-positions are introduced, which were used for subsequent nucleophilic aromatic substitutions. Finally, it was demonstrated that the *trans*-A₂B₂-porphyrins carrying polar hydroxy/amino substituents exhibit *in vitro* PDT activity against several tumor cell lines.

Experimental Section

General

The nomenclature and numbering (¹³C and ¹⁹F NMR spectra) are in accordance with IUPAC recommendations. THF and DMSO used as solvents for the reactions were stored over molecular sieves. All liquid reagents were added through syringes. Purchased reagents were used as received without further purification. All reactions were monitored by TLC analysis. A variable UV detector (λ = 254/366 nm) was used for detection. The preparative purification of mixtures by column chromatography was conducted on silica gel (60 M, 40–63 μm). The yields refer to analytically pure compounds. NMR spectra were recorded on a 400, 500 and 700 MHz instruments, respectively. Chemical shifts are given in parts per million (ppm) relative to the resonance of the solvent. As deuterated solvents chloroform (δ = 7.26, 77.0 ppm) and acetone (δ = 2.05, 29.0 ppm) were used. Integrals are in accordance to assignments and coupling constants are given in hertz (Hz). All ¹³C-NMR spectra are proton decoupled. In the ¹³C NMR spectra of the porphyrinoids not all expected ¹³C NMR signals could be observed; especially the signal intensity of the α-carbon atoms (carrying no hydrogen) was sometimes too low to be detected. The multiplicity is indicated as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), m (multiplet), m_c (centered multiplet) dd (doublet of doublets), td (triplet of doublets). The *ortho*- and *meta*-fluorine signals in the ¹⁹F NMR spectra of the substituted tetrafluorophenyl moieties exhibit the A,A',B,B' and A,A',X,X' coupling pattern typical for *para*-substituted aromatic compounds, in the ¹⁹F NMR spectra these signals are denoted as m_c. HRMS analyses were performed by ESI-TOF, the solvent flow rate was adjusted to 4 μL/min and spray voltage was set to 4 kV. Drying gas flow rate was set to 15 psi (1 bar) and all other parameters were adjusted for a maximum abundance of the respective [M+H]⁺. Melting points are uncorrected. Compounds **1**,^[21] **4**,^[16] 3-azidopropyl-1-amine,^[22] **10a-c**^[16] and **15**^[16] were prepared according to the literature.

General Procedures

General procedure for synthesis of substituted dipyrroles. A mixture of PFP-dipyrrole and amine in dry DMSO was stirred at 80 °C for the specific time given for each individual experiment in table 1. After the indicated time the mixture was diluted with DCM and washed several times with water. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography (the specific solvent mixture for each compound is given in the Supporting Information). The product was isolated and analyzed by ¹H, ¹³C, ¹⁹F NMR analysis and HRMS.

General procedure for synthesis of substituted BODIPYs. Under argon atmosphere the amino-substituted dipyrrole was dissolved in DCM, DDQ was added and the mixture stirred at rt temperature for 5 min. After addition of DIPEA and stirring for another 15 min, finally BF₃·OEt₂ was added and the reaction stirred for 20 min. The reaction was stopped by the addition of water, washed with water several times and the organic layer was dried with sodium sulfate, filtered and evaporated to dryness. Further purification was achieved by silica gel column chromatography (the specific solvent mixture for each compound is given in the Supporting Information). The product was isolated and analyzed by ¹H, ¹³C, ¹⁹F NMR analysis, HRMS, melting point, UV/Vis and fluorescence emission.

