New Flavins and Their Application to Chemical Photocatalysis

Dissertation

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vorgelegt von

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A good scientist is a person
in whom the childhood quality
of perennial curiosity lingers on.
Once he gets an answer,
he has other questions.

Frederick Seitz

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Table of contents

Summary

The presented dissertation comprises the synthesis of substituted flavins and their application as photocatalysts. Chapter 1 contains a short introduction into possible redox states of flavins, especially under light irradiation and previous applications of flavin-based photocatalysts in particular of our working group are presented. The synthesis of various flavin-thiourea derivatives is described in chapter 2. These compounds and mixtures of flavins with thiourea were successfully applied to the photooxidation of 4-methoxybenzyl alcohol. High conversions were achieved with such catalytic systems and also the use in preparative experiments. However, in water as reaction media, the reaction proceeds faster and with increased efficiency. In contrast to reactions in acetonitrile, also non activated benzyl alcohols can be oxidized. Chapter 3 contains the experiments in water and the immobilization of flavins on solid support or in polyethylene. Simple separation from the reaction mixture and possible recycling make these catalysts valuable for application, however, showing the same reactivity compared to homogeneous solution. Templated flavins were synthesized by fixing the chromophore together with a substrate binding site on a platform (chapter 4). Such assemblies increase the probability for a photoinduced electron transfer reaction, therefore optimizing the reactivity of flavins under light irradiation. A novel synthetic approach to 3-N-arylation by reaction with phenyl boronic acids is presented in chapter 5. For the first time, this method enables a direct coupling of aromatic systems to the 3-N-position of a flavin. Terminatory, chapter 6 contains the synthesis of a new diamin derived from Kemp´s Acid. This easily accessible rigid platform makes the composition of structurally defined compositions feasible.

Zusammenfassung

Die vorliegende Dissertation beinhaltet die Synthese von artifiziellen Flavinen und deren Einsatz als Photokatalysatoren. Kapitel 1 enthält eine kurze Einführung in mögliche Oxidationszustände von Flavin-Systemen, insbesondere unter Lichteinstrahlung und beschreibt bisherige Anwendungen von Flavin-basierten Photokatalysatoren speziell in unserer Arbeitsgruppe. Im zweiten Kapitel wird die Synthese zahlreicher Flavin-Thioharnstoff-Konjugate vorgestellt. Diese Katalysatoren und Mischungen von unfunktionalisierten Flavinen mit Thioharnstoff wurden für die Photooxidation von 4-Methoxybenzylalkohol in Acetonitril eingesetzt. Diese Katalysatorsysteme erreichen sehr hohe Umsätze und können auch in präparativen Ansätzen verwendet werden. In Wasser als Reaktionsmedium läuft die Photooxidation deutlich schneller ab als in Acetonitril, was zu noch höherer Effektivität der Flavin-Katalysatoren führt. Im Gegensatz zu Reaktionen in Acetonitril können auch verschiedene nicht aktivierte Benzylalkohole oxidiert werden. Kapitel 3 beinhaltet die Experimente in Wasser und auch die Immobilisierung von Flavinen auf Kieselgel und in Polyethylen. Die immobilisierten Flavin-Photokatalysatoren zeichnen sich durch einfache Separation vom Reaktionsgemisch und durch mögliches Recycling aus, wobei die gleichen Substrate wie in homogener Lösung oxidiert werden. Um die Reaktivität angeregter Flavine noch besser nutzen zu können, wurden Flavin-Template synthetisiert, bei denen das Chromophor gemeinsam mit einer Substrat-Bindungsstelle starr auf einer Plattform fixiert wurde (Kapitel 4). Dadurch wird die Wahrscheinlichkeit für einen photoinduzierten Elektronentransfer zwischen angeregtem Flavin und Substrat erhöht. Kapitel 5 beschäftigt sich mit einer neuartigen Methode zur Funktionalisierung von Flavinen in 3-N-Position – der Kupplung mit Phenylboronsäuren. Diese Methode erlaubt erstmals das Einführen eines aromatischen Systems direkt an die 3-N-Position eines fertig aufgebauten Flavins. Abschließend widmet sich Kapitel 6 der Synthese eines Diamins, das von Kemp´s Trisäure abgeleitet ist und eine leicht zugängliche, inerte und starre Plattform für den Aufbau geometrisch vororientierter Verbindungen darstellt.

Chapter 1

Flavin Photocatalysts with Substrate Binding Sites*

Introduction

Photochemical activation of inert substrates is desirable whenever chemical storage of light energy is attempted. The best example of this process is found in nature with its highly efficient and sophisticated photosynthesis. To mimic photosynthesis by a technical process is one of the engaging challenges in chemistry, molecular biology, and physics. Recent heterogeneous approaches addressed the photocatalytic reduction of carbon dioxide with silicates,[1] semiconductors[2] or metal oxides and hydrogen.[3] Homogeneous photocatalysts may allow a more rational optimization, due to their defined structure. Examples of molecular photocatalysts are cyclodextrin-stabilized palladium clusters used for the reduction of hydrogen carbonate,[4] the photohydrogenation of alkynes[5] or the photooxidation of benzyl alcohol.[6]

The initial key step of photoredox catalysis is the light induced transfer of an electron. Such processes have been intensively studied with the help of covalent and non-covalent connected electron-donor-acceptor dyads.[7] As expected from Marcus theory,[8] the efficiency of the electron transfer was

* This chapter was written by H.S. as a summary of the contribution of our group in the DFG priority programm "Use of Secondary Interaction for Directed Functionalization of Less Reactive Substrates" (SPP 1118) and will be published in a book in March 2009.

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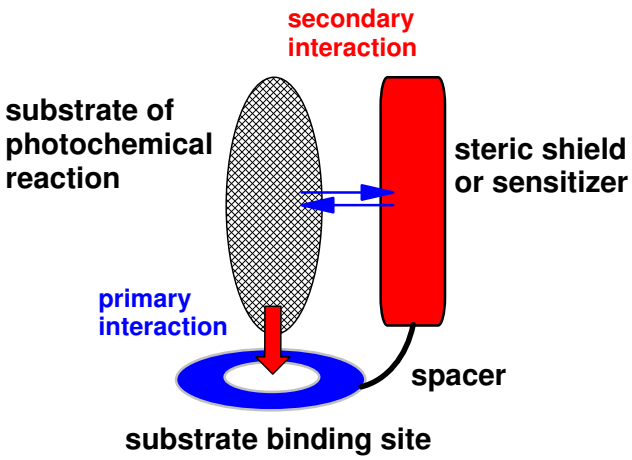
shown to be strongly dependent on the distance and the orientation of the reaction partners. An efficient and selective photocatalyst should therefore reversibly bind the reaction substrate, rather than undergo a diffusion controlled reaction, to ensure optimal interaction with the chromophore of the catalytic system. Examples of such templated photochemistry[9] showed high selectivity; chiral templates even allow controlling the absolute stereochemistry of a reaction.[10] Scheme 1.1 shows the general structure of a template guiding a photochemical reaction. The shield restrains the orientation of the photoactive reactants or participates in the reaction, if it is a sensitizer. A recent review has summarized the achievements in the field of photochemical reactions with topological control.[11] In this report we will focus on photocatalysts with substrate binding site bearing flavin* as chromophore.

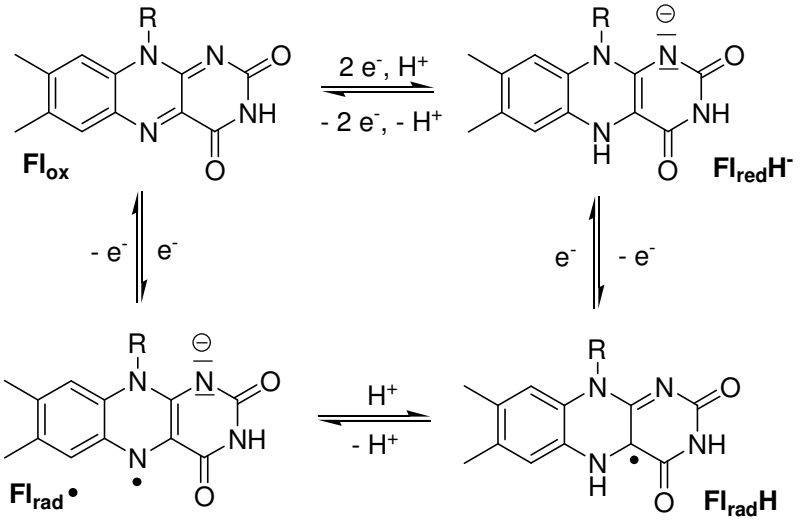


Scheme 1.1 General structure of a template controlling and enhancing photochemical homogeneous reactions

Flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) are prominent redox co-factors in many enzymes. Their redox properties, UV absorption and reactivity change with substitution, non-covalent interactions, such as hydrogen bonds, and the nature of the surrounding protein.[12] Numerous flavoenzyme models which try to simulate a particular feature of the protein have been studied.[13] Nearly all of them investigate

* Throughout this work, the term flavin is used synonymously with 7,8-dimethyl-benzo[*g*]-pteridine-2,4-(3*H*,10*H*)-dione (7,8-dimethylisoalloxazine).

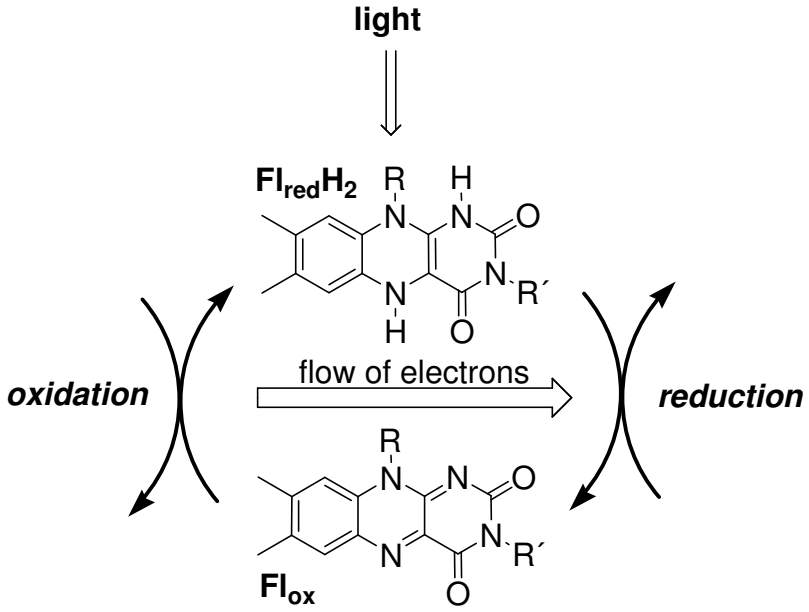
changes of the chromophores redox potential, but the use of modified flavins in chemical catalysis is less common.[14] Scheme 1.2 shows the typical redox and protonation states of flavin.[15] The oxidized form of flavin is reduced via a direct two-electron transition to the flavohydroquinone anion. On the other hand, after one-electron reduction to the semiquinone radical or radical anion, it can accept a second electron to reach the fully reduced form. The different states are easily distinguished by UV/Vis spectroscopy.



Scheme 1.2 Typical redox and protonation states of flavins

Principally, both halves of the flavin redox cycle can be utilized for photocatalytic conversions (scheme 1.3). If substrates are to be reduced (right side), a sacrificial electron donor is added to regenerate the reduced form of flavin. Typical electron donors are EDTA or triethyl amine, which reduce flavins efficiently upon irradiation by visible light.[13] For the oxidation of substrates (left side) in most cases oxygen serves as terminal oxidant regenerating the oxidized flavin. The excited states of reduced and oxidized flavin provide sufficient redox energy,[16] as estimated by the Rehm-Weller equation,[17] to convert even substrates with low chemical reactivity, which recommends its use in photocatalysis.

The survey of templated flavin photocatalysis starts with examples of photoreductions and will continue with photooxidations.

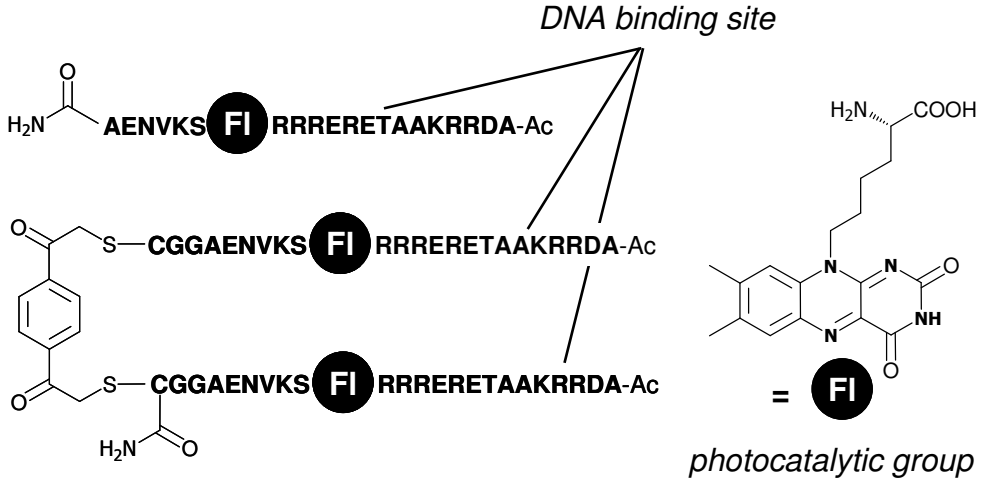


Scheme 1.3 Photocatalysis with flavins

Templated flavin photoreductions

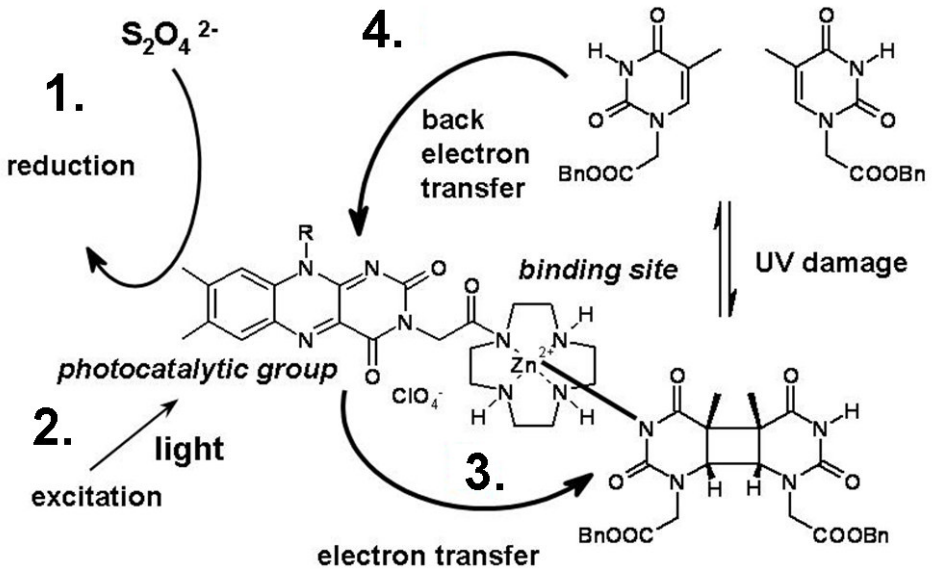
Flavin derivatives have been used as the sensitizing chromophore for the reductive cycloreversion of pyrimidine photocycloadducts in DNA strands. These cyclobutanes occur in nature as a result of environmental damage to DNA exposed to UV-light. A bis-pyrimidine cyclobutane is formed e.g. between two adjacent thymine residues in DNA-strands, thus, destroying the genetic information and leading to cell death or skin cancer.[18] The DNA lesions are selectively recognized by the bacterial enzyme DNA photolyase and repaired by photoinduced electron transfer using a non-covalently bound reduced flavin as electron donor. To mimic and understand this repair mechanism, artificial DNA-repair systems were prepared.[19] Covalent constructs of flavins and synthetic bis-pyrimidine cyclobutanes proved the principle of photo repair. Carell and co-workers incorporated flavin as an artificial amino acid into oligopeptides via a modified Fmoc peptide synthesis protocol.[20] These peptides were able to repair short oligonucleotide sequences containing bis-pyrimidine cyclobutanes, such as 5´-CGCGT-U=U-TGCGC-3´. Irradiation in the presence of EDTA led to fully reduced flavin species, which are the active compounds in nature´s photolyase, too. The

reduced flavin then cycloreverts the cyclobutane and thus repairs the DNA lesions (scheme 1.4). Dimerized oligopeptides were synthesized to mimic helix-loop-helix proteins and to maximize the DNA-binding properties.



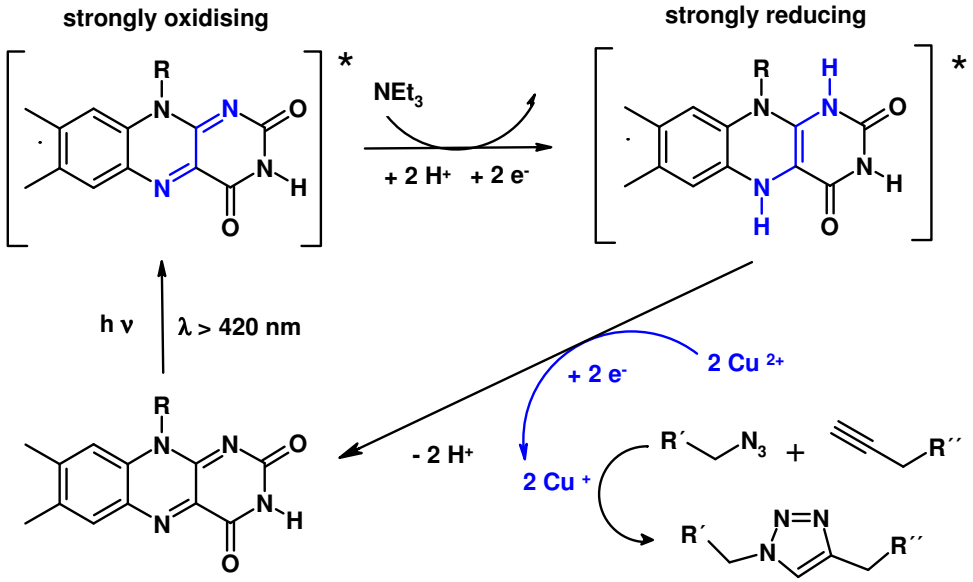
Scheme 1.4 Artificial flavin-containing peptides for DNA repair

In 2004 Wiest et al. described an even more simplified photolyase model which reversibly coordinates bis-pyrimidine cyclobutanes with millimolar affinity in both protic and non-protic solvents.[21] Irradiation by visible light cycloreverts the dimeric compounds into monomeric pyrimidines: The excited flavin chromophore is reduced (1), transfers an electron onto the nucleobase cyclobutane dimer (2), which after cycloreversion (3) returns the electron to flavin (4) to close the catalytic cycle. The substrate binding site is essential to achieve an efficient conversion. However, the reaction ceases at about 75% conversion. The monomeric heterocyclic products of the reaction compete with their imide groups for coordination to the metal complex similar to enzymatic product inhibition and block further binding of bis-pyrimidine cyclobutanes (scheme 1.5).



Scheme 1.5 A functional model of photolyase activity

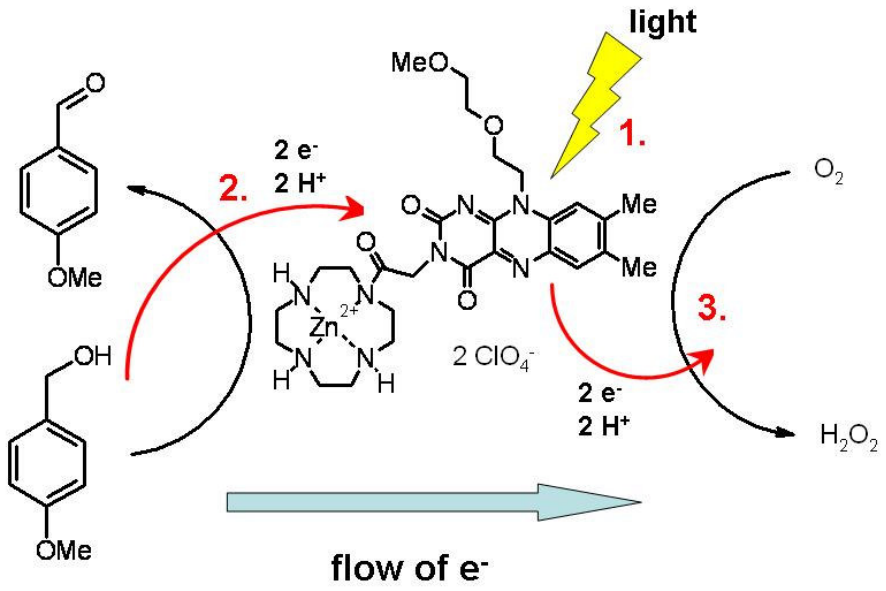
If the product of a flavin photoreduction is itself a catalytic active species, modulation of a catalytic reaction by light becomes possible. This was realized with tetraacetyl riboflavin and copper(II) ions as substrate of the photoreduction in the presence of amines as electron donor.[22] No additional substrate binding sites on flavin are necessary for an efficient photoreduction to copper(I), as the metal ions coordinate to heteroatoms of the flavin.[23] The generated copper(I) ions serve as catalyst for a subsequent azide–alkyne cycloaddition (Huisgen reaction, scheme 1.6). It was shown that the light quantity correlates with the amount of copper(I) and the rate of the cycloaddition. The system is an example of signal amplification by regulated catalysis: one photon induces the synthesis of 15 triazoles by catalyzed cycloaddition.



Scheme 1.6 Flavin photoreduction of copper(II) to copper(I) and subsequent copper(I)-catalyzed cycloaddition

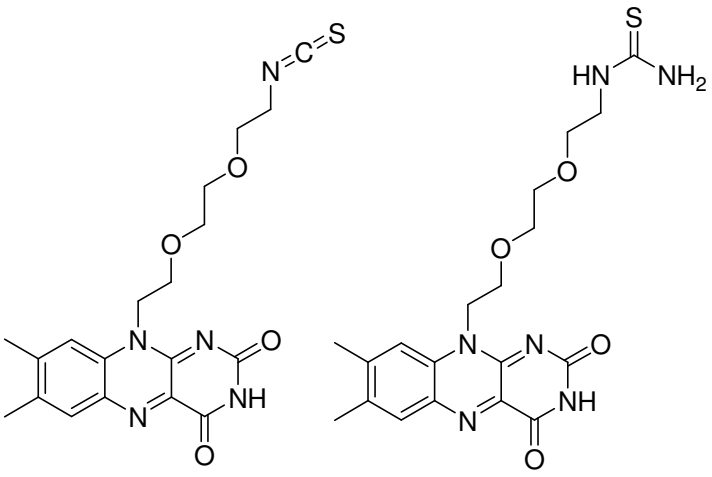
Templated flavin photooxidations

The use of flavin as photooxidant has been described in many examples.[24] However, observed selectivity and stability are not satisfactory for many cases. Therefore, optimization by the addition of a substrate binding site was attempted. Azamacrocyclic complexes, such as zinc(II)-cyclene, are Lewis-acids and coordinate Lewis-basic functional groups even in polar protic solvents. A hybrid compound of zinc(II)-cyclene and flavin was therefore prepared and its properties in the oxidation of 4-methoxybenzyl alcohol were tested (scheme 1.7).[25] The coordination of the substrates hydroxyl group by the metal complex brings it in close proximity to the flavin. After light irradiation (1), a photoinduced electron transfer from the alcohol to the flavin occurs (2). Reoxidation (3) of the flavin by oxygen dissolved in the solution regenerates the oxidized form of the flavin photocatalyst. The reaction proceeds in acetonitrile and aqueous solutions with catalytic amounts of the flavin sensitizer (10 mol%) leading to 90% conversion after two hours of irradiation.



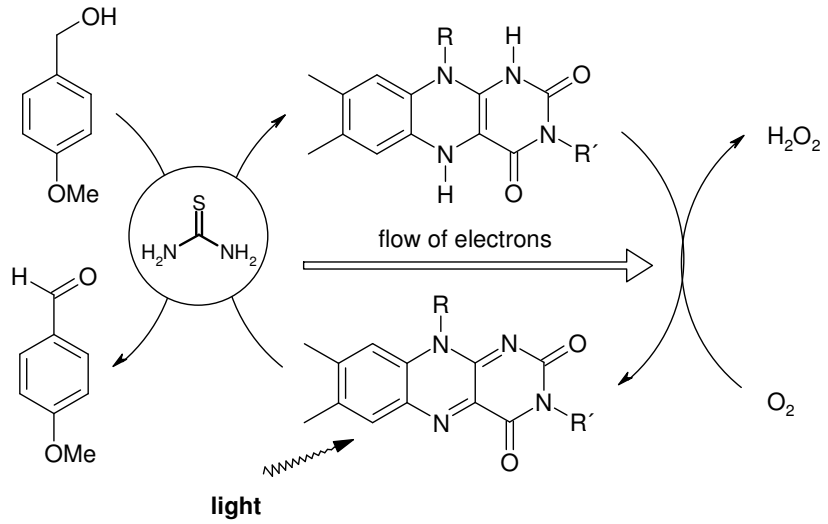
Scheme 1.7 Schematic representation of the catalytic oxidation of 4-methoxy-benzyl alcohol by a flavin unit

Thiourea is well known for its ability to reversibly form hydrogen bonds with a variety of functional groups. This has been widely used in the design of supramolecular aggregates and organocatalysts. Thiourea derivatives of flavin were therefore selected as a potential photocatalyst lead structure.[26] Their preparation uses highly reactive flavin isothiocyanates, which were derived from flavin amines, accessible by modified Kuhn synthesis. Scheme 1.8 shows two of the compounds from a larger series that was prepared.



Scheme 1.8 Flavin isothiocyanate and thiourea derivatives

Thiourea derivatives of flavin showed high activity in the catalytic photooxidation of benzyl alcohol. In a very clean reaction, the complete conversion of the alcohol was achieved within one hour of irradiation by a light emitting diode (440 nm, 5 W) in air and 10 mol% of flavin derivative as photocatalyst. The photostability of the catalyst is good and up to five times recycling is possible. With a catalyst loading of 0.1%, high turn over numbers of up to 580 were achieved. The quantum yield of the intermolecular reaction is in the order of Φ~0.02. Values for comparison of the efficiency are available for the enzyme photolyase (Φ=0.7–0.9)[19] and artificial photolyase models (Φ=0.005–0.11)[13j,27] cleaving pyrimidine cyclobutanes intramolecularly. A series of control experiments was performed to reveal the role of thiourea enhancing the oxidation. Surprisingly, mixtures of thiourea and flavins show a similar rate enhancing effect on the alcohol oxidation than covalent flavin-thiourea hybrid compounds, which disproves the idea of thiourea acting as a binding site. A comparison of the redox potentials of flavin, thiourea and the benzyl alcohol substrate indicates the possible role of thiourea as an electron transfer mediator between the alcohol and flavin (scheme 1.9).



Scheme 1.9 Thiourea assisted flavin photooxidation of 4-methoxybenzyl alcohol

Summary and outlook

Flavin derivatives have been successfully used as photocatalysts for reductions and oxidations. The introduction of binding sites typically enhances the selectivity and the efficiency of the reactions if compared to diffusion controlled processes.

The photostability of flavins remains a concern in the development of efficient catalysts. However, fine tuning of the reaction conditions may allow overcoming the problem. Even if all physical parameters, such as redox potential, excitation energies and lifetimes of excited states are available, the coupling of the physical processes of chromophore excitation and electron transfer with a chemical reaction is difficult and still has to relay on experimental trials. Flavin mediated photocatalytic reactions leading to nucleophilic products, such as the reduction of carbonyl compounds to alcohols, are still a challenge, because of the facile covalent addition of the products to flavin destroying the chromophore. Reactions at interfaces and new techniques of non-covalent immobilization of catalyst in ionic liquids or fluorous phases may provide solutions to this problem and pave the way for more frequent use of flavins as photoactive groups in photocatalysis activating less reactive molecules.

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Chapter 2

Thiourea-Enhanced Flavin Photooxidation of Benzyl Alcohol*

Introduction

Flavins are nature's beloved redox co-factors.[1,2] They occur ubiquitously in a number of enzymes that bring the most essential biochemical processes about, mostly in the form of flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) co-factors. Their redox properties, reactivity and selectivity for the desired process are fine-tuned by substitution, non-covalent interactions and the presence of the surrounding protein, and their function can therefore be tailored to the task required. Their reactivity even increases upon irradiation, making them strong oxidizing agents.[3–6] A large number of flavoenzyme models which try to simulate a particular feature of the protein in a minimized system have been studied.[7–29] Most of them focus on the changes of the flavin chromophore redox potentials caused by non-covalent interactions. However, examples where the modification of flavin reactivity was applied to chemical catalysis are less common.[30–39] In this work, we report flavin molecules functionalized with a thiourea group[40-42] which was supposed to bind reversibly substrates of photooxidation reactions to keep them in the vicinity of the excited chromophore. This should increase the electron transfer efficiency by making the process intramolecular rather then diffusion-controlled.[33,34,43]

* The investigations presented in this chapter were carried out together with Dr. Jiří Svoboda and have already been published. J.S. synthesized the molecules **4**, **7**, **12**, **16**, **18**, **27** and **28** and performed the ^{19}F NMR titrations. The kinetic experiments were equally shared between J.S. and H.S.

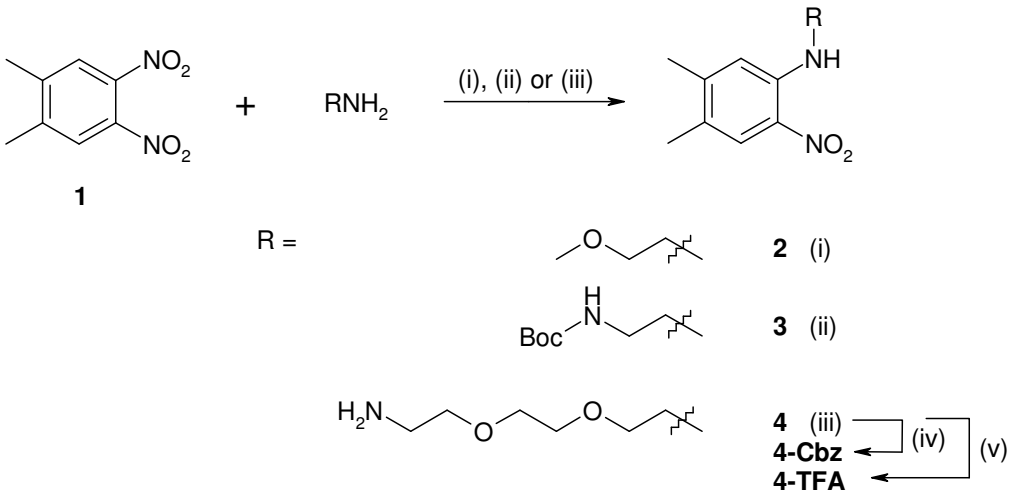
J. Svoboda, H. Schmaderer, B. König, *Chem. Eur. J.* **2008**, *14*, 1854–1865.

To investigate possible effects of thiourea functionalization, the activity of the new flavin molecules was studied on the photooxidation of 4-methoxybenzyl alcohol in aerial environment.[44]

Results and discussion

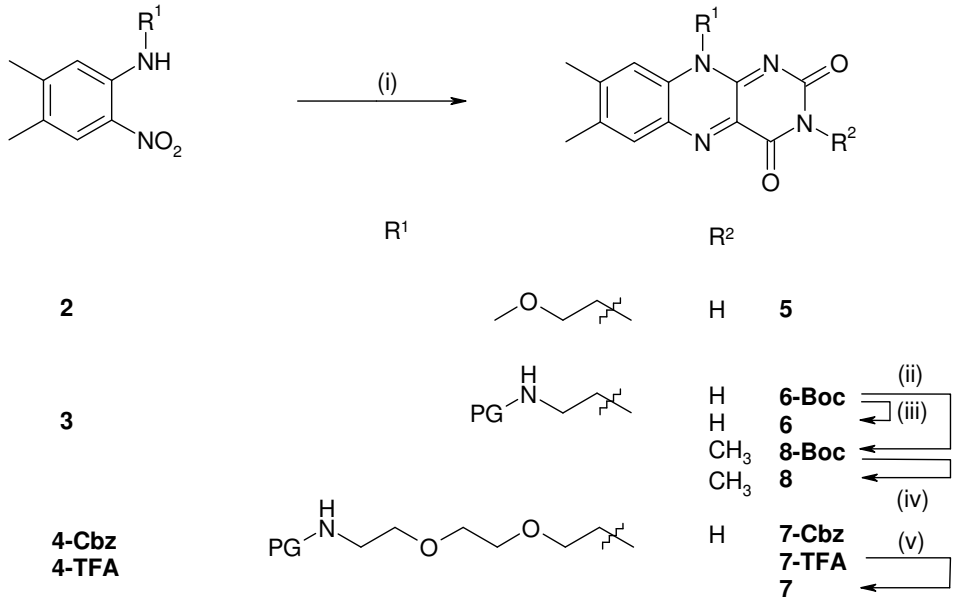
Synthesis

The synthesis of the new compounds follows the Kuhn synthesis.[45] The preparation of 4,5-dimethyl-1,2-dinitrobenzene (**1**) was optimized to obtain the starting material in sufficient quantities (see appendix A). Heating dinitro compound **1** with 3-oxabut-1-yl amine, 2-(*tert*-butyloxycarbonyl-amino)ethyl amine or symmetrical 3,6-dioxaoctyl-1,8-diyl diamine led to *N*-substituted 2-nitroanilines **2–4** (scheme 2.1). The glycol chains increase the solubility of the target molecules in polar solvents, and the amino groups were converted to thiourea moieties later on. Although 3,6-dioxaoct-1,8-diyl diamine was not mono-protected, twofold substitution was not observed. However, the side chain amino group disturbs the course of the cyclocondensation reaction of the phenylene diamine intermediate with alloxane hydrate, and had to be protected before completion of the flavin synthesis. The flavin skeleton is sensitive to bases,[46,47] and protective groups which require removal by base are therefore not suitable. Suitable protective groups were benzyloxycarbonyl and trifluoroacetyl protective group.



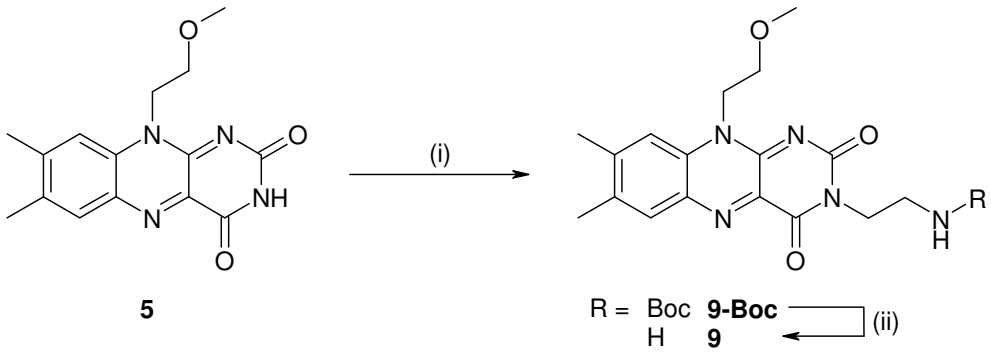
Scheme 2.1 *ipso*-Substitution of dinitro compound **1** with amines and protection of the side chain amino group. Conditions: (i) 3-Oxabut-1-yl amine (neat), 80 °C, 6 h, 99% (ii) Pyridine, 24 h, 90 °C, 46% (iii) EtOH, ∆, 62 h, 51% (iv) Cbz-Cl, TEA, DCM, r.t., 30 min, 64% (v) Ethyl trifluoroacetate, TEA, MeOH, r.t., 24 h, 83%

The synthesis of the flavin skeleton was completed by reduction of the remaining nitro group and cyclocondensation of the resulting phenylene diamine intermediates with alloxane hydrate in the presence of boric acid to yield flavins **5**, **6-Boc**, **7-Cbz**, and **7-TFA** (scheme 2.2). Flavin **6-Boc** was *N*-methylated by dimethyl sulphate to give the corresponding analogue **8-Boc**. *tert*-Butyl carbamates **6-Boc** and **8-Boc** were cleaved by hydrogen chloride and yielded 10-(2'-aminoethyl) flavins **6●HCl** and **8●HCl**. Unfortunately, the benzyloxycarbonyl protective group of flavin **7-Cbz** could not be removed by any of the usual methods.[48,49] Cleavage of the trifluoroacetamide **7-TFA** in strongly acidic environment[50] led to the quantitative formation of aminoglycol flavin **7●HCl**.



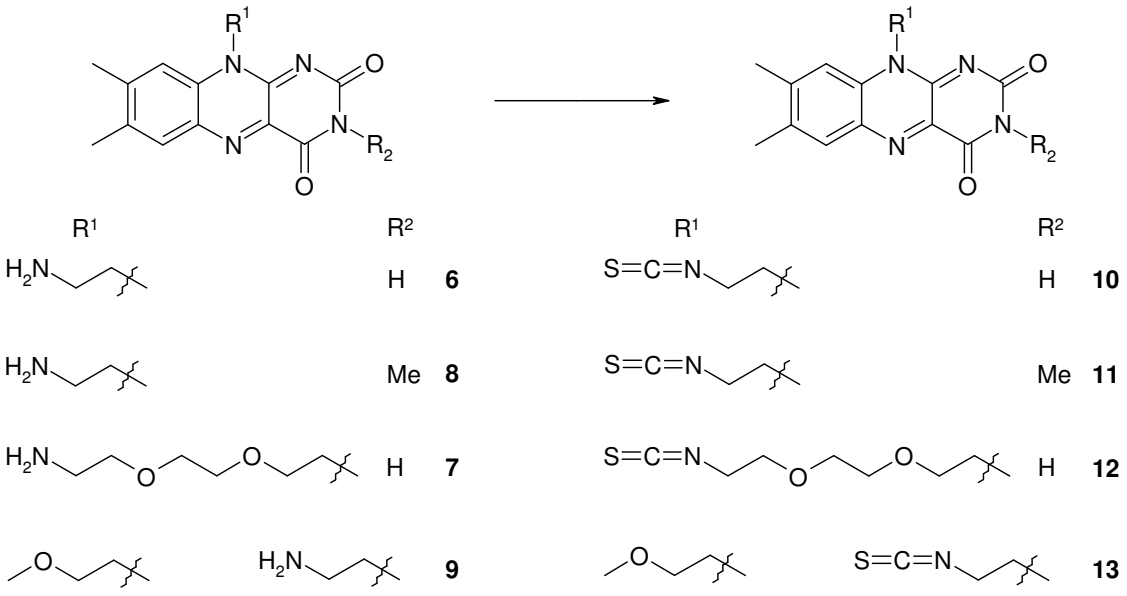
Scheme 2.2 Completion of flavin synthesis. Conditions: (i) 1. H_2, 10% Pd/C, AcOH (compounds **2**, **3**, and **4-TFA**), or tin(II) chloride, EtOH, Δ, 72 h (compound **4-Cbz**) 2. Alloxane hydrate, H_3BO_3, AcOH, r.t., 50% (**5**), 47% (**6-Boc**), 71% (**7-Cbz**), 48% (**7-TFA**) (ii) Dimethyl sulphate, Cs_2CO_3, DMF (dry), r.t., overnight, 53% (iii) HCl, DE, $CHCl_3$, r.t., overnight, 83% (iv) HCl, DE, CHCl3, rt, overnight, 100% (v) HCl (aq) (6 M), 95–100 °C, 90 min, 100%

Flavin **5** was N-alkylated by 2-(*tert*-butyloxycarbonylamino)ethyl bromide (scheme 2.3). Cleavage of *tert*-butylcarbamate **9-Boc** by hydrogen chloride yielded the corresponding 3-(2'-aminoeth-1'-yl) flavin **9•HCl**.



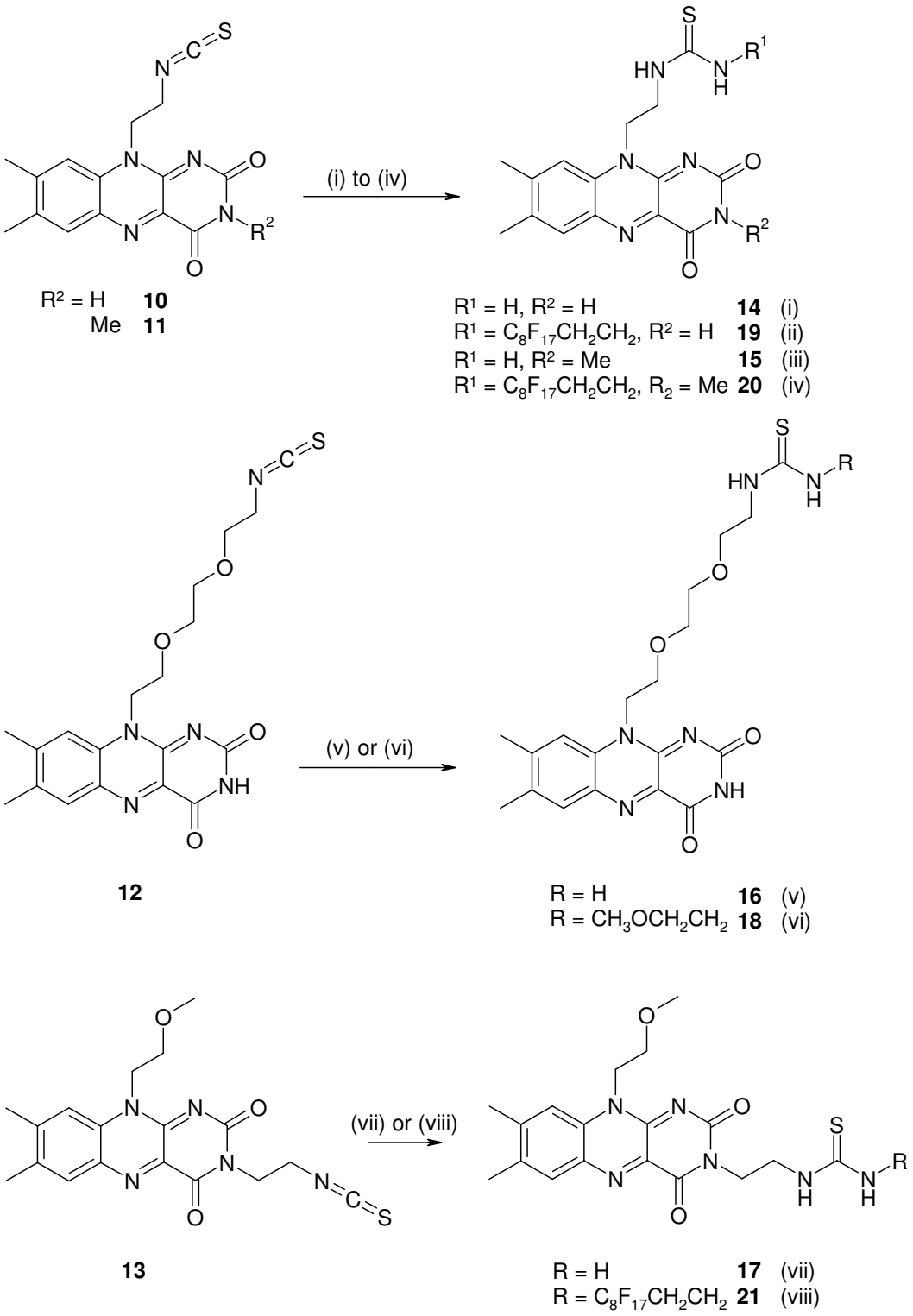
Scheme 2.3 Synthesis of 3-(2'-aminoeth-1'-yl) flavin **9**. Conditions: (i) 2-(*tert*-Butyloxycarbonylamino)eth-1-yl bromide, K_2CO_3, NaI, DMF (dry), r.t., 3 d, 54% (ii) HCl, DE, r.t., 95%

Amines **6**–**9** were then converted to the corresponding isothiocyanates **10-13** by reaction with thiophosgene in a two-phase solvent mixture (scheme 2.4). The reactions were clean, rapid and very good yields of the isothiocyanates were obtained.



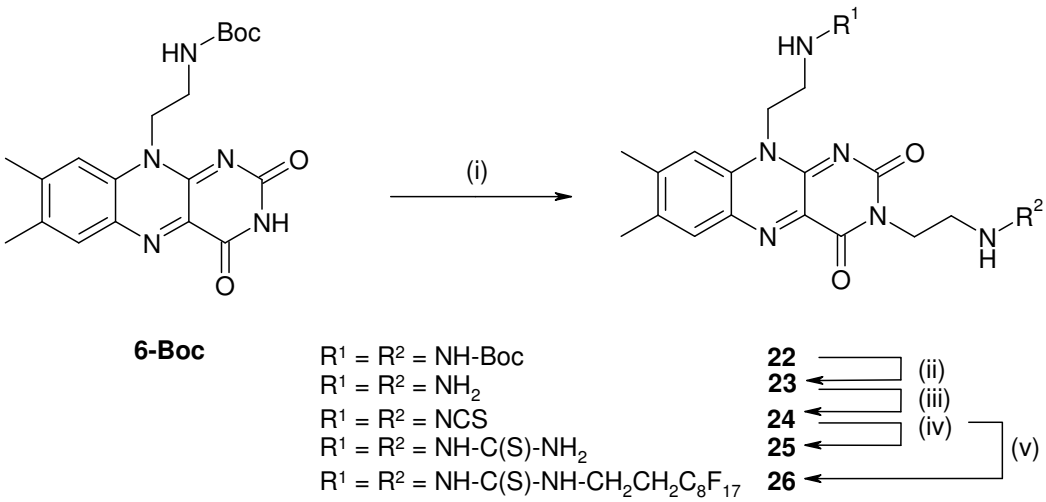
Scheme 2.4 Synthesis of isothiocyanates **10–13**. Conditions: thiophosgene, DCM, $CaCO_3$, H_2O, r.t., 87% (**10**), 79% (**11**), 97% (**12**), 89% (**13**)

The reaction of isothiocyanates with amines leads to the formation of substituted thioureas.[40,51] Flavin isothiocyanates **10–13** show high reactivity, and corresponding thioureas are obtained with excellent yields.
Passing gaseous ammonia through the solution of a given isothiocyanate leads to mono-substituted thioureas **14–17** (scheme 2.5) which are less soluble than the starting materials and were isolated by filtration or trituration in 44–100% yield. Reaction with primary amines led to *N,N'*-substituted thioureas **18–21**. A hydrophilic chain (thiourea **18**) or fluorophilic chain (thioureas **19–21**) were introduced to increase the solubility of the molecules in hydrophilic or fluorophilic solvents, respectively.



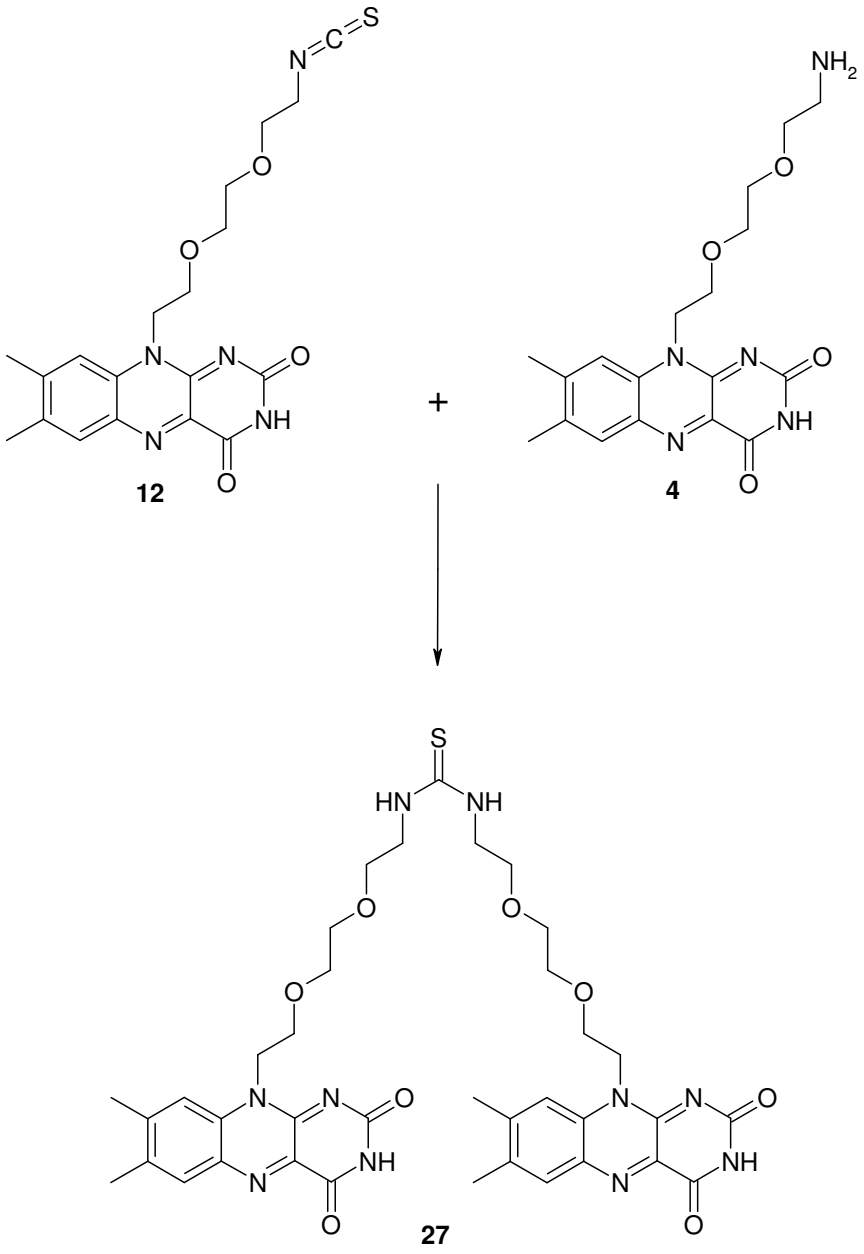
Scheme 2.5 Synthesis of thioureas **14–21** from isothiocyanates **10–13**. Conditions: (i) NH_3 (g), MeOH, r.t., 3 h, 76% (ii) Perfluorooctylethyl amine, TEA, $CHCl_3$, Δ, overnight, 68% (iii) NH_3 (g), $CHCl_3$, r.t., 2 h, 68% (iv) Perfluorooctylethyl amine, TEA, $CHCl_3$, Δ, overnight, 79% (v) NH_3 (g), $CHCl_3$, r.t., 3 h, 44% (vi) 3-Oxa-but-1-yl amine, $CHCl_3$, Δ, 2.5 h, 100% (vii) NH_3 (g), $CHCl_3$, r.t., 3 h, 100% (viii) Perfluorooctylethyl ammonium chloride, TEA, Δ, 18 h, 67%

Flavins containing two thiourea groups were prepared starting from flavin **6-Boc** which was alkylated with 2-(*tert*-butyloxycarbonylamino)ethyl bromide yielding flavin **22** (scheme 2.6). Removal of both Boc protective groups led to bis(2'-aminoethyl) flavin dihydrochloride **23●2HCl** in quantitative yield. Two-fold reaction with thiophosgene under the conditions mentioned above led to bis(isothiocyanatoethyl) flavin **24**. Reaction of both isothiocyanate groups with ammonia gave compound **25** containing two mono-substituted thiourea groups, and reaction with perfluorooctylethyl amine yielded compound **26** containing two *N,N'*-substituted thiourea groups.