Reaction of 5,15-bis[(*N*-4-prop-2-ynylamino)-2,3,5,6-tetrafluorophenyl]-10-(3-hydroxyphenyl)corrole (6**) with 8-(*N*-4-prop-2-ynylamino)-2,3,5,6-tetrafluorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**3b**).** Under argon atmosphere corrole **6** (21 mg, 24 μmol) was dissolved in dry DMSO (3.0 mL). After addition of BODIPY **3b** (20 mg, 50 μmol, 2.1 eq.), CuSO₄·(H₂O)₅ (12 mg, 70 μmol, 3.2 eq.) and sodium ascorbate (57 mg, 0.28 mmol, 12 eq.) the reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with DCM, washed with water several times, dried with sodium sulfate, filtered and evaporated to dryness. The crude product was purified by column chromatography (silica gel, DCM/*n*-hexane = 1:1) to obtain the product **7** as a red-brown solid (17 mg, 41%). m.p. 185 °C. ¹H NMR (700 MHz, CDCl₃): δ = 2.32 (dt, *J* = 13.0, 6.4 Hz, 4 H, CH₂), 3.55 (dd, *J* = 13.0, 6.5 Hz, 4 H, CH₂), 4.20 (br s, 2 H, NH), 4.58 (t, *J* = 6.6 Hz, 4 H, CH₂), 4.80 (d, *J* = 6.2 Hz, 4 H, CH₂), 4.85 (br s, 2 H, NH), 6.51 (d, *J* = 3.6 Hz, 4 H, H_{pyrrole}), 6.84 (d, *J* = 3.7 Hz, 4 H, H_{pyrrole}), 6.97–6.98 (m, 1 H, Ar-H), 6.99 (d, *J* = 8.2 Hz, 1 H, Ar-H), 7.11 (d, *J* = 8.2 Hz, 1 H, Ar-H), 7.19 (d, *J* = 4.2 Hz, 2 H, β-H), 7.22–7.24 (m, 2 H, β-H), 7.32 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.45–7.47 (br s, 2 H, H_{Triazol}), 7.60–7.61 (m, 2 H, β-H), 7.89–7.82 (br s, 6 H, H_{pyrrole}, β-H) ppm. ¹³C NMR (176 MHz, CDCl₃): The signal to noise ratio of the recorded ¹³C NMR spectrum did not allow a meaningful interpretation. ¹⁹F NMR (376 MHz, CDCl₃): δ = -159.79 (m_c, *J* = 18.4 Hz, 4 F, Ar-F_{meta}), -158.48 (m_c, *J* = 16.0 Hz, 4 F, Ar-F_{ortho}), -144.70 (q, *J* = 28.4 Hz, 4 F, BF₂), -139.23 (m_c, *J* = 16.5 Hz, 8 F, Ar-F_{ortho}, Ar-F_{meta}) ppm. HRMS (ESI-TOF): *m/z* calcd. for C₇₉H₄₇B₂CuF₂₀N₁₈NaO⁺ [M+Na]⁺ 1751.3235; found 1751.3287. UV/Vis (DCM), λ_{max} [log ε (L·mol⁻¹·cm⁻¹)] 412 (5.00), 517 (4.95) nm.

General procedure for the synthesis of substituted corroles. At rt the amino-substituted dipyrrole was dissolved in MeOH and the aldehyde was added. After addition of water and hydrochloric acid the mixture was stirred at rt for 1 h. The reaction mixture was extracted with DCM several times, after that the organic layer was washed with water several times. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The residue was dissolved in DCM, DDQ was added and the mixture refluxed for 1 h. After filtration through silica gel the crude product was purified by silica gel column chromatography (the specific solvent mixture is given in the Supporting Information) and recrystallization (MeOH/water). The product was isolated and analyzed

by ^1H , ^{13}C , ^{19}F NMR analysis, HRMS, melting point and UV/Vis spectroscopy.

General procedure for the synthesis of substituted A_2B_2 -porphyrins.