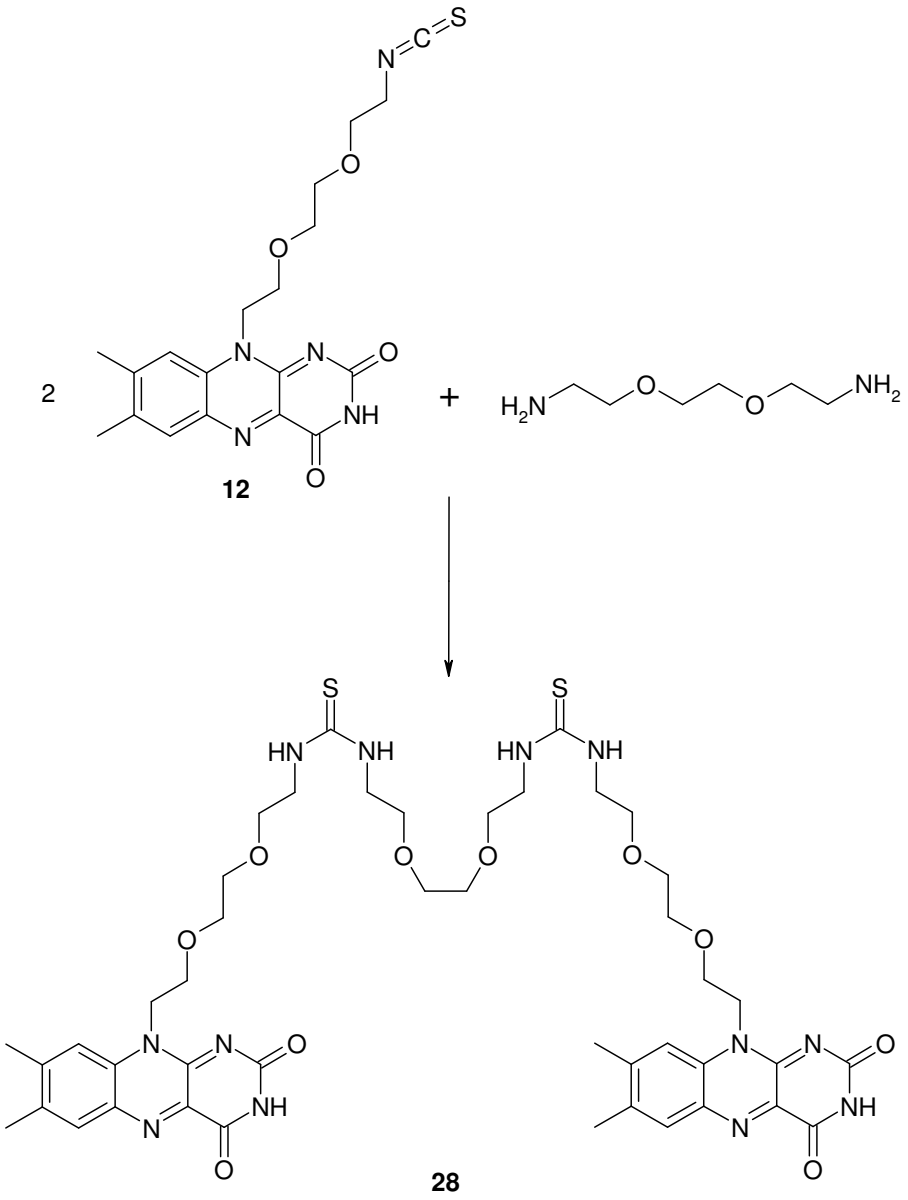


Scheme 2.6 Synthesis of flavin–bis(thiourea) **25** and **26**. Conditions: (i) 2-(tert-Butyloxycarbonylamino)eth-1-yl bromide, K_2CO_3, NaI, DMF (dry), 3 d, 52% (ii) HCl, DE, MeOH, r.t., overnight, 100% (iii) Thiophosgene, DCM, $CaCO_3$, H_2O, overnight, 81% (iv) NH_3 (g), MeOH, $CHCl_3$, 100%, r.t., 1 h (v) Perfluorooctylethyl amine, TEA, $CHCl_3$, Δ, 51%

The reaction of isothiocyanate **12** with aminoglycol flavin **4** (scheme 2.7), and two-fold reaction of isothiocyanate **12** with 3,6-dioxaoct-1,8-diyl diamine (scheme 2.8) yielded bis-flavins **27** and **28**, respectively, containing one or two thiourea groups and a glycol linker of varying length.[21,26,37] Both reactions gave high yields of the bis-flavins **27** and **28**.



Scheme 2.7 Synthesis of bis-flavin **27**. Conditions: TEA, $CHCl_3$, Δ, 22 h, 100%



Scheme 2.8 Synthesis of bis-flavin **28**. Conditions: $CHCl_3$, Δ, 8 h, 93%

Photocatalytic Oxidations

Flavin-mediated photooxidation of 4-methoxybenzyl alcohol to the corresponding aldehyde using air as terminal oxidant was chosen as the model reaction to study the catalytic activity of the new flavin–thiourea compounds. Other photocatalysts, such as titanium dioxide, can mediate this oxidation as well, but they require intense UV irradiation.[52] The catalytic flavin cycle starts with the oxidized form of flavin which is irradiated by visible light (λ=440 nm, absorption maximum of flavins in the visible region). The excited chromophore is a strong oxidizing agent,[3–6] and

accepts stepwise electrons and protons from the benzyl alcohol substrate. The aldehyde is formed, along with the reduced flavin which reacts rapidly with oxygen dissolved in the reaction mixture to yield the hydroperoxide intermediate. The hydroperoxide intermediate then instantaneously releases hydrogen peroxide and regenerates the oxidized flavin, thus completing the catalytic cycle.[53,54] The oxidation of benzyl alcohol to benzaldehyde by oxygen is an exothermic process, but it does not proceed in the absence of flavin or light. The efficiency of the flavin photooxidation increases, if substrate binding sites are present at the chromophore,[23,33,34] and the experiments we describe in the following aim to clarify the effect of thiourea substituents on the photooxidation process.

The reaction was monitored in a mixture of MeCN-d_3 and DMSO-d_6 (98:2 v/v) by ^{1}H NMR.[55] Upon irradiation, the intensity of the resonance signals corresponding to the benzyl alcohol decreased, while benzaldehyde resonance signals appeared in a very clean conversion (figure 2.1, table 2.1). At the concentrations used (flavin 2×10^{-4} M, 4-methoxybenzyl alcohol 2×10^{-3} M), the resonance signals of the photocatalysts are only observed as minor peaks in the baseline noise. Hydrogen peroxide was not detected by NMR, presumably due to fast deuterium exchange with the solvent.[56]

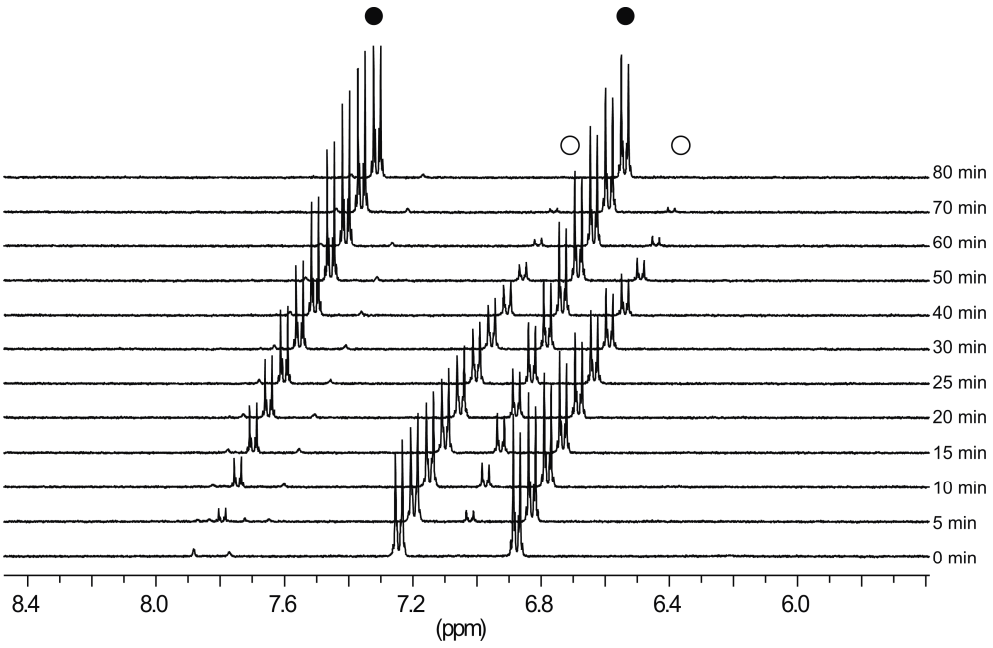


Figure 2.1 Stack plot of the aromatic region of the ^{1}H NMR spectra recorded during the irradiation of 4-methoxybenzyl alcohol in the presence of flavin **16**. Perspective view of the spectra is used (no change of the chemical shift of the signals). ○ 4-Methoxybenzyl alcohol aromatic signals, ● 4-Methoxy benzaldehyde aromatic signals. Resonance signals in the baseline noise belong to flavin **16**. Initial concentration of 4-methoxybenzyl alcohol 2×10^{-3} M, concentration of flavin 2×10^{-4} M

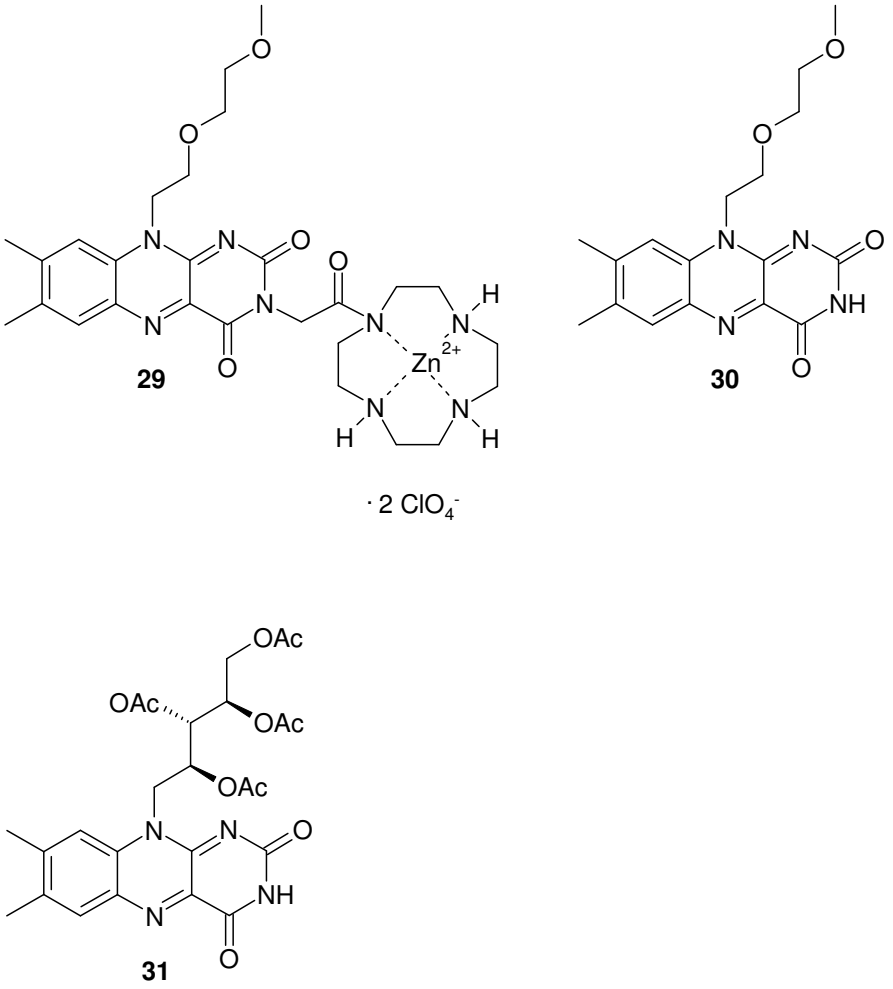
Table 2.1a Results of flavin-mediated photooxidation of 4-methoxybenzyl alcohol to 4-methoxy benzaldehyde

Entry	Flavin catalyst [mol×L^{-1}]	4-Methoxybenzyl alcohol [mol×L^{-1}]	Ratio substrate:catalyst	Irradiation time [h]	Conversion [%]	TON	TOF [h^{-1}]	Quantum yield Φ (×100)
			Flavin-catalyzed photooxidations					
1	**16** (2×10^{-4})	2×10^{-3}	10:1	1	92	9.2	9.2	0.93
2	**17** (2×10^{-4})	2×10^{-3}	10:1	1	64	6.4	6.4	0.65
3	**19** (3×10^{-5})	2×10^{-3}	70:1	1	64	45	45	0.65
4	**14** (2×10^{-4})	2×10^{-3}	10:1	1	47	4.7	4.7	0.48
5	**18** (2×10^{-4})	2×10^{-3}	10:1	1	41	4.1	4.1	0.42
6	**15** (2×10^{-4})	2×10^{-3}	10:1	1	40	4	4	0.41
7	**21** (2×10^{-4})	2×10^{-3}	10:1	1	39	3.9	3.9	0.4
8	**25** (5×10^{-5})	2×10^{-3}	40:1	1	27	11	11	0.27
9	**29** (2×10^{-4})	2×10^{-3}	10:1	1	25	2.5	2.5	0.25
10	**20** (2×10^{-5})	2×10^{-3}	100:1	1	20	20	20	0.2
11	**5** (2×10^{-4})	2×10^{-3}	10:1	1	9	0.9	0.9	0.09
12	**31** (2×10^{-4})	2×10^{-3}	10:1	1	7	0.7	0.7	0.07
13	**27** (2×10^{-4})	2×10^{-3}	10:1	1	6	0.6	0.6	0.06
14	**28** (2×10^{-4})	2×10^{-3}	10:1	1	6	0.6	0.6	0.06
15	**26** (1×10^{-5})	2×10^{-3}	200:1	1	3	6	6	0.03
16	**30** (2×10^{-4})	2×10^{-3}	10:1	1	2	0.2	0.2	0.02

Table 2.1b Results of flavin-mediated photooxidation of 4-methoxybenzyl alcohol to 4-methoxy benzaldehyde

Entry	Flavin catalyst [mol×L^{-1}]	4-Methoxybenzyl alcohol [mol×L^{-1}]	Ratio substrate:catalyst	Irradiation time [h]	Conversion [%]	TON	TOF [h^{-1}]	Quantum yield Φ (×100)
Experiments without light, oxygen or flavin								
17	**16** (2 10^{-4})	2×10^{-3}	10:1	1[a]	5	0.5	0.5	0.05
18	**16** (2×10^{-4})	2×10^{-3}	10:1	1[b]	0	–	–	–
19	None	2×10^{-3}	N/A	1	0	–	–	–
20	None[c]	2×10^{-3}	N/A	1	0	–	–	–
Experiments with lower catalyst loading								
21	**16** (2×10^{-4})	2×10^{-2}	100:1	16	84[d]	87	5.4	0.55
22	**16** (2×10^{-5})	2×10^{-3}	100:1	156	61	61	0.4	0.004
23	**16** (2×10^{-4})	2×10^{-1}	1000:1	96	50[e]	580	6	0.006
Stoichiometric mixtures of flavin and thiourea and miscellaneous experiments								
24	**5** (2×10^{-4})[c]	2×10^{-3}	10:1	1	91	9.1	9.1	0.92
25	**30** (2×10^{-4})[c]	2×10^{-3}	10:1	1	95	9.5	9.5	0.97
26	**31** (2×10^{-4})[c]	2×10^{-3}	10:1	0.5	89	8.9	18	1.81
27	**30** (2×10^{-4})[f]	2×10^{-3}	10:1	1	99	9.9	9.9	1.01
28	**5** (2×10^{-4})[g]	2×10^{-3}	10:1	1	3	0.3	0.3	0.03

[a] Reaction mixture was thoroughly purged by argon prior to irradiation [b] Instead of irradiation, the reaction mixture was left standing in the dark [c] Thiourea (2×10^{-4} M) was added to the reaction mixture [d] Mixture of 4-methoxy benzaldehyde (81%) and 4-methoxybenzoic acid (3%) [e] Mixture of 4-methoxy benzaldehyde (42%) and 4-methoxybenzoic acid (8%) [f] *N,N,N′,N′*-Tetramethylthiourea (2×10^{-4} M) was added to the reaction mixture [g] Urea (2×10^{-4} M) was added to the reaction mixture



Scheme 2.9. Flavin molecules, which do not contain a thiourea group, used for comparison

In the absence of flavin, light, or oxygen, or in the presence of thiourea alone, the reaction did not proceed (table 2.1, entries 17–20).[57] Using simple flavins **5**, **30** and **31** (scheme 2.9) which do not contain the thiourea group, some amount of the product was formed, but the conversion remained very low (entries 11, 12 and 16). Bis-flavins **27** and **28** (entries 13 and 14) were not very efficient either, presumably due to steric reasons or unproductive excimer formation.[25] Thiourea groups connected to the 3- or 10-position lead to similar rate enhancements: 3-(2'-thioureidoethyl) flavin **17** oxidized 64% of the alcohol within 60 min, while 10-(2'-thioureidoethyl) flavin **14** oxidized 47% (entries 2 vs. 4). The distance of the thiourea group to the chromophore plays a significant

role:[58] With the thiourea group located at the end of the dioxaoctyl chain (catalyst **16**), the conversion reached 92%, while with a short ethylene spacer (catalyst **14**), only 47% was observed (entries 1 vs. 4).

Figure 2.2 shows the course of selected kinetic experiments with flavin-thiourea photocatalysts or with stoichiometric mixtures of simple flavin molecules and thiourea.

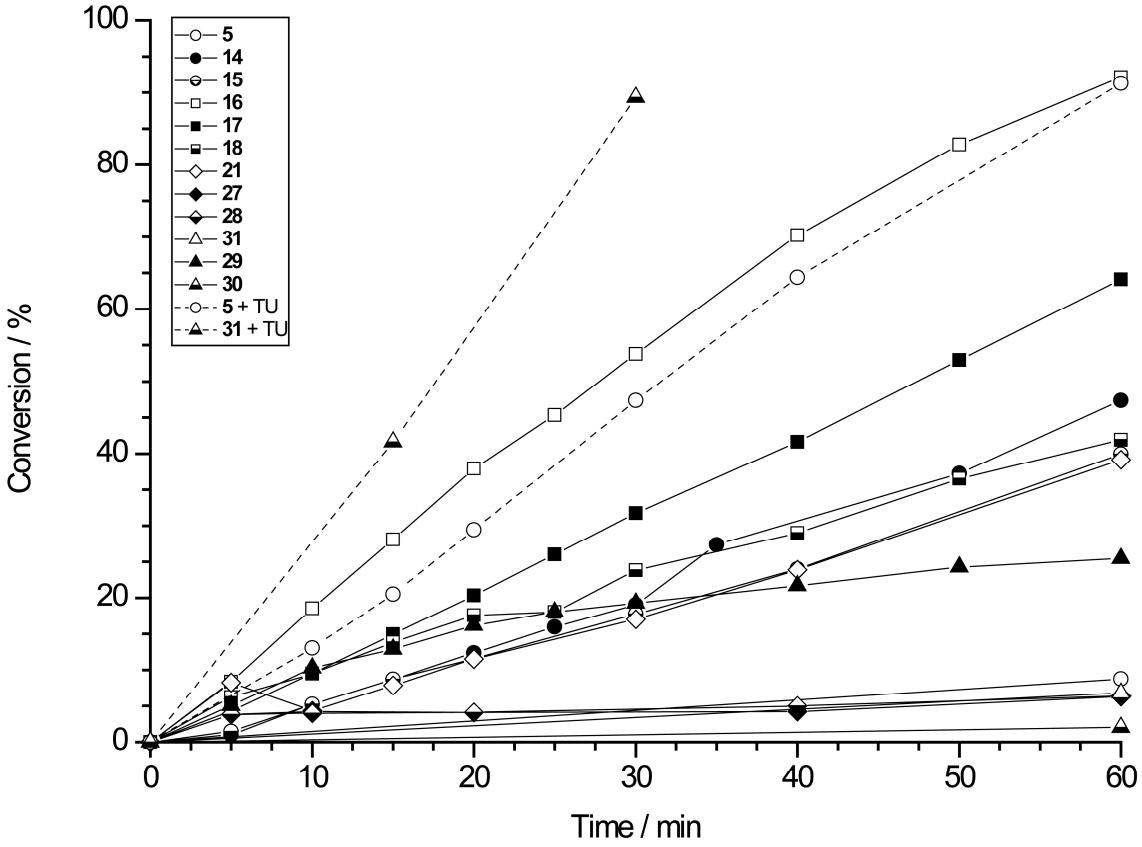


Figure 2.2 Flavin-mediated photooxidation of 4-methoxybenzyl alcohol to 4-methoxy benzaldehyde. Conditions: Initial concentration of 4-methoxybenzyl alcohol 2×10^{-3} M, concentration of flavin sensitizer 2×10^{-4} M. "TU" denotes the addition of thiourea to the reaction mixture (2×10^{-4} M). The conversion was calculated from the ratio of the integrals of the aromatic signals in ^{1}H NMR spectra recorded during the experiment

The flavin–thiourea photocatalysts remain active for several subsequent cycles (figure 2.3). After every hour, the conversion of 4-methoxybenzyl alcohol to the aldehyde was determined by ^{1}H NMR, and an aliquot of concentrated alcohol stock solution was added to restore the initial alcohol-

to-sensitizer ratio. While high conversion within 1 h was observed in the first cycles, the activity of the photocatalyst then decayed due to photodecomposition of the flavin chromophore.

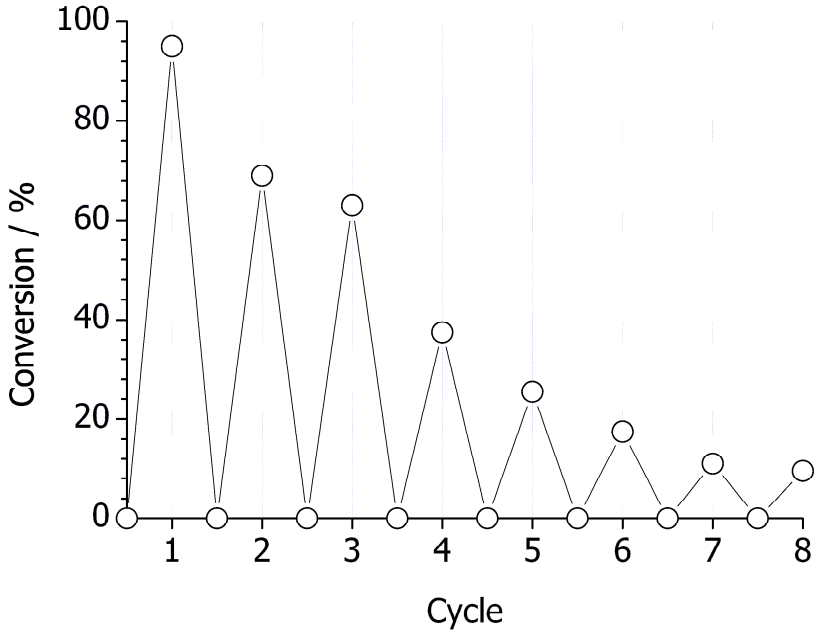


Figure 2.3 Repeated oxidation of 4-methoxybenzyl alcohol. Conditions: flavin–thiourea **16** 2×10^{-4} M, 4-methoxybenzyl alcohol 2×10^{-3} M before every cycle (1 h). Products accumulated in the reaction mixture

To probe the activity of the most efficient compound **16** further, experiments with higher substrate-to-photocatalyst ratios were carried out (table 2.1, entries 21–23). Regardless of whether the concentration of the substrate was higher or concentration of the flavin sensitizer lower to reach the higher ratio, the reaction was significantly slower and longer irradiation times were therefore required. Nevertheless, unprecedented turnovers were observed: Using mere 0.1 mol% of the flavin photocatalyst, a total conversion of 50% after 4 days of irradiation was observed. 4-Methoxybenzyl alcohol (42%) was in this case accompanied by 4-methoxy benzoic acid (8%), the product of a subsequent oxidation which was not observed in the experiments with 10 mol% of flavin sensitizers even upon prolonged irradiation of the fully converted reaction mixtures or mixtures with authentic 4-methoxy benzaldehyde. This result corresponds to a TON

of 580, significantly exceeding the highest turnover reported for this reaction.[33] Fluorophilic catalysts **19** and **20** and bis-thiourea catalysts **25** and **26** (entries 3, 8, 10, and 15) were not sufficiently soluble to test their efficiency at 2×10^{-4} M. However, they were highly active even at lower concentrations, especially compound **19** which was able to oxidise 64% of the substrate while present at 1.5 mol%, thus achieving a TOF of 45 h^{-1}.

Surprisingly, the covalent linkage between the flavin chromophore and the thiourea group was not decisive for the catalytic activity. Mixtures of related flavin molecules, which do not contain the covalently-linked thiourea group, and stoichiometric amounts of thiourea worked comparably well (table 2.1, entries 24–26). This made us revise the hypothesis of reversible non-covalent binding of substrate to the thiourea group. Indeed, addition of 4-methoxybenzyl alcohol to the most active catalyst **16** did not cause any quenching of flavin fluorescence and induced no changes in the UV/Vis spectra, suggesting no direct binding between the substrate and the thiourea group. This assumption was supported by ^{19}F NMR titration of flavin–thiourea **16** and 2-fluorobenzyl alcohol. Upon addition of the flavin–thiourea, no change in the chemical shift of the fluorine atom was observed, again indicating no direct interaction.

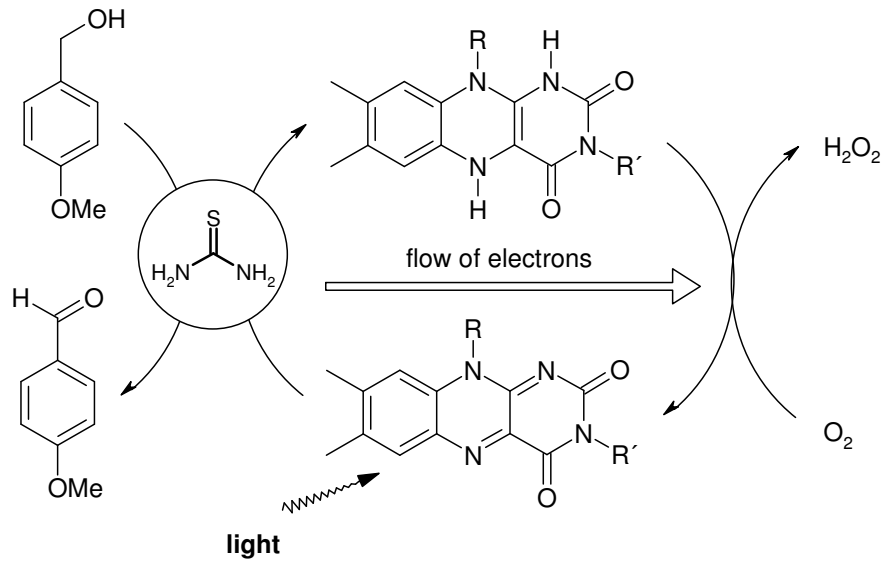
To assess whether the presence of thiourea influences the flavin redox potential by hydrogen binding, as observed in natural flavoenzymes and their models,[15,16,20,21,24,59–65] the reduction potentials of 10-thioureidoglycol flavin **16** and 10-(3′,6′-dioxahept-1′-yl) flavin **30** was determined by cyclic voltammetry (see appendix A). The measurement revealed a shift of the reduction potential by +90 mV for flavin–thiourea **16** compared to **30**. However, this shift is not as pronounced as in related flavin molecules which catalyze the oxidation of 4-methoxybenzyl alcohol less efficiently (e.g., compound **29**, reduction potential is shifted by +200 mV compared to compound **30**),[33] and cannot justify the high activity in the oxidation reactions. To disprove a hydrogen-bond-mediated change of the flavin redox potential as the source of reactivity increase in alcohol photooxidation, experiments with a mixture of 10-(3′,6′-dioxahept-1′-yl) flavin **30** and either thiourea or *N,N,N′,N′*-tetramethylthiourea were carried out giving comparable results (table 2.1, entries 25 vs. 27).

Another potential effect of thiourea, which is a mild organic base, is the deprotonation of the alcohol, making it more electron-rich and facilitating its oxidation. Although thiourea is more basic than alcohols in aqueous environment, the situation changes in organic media due to less effective solvation of the alcoholate anion, making deprotonation by thiourea virtually impossible.[66,67]

Having disproved the hypotheses described above, we turned our attention to the possibility that thiourea works as an electron mediator between the substrate and the flavin moiety, and assists the chromophore in bringing the oxidation about (scheme 2.10). To assess whether electron transfer between the flavin unit and thiourea and other entities participating in the system are thermodynamically feasible, their redox potentials were determined by cyclic voltammetry and ΔG of the electron-transfer reactions was calculated using the Rehm–Weller equation (see appendix A).[68,69] Indeed, the excited flavin can oxidize either the alcohol (ΔG=−29 kJ/mol) or thiourea (ΔG=−100 kJ/mol). The reduced form of flavin may also reduce thiourea (ΔG=−55 kJ/mol) or be re-oxidized by oxygen (ΔG=−35 kJ/mol); however, the rate-determining step is the oxidation of the substrate, not the re-oxidation of the reduced flavin form, as only the oxidized form can be observed in UV/Vis spectra recorded during the reaction. Thiourea must therefore exert its positive effect on the oxidation of the substrate. The ability of thiourea to enhance the reactivity of flavin may stem from its capability to undergo oxidation to highly reactive (radical) intermediates.[70–72] In accordance, urea which cannot tautomerize to the isourea form,[73] which is necessary to undergo the oxidation,[74] does not increase the efficiency of the flavin photocatalyst (table 2.1, entry 28). The situation may be analogous to certain oxidases, which contain a stabilized sulphenic acid based on the cysteine side chain in the vicinity of the flavin-dependent active site.[75–80]

The effect of thiourea on the reaction rate is a diffusion-controlled process rather than a photochemical reaction within a non-covalent assembly: When excess of thiourea with respect to flavin is used, the oxidation proceeds significantly faster compared to stoichiometric mixtures of flavin and thiourea. In addition, the difference in photocatalyst efficiency with

covalently tethered thiourea and stoichiometric mixtures of flavin and thiourea is small.



Scheme 2.10 Proposed catalytic cycle of the thiourea-mediated photooxidation of 4-methoxybenzyl alcohol

Conclusion

Flavin–thioureas **14**–**21** and **25**–**28** were prepared by the Kuhn synthesis and the application of isothiocyanate chemistry. The photocatalysts were successfully applied to the oxidation of 4-methoxybenzyl alcohol to 4-methoxy benzaldehyde using oxygen as the terminal oxidizing agent. The activity of some of the catalysts exceeded known systems and high TONs of up to 580 have been observed. The presence of thiourea, either covalently bound to a flavin derivative or added stoichiometrically, led to a 30-fold increase of the reactions quantum yield in some examples. Our investigations revealed that thiourea presumably acts as an efficient electron mediator between the photoactive flavin chromophore and the substrate.

Experimental part

General

10-(3′-Oxabut-1′-yl) flavin **5**,[81] 10-[2′-(*tert*-butyloxycarbonylamino)-eth-1′-yl] flavin **6-Boc**,[17] 10-(2′-aminoeth-1′-yl) flavin **6**,[17] 2-perfluoro-octylethyl amine,[82] 2-(*tert*-butyloxycarbonylamino)ethyl bromide,[83] and (3′,6′-dioxahept-1′-yl) flavin **30**[33] were prepared by known methods. Flavin–zinc(II)–cyclene was a gift from Dr. Radek Cibulka. All other chemicals were purchased from commercial suppliers, checked by ^{1}H NMR spectrometry and then used as received. Solvents were distilled before use and dried by usual methods if required by the experimental procedure. Dry DMAP was purchased from Fluka. Thin layer chromatography (TLC) was carried out on Silica gel 60 F_{254} aluminium sheets (Merck) or on pre-coated plastic sheets Polygram SIL G/UV_{254} (Macherey-Nagel, Düren, Germany), with detection under 254 nm or 333 nm UV light, by naked eye (flavins are intensively yellow-coloured), or by staining with ninhydrin solution. Preparative thin-layer chromatography (PTLC) was carried out on home-made glass plates (20×20 cm) coated with silica gel 60 GF_{254} (20 g, Merck). Column chromatography was carried out on silica gel Geduran 60 (Merck) or silica gel 60 M (Macherey-Nagel). Flash chromatography was carried out on silica gel 35–70 μm, 60 Å from Acros. Nuclear magnetic resonance spectra were recorded at Bruker spectrometer equipped with a robotic sampler at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR), unless otherwise indicated. Tetramethylsilane (TMS) was used as an external standard. Electron-impact (EI-MS) and chemical ionisation (CI-MS) mass spectra were measured on Finnigan TSQ 710 spectrometer, and electronspray ionisation (ES-MS) mass spectra were measured on ThermoQuest Finnigan TSQ 7000 spectrometer. All methods of high resolution mass spectrometry (HR-MS) were measured on ThermoQuest Finnigan MAT 95 spectrometer. Elemental composition (C, H, N, S) of new compounds was determined either by HR-MS or by combustion elementary analysis. Melting points were measured on a melting point apparatus Büchi SMP-20 using a glass capillary tube immersed in heated silicon oil, and are uncorrected. UV/Vis spectra were recorded at Varian Cary 50 Bio UV/Vis spectrometer against air. Fluorescence spectra were recorded at Varian Cary Eclipse.

Kinetic experiments

The kinetic experiments were carried out in a mixture of MeCN-d_3 and DMSO-d_6. The latter was required to improve solubility of flavin–thiourea photocatalysts. A typical reaction mixture, prepared in an NMR tube,[84] contained 4-methoxybenzyl alcohol (2×10^{-3} M) and the flavin derivative (2×10^{-4} M, 10 mol%) and had a total volume of 1 mL. The reaction mixture was prepared under aerobic conditions, but the solution was not additionally saturated with oxygen. The reaction mixture was irradiated by a LED with emission wavelength of 440 nm and an electric power of 6 W. The NMR tube was placed vertically above the aperture of the LED. Optical path using this setup was 73–75 mm. The reaction mixture was irradiated for the desired time, and ^{1}H NMR spectra of the mixture were recorded using a Bruker spectrometer with a working frequency of 400 or 300 MHz using 64 transitions to achieve better signal-to-noise ratio and hence more accurate integration. Sodium 3-(trimethylsilyl)-2,2,3,3-tetradeutero-propionate (2×10^{-3} M) was used as an internal standard. The concentration of substrate and product was derived from the integration of the peaks of the aromatic doublets (see figure 1) and compared to the integral value of the trimethylsilyl peak of the TSP internal standard. Quantum yield was estimated using the standard ferrioxalate actinometry.[85]

Cyclic voltammetry

The cyclic voltammograms were recorded on an Autolab potentiostat, using glassy carbon working electrode, platinum auxiliary electrode, saturated calomel reference electrode, 0.1 M tetrabutylammonium tetrafluoroborate as auxiliary electrolyte, and a mixture of MeCN and DMSO (98:2 v/v) as solvent, at 1×10^{-3} M concentration of analytes. The solution was degassed before the measurement by a stream of argon, and left under a gentle stream of argon during the measurement; a step potential of 0.1 V×s^{-1} was used.

***N*-(3'-Oxabut-1'-yl)-4,5-dimethyl-2-nitroaniline (2)** Dinitrobenzene **1** (2.94 g, 15 mmol) was dissolved in 3-oxabut-1-yl amine (25 mL) and the reaction mixture was heated to 80 °C for 6 h. The mixture was diluted with DCM (100 mL) and then washed with water (2×100 mL) and brine

(100 mL). The organic phase was dried over magnesium sulphate and evaporated. The product partially solidified upon drying.

Yield 3.35 g, 15 mmol, quant., brown oil

^{1}H NMR ($CDCl_3$) δ = 2.14 (s, 3 H, CH_3-4), 2.23 (s, 3 H, CH_3-5), 3.40 (s, 3 H, CH_3-4′), 3.42–3.47 (m, 2 H, CH_2-1′), 3.65 (m, 2 H, CH_2-2′), 6.60 (s, 1 H, H-6), 7.87 (s, 1 H, H-3), 8.07 (br s, 1 H, NH)

^{13}C NMR ($CDCl_3$) δ = 18.4, 20.6 (2×CH_3), 42.6 (CH_2), 58.9 (CH_3), 70.4 (2×CH_2), 114.0 (CH), 124.4 (C_{qu}), 126.3 (CH), 129.8, 143.9, 147.1 (C_{qu})

CI-MS *m/z* (%): 225.1 (100) $[M+H]^+$, 195.2 $[M+H–NO]^+$

N-(8′-Amino-3′,6′-dioxaoct-1′-yl)-4,5-dimethyl-2-nitroaniline (4)

The procedure is analogous to the one described by Sawhney et al.[86] Thus, dinitro compound **1** (5.88 g, 30 mmol) was dissolved in EtOH (3.0 L). 1,8-Diamino-3,6-dioxaoctane (23.8 g, 160 mmol, 5.3 eq) was added and the reaction mixture was heated to reflux for 62 h. The reaction mixture was evaporated, the residue was dissolved in DCM, extracted by diluted hydrochloric acid. The aqueous phase was separated and neutralized by dilute sodium hydroxide solution. The solution was extracted by DCM, the organic phase was separated and evaporated, the residue was co-evaporated with toluene and dried.

Yield 4.55 g, 15.3 mmol, 51%) red oil

R_f=0.17 (DCM:MeOH:TEA – 50:2:1)

^{1}H NMR ($CDCl_3$) δ = 2.15 (s, 3 H, CH_3-4), 2.24 (s, 3 H, CH_3-5), 2.86, 3.52, 3.66, 3.77 (4×m, 12 H, 6×CH_2), 6.61 (s, 1 H, H-6), 7.90 (s, 1 H, H-3), 8.13 (br s, 1 H, Ar–NH)

^{13}C NMR ($CDCl_3$) δ = 18.6, 20.7 (2×CH_3), 41.1, 42.7, 69.1, 70.3, 70.6, 71.7 (6×CH_2), 114.2 (CH), 117.8, 124.6 (2×C_{qu}), 126.5 (CH), 144.1, 147.3 (2×C_{qu})

ES-MS *m/z* (%): 298.2 (100) $[M+H]^+$

HRMS-EI *m/z*: calcd for $C_{14}H_{23}N_3O_4$ $[M]^{+\bullet}$: 297.1689; found: 297.1689 [Δ 0.00 ppm]

N-[8′-(Benzyloxycarbonylamino)-3′,6′-dioxaoct-1′-yl]-4,5-dimethyl-2-nitroaniline (4-Cbz)

The procedure is analogous to the one described by Nicola et al.[87] Thus, free amine **4** (650 mg, 2.20 mmol) was dissolved in dry DCM (100 mL). A solution of benzyl chloroformate (380 mg, 2.20 mmol, 1 eq) in dry DCM (50 mL) was added dropwise. TEA (750 μL) was added to the reaction mixture and the reaction was monitored by TLC (DCM:MeOH:TEA – 50:2:1, staining with ninhydrin). After 30 min, the starting material disappeared. The reaction mixture was evaporated, the residue was dissolved in a minimal amount of MeOH and the solution was applied to four PTLC plates. The mixture was separated using the aforementioned mobile phase, and the corresponding zone was thoroughly extracted with $CHCl_3$. The extract was evaporated and the residue was dried.

Yield 610 mg, 1.41 mmol, 64%, red oil

R_f=0.58 ($CHCl_2$:MeOH:TEA – 50:2:1)

^{1}H NMR ($CDCl_3$) δ = 2.13 (s, 3 H, CH_3-4), 2.22 (s, 3 H, CH_3-5), 3.41, 3.55, 3.63, 3.77 (4×m, 12 H, 6×CH_2), 5.05 (s, 2 H, CH_2Ph), 5.44 (br s, 1 H, H-8′), 6.57 (s, 1 H, H-6), 7.30 (m, 5 H, Ph), 7.86 (s, 1 H, H-3), 8.13 (s, 1 H, NH aniline)

^{13}C NMR ($CDCl_3$) δ = 18.6, 20.7 (2×CH_3), 42.7 (*C*H_2Ph), 65.1, 66.6, 69.1, 70.2, 70.3, 70.5 (6×CH_2), 114.2 (CH), 124.5 (C_{qu}), 126.4 (CH), 126.8 (C_{qu}), 128.0, 128.5, 130.0 (3×CH), 137.7, 144.0, 147.3 (4×C_{qu}), 156.5 (C=O)

EI-MS *m/z* (%): 91.1 (100) $[C_7H_7]^+$, 179.1 $[ArNH{=}CH_2]^+$, 431.2 $[M]^{+\bullet}$

EA (%) calcd for $C_{22}H_{29}N_3O_6$: C 61.24, H 6.77, N 9.74, O 22.25; found: C 61.44, H 6.91, N 9.65

N-[8′-(Trifluoroacetamido)-3′,6′-dioxaoct-1′-yl]-4,5-dimethyl-2-nitroaniline (4-TFA)

Free amine **4** (5.8 g, 20 mmol) was dissolved in MeOH (200 mL) and ethyl trifluoroacetate (13 g, 92 mmol, 4.6 eq) and TEA (11 g, 110 mmol, 5.4 eq) were added to the solution. The reaction mixture was stirred at room temperature and monitored by TLC (DCM:MeOH:TEA – 50:2:1). After 24 h, the starting material disappeared. The reaction mixture was evaporated, the residue was dissolved in DCM (100 mL) and the solution was washed with

water (3×100 mL). The organic phase was separated, evaporated and the residue was dried.

Yield 6.5 g, 16.6 mmol, 83%, red oil

R_f =0.46 (DCM:MeOH:TEA – 50:2:1)

^{1}H NMR ($CDCl_3$) δ = 2.10 (s, 3 H, CH_3-4), 2.20 (s, 3 H, CH_3-5), 3.43, 3.53, 3.60, 3.63, 3.72 (5×m, 12 H, 6×CH_2), 6.57 (s, 1 H, H-6), 7.42 (br s, 1 H, NH–CO), 7.81 (s, 1 H, H-3), 8.15 (br, 1 H, Ar–NH)

^{19}F NMR ($CDCl_3$) δ = –76.4

ES-MS *m/z* (%): 394.2 (100) $[M+H]^+$

EI-MS *m/z* (%): 393.3 (100) $[M]^{+\bullet}$

HRMS-EI *m/z*: calcd for $C_{16}H_{22}F_3N_3O_5$ $[M]^{+\bullet}$: 393.1512; found: 393.1509 [Δ –0.76 ppm]

10-[8'-(Benzyloxycarbonylamino)-3',6'-dioxaoct-1'-yl]-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (7-Cbz)

The reduction procedure is analogous to the literature.[88,89] Thus, *o*-nitro-aniline **4-Cbz** (430 mg, 1.00 mmol) was dissolved in EtOH (100 mL), and tin(II)-chloride dihydrate (1.7 g, 7.5 mmol, 7.5 eq) was added. The reaction mixture was heated to reflux and monitored by TLC (DCM:MeOH:TEA – 50:2:1). After 72 h, the starting material disappeared. The reaction mixture was evaporated and the residue was redissolved in EE. The solution was washed with a 2 M NaOH solution, the organic phase was separated, dried over magnesium sulphate, evaporated and the residue was dried. The crude reduction product was dissolved in AcOH (25 mL), and alloxane hydrate (1.1 g, 6.9 mmol, 6.9 eq) and boric acid (1.0 g, 16 mmol, 16 eq) were added. The flask was wrapped in aluminium foil and the mixture was stirred at room temperature for 22 h, diluted with water (25 mL) and extracted with DCM (50 mL). The organic phase was evaporated and the residue was co-evaporated with toluene to remove traces of H_2O and AcOH. The crude product was dissolved in a minimal amount of MeOH and separated on four PTLC plates (DCM:MeOH:TEA – 50:2:1, eluting twice). The corresponding zone was extracted by MeOH, the extract was evaporated and the residue dried.

Yield 360 mg, 710 μmol, 71%, orange solid

R_f=0.43 (DCM:MeOH:TEA – 50:2:1)

m.p. 232 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.41 (s, 3 H, CH_3-7), 2.50 (s, 3 H, CH_3-8), 3.31, 3.47, 3.55, 3.97 (4×m, 8 H, 4×CH_2 glycol), 4.86 (br, 2 H, CH_2-2′), 5.06 (s, 2 H, $PhCH_2$), 5.30 (br, 2 H, CH_2-1′), 7.15–7.38 (m, 5 H, Ph), 7.66 (s, 1 H, H-9), 7.97 (s, 1 H, H-6)

^{13}C NMR spectrum could not be recorded due to very low solubility of the title compound in organic solvents

EI-MS *m/z* (%): 242.0 (100) $[M–side\ chain]^{+\bullet}$, 507.2 $[M]^{+\bullet}$ [90]

EA (%): calcd for $C_{26}H_{29}N_5O_6$: C 61.53, H 5.76, N 13.80, O 18.91; found: C 61.33, H 5.84, N 13.85

7,8-Dimethyl-10-[8′-(trifluoroacetamido)-3′,6′-dioxaoct-1′-yl]benzo[*g*]pteridin-2,4-dione (7-TFA)

Trifluoroacetamide **4-TFA** (2.0 g, 5.0 mmol) was dissolved in AcOH (60 mL), and palladium on activated charcoal (15 mg, 10% Pd/C) was added. The reaction mixture was placed in an autoclave which was flushed three times with hydrogen and then filled up to 50 bar. The reaction mixture was stirred at room temperature for 16 h. Afterwards, the reaction mixture was filtered over celite to remove the catalyst, and the filtrate was transferred to a round-bottom flask. Alloxane hydrate (2.1 g, 13 mmol, 2.6 eq) and boric acid (7.0 g, 110 mmol, 22 eq) were added to the filtrate. The flask was wrapped in aluminium foil and the reaction mixture was stirred at room temperature for 6 d. The reaction mixture was evaporated, the residue was dissolved in water (300 mL), and the solution was extracted with DCM (2×250 mL). The organic phase was separated, dried over magnesium sulphate, evaporated and dried.

Yield 1.13 g, 2.4 mmol, 48%, orange crystals

R_f=0.27 (DCM:MeOH:TEA – 50:2:1)

m.p. 215 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.40 (s, 3 H, CH_3-7), 2.50 (s, 3 H, CH_3-8), 3.25–3.46 (m, 8 H, 4×CH_2), 3.81 (tr, *J*=5.9 Hz, 2 H, CH_2-2′), 4.78 (tr, *J*=5.9 Hz, 2 H, CH_2-1′), 7.85 (s, 1 H, H-9), 7.88 (s, 1 H, H-6), 9.47, 11.33 (2×br s, 2 H, 2×NH)

^{13}C NMR spectrum could not be recorded due to very low solubility of the title compound in organic solvents

ES-MS *m/z* (%): 470.3 (100) $[M+H]^+$

EA (%): calcd for $C_{20}H_{22}F_3N_5O_5$: C 51.17, H 4.72, F 12.14, N 14.92, O 17.04; found: C 51.34, H 4.87, N 14.83

10-[2'-(*tert*-Butyloxycarbonylamino)eth-1'-yl]-3,7,8-trimethylbenzo[*g*]pteridin-2,4-dione (8-Boc)

Flavin **6-Boc** (800 mg, 2.1 mmol) was dissolved in dry DMF (80 mL). Caesium carbonate (900 mg, 2.8 mmol, 1.3 eq) and dimethyl sulphate (2.7 g, 2.0 mL, 21 mmol, 10 eq) were added, and the mixture was stirred at room temperature in the dark overnight. The suspension was diluted with $CHCl_3$ (250 mL) and washed with water (3×100 mL), 5% aqueous NH_3 (100 mL) and water (100 mL). The organic phase was separated, dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography ($CHCl_3$:MeOH – 20:1).

Yield 440 mg, 1.11 mmol, 53%, orange solid

R_f=0.38 ($CHCl_3$:MeOH – 20:1)

m.p. 232 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 1.21 (s, 9 H, Boc), 2.41 (s, 3 H, CH_3-7), 2.51 (s, 3 H, CH_3-8), 3.28 (s, 3 H, CH_3-3), 3.41 (m, 2 H, CH_2-1'), 4.67 (tr, *J*=5.8 Hz, 2 H, CH_2-2'), 6.99 (tr, *J*=5.8 Hz, 1 H, NH), 7.87 (s, 1 H, H-9), 7.95 (s, 1 H, H-6)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.9, 28.0, 28.2 (4×CH_3), 37.0, 44.1 (2×CH_2), 77.9 (C_{qu}), 116.2, 131.0 (CH), 131.5, 134.2, 135.8, 135.9, 146.5, 148.9, 155.1, 155.8, 159.7 (9×C_{qu})

ES-MS *m/z* (%): 300.1 $[M+H-Boc]^+$, 344.1 $[M+H-C_4H_8]^+$, 400.2 (100) $[M+H]^+$, 422.2 $[M+NH_4]^+$, 438.2 $[M+K]^+$

10-(2'-Aminoeth-1'-yl)-3,7,8-trimethylbenzo[*g*]pteridin-2,4-dione (8)

Flavin **8-Boc** (100 mg, 250 μmol) was dissolved in $CHCl_3$ (25 mL) and hydrogen chloride in ether (3 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight, and was then evaporated.

Yield 84 mg, 250 μmol, quant., yellow solid

m.p. 257 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.42 (s, 3 H, CH_3-7), 2.54 (s, 3 H, CH_3-8), 3.19–3.21 (m, 2 H, CH_2-2′), 3.29 (s, 3 H, CH_3-3), 4.92 (tr, *J*=6.5 Hz, 2 H, CH_2-1′), 7.99 (s, 1 H, H-9), 8.06 (s, 1 H, H-6), 8.18 (br s, 3 H, NH_3^+)
^{13}C NMR could not be measured due to extremely low solubility of the title compound
ES-MS *m/z* (%): 300.1 (100) $[M+H]^+$

10-(8′-Amino-3′,6′-dioxaoct-1′-yl)-7,8-dimethylbenzo[*g*]pter-idin-2,4-dione (7)

Trifluoroacetamide **7-TFA** (1.1 g, 2.3 mmol) was dissolved in 6 M aqueous solution of hydrochloric acid (200 mL, 1.2 mol, 520 eq), and the reaction mixture was heated to 90–95 °C and monitored by TLC ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5). After 90 min, the starting material disappeared. The reaction mixture was evaporated and the residue was dried.
Yield 940 mg, 2.3 mmol, quant., dark brown oil
R_f=0.04 ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5)
^{1}H NMR (MeOH-d_4) δ = 2.46 (s, 3 H, CH_3-7), 2.58 (s, 3 H, CH_3-8), 3.06 (tr, *J*=4.9 Hz, 2 H, CH_2-8′), 3.60–3.68 (m, 6 H, 3×CH_2), 4.00 (tr, *J*=5.6 Hz, 2 H, CH_2-2′), 5.00 (tr, *J*=5.6 Hz, 2 H, CH_2-1′), 7.86 (s, 1 H, H-9), 7.91 (s, 1 H, H-6)
^{13}C NMR (MeOH-d_4) δ = 19.5, 21.4 (2×CH_3), 40.7, 46.3, 68.0, 68.7, 71.3, 71.8 (6×CH_2), 118.1 (CH), 132.5, 133.3, 138.9, 139.0, 141.3, 149.7, 151.7, 158.4 (8×C_{qu}), 172.8 (CH)
ES-MS *m/z* (%): 374.3 (100) $[M+H]^+$
HRMS-EI *m/z*: calcd for $C_{18}H_{23}N_5O_4$ $[M+H]^+$: 374.1828; found: 374.1834 [Δ 1.69 ppm]

3-[2′-(*tert*-Butyloxycarbonylamino)eth-1′-yl]-7,8-dimethyl-10-(3″-oxabut-1″-yl)benzo[*g*]pteridin-2,4-dione (9-Boc):

Flavin **5** (1.2 g, 4.0 mmol, 1 eq) was dissolved in dry DMF (150 mL) at 80 °C. After cooling to room temperature, potassium carbonate (2.8 g, 20 mmol, 5 eq) was added and the mixture was stirred for 30 min. 2-(*tert*-Butyloxycarbonylamino)ethyl bromide (2.3 g, 10 mmol, 2.5 eq) in DMF (5 mL) was added dropwise. Sodium iodide (900 mg, 6.0 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for one

day. Another portion of the bromide (2.3 g, 10 mmol, 2.5 eq) was added, and the reaction mixture was stirred for two more days at room temperature, evaporated, the residue was dissolved in DCM (400 mL) and the solution was washed with aqueous sodium hydrogen carbonate (250 mL), water (250 mL) and brine (250 mL). The organic phase was separated, dried over magnesium sulphate and evaporated. The remaining dark oil was purified by column chromatography (EE/MeOH 20:1).

Yield 950 mg, 2.16 mmol, 54%, yellow solid

R_f=0.42 (EE:MeOH – 10:1)

m.p. 176 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 1.32 (s, 9 H, Boc), 2.40 (s, 3 H, CH_3-7), 2.51 (s, 3 H, CH_3-8), 3.19–3.21 (m, 2 H, CH_2-2′), 3.24 (s, 3 H, CH_3-4″), 3.76 (tr, *J*=5.6 Hz, 2 H, CH_2-1″), 3.96 (tr, *J*=5.9 Hz, 2 H, CH_2-1′), 4.83 (tr, *J*=5.6 Hz, 2 H, CH_2-2″), 6.82 (tr, *J*=5.9 Hz, 1 H, NH), 7.89 (s, 1 H, H-9), 7.95 (s, 1 H, H-6)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.7, 28.2 (3×CH_3), 37.7, 40.9, 43.8 (3 × CH_2), 58.5 (CH_3), 68.4 (CH_2), 77.6 (C_{qu}), 116.8, 130.8 (2×CH), 131.4, 133.9, 136.0, 136.4, 146.5, 148.8, 154.8, 155.7, 159.7 (9×C_{qu})

ES-MS *m/z* (%): 388.1 $[M+H-C_4H_8]^+$, 444.2 (100) $[M+H]^+$

3-(2′-Aminoeth-1′-yl)-7,8-dimethyl-10-(3″-oxabut-1″-yl)benzo-[*g*]pteridin-2,4-dione (9)

Flavin **9-Boc** (850 mg, 1.9 mmol) was dissolved in DCM (150 mL) and hydrogen chloride in DE (10 mL) was added dropwise. The reaction mixture was stirred for 15 h at room temperature. The brown precipitate was filtered off and dried.

Yield 690 mg, 1.81 mmol, 95%, brown solid

m.p. 150 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.41 (s, 3 H, CH_3-7), 2.51 (s, 3 H, CH_3-8), 3.07–3.09 (m, 2 H, CH_2-2′), 3.24 (s, 3 H, CH_3-4″), 3.79 (tr, *J*=5.5 Hz, 2 H, CH_2-1″), 4.16 (tr, *J*=5.9 Hz, 2 H, CH_2-1′), 4.87 (tr, *J*=5.8 Hz, 2 H, CH_2-2″), 7.94 (s, 1 H, H-9), 7.94–7.96 (br, 3 H, NH_3^+), 7.96 (s, 1 H, H-6)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.7 (2×CH_3), 37.3, 39.9, 44.0 (3×CH_2), 58.5 (CH_3), 68.4 (CH_2), 117.0, 130.8 (CH), 131.4, 133.9, 136.3, 136.4, 146.8, 148.9, 154.9, 160.2 (8×C_{qu})

ES-MS *m/z* (%): 344.1 (100) $[M+H]^+$

General procedure 1 for the preparation of isothiocyanates (10–13 and 24)

Flavin was dissolved in water and calcium carbonate (2.5 eq) was added. The solution was then added to a rapidly stirred solution of thiophosgene, prepared by the dilution of 0.1 M stock solution in DCM (2 eq) with DCM, cooled to 0 °C. The reaction mixture was stirred overnight at room temperature, diluted with DCM, the organic phase was separated, washed with water, dried over magnesium sulphate and evaporated. The crude product was purified by chromatography if required.

10-(2'-Isothiocyanatoeth-1'-yl)-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (10)

Prepared according to general procedure 1 from **6●HCl** (150 mg, 466 μmol).

Yield 130 mg, 397 μmol, 85%, orange solid

R_f=0.39 (EE:MeOH – 10:1)

m.p. 182 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.41 (s, 3 H, CH_3-7), 2.50 (s, 3 H, CH_3-8), 4.14 (tr, *J*=5.8 Hz, 2 H, CH_2-2'), 4.95 (tr, *J*=5.8 Hz, 2 H, CH_2-1'), 7.92 (s, 1 H, H-9), 8.00 (s, 1 H, H-6). 11.37 (s, 1 H, NH)

ES-MS *m/z* (%): 328 (100) $[M+H]^+$

10-(2'-Isothiocyanatoeth-1'-yl)-3,7,8-trimethylbenzo[*g*]pteridin-2,4-dione (11)

Prepared according to general procedure 1 from **8●HCl** (109 mg, 325 μmol).

Yield 88 mg, 258 μmol, 79%, orange solid

R_f=0.35 ($CHCl_3$:MeOH – 20:1)

m.p. 195 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.46 (s, 3 H, CH_3-7), 2.59 (s, 3 H, CH_3-8), 3.52 (s, 3 H, CH_3-3), 4.17 (tr, *J*=5.8 Hz, 2 H, CH_2-2'), 4.97 (tr, *J*=5.6 Hz, 2 H, CH_2-1'), 7.55 (s, 1 H, H-9), 8.09 (s, 1 H, H-6)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.6, 30.0 (3×CH_3), 41.9, 42.8 (2×CH_2), 116.3 (CH), 130.8 (Cqu), 131.1 (CH), 133.9, 136.0, 136.3, 146.9, 148.9, 155.0, 159.6 (7×Cqu) Signal of the isothiocyanate group was not observed, presumably due to long relaxation time
ES-MS *m/z* (%): 342.1 (100) $[M+H]^+$

10-(8′-Isothiocyanato-3′,6′-dioxaoct-1′-yl)-7,8-dimethylbenzo-[*g*]pteridin-2,4-dione (12)

Prepared according to general procedure 1 from **7●HCl** (100 mg, 244 μmol)
Yield 98 mg, 236 μmol, 97%, orange solid
R_f=0.84 ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5)
m.p. 178 °C (decomp.)
NMR signals were completely assigned with the help of 2D experiments (NOESY, HMBC, HSQC) and reported data of analogous compounds[91]
^{1}H NMR ($CDCl_3$) δ = 2.45 (s, 3 H, CH_3-7), 2.56 (s, 3 H, CH_3-8), 3.57–3.62 (m, 8 H, 4×CH_2-4′,5′,7′,8′), 4.04 (tr, *J*=5.5 Hz, 2 H, CH_2-2′), 4.95 (tr, *J*=5.5 Hz, 2 H, CH_2-1′), 7.73 (s, 1 H, H-9), 8.03 (s, 1 H, H-6), 8.58 (s, 1 H, H-3)
^{13}C NMR ($CDCl_3$) δ = 19.5 (CH_3-7), 21.5 (CH_3-8), 45.3 (C-4′), 45.6 (C-1′), 67.9 (C-2′), 69.2, 70.6, 70.8 (C-5′, 7′, 8′), 132.1 (C-9a), 132.4 (C-6), 133.0 (NCS), 135.0 (C-5a), 136.0 (C-4a), 137.1, 148.1 (C-7, 8), 150.4 (C-10a), 155.1, 159.6 (C-2, 4), 166.8 (C-9)
EI-MS *m/z* (%): 91.2 (100) $[C_7H_7]^+$, 242.2 [M–side chain]$^{+\bullet}$, 415.3 $[M]^{+\bullet}$ [90]
ES-MS *m/z* (%): 416.1 (100) $[M+H]^+$
HRMS-EI *m/z*: calcd for $C_{19}H_{21}N_5O_4S$ $[M]^{+\bullet}$: 415.1314; found: 415.1320 [Δ – 1.39 ppm]

3-(2′-Isothiocyanatoeth-1′-yl)-7,8-dimethyl-10-(3″-oxabut-1″-yl)benzo[*g*]pteridin-2,4-dione (13)

Prepared according to general procedure 1 from **9●HCl** (600 mg, 1.58 mmol).
Yield 540 mg, 1.40 mmol, 89%, yellow solid
R_f=0.33 (EE)
m.p. 190–193 °C

^{1}H NMR (DMSO-d_6) δ = 2.41 (s, 3 H, CH_3-7), 2.51 (s, 3 H, CH_3-8), 3.24 (s, 3 H, CH_3-4″), 3.77 (tr, *J*=5.8 Hz, 2 H, CH_2-1″), 3.95 (tr, *J*=5.9 Hz, 2 H, CH_2-1′), 4.20 (tr, *J*=5.8 Hz, 2 H, CH_2-2′), 4.84 (tr, *J*=5.6 Hz, 2 H, CH_2-2″), 7.91 (s, 1 H, H-9), 7.96 (s, 1 H, H-6)
^{13}C NMR (DMSO-d_6) δ = 18.8, 20.7 (2×CH_3), 40.0, 42.8, 44.0 (3×CH_2), 58.5 (CH_3), 68.3 (CH_2), 116.9, 130.8 (2×CH), 131.5, 134.1, 136.0, 136.2, 146.8, 149.0, 154.4, 159.6 (8×C_{qu}); the signal of the isothiocyanate group was not observed, presumably due to long relaxation time
EI-MS *m/z* (%): 242.2 (100) [M–$CH_2OCH_2CH_2$–CH_2CH_2NCS]$^{\bullet+}$, 385.2 [M]$^{\bullet+}$[90]

General procedure 2 for the preparation of flavin photocatalysts with primary thiourea group (14–17 and 25)

Flavin was dissolved in $CHCl_3$ and gaseous NH_3 was passed through the solution for 3 h. The precipitate was filtered off and purified by trituration or chromatography if required.

7,8-Dimethyl-10-(2′-thioureidoeth-1′-yl)benzo[*g*]pteridin-2,4-dione (14)

Prepared according to general procedure 2 from **10** (60 mg, 183 μmol).
Yield 48 mg, 139 μmol, 76%, yellow solid
m.p. 178 °C (decomp.)
^{1}H NMR (DMSO-d_6) δ = 2.40 (s, 3 H, CH_3-7), 2.48 (s, 3 H, CH_3-8), 3.78 (m, 2 H, CH_2-2′), 4.71 (m, 2 H, CH_2-1′), 7.16 (br s, 2 H, NH_2), 7.72 (m, 1 H, NH), 7.87 (s, 1 H, H-9), 8.14 (s, 1 H, H-6), 11.27 (s, 1 H, H-3)
^{13}C NMR (DMSO-d_6) δ = 18.8, 20.6 (2×CH_3), 39.5, 43.6 (2×CH_2), 116.5, 130.8 (2×CH), 131.5, 133.7, 135.8, 136.8, 146.5, 150.3, 155.6, 159.9, 183.8 (9×C_{qu})
ES-MS *m/z* (%): 345.0 (100) [M+H]$^+$
EA (%): calcd for $C_{15}H_{16}N_6O_2S$: C 52.31, H 4.68, N 24.40, O 9.29, S 9.31; found: C 52.55, H 4.53, N 24.51, S 9.20

3,7,8-Trimethyl-10-(2′-thioureidoeth-1′-yl)benzo[*g*]pteridin-2,4-dione (15)

Prepared according to general procedure 2 from **11** (50 mg, 146 μmol).
Yield 36 mg, 100 μmol, 68%, yellow solid
R_f=0.70 ($CHCl_3$:MeOH – 7:1)
m.p. 252 °C (decomp.)
^{1}H NMR (DMSO-d_6) δ = 2.38 (s, 3 H, CH_3-7), 2.47 (s, 3 H, CH_3-8), 3.29 (s, 3 H, CH_3-3), 3.77 (m, 2 H, CH_2-2′), 4.70 (m, 2 H, CH_2-1′), 7.18 (m, 2 H, NH_2), 7.75 (m, 1 H, NH), 7.87 (s, 1 H, H-9), 8.14 (s, 1 H, H-6)
^{13}C NMR (DMSO-d_6) δ = 18.8, 20.7, 28.0 (3×CH_3), 39.5, 43.6 (2×CH_2), 116.5, 130.8 (2×CH), 131.5, 133.7, 135.8, 136.8, 146.5, 150.3, 155.6, 159.9, 183.8 ppm (9×C_{qu})
ES-MS *m/z* (%): 357.1 (100) $[M–H^+]^-$, 417.2 $[M+AcO]^-$, 471.1 $[M+TFA]^-$
HRMS-EI *m/z*: calcd for $C_{16}H_{19}N_6O_2S$ $[M]^{+\bullet}$: 359.1290; found: 359.1297 [Δ -1.89 ppm]

7,8-Dimethyl-10-(3′,6′-dioxa-8′-thioureidooct-1′-yl)benzo[*g*]pteridin-2,4-dione (16)

Prepared according to general procedure 2 from **12** (500 mg, 1.20 mmol).
Yield 230 mg, 515 μmol, 43%, brown solid
R_f=0.60 ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5)
m.p. 170 °C (decomp.)
^{1}H NMR (DMSO-d_6) δ = 2.40 (s, 3 H, CH_3-7), 2.50 (s, 3 H, CH_3-8), 3.35–3.56 (m, 8 H, CH_2-4′,5′,7′,8′), 3.81 (tr, *J*=5.9 Hz, 2 H, CH_2-2′, 4.80 (tr, *J*=5.5 Hz, 2 H, CH_2-1′), 7.01 (br s, 2 H, NH_2), 7.54 (br s, 1 H, *NH*–C(S)NH_2), 7.88 (s, 2 H, CH-6,9), 11.33 (s, 1 H, H-3)
^{13}C NMR (DMSO-d_6) δ = 18.8, 20.6 (2×CH_3), 43.8 (CH_2), 44.0 (CH_2-1′), 66.7 (CH_2-2′), 69.0, 69.5, 70.1 (3×CH_2), 116.8, 130.7 (2×CH), 131.4 (C-9a), 133.7 (C-5a), 135.8, 136.0, 137.1, 146.2, 155.6, 159.9 (6×C_{qu}), 182.9 (C=S)
ES-MS *m/z* (%): 433.1 (100) $[M+H]^+$
ES-MS *m/z* (%): 431.1 (100) $[M–H]^+$, 467.1 $[M+Cl]^-$, 491.3 $[M+AcO]^-$
HRMS-EI *m/z*: calcd for $C_{19}H_{24}N_6O_4S$ $[M]^{+\bullet}$: 432.1580; found: 432.1575 [Δ 1.10 ppm]

3-(2′-Thioureidoeth-1′-yl)-10-(3″-oxabut-1″-yl) Flavin (17)

Prepared according to general procedure 2 from **13** (100 mg, 259 μmol).

Yield 104 mg, 258 μmol, quant., orange solid

R_f=0.30 (EE:MeOH – 10:1)

m.p. 171 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.39 (s, 3 H, CH_3-7), 2.49 (s, 3 H, CH_3-8), 3.24 (s, 3 H, CH_3-4″), 3.66 (br, 2 H, CH_2-1′), 3.76 (tr, J=5.6 Hz, 2 H, CH_2-1″), 4.03 (br, 2 H, CH_2-2′), 4.82 (tr, J=5.5 Hz, 2 H, CH_2-2″), 6.98, 7.62 (m, 3 H, NH), 7.88 (s, 1 H, H-9), 7.90 (s, 1 H, H-6)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.7 (2×CH_3), 39.5, 42.1, 43.9 (3×CH_2), 58.5 (CH_3), 68.3 (CH_2), 116.8, 130.8 (2×CH), 131.4, 133.9, 136.1, 136.2, 146.6, 148.8, 154.9, 159.7, 183.5 (9×C_{qu})

ES-MS *m/z* (%): 403.1 (100) $[M+H]^+$

HRMS-EI *m/z*: calcd for $C_{18}H_{22}N_6O_3S$ $[M]^{+\bullet}$: 402.1474; found: 402.1479 [Δ -1.22 ppm]

General procedure 3 for the preparation of *N,N′*-substituted flavin–thiourea compounds (18–21 and 26–28)

Flavin isothiocyanate was dissolved in $CHCl_3$, and the corresponding amine (2.5 eq) and TEA (2 eq) were added. The reaction mixture was heated to reflux until monitoring by TLC indicated complete conversion. The reaction mixture was then evaporated and the crude product was purified by chromatography if required.

10-(9',11'-Diaza-3',6',14'-trioxa-10'-thioxopentadec-1'-yl)-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (18)

Prepared according to general procedure 3 from **12** (20 mg, 48 μmol).

Yield 24 mg, 48 μmol, quant., orange solid

R_f=0.69 ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5)

m.p. 178 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.43 (s, 3 H, CH_3-7), 2.54 (s, 3 H, CH_3-8), 3.14–3.72 (m, 15 H, CH_2-4′,5′,7′,8′,12′,13′), 4.05 (br, 2 H, CH_2-2′), 4.99 (br, 2 H, CH_2-1′), 7.59 (s, 1 H, H-9), 8.01 (s, 1 H, H-6)

^{13}C NMR ($CDCl_3$) δ = 19.5 (CH_3-7), 21.6 (CH_3-8), 44.3 (C-4′), 44.9 (C-1′), 58.5 (C-15′), 70.1, 70.3, 70.6, 70.9, 71.5, 71.5 (C-2′,5′,7′,8′,12′,13′),

116.0 (C-9), 131.5 (C-9a), 132.6 (C-6), 135.1 (C-5a), 136.0 (C-4a), 137.3, 148.3 (C-7,8), 150.5 (C-10a), 156.5, 159.7 (C-2,4), 183.1 (C=S)
ES-MS *m/z* (%): 491.3 (100) $[M+H]^+$
HRMS-LSI *m/z*: calcd for $C_{22}H_{31}N_6O_5S$ $[M+H]^+$: 491.2077; found: 491.2086 [Δ –1.90 ppm]

10-(3',5'-Diaza-8',8',9',9',10',10',11',11',12',12',13',13',-14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl)-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (19)

Prepared according to general procedure 3 from isothiocyanate **10** (50 mg, 153 μmol).
Yield 82 mg, 104 μmol, 68%, yellow solid
m.p. 237 °C (decomp.)
^{1}H NMR (DMSO-d_6) δ = 2.38 (s, 3 H, CH_3-7), 2.46 (br, 5 H, CH_3-8, CH_2), 3.50–4.00 (m, 4 H, 2×CH_2), 4.72 (m, 2 H, CH_2), 7.78 (tr, *J*=5.4 Hz, 1 H, NH), 7.88 (s, 1 H, H-9), 8.03 (s, 1 H, H-6), 11.37 (s, 1 H, H-3)
^{13}C NMR spectrum could not be measured to extremely low solubility of the title compound
^{19}F NMR (DMSO-d_6) δ = –125.2 (m, 2 F), –122.6 (m, 2 F), –121.9 (m, 2 F), –121.2 (m, 6 F), –112.7 (m, 2 F), –79.7 ppm (t, *J*=9.5 Hz, 3 F, CF_3)
ES-MS *m/z* (%): 791.2 (100) $[M+H]^+$
HRMS-LSI *m/z*: calcd for $C_{25}H_{20}F_{17}N_6O_2S$ $[M+H]^+$: 791.1097; found: 791.1102 [Δ 0.64 ppm]

10-(3',5'-Diaza-8',8',9',9',10',10',11',11',12',12',13',13',-14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl)-3,7,8-trimethylbenzo[*g*]pteridin-2,4-dione (20)

Prepared according to general procedure 3 from isothiocyanate **11** (15 mg, 44 μmol).
Yield 28 mg, 35 μmol, 79%, orange solid
m.p. 208 °C (decomp.)
^{1}H NMR (DMSO-d_6) δ = 2.37 (s, 3 H, CH_3-7), 2.45 (br, 5 H, CH_3-8, CH_2), 3.30 (s, 3 H, CH_3-3), 3.52–3.98 (m, 4 H, 2×CH_2), 4.69 (m, 2 H, CH_2), 7.79 (tr, *J*=5.4 Hz, 1 H, NH), 7.89 (s, 1 H, H-9), 8.05 (s, 1 H, H-6)

^{13}C NMR spectrum could not be measured due to extremely low solubility of the title compound

^{19}F NMR ($CDCl_3$) δ = –126.6 (m, 2 F), –123.9 (m, 2 F), –123.2 (m, 2 F), –122.4 (m, 2 F), –122.1 (m, 2 F), –114.2 (m, 2 F), –81.2 (t, *J*=9.8 Hz, 3 F)

ES-MS *m/z* (%): 805.2 (100) $[M+H]^+$

HRMS-LSI *m/z*: calcd for $C_{26}H_{22}F_{17}N_6O_2S$ $[M+H]^+$: 805.1253; found: 805.1281 [Δ –3.42 ppm]

3-(3′,5′-Diaza-8′,8′,9′,9′,10′,10′,11′,11′,12′,12′,13′,13′,-14′,14′,15′,15′,15′-heptadecafluoro-4′-thioxopentadec-1′-yl)-7,8-dimethyl-10-(3″-oxabut-1″-yl)benzo[*g*]pteridin-2,4-dione (21)

Prepared according to general procedure 3 from isothiocyanate **13** (40 mg, 104 μmol).

Yield 59 mg, 70 μmol, 67%, orange solid

R_f=0.63 (DCM:MeOH – 10:1)

m.p. 186 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.45 (s, 3 H, CH_3-7), 2.55 (m, 5 H, CH_3-8 and CH_2-6′), 3.27 (s, 3 H, CH_3-4″), 3.65 (m, 2 H, CH_2-2′), 3.91 (tr, *J*=5.1 Hz, 2 H, CH_2-1″), 3.99 (m, 2 H, CH_2-7′), 4.30 (tr, *J*=6.2 Hz, 2 H, CH_2-1′), 4.91 (tr, *J*=5.1 Hz, 2 H, CH_2-2″), 7.71 (s, 1 H, H-9), 8.04 (s, 1 H, H-6)

^{13}C NMR ($CDCl_3$) δ = 19.6, 21.8 (2×CH_3), 30.6, 40.6, 40.7, 45.6, 45.7 (5×CH_2), 59.3 (CH_3), 69.5 (CH_2), 117.0, 132.1 (2×CH), 132.2, 134.9, 135.4, 137.6, 137.6, 148.6, 148.8, 156.5, 160.5 (9×C_{qu})

^{19}F NMR ($CDCl_3$) δ = –126.7 (m, 2 F), –124.0 (m, 2 F), –123.3 (m, 2 F), –122.5 (m, 4 F), –122.2 (m, 2 F), –114.3 (t, *J*=13.5 Hz, 2 F, CF_2-8′), –81.3 ppm (t, *J*=9.8 Hz, 3 F, CF_3-16′)

ES-MS *m/z* (%): 849.3 (100) $[M+H]^+$

HRMS-EI *m/z*: calcd for $C_{28}H_{25}F_{17}N_6O_6S$ $[M]^{+\bullet}$: 848.1437; found: 848.1438 [Δ –0.07 ppm]

3,10-Bis[2′-(*tert*-butyloxycarbonylamino)eth-1′-yl]-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (22)

Flavin **6-Boc** (300 mg, 0.78 mmol, 1 eq) was dissolved in dry DMF (40 mL) at 80 °C. The solution was allowed cool to room temperature, potassium carbonate (540 mg, 3.9 mmol, 5 eq) was added and the mixture was stirred

for 30 min. 2-(*tert*-Butyloxycarbonylamino)ethyl bromide (520 mg, 2.3 mmol, 3 eq) and sodium iodide (180 mg, 1.2 mmol, 1.5 eq) were added, and the reaction mixture was stirred at room temperature. After the first and second day of stirring, another portions of the bromide (520 mg, 2.3 mmol, 3 eq each portion) were added. After 3 days, the reaction mixture was diluted with $CHCl_3$ (300 mL), washed with aqueous sodium hydrogen carbonate (100 mL), water (3×100 mL), and brine (100 mL), and the organic phase was evaporated. Compound **22** was isolated by flash column chromatography ($CHCl_3$/MeOH 15:1).

Yield 210 mg, 406 μmol, 52%, orange solid

R_f=0.34 ($CHCl_3$:MeOH – 15:1)

m.p. 136 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 1.24 (s, 9 H, *tert*-Bu), 1.34 (s, 9 H, *tert*-Bu), 2.41 (s, 3 H, CH_3-7), 2.50 (s, 3 H, CH_3-8), 3.19 (d, *J*=6.0 Hz, 2 H, CH_2-2′), 3.40 (d, *J*=5.8 Hz, 2 H, CH_2-2′), 3.96 (tr, *J*=6.0 Hz), 2 H, CH_2-1′), 4.66 (tr, *J*=5.6 Hz, 2 H, CH_2-1′), 6.83 (tr, *J*=5.8 Hz, 1 H, NH), 7.03 (tr, *J*=5.8 Hz), 1 H, NH), 7.89 (s, 1 H, H-9), 7.95 (s, 1 H, H-6)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.8, 27.9, 28.1 (4×CH_3), 36.9, 37.8, 40.8, 43.9 (4×CH_2), 77.5, 77.8 (2×C_{qu}), 116.1, 130.9 (2×CH), 131.3, 134.0, 135.7, 135.8, 146.5, 148.7, 154.7, 155.6, 155.8, 159.6 (10×C_{qu})

ES-MS *m/z* (%): 429.2 $[M+H–Boc]^+$, 473.3 $[M+H–Bu]^+$, 529.3 (100) $[M+H]^+$, 551.4 $[M+Na]^+$

3,10-Bis(2′-aminoeth-1′-yl)-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (23)

Flavin **22** (150 mg, 290 μmol) was dissolved in MeOH (30 mL) and hydrogen chloride in ether (3 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature. The mixture was evaporated and dried.

Yield 114 mg, 290 μmol, quant., yellow brownish solid

m.p. 268 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.42 (s, 3 H, CH_3-7), 2.55 (s, 3 H, CH_3-8), 3.07 (d, *J*=5.5 Hz, 2 H, CH_2-2′), 3.18 (d, *J*=5.2 Hz, 2 H, CH_2-2′), 4.18 (tr, *J*=5.9 Hz, 2 H, CH_2-1′), 4.97 (tr, *J*=6.6 Hz, 2 H, CH_2-1′), 7.97 (s, 1 H, H-9), 8.13 (br s, 3 H, NH_3), 8.30 (s, 1 H, H-6), 8.57 (br s, 3 H, NH_3)

^{13}C NMR (DMSO-d_6) δ = 18.8, 20.5 (2×CH_3), 35.8, 37.1, 38.5, 41.2 (4×CH_2), 116.3 (CH), 130.5 (C_{qu}), 131.2 (CH), 134.2, 136.4, 136.5, 147.6, 149.4, 154.9, 160.0 (7×C_{qu})
ES-MS *m/z* (%): 329.1 (100) $[M+H]^+$

3,10-Bis(2'-isothiocyanatoeth-1'-yl)-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (24)

Prepared according to general procedure 1 from **23•2HCl** (114 mg, 284 μmol).
Yield 95 mg, 230 μmol, 81%, yellow solid
R_f=0.35 ($CHCl_3$:MeOH – 25:1)
m.p. 140 °C (decomp.)
^{1}H NMR ($CDCl_3$) δ = 2.47 (s, 3 H, CH_3-7), 2.60 (s, 3 H, CH_3-8), 3.91 (tr, *J*=6.3 Hz, 2 H, CH_2-2'), 4.19 (tr, *J*=5.6 Hz, 2 H, CH_2-2'), 4.43 (tr, *J*=6.3 Hz, 2 H, CH_2-1'), 4.99 (tr, *J*=5.9 Hz, 2 H, CH_2-1'), 7.57 (s, 1 H, H-9), 8.10 (s, 1 H, H-6)
^{13}C NMR ($CDCl_3$) δ = 18.8, 20.9 (2×CH3), 40.4, 42.0, 42.3, 43.8 (4×CH_2), 115.6 (CH), 131.1 (C_{qu}), 132.0 (CH), 134.6, 135.0, 137.6, 148.6, 149.4, 155.4, 159.9 (7×C_{qu}); the signal of the isothiocyanate groups were not observed, presumably due to long relaxation time
ES-MS *m/z* (%): 413.1 (100) $[M+H]^+$

7,8-Dimethyl-3,10-bis(2'-thioureidoeth-1'-yl)benzo[*g*]pteridin-2,4-dione (25)

Prepared according to general procedure 2 from isothiocyanate **24** (60 mg, 145 μmol).
Yield 65 mg, 145 μmol, quant., orange-red solid
R_f=0.30 ($CHCl_3$:MeOH – 10:1)
m.p. 235 °C (decomp.)
^{1}H NMR (DMSO-d_6) δ = 2.42 (s, 3 H, CH_3-7), 2.50 (s, 3 H, CH_3-8), 3.67–3.69 (m, 4 H, 2×CH_2), 4.06 (m, 2 H, CH_2-2'), 4.76 (m, 2 H, CH_2-1'), 6.98–7.77 (m, 6 H, NH and NH_2), 7.95 (s, 1 H, H-9), 8.21 (s, 1 H, H-6)
^{13}C NMR spectrum could not be measured due to extremely low solubility of the title compound
ES-MS *m/z* (%): 447.2 (100) $[M+H]^+$

HRMS-LSI *m/z*: calcd for $C_{18}H_{23}N_8O_2S_2$ $[M+H]^+$: 447.1385; found: 447.1372 [Δ –3.00 ppm]

3,10-Bis[2'-(3',5'-diaza-8',8',9',9',10',10',11',11',12',12',-13',13',14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl)-eth-1'-yl]-7,8-dimethylbenzo[*g*]pteridin-2,4-dione (26)

Prepared according to general procedure 3 from isothiocyanate **24** (60 mg, 145 μmol).

Yield 99 mg, 74 μmol, 51%, red solid

R_f=0.50 ($CHCl_3$:MeOH – 10:1)

m.p. 211 °C (decomp.)

^{1}H NMR and ^{13}C NMR spectra could not be measured due to extremely low solubility of the title compound

^{19}F NMR (DMSO-d_6) δ = –125.4 (m, 4 F), –122.6 (m, 4 F), –122.0 (m, 4 F), –121.2 (m, 12 F), –112.8 (m, 4 F), –79.7 (m, 6 F)

ES-MS *m/z* (%): 1339.2 (100) $[M+H]^+$, 1361.2 $[M+Na]^+$

EA (%) calcd for $C_{38}H_{28}F_{34}N_8O_2S_2$: C 34.09, H 2.11, F 48.25, N 8.37, O 2.39, S 4.79; found: C 34.31, H 1.95, N 8.24, S 4.91

Bis-flavin 27

Prepared according to general procedure 3 from isothiocyanate **12** (40 mg, 96 μmol) and amine **7●HCl** (80 mg, 195 μmol).

Yield 76 mg, 96 μmol, quant., orange solid

R_f: 0.62 ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5)

m.p. 165 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.44 (s, 6 H, CH_3-7), 2.56 (s, 6 H, CH_3-8), 3.59–3.72 (m, 16 H, CH_2-4',5',7',8',12',13',15',16'), 4.05 (tr, *J*=5.1 Hz, 4 H, CH_2-2',18'), 4.11 (tr, *J*=5.1 Hz, 4 H, CH_2-1',19'), 7.02 (br s, 2 H, H-9',11'), 7.64 (s, 2 H, H-9), 7.99 (s, 2 H, H-6), 9.38 (br s, 2 H, H-3)

^{13}C NMR spectrum could not be measured due to very low solubility of the compound

ES-MS *m/z* (%): 395.3 $[M+2H]^{2+}$, 414.3 $[M+H+K]^{2+}$, 798.4 (100) $[M+H]^+$, 811.4 $[M+Na]^+$, 827.3 $[M+K]^+$

EA (%) calcd for $C_{37}H_{44}N_{10}O_8S$: C 56.33, H 5.62, N 17.75, O 16.22, S 4.06; found: C 56.47, H 5.42, N 17.91, S 4.05

Bis-flavin 28

Prepared according to general procedure 3 from isothiocyanate **12** (60 mg, 144 μmol) and 3,6-dioxaoct-1,8-diyl diamine.

Yield 66 mg, 67 μmol, 93%, orange solid

R_f=0.55 ($CHCl_3$:MeOH:AcOH – 77.5:15:7.5)

m.p. 117 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.42 (s, 6 H, CH_3-7), 2.55 (s, 6 H, CH_3-8), 3.54–3.87 (m, 28 H, CH_2), 4.05 (br, 4 H, CH_2-2′,29′), 4.95 (br, 4 H, CH_2-1′,30′), 7.07 (br, 2 H, H-3), 7.66 (s, 2 H, H-9), 7.95 (s, 2 H, H-6), 8.39 (br, 4 H, H-9′,11′,20′,22′)

^{13}C NMR ($CDCl_3$) δ = 19.4, 21.5, 45.3, 67.7, 69–72 (unresolved glycol CH_2), 132.2, 136.3, 138.8, 148.2; due to low solubility of the compound, ^{13}C NMR was reconstructed from HSQC and HMBC experiments; signals of the remaining carbon atoms could not be observed

ES-MS *m/z* (%): 490.5 (100) $[M+2H]^{2+}$, 491.5 $[M+H+Na]^{2+}$, 979.5 $[M+H]^+$, 1001.5 $[M+Na]^+$

HRMS-EI *m/z*: calcd for $C_{44}H_{59}N_{12}O_{10}S_2$ $[M+H]^+$: 979.3919, found 979.3882 [Δ 3.73 ppm]

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Chapter 3

Photooxidation of Benzyl Alcohols with Immobilized Flavins*

Introduction

Flavin is a prosthetic group of flavoproteins and a versatile electron carrier in biological systems. In nature, flavins occur mostly in the form of flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN) or riboflavin co-factors.[1] The presence and structure of the surrounding protein, substitutions, and non-covalent interactions significantly alters the redox properties of these compounds. Furthermore, irradiation has a major effect on the reactivity of flavins increasing their redox power.[2]

Recently, flavins have received interest as flavoenzyme models[3] and for applications in chemical catalysis.[4,5] Photooxidation of alcohols using catalytic amounts of flavin is particularly advantageous due to the low toxicity of the reagent. The flavin-mediated photooxidation of benzyl alcohols is an efficient process using air as terminal oxidant; the reaction was recently investigated and optimized for reaction in homogeneous acetonitrile solution.[6] High power LEDs serve as selective and efficient light source for the reaction, which makes applications to synthesis very easy.

* The investigations presented in this chapter were performed together with Dr. Petra Hilgers and Robert Lechner and have already been published. P.H. performed the main part of the catalytic testing reactions with the catalysts immobilized on fluorinated silica gel. R.L. carried out the experiments to verify the electron transfer mechanism of the photooxidation reaction. All other investigations were performed by H.S.

H. Schmaderer, P. Hilgers, R. Lechner, B. König, *Adv. Synth. Catal.* **2009**, *351*, 163–174.

Although a typical catalyst loading in the photooxidation reactions is about 1 mol%, it is advantageous to immobilize the catalyst to facilitate its separation from the reaction mixture and a potential reuse. Furthermore, for the synthesis of larger quantities of carbonyl compounds, it would be desirable to accomplish the catalytic oxidation of alcohols in a continuous reaction process which requires catalysts that are immobilized on a suitable surface and are available for a number of reaction cycles.

Only few examples of immobilized flavins have been published: Bäckvall et al. described the catalytic oxidation of sulfides to sulphoxides by H_2O_2 or NMM to NMO in the osmium-catalyzed dihydroxylation with flavin-derivatives immobilized in an ionic liquid.[4a,7] Rotello et al. reported on the development of flavin derivatives appended on polystyrene copolymers to study their redox properties.[3b] To the best of our knowledge no use of heterogeneously immobilized flavins as catalysts in organic reactions has been reported.

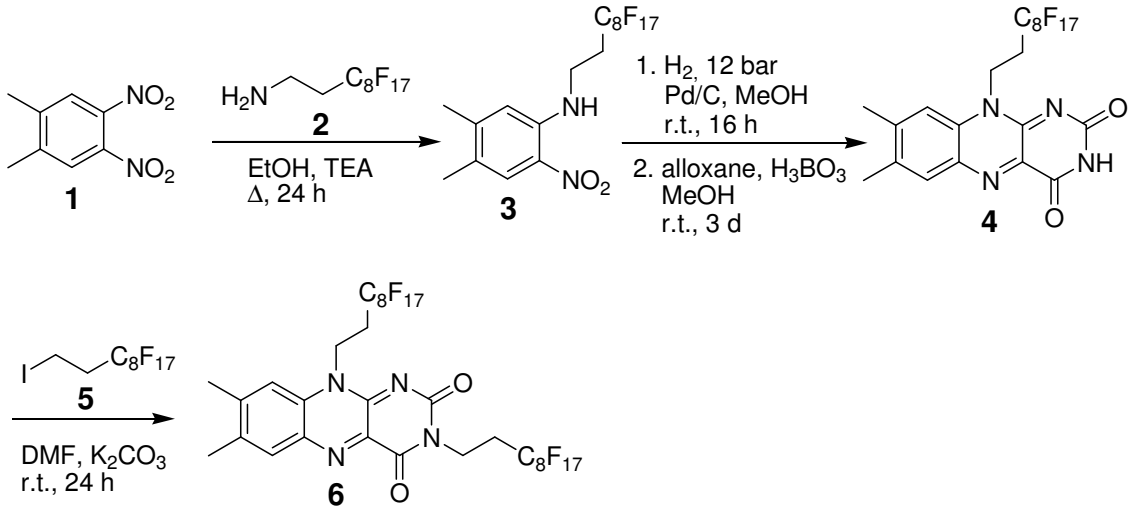
Typical immobilization strategies for catalysts are covalent binding to a solid support, physical or electrostatic adsorption,[8] and entrapment of catalysts in porous materials. From these methods, electrostatic and physical adsorption are the most simple to implement; however, both approaches are prone to catalyst leaching. A special case of surface adsorption that partly overcomes this drawback uses perfluorinated alkyl chains as tags to impose fluorous properties on a given molecule. This allows separation of the perfluorinated compound from a complex reaction mixture by fluorous phase extraction or adsorption on fluorous silica or perfluorinated polymers.[9] Fluorous technology has been applied to catalyst recovery in transition metal-[10] and organocatalysis.[11]

We have investigated the immobilization of flavin photocatalysts on unmodified, fluorous and reversed phase silica gel, and the flavin entrapment in PE pellets and glue. The catalytic activity of the heterogeneous photocatalysts was determined in benzyl alcohol photooxidations in aqueous solution and compared to the analogous reactions in homogeneous solution. We discuss and compare here the stability of different immobilized catalysts and their photooxidation efficacy.

Results and discussion

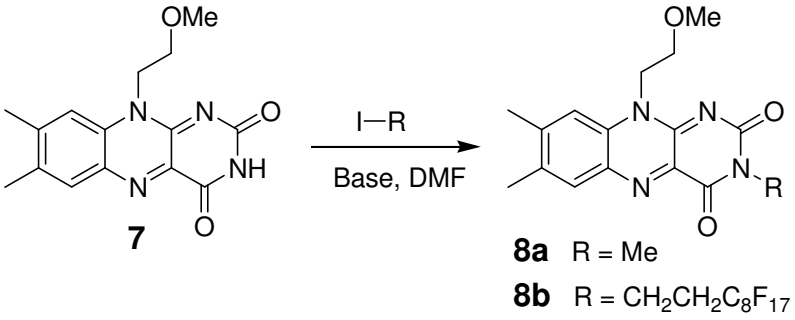
Synthesis

The new flavin derivatives were synthesized according to the Kuhn protocol.[12] Dinitro compound **1** was obtained in an optimized route from commercially available 4,5-dimethyl-nitroaniline.[13] Fluorinated amine **2** was synthesized *via* azide substitution of iodide **5** and subsequent reduction.[14]



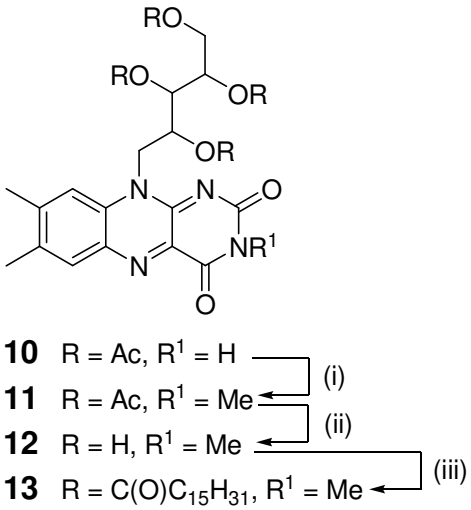
Scheme 3.1 Synthesis of flavin **6** bearing a fluorinated side chain

In a nucleophilic aromatic substitution, dinitro compound **1** was reacted with fluorinated amine **2**. After reduction of the remaining nitro group, the resulting amine was instantly used without isolation due to its sensitivity to air. Cyclocondensation with alloxane hydrate yielded flavin **4** in 38% over two steps. The fluorine mass content of the compound reaches 47%. In order to enhance fluorine interactions, molecules with even higher fluorine content are required. Therefore, flavin **4** was alkylated with iodide **5** and potassium carbonate in dry DMF to obtain flavin **6** in 62% yield. Flavin **6** exhibits a fluorine mass content of 57% (scheme 3.1).



Scheme 3.2 Preparation of N-methylated and fluorinated flavins **8**

The synthesis and use of flavin **7** was recently reported.[6] 3-*N*-Methylation of the compound was accomplished in dry DMF with methyl iodide and caesium carbonate as base yielding 91% of flavin **8a**. The use of a perfluorinated alkylation agent **5** gave flavin **8b** in 23% yield (scheme 3.2).

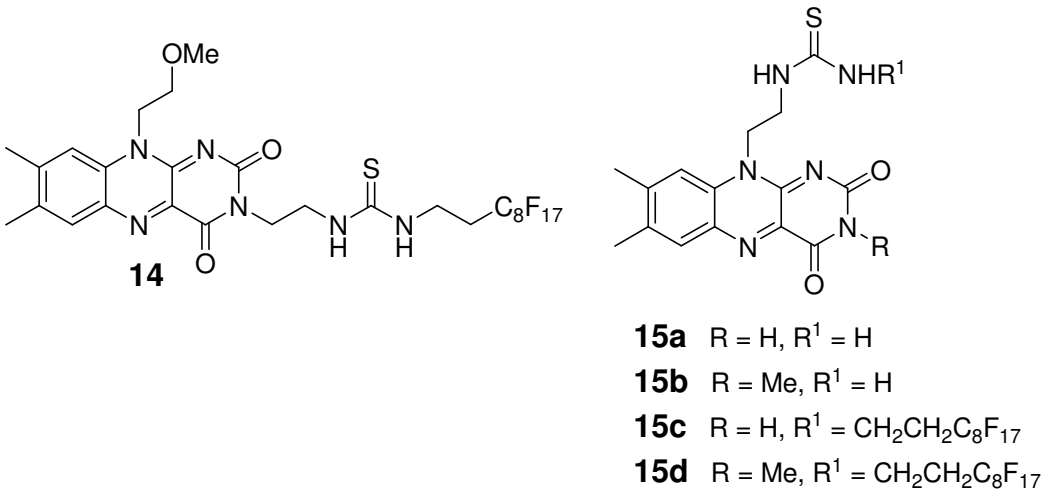


Scheme 3.3 Synthesis of riboflavin derivatives **11**–**13**. Conditions: (i) MeI, Cs_2CO_3, DMF, r.t., 16 h (ii) *p*-TsOH, EtOH, Δ, 17 h (iii) $C_{16}H_{31}OCl$, pyridine, $CHCl_3$, r.t., 24 h

The synthesis of a hydrophobic flavin **13** started from commercially available riboflavin. Tetraacetyl riboflavin (**10**), which is easily available in large amounts from riboflavin,[15] was methylated as described before yielding flavin **11**[16] in 71% yield. The acetyl groups of the ribityl chain were cleaved by *p*-toluene sulfonic acid to give 3-methyl riboflavin (**12**)[16] (73%). Reaction with palmityl chloride gave 3-methyl tetrapalmityl riboflavin (**13**) as an orange soft solid in 52% yield (scheme 3.3). This

flavin shows high solubility in organic solvents and its hydrophobic properties are desired for immobilization on reversed phase silica gel.

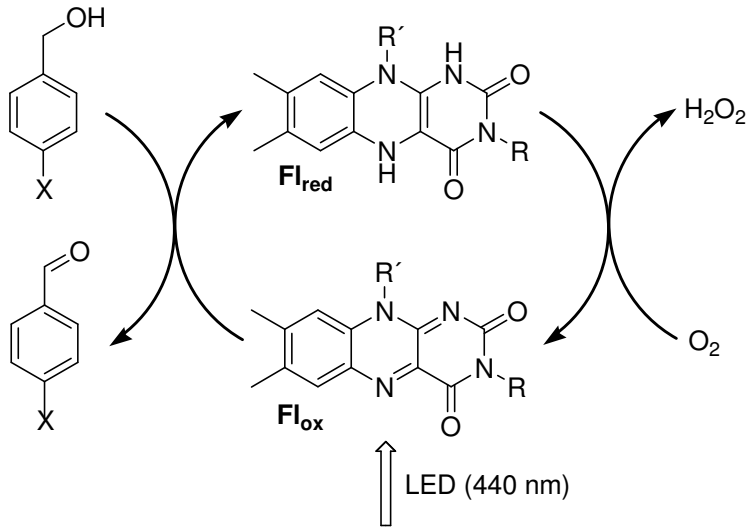
In addition, some previously prepared flavin derivatives,[6] shown in scheme 3.4, were tested for immobilization and as catalysts.



Scheme 3.4 Thiourea-flavin derivatives investigated for catalytic activity

Photooxidations in aqueous homogeneous solution

Recently, we studied the photooxidation of 4-methoxybenzyl alcohol in the presence of various flavin catalysts in acetonitrile solution.[6] In the catalytic cycle, oxidized flavin (**Fl_{ox}**) is excited by irradiation with light of suitable wavelength. As light source we used commercially available high power LEDs with an emission maximum at 440 nm which matches the longest wavelength absorption maximum of oxidized flavin. After irradiation, the flavin becomes strongly oxidizing and benzyl alcohol is converted into the corresponding aldehyde. If oxygen is present in the reaction mixture, the reduced flavin species (**Fl_{red}**) is instantly reoxidized, forming hydrogen peroxide as the second reaction product. [4d,6,17,18] Overall, benzyl alcohol is oxidized in a light driven catalytic cycle by aerial oxygen as terminal oxidant (scheme 3.5).[17–20] In these experiments, we were able to almost completely convert the alcohol starting material in a typical setup within one hour, corresponding to a TOF of up to 10 h^{-1}.



Scheme 3.5 Catalytic cycle for the photooxidation of benzyl alcohols

However, we realized that this reaction is even more efficient in aqueous solution. Figure 3.1 shows a standard screening setup (left without irradiation; right with irradiation). The photocatalytic activity of different flavins was tested in solutions of benzyl alcohol in D_2O (for detailed setup see experimental part).

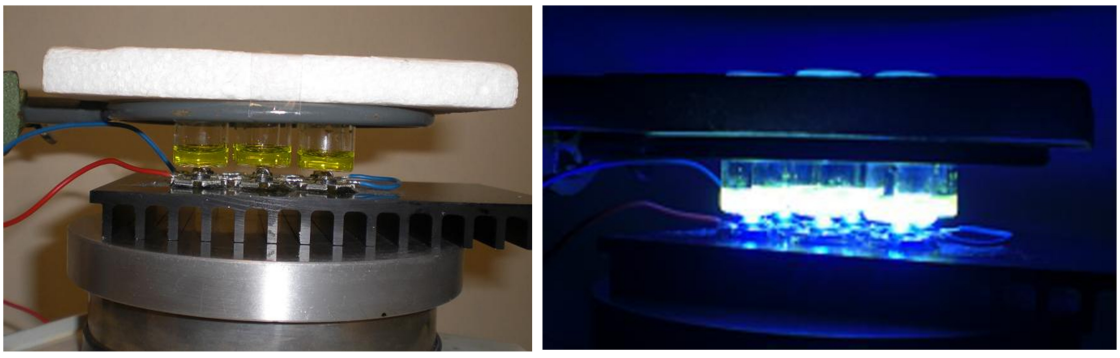


Figure 3.1 Experimental setup for photocatalytic screening

With 10 mol% of tetraacetyl riboflavin (**10**) as photocatalyst the reaction was completed within five minutes (table 3.1, entry 1). Within one minute, it was possible to convert 58% of the alcohol corresponding to a TOF of 350 h^{-1} (entry 2) and lower catalyst loadings led to TOF of more than 800 h^{-1} (entry 3). If the reaction mixture is not stirred, the TOF drops by a factor of 5, demonstrating the importance of efficient mixing during the

course of the reaction, especially for longer irradiation times (entry 4). Our previous investigations in acetonitrile solution showed, that the addition of thiourea dramatically accelerates this photooxidation.[6] Therefore, we also tried to further improve the rates in aqueous solution by the addition of thiourea. However, in water the addition of thiourea decreases the reaction rates (entries 5+6). While in acetonitrile electronically activated substrates, such as 4-methoxybenzyl alcohol were required for the conversion into the aldehyde,[6] the scope of convertible substrates is significantly extended in water. Alteration of the redox potentials or a tighter catalyst–substrate interaction in the more polar solvent may explain the observation. We were able to convert unsubstituted benzyl alcohol (entry 8) and electron poor benzyl alcohols in moderate to good yields (entries 9–11). As expected, due to the electronic deactivation, the reaction rates drop compared to 4-methoxybenzyl alcohol.

Table 3.1 Catalytic photooxidations with flavins in homogeneous aqueous solution

Entry	Flavin	X	t [min]	Aldehyde [%]	TON	TOF [1/h]
1	**10**	OMe	5	100	10	—
2	**10**	OMe	1	58	5.8	348
3[a]	**10**	OMe	5	68	68	816
4[b]	**10**	OMe	5	59	5.9	71
5[b,c]	**10**	OMe	15	79	7.9	32
6[b,c,d]	**10**	OMe	15	48	4.8	19
7[b,c]	**11**	OMe	15	48	4.8	19
8	**10**	H	25	75	7.5	18
9	**10**	COONa	25	74	7.4	18
10	**10**	COOMe	25	58	5.8	14
11	**10**	COOH	25	47	4.7	11

Conditions: V=1 mL, 2% DMSO-d_6 in D_2O, alcohol: 2×10^{-3} M, 10 mol% of catalyst [a] 1 mol% of catalyst [b] Without stirring [c] Reaction in an NMR-tube instead of a small glass vial [d] Addition of thiourea (2×10^{-4} M)

A larger experiment with 2.5 mmol of 4-methoxybenzyl alcohol and a catalyst loading of 1 mol% of tetraacetyl riboflavin (**10**) in 250 mL of water demonstrates the applicability on preparative lab scale. After irradiation with six LEDs (440 nm, 5 W each) at room temperature, full conversion was

obtained after 20 h in a very clean reaction. The kinetics of this reaction were determined by removing aliquots after several time steps and recording ^{1}H NMR spectra of the reaction mixture (figure 3.2, for details see appendix B).