Under argon atmosphere the amino-substituted dipyrane was dissolved in DCM, aldehyde and a specific catalyst as indicated for each individual experiment in table 3 was added. The reaction mixture was shielded from ambient light and stirred at rt for 16 h. DDQ was added, the mixture stirred for another 4 h and TEA was also added and stirred for another 15 min. After filtration through silica gel the solvent was evaporated to dryness. Further purification was achieved by silica gel column chromatography (specific solvent mixture is given in the Supporting Information) to obtain several successive fractions. The products were isolated and analyzed by ^1H , ^{13}C , ^{19}F NMR analysis, HRMS, melting point and UV/Vis spectroscopy.

General procedure for the synthesis of multifunctionalized A_3B - and *trans*- A_2B_2 -porphyrins, starting from porphyrins carrying PFP-substituents.

Under argon atmosphere the porphyrin was dissolved in dry THF or dry DMSO, the specific nucleophile was added (for alcohols as nucleophiles also the indicated amount of potassium hydroxide was added) and stirred for the time indicated for each individual experiment in table 4 and 5, respectively. The mixture was diluted with DCM and washed with water several times. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography (the specific solvent mixture is given in the Supporting Information) and recrystallization. The product was isolated and analyzed by ^1H , ^{13}C , ^{19}F NMR analysis, HRMS, melting point and UV/Vis spectroscopy.

General procedure for the synthesis of substituted hexaphyrins.

Under argon atmosphere the substituted dipyrane was dissolved in DCM, PFP-aldehyde and $\text{BF}_3\cdot\text{OEt}_2$ were added and the mixture stirred at 0°C for 2 h. DDQ was added and the reaction mixture was stirred at rt for 16 h. After neutralization with TEA the mixture was stirred for another 30 min and the reaction mixture was filtered (aluminum oxide) and the filtrate was evaporated to dryness. The residue was purified several times by silica gel column chromatography (the specific solvent mixture is given in the Supporting Information) to obtain two successive fractions. The first band refers to the A_2B_2 -porphyrin and the second band refers to the hexaphyrin. The products were isolated and analyzed by ^1H , ^{13}C , ^{19}F NMR analysis, HRMS, melting point and UV/Vis spectroscopy.

X-ray crystallography

Crystals were grown by dissolving the compounds in DCM and layering with MeOH. Diffraction data for all compounds were collected on a Bruker APEX 2 DUO CCD diffractometer using graphite-monochromated MoK_α ($\lambda = 0.71073\text{ \AA}$) radiation. Crystals were mounted on a MiTeGen MicroMount and collected at 100(2) K using an Oxford Cryosystems Cobra low temperature device. Data was collected using omega and phi scans and were corrected for Lorentz and polarization effects using the APEX software suite.^[53] The structures were solved with Direct Methods and refined against $|F^2|$ with the program SHELX using all data.^[54] Hydrogen atoms were fixed geometrically and allowed to ride on the parent carbon atoms, with aromatic C-H = 0.93 Å, and methyl C-H = 0.97 Å. The displacement parameters were set for aromatic H atoms at $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$, and methyl H atoms at $U_{\text{iso}}(\text{H}) = 1.5 U_{\text{eq}}(\text{C})$.

Crystal data and refinement of 3a: Crystal Data: $\text{C}_{18}\text{H}_{12}\text{BF}_6\text{N}_3$, $M = 395.12$, monoclinic, space group $P2_1/c$, $a = 10.3054(7)\text{ \AA}$, $b = 13.6051(10)\text{ \AA}$, $c = 12.1578(8)\text{ \AA}$, $\alpha = 90^\circ$, $\beta = 104.183(2)^\circ$, $\gamma = 90^\circ$, $V =$

$1652.6(2)\text{ \AA}^3$, $Z = 4$, $T = 99.99\text{ K}$, $\mu(\text{MoK}_\alpha) = 0.143\text{ mm}^{-1}$, $D_{\text{calc}} = 1.588\text{ g.cm}^{-3}$, 38280 reflections measured ($4.076^\circ \leq 2\theta \leq 50.756^\circ$), 3035 unique ($R_{\text{int}} = 0.0451$, $R_{\text{sigma}} = 0.0220$) which were used in all calculations. The final R_1 was 0.0390 ($I > 2\sigma(I)$) and wR_2 was 0.1044 (all data). *Refinement:* The structure was solved with disorder present in the allylamino moiety at N27 with both disordered parts being modelled with restraints (DFIX, SADI, ISOR) in a 51 and 49% occupancy.