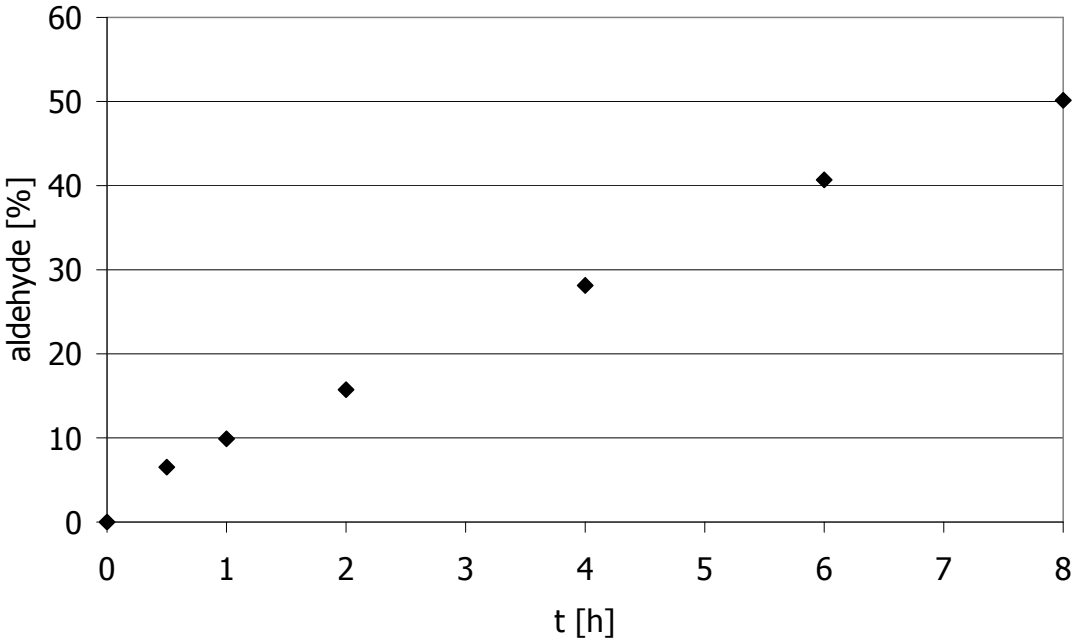
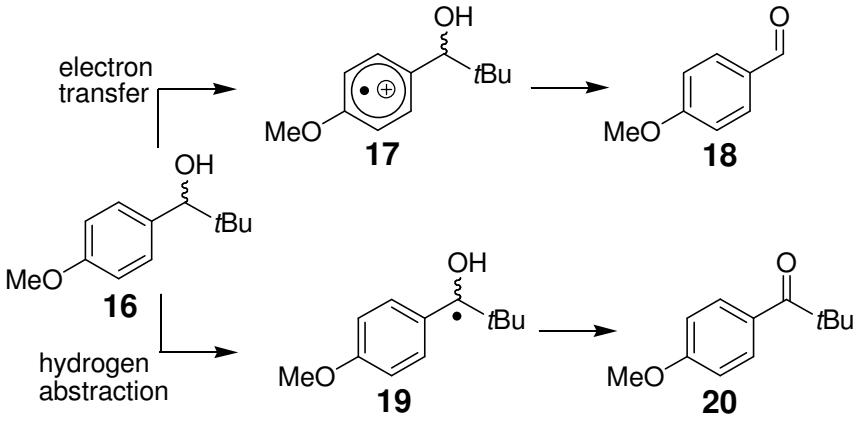


Figure 3.2 Kinetic data of the reaction on preparative scale (yield of aldehyde *versus* reaction time)

Earlier, Fukuzumi et al. presented a mechanism for this reaction starting with an initial electron transfer from the alcohol substrate to the oxidized flavin catalyst, leading to the aldehyde and hydrogen peroxide as products.[17,19] Later, this mechanism was supported by calculations[20] and we observed stoichiometric hydrogen peroxide formation in previous studies.[4d,6] To get an insight in the mechanism of the oxidation reaction, we used the secondary alcohol 2,2-dimethyl-1-phenyl-1-propanol (**16**) as a probe to discriminate between an electron transfer and a hydrogen abstraction mechanism.[21] In the case of an initial electron transfer, a cationic radical **17** is formed, which leads after abstraction of a tertiary butyl radical to aldehyde **18**. If instead the first step is a hydrogen abstraction, the formation of a neutral benzyl radical **19** finally leads to ketone **20** (scheme 3.6). In our experiments with tetraacetyl riboflavin (**10**)

in aqueous homogeneous solution we exclusively observed aldehyde **18** as the product of this reaction, proving the electron transfer mechansim.



Scheme 3.6 Electron transfer *versus* hydrogen abstraction mechanism in the photooxidation of benzyl alcohol

Photooxidation with silica gel-immobilized flavins

After the optimization of the photooxidation conditions in homogeneous solution, heterogeneous flavin catalysts immobilized on silica gel were investigated. Initially, flash silica gel particles with diameters of 35–70 μm were used as solid support for immobilization due to their large surface areas. Immobilization of the catalysts was accomplished by soaking flash silica gel with solutions of flavins in $CHCl_3$ and evaporation of the solvent, which gave homogenous yellow powders of flavin coated silica gel (figure 3.3 and 3.4).

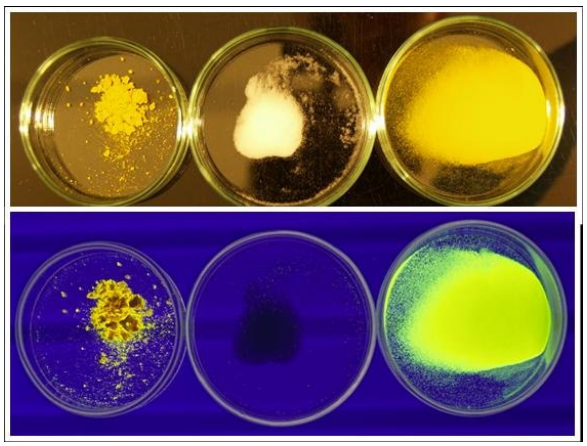


Figure 3.3 Top: Normal light irradiation, bottom: UV-blue light irradiation, left: solid flavin **10**, middle: non-modified silica gel, right: immobilized catalyst

Fluorinated flavins **4**, **6** and **8b** and non-fluorinated flavins **7**, **8a**, **13**, **14**, and **15** were immobilized on silica gel and fluorinated silica gel. The nature of the support has a dramatic effect on the stability of the immobilized catalyst in aqueous solution: Fluorinated flash silica gel turned out to be a more suitable support for all flavins compared to standard flash silica gel. In water, considerable amounts of the chromophore were washed off from not fluorinated flash silica gel, giving yellow and fluorescing solutions. No leaching of flavins from the fluorinated support was observed in aqueous media and in toluene, even if flavins without fluorous tags were applied. It was also checked whether tetraacetyl riboflavin (**10**) was washed off from

the support in a reaction mixture containing 4-methoxybenzyl alcohol. After stirring for 30 min under standard conditions, the characteristic absorption of flavin was not detectable in a UV/Vis spectrum indication a flavin concentration in solution less than c = 1×10^{-7} M (see appendix B).

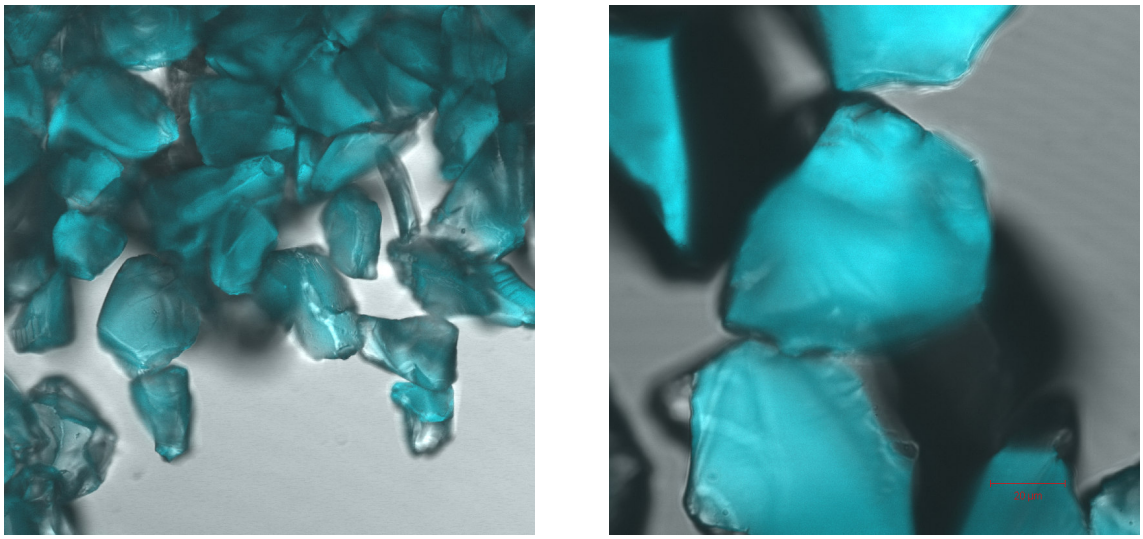


Figure 3.4 Confocal microscopy images of silica gel particles with immobilized flavin (tetraacetyl riboflavin (**10**) (1% per mass on fluorinated silica gel))

The photocatalytic activity of immobilized flavins on silica supports (1% per mass) was tested in solutions of benzyl alcohol in D_2O (for detailed setup see experimental part).

Table 3.2 Catalytic Photooxidations with flavins immobilized on silica gel

Entry	Flavin	X	t [h]	Aldehyde [%]	Acid [%]	TON	TOF [h^{-1}]
1	**10**	OMe	2	71	29	7.1	3.6
2	**10**	OMe	1	83	17	8.3	8.3
3	**10**	OMe	0.5	78	3	7.8	16
4	**10**	OMe	0.25	65	3	6.5	26
5[a]	**10**	OMe	1	46	0	4.6	4.6
6[a]	**10**	OMe	0.5	33	0	3.3	6.6
7[a]	**10**	OMe	0.25	29	0	2.9	12
8[b]	**10**	OMe	2	52	8	5.2	2.6
9[c]	**10**	OMe	2	55	12	5.5	2.8
10	**10**	Me	2	41	9	4.1	2.1
11	**10**	H	2	44	0	4.4	2.2
12	**10**	COOMe	2	36	0	3.6	1.8
13	**10**	COOH	2	24	0	2.4	1.2
14	**10**	COONa	2	<3	0	<0.3	<0.15
15	**4**	OMe	2	61	9	6.1	3.1
16	**7**	OMe	2	93	4	9.3	4.7
17	**8a**	OMe	2	46	3	4.6	2.3
18	**8b**	OMe	2	10	0	1	0.5
19	**11**	OMe	2	54	1	5.4	2.7
20	**14**	OMe	2	10	0	5	2.5
21	**15a**	OMe	2	97	3	9.7	4.9
22	**15b**	OMe	2	77	8	7.7	3.9
23	**15c**	OMe	2	59	4	5.9	3
24	**15d**	OMe	2	18	3	1.8	0.9
25[d]	**13**	OMe	15.5	2.8	—	280	18
26[e]	**6**	OMe	4	<3	—	—	—

Conditions: V=1 mL, 1% per mass flavin on fluorinated silica gel, 10mol% of catalyst, alcohol: 2×10^{-3} M

[a] Oxygen atmosphere [b] Addition of thiourea (2×10^{-3} M) [c] Addition of thiourea (1×10^{-3} M) [d] Reversed phase silica gel instead of fluorinated, pure alcohole solution [e] Immobilized on fluorinated glass instead of fluorous silica gel, V=7 mL, alcohol: 1×10^{-2} M, without stirring

With tetraacetyl riboflavin (**10**) as catalyst, the system retains its activity compared to homogeneous solution and 4-methoxybenzyl alcohol was completely converted within one hour (table 3.2, entries 1+2). However, in some reactions, oxidation to minor amounts of 4-methoxybenzoic acid

occurs. Shorter reaction times of 30 or 15 minutes, respectively, suppress the undesired acid by-product (entries 3+4).

Oxygen is the terminal oxidant of this reaction. Therefore, it was investigated whether the photooxidation is accelerated under oxygen atmosphere (entries 5–7). However, the conversion drops by a factor of two compared to the standard experiments in aerial environment (entries 2–4). The adverse effect of high oxygen concentrations may be due to the quenching of the flavin excited state by oxygen.

Hydrogen peroxide, the second product of the reaction, is not able to oxidize 4-methoxybenzyl alcohol.[4d] A standard reaction mixture with 10 equivalents of hydrogen peroxide instead of a flavin catalyst does not show any conversion after stirring for 30 min (see appendix B).

Like in homogeneous solution (table 3.1), the addition of thiourea decelerates the conversion (entries 8+9),[6] but a larger scope of possible substrates is observed. Electronically not activated benzyl alcohols were oxidized with the catalysts on fluorinated silica gel with reasonable TOFs and good overall conversions (entries 10–13).

A surprising correlation arises from the analysis of the catalytic activity of different immobilized flavins (entries 1, 16–24). All 3-N-substituted flavins show a reduced catalytic activity in the photooxidation of 4-methoxybenzyl alcohol in aqueous solution when immobilized on silica support. In homogeneous reaction conditions the catalytic activity of 3-N-alkylated and 3-N-H flavins is comparable (table 3.1, entries 5+7), indicating that this difference has to be attributed to the immobilization. Neither the redox potentials[4d] nor the shape of HOMO and LUMO[22] of the flavin chromophore are significantly influenced by 3-N alkylation. A different orientation of the flavin chromophore on the support surface may be envisaged to cause the differences in reactivity.

Flavins **7** and **15a** showed considerable higher TOFs of 4.7 and 4.9 h^{-1} respectively, compared to all other tested derivatives, exceeding tetraacetyl riboflavin (**10**) as catalyst (3.6 h^{-1} under comparable conditions).

Table 3.3 Comparison of homogeneous, silica gel and polyethylene based catalysis

Entry	X	System	t [min]	Aldehyde [%]	TON	TOF [h^{-1}]
1	OMe	in solution	1	58	5.8	348
2	OMe	on silica gel	30	78	7.8	16
3	H	in solution	25	75	7.5	18
4	H	on silica gel	120	44	4.4	2.2
5	COOMe	in solution	25	58	5.8	14
6	COOMe	on silica gel	120	36	3.6	1.8
7[a]	OMe	in solution	5	59	—	—
8[a,b]	OMe	PE-pellet	240	65	—	—

Conditions: V=1 mL, D_2O, tetraacetyl riboflavin (**10**) as catalyst, alcohol: 2×10^{-3} M
[a] Without stirring [b] Alcohol: 1×10^{-2} M

In general, the TOF of the photoreaction with immobilized flavins drops compared to experiments in homogeneous solution by a factor of 8–20, while TON and aldehyde yields remain comparable (table 3.3, entries 1–6). Recycling of the immobilized photocatalysts was demonstrated by placing a reaction mixture into a syringe with a filter. After each 15 minutes of irradiation and stirring, the reaction mixture was removed and the conversion was monitored by ^{1}H NMR. To the remaining immobilized catalyst in the syringe, a fresh benzyl alcohol solution was added and the procedure was repeated (see appendix B). The activity of the immobilized photocatalyst remained almost unchanged for three cycles with high TOFs of 10 h^{-1} and then dropped by 30% in the next two cycles (table 3.4, entries 1–5). These results confirm that the immobilized flavins are catalytically active and not chromophore molecules that are leaching from the support. As an additional experiment, we removed the immobilized catalyst from a reaction mixture that was irradiated for 30 min (yield: 72% of aldehyde). Continued irradiation of the same solution without the catalyst under identical conditions for 30 min did not result in further reaction conversion (see appendix B). The photooxidation proceeds only in the presence of the heterogeneous photocatalyst.

Table 3.4 Recycling experiments with immobilized catalysts
(Alc. = 4-methoxybenzyl alcohol, Ald. = 4-methoxy benzaldehyde)

Entry	Alc. [M]	Immobilization	t [min]	Ald. [%]	Run	TON	TOF [h^{-1}]
1[a]	2×10^{-3}	on SiO2	15	22	1	2.2	8.8
2[a]	2×10^{-3}	on SiO2	15	25	2	2.5	10
3[a]	2×10^{-3}	on SiO2	15	24	3	2.4	9.6
4[a]	2×10^{-3}	on SiO2	15	15	4	1.5	6
5[a]	2×10^{-3}	on SiO2	15	8	5	0.8	3.2
6	1×10^{-2}	PE	240	46	1	—	—
7	1×10^{-2}	PE	240	29	2	—	—

Conditions: V=1 mL, D_2O, tetraacetyl riboflavin (**10**) as catalyst
[a] 10 mol% of catalyst

To show the applicability of the photooxidation to preparative lab-scale we used 4-methoxybenzyl alcohol as substrate and solvent. 3-Methyl tetrapalmityl riboflavin (**13**), which is a very low melting oily solid and completely insoluble in water was immobilized on reversed phase silica gel, comprising C_{18}-alkyl chains and was used as catalyst. Preparation of the supported catalyst was carried out the same way as with fluorinated silica gel. The photooxidation in neat 4-methoxybenzyl alcohol allows an overall conversion of 2.8% to the aldehyde with a TOF of 18 h^{-1} and high TON of 280 (table 3.2, entry 25).
An attempt to create an active photocatalyst by immobilization of flavin **6** on commercially available fluorinated glass[23] failed due to the small amount of deposited photoactive compound. No significant conversion was observed with this catalyst even after 4 h of irradiation (table 3.2, entry 26).

Flavin immobilization by entrapment in PE-pellets or glues

In some solvents, the catalysts were washed off from the silica gel support. Therefore, an entrapment of flavins in polymer pellets and in simple glue was tried. As water is the best solvent for the photocatalytic oxidation completely insoluble polyethylene (PE) was selected as material for the entrapment. The preparation of flavin containing PE-pellets is simple: The

flavin chromophore and commercially available PE-powder are mixed in a ratio of 1:100 by weight. This mixture is compressed to 125 MPa at 80 °C yielding yellow fluorescing pellets (figure 3.5).

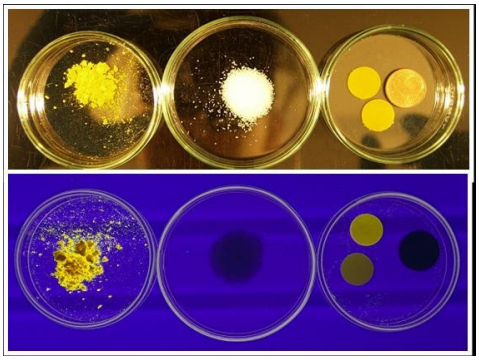


Figure 3.5 Top: normal light, bottom: UV-light, left: solid flavin **10**, middle: PE-powder, right: immobilized catalyst + 1 €-cent coin for comparison

To determine the catalytic activity, the flavin-PE-pellets were placed at the top of 1 mL of an aqueous 4-methoxybenzyl alcohol solution (1×10^{-2} M in D_2O) in a small glass reaction vessel, which was irradiated from the bottom by an LED (440 nm) without stirring. The reaction conversion was monitored by ^1H NMR.

Table 3.5 Catalytic photooxidations with entrapped flavins

Entry	Flavin	Alcohol [M]	t [h]	Immobilization method	Aldehyde [%]
1	**10**	1×10^{-2}	4	PE	65
2	**11**	1×10^{-2}	4	PE	55
3	**8a**	1×10^{-2}	4	PE	14
4	**7**	1×10^{-2}	4	PE	n.s.c.[a]
5	–	1×10^{-2}	4	pure PE	n.s.c.[a]
6	**13**	2×10^{-3}	1	coated on glass	29
7	**10**	2×10^{-3}	12	superglue	n.s.c.[a]

Conditions: V=1 mL, D_2O

[a] n.s.c. = no significant conversion[24]

Riboflavin tetraacetates **10** and **11** were found to be the most active catalysts if immobilized in PE-pellets. A conversion of the benzyl alcohol to the aldehyde in 55–65% yield was observed after 4 h (table 3.5,

entries 1+2). In absolute numbers, 5.5–6.5 μmol were converted in such a reaction. However, compared to the reaction in homogeneous aqueous solution which reaches under identical conditions the same conversion after 5 min (table 3.1, entry 4), the efficiency is drastically reduced by a factor of 50. In addition, one pellet contains about 4.6 μmol of flavin, which means, that the catalyst loading is 45%. Obviously, not all flavin molecules are accessible for the photocatalytic reaction as they are trapped in the bulk of the pellet leading to a lower effective loading. Other entrapped flavins **7** and **8a** (entries 3+4) showed only low or no significant photooxidation activity. As expected, no conversion was obtained if a PE-pellet without flavin was used. Recycling of flavin catalyst pellets is limited; the activity drops by 50% in the second run (table 3.4, entries 6+7).

In order to obtain stable immobilized flavin layers, we entrapped tetraacetyl riboflavin (**10**) by mixing a chloroform solution with superglue[25] and evaporating the mixture. This yielded a stable polymer layer containing the chromophore in a glass, which unfortunately showed no conversion when irradiated in the presence of substrate solution for 12 h (entry 7). Simple evaporation of a chloroform solution of tetrapalmityl riboflavin (**13**) without adding glue yielded a stable chromophore layer in a glass vial. This layer is stable in aqueous solution, but is destroyed by stirring. Therefore, the photooxidation was investigated by irradiation of the flavin layer with a solution of 4-methoxybenzyl alcohol without stirring. Within 1 h, 29% of the substrate was converted into the corresponding aldehyde (entry 6).

Conclusion

The photooxidation of benzyl alcohols to the corresponding aldehydes with flavin catalysts using oxygen as the terminal oxidising agent proceeds very fast and efficient in aqueous solution. TOF of more than 800 h^{-1} and TON of up to 68 were observed. It was possible to oxidize benzyl alcohols which are electronically not activated for this reaction.

To create heterogeneous photocatalysts, several new flavin derivatives were prepared and immobilized on solid supports (fluorous silica gel, reversed phase silica gel, PE-pellets). The immobilized photocatalysts retained their

catalytic activity for benzyl alcohol oxidation. In comparison to the analogous homogeneous reactions, the reaction rates decrease by a factor of 8–20 for immobilization on silica gel and by a factor of 50 for the catalyst entrapment in polyethylene pellets.

The highest catalytic activity (TOF 26 h^{-1}), best stability (TON 280) and up to 3 reaction cycles without loss of performance are possible with flavins **7**, **10** and **13** immobilized on fluorous silica gel and reversed phase silica gel, respectively.

In summary, we have shown that heterogeneous photocatalysts can be derived from functionalized flavins by physical adsorption on fluorinated silica gel support or by mechanical entrapment. The immobilized chromophores are the catalytically active species, as the photooxidation reactions stops immediately when the heterogeneous catalyst is removed. The heterogeneous catalysts significantly facilitate product isolation and catalyst recycling. Flavin-catalyzed photooxidations are suited for preparative lab scale conversions. The introduced heterogeneous catalysts facilitate the use of flavin photooxidation catalysts in synthesis and pave the way to applications of the energy efficient transformations in continuous flow reactions.

Experimental part

General

Dinitrobenzene **1**,[13] fluorinated amine **2**,[14] 10-(2-methoxyethyl)-7,8-dimethyl-benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (**7**)[6] and tetraacetyl ribo-flavin (**10**)[15] were prepared by known methods. All other chemicals were purchased from commercial suppliers, checked by ^{1}H NMR spectrometry and then used as received. Before use, solvents were distilled. Dry DMAP was purchased from Fluka. Fluorinated silica gel with a particle size of 35–70 μm and reversed phase silica gel (40–63 μm) were purchased from Fluka. Thin layer chromatography was carried out on Silica gel 60 F254 aluminium sheets (Merck) or on precoated plastic sheets Polygram SIL G/UV254 (Macherey-Nagel, Düren, Germany), with detection under 254 nm or

333 nm UV light or by naked eye (flavins are intensively yellow-coloured). Flash column chromatography was carried out on silica gel 35–70 μm, 60 Å from Acros. NMR spectra were recorded at Bruker spectrometer equipped with a robotic sampler at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C-NMR). Tetramethylsilane (TMS) was used as an external standard. Electrospray ionisation (ES-MS) mass spectra were measured on ThermoQuest Finnigan TSQ 7000 spectrometer. High resolution mass spectrometry (HRMS) was measured on ThermoQuest Finnigan MAT 95 spectrometer. Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected. IR spectra were measured on Biorad Spectrometer Excalibur FTS 3000.

General procedure for the immobilization of flavins on fluorous silica gel

Flavins (2–5 mg) were dissolved in $CHCl_3$ (20–30 mL) in a flask (50 mL) and the appropriate amount of silica gel (200–500 mg) was added. The solvent was slowly evaporated. Drying gave flavin catalysts on fluorous silica with a loading of 1% per mass as yellow powders. In the case of tetraacetyl riboflavin (**10**) which was mainly used in our experiments, this represents 18 μmol flavin/g silica gel.

General procedure for the immobilization of flavins in polyethylene pellets

Flavin (2.5 mg) and polyethylene powder (247.5 mg) were mixed and brought into a press. A pressure of 125 MPa was adjusted and the pressing tool was heated to 80–100 °C until the pressure decreased. The apparatus was allowed to cool down to room temperature and the yellow pellets (1-2 mm thick, 1.3 cm diameter) were removed. To remove traces of flavin that was not completely incorporated, the pellets were washed with water three times.

General procedure for testing of the photocatalytic activity of flavins

The photocatalytic activity of flavins was tested in solutions of different benzyl alcohols (2×10^{-3} M) in D_2O (V=1 mL). Flavins (10 mol%) were added as DMSO-d_6 stock solution (1×10^{-2} M) for the experiments in homogeneous solution or as immobilized flavins on silica gel (1% per mass) for

heterogeneous experiments. The reaction mixture was stirred and irradiated at room temperature with an array of six LEDs (440 nm, 5 W each) in small glass vials (see figure 1). The progress of the reaction was monitored by ^{1}H NMR. Heterogeneous catalysts were removed by filtration before the measurement. The ^{1}H NMR resonance signals of the alcohol and the aldehyde are well separated and were assigned unambiguously. The clean conversion allows the quantitative monitoring of the reaction progress by integration of the aromatic resonance signals (see also appendix B).

_N_-1_H_,1_H_,2_H_,2_H_-Perfluorodecyl-4,5-dimethyl-2-nitroaniline (3)

Dinitro-*o*-xylol **1** (392 mg, 2.0 mmol) was dissolved in EtOH (50 mL). Subsequently, TEA (416 µL, 3.0 mmol) and the fluorinated amine **2** (1.31 g, 2.83 mmol) in EtOH (3 mL) were added and the mixture was refluxed for one day. Another portion of amine **2** (300 mg, 648 µmol) was added. After refluxing for five more days, the solvent was evaporated yielding a yellow-orange solid. Flash column chromatography (R_f=0.25; PE:$CHCl_3$ – 4:1) gave an orange solid.

Yield 294 mg, 480 µmol, 24%, orange solid

R_f=0.25 (PE:CHCl3 – 4:1)

m.p. 85 °C

^{1}H NMR ($CDCl_3$) δ = 2.20 (s, 3 H, Ar-CH_3), 2.30 (s, 3 H, Ar-CH_3), 2.42–2.59 (m, 2 H, CH_2C$_8$F$_{17}$), 3.65–3.72 (m, 2 H, NH-CH_2), 6.61 (s, 1 H, Ar-*H*), 7.96 (s, 1 H, Ar-*H*), 8.02 (tr, *J*=5.49 Hz, 1 H, N*H*)

^{13}C NMR ($CDCl_3$) δ = 18.7 (Ar-*C*H$_3$), 20.9 (Ar-*C*H$_3$), 30.8 (CH$_2$-C$_8$F$_{17}$), 35.1 (N-CH$_2$), 113.5, 125.5, 127.0, 130.7, 143.1 and 147.7 (6×Ar-*C*)

^{19}F NMR ($CDCl_3$) δ = -126.6 (m, 2 F, CF_2), -123.8 (m, 2 F, CF_2), -123.2 (m, 2 F, CF_2), -122.4 (m, 4 F, 2×CF_2), -122.1 (m, 2 F, CF_2), -114.3 (quin, *J*=15.3 Hz, 2 F, CH$_2$CF_2), -81.2 (tr, *J*=9.82 Hz, 3 F, CF_3)

ES-MS *m/z* (%): 613.2 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{18}H_{13}F_{17}N_2O_2$ $[M]^{+\bullet}$: 612.0706; found: 612.0714 [Δ –1.38 ppm]

IR (ATR): ν = 3348, 1633, 1578, 1505, 1333, 1242, 1193, 1146, 1007 cm^{-1}

10-1*H*,1*H*,2*H*,2*H*-Perfluorodecyl-flavin (4)

Nitro compound **3** (127 mg, 207 μmol) was dissolved in MeOH (30 mL) and $CHCl_3$ (5 mL). Palladium on activated charcoal (28 mg) was added and the mixture was hydrogenated with 12 bar at room temperature for 16 h. After filtration, alloxane monohydrate (365 mg, 2.57 mmol) and boric acid (700 mg, 11.3 mmol) was added and the mixture was stirred at room temperature for three days in the dark. After evaporation of the solvents, $CHCl_3$ (300 mL) was added and the organic phase was washed with water and brine. The organic phase was dried over magnesium sulphate and evaporated. The crude product was purified by flash column chromatography ($CHCl_3$:EE:MeOH – 20:10:3).

Yield 66 mg, 96 μmol, 46%, yellow solid

R_f=0.3 ($CHCl_3$:EE:MeOH – 20:10:3)

m.p. 310 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.47 (s, 3 H, Ar-CH_3), 2.58 (s, 3 H, Ar-CH_3), 2.68–2.85 (m, 2 H, C$H_2C_8F_{17}$), 4.99 (tr, J=7.55 Hz, 2 H, N-CH_2), 7.42 (s, 1 H, Ar-*H*), 8.10 (s, 1 H, Ar-*H*), 8.43 (br s, 1 H, N*H*)

^{13}C NMR not measured due to low solubility

^{19}F NMR ($CDCl_3$) δ = -126.6 (m, 2 F, CF_2), -123.4 (m, 2 F, CF_2), -123.1 (m, 2 F, CF_2), -122.3 (m, 4 F, 2×CF_2), -122.0 (m, 2 F, CF_2), -113.9 (tr, J=13.2 Hz, 2 F, CH_2CF_2), -81.2 (tr, J=9.82 Hz, 3 F, CF_3)

ES-MS *m/z* (%): 689.2 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{22}H_{13}F_{17}N_4O_2$ $[M]^{+\bullet}$: 688.0767; found: 688.0767 [Δ 0.00 ppm]

IR (ATR): ν = 3182, 3069, 1724, 1672, 1581, 1538, 1509, 1196, 1141, 824 cm^{-1}

3,10-Bis-1*H*,1*H*,2*H*,2*H*-perfluorodecyl-flavin (6)

Flavin **4** (68 mg, 100 μmol) was dissolved in dry DMAP (15 mL) and subsequently, potassium carbonate (72 mg, 521 μmol) and fluorinated iodide **5** (1.30 g, 2.26 mmol) were added and the mixture was stirred for 24 h at room temperature in the dark. The suspension was diluted with $CHCl_3$ and washed with water (5x100 mL) and brine (2x100 mL). The organic phase was dried over magnesium sulphate and the solvents were

evaporated. The crude product was purified by flash column chromatography (DCM:MeOH – 100:1).

Yield 71 mg, 62 µmol, 62%, yellow solid

R_f=0.2 (DCM:MeOH – 100:1)

m.p. 155 °C

^{1}H NMR ($CDCl_3$) δ = 2.45 (s, 3 H, Ar-CH_3), 2.46–2.83 (m, 7 H, Ar-CH_3+CH_2C$_8$F$_{17}$), 4.43 (tr, J=7.14 Hz, 2 H, N-CH_2), 4.96 (tr, J=7.00 Hz, 2 H, N-CH_2), 7.41 (s, 1 H, Ar-H), 8.07 (s, 1 H, Ar-H)

^{13}C NMR not measured due to low solubility

^{19}F NMR ($CDCl_3$) δ = -126.6 (m, 4 F, 2×CF_2), -124.0 (m, 2 F, CF_2), -123.5 (m, 2 F, CF_2), -123.2 (m, 4 F, 2×CF_2), -122.3–-122.1 (m, 12 F, 6×CF_2), -114.8 (tr, J=12.9 Hz, 2 F, CH$_2$CF_2), -113.9 (tr, J=13.5 Hz, 2 F, CH$_2$CF_2), -81.3–-81.2 (m, 6 F, CF_3)

ES-MS m/z (%): 1135.2 (100) $[M+H]^+$

HRMS–EI m/z: calcd for $C_{32}H_{16}F_{34}N_4O_2$ $[M]^{+\bullet}$: 1134.0730; found: 1134.0722 [Δ 0.73 ppm]

IR (ATR): ν = 1664, 1585, 1546, 1196, 1144, 656 cm^{-1}

10-Methoxyethyl-3-methyl-flavin (8a)[16]

Flavin **7** (306 mg, 1.02 mmol) was dissolved in dry DMAP (40 mL) and subsequently, caesium carbonate (488 mg, 1.50 mmol) and methyl iodide (1.37 g, 9.64 mmol) were added and the mixture was stirred for 18 h at room temperature in the dark. The suspension was diluted with $CHCl_3$ and washed with water (3x100 mL) and brine. The organic phase was dried over magnesium sulphate and the solvents were evaporated. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH – 100:1).

Yield 293 mg, 930 µmol, 91%, yellow solid

R_f=0.2 ($CHCl_3$:MeOH – 100:1)

m.p. 255 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 2.41 (s, 3 H, Ar-CH_3), 2.51 (s, 3 H, Ar-CH_3), 3.26 (s, 3 H, O-CH_3), 3.49 (s, 3 H, N-CH_3), 3.88 (tr, J=5.21 Hz, 2 H, O-CH_2), 4.87 (tr, J=5.08 Hz, 2 H, N-CH_2), 7.62 (s, 1 H, Ar-H), 7.99 (s, 1 H, Ar-H)

^{13}C NMR ($CDCl_3$) δ = 19.6 (Ar-CH$_3$), 21.6 (Ar-CH$_3$), 45.4 (N-CH$_2$), 59.3 (O-CH$_3$), 69.6 (O-CH$_2$), 116.7 (C-9), 132.2 (C-9a), 132.3 (C-6), 135.0 (C-5a),

135.5 (*C*-4a), 136.7 (*C*-7), 147.6 (*C*-8), 148.7 (*C*-10a), 156.0 (*C*-2), 160.2 (*C*-4)

ES-MS *m/z* (%): 315.0 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{16}H_{18}N_4O_3$ $[M]^{+\bullet}$: 314.1379; found: 314.1374 [Δ 1.56 ppm]

IR (ATR): ν = 2921, 1703, 1651, 1582, 1540, 1451, 1231, 1110, 1014, 970 cm^{-1}

3-1*H*,1*H*,2*H*,2*H*-Perfluorodecyl-10-methoxyethyl-flavin (8b)

Flavin **7** (109 mg, 363 μmol) was dissolved in dry DMAP (15 mL) and potassium carbonate (251 mg, 1.81 mmol) was added. After stirring for 20 min, fluorinated iodide **5** (625 mg, 1.09 mmol) in dry DMAP (5 mL) was added. After one day, another portion of iodide **5** (417 mg, 726 μmol) was added and the mixture was stirred for three days at room temperature in the dark. The mixture was diluted with $CHCl_3$ and washed with water (3x100 mL) and brine (100 mL). The organic phase was dried over magnesium sulphate and the solvents were evaporated. The crude brown solid was purified by flash column chromatography ($CHCl_3$:MeOH – 20:1).

Yield 63 mg, 84 μmol, 23%, yellow solid

R_f=0.2 ($CHCl_3$:MeOH – 20:1)

m.p. 175 °C

^{1}H NMR ($CDCl_3$) δ = 2.44 (s, 3 H, Ar-C*H*$_3$), 2.49–2.67 (m, 5 H, Ar-C*H*$_3$+3-N-C*H*$_2$), 3.29 (s, 3 H, O-C*H*$_3$), 3.91 (tr, *J*=5.08 Hz, 2 H, 10-N-C*H*$_2$), 4.45 (tr, *J*=7.55 Hz, 2 H, C*H*$_2$C$_8$F$_{17}$), 4.89 (tr, *J*=5.21 Hz, 2 H, O-C*H*$_2$), 7.67 (s, 1 H, Ar-*H*), 8.03 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.6 (Ar-*C*H$_3$), 21.7 (Ar-*C*H$_3$), 29.8 ($CH_2C_8F_{17}$), 34.3 (N-CH_2), 45.6 (N-CH_2), 59.4 (O-CH_3), 69.6 (O-CH_2), 116.8 (*C*-9), 132.4 (*C*-9a, *C*-6, *C*-5a), 135.3 (*C*-4a), 137.0 (*C*-7), 148.1 (*C*-8), 148.9 (*C*-10a), 155.1 (*C*-2), 159.9 (*C*-4)

^{19}F NMR ($CDCl_3$) δ = -126.6 (m, 2 F, C*F*$_2$), -124.0 (m, 2 F, C*F*$_2$), -123.2 (m, 2 F, C*F*$_2$), -122.4 (m, 4 F, 2×C*F*$_2$), -122.2 (m, 2 F, C*F*$_2$), -114.8 (quin, *J*=16.6 Hz, 2 F, CH_2C*F*$_2$), -81.2 (tr, *J*=10.1 Hz, 3 F, C*F*$_3$).

ES-MS *m/z* (%): 747.3 (100) $[M+H]^+$, 769.3 $[M+Na]^+$

HRMS–EI *m/z*: calcd for $C_{25}H_{19}F_{17}N_4O_3$ $[M]^{+\bullet}$: 746.1186; found: 746.1178 [Δ 1.03 ppm]

IR (ATR): ν = 2952, 1708, 1663, 1585, 1552, 1197, 1144, 1111, 1003, 958, 719, 657 cm^{-1}

3-Methyl-tetraacetyl riboflavin (11)[16,26]

Tetraacetyl riboflavin **10** (1.63 g, 3.0 mmol) was dissolved in dry DMAP (20 mL) and subsequently, caesium carbonate (1.47 g, 4.50 mmol) and methyl iodide (1.8 mL, 29.0 mmol) were added. After stirring for 16 h at room temperature in the dark, water (5 mL) was added and the solvents were evaporated. The crude product was dissolved in $CHCl_3$ (250 mL) and washed with water (2x100 mL) and brine. The organic phase was dried over magnesium sulphate and the solvents were evaporated. Purification was done by flash column chromatography ($CHCl_3$:MeOH – 50:1).

Yield 1.19 g, 2.13 mmol, 71%, orange solid

R_f=0.15 ($CHCl_3$:MeOH – 50:1)

m.p. 183 °C

^{1}H NMR ($CDCl_3$) δ = 1.70 (s, 3 H, Ac-C*H*$_3$), 2.05 (s, 3 H, Ac-C*H*$_3$), 2.20 (s, 3 H, Ac-C*H*$_3$), 2.27 (s, 3 H, Ac-C*H*$_3$), 2.40 (s, 3 H, Ar-C*H*$_3$), 2.52 (s, 3 H, Ar-C*H*$_3$), 3.45 (s, 3 H, N-C*H*$_3$), 4.22 (dd, *J*=12.35 Hz, *J*=5.76 Hz, 1 H, C*H*), 4.40 (dd, *J*=12.21 Hz, *J*=2.61 Hz, 1 H, C*H*), 4.59–5.26 (m, 2 H, C*H*), 5.35–5.45 (m, 2 H, C*H*), 5.62–5.65 (m, 1 H, C*H*), 7.51 (s, 1 H, Ar-*H*), 7.97 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.5 (Ar-*C*H$_3$), 20.4 (Ac-*C*H$_3$), 20.8 (Ac-*C*H$_3$), 20.9 (Ac-*C*H$_3$), 21.1 (Ac-*C*H$_3$), 21.5 (Ar-*C*H$_3$), 28.7 (N-*C*H$_3$), 44.6 (*C*H$_2$), 61.9 (*C*H$_2$), 69.0 (*C*H), 69.4 (*C*H), 70.4 (*C*H), 115.4 (*C*-9), 131.2 (*C*-9a), 132.9 (*C*-6), 134.7 (*C*-5a), 135.6 (*C*-4a), 136.7 (*C*-7), 147.6 (*C*-8), 149.1 (*C*-10a), 155.3 (*C*-2), 160.0 (*C*-4), 169.7 (*C*O), 169.9 (*C*O), 170.4 (*C*O), 170.7 (*C*O)

ES-MS *m/z* (%): 559.2 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{26}H_{30}N_4O_{10}$ $[M]^{+\bullet}$: 558.1962; found: 558.1962 [Δ –0.01 ppm]

IR (ATR): ν = 2920, 1737, 1709, 1659, 1532, 1373, 1209, 1034 cm^{-1}

3-Methyl-riboflavin (12)[16,27]

3-Methyl-tetraacetyl riboflavin **11** (280 mg, 501 μmol) was dissolved in EtOH (50 mL) and *p*-toluene sulfonic acid (98 mg, 569 μmol) was added. After refluxing for 17 h, another portion of *p*-toluene sulfonic acid (49 mg,

285 μmol) was added and the mixture was refluxed for 3 h. After cooling to room temperature, the solution was stored in the refrigerator over night and a yellow solid precipitated which was filtered off and dried.

Yield 142 mg, 364 μmol, 73%, yellow solid

m.p. 275 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 2.38 (s, 3 H, Ar-CH_3), 2.47 (s, 3 H, Ar-CH_3), 3.27 (s, 3 H, N-CH_3), 3.44–3.48 (m, 1 H, O*H*), 3.64 (br s, 3 H, 3×O*H*), 4.23–4.26 (m, 1 H, C*H*), 4.51 (tr, *J*=5.63 Hz, 1 H, C*H*), 4.58–4.62 (m, 1 H, C*H*), 4.77 (d, *J*=5.49 Hz, 1 H, C*H*),4.88–5.00 (m, 2 H, C*H*), 5.13 (d, *J*=4.67 Hz, 1 H, C*H*), 7.89 (s, 1 H, Ar-*H*), 7.91 (s, 1 H, Ar-*H*)

^{13}C NMR (DMSO-d_6) δ = 18.8 (Ar-*C*H_3), 20.8 (Ar-*C*H_3), 28.0 (N-*C*H_3), 47.1 (*C*H_2), 63.4 (*C*H_2), 68.8 (*C*H), 72.8 (*C*H), 73.6 (*C*H), 117.4 (*C*-9), 130.7 (*C*-6), 132.0 (*C*-9a), 134.2 (*C*-5a), 135.7 (*C*-4a), 135.9 (*C*-7), 146.2 (*C*-8), 149.3 (*C*-10a), 155.0 (*C*-2), 159.7 (*C*-4)

ES-MS *m/z* (%): 391.0 (100) $[M+H]^+$

HRMS–LSI *m/z*: calcd for $C_{18}H_{23}N_4O_6$ $[M+H]^+$: 391.1618; found: 391.1621 [Δ –0.87 ppm]

IR (ATR): ν = 3230, 1716, 1617, 1579, 1532, 1235 cm^{-1}

3-Methyl-tetrapalmityl-riboflavin (13)

3-Methyl-riboflavin **12** (280 mg, 501 μmol) was suspended in a mixture of dry $CHCl_3$ (15 mL) and pyridine (15 mL). A solution of palmityl chloride (1.55 mL, 5.13 mmol) in dry $CHCl_3$ (5 mL) was added dropwise within 1 h at 0 °C. Afterwards, the mixture was stirred for 24 h at room temperature. After addition of water (5 mL), the suspension was heated to 60 °C for 1 h and the solvents were evaporated afterwards. The crude product was dissolved in $CHCl_3$ (30 mL) and was washed with sodium hydrogen carbonate solution (2x100 mL) and brine (2x100 mL). The organic phase was dried over magnesium sulphate and the solvents were evaporated. The orange solid was purified by flash column chromatography (PE:EE – 2:1).

Yield 173 mg 129 μmol, 52%, orange solid

R_f=0.2 (PE:EE – 2:1)

m.p. 50–53 °C

^{1}H NMR ($CDCl_3$) δ = 0.86–2.53 (m, 130 H, 2×Ar-CH_3+4×$C_{15}H_{31}$), 3.48 (s, 3 H, N-CH_3), 4.17–4.23 (m, 1 H, C*H*), 4.43–4.48 (m, 1 H, C*H*), 4.92 (br s, 2

H, C*H*), 5.39–5.49 (m, 2 H, C*H*), 5.67–5.69 (m, 1 H, C*H*), 7.54 (s, 1 H, Ar-*H*), 8.02 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 14.2 (*C*H_3), 19.5 (Ar-*C*H_3), 21.5 (Ar-*C*H_3), 28.8 (N-*C*H_3), 44.6 (*C*H_2), 61.9 (*C*H_2), 69.1 (*C*H), 70.4 (2×*C*H), 115.6 (*C*-9), 131.4 (*C*-9a), 133.0 (*C*-6), 134.7 (*C*-5a), 135.7 (*C*-4a), 136.5 (*C*-7), 147.4 (*C*-8), 149.2 (*C*-10a), 155.3 (*C*-2), 160.0 (*C*-4), 172.5 (*C*O), 172.6 (*C*O), 173.1 (*C*O), 173.5 (*C*O); $C_{15}H_{31}$ signals not assigned

ES-MS *m/z* (%): 1344.4 (100) $[M+H]^+$

IR (ATR): ν = 2917, 2850, 1741, 1664, 1584, 1545, 1466, 1151, 721 cm^{-1}

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[24] Under these experimental conditions with long reaction times, a slow background reaction was detectable which leads to conversions of 2–3% per hour.
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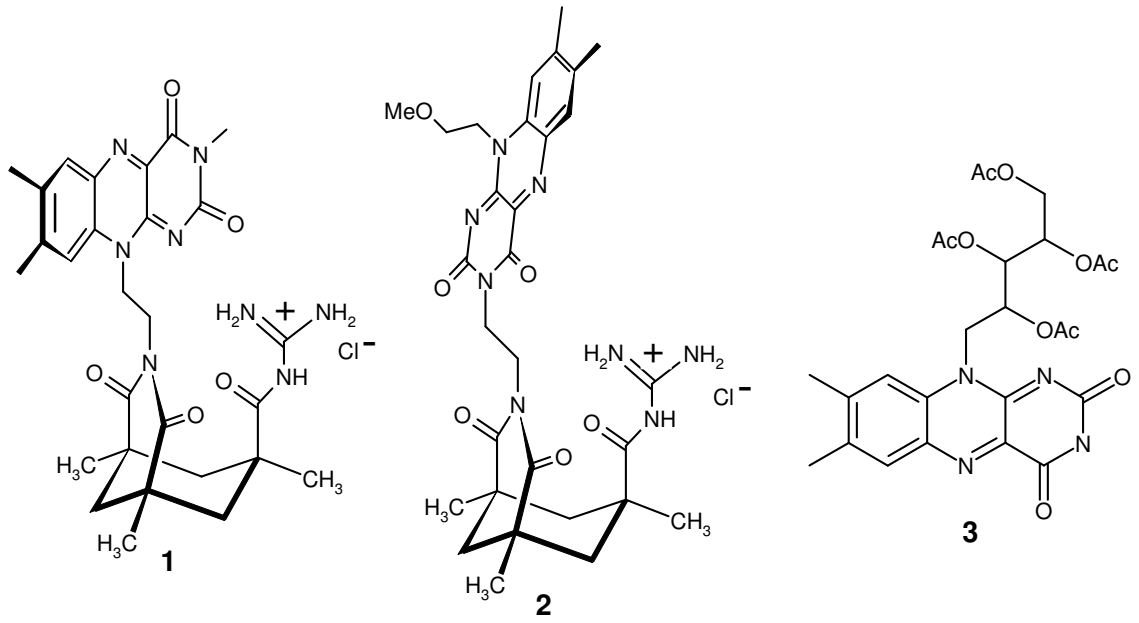
Chapter 4

Synthesis of Rigidified Flavin–Guanidinium Ion Conjugates and Investigation of Their Photocatalytic Properties*

Introduction

Flavins are redox-active chromophores[1] and represent one of the most abundant classes of natural enzyme co-factors.[2] Recently, the photo redox properties of flavins have been used to catalyze chemical reactions.[3] A drawback of photochemical processes in homogeneous solution is the limited preorganization of the reactants and the chromophore, which may lead to low selectivities and slow conversions in diffusion controlled reactions. To overcome this problem, Kemp´s acid[4] derivatives have been used as sterically defined templates enhancing the efficiency and selectivity of photoreactions.[5] Flavins with geometrically defined substrate binding sites are not known so far. The close vicinity of substrate and flavin should enhance the rate of photoinduced electron transfer processes, which strongly depend on distance.[6] We present here the synthesis of geometrically defined flavin-guanidinium ion conjugates based on a Kemp´s acid skeleton (scheme 4.1). The guanidinium moiety should serve as a hydrogen bonding site for oxoanions or carbonyl groups.[7] The structure of the new flavins was determined in solid state and in solution and their photocatalytic properties were tested.

* Manuscript in preparation. All experiments presented in this chapter were carried out by H.S.

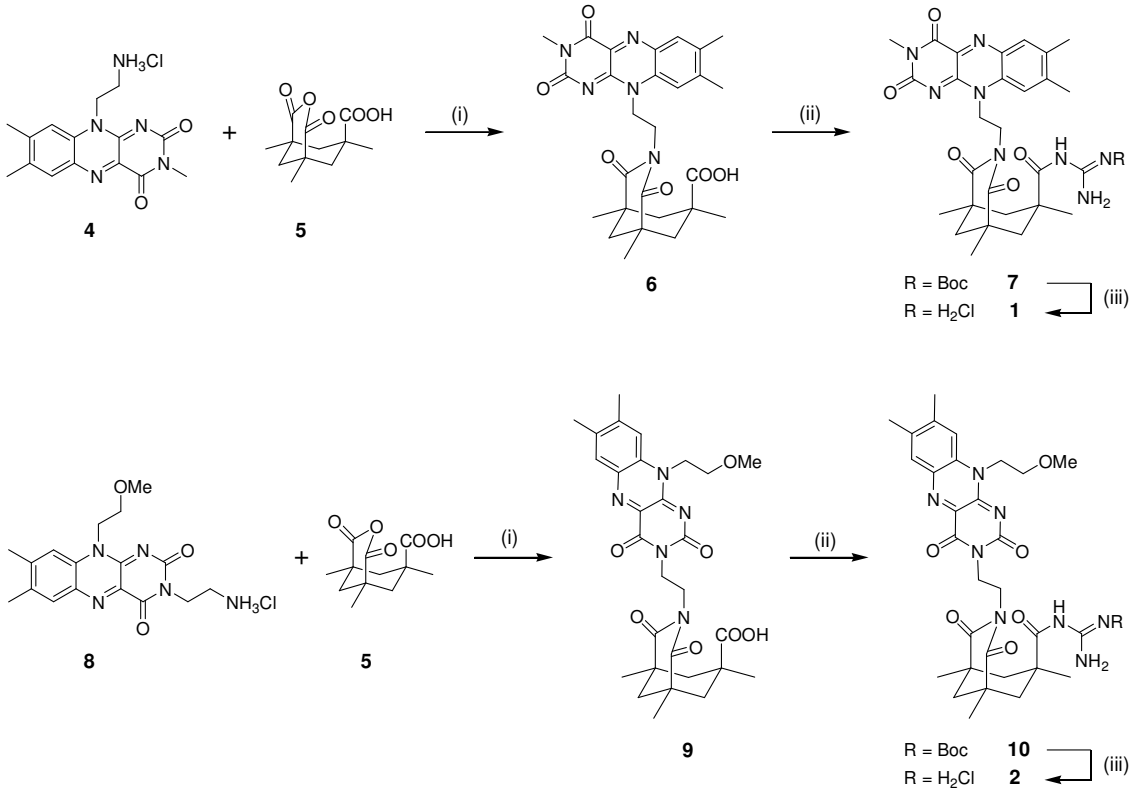


Scheme 4.1 Flavin–guanidinium ion conjugates **1** and **2** and tetraacetyl riboflavin (**3**)

Results and discussion

Synthesis

The synthesis of the potential photocatalysts **1** and **2**, consisting of the flavin chromophore, the guanidinium substrate binding site and a Kemp´s acid derived rigid linker, starts from Kemp´s acid anhydride (**5**).[8] The anhydride **5** was allowed to react with previously prepared flavins **4** and **8**[3l] in the presence of DMAP as catalyst. The amide formation of the carboxyl group with Boc-protected guanidine was achieved using standard peptide coupling conditions. Boc-deprotection with hydrogen chloride in diethyl ether yielded the guanidinium chloride salts **1** and **2** (scheme 4.2). The guanidinium salts are soluble in water and methanol, but also in chloroform and acetonitrile.



Scheme 4.2 Synthesis of flavins **1** and **2**
Conditions: (i) DMAP, H_2O, Δ, 20 h, 71–78% (ii) HOBt, EDC, DIPEA, mono-Boc guanidine, DCM, r.t., 20 h, 58–82% (iii) HCl/DE, DCM/$CHCl_3$, r.t., 24 h, 83–90%

Structural investigations

The structure of compounds **1**, **2**, **6**, and **9** was examined in the solid state and in solution. Figure 4.1 shows the X-ray crystal structures of **6** and **9**. The planar flavin chromophore is turned outward relative to the Kemp´s acid. Intermolecular π-π-interactions between the flavin heteroarenes are observed.

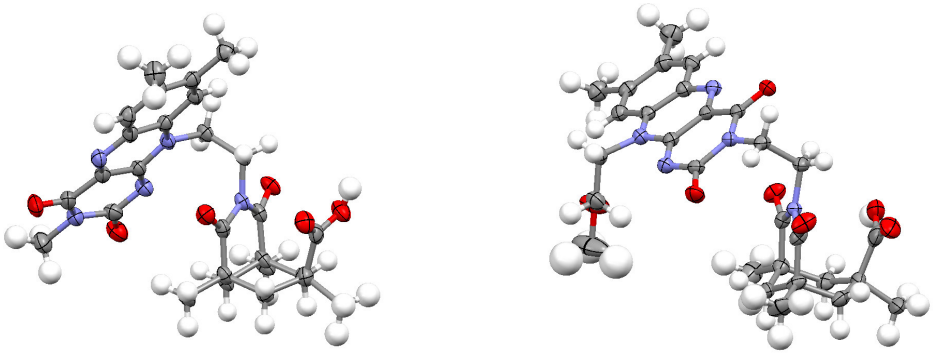


Figure 4.1 X-ray crystal structures of the flavin-Kemp´s acids **6** (left) and **9** (right)

The structure of compound **1** in the solid state (figure 4.2) shows an almost identical orientation of the flavin group as in the acid **6**. The acyl guanidinium ion group is almost planar and in a parallel orientation relative to the Kemp´s acid imide group.

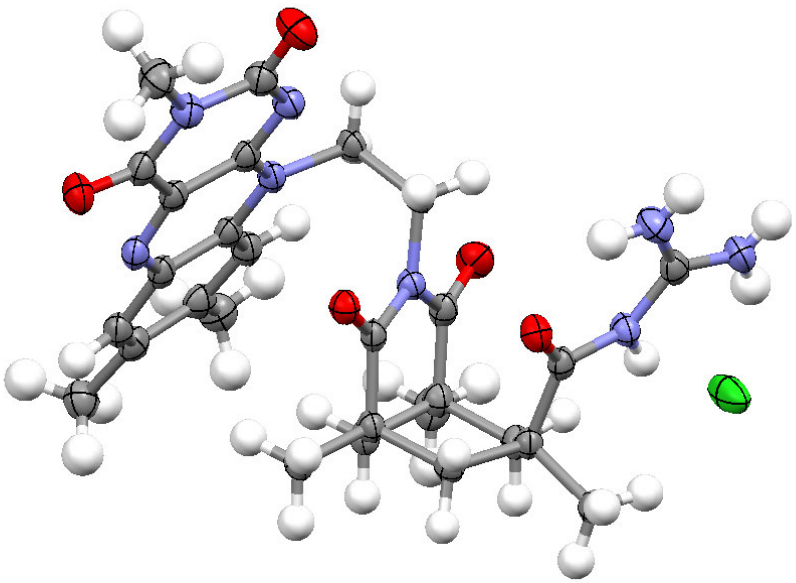


Figure 4.2 Structure of compound **1** in the solid state

The most stable conformer of compound **1** in the gas phase was determined by computational methods (semi-empirical AM1, Spartan program package, figure 4.3, see also appendix C).[9] In this structure the flavin is turned towards the guanidinium ion forming a hydrogen bond between the flavin carbonyl oxygen atom and the guanidinium moiety (distance ~2.1 Å). However, simple gas phase calculations overestimate the effect of hydrogen bonds[10] and in solution the flavin chromophore is expected to rotate freely around the C-C single bonds of the ethane linker.

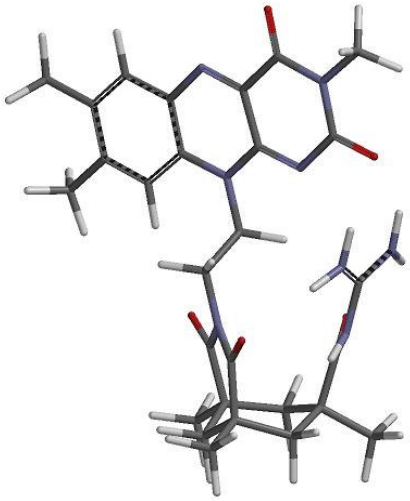
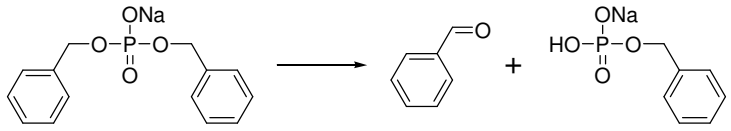


Figure 4.3 Calculated lowest energy conformation of **1** in the gas phase (AM1, Spartan program package)

Preliminary catalytic reactions

Compounds **1** and **2** were tested as photocatalysts in three different reactions and their performance was compared to tetraacetyl riboflavin **3** or compound **8**. Dibenzyl phosphate esters are oxidatively cleaved by blue light irradiation (440 nm) in the presence of compounds **1** and **2** (scheme 4.3). The acceleration of the reaction in acetonitrile by **1** and **2**, bearing a guanidinium ion binding site with phosphate affinity, is significantly larger (table 4.1, entries 1+2) in comparison to the ammonium salt **8** (entry 3). In water, however, the accelerating effect is not observed (entries 5–8). The presence of the photocatalyst is essential in all cases, as

the non-catalyzed hydrolysis is slow under the reaction conditions (<5% conversion).



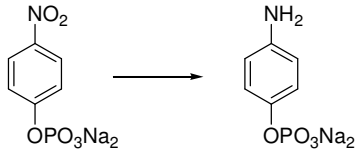
Scheme 4.3 Oxidative photocleavage of dibenzyl phosphate

Table 4.1 Oxidative photocleavage of dibenzyl phosphate

Entry	Catalyst	Solvent	t [h]	Conversion [%]
1[a]	**1**	MeCN-d_3	4	53
2[a]	**2**	MeCN-d_3	4	58
3[a]	**8**	MeCN-d_3	4	12
4[a]	–	MeCN-d_3	4	<5
5	**1**	D_2O	2	44
6	**2**	D_2O	2	15
7	**8**	D_2O	2	50
8	–	D_2O	2	<5

Conditions: V=1 mL, dibenzyl phosphate 10^{-2} M, catalyst 20 mol%, 40 °C, LED (440 nm)
[a] Dibenzyl phosphate ester was neutralized previous to the reaction

In the presence of sacrificial electron donor substrates, such as aliphatic amines, flavins can photoreduce nitro arenes to anilines under blue light irradiation (scheme 4.4). 4-Nitrophenyl phosphate was used as a substrate for photoreduction in water and in acetonitrile. The results summarized in table 4.2 show that 10 mol% of flavin **2**, the same amount of tetraacetyl riboflavin (**3**) or compound **8** catalyze the photoreaction equally well. The guanidinium binding site of **1** and **2** does not lead to a more effective conversion.



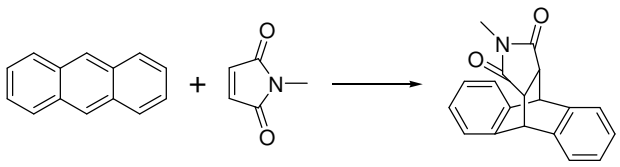
Scheme 4.4 Photoreduction of 4-nitrophenyl phosphate

Table 4.2 Results of nitrobenzene photoreduction

Entry	Catalyst	Solvent	Conversion [%]
1	**1**	H_2O	36
2	**2**	H_2O	72
3	**2**	H_2O[a]	73
4	**3**	H_2O[a]	89
5	**8**	H_2O	79
6[b]	**1**[c]	MeCN	15
7[b]	**2**	MeCN	55
8[b]	**3**	MeCN	81
9[b]	**8**	MeCN	59

Conditions: V=5 mL, nitrobenzene 10^{-2} M, catalyst 10 mol%, TEA 10 eq., t=4 h, 40 °C, LED (440 nm), UV-lamp (370 nm)
[a] 10% DMSO added to increase solubility [b] 4-Nitrophenyl phosphate was neutralized previous to the reaction [c] The catalyst is barely soluble in MeCN, which explains the lower conversion in this case

Photo Diels-Alder reactions in the presence of a sensitizer and light have been described.[11] Therefore flavins **1** and **2** were tested as catalyst for the cycloaddition of maleinimide to anthracene in toluene (scheme 4.5). Table 4.3 summarizes the results. A significantly higher yield of the cycloaddition product was obtained after 8 h at 40 °C in the presence of compound **2** (entry 3), if compared to the control reaction (entry 6). Upon irradiation with blue light the yield after 8 h reaction time increased further (entry 2) and was significantly higher as in the absence of a photocatalyst (entry 5). However, a comparison with tetraacetyl riboflavin (**3**) under identical reaction conditions showed an even more pronounced acceleration of the reaction (entry 4). Blue light irradiated flavins accelerate the anthracene maleinimide cycloaddition significantly, but flavins **1** and **2** do not provide additional benefit if compared to tetraacetyl flavin **3**.



Scheme 4.5 Photo Diels-Alder-reaction of anthracene with N-methyl-maleinimide

Table 4.3 Results of photoinduced Diels-Alder-reaction

Entry	Catalyst	hν	Yield [%]	TON	TOF [h^{-1}]
1	**1**	**+**	45	22.5	2.8
2	**2**	**+**	85	42.5	5.3
3	**2**	–	59	28.5	3.6
4	**3**	**+**	100	50	6.3
5	–	**+**	30	–	–
6	–	–	9	–	–
7[a]	–	–	100	–	–

Conditions: Toluene, V=1.2 mL, anthracene 33×10^{-3} M, maleinimide 2.5 eq., catalyst 2 mol%, t=8 h, 40 °C, LED (440 nm)
[a] Anthracene 500 μmol, methyl maleinimide 1.25 mmol, toluene 10 mL, 100 °C, 16 h

Conclusion

We have prepared new flavin derivatives that bear an acyl guanidinium group, which is linked to the chromophore via a rigid Kemp´s acid spacer. The connectivity and expected relative geometry of **1** and of the carboxylic acids **6** and **9** was confirmed by X-ray structure analysis. Guanidinium cations are known to bind oxoanions, such as phosphates, via hydrogen bonds. Therefore a benefit to the photocatalytic activity of **1** and **2** was expected, as the binding site could keep reaction substrates in close proximity to the redox active chromophore, facilitating photoinduced electron transfer processes. Initial exemplary photocatalytic experiments showed that flavin-derivatives **1** and **2** catalyze oxidative benzyl ether cleavage, nitro arene reductions and Diels-Alder reactions. However, no

significant gain in photocatalytic performance by the guanidinium ion substrate binding site was observed in comparison to flavins lacking the binding site and the rigid Kemp´s acid skeleton. The primary interaction between the aromatic substrates and the heteroaromatic flavin chromophore seems to dominate the formation of the substrate-catalyst aggregate. Hydrogen bonds between the substrate and the acylguanidinium group are not decisive for their interaction. The rigidity of the Kemp´s triacid skeleton is not effectively transferred in **1** and **2** to the relative flavin–guanidinium ion orientation, which is due to the flexible ethane linker between imide and flavin. Derivatives with a more constrained conformation of the flavin chromophore and the substrate binding sites may lead to chemical photocatalysts with better performance.

Experimental part

General

The flavin salts **4** and **8**, Kemp´s acid anhydride **5** and mono Boc-protected guanidine were prepared by known methods.[8,3l] All other chemicals were purchased from commercial suppliers, checked by ^{1}H NMR spectrometry and then used as received. Solvents were distilled before use. Flash column chromatography was carried out on silica gel 35–70 μm, 60 Å from Acros. NMR spectra were recorded at a Bruker Avance 300 spectrometer (300 MHz) or at a Bruker Avance 600 spectrometer (600 MHz). Electrospray ionisation (ES-MS) mass spectra were measured on ThermoQuest Finnigan TSQ 7000 spectrometer. High resolution mass spectrometry (HRMS) was measured on ThermoQuest Finnigan MAT 95 spectrometer. Melting points were measured on a Büchi SMP-20 apparatus and are not corrected. IR spectra were measured on Biorad Spectrometer Excalibur FTS 3000. UV/Vis spectra were recorded at Varian Cary 50 Bio UV/VIS spectrometer against air. Fluorescence spectra were recorded at Varian Cary Eclipse.

Flavin–Kemp´s acid 6

DMAP (230 mg, 1.9 mmol) and Kemp´s acid anhydride (**5**) (180 mg, 750 μmol) were added successively to a solution of flavin salt **4** (250 mg,

750 μmol) in water (22 mL) and the solution was refluxed for 20 h. After cooling, the mixture was brought to pH 1 with hydrochloric acid (5 M), and the precipitating orange product was collected by filtration. As thin layer chromatography showed considerable amounts of the product in the filtrate, it was concentrated and purified by flash column chromatography ($CHCl_3$:MeOH – 15:1), to yield another portion of orange solid.

Yield 302 mg, 580 μmol, 78%, orange solid

R_f=0.2 ($CHCl_3$:MeOH – 10:1)

m.p. 292 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 0.87 (s, 6 H, 2xKemps-CH_3), 1.00 (s, 3 H, Kemps-CH_3), 1.07–1.26 (m, 3 H, H_{ax}), 2.20–2.24 (m, 3 H, H_{eq}), 2.41 (s, 3 H, Ar-CH_3), 2.50 (s, 3 H, Ar-CH_3, hidden by DMSO), 3.28 (s, 3 H, N-CH_3), 3.90 (s, 2 H, CH_2), 4.87 (s, 2 H, CH_2), 7.77 (s, 1 H, Ar-*H*), 7.98 (s, 1 H, Ar-*H*), 12.24 (br s, 1 H, COO*H*)

^{13}C NMR (DMSO-d_6) δ = 18.8 (Ar-*C*H$_3$), 20.9 (Ar-*C*H$_3$), 24.7 (2×*C*H$_3$), 28.0 (N-*C*H$_3$), 29.7 (*C*H$_3$), 37.3 (N-CH$_2$), 39.4 (2×C_{qu}), 40.9 (2×*C*H$_2$), 41.1 (C_{qu}), 42.1 (*C*H$_2$), 43.0 (N-CH$_2$), 116.0(*C*-9), 131.1 (*C*-9a), 131.3 (*C*-6), 134.2 (*C*-5a), 135.5 (*C*-4a), 136.2 (*C*-7), 146.9 (*C*-8), 149.4 (*C*-10a), 154.9 (*C*-2), 159.5 (*C*-4), 176.2 (2×*C*O), 176.5 (*C*O)

ES-MS *m/z* (%): 522.4 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{23}H_{32}N_5O_6$ $[M+H]^+$: 522.2353; found: 522.2342 [Δ 2.03 ppm]

IR (ATR): ν = 1717, 1649, 1583, 1545, 1451, 1250, 1193, 1096, 1053, 970, 756 cm^{-1}

Flavin–Kemp´s acid 9

DMAP (460 mg, 2.8 mmol) and Kemp´s anhydride (**5**) (370 mg, 1.54 mmol) were added successively to a solution of flavin salt **8** (570 mg, 1.50 mmol) in water (50 mL) and the solution was refluxed for 20 h. After cooling, the mixture was brought to pH 1 with hydrochloric acid (5 M), and the precipitating dark orange product was collected by filtration. As thin layer chromatography showed considerable amounts of the product in the filtrate, it was concentrated and purified by flash column chromatography ($CHCl_3$:MeOH – 15:1), to yield another portion of orange solid.

Yield 597 mg, 1.06 mmol, 71%, orange solid

R_f=0.2 ($CHCl_3$:MeOH – 10:1)

m.p. 305 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 0.97 (s, 6 H, 2xKemps-CH_3), 1.04 (s, 3 H, Kemps-CH_3), 1.15 (d, J=13.72 Hz, 2 H, H_{ax}), 1.32 (d, J=12.62 Hz, 1 H, H_{ax}), 1.82 (d, J=12.62 Hz, 1 H, H_{eq}), 2.25 (d, J=13.17 Hz, 2 H, H_{eq}), 2.41 (s, 3 H, Ar-CH_3), 2.50 (s, 3 H, Ar-CH_3, hidden by DMSO), 3.22 (s, 3 H, O-CH_3), 3.74–3.77 (m, 4 H, 2xCH_2), 4.06–4.07 (m, 2 H, N-CH_2), 4.83 (tr, J=5.35 Hz, 2 H, O-CH_2), 7.91 (s, 1 H, Ar-H), 7.98 (s, 1 H, Ar-H), 12.25 (br s, 1 H, COOH)

^{13}C NMR (DMSO-d_6) δ = 18.8 (Ar-CH$_3$), 20.8 (Ar-CH$_3$), 25.0 (CH$_3$), 29.9 (CH$_3$), 37.4, 41.0, 41.6 and 43.1 (C_{qu} and CH$_2$), 44.0 (10-N-CH$_2$), 58.5 (O-CH$_3$), 68.3 (O-CH$_2$), 116.9 (*C9*), 130.9 (*C6*), 131.5 (*C9a*), 134.0 (*C5a*), 135.6 (*C4a*), 136.3 (*C7*), 147.0 (*C8*), 148.6 (*C10a*), 155.0 (*C2*), 159.7 (*C4*), 176.1 und 176.6 (*C*OOH und *C*ONH)

ES-MS *m/z* (%): 566.3 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{29}H_{36}N_5O_7$ $[M+H]^+$: 566.2615; found: 566.2623 [Δ -1.46 ppm]

IR (ATR): ν = 1719, 1673, 1621, 1581, 1548, 1234, 1119, 953, 886, 806, 758 cm^{-1}

Flavin-Boc-guanidin *7*

To a solution of HOBt•H_2O (89 mg, 580 μmol), EDC (90 mg, 580 μmol) and DIPEA (171 μL, 970 μmol) in DCM (6.5 mL) were added compound **6** (252 mg, 480 μmol) and mono Boc-protected guanidine (86 mg, 530 μmol) at 0 °C. The mixture was stirred at room temperature for 20 h, diluted with $CHCl_3$ (150 mL) and washed with brine twice. The organic phase was separated, dried over magnesium sulphate and the solvents were evaporated to yield an orange solid. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH – 50:1).

Yield 186 mg, 280 μmol, 58%, orange solid

R_f=0.15 ($CHCl_3$:MeOH – 50:1)

m.p. 255–259 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 0.91–1.05 (m, 12 H, 3xCH_3+3xH_{ax}), 1.48 (s, 9 H, Boc-CH_3), 2.39 (s, 3 H, Ar-CH_3), 2.48 (s, 3 H, Ar-CH_3), 2.64–2.69 (m, 3 H, H_{eq}), 3.48 (s, 3 H, N-CH_3), 3.98 (tr, J=4.53 Hz, 2 H, CH_2), 4.84 (br s, 2 H, CH_2),

7.30 (s, 1 H, Ar-*H*) 7.99 (s, 1 H, Ar-*H*), 8.33 (br s, 1 H, N-*H*), 8.85 (br s, 1 H, N-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.5 (Ar-*C*H_3) 21.9 (Ar-*C*H_3), 25.5 (2×*C*H_3), 28.1 (Boc-*C*H_3), 28.8 (N-*C*H_3), 31.3 (*C*H_3), 37.2 (N-*C*H_2), 40.1 (2×C_{qu}), 42.3 (*C*H_2), 43.3 (*C*H_2), 44.1 (N-*C*H_2), 44.5 (C_{qu}), 83.8 (Boc-C_{qu}), 115.1 (*C*9), 131.9 (*C*9a), 132.8 (*C*6), 134.7 (*C*5a), 135.8 (*C*4a), 136.3 (*C*7), 146.8 (*C*8), 149.3 (*C*10a), 153.0 (NH*C*O), 156.0 (*C*2), 158.7 (Boc-*C*O), 160.2 (*C*4), 177.5 (NH*C*O)

ES-MS *m/z* (%): 681.4 $[M+NH_4]^+$, 663.4 (100) $[M+H]^+$, 563.3 $[M+H\text{-}Boc]^+$

HRMS–EI *m/z*: calcd for $C_{33}H_{43}N_8O_7$ $[M+H]^+$: 663.3255; found: 663.3242 [Δ 1.92 ppm]

IR (ATR): ν = 1716, 1668, 1634, 1584, 1543, 1455, 1367, 1327, 1236, 1144, 968, 756 cm^{-1}

Flavin-Boc-guanidin 10

To a solution of HOBt•H_2O (226 mg, 1.67 mmol), EDC (226 mg, 1.45 mmol) and DIPEA (498 µL, 970 µmol) in $CHCl_3$ (10 mL) was added compound **9** (548 mg, 969 µmol) and mono Boc-protected guanidine (231 mg, 1.45 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h, diluted with $CHCl_3$ (250 mL) and washed with water and brine. The organic phase was separated, dried over magnesium sulphate and the solvents were evaporated. The crude brown product was purified by flash column chromatography ($CHCl_3$:MeOH:TEA – 70:1:1).

Yield 564 mg, 798 µmol, 82%, yellow solid

R_f=0.1 ($CHCl_3$:MeOH:TEA – 50:1:1)

m.p. 229–231 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 0.93–1.21 (m, 12 H, 3xCH_3+3xH_{ax}), 1.46 (s, 9 H, Boc-CH_3), 2.15 (d, *J*=12.90 Hz, 1 H, H_{eq}), 2.38 (s, 3 H, Ar-CH_3), 2.48 (s, 3 H, Ar-CH_3), 2.68 (d, *J*=13.44 Hz, 2 H, H_{eq}), 3.22 (s, 3 H, O-CH_3), 3.80–3.84 (m, 4 H, 2xCH_2), 4.20–4.22 (m, 2 H, CH_2), 4.79 (tr, *J*=5.08 Hz, 2 H, CH_2), 7.58 (s, 1 H, Ar-*H*) 7.94 (s, 1 H, Ar-*H*), 8.27 (br s, 1 H, N-*H*), 8.75 (br s, 1 H, N-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.5 (Ar-*C*H_3) 21.5 (Ar-*C*H_3), 25.5 (2×*C*H_3), 28.1 (Boc-*C*H_3), 31.3 (*C*H_3), 38.4 (N-*C*H_2), 40.2 (2×C_{qu}), 40.8 (N-*C*H_2), 43.2 (N-*C*H_2), 44.2 (2×*C*H_2), 44.6 (C_{qu}), 45.2 (*C*H_2), 59.2 (O-*C*H_3), 69.6 (O-*C*H_2), 83.4

(Boc-C_{qu}), 116.6 (*C*9), 132.2 (*C*9a), 132.2 (*C*6), 134.9 (*C*5a), 135.6 (*C*4a), 136.4 (*C*7), 147.2 (*C*8), 148.7 (*C*10a), 153.4 (NH*C*O), 156.1 (*C*2), 158.5 (Boc-*C*O), 160.4 (*C*4), 177.5 (NH*C*O), 188.7 (C_{qu})

ES-MS *m/z* (%): 707.3 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{35}H_{47}N_8O_8$ $[M+H]^+$: 707.3517; found: 707.3531 [Δ -2.00 ppm]

IR (ATR): ν = 1706, 1655, 1634, 1583, 1540, 1457, 1366, 1325, 1226, 1146, 758 cm^{-1}

Flavin-guanidinium 1

Compound **7** (210 mg, 317 µmol) was dissolved in $CHCl_3$ (25 mL) and hydrogen chloride saturated diethyl ether (3 mL) was added dropwise. After stirring for 24 h, the solution was evaporated to 5 mL and diethyl ether (15 mL) was added to precipitate the product. The mixture was cooled to 0 °C and the solid was filtered off, washed with diethyl ether and dried.

Yield 157 mg, 262 µmol, 83%, orange-yellow solid

R_f=0.1 ($CHCl_3$:MeOH – 10:1)

m.p. 320–322 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 0.91 (s, 6 H, 2xCH_3), 1.16 (s, 3 H, CH_3), 1.28–1.31 (m, 4 H, 3×CH_{ax} and CH_{eq}), 2.41 (Ar-CH_3), 2.47 (d, *J*=14.39 Hz, 2 H, H_{eq}), 2.50 (Ar-CH_3, hidden by DMSO), 3.28 (s, 3 H, N-CH_3), 3.90 (tr, *J*=5.01 Hz, 2 H, CH_2), 4.84 (s, 2 H, CH_2), 7.74 (Ar-*H*), 7.97 (Ar-*H*), 8.36–8.44 (m, 4 H, N*H*), 11.38 (s, 1 H, N*H*CO)

^{13}C NMR (DMSO-d_6) δ = 18.7 (Ar-*C*H_3) 21.0 (Ar-*C*H_3), 24.7 (2×*C*H_3), 28.0 (N-*C*H_3), 29.0 (*C*H_3), 36.8 (*C*H_2), 40.1 (C_{qu}), 40.7 (*C*H_2), 42.0 (*C*H_2+C_{qu}), 43.6 (*C*H_2), 116.0 (*C*9), 131.1 (*C*5a), 131.3 (*C*6), 134.0 (*C*9a), 135.5 (*C*4a), 136.2 (*C*7), 146.8 (*C*8), 149.3 (*C*10a), 154.9 (*C*2), 155.0 (C_{qu}), 159.4 (*C*4), 176.0 (*C*O), 177.3 (*C*O)

ES-MS *m/z* (%): 563.3 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{28}H_{35}N_8O_5$ $[M+H]^+$: 563.2730; found: 563.2746 [Δ -2.77 ppm]

IR (ATR): ν = 1700, 1643, 1584, 1546, 1452, 1306, 1238, 1190, 1127, 1098, 1048, 753 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 272 (41500), 343 (9130), 447 nm (11060)

Fluorescence (MeCN): λ_{max} (emission) = 507 nm (excitation: 445 nm)

Flavin-guanidinium 2

Compound **10** (493 mg, 698 μmol) was dissolved in $CHCl_3$ (50 mL) and hydrogen chloride saturated diethyl ether (6 mL) was added dropwise. After stirring for 24 h, the solution was evaporated to 5 mL and diethyl ether (25 mL) was added to precipitate the product. The mixture was cooled to 0 °C and the solid was filtered off, washed with diethyl ether and dried.

Yield 402 mg, 625 μmol, 90%, yellow solid

R_f=0.15 ($CHCl_3$:MeOH – 10:1)

m.p. 245–247 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 0.99 (s, 6 H, 2xCH_3), 1.17 (s, 3 H, CH_3), 1.30 (d, J=14.39 Hz, 2 H, 2×CH_{ax}), 1.38 (d, J=12.59 Hz, 1 H, CH_{ax}), 1.84 (d, J=12.59 Hz, H, CH_{eq}), 2.39 (s, 3 H, Ar-CH_3), 2.51 (s, 3 H, Ar-CH_3), 2.52 (d, J=14.39 Hz, 2 H, 2×CH_{ax}), 3.21 (s, 3 H, O-CH_3), 3.73–3.75 (m, 4 H, 2×CH_2), 4.02–4.04 (m, 2 H, CH_2), 4.82 (tr, J=5.52 Hz, 2 H, CH_2), 7.89 (Ar-*H*), 7.95 (Ar-*H*), 8.34–8.43 (m, 4 H, N*H*), 11.42 (s, 1 H, N*H*CO)

^{13}C NMR (DMSO-d_6) δ = 18.8 (Ar-*C*H_3) 20.7 (Ar-*C*H_3), 24.9 (2×*C*H_3), 28.6 (*C*H_3), 37.3 (*C*H_2), 39.5 (*C*H_2), 40.1 (C_{qu}), 41.2 (*C*H_2), 42.1 (2×*C*H_2), 43.8 (C_{qu}), 44.0 (*C*H_2), 116.9 (*C*9), 130.9 (*C*6), 131.4 (*C*5a), 134.1 (*C*9a), 135.5 (*C*4a), 136.3 (*C*7), 147.0 (*C*8), 148.5 (*C*10a), 154.9 (*C*2), 155.1 (C_{qu}), 159.7 (*C*4), 176.0 (*C*O), 177.3 (*C*O)

ES-MS *m/z* (%):607.3 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{30}H_{39}N_8O_6$ $[M]^+$: 607.2993; found: 607.2981 [Δ 1.90 ppm]

IR (ATR): ν = 1692, 1669, 1579, 1545, 1456, 1328, 1235, 1173, 747 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 275 (96000), 344 (8760), 445 nm (10510)

Fluorescence (MeCN): λ_{max} (emission) = 509 nm (excitation: 445 nm)

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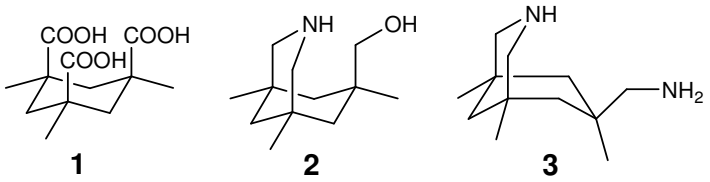
Chapter 5

Synthesis of a Bicyclic Diamine Derived from Kemp´s Acid*

Introduction

Derivatives of cis,cis-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp´s acid) (**1**)[1] are used as scaffolds in enantioselective photocatalysis as chiral auxiliary and in combinatorial library synthesis,[2–8] for the stereoselective protonation of lithium enolates,[9,10] and in molecular recognition.[11,12] Typically, the carbonyl groups of imide and amide derivatives of Kemp´s triacid (**1**) act as hydrogen binding sites. A reduced Kemp´s triacid derivative, such as a bicyclic amino alcohol **2**, was also reported.[13] The diamino compound **3** represents a missing piece in the family of Kemp´s triacid derived molecules and the details of the synthesis of the imide amide precursor **4** were not published until now. We therefore present an improved and documented synthesis of the amide imide precursor **4** and the first synthesis and structural characterization of the bicyclic diamine **3** derived from Kemp´s triacid (**1**).



1 **2** **3**

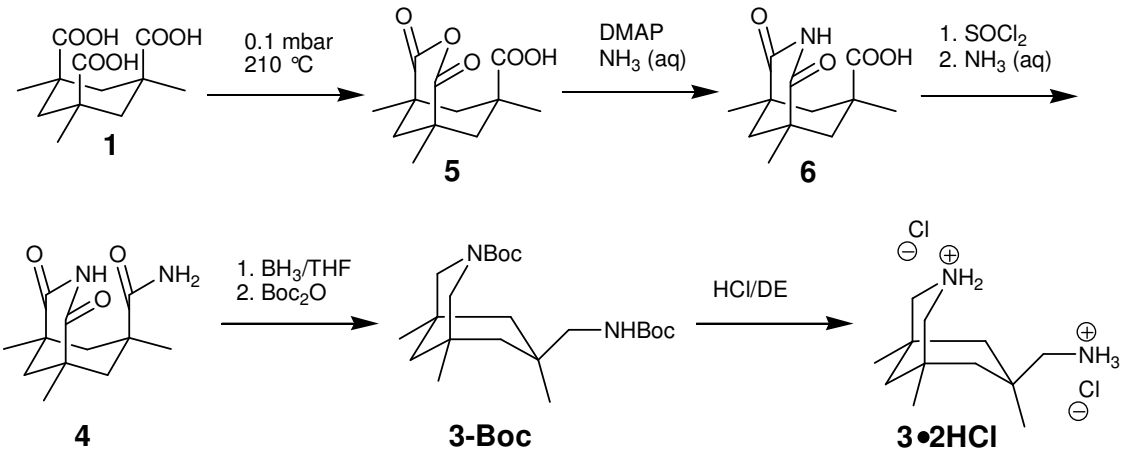
Scheme 5.1 Kemp´s triacid (**1**) and fully reduced derivatives **2** and **3**

* The results of this chapter have already been published. All experiments presented in this chapter were performed by H.S. Andreas Hohenleutner repeated the synthetic route within his research internship in our group.
H. Schmaderer, A. Hohenleutner, B. König, *Syn. Commun.* **2009**, *accepted*.

Results and discussion

Synthesis

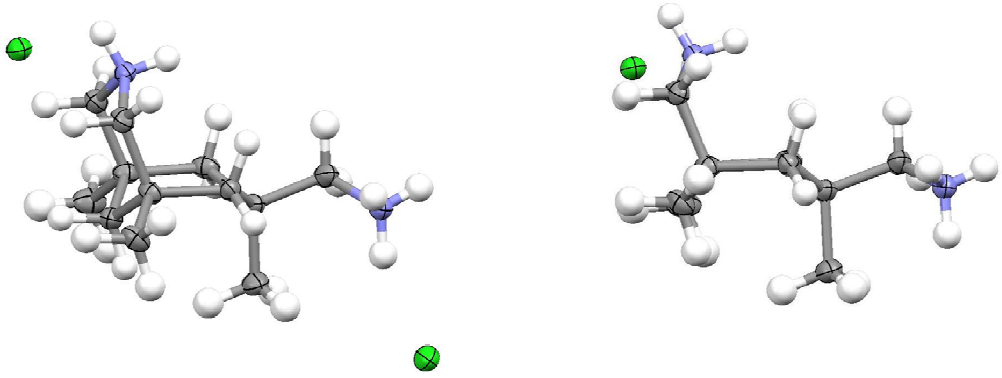
The synthetic route starts from Kemp´s acid (**1**) which is commercially available or can be obtained in four steps from trimesic acid (1,3,5-benzene tricarboxylic acid).[14] In a condensation reaction, Kemp´s acid (**1**) was sublimated on a 4 mmol scale to give anhydride **5** with an improved yield of 93%.[11] Reaction in aqueous ammonia solution and with DMAP as a catalyst yielded the imide acid **6** also in an improved yield of 95%.[11] The imide acid **6** was then converted to the imide amide **4** via an intermediate acid chloride[11] of the remaining carboxylic acid. After refluxing with thionyl chloride and quenching with aqueous ammonia solution, imide amide **4** was obtained in 84% yield. Complete reduction of the carbonyl groups of both, the amide as well as the imide group of **4** was achieved by the use of borane in tetrahydrofuran. However, like in comparable literature procedures,[15–17] the yield was moderate. Purification of the crude reduction product by double Boc-protection and subsequent column chromatography was superior to direct isolation of diamine **3**. By this procedure, it was possible to isolate double Boc-protected diamine **3-Boc** in 30% yield (two steps). The target compound **3●2HCl** was received by deprotection with hydrogen chloride in diethyl ether in 93% yield. The overall yield for this seven step synthesis from Kemp´s triacid (**1**) is 21%. Although the yield -especially for the reduction step– is moderate, the synthesis is straight-forward, fast and only a single purification by column chromatography is necessary.



Scheme 5.2 Synthesis of diamine **3•2HCl** starting from Kemp´s acid (**1**)

Crystal structure

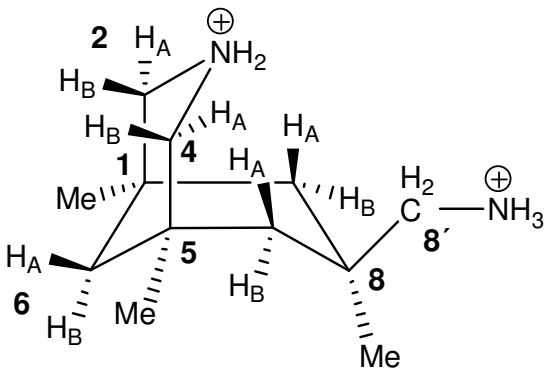
An X-ray crystal structure of diammonium salt **3•2HCl** was obtained.[18] An interesting feature of the structure is the mixed chair/boat conformation of this bicyclic system (scheme 5.3). The six-membered ring of the Kemp´s acid (**1**) derived cyclohexane is in a boat conformation. The N-heterocyclic ring which was closed later in the synthesis is in a chair conformation. In this chair/boat conformation, the molecule overcomes the high electrostatic repulsion of the two positively charged nitrogen atoms. Moreover, a double chair conformation would position the hydrogen atoms of the 8´-methylene group close to the 3-nitrogen, leading to vast steric strain. The distance of the two nitrogen atoms in the crystal structure is 5.6 Å.



Scheme 5.3 X-ray crystal structure analysis of diamine **3•2HCl** (right: projection along C1-C5-axis) in the solid state

Two dimensional NMR experiments

In addition to the solid state structure, an estimation of the geometry of diamine **3●2HCl** in solution was carried out by means of NOESY-NMR experiments. Therefore, all proton and carbon resonances were assigned by one- and two-dimensional NMR experiments in deuterated DMSO. Due to similar chemical shifts of some resonance signals, only significant crosspeaks were used for the structure determination. The NOESY-contact of the 8-methyl group to the H_B of the 6-methylene group was detected unambiguously, proving the vicinity of both protons (see numbering in scheme 5.4). This is only possible in the chair/boat conformation as depicted in the crystal structure (scheme 5.3). Furthermore, no contact of 2,4-H_A with the protons of 8´-methylene was observed. Both findings support the chair/boat conformation. Overall, the pattern of all NOESY crosspeaks clearly indicates a solution structure which is similar to the solid state structure as obtained from X-ray crystallography. In addition it was examined, whether the electrostatic interaction of the positively charged nitrogen atoms is crucial for this chair/boat conformation. Therefore, the two dimensional NMR experiments were also carried out with the free diamine molecule **3**, which was obtained by addition of base to the NMR solution. The pattern and the relative intensity of the NOESY crosspeaks were not affected significantly, indicating that molecule **3** does not undergo major structural changes upon variation of the pH.



Scheme 5.4 Structure of diamine **3●2HCl** with numbering of the atoms

Experimental part

General

Kemp´s acid (**1**) was prepared by a known method.[14] All other chemicals were purchased from commercial suppliers, checked by ^{1}H NMR spectrometry and then used as received. Solvents were distilled before use. Flash column chromatography was carried out on silica gel 35–70 μm, 60 Å from Acros. NMR spectra were recorded at a Bruker Avance 300 spectrometer (300 MHz) or at a Bruker Avance 600 spectrometer (600 MHz). Electrospray ionisation (ES-MS) mass spectra were measured on ThermoQuest Finnigan TSQ 7000 spectrometer. High resolution mass spectrometry (HRMS) was measured on ThermoQuest Finnigan MAT 95 spectrometer. Melting points were measured on a Büchi SMP-20 apparatus and are not corrected. IR spectra were measured on Biorad Spectrometer Excalibur FTS 3000.

Anhydride 5[11]

Kemp´s triacid (**1**) (1.03 g, 3.99 mmol) was sublimated at 190 °C and 0.1 mbar yielding anhydride **5**.

Yield 888 mg, 3.70 mmol, 93%, colourless powder

m.p. 243–245 °C

^{1}H NMR (DMSO-d_6) δ = 1.13 (s, 3 H), 1.20 (s, 6 H), 1.36 (d, *J*=14.0 Hz, 2 H), 1.43 (d, *J*=13.2 Hz, 1 H), 2.18 (d, *J*=13.2 Hz, 1 H), 2.42 (d, *J*=13.2 Hz, 2 H), 12.67 (1H, s)

^{13}C NMR (DMSO-d_6) δ = 24.6, 29.8, 39.5, 39.8, 41.0, 43.1, 171.7, 176.2

CI-MS *m/z* (%): 258.3 (100) $[M+NH_4]^+$

IR (ATR): ν = 1794, 1766, 1699, 1467, 1282, 1214, 1130, 1091, 998, 747, 616 cm^{-1}

Imide acid 6[11]

To a solution of DMAP (111 mg, 910 μmol) in aqueous NH_3 solution (25%, 60 mL), anhydride **5** (1.09 g, 4.54 mmol) was added in small portions, refluxed for 18 h, and cooled afterwards. The solution was adjusted to pH 1 with concentrated hydrochloric acid. The precipitate was filtered off, washed and dried, yielding imide acid **6**.

Yield 1.03 g, 4.30 mmol, 95%, colourless powder

m.p. 370 °C (decomp.)

^{1}H NMR (DMSO-d_6) δ = 1.08 (s, 6 H), 1.10 (s, 3 H), 1.18 (d, *J*=13.7 Hz, 2 H), 1.37 (d, *J*=12.9 Hz, 1 H), 1.88 (d, *J*=12.9 Hz, 1 H), 2.36 (d, *J*=13.2 Hz, 2 H), 10.35 (s, 1 H), 12.20 (s, 1 H)

^{13}C NMR (DMSO-d_6): δ = 24.4, 30.7, 39.2, 41.0, 42.8, 43.2, 176.6, 176.7

ES-MS *m/z* (%): 237.9 $[M-H]^+$, 477.0 (100) $[2M-H]^+$

IR (ATR): ν = 3135, 3089, 2875, 1703, 1656, 1459, 1376, 1327, 1218, 1183, 879, 666 cm^{-1}

Imide amide 4

Imide acid **6** (1.03 g, 4.30 mmol) was added to thionyl chloride (12 mL) in small portions and refluxed for 3 h. After removing the excess of thionyl chloride by distillation, the colourless solid was dried in vacuo. The acid chloride was added in small portions to an aqueous NH_3 solution (25%, 20 mL). After stirring for 1 h at room temperature, the precipitate was filtered off, washed with cold water and dried, yielding imide amide **4**.

Yield 862 mg, 3.62 mmol, 84%, pale brown powder

m.p. 303–306 °C

^{1}H NMR (DMSO-d_6) δ = 1.04–1.11 (m, 11 H), 1.33 (d, *J*=12.9 Hz, 1 H), 1.84 (d, *J*=12.6 Hz, 1 H), 2.47 (m, 2 H, partially hidden by DMSO), 6.60 (s, 1 H), 7.04 (s, 1 H), 10.23 (s, 1 H)

^{1}H NMR (MeOD) δ = 1.19–1.21 (m, 9 H), 1.26 (d, *J*=14.3 Hz, 2 H), 1.44 (d, *J*=13.2 Hz, 1 H), 1.96 (d, *J*=13.2 Hz, 1 H), 2.57 (d, *J*=13.4 Hz, 2 H)

^{13}C NMR (DMSO-d_6) δ = 24.7, 31.4, 39.3, 41.2, 43.0, 43.7, 176.2, 176.8

ES-MS *m/z* (%): 236.9 (100) $[M-H]^+$

HRMS-EI *m/z*: calcd for $C_{12}H_{18}N_2O_3$ $[M]^{+\bullet}$: 238.1318; found: 238.1309 [Δ 3.54 ppm]

IR (ATR): ν = 3417, 3220, 3085, 2857, 1703, 1665, 1605, 1450, 1375, 1206, 1103, 1079, 855, 593 cm^{-1}

EA (%): calcd for C1H2N3 C 60.49, H 7.61, N 11.76, found C 60.34, H 7.69, N 11.81

Boc-protected diamine 3-Boc

To a solution of borane in tetrahyrofuran (1 M, 24 mL, 24 mmol) in a Schlenk tube under nitrogen atmosphere, imide amide **4** (858 mg, 3.60 mmol) was added in small portions. The closed vessel was heated to reflux for 20 h. After cooling to room temperature, the mixture was slowly quenched by addition of MeOH (12 mL) and the solvents were evaporated afterwards. The crude product was heated with a mixture of hydrochloric acid (10%, 20 mL) and EtOH (20 mL) to 60 °C for 1 h and the solvents were evaporated afterwards.

For the Boc-protection, the crude diamine **3** was dissolved in DCM (60 mL) with TEA (36 mmol, 4.9 mL) and Boc-anhydride (18 mmol, 3.93 g, dissolved in DCM (15 mL)) was added. The solution was stirred at room temperature overnight. Afterwards, water (30 mL) was added and the mixture was stirred at room temperature for 1 h. The organic phase was separated, dried over magnesium sulphate, and evaporated. The colourless oil was purified by flash column chromatography (toluene:EE:TEA – 100:10:1) yielding the double Boc-protected diamine **3-Boc**.

Yield 397 mg, 1.08 mmol, 30%, colourless solid

m.p. 90 °C

^{1}H NMR ($CDCl_3$) δ = 0.91 (s, 6 H), 0.96–0.98 (m, 4 H); 1.12 (d, *J*=14.5 Hz, 2 H), 1.36 (d, *J*=14.5 Hz, 2 H), 1.40–1.43 (m, 19 H), 2.29–2.34 (m, 2 H), 2.82–2.92 (m, 2 H), 3.56–3.65 (m, 2 H), 4.58 (tr, *J*=6.0 Hz, 1 H)

^{13}C NMR ($CDCl_3$) δ = 28.4, 28.5, 29.7, 31.3, 31.9, 34.2, 45.0, 45.3, 52.1, 55.1, 56.0, 78.8, 79.7, 155.4, 156.3

ES-MS *m/z* (%): 397.1 (100) $[M+H]^+$, 810.6 $[2M+NH_4]^+$

HRMS-EI *m/z*: calcd for $C_{22}H_{40}N_2O_4$ $[M]^{+\bullet}$: 396.2988; found: 396.2995 [Δ –1.75 ppm]

IR (ATR): ν = 3280, 2954, 2891, 2838, 1683, 1389, 1362, 1294, 1159, 1117, 1007, 912, 876, 762, 574 cm^{-1}

Diamine 3●2HCl

Double Boc-protected diamine **3-Boc** (395 mg, 996 μmol) was dissolved in DCM (20 mL) and hydrogen chloride saturated DE (4 mL) was added dropwise. After stirring at room temperature over night, the mixture was concentrated and DE (15 mL) was added to precipitate the product, which was filtered off, washed with cold DE, and dried, yielding diamine **3●2HCl**.

Yield 251 mg, 929 μmol, 93%, colourless solid

m.p. 248–250 °C

^{1}H NMR (DMSO-d_6) δ 0.97 (s, 6 H),1.06–1.07 (m, 4 H), 1.32 (d, *J*=15.3 Hz, 2 H), 1.58 (d, *J*=15.3 Hz, 2 H), 1.82 (d, *J*=13.6 Hz, 1 H), 2.43 (d, *J*=12.3 Hz, 2H), 2.76 (d, *J*=12.3 Hz, 2 H), 2.81 (s, 2 H), 7.50–10.50 (m, 5 H)

^{13}C NMR (DMSO-d_6) δ 27.8, 28.7, 29.5, 32.1, 39.6, 40.5, 51.0, 54.5

ES-MS *m/z* (%): 196.8 (100) $[M+H]^+$, 139.8 $[M+2H+2MeCN]^+$

HRMS-EI *m/z*: calcd for $C_{12}H_{24}N_2$ $[M]^{+\bullet}$: 196.1939; found: 196.19377 [Δ 1.27 ppm]

IR (ATR): ν = 3459, 2922, 1621, 1585, 1498, 1460, 1142, 1105, 1057, 996, 979, 855, 588 cm^{-1}

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[18] CCDC 710819 contains 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.

Chapter 6

Copper-Mediated 3-N-Arylation of Flavins*

Introduction

Flavins are abundant redox cofactors of key importance for many biological processes;[1–2] typical examples are flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN). Their redox properties are tuned for the desired purpose either by substitution or by specific hydrogen bonds to the protein they are embedded in.[3–8] Many flavoenzyme models have been developed to investigate photo- and redox properties or utilizing flavins for organocatalytic reactions. [8–14] The synthesis of such flavoenzyme models or catalysts requires selective modification of the parent flavin structure.[8–11] The nitrogen atom in 3-N-position is particular suitable for the introduction of substituents at a late stage of the flavin synthesis.[15] Typically, alkylations in 3-N-position exhibit only moderate yields due to decomposition of flavins in basic solutions.[11d,15–16] So far, only few examples are known with aryl substitution at the 3-N-position.[17–22] However, introduction of these aryl substituents requires additional steps before the flavin ring system is cyclized. Direct arylation of flavins at this position may provide a short cut creating valuable flavin derivatives. Interesting optical properties are expected from the orthogonal orientation of the additional π-system to the flavin aromatic system.

* The investigations described in this chapter were carried out together with Bianca Attenberger and have already been published. B.A. synthesized all compounds **3** within her final thesis for her studies as a teacher.

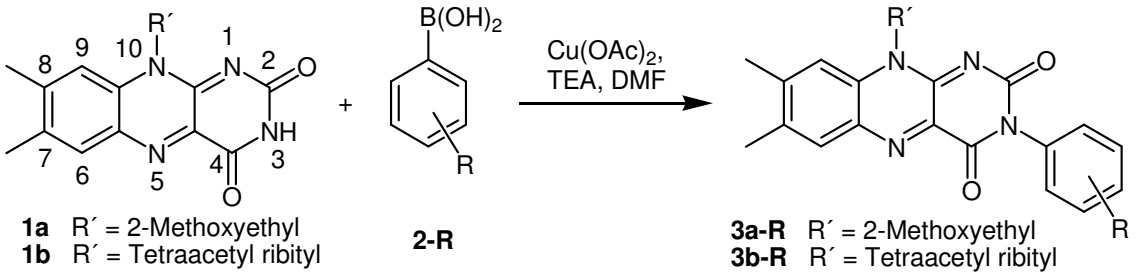
B. Attenberger, H. Schmaderer, B. König, *Synthesis* **2008**, *11*, 1767–1774.

In this work, we present the first method for direct 3-N-arylation of flavins. The aromatic substituent is introduced to the flavin skeleton in a general applicable copper catalyzed reaction with aryl boronic acids.

Results and discussion

Copper-mediated flavin 3-N-arylation

In recent years, several synthetic methods were developed to directly arylate imides.[23] Generally, the yields of this C(aryl)-N(imide)-bond formation are moderate. Initial attempts to react flavin **1a** with aryl iodide and glycin under copper(I)-catalysis at 80 °C failed. Other reported procedures use boronic acids and show a wider scope of substrates. In most instances, solvents like $CHCl_3$ and DCM or MeOH gave the best results. Unfortunately, a direct application of these conditions is complicated, because many flavins are not well soluble in such solvents. In a reaction of flavin **1a** with benzene boronic acid (**2-H**) moderate yields of flavin **3a-H** were obtained in $CHCl_3$. In MeOH, however, no product **3a-H** was observed. DMF as solvent allowed high concentrations of starting materials and gave the best results in 3-N-alkylation reactions in our hands. 10-(2-Methoxyethyl)-7,8-dimethylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (**1a**)[14,24] was used as a standard to optimize the reaction conditions and explore the scope of the reaction. Flavins **1** were reacted with various benzene boronic acids **2–R** under different conditions (scheme 6.1).



Scheme 6.1 3-N-Arylation of flavins **1** with boronic acids **2**

To a mixture of flavin **1a** (250 μmol), benzene boronic acid **2–R** (3 eq), copper acetate (2 eq), and TEA (3 eq), dry DMF (3 mL) was added and the mixture was stirred at room temperature in the dark. To compare the coupling efficiency of different boronic acids, every reaction was terminated after two days. After extraction and chromatography, purified products and remaining starting material were isolated (entries 1–7). Table 6.1 summarizes the results of all experiments with reaction conditions, yields of products **3** (corrected by conversion), recovered starting material **1** and observed by-products.

Table 6.1 Results of flavin **1** 3-N-arylation with boronic acids

Entry	Flavin	Boronic acid 2–R	Reaction conditions	Recovered flavin 1 [%]	Yield 3 [%][a]
1	**1a**	H	r.t., 48 h	n.d.[b]	56
2	**1a**	4–Me	r.t., 48 h	36	47 (74)
3	**1a**	4–OMe	r.t., 48 h	23	34 (50)[f]
4	**1a**	4–Br	r.t., 48 h	32	29 (43)
5	**1a**	3–Br	r.t., 48 h	62	34 (89)
6	**1a**	4–$B(OH)_2$	r.t., 48 h	5	–[g]
7	**1a**	4–$B(OH)_2$[c]	r.t., 48 h	13	–[h]
8	**1a**	H	40–50 °C[d], 2–3 h	n.d.[b]	22
9	**1a**	4–Me	40–50 °C[d], 2–3 h	n.d.[b]	25
10	**1a**	4–OMe	40–50 °C[d], 2–3 h	19	18 (22)
11	**1a**	3–Br	40–50 °C[d], 2–3 h	n.d.[b]	33
12	**1a**	4–$B(OH)_2$	40–50 °C[d], 2–3 h	28	–
13	**1a**	H	80 °C, 5 h	–	<5[i]
14	**1a**	H	0 °C, 24 h	58	40 (95)
15	**1a**	H	r.t., 96 h, O_2[e]	–	68
16	**1b**	H	r.t., 48 h	n.d.[b]	39
17	**1b**	H	40–50 °C[d], 2–3 h	n.d.[b]	16
18	**1a**	**9**	r.t., 48 h	23	19 (25)
19	**1a**	**10**	r.t., 48 h	n.d.[b]	–
20	**1a**	**10**	40–50 °C[d], 2–3 h	n.d.[b]	–

[a] Yield isolated and corrected by recovered starting material **1a** (in parantheses) [b] n.d. = not determined [c] 0.5 equivalents [d] Heating in laboratory microwave [e] Addition of molecular sieves (4 Å, 250 mg) [f] 9% of **4** as by-product [g] <5% of **3a-H** and 9% of **5** as by-products [h] <5% of **7** as by-product [i] 42% of **6** as by-product

The survey showed moderate to good yields for the C-N-bond formation reaction with bromo-, methoxy-, methyl- and unsubstituted mono boronic acids (entries 1–5). In all cases, the reactions were not completed after two days and different amounts of unreacted flavin **1a** were recovered after column chromatography. Monitoring by thin layer chromatography indicates the occurrence of by-products. In the case of 4-methoxy phenyl (entry 3), product **3a–(*p*–OMe)** is oxidized at the C-8-methyl group under the reaction conditions, yielding additional 9% of aldehyde **4** (figure 6.2).

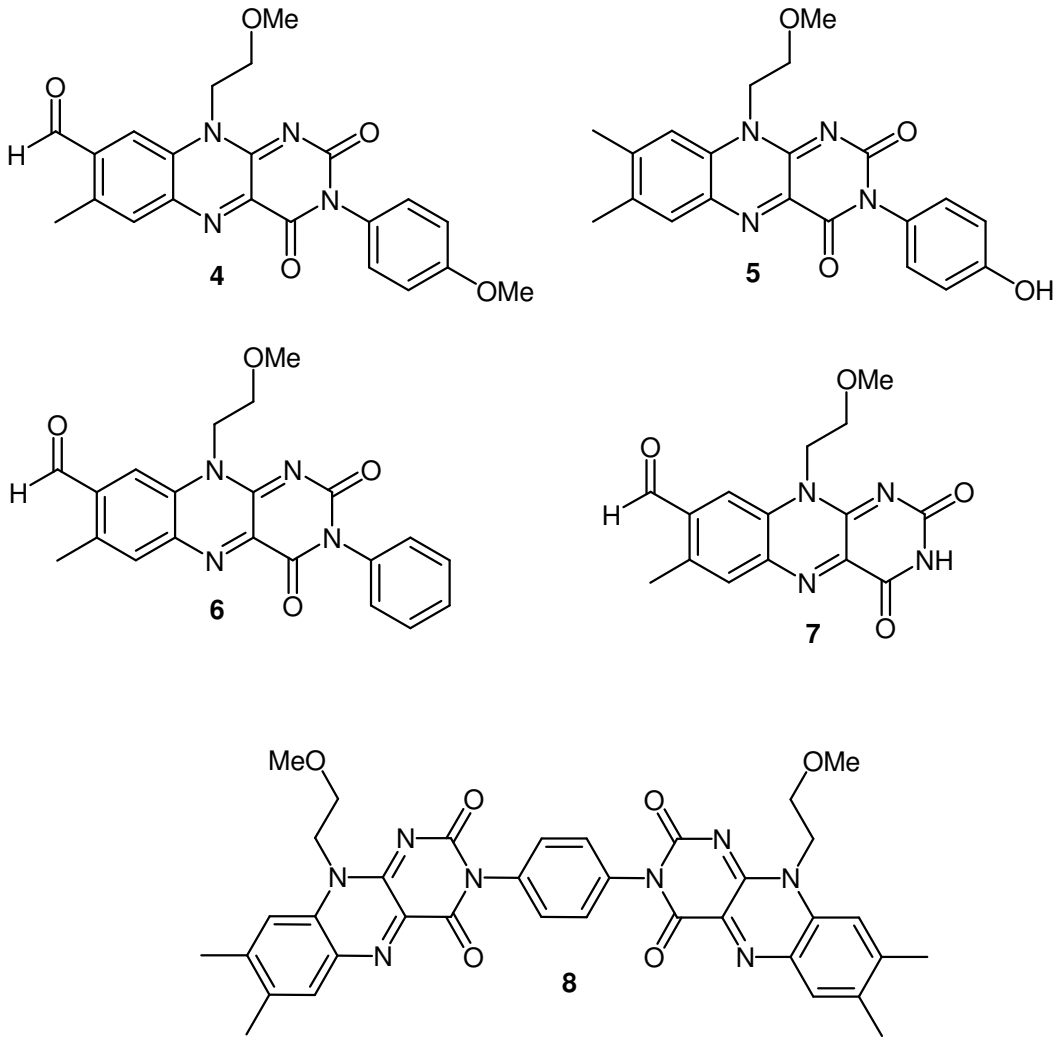


Figure 6.2 Other products of the reaction

Reaction with excess (3 eq) of 1,4-benzene diboronic acid (**2–4–B(OH)$_2$**) (entry 6) was expected to afford a 3-N-aryl flavin with a remaining boronic acid function in *p*-position for subsequent functionalization. However, in that

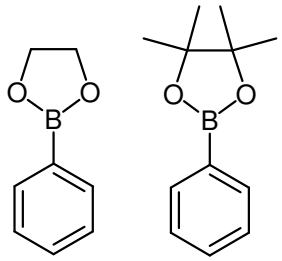
case only small amounts of unsubstitued 3-N-phenyl flavin **3a–H** and its *p*-hydroxy derivative **5** were isolated (figure 6.2), resulting from defunctionalization of diboronic acid **2–4–B(OH)$_2$** under these conditions. The reaction with 0.5 eq of diboronic acid **2–4–B(OH)$_2$** (entry 7) yielded aldehyde **7**, an oxidation product of starting material **1a**, instead of a phenylene connected flavin dimer **8** (figure 6.2).

To explore the possible improvement and acceleration of the reaction at elevated temperatures, a set of experiments was performed in a laboratory microwave at 40–50 °C (entries 8–12). Every 15–30 minutes, the progress was monitored by thin layer chromatography. A second portion of boronic acid **2–R** (3 eq), copper acetate (2 eq) and TEA (3 eq) was added after one hour. After 2–3 h, no further reaction progress was observed and the reaction was worked up as described before. As expected, the reaction time decreased significantly but more by-products and general lower yields are observed, making the product purification more complicated. Overall, microwave conditions did not improve the reaction although the conversion of starting material is significantly accelerated. In another experiment, flavin **1a** and unsubstituted boronic acid **2–H** were allowed to react at 80 °C thermal heating for 5 h (entry 13). Monitoring by thin layer chromatography showed fast and complete conversion of all starting material **1a**. After purification, beside little amounts of 3-N-aryl flavin **3a-H**, 42% of aldehyde **6** (figure 6.2) was isolated. Apparently, the desired product **3a-H** is further oxidized at C-8 under these conditions.

To extend the 3-N-arylation reaction to other flavins, tetraacetyl riboflavin (**1b**)[25] was used as starting material (entry 16–17). At room temperature, 39% of N-arylated flavin **3b–H** was obtained after two days; 16% after 2 h in a microwave reaction. These yields are a slightly lower if compared to flavin **1a**, because work up of the more sensitive flavin emerged more complex.

The application of boronic acid esters **9** and **10** (figure 6.3), instead of boronic acids **2-R**, gave ambivalent results (entries 18–20). Under standard reaction conditions, with ethylene ester **9** a yield of 19% (25% corrected by

conversion, 23% recovered flavin **1a**) was achieved. A reaction with commercially available pinacole ester **10** at room temperature and in the microwave (40–50 °C) yielded no conversion.



9 **10**

Figure 6.3 Boronic acid ester **9** and **10** used for the 3-N-Arylation

In addition, neither the application of copper acetate in larger amounts (5-10 equivalents), nor the addition of catalytic amounts of palladium to the mixture could improve the reaction of flavin **1a** with benzene boronic acid (**2-H**).

As elevated temperatures lead to more decomposition of the starting material and an increased number of by-products, reaction of flavin **1a** with boronic acid **2-H** was carried out at 0 °C in an ice bath (entry 14). Under these conditions, 40% (95% corrected by recovered starting material) of the desired product **3a–H** and 58% of flavin **1a** were isolated after one day. The reaction proceeds more cleanly, facilitating the workup and product isolation. In another run, the reaction was conducted at room temperature in the presence of molecular sieves under oxygen atmosphere (entry 15). Here, 68% of the product **3a-H** was isolated after extending the reaction time to 4 days to complete conversion, representing the highest absolute yield of all reactions.

UV/Vis and fluorescence spectra of 3-N-aryl flavins

The influence of the additional aromatic system in 3-N-position on the electronic properties of the flavin moiety was examined with optical spectroscopy. UV/Vis spectra for flavins **1a**, **3**, **4**, **5**, and **6** are shown in figure 6.4 (MeCN, 2.5×10^{-5} M).

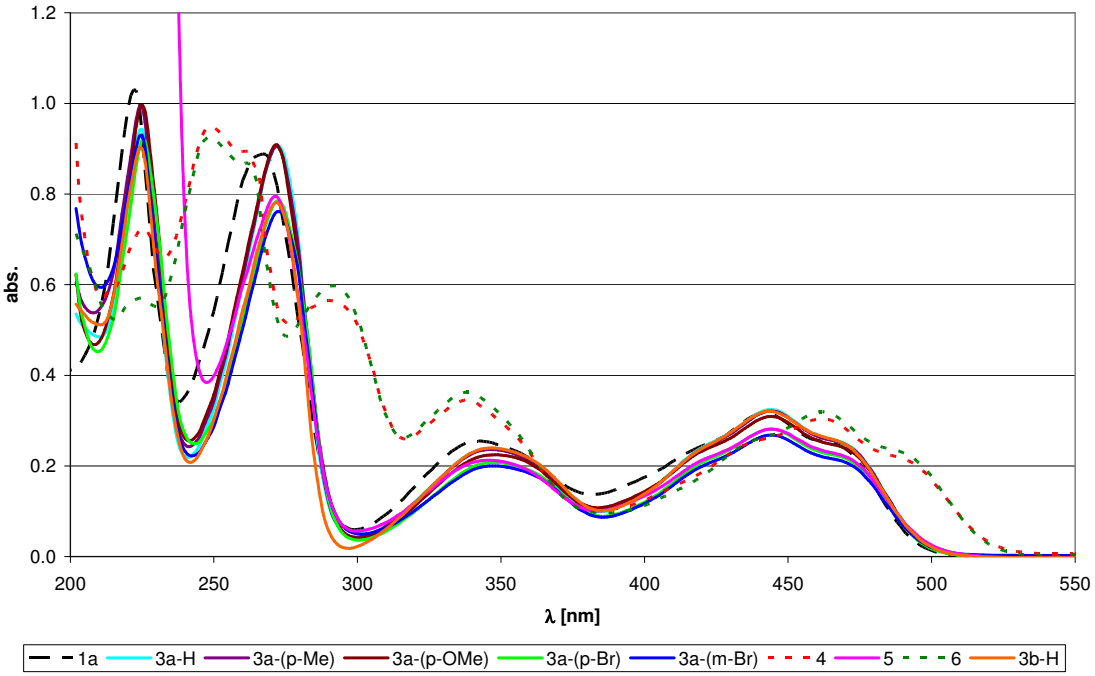


Figure 6.4 UV/Vis spectra of flavins **1a** and **3**–**6**

As expected from the orthogonal orientation of the π-system, UV/Vis spectra of all 3-N-arylated flavins **3** and **5** look similar and differ only slightly from the parent flavin **1a**. The absorption maxima in the visible and UV region are slightly shifted and the extinction coefficients are similar (table 6.2). Aldehydes **4** and **6** show different absorption properties. The absorption maximum in the visible range is bathochromically shifted by 17–18 nm. This clearly indicates the significant influence of the carbonyl group at C-8-position on the electronic structure of the flavin as reported previously in literature.[7,8]

Table 6.2 UV/Vis data of flavins **1a**, **3**, **4**, **5**, and **6** in MeCN (2.5×10^{-5} M)

Entry	Flavin	λ_{max} [nm]	λ_{max} [nm]	λ_{max} [nm]	λ_{max} [nm]
		ε [L×mol^{-1}×cm^{-1}]	ε [L×mol^{-1}×cm^{-1}]	ε [L×mol^{-1}×cm^{-1}]	ε [L×mol^{-1}×cm^{-1}]
1	**1a**	222 41200	267 35550	343 10200	441 12700
2	**3a–H**	225 37650	272 36300	340 9500	444 12950
3	**3a–(*p*-Me)**	225 39650	272 36200	346 9450	444 12850
4	**3a–(*p*-OMe)**	225 39850	272 36350	349 9000	444 12350
5	**3a–(*p*-Br)**	225 36750	272 31350	348 8300	444 11250
6	**3a–(*m*-Br)**	225 37150	272 30450	347 8000	444 10700
7	**3b–H**	224 36050	272 31250	348 9600	444 12800
8	**4**	249 37750	290 22350	338 13600	462 11900
9	**5**	– –	271 31750	346 8500	444 11250
10	**6**	248 36750	292 23650	339 14250	461 12550

Figure 6.5 shows the fluorescence spectra of flavins **1a**, **3**, **4**, **5**, and **6** in MeCN (2.5×10^{-6} M) upon excitation at 440 nm

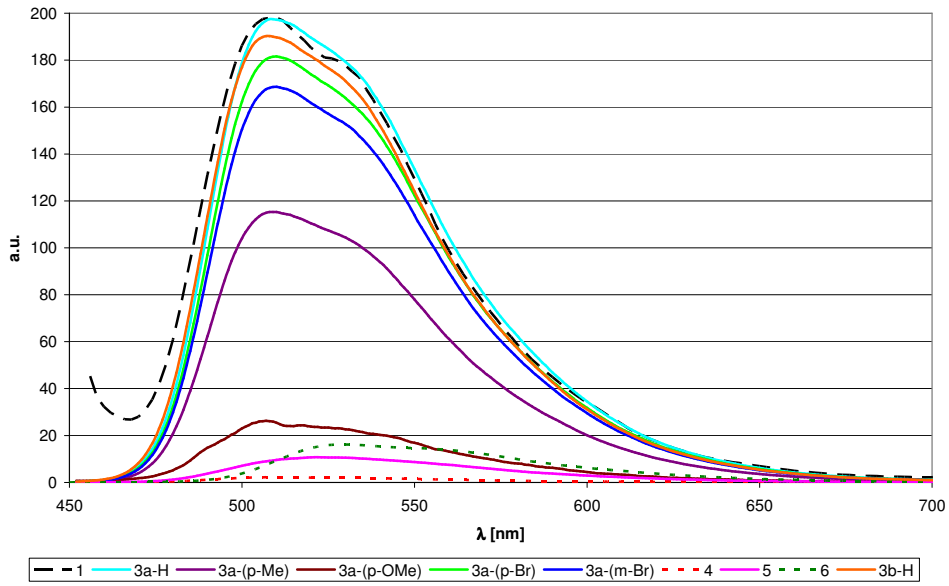


Figure 6.5 Fluorescence-spectra of flavins **1a** and **3**–**6** upon excitation at 440 nm

The maximum of emission of flavin **5** is shifted to longer wavelength (+13 nm) compared to the other 3-N-aryl flavins **3a** and flavin **1a** (table 6.3). Fluorescence of *p*-methylphenyl-flavin **3a–(*p*–Me)** is slightly and of *p*-methoxy- and *p*-hydroxy-derivatives **3a–(*p*–OMe)** and **5** is strongly quenched. This indicates that high electron density in the 3-N aromatic substituent decreases the emission of the flavin. Emission intensities of aldehydes **4** and **6** are also decreased. The emission maximum of flavin **6** is shifted by about 20 nm to longer wavelength.

Table 6.3 Fluorescence data of flavins **1a**, **3**, **4**, **5**, and **6** in MeCN (2.5×10^{-6} M) after excitation at 440 nm

Entry	Flavin	λ_{max} [nm]	Emission intensity [a.u.]
1	**1a**	510	198
2	**3a–H**	508	197
3	**3a–(*p*-Me)**	509	115
4	**3a–(*p*-OMe)**	507	26
5	**3a–(*p*-Br)**	510	182
6	**3a–(*m*-Br)**	510	169
7	**3b–H**	508	190
8	**4**	510	1
9	**5**	522	11
10	**6**	529	16

Figure 6.6 shows equally concentrated solutions of flavins **3**, **4** and **5** in MeCN under an UV-lamp with black (top) and white (bottom) background. The differences in the emission intensities are clearly visible. More detailed photophysical investigations are currently in progress and results will be disclosed later.

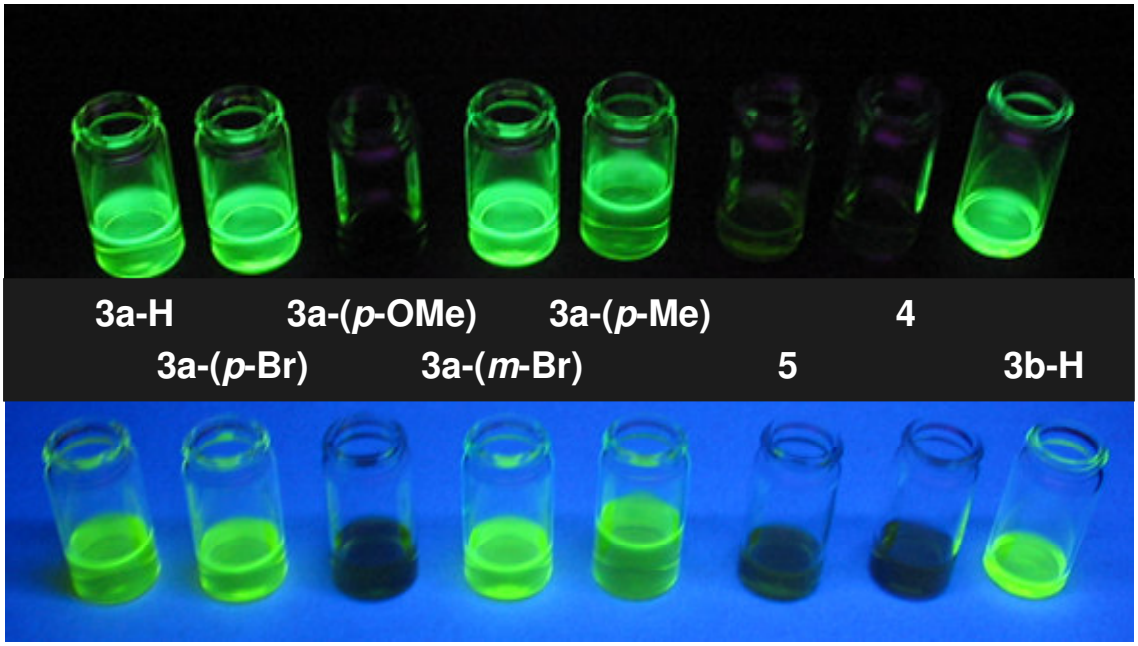


Figure 6.6 Pictures of flavins **3**–**5** under UV-irradiation with black (top) and white (bottom) background.

Summary

We have established a method for the direct 3-N-arylation of flavins using various benzene boronic acids and copper acetate giving moderate to good yields of C(aryl)-N(imide)-bond formation. The new reaction provides a more facile access to a class of flavins that was difficult to prepare and was therefore sparse investigated. The reaction conditions were optimized considering the lability of flavins under basic conditions and heating. Best product yields were achieved at low reaction temperatures or under oxygen atmosphere with addition of molecular sieves. The additional orthogonal aromatic system at 3-N is not electronically coupled to the original flavin-π-system as proven by optical spectroscopy. Some of the new compounds show reduced or quenched emission intensity.

Experimental part

General

10-(2-Methoxyethyl)-7,8-dimethylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (**1a**),[14] tetraacetyl riboflavin (**1b**),[25] and phenyl boronic ester **9**[26] were prepared by known methods. All other chemicals were purchased from commercial suppliers, checked by ^{1}H NMR spectrometry and then used as received. Before use, solvents were distilled. Dry DMAP was purchased from Fluka. Thin layer chromatography was carried out on Silica gel 60 F254 aluminium sheets (Merck) or on precoated plastic sheets Polygram SIL G/UV254 (Macherey-Nagel, Düren, Germany), with detection under 254 or 333 nm UV light or by naked eye (flavins are intensively yellow-coloured). Preparative thin layer chromatography was carried out on home-made glass plates (20×20 cm) coated with silica gel 60 GF254 (20 g, Merck). Flash column chromatography was carried out on silica gel 35–70 μm, 60 Å from Acros. NMR spectra were recorded at Bruker spectrometer equipped with a robotic sampler at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR). Tetramethylsilane (TMS) was used as an external standard. Electron-impact (EI-MS) and chemical ionisation (CI-MS) mass spectra were measured on Finnigan TSQ 710 spectrometer, and electrospray ionisation (ES-MS) mass spectra were measured on ThermoQuest Finnigan TSQ 7000 spectrometer. All methods of HRMS were measured on ThermoQuest Finnigan MAT 95 spectrometer. Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected. UV/Vis spectra were recorded at Varian Cary 50 Bio UV/VIS spectrometer against air. Fluorescence spectra were recorded at Varian Cary Eclipse. IR spectra were measured on Biorad Spectrometer Excalibur FTS 3000. Microwave heating was carried out with Microwave Discover System S-Class from CEM.

General procedure 1

Flavin **1a** (75 mg, 250 μmol), benzene boronic acid **2–R** (3 eq), copper acetate (100 mg, 500 μmol, 2 eq) and TEA (76 mg, 750 μmol, 3 eq), were stirred in dry DMAP (3 mL) for two days at room temperature in the dark. Afterwards, the reaction mixture was diluted with $CHCl_3$ and washed with water and brine. The organic phase was dried over magnesium sulphate and

the solvent was evaporated yielding dark oil. After purification by flash column chromatography (EE:MeOH – 20:1) and/or preparative thin layer chromatography ($CHCl_3$:MeOH – 25:1) a yellow solid was obtained.

10-(2-Methoxyethyl)-7,8-dimethyl-3-phenylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (3a–H)

Prepared with benzene boronic acid (**2–H**) (91 mg, 750 μmol) according to general procedure 1.

Yield 53 mg, 141 μmol, 56%, yellow solid

R_f=0.65 ($CHCl_3$:MeOH – 10:1)

m.p. 237 °C

^{1}H NMR ($CDCl_3$) δ = 2.42 (s, 3 H, Ar-CH_3), 2.53 (s, 3 H, Ar-CH_3), 3.30 (s, 3 H, O-CH_3), 3.93 (tr, *J*=5.21 Hz, 2 H, N-CH_2), 4.92 (tr, *J*=5.21 Hz, 2 H, O-CH_2), 7.28–7.30 (m, 2 H, Ph-*H*), 7.41 (tr, *J*=7.27 Hz, 1 H, Ph-*H*), 7.50 (tr, *J*=7.55 Hz, 2 H, Ph-*H)*, 7.68 (s, 1 H, Ar-*H*), 8.02 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.5 (*C*7´), 21.7 (*C*8´), 45.5 (N-*C*H_2), 59.3 (O-*C*H_3), 69.6 (O-*C*H_2), 116.8 (*C*9), 128.3, 128.6 and 129.4 (Ph-*C*), 132.3 (*C*9a), 132.4 (*C*6), 135.2 (Ph-*C*), 135.8 (*C*5a), 136.0 (*C*4a), 136.8 (*C*7), 147.8 (*C*8), 149.2 (*C*10a), 155.5 (*C*2), 160.0 (*C*4)

ES-MS *m/z* (%): 377.1 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{21}H_{20}N_4O_3$ $[M]^{+\bullet}$: 376.1535; found: 376.1537 [Δ -0.42 ppm]

IR (ATR): ν = 1712, 1654, 1577, 1535, 1453, 1400, 1344, 1311, 1273, 1223, 1208, 1157, 1088 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 225 (37650), 272 (36300), 340 (9500), 444 nm (12950)

10-(2-Methoxyethyl)-7,8-dimethyl-3-(4-methylphenyl)-benzo-[*g*]pteridine-2,4(3*H*,10*H*)-dione (3a–(*p*–Me))

Prepared with 4-methylbenzene boronic acid (**2–(4–Me)**) (102 mg, 750 μmol) according to general procedure 1. Recovery of unreacted starting material flavin **1a** after column chromatography: 27 mg, 90 μmol, 36%.

Yield 46 mg, 118 μmol, 47%, yellow solid

R_f=0.55 ($CHCl_3$:MeOH – 10:1)

m.p. 185 °C

^{1}H NMR ($CDCl_3$) δ = 2.41 (s, 3 H, Ph-C*H*$_3$), 2.44 (s, 3 H, Ar-C*H*$_3$), 2.55 (s, 3 H, Ar-C*H*$_3$), 3.31 (s, 3 H, O-C*H*$_3$), 3.94 (tr, *J*=5.08 Hz, 2 H, N-C*H*$_2$), 4.93 (tr, *J*=5.21 Hz, 2 H, O-C*H*$_2$), 7.19 (d, *J*=8.33 Hz, 2 H, Ph-*H*), 7.32 (d, *J*=7.96 Hz, 2 H, Ph-*H*), 7.68 (s, 1 H, Ar-*H*), 8.04 (s, 1 H, Ar-*H*)
^{13}C NMR ($CDCl_3$) δ = 19.6 (*C*7´), 21.4 (Ph-*C*H$_3$), 21.7 (*C*8´), 45.5 (N-*C*H$_2$), 59.4 (O-*C*H$_3$), 69.6 (O-*C*H$_2$), 116.8 (*C*9), 128.0 and 130.2 (Ph-*C*), 132.3 (*C*6), 132.4 (*C*9a), 133.2 (Ph-*C*), 135.1 (*C*5a), 136.0 (*C*4a), 136.8 (*C*7), 138.6 (Ph-*C*), 147.8 (*C*8), 149.2 (*C*10a), 155.6 (*C*2), 160.1 (*C*4)
ES-MS *m/z* (%): 391.2 (100) $[M+H]^+$
HRMS–EI *m/z*: calcd for $C_{22}H_{22}N_4O_3$ $[M]^{+\bullet}$: 390.1692; found: 390.1689 [Δ 0.74 ppm]
IR (ATR): ν = 3554, 3491, 2919, 2850, 2360, 1708, 1664, 1581, 1542, 1513, 1455, 1401, 1346, 1270, 1241, 1149, 1079, 1066, 1014 cm^{-1}
UV/Vis (MeCN): λ_{max} (ε) = 225 (39650), 272 (36200), 346 (9450), 444 nm (12850)

10-(2-Methoxyethyl)-3-(4-methoxyphenyl)-7,8-dimethylbenzo-[*g*]pteridine-2,4(3*H*,10*H*)-dione (**3a–(*p*–OMe)**)
Prepared with 4-methoxybenzene boronic acid (**2–(4-OMe)**) (114 mg, 750 µmol) according to general procedure 1. Recovery of unreacted starting material flavin **1a** after column chromatography: 17 mg, 57 µmol, 23%. Yield 35 mg, 86 µmol, 34%, yellow solid
R_f=0.60 ($CHCl_3$:MeOH – 10:1)
m.p. 155 °C
^{1}H NMR ($CDCl_3$) δ = 2.43 (s, 3 H, Ar-C*H*$_3$), 2.53 (s, 3 H, Ar-C*H*$_3$), 3.30 (s, 3 H, O-C*H*$_3$), 3.83 (s, 3 H, Ph-OC*H*$_3$), 3.92 (tr, *J*=5.08 Hz, 2 H, N-C*H*$_2$), 4.92 (tr, *J*=5.08 Hz, 2 H, O-C*H*$_2$), 6.99 (d, *J*=9.06 Hz, 2 H, Ph-*H*), 7.21 (d, *J*=8.78 Hz, 2 H, Ph-*H*), 7.67 (s, 1 H, Ar-*H*), 8.02 (s, 1 H, Ar-*H*)
^{13}C NMR ($CDCl_3$) δ = 19.4 (*C*7´), 21.6 (*C*8´), 45.5 (N-*C*H$_2$), 55.4 (Ph-O*C*H$_3$), 59.2 (O-*C*H$_3$), 69.4 (O-*C*H$_2$), 114.7 (Ph-*C*), 116.8 (*C*9), 128.1 and 129.1 (Ph-*C*), 132.1 (*C*6), 132.3 (*C*9a), 135.2 (*C*5a), 135.6 (*C*4a), 137.2 (*C*7), 148.2 (*C*8), 149.0 (*C*10a), 156.0 (*C*2), 159.5 (Ph-*C*), 160.4 (*C*4)
ES-MS *m/z* (%): 407.2 (100) $[M+H]^+$
HRMS–EI *m/z*: calcd for $C_{22}H_{22}N_4O_4$ $[M]^{+\bullet}$: 406.1641; found: 406.1645 [Δ -0.97 ppm]

IR (ATR): ν = 2924, 2361, 2343, 1711, 1665, 1577, 1538, 1510, 1449, 1400, 1351, 1301, 1241, 1154, 1111, 1084, 1025 cm^{-1}
UV/Vis (MeCN): λ_{max} (ε) = 225 (39850), 272 (36350), 349 (9000), 444 nm (12350)

3-(4-Bromophenyl)-10-(2-methoxyethyl)-7,8-dimethylbenzo-[*g*]pteridine-2,4(3*H*,10*H*)-dione (3a–(*p*–Br))

Prepared with 4-bromobenzene boronic acid (**2–(4–Br)**) (151 mg, 750 μmol) according to general procedure 1. Recovery of unreacted starting material flavin **1a** after column chromatography: 24 mg, 80 μmol, 32%.
Yield 33 mg, 73 μmol, 29%, yellow solid
R_f=0.60 ($CHCl_3$:MeOH – 10:1)
m.p. 246 °C
^{1}H NMR ($CDCl_3$) δ = 2.44 (s, 3 H, Ar-CH_3), 2.55 (s, 3 H, Ar-CH_3), 3.30 (s, 3 H, O-CH_3), 3.94 (tr, *J*=5.08 Hz, 2 H, N-CH_2), 4.93 (tr, *J*=5.08 Hz, 2 H, O-CH_2), 7.19 (d, *J*=8.51 Hz, 2 H, Ph-*H*), 7.62 (d, *J*=8.51 Hz, 2 H, Ph-*H*), 7.69 (s, 1 H, Ar-*H*), 8.04 (s, 1 H, Ar-*H*)
^{13}C NMR ($CDCl_3$) δ = 18.6 (*C*7´), 20.8 (*C*8´), 44.7 (N-*C*H_2), 58.4 (O-*C*H_3), 68.6 (O-*C*H_2), 115.9 (*C*9), 121.7 and 129.1 (Ph-*C*), 131.4 (*C*9a), 131.4 (*C*6), 131.7 and 133.8 (Ph-*C*), 134.3 (*C*5a), 134.8 (*C*4a), 136.1 (*C*7), 147.2 (*C*8), 148.2 (*C*10a), 154.5 (*C*2), 158.9 (*C*4)
ES-MS *m/z* (%): 455.1 (100) $[M+H]^+$, 911.3 $[2M+H]^+$
HRMS–EI *m/z*: calcd for $C_{21}H_{19}BrN_4O_3$ $[M]^{+\bullet}$: 454.0641; found: 454.0636 [Δ 1.02 ppm]
IR (ATR): ν = 2918, 2849, 1707, 1658, 1587, 1539, 1487, 1445, 1400, 1351, 1262, 1228, 1193, 1113, 1066, 1012 cm^{-1}
UV/Vis (MeCN): λ_{max} (ε) = 225 (36750), 272 (31350), 348 (8300), 444 nm (11250)

3-(3-Bromophenyl)-10-(2-methoxyethyl)-7,8-dimethylbenzo-[*g*]pteridine-2,4(3*H*,10*H*)-dione (3–(*m*–Br))

Prepared with 3-bromobenzene boronic acid (**2–(3–Br)**) (151 mg, 750 μmol) according to general procedure 1. Recovery of unreacted starting material flavin **1a** after column chromatography: 24 mg, 80 μmol, 32%.

Yield 39 mg, 86 μmol, 34%, yellow solid

R_f=0.70 ($CHCl_3$:MeOH – 10:1)

m.p. 179 °C

^{1}H NMR ($CDCl_3$) δ = 2.45 (s, 3 H, Ar-CH_3), 2.56 (s, 3 H, Ar-CH_3), 3.30 (s, 3 H, O-CH_3), 3.94 (tr, *J*=5.08 Hz, 2 H, N-CH_2), 4.94 (tr, *J*=5.21 Hz, 2 H, O-CH_2), 7.25–7.28 (m, 1 H, Ph-*H*), 7.39 (tr, *J*=8.10 Hz, 1 H, Ph-*H*), 7.48 (tr, *J*=1.78 Hz, 1 H, Ph-*H)*, 7.55–7.58 (m, 1 H, Ph-*H*), 7.70 (s, 1 H, Ar-*H*), 8.05 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.6 (*C*7´), 21.7 (*C*8´), 45.6 (N-*C*H_2), 59.4 (O-*C*H_3), 69.6 (O-*C*H_2), 116.9 (*C*9), 122.6, 127.3, 130.6, 131.7 and 131.9 (Ph-*C*), 132.4 (*C*6), 132.4 (*C*9a), 135.3 (Ph-*C*), 136.0 (*C*5a), 137.0 (*C*4a), 137.1 (*C*7), 148.2 (*C*8), 149.2 (*C*10a), 155.1 (*C*2), 159.8 (*C*4)

ES-MS *m/z* (%): 455.1 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{21}H_{19}BrN_4O_3$ $[M]^{+\bullet}$: 454.0641; found: 454.0640 [Δ 0.14 ppm]

IR (ATR): ν = 2922, 2851, 2360, 1708, 1657, 1581, 1539, 1457, 1400, 1350, 1267, 1225, 1193, 1112, 1065 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 225 (37650), 272 (36300), 340 (9500), 444 nm (12950)

10-Tetraacetyl-ribityl-7,8-Dimethyl-3-phenylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (3b–H)

Prepared with tetraacetyl riboflavin (**1b**) (155 mg, 250 μmol) and benzene boronic acid (**2–H**) (91 mg, 750 μmol) according to general procedure 1.

Yield 60 mg, 97 μmol, 39%, yellow solid

R_f=0.65 (EE:MeOH – 20:1)

m.p. 250 °C (decomp.)

^{1}H NMR ($CDCl_3$) δ = 1.74 (s, 3 H, Ac-CH_3), 2.05 (s, 3 H, Ac-CH_3), 2.21 (s, 3 H, Ac-CH_3), 2.27 (s, 3 H, Ac-CH_3), 2.42 (s, 3 H, Ar-CH_3), 2.55 (s, 3 H, Ar-CH_3), 4.19–4.25 (m, 1 H, ribityl), 4.42 (dd, *J*=12.35 Hz, *J*=2.47 Hz, 1 H,

ribityl), 4.97 (br s, 2 H, ribityl), 5.40 (s, 1 H, ribityl), 5.47 (s, 1 H, ribityl), 5.71 (d, *J*=6.86 Hz, 1 H, ribityl), 7.29 (s, 2 H, Ph-*H*), 7.41 (tr, *J*=7.27 Hz, 1 H, Ph-*H*), 7.49 (tr, *J*=7.55 Hz, 2 H, Ph-*H)*, 7.56 (s, 1 H, Ar-*H*), 8.01 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.5 (*C*7´), 20.4 (*C*8´), 20.8, 20.9, 21.2 and 21.5 (Ac-*C*H_3), 44.7 (*C*α), 61.9 (*C*ε), 69.0, 69.5 and 70.3 (*C*-β,χ,δ), 115.5 (*C*9), 128.2, 128.7 and 129.4 (Ph-*C*), 131.4 (*C*9a), 133.0 (*C*6), 134.8 (*C*5a), 135.7 (Ph-*C*), 136.1 (*C*4a), 136.8 (*C*7), 147.8 (*C*8), 149.6 (*C*10a), 154.9 (*C*2), 159.7 (*C*4), 169.8, 170.0, 170.5 and 170.7 (*C*O)

ES-MS *m/z* (%): 621.3 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{31}H_{33}N_4O_{10}$ $[M+H]^+$: 621.2197; found: 621.2185 [Δ 1.88 ppm]

IR (ATR): ν = 2361, 1741, 1669, 1584, 1546, 1369, 1203, 1044 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 224 (36050), 272 (32150), 348 (9600), 444 nm (12800)

8-Formyl-10-(2-methoxyethyl)-3-(4-methoxyphenyl)-7-methyl-benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (4)

Obtained after chromatographic purification as a by-product of the reaction of flavin **1a** with 4-methoxybenzene boronic acid (**2–(4–OMe)**) (114 mg, 750 μmol) according to general procedure 1.

Yield 9 mg, 21 μmol, 9%, orange-red solid

R_f=0.50 (EE–MeOH – 20:1)

m.p. 212 °C

^{1}H NMR ($CDCl_3$) δ = 2.83 (s, 3 H, Ar-C*H*$_3$), 3.29 (s, 3 H, O-C*H*$_3$), 3.86 (s, 3 H, Ph-OC*H*$_3$), 3.96 (tr, *J*=4.94 Hz, 2 H, N-C*H*$_2$), 4.97 (tr, *J*=4.94 Hz, 2 H, O-C*H*$_2$), 7.03 (d, *J*=8.78 Hz, 2 H, Ph-*H*), 7.22 (d, *J*=9.06 Hz, 2 H, Ph-*H*), 8.19 (s, 1 H, Ar-*H*), 8.36 (s, 1 H, Ar-*H*), 10.47 (s, 1 H, CO-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.0 (*C*7´), 45.9 (N-*C*H_2), 55.6 (Ph-O*C*H_3), 59.4 (O-*C*H_3), 69.6 (O-*C*H_2), 114.9 (Ph-*C*), 120.4 (*C*9), 127.9 and 129.2 (Ph-*C*), 132.3 (*C*9a), 135.2 (*C*6), 137.4 (*C*8), 137.8 (*C*5a), 138.3 (*C*4a), 139.7 (*C*7), 149.3 (*C*10a), 155.2 (*C*2), 159.4 (*C*4), 159.7 (Ph-*C*), 191.0 (*C*O)

CI-MS *m/z* (%): 421.1 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{22}H_{20}N_4O_5$ $[M]^{+\bullet}$: 420.1434; found: 420.1431 [Δ 0.64 ppm]

IR (ATR): ν = 2836, 2361, 1701, 1664, 1620, 1581, 1546, 1510, 1451, 1348, 1304, 1253, 1198, 1154, 1112, 1033 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 249 (37750), 290 (22350), 338 (13600), 462 nm (11900)

3-(4-Hydroxyphenyl)-10-(2-Methoxyethyl)-7,8-dimethylbenzo-[*g*]pteridine-2,4(3*H*,10*H*)-dione (5)

Obtained after chromatographic purification as a by-product of the reaction of flavin **1a** with 1,4-benzene diboronic acid (**2–(4-B(OH)$_2$)**) (92 mg, 750 μmol) according to general procedure 1.

Yield 9 mg, 23 μmol, 9%, yellow solid

R_f=0.25 (EE:MeOH – 20:1)

^{1}H NMR (DMSO-d_6) δ = 2.41 (s, 3 H, Ar-CH_3), 2.54 (s, 3 H, Ar-CH_3), 3.27 (s, 3 H, O-CH_3), 3.79 (tr, *J*=5.49 Hz, 2 H, N-CH_2), 4.85 (tr, *J*=5.63 Hz, 2 H, O-CH_2), 6.83 (d, *J*=8.78 Hz, 2 H, Ph-*H*), 7.02 (d, *J*=8.78 Hz, 2 H, Ph-*H*), 7.91 (s, 1 H, Ar-*H*), 7.95 (s, 1 H, Ar-*H*), 9.60 (s, 1 H, Ph-O*H*)

ES-MS *m/z* (%): 393.2 (100) $[M+H]^+$

IR (ATR): ν = 3383, 3096, 2953, 2926, 2857, 2255, 1651, 1463, 1325, 1104 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 227 (154300), 271 (31750), 346 (8500), 444 nm (11250)

8-Formyl-10-(2-methoxyethyl)-7-methyl-3-phenylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (6)

Prepared with benzene boronic acid (**2–H**) (91 mg, 750 μmol) according to general procedure 1 but with stirring at 80 °C for 5 h. Minor amounts of product **3a–H** were also obtained.

Yield 41 mg, 105 μmol, 42%, orange solid

R_f=0.65 (DCM:MeOH – 10:1)

m.p. 234 °C

^{1}H NMR ($CDCl_3$) δ = 2.83 (s, 3 H, Ar-CH_3), 3.29 (s, 3 H, O-CH_3), 3.97 (tr, *J*=4.80 Hz, 2 H, N-CH_2), 4.98 (tr, *J*=4.67 Hz, 2 H, O-CH_2), 7.29–7.32 (m, 2 H, Ph-*H*), 7.43–7.56 (m, 3 H, Ph-*H*), 8.19 (s, 1 H, Ar-*H*), 8.37 (s, 1 H, Ar-*H*), 10.48 (s, 1 H, CO-*H*)

^{13}C NMR ($CDCl_3$) δ = 18.9 (*C*7´), 45.9 (N-*C*H_2), 59.3 (O-*C*H_3), 69.5 (O-*C*H_2), 120.5 (*C*9), 128.2, 128.9 and 129.5 (Ph-*C*), 132.3 (*C*9a), 135.1 (*C*6), 135.3 (Ph-*C*), 137.4 (*C*8), 137.7 (*C*5a), 138.2 (*C*4a), 139.6 (*C*7), 149.3 (*C*10a), 154.9 (*C*2), 159.1 (*C*4), 191.0 (*C*O)

CI-MS *m/z* (%): 391.1 (100) $[M+H]^+$

HRMS–EI *m/z*: calcd for $C_{21}H_{18}N_4O_4$ $[M]^{+\bullet}$: 390.1328; found: 390.1328 [Δ 0.01 ppm]

IR (ATR): ν = 2920, 1693, 1665, 1622, 1582, 1548, 1520, 1454, 1349, 1319, 1196, 1155, 1115, 1014 cm^{-1}

UV/Vis (MeCN): λ_{max} (ε) = 248 (36750), 292 (23650), 339 (14250), 461 nm (12550)

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List of abbreviations

ATR	Attenuated total reflectance
ax	Axial
Boc	*tert*-Butoxycarbonyl
br	Broad
calcd	Calculated
Cbz	Benzyloxycarbonyl
CI	Chemical ionisation
d	Doublet
DCM	Dichloromethane
DE	Diethyl ether
decomp.	Decomposition
DIPEA	Diisopropyl-ethyl amine
DMAP	4-Dimethylamino pyridine
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethyl sulphoxide
DNA	Deoxyribonucleic acid
EA	Combustion elementary analysis
EDC	*N*-(3-Dimethylaminopropyl)-*N´*-ethyl-carbodiimide
EDTA	Ethylenediaminetetraacetic acid
EE	Ethyl acetate
EI	Electron impact
eq	Equivalents
eq	Equatorial
ES	Electron spray
FAD	Flavin adenine dinucleotide
Fl	Flavin
FMN	Flavin mononucleotide
HMBC	Heteronuclear multiple bond correlation
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HR	High resolution

HSQC	Heteronuclear single quantum correlation
IR	Infrared
LED	Light emitting diode
LSI	Liquid secondary ion
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m.p.	Melting point
MS	Mass spectrometry
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nucleon magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy
PE	Petrol ether
ppm	Parts per million
PTLC	Preparative thin layer chromatography
qu	Quartet
quant.	Quantitatively
quin	Quintet
r.t.	Room temperature
R_f	Retention factor
SCE	Saturated calomel electrode
TEA	Triethyl amine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TOF	Turnover frequency
TON	Turnover number
tr	Triplet
UV	Ultraviolet
Vis	Visible

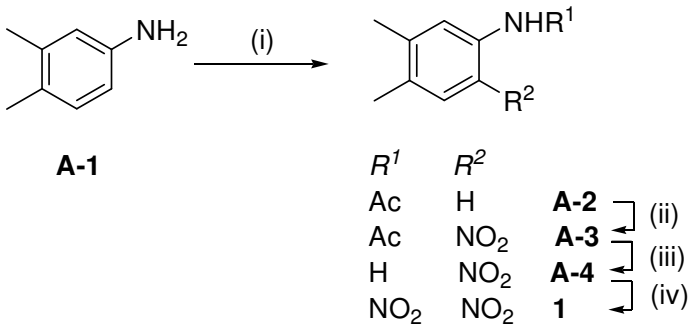
Appendix A

Supporting Information to Chapter 2 – Thiourea-Enhanced Flavin Photooxidation of Benzyl Alcohol

The numbering of the molecules in this appendix refers to chapter 2

Contents

Scheme A.1 shows the synthesis of the starting material, dinitro compound **1**, from 3,4-dimethyl aniline (**A-1**).



Scheme A.1 Synthesis of dinitro compound **1** from 3,4-dimethyl aniline (**A-1**) Conditions: (i) Ac_2O, AcOH (ii) HNO_3, AcOH (iii) H_2SO_4 (iv) H_2O_2, AcOH

3,4-Dimethyl-acetanilid (A-2)

3,4-Dimethylanilin (**A-1**) (24.2 g, 200 mmol) was dissolved in acetic acid (30 mL) and acetic anhydride (30 mL). After refluxing for 15 min, the mixture was cooled and added dropwise to ice/water with stirring. The pale brown precipitate was collected on a buechner funnel and dried.

yield 29.5 g, 181 mmol, 91% (72-87%[1]), brown solid

^{1}H NMR ($CDCl_3$) δ = 2.13 (s, 3 H, COC*H*$_3$), 2.20 (s, 3 H, Ar-C*H*$_3$), 2.21 (s, 3 H, Ar-C*H*$_3$), 7.04 (d, *J*=7.96 Hz, 1 H, Ar-*H*), 7.21 (dd, *J*=7.96 Hz, *J*=2.20 Hz, 1 H, Ar-*H*), 7.28 (d, *J*=2.20 Hz, 1 H, Ar-*H*), 7.59 (br s, 1 H, N-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.1 (Ar-*C*H$_3$), 19.8 (Ar-*C*H$_3$), 24.4 (CO*C*H$_3$), 117.5, 121.4, 129.8, 132.5, 135.6, 137.1 (6×Ar-*C*), 168.4 (*C*O)

3,4-Dimethyl-4-nitro-acetanilid (A-3)

A mixture of nitric acid (100 mL) and acetic acid (35 mL) was cooled to 15 °C. A solution of anilid **A-2** in acetic acid (35 mL) was added dropwise and the solution was stirred at 15 °C for 2 hours. The brown solution was added dropwise to ice/water and the yellow precipitate was filtered off and dried.[2]

yield 10.6 g, 50.9 mmol, 56%, yellow solid

^{1}H NMR ($CDCl_3$) δ = 2.27 (m, 6 H, 2×Ar-C*H*$_3$), 2.34 (s, 3 H, COC*H*$_3$), 7.97 (s, 1 H, Ar-*H*), 8.53 (s, 1 H, Ar-*H*), 10.30 (br s, 1 H, N-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.1 (Ar-*C*H_3), 20.5 (Ar-*C*H_3), 25.6 (CO*C*H_3), 122.6, 125.9, 132.3, 132.7, 134.1, 146.9 (6×Ar-*C*), 168.9 (*C*O)

3,4-Dimethyl-2-nitroanilin (A-4)

Nitroanilid **A-3** (21.1 g, 101 mmol) was slowly added to sulfuric acid (250 mL) and stirred for 30 min at 100 °C. The solution was added dropwise to ice/water after cooling and the brown precipitate was filtered off and dried.

yield 13.8 g, 83.0 mmol, 82% (71-93%[1]), brown solid

^{1}H NMR ($CDCl_3$) δ = 2.17 (s, 3 H, Ar-C*H*$_3$), 2.22 (s, 3 H, Ar-C*H*$_3$), 5.66 (br s, 2 H, N*H*$_2$), 6.59 (s, 1 H, Ar-*H*), 7.86 (s, 1 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 18.6 (Ar-*C*H_3), 20.1 (Ar-*C*H_3), 119.0, 125.6, 126.1, 130.2, 143.0 and 146.6 (6×Ar-*C*)

EI-MS *m/z* (%): 166.1 (100) $[M]^{+\bullet}$

4,5-Dinitro-o-xylol (1)

Nitroanilin **A-4** (5.09 g, 30.6 mmol) was dissolved in acetic acid (150 mL) and H_2O_2 (30 mL, 40% in water) was added dropwise. The solution was stirred at 50 °C over night. Adding the solution dropwise to ice/water after cooling gave a yellow solid that was filtered off and dried.

yield 3.73 g, 19.0 mmol, 62%, yellow solid

^{1}H NMR ($CDCl_3$) δ = 2.42 (s, 6 H, C*H*$_3$), 7.68 (s, 2 H, Ar-*H*)

^{13}C NMR ($CDCl_3$) δ = 19.9 (Ar-*C*H_3), 125.7 (Ar-*C*-H), 140.6 (Ar-*C*-NO_2), 143.6 (Ar-*C*-Me)

CI-MS *m/z* (%): 214.2 (100) $[M+NH_4]^+$, 184.1 $[M+NH_4–NO]^{+\bullet}$, 231.2 $[M+2NH_3+H]^+$

Cyclic voltammetry I

Reduction potential of simple flavin **30** and flavin–thiourea **16** were measured by cyclic voltammetry and compared (figure A.1). Reduction potential of the thiourea-containing flavin **16** is shifted by +90 mV. The experiment was measured using the conditions described in chapter 2, experimental part.

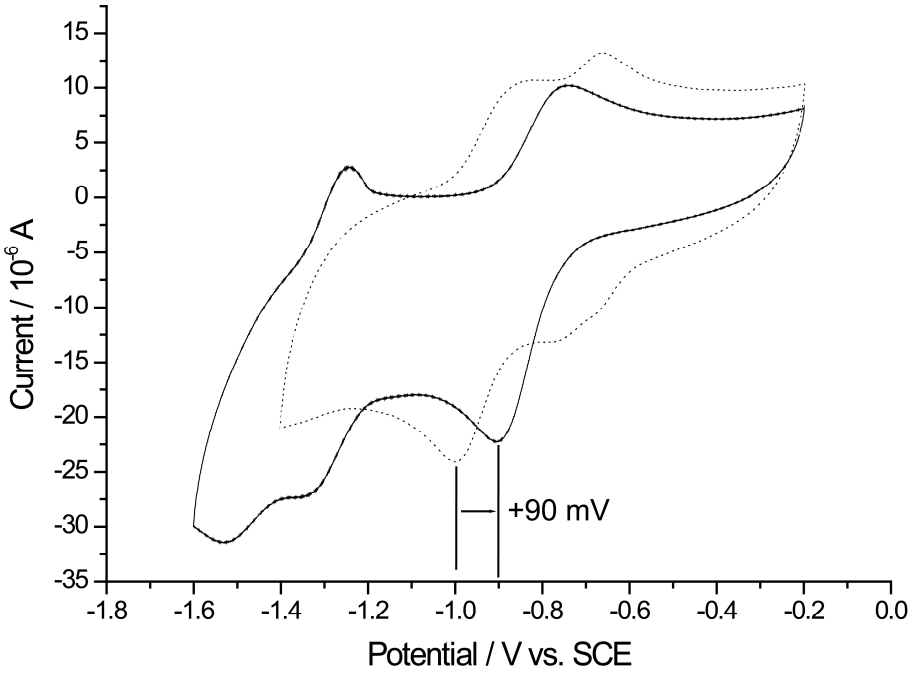


Figure A.1 Cyclic voltammograms of flavin-thiourea **16** (solid line) and 10-glycol flavin **30** (dashed line)

Cyclic voltammetry II

Half-wave reduction or oxidation potentials were determined by cyclic voltammetry (table A.1) as described in the experimental Part. ΔG energy of various possible redox processes (table A.2) was calculated using the Rehm–Weller equation.[3,4]

$$\Delta G = 96.4\left(E_{\frac{1}{2}}^{ox} - E_{\frac{1}{2}}^{red} \right) - \frac{e^2}{\varepsilon \times a} - E^{O-O}$$

Typical values for the Coulombic ($e^2/(\varepsilon \times a)$=5.4 kJ/mol) and flavin excitation term (E^{O-O}=241 kJ/mol were used, neglecting entropy changes from the ground to the excited state (table A.2).

Table A.1 Redox potentials of species participating in the catalytic cycle

Redox process	**$E_{1/2}$ vs. SCE [V]**	**$E_{1/2}$ vs. Fc/Fc^+ [V]**
4-Methoxy benzylalcohol ox.	1.547	1.086
Flavin **30** red.	–0.717	–1.178
Fl_{red} **30** ox.	–1.234	–1.695
Oxygen red.	–0.923	–1.384
Thiourea ox.	0.8	0.339
Thiourea red.	–0.720	–1.181

Table A.2 ΔG of redox processes

ΔG [kJ/mol]		Oxidized species		
		Alcohol	Thiourea	Fl_{red}
Reduced species	Flavin	212	141	—
	Flavin*	–29	–100	—
	Thiourea	213	—	–55
	Oxygen	232	160	–35

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Appendix B

Supporting Information to Chapter 3 – Photooxidation of Benzyl Alcohols with Immobilized Flavins

The numbering of the molecules in this appendix refers to chapter 3

Contents

Reaction monitoring: Photocatalytic oxidation of 4-methoxybenzyl alcohol on 2.5 mmol scale

4-Methoxybenzyl alcohol (345 mg, 2.5 mmol) was dissolved in water (250 mL, containing 0.2% DMSO) and tetraacetyl riboflavin (**10**) (13.6 mg, 0.025 mmol, 1 mol%) was added. The stirred solution was irradiated by an array of six LEDs (440 nm, 5 W each) at room temperature. To monitor the reaction progress, 10 mL-aliquots of the reaction mixture were removed at certain intervals and extracted with DCM. The organic phase (containing the starting material and the product) was dried and the solvent was evaporated. Amounts of starting material and product were determined by integration of the ^{1}H NMR resonance signals of the aromatic protons of alcohol and corresponding aldehyde. The spectra confirm a very clean reaction with the alcohol and the aldehyde as the only detectable compounds. After 8 h, the reaction conversion is 50%; full conversion of the starting material requires 20 h.

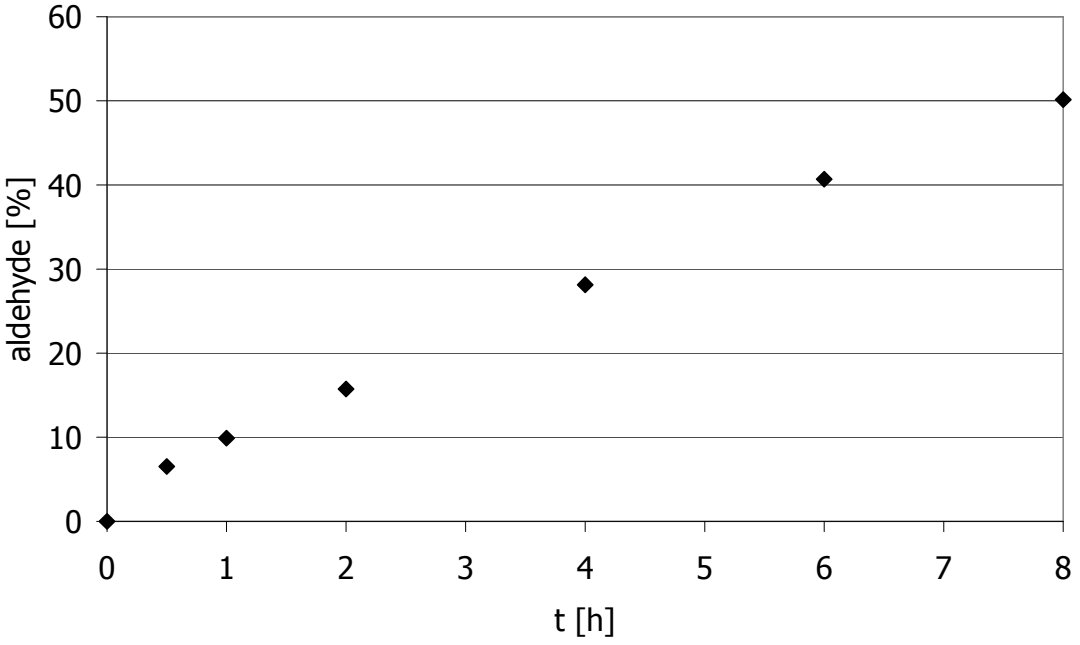


Figure B.1 Kinetic data of the reaction on preparative scale (yield of aldehyde *versus* reaction time)

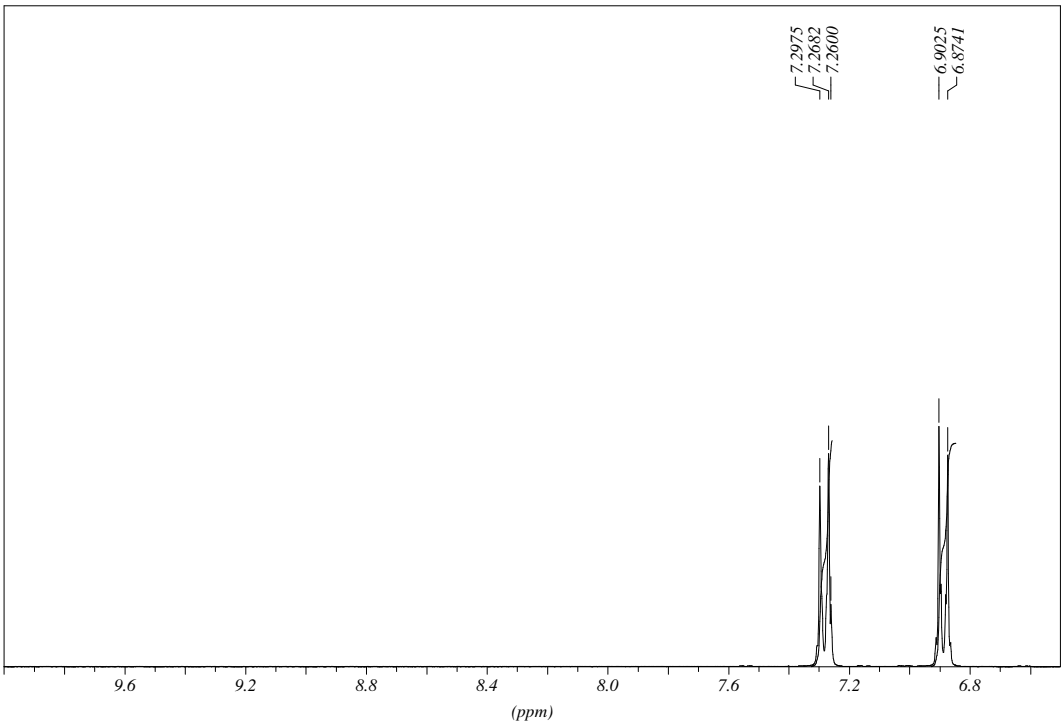


Figure B.2 ^{1}H NMR ($CDCl_3$) of the starting material 4-methoxybenzyl alcohol

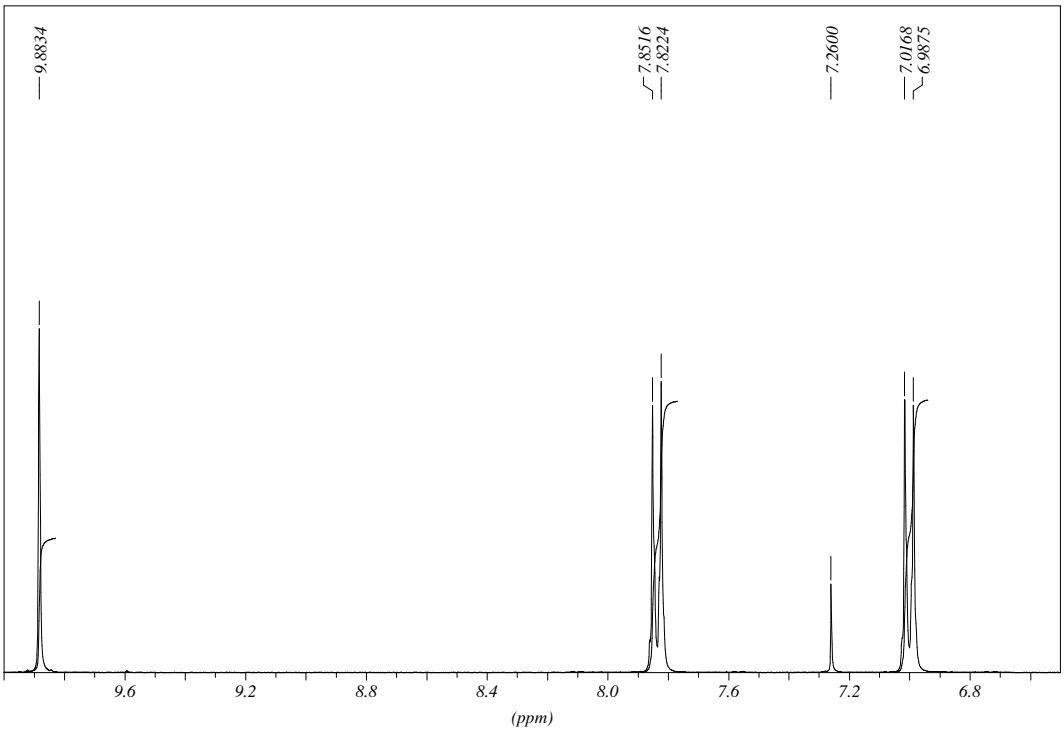


Figure B.3 ^{1}H NMR ($CDCl_3$) of the reaction product 4-methoxy benzaldehyde

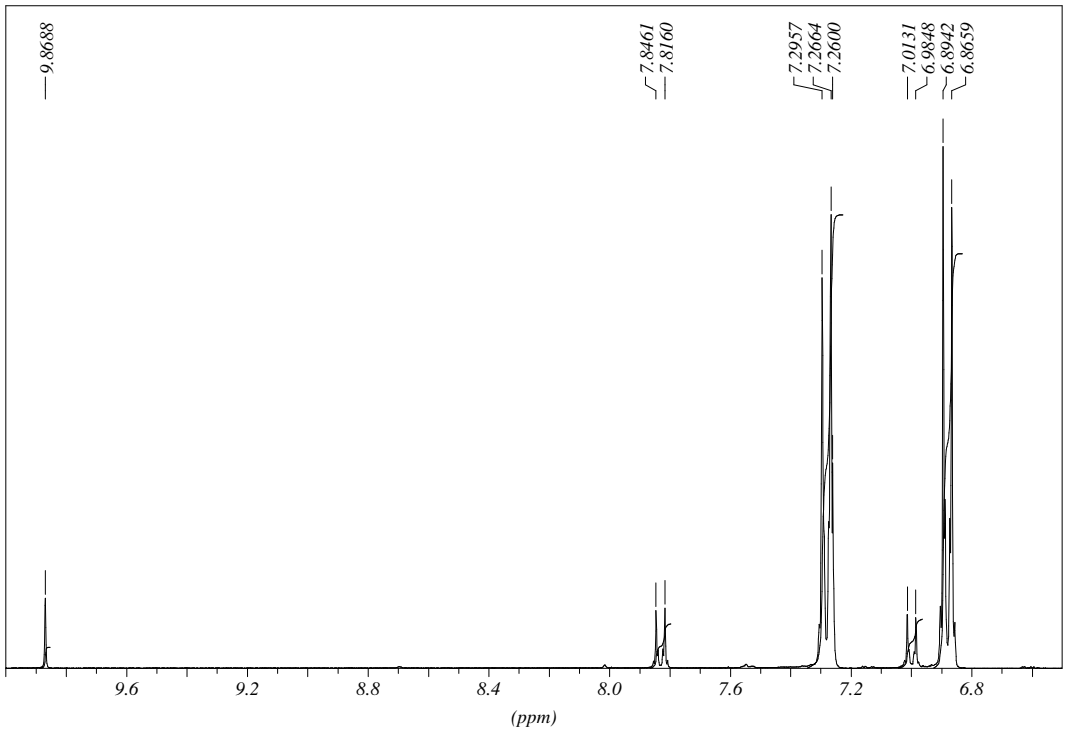


Figure B.4 ^{1}H NMR ($CDCl_3$) of the reaction mixture after 1 h

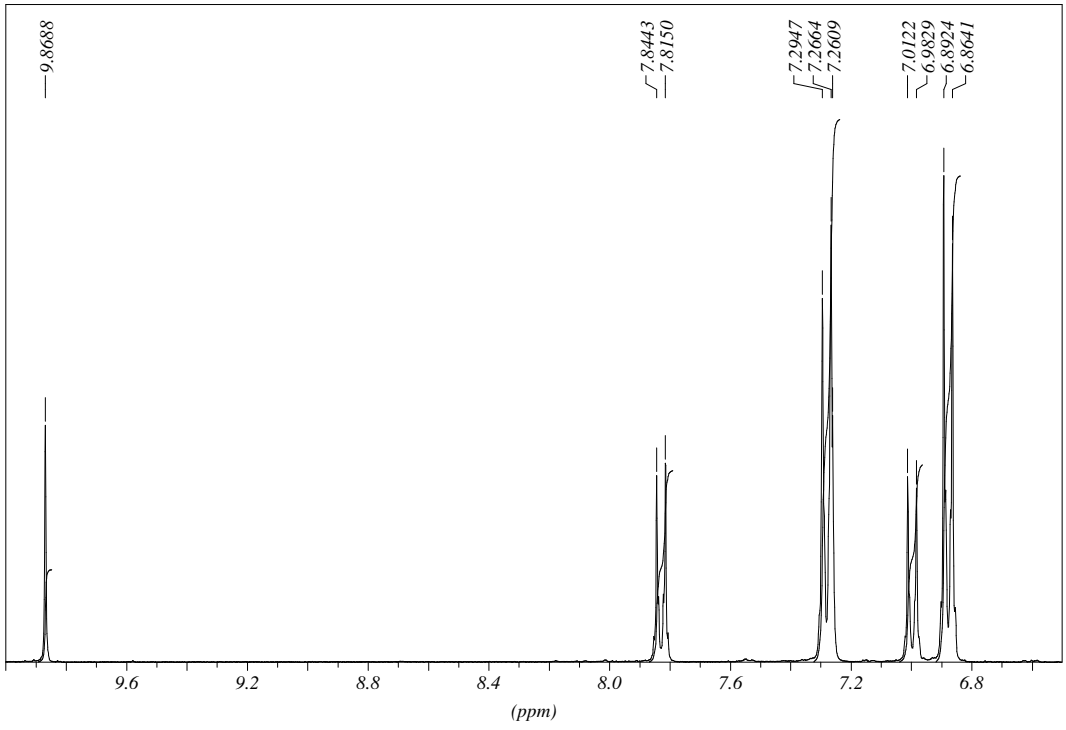


Figure B.5 ^{1}H NMR ($CDCl_3$) of the reaction mixture after 4 h

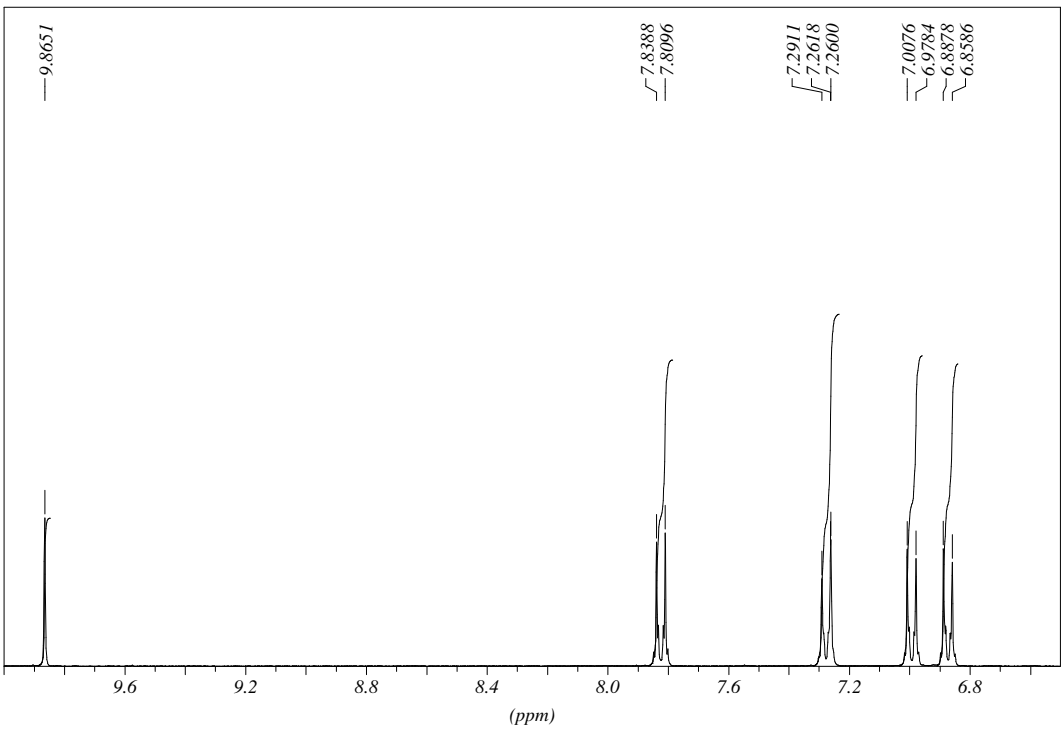
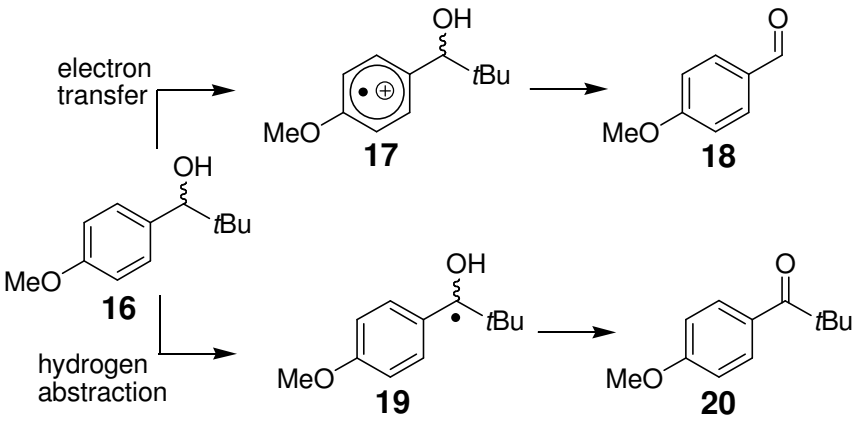


Figure B.6 ^{1}H NMR ($CDCl_3$) of the reaction mixture after 8 h

Control experiment 1: Determination of the reaction mechanism

Fukuzumi et al. proposed a mechanism of the benzyl alcohol photooxidation reaction, which was further discussed and supported.[1–4] It is well documented, that reduced flavin species are re-oxidized by oxygen giving the oxidized form of flavin and hydrogen peroxide.[2,3] We observed this reaction and detected stoichiometric amounts of hydrogen peroxide in earlier experiments.[5,6] To get an insight in the mechanism of the oxidation reaction, we used the secondary alcohol **16** as a probe.[7–10] In the case of an initial electron transfer, a cationic radical **17** is formed, which leads after abstraction of an tertiary butyl radical to aldehyde **18**. If instead the first step is a hydrogen abstraction, the formation of a neutral benzyl radical **19** finally leads to ketone **20**. In our experiments with tetraacetyl riboflavin (**10**) in aqueous homogeneous solution we obtained exclusively aldehyde **18** as the product of this reaction. This mechanism of an initial electron transfer is in accordance to earlier literature results.



Scheme B.1 Electron transfer *versus* hydrogen abstraction mechanism in the photooxidation of benzyl alcohol

Control experiment 2: Determination of catalyst leaching from the heterogeneous flavin photocatalysts

A standard reaction mixture (V=1 mL, H_2O, 4-methoxybenzyl alcohol 2×10^{-3} M, tetraacetyl riboflavin (**10**) (1% per mass on fluorinated silica gel, 10 mol%)) was stirred for 30 min without irradiation. The catalyst was filtered off and a UV/Vis spectrum of the solution was recorded. The typical absorption bands of flavin (345 nm, ε=8200 $L\times mol^{-1}\times cm^{-1}$, 440 nm, ε=12000 $L\times mol^{-1}\times cm^{-1}$) were not detectable, which indicates that the concentration of flavin leached from the heterogeneous catalyst has to be smaller that c = 1×10^{-7} M.

To achieve photoconversions, an estimated minimal concentration of 4×10^{-6} M flavin in solution is necessary, which would lead to a clearly detectable UV/Vis absorption larger than 0.05.

Control experiment 3: Proof of the immobilized flavin as the active catalyst

To proof that the immobilized flavins are the only catalytic active species, the catalyst was removed from the reaction mixture after 30 min of irradiation. The aldehyde yield was 72% after this reaction time. The catalyst was filtered off and the solution was again irradiated and stirred for another 30 min. The ^{1}H NMR measurement indicated no significant further conversion within the error of the analytic detection (aldehyde yield 74%). The small additional amount of aldehyde product originates from the slow non-catalyzed background oxidation. The experiment confirms that the catalyzed photooxidation reaction terminates immediately after removing the immobilized catalyst. Therefore it must be the catalytically active species.

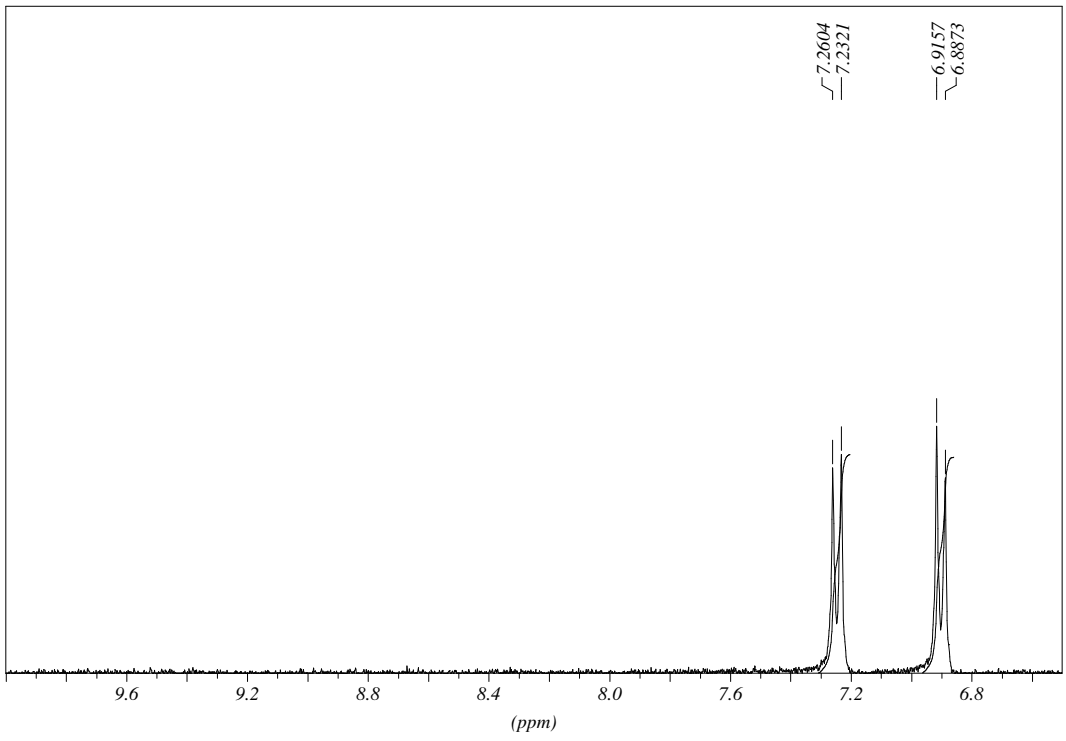


Figure B.7 ^{1}H NMR (D_2O) of the reaction mixture before irradiation

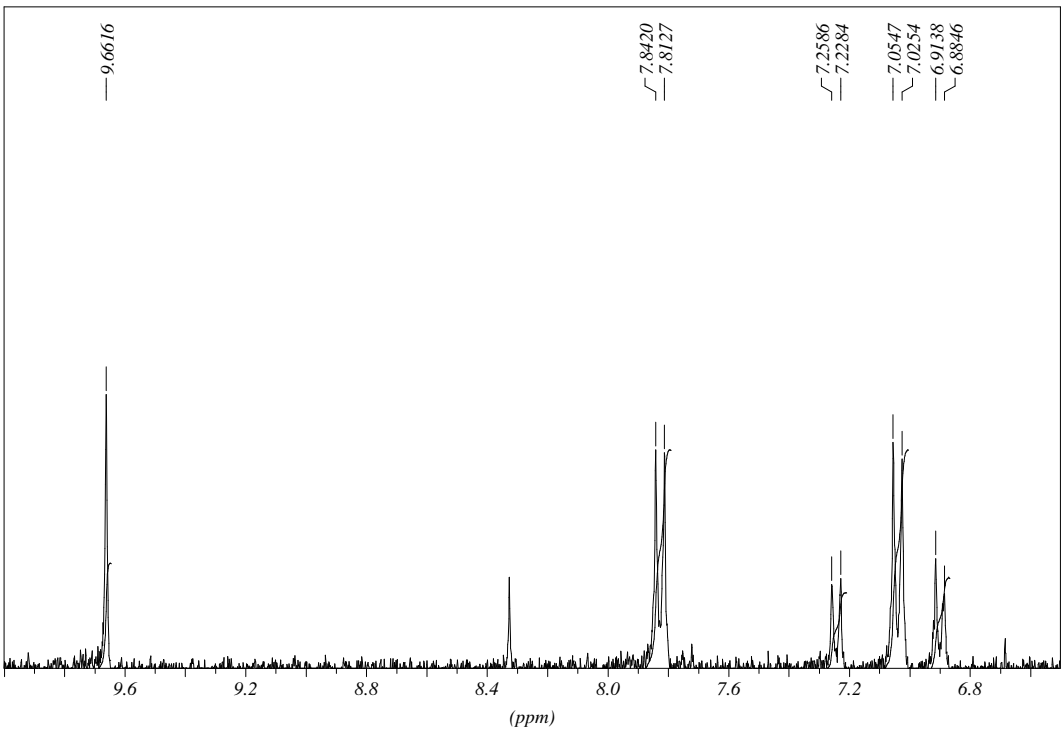


Figure B.8 ^{1}H NMR (D_2O) of the reaction mixture after irradiation in the presence of the photocatalyst for 30 min

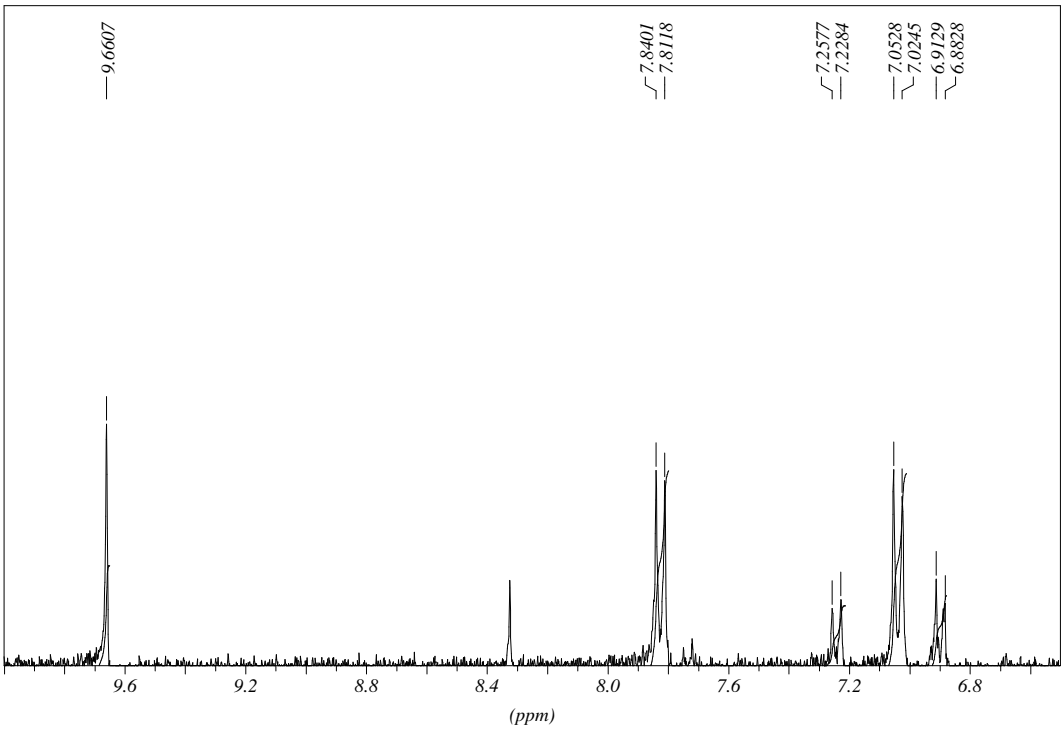


Figure B.9 ^{1}H NMR (D_2O) of the filtered solution after additional irradiation for 30 min

Control experiment 4: Hydrogen peroxide does not oxidize 4-methoxybenzyl alcohol

10 Equivalents of hydrogen peroxide were added to a solution of 4-methoxybenzyl alcohol (2×10^{-3} M) in D_2O. After one hour of stirring, no aldehyde was detectable in this solution. Like in MeCN solutions,[6] hydrogen peroxide is not able to oxidize the alcohol under the experimental conditions. This proves that the benzyl alcohol oxidation originates from the photooxidation by immobilized flavins as catalysts and not from hydrogen peroxide.

^{1}H NMR of a standard reaction with immobilized flavin

In the ^{1}H NMR spectrum of a standard reaction setup (chapter 3, table 2, entry 4) with an immobilized flavin in D_2O the alcohol and aldehyde signals are detected exclusively, indicating that no other species are formed.

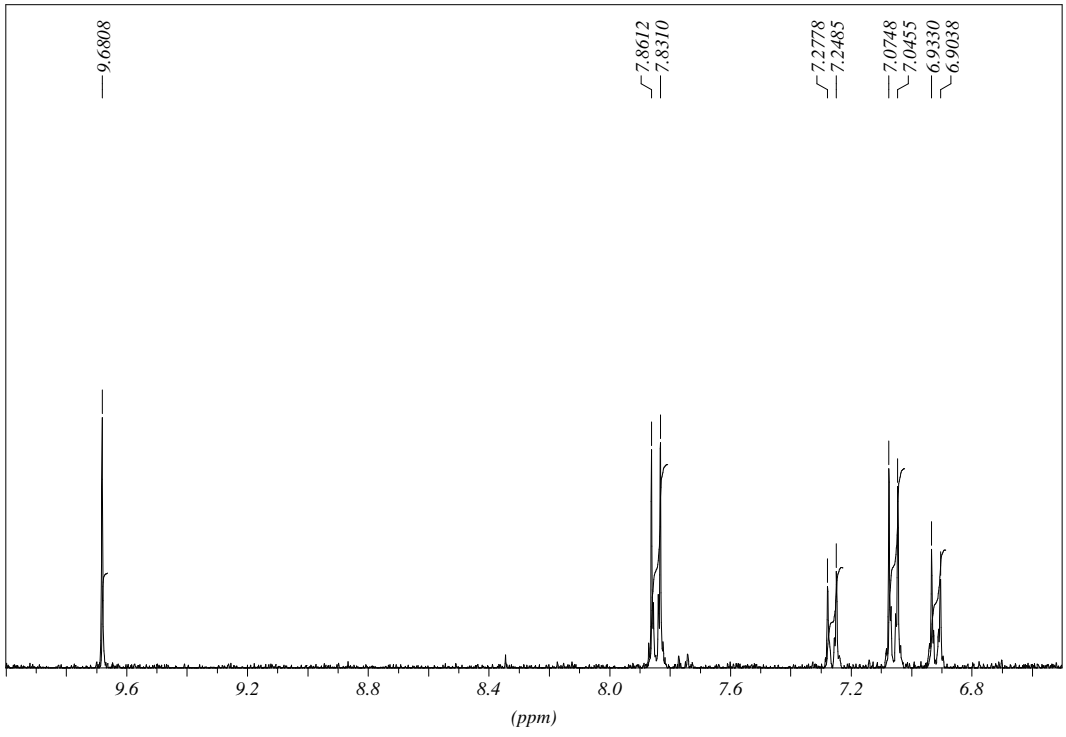


Figure B.10 ^{1}H NMR (D_2O) of the reaction mixture (chapter 3, table 3.2, entry 4) after irradiation

Recycling experiment with immobilized flavin

Tetraacetyl riboflavin (**10**) as immobilized catalyst (55 mg, 10 mol% 1% per mass on fluorinated silica gel) and a stirring bar were placed in a 10 mL-syringe with a filter. Oxygen saturated water (5 mL) was added before every catalytic run and the mixture was stirred for 5 min to completely oxidize the catalyst. The water was removed and the substrate solution (4-methoxybenzyl alcohol, 2×10^{-3} M in H_2O, 5 mL) was sucked into the syringe. In each run, the reaction mixture was stirred and irradiated (LED, 440 nm, 5 W) for 15 min. The solution was pressed out of the syringe. After washing with water two times, the syringe containing the immobilized catalyst was used for the next experiment. The organic compounds were extracted from the aqueous phase with DCM. The organic phase was separated, dried (magnesium sulphate) and the solvent was evaporated. The conversion of each run was determined by ^{1}H NMR measurements. The results show that the activity of the immobilized catalyst remains unchanged for three experiments with high TOFs of 10 h^{-1}. However, after three cycles the catalysts activity drops by 30%.

Conversions of alcohol to aldehyde [%] for each run: 1: 22% – 2: 25% – 3: 24% – 4: 15% – 5: 8%

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Appendix C

Supporting Information to Chapter 4 – Synthesis of Rigidified Flavin–Guanidinium Ion Conjugates and Investigation of Their Photocatalytic Properties

The numbering of the molecules in this appendix refers to chapter 4

Contents

Oxidative photocleavage of dibenzyl phosphate

The photocleavage of dibenzyl phosphate was tested in small glass vials with deuterated solvents (1 mL, MeCN-d_3 or D_2O), containing the phosphate starting material (10×10^{-3} M) and flavin catalyst (2×10^{-3} M, 20 mol%). The mixture was stirred and irradiated by a LED (440 nm, 5 W) at 40 °C for 2 h (D_2O) or 4 h (MeCN-d_3), respectively. The products were identified by ^{1}H NMR and mass spectrometry and the conversion was determined by integration of the aromatic protons in the ^{1}H NMR.

Photoreduction of 4-nitrophenyl phosphate

The photocleavage of dibenzyl phosphate was tested in small glass vials in MeCN or water (5 mL), containing the 4-nitrophenyl phosphate starting material (10×10^{-3} M), triethanol amine as sacrificial electron donor (100×10^{-3} M, 10 equivalents), and flavin catalyst (1×10^{-3} M, 10 mol%). The solution was degassed by three consecutive pump and freeze circles and afterwards, the solution was stirred and irradiated by a LED (440 nm, 5 W) and a UV-lamp (370 nm) at 40 °C for 4 h. Reaction mixtures in MeCN were evaporated and dried. The mixtures of the experiments in water were lyophilized. 4-aminophenyl phosphate and 4-amino phenol as by-product were identified by ^{1}H NMR and mass spectrometry, respectively. The conversion was determined by integration of the aromatic protons in the ^{1}H NMR.

Photo Diels-Alder-reaction of anthracene with N-methyl-maleinimide

Photoinduced Diels-Alder-reactions were carried out in small glass vials in dry toluene (1.2 mL), containing anthracene (33×10^{-3} M), methyl maleinimide (83×10^{-3} M, 2.5 equivalents), and flavin catalyst (0.67×10^{-3} M, 2 mol%). The mixture was stirred and irradiated by a LED (440 nm, 5 W) at 40 °C for 8 h. Afterwards, the solvent was evaporated and the mixture was dried. The products were identified by ^{1}H NMR and mass spectrometry and the conversion was determined by integration of the aromatic protons in the ^{1}H NMR.

Calculated gas phase conformations

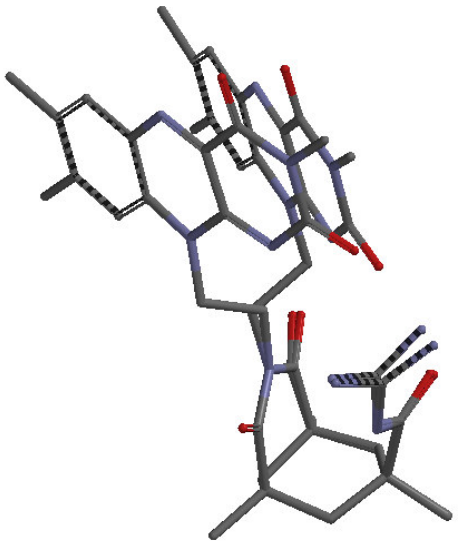
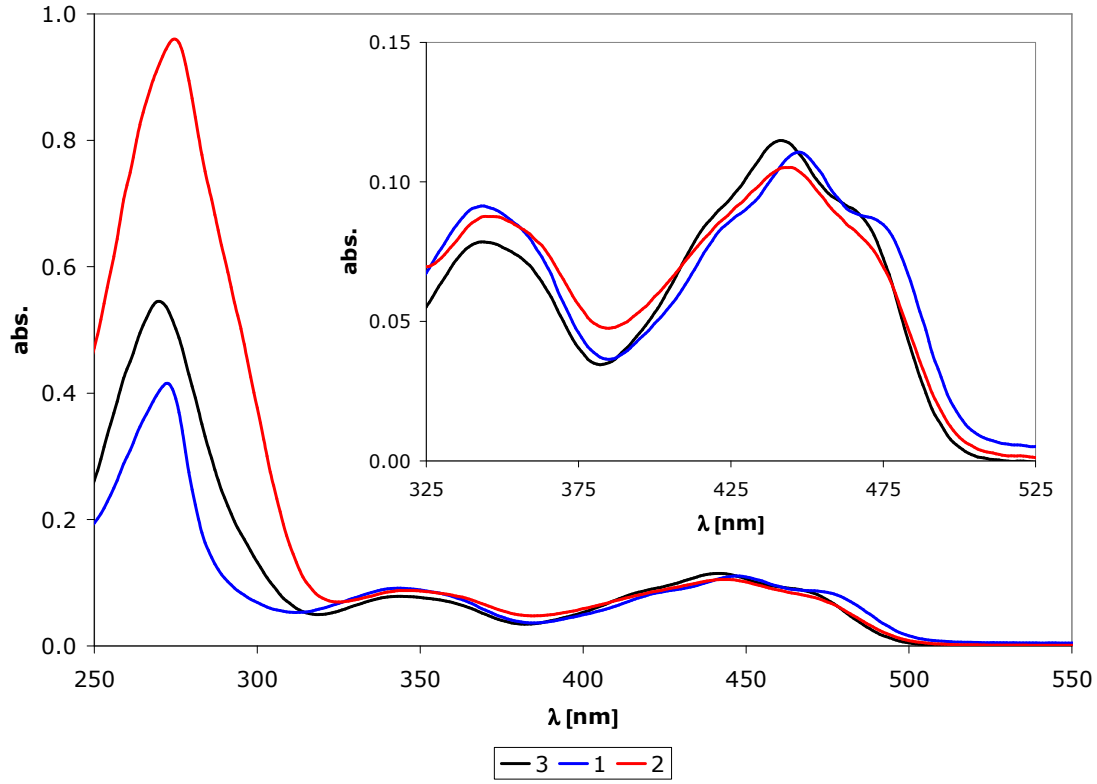


Figure S.1 Calculated conformations of **1** in the gas phase (AM1, Spartan program package).

Figure S.1 shows the two lowest energy conformations of compound **1** in the gas phase (semi-empirical AM1, Spartan program package, difference: 13.5 kJ/mol). It is possible to transform the structures into each other by rotation of the C-C single bonds of the ethane linker that are expected to rotate freely in solution.

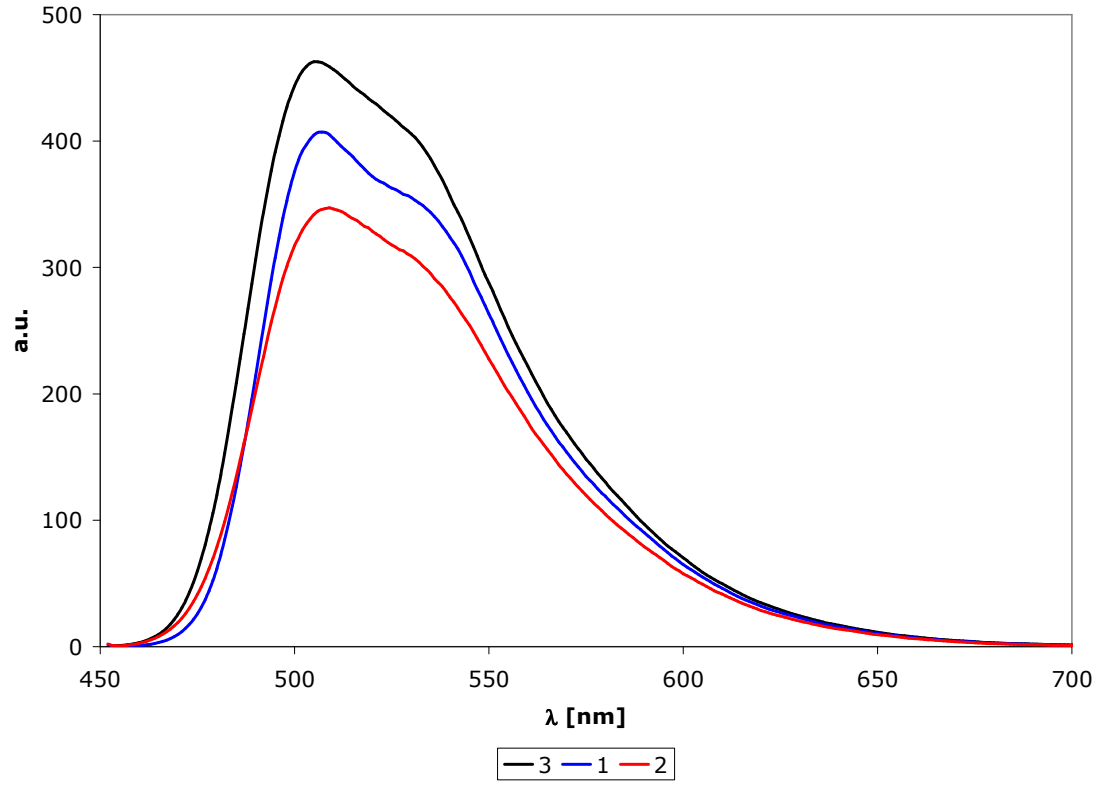
UV/Vis spectra of 1, 2 and 3

(MeCN + 1% DMSO, 1×10^{-5} M)

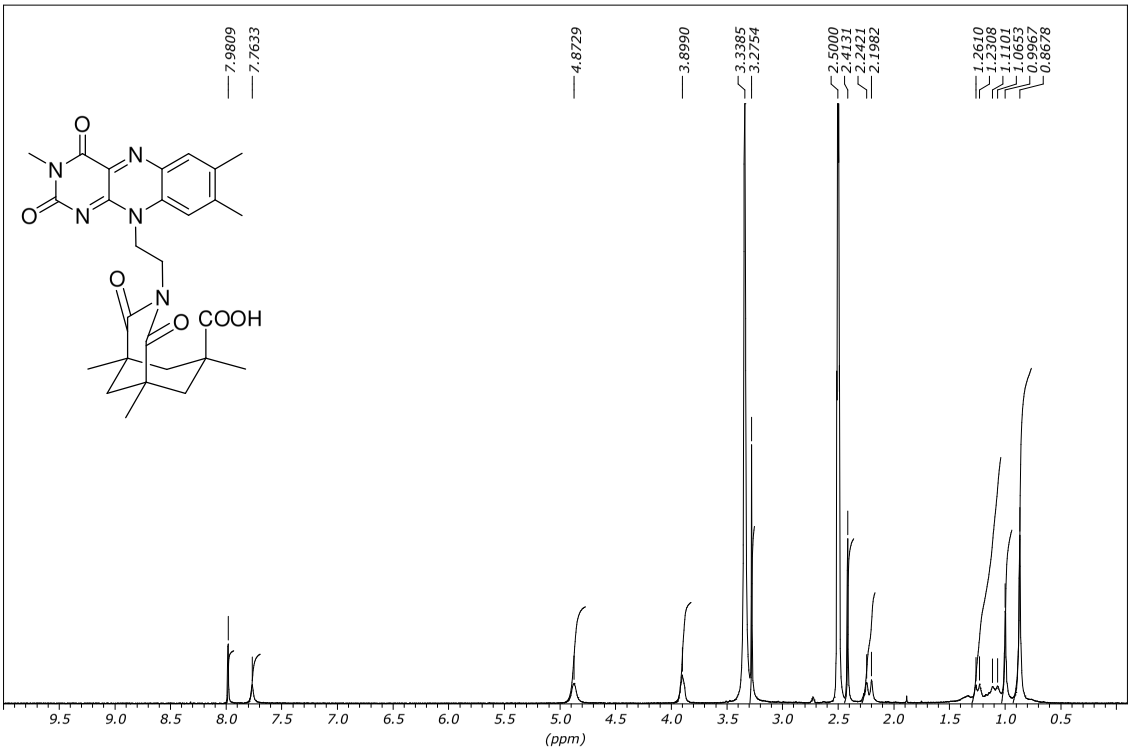


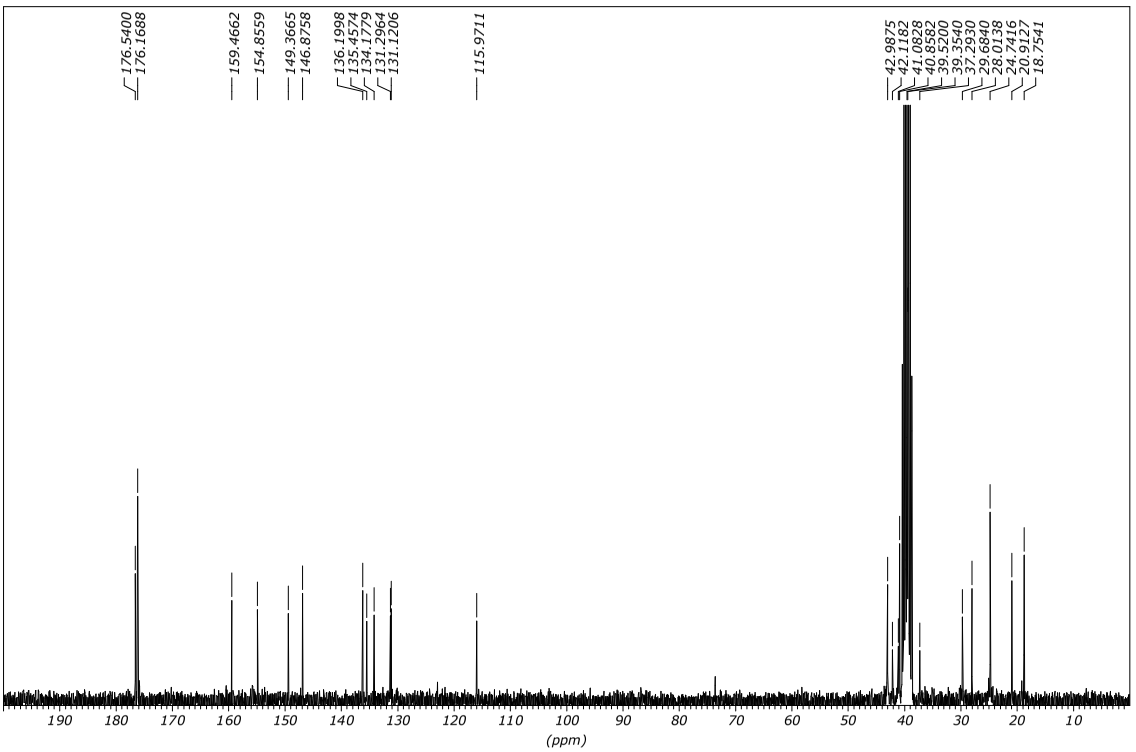
Fluorescence spectra of 1, 2 and 3

(MeCN + 1% DMSO, 1×10^{-5} M, excitation at 445 nm (**1**+**2**) and 440 nm (**3**))

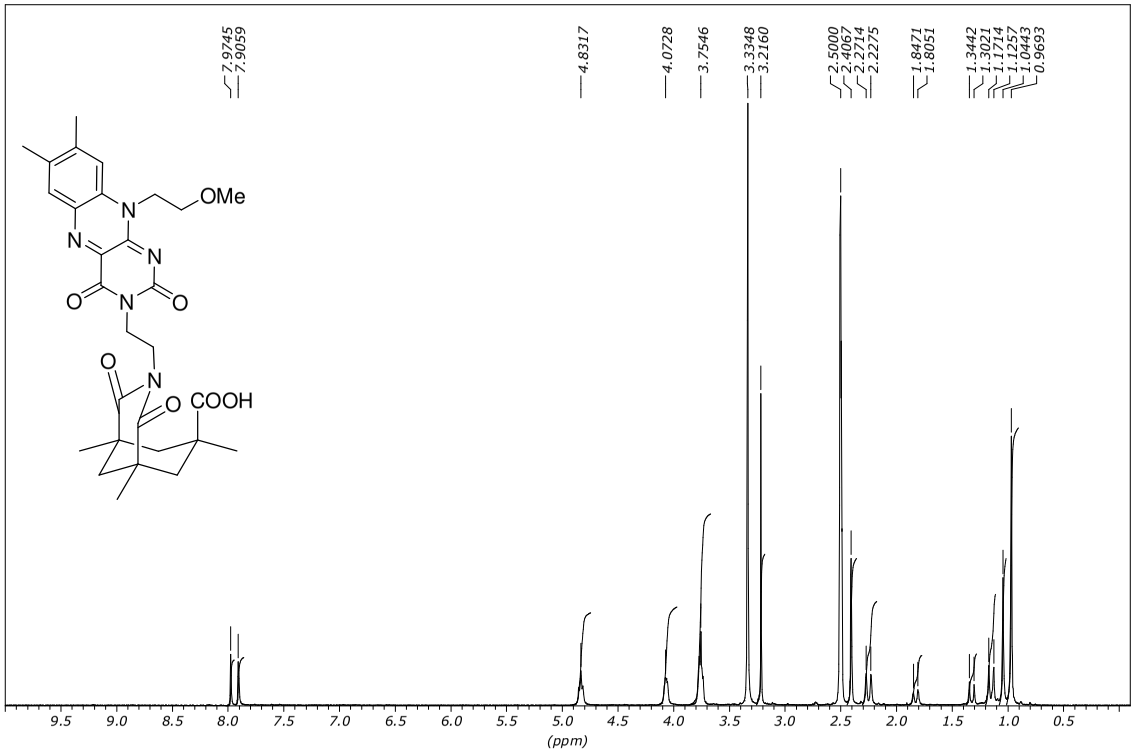


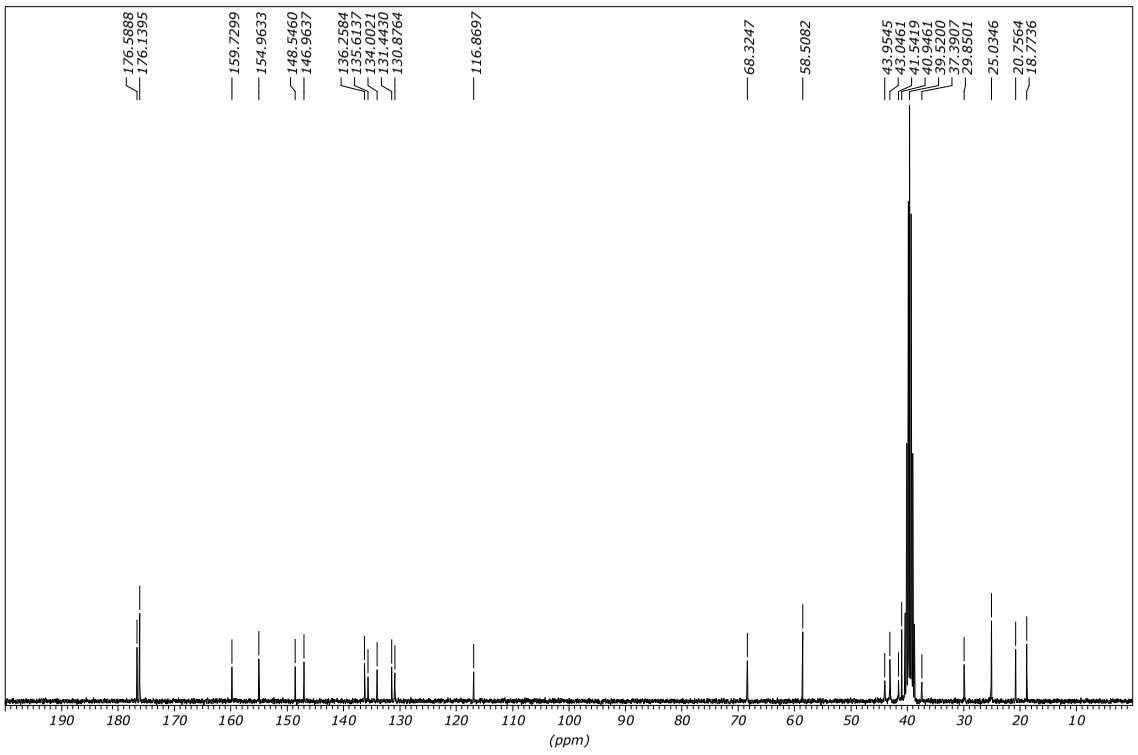
^{1}H NMR spectrum (300 MHz, DMSO-d_6) (top) and ^{13}C NMR (75 MHz, DMSO-d_6) of compound **6**



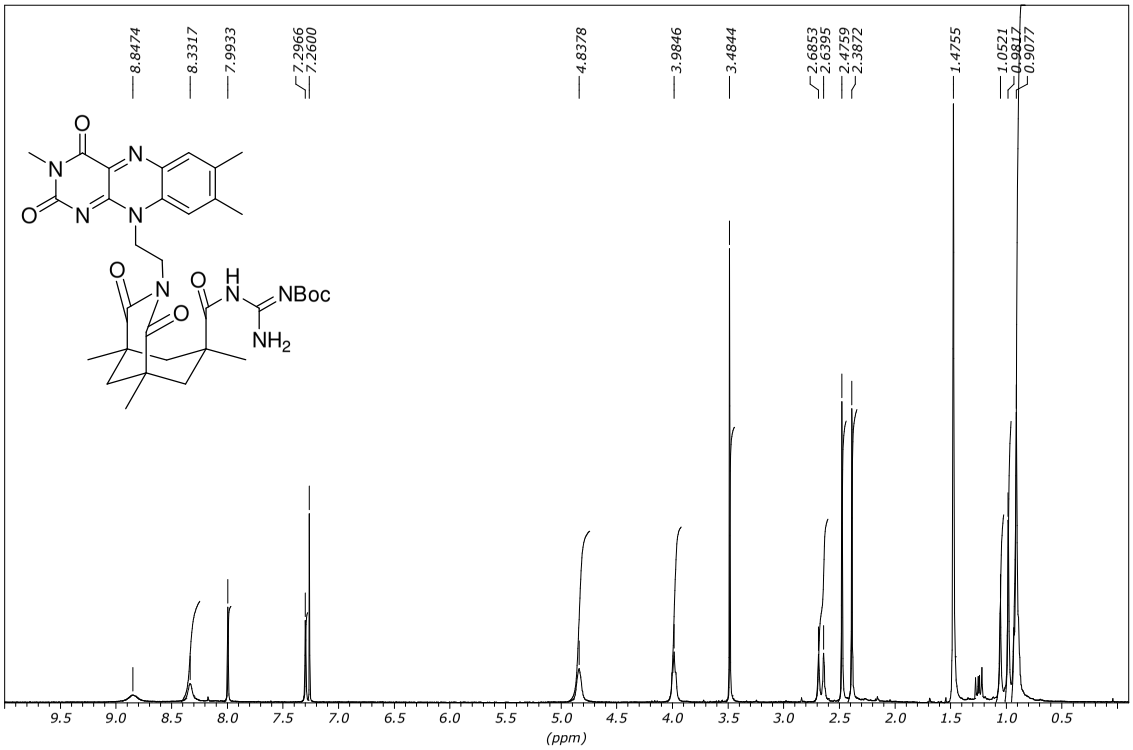


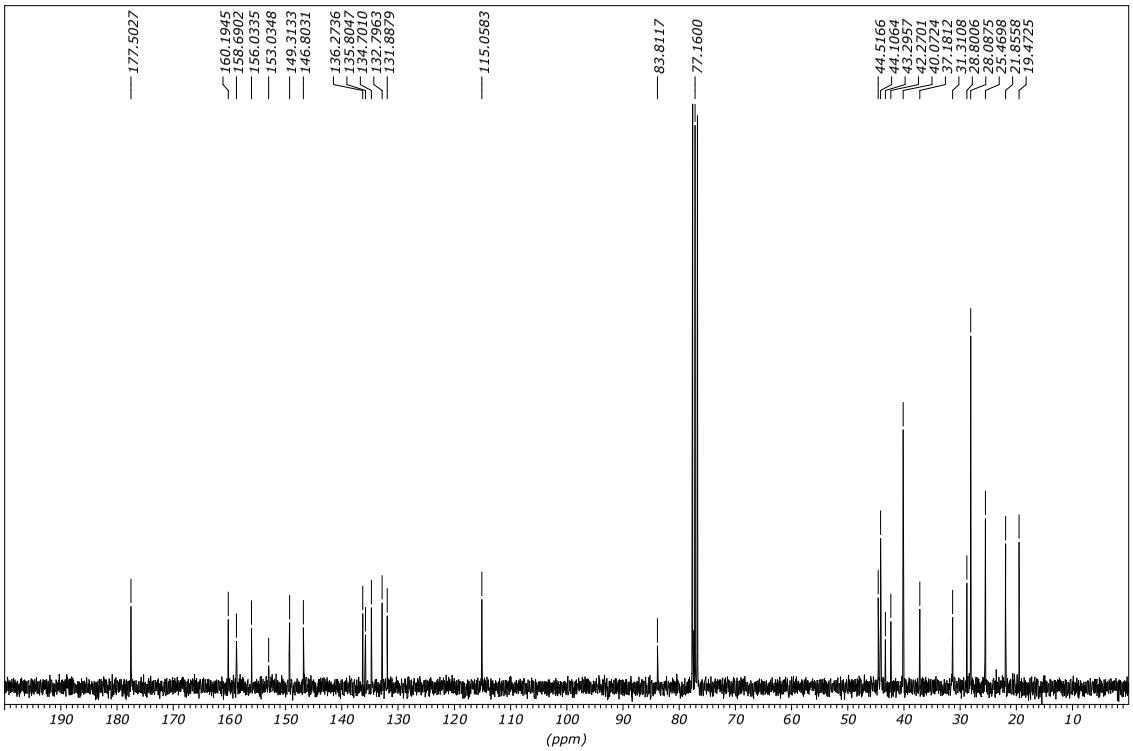
^{1}H NMR spectrum (300 MHz, DMSO-d_6) (top) and ^{13}C NMR (75 MHz, DMSO-d_6) of compound **9**



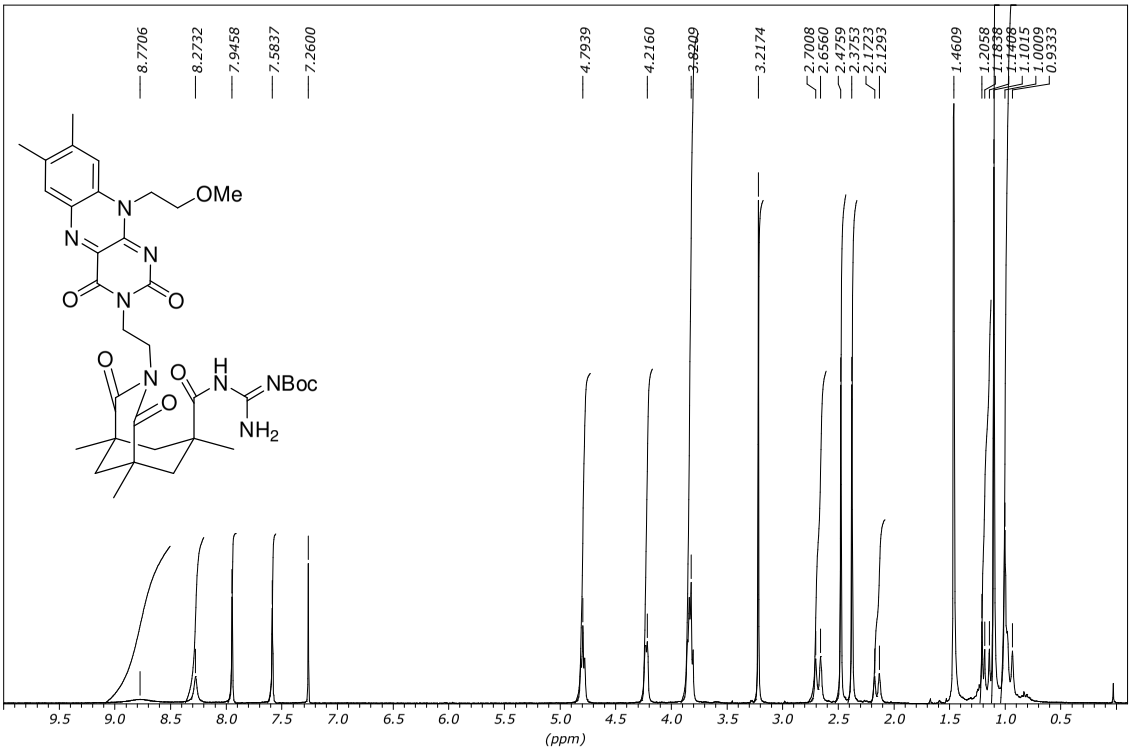


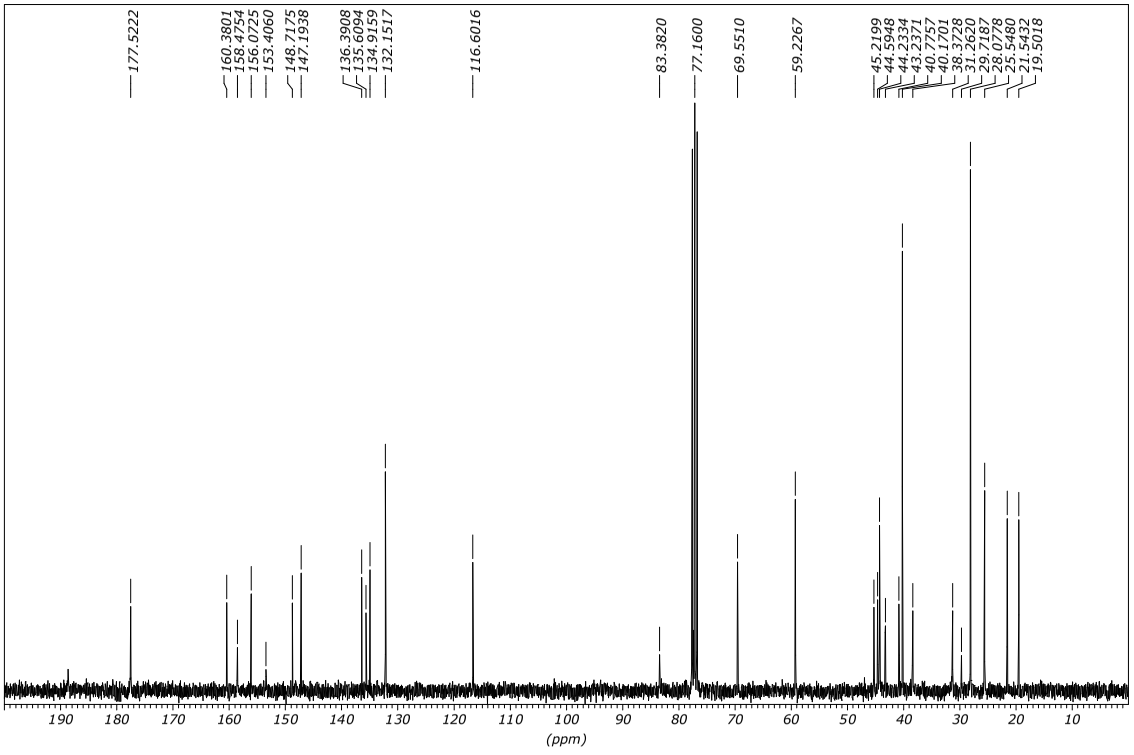
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of compound **7**



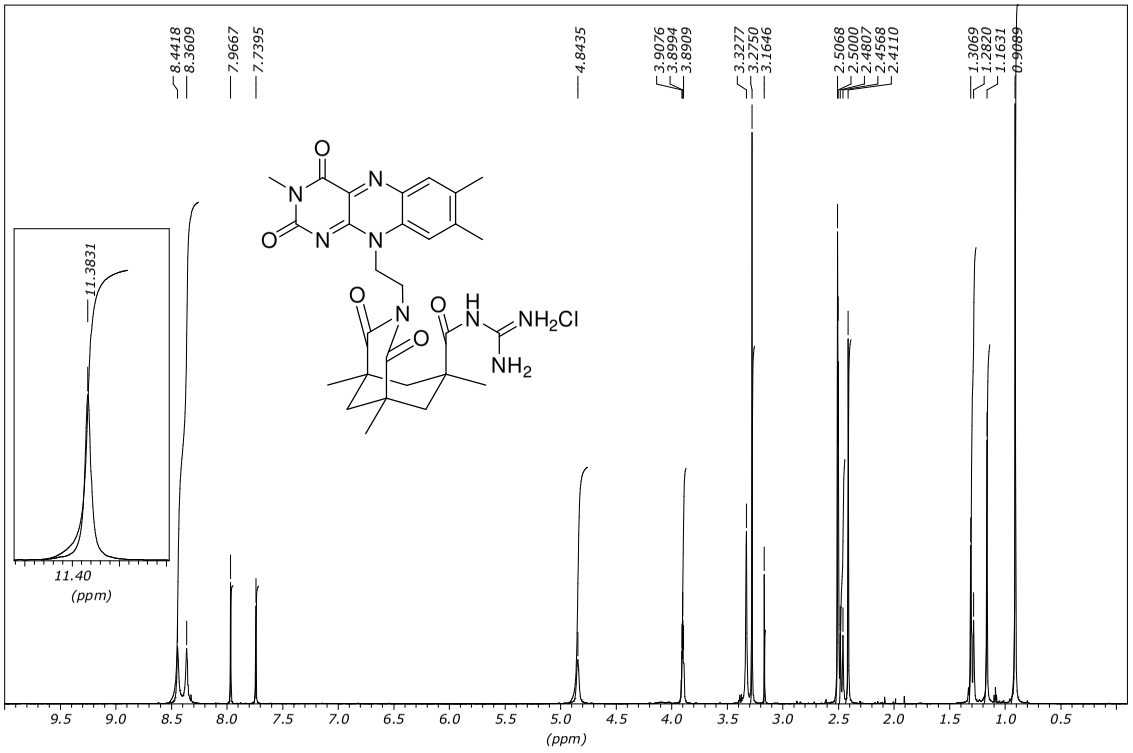


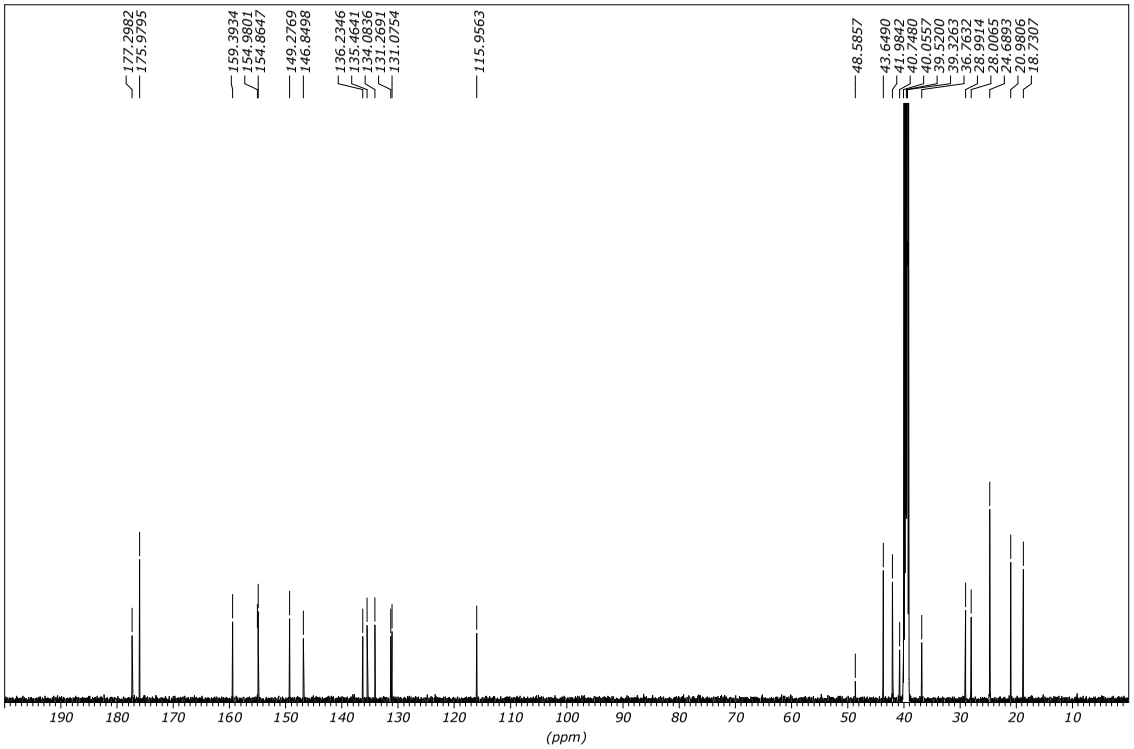
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of compound **10**



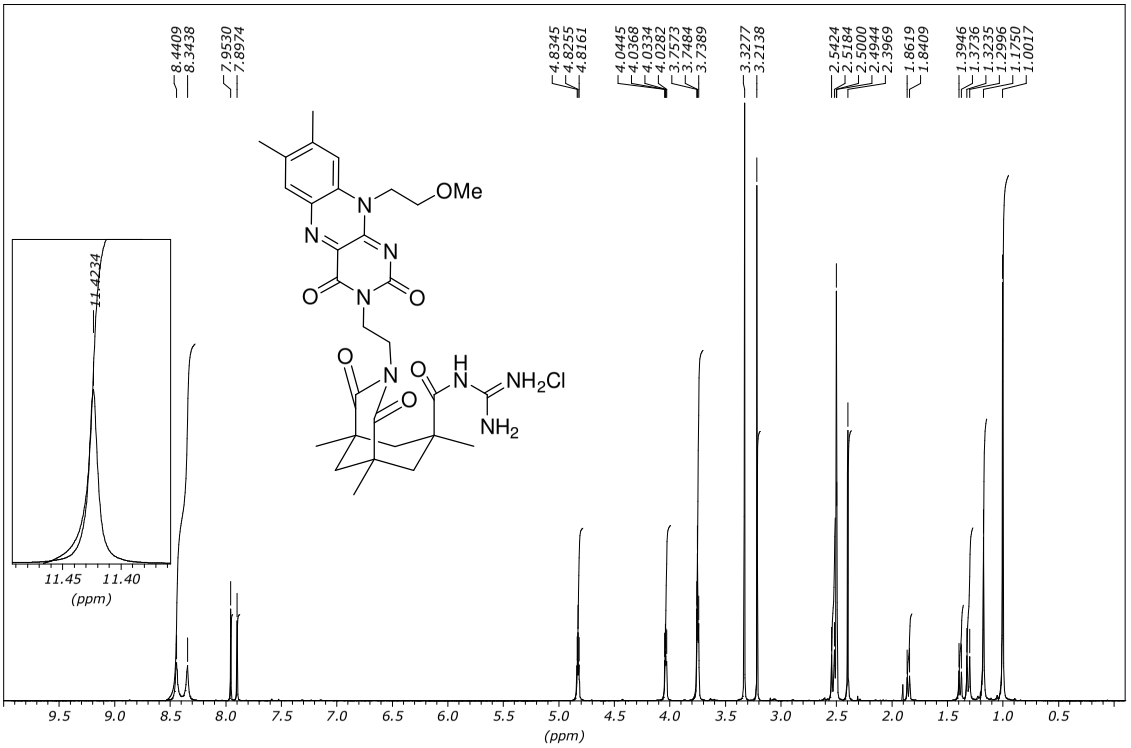


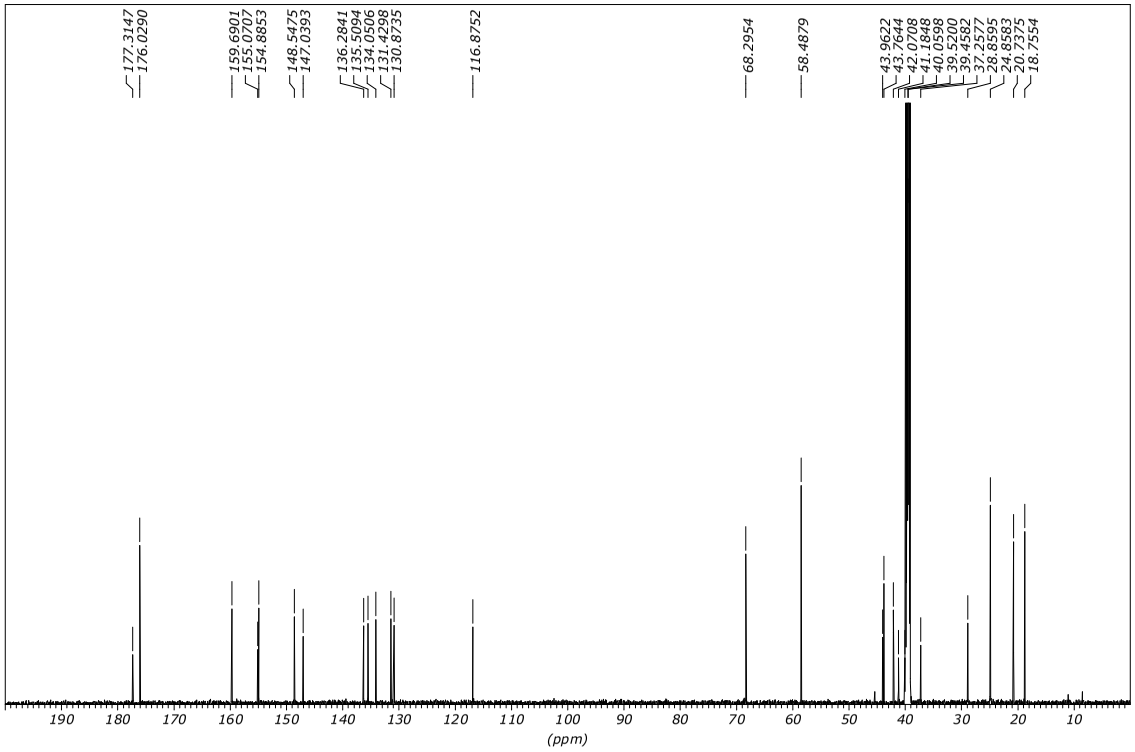
^{1}H NMR spectrum (600 MHz, DMSO-d_6) (top) and ^{13}C NMR (150 MHz, DMSO-d_6) of compound **1**





^{1}H NMR spectrum (600 MHz, DMSO-d_6) (top) and ^{13}C NMR (150 MHz, DMSO-d_6) of compound **2**





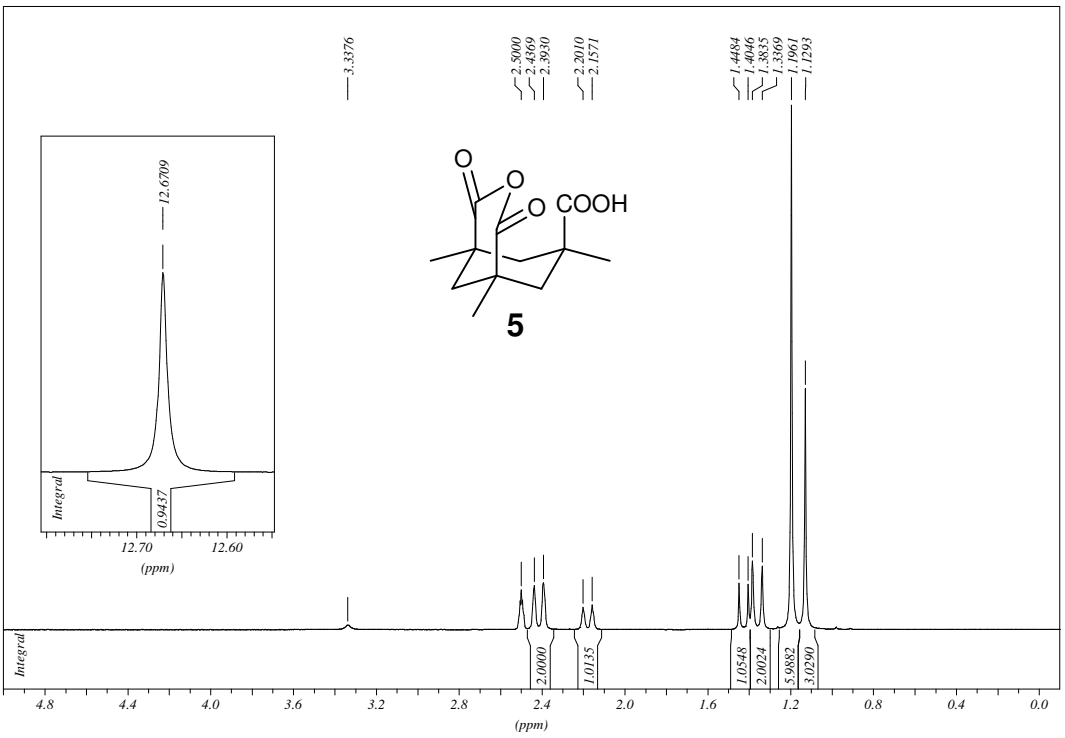
Appendix D

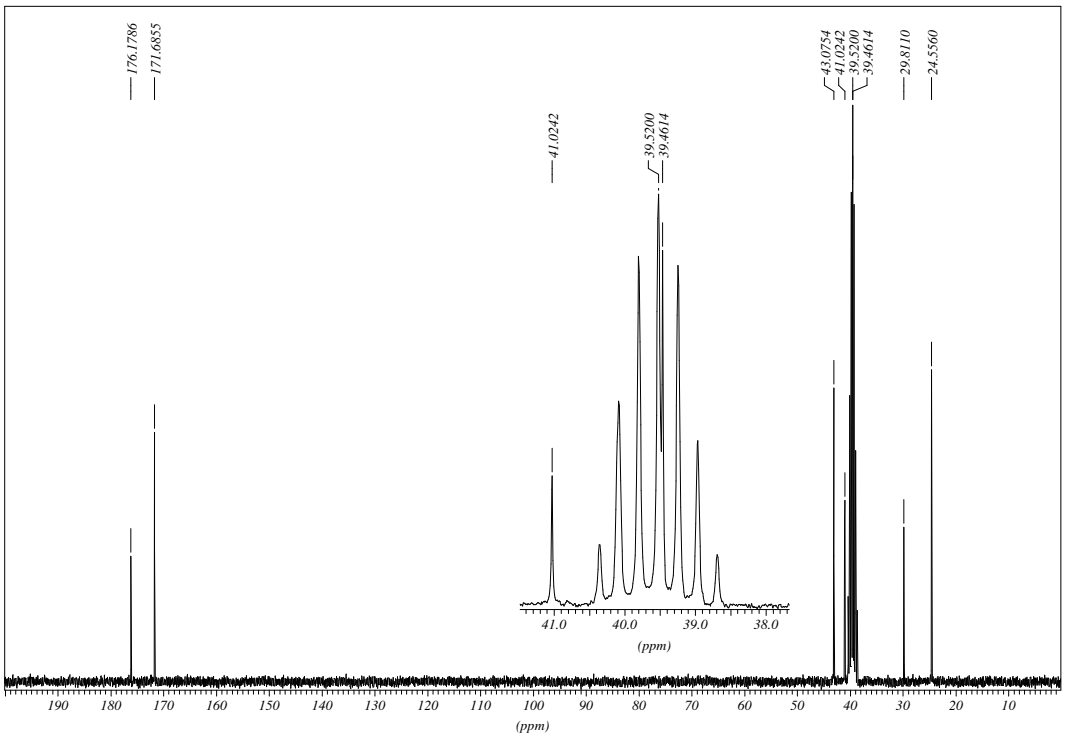
Supporting Information to Chapter 5 – Synthesis of a Bicyclic Diamine Derived from Kemp´s Acid

The numbering of the molecules in this appendix refers to chapter 5

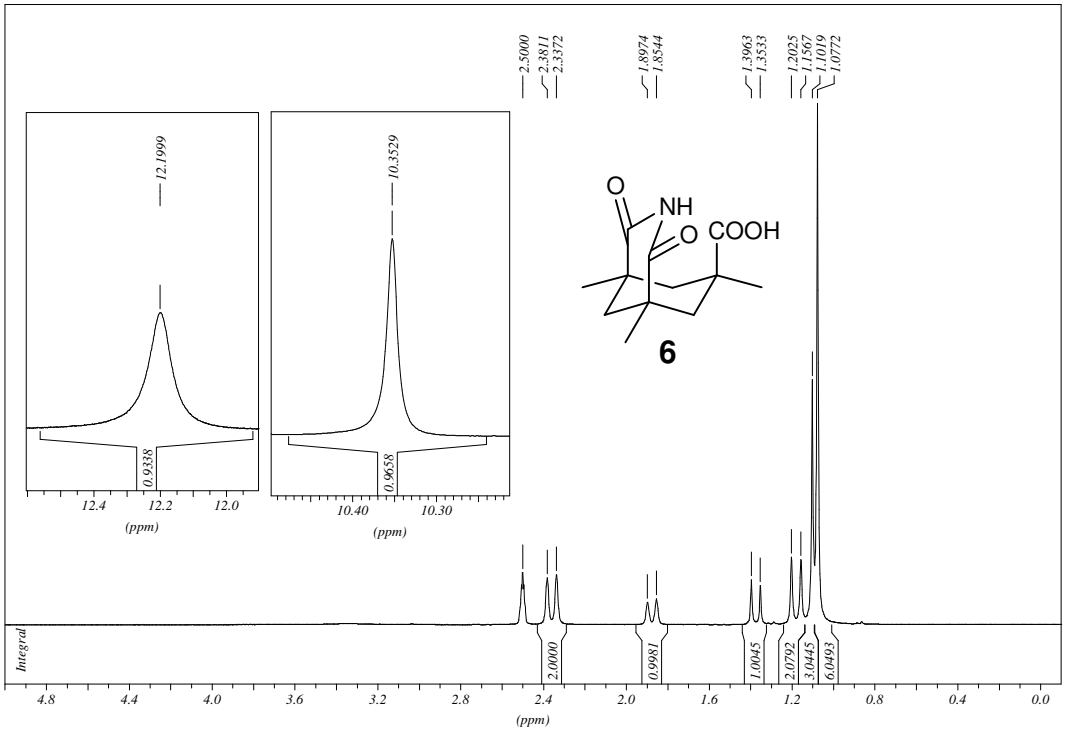
Contents

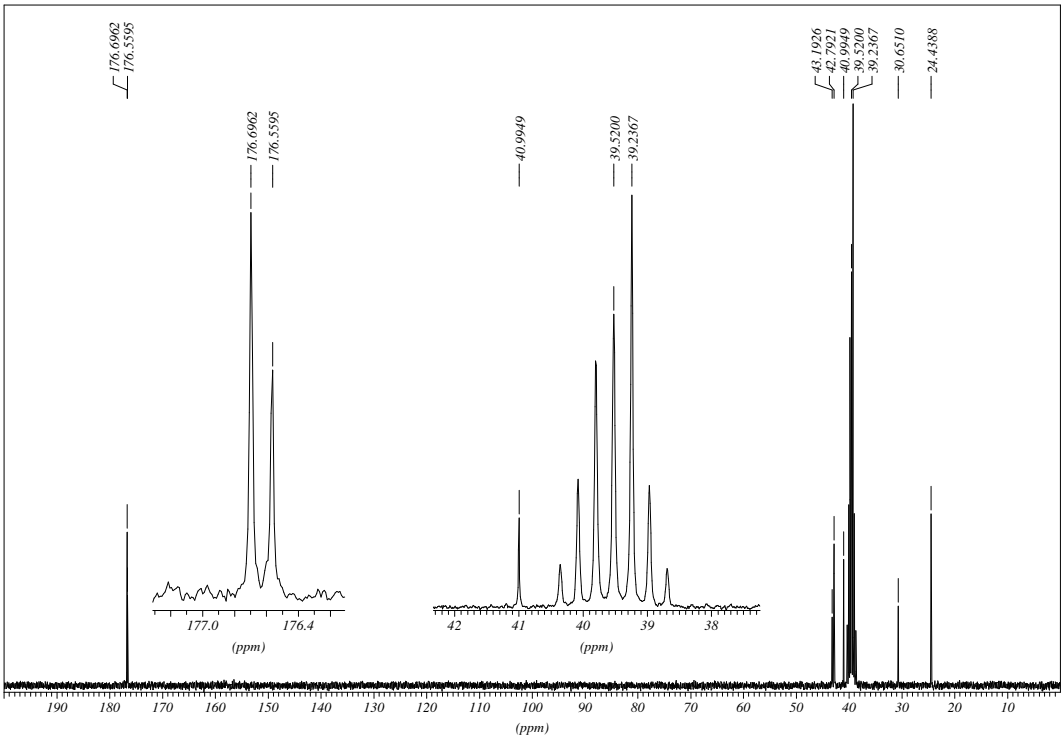
^{1}H NMR spectrum (300 MHz, DMSO-d_6) (top) and ^{13}C NMR (75 MHz, DMSO-d_6) of anhydride **5**



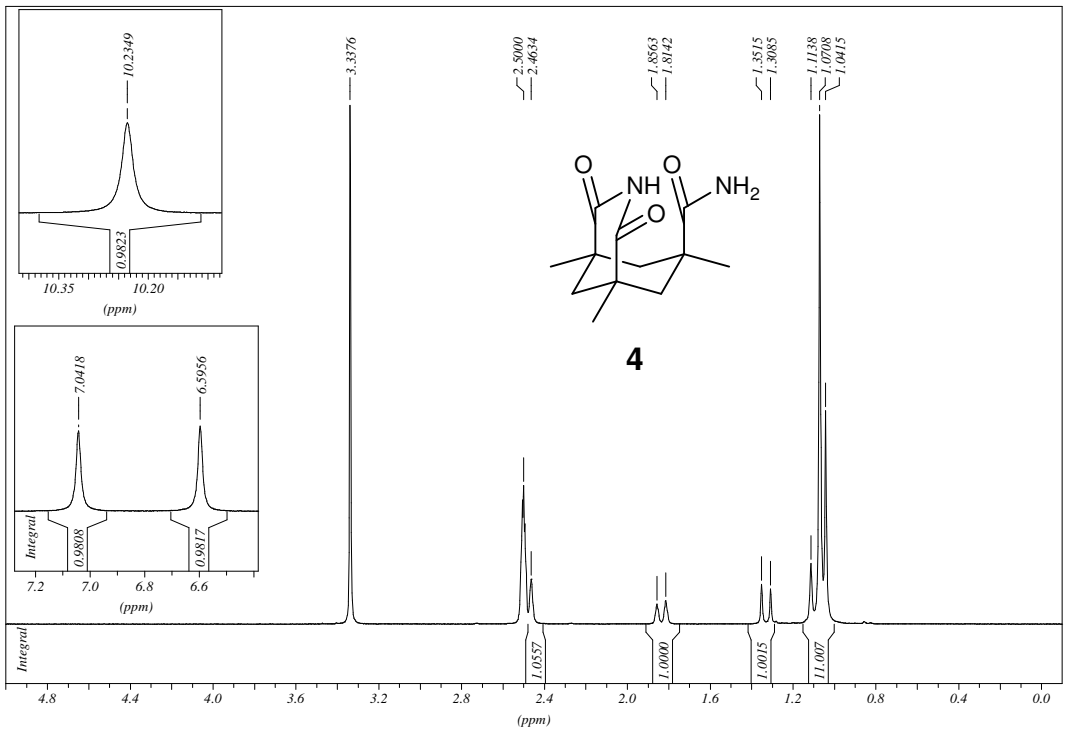


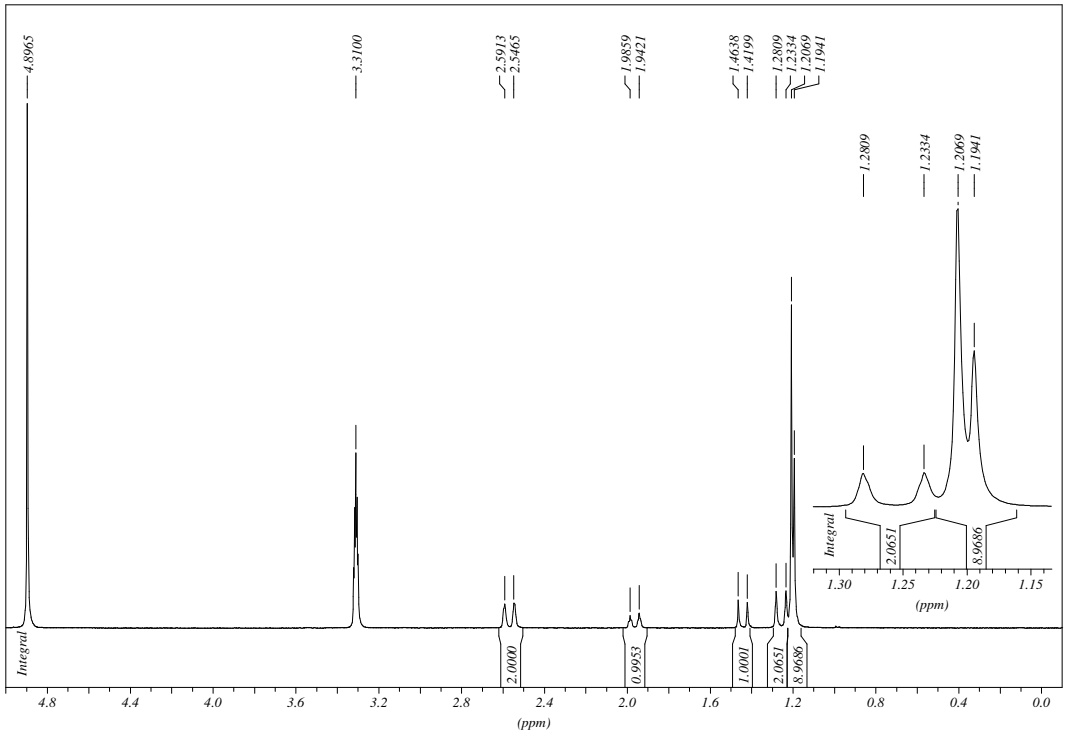
^{1}H NMR spectrum (300 MHz, DMSO-d_6) (top) and ^{13}C NMR (75 MHz, DMSO-d_6) of imide acid **6**



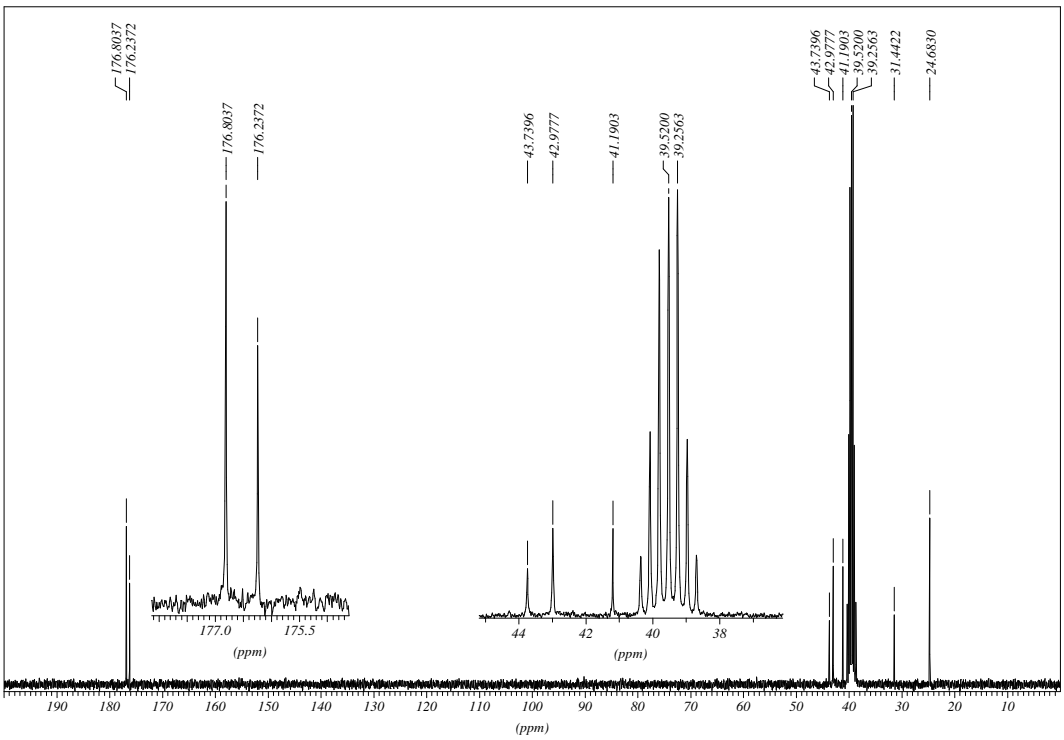


^{1}H NMR spectrum (300 MHz, DMSO-d_6) (top) and (300 MHz, MeOH-d_4) of imide amide **4**

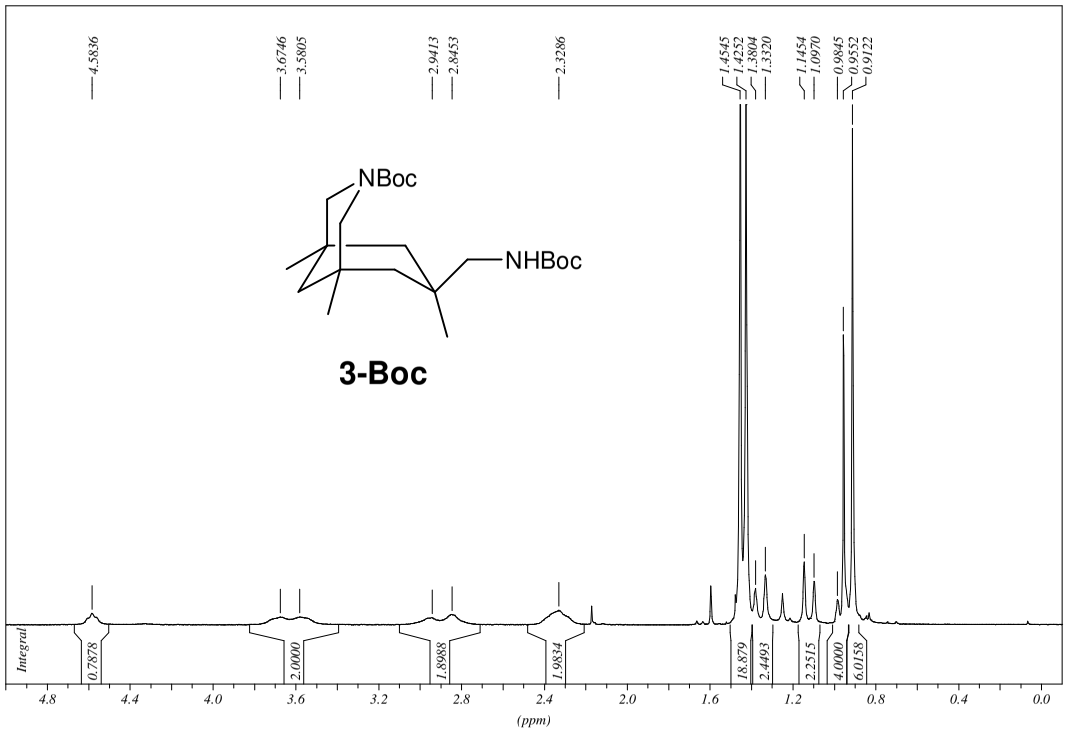


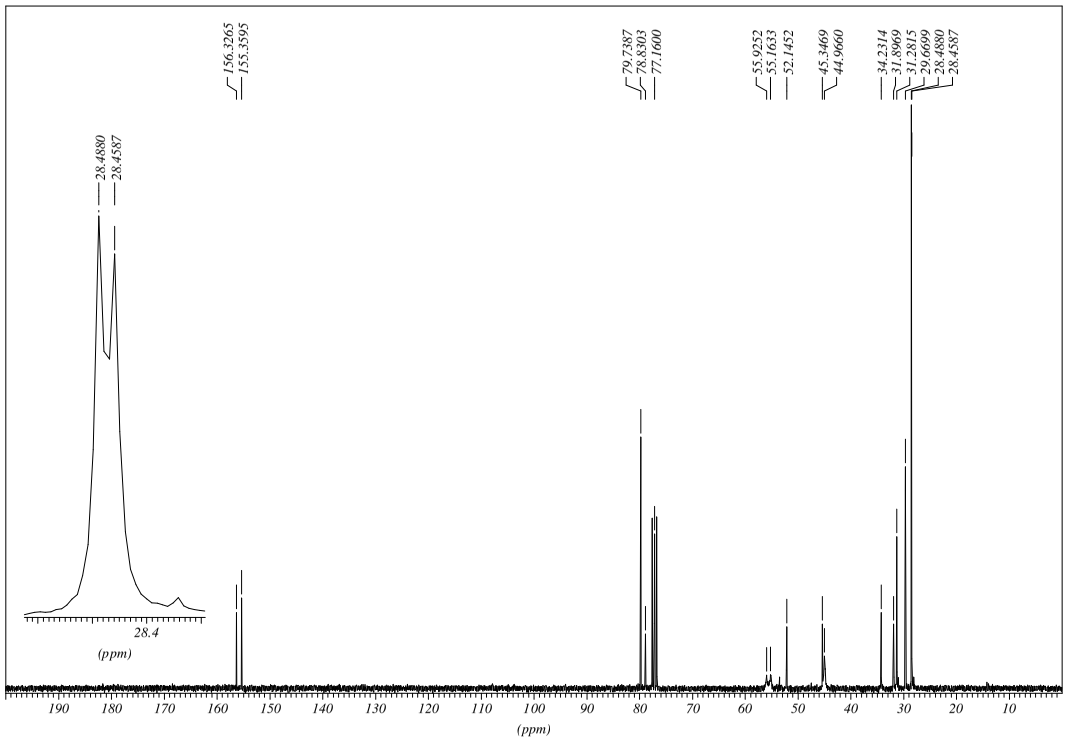


^{13}C NMR (75 MHz, DMSO-d_6) of imide amide **4**

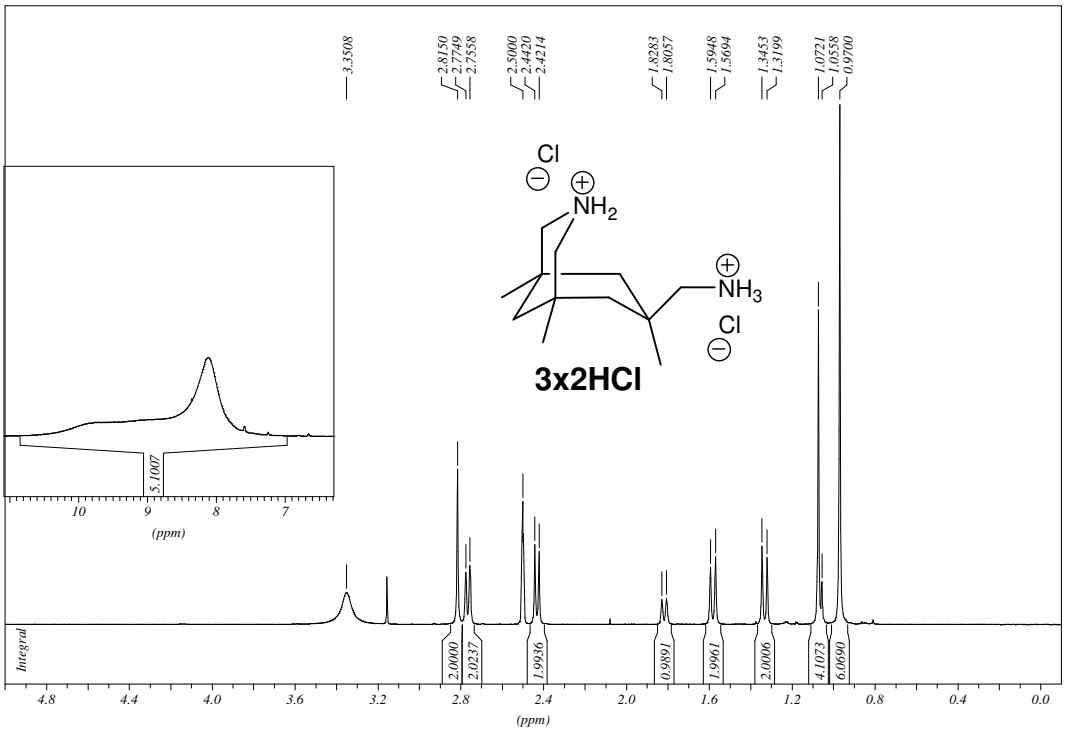