Crystal data and refinement of 3d: Crystal Data: $\text{C}_{17}\text{H}_{12}\text{BF}_6\text{N}_3\text{O}$, $M = 399.11$, monoclinic, space group $C2/c$, $a = 24.1941(14)\text{ \AA}$, $b = 7.0067(4)\text{ \AA}$, $c = 19.3763(11)\text{ \AA}$, $\alpha = 90^\circ$, $\beta = 97.4840(10)^\circ$, $\gamma = 90^\circ$, $V = 3256.7(3)\text{ \AA}^3$, $Z = 8$, $T = 100.0\text{ K}$, $\mu(\text{MoK}_\alpha) = 0.150\text{ mm}^{-1}$, $D_{\text{calc}} = 1.628\text{ g.cm}^{-3}$, 44181 reflections measured ($3.396^\circ \leq 2\theta \leq 60.29^\circ$), 4802 unique ($R_{\text{int}} = 0.0174$, $R_{\text{sigma}} = 0.0086$) which were used in all calculations. The final R_1 was 0.0326 ($I > 2\sigma(I)$) and wR_2 was 0.0935 (all data).

In vitro testing

Human epidermoid carcinoma cells A431 (DSMZ) and A253 (ATCC), squamous carcinoma cells CAL-27 (DSMZ), and colorectal adenocarcinoma cells HT29 (DSMZ) were grown in Dulbecco's modified eagle medium (DMEM) from cc-pro GmbH with 10% heat inactivated fetal calf serum (FCS) from cc-pro GmbH, 1% penicillin (10 000 IU) and streptomycin (10 000 $\mu\text{g mL}^{-1}$) from cc-pro GmbH. A stock solution (2 mM) of the photosensitizer (PS) was prepared at 4°C in DMSO and kept in the dark. DMEM (without phenol red) with 10% FCS was used for further dilution to reach concentration 2 or 10 mM of the PS, respectively. In micro plates 2×10^4 cells/well were seeded with fresh medium (DMEM without phenol red) containing 10% FCS with 0 μM , 2 μM or 10 μM of the PS and incubated for 24 h. After exchange of medium (to remove any PS not taken up by the cells) the photosensitization was performed at RT with a diode laser at 652 nm and 50 J cm^{-2} (Ceralas PDT 652, CeramOptec GmbH). The cell viability of the samples was measured with a Tecan Infinite 200 microplate reader at a wavelength of 490 nm and assessed using the XTT assay^[55] and the absorbance. A wavelength of 630 to 690 nm was used to measure the reference absorbance (for measuring the non-specific readings).

Supporting Information

See footnote on the first page of this article: Synthesis details and ^1H , ^{13}C , and ^{19}F NMR and HRMS spectra for all new compounds. CCDC 1473017 (3a) and CCDC 1473016 (3d) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Entry for the Table of Contents

FULL PAPER

(Key Topic) Porphyrinoids

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Susanna Gräfe, Keith J. Flanagan,
Mathias O. Senge, Hans-Ulrich Reissig,
Nora Kulak, Arno Wiehe

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**Nucleophilic Aromatic Substitution
on Pentafluorophenyl-substituted
Dipyrranes and Tetrapyrroles as a
Route to Multifunctionalized
Chromophores for a Potential
Application in Photodynamic Therapy**

Alternatively to an amino-substitution on the final porphyrinoid or BODIPY the precursor PFP-dipyrane can be modified with different amines (or alcohols). These dipyranes were transformed to specifically substituted corroles, porphyrins, hexaphyrins and BODIPYs. Selected porphyrins were tested for their PDT activity.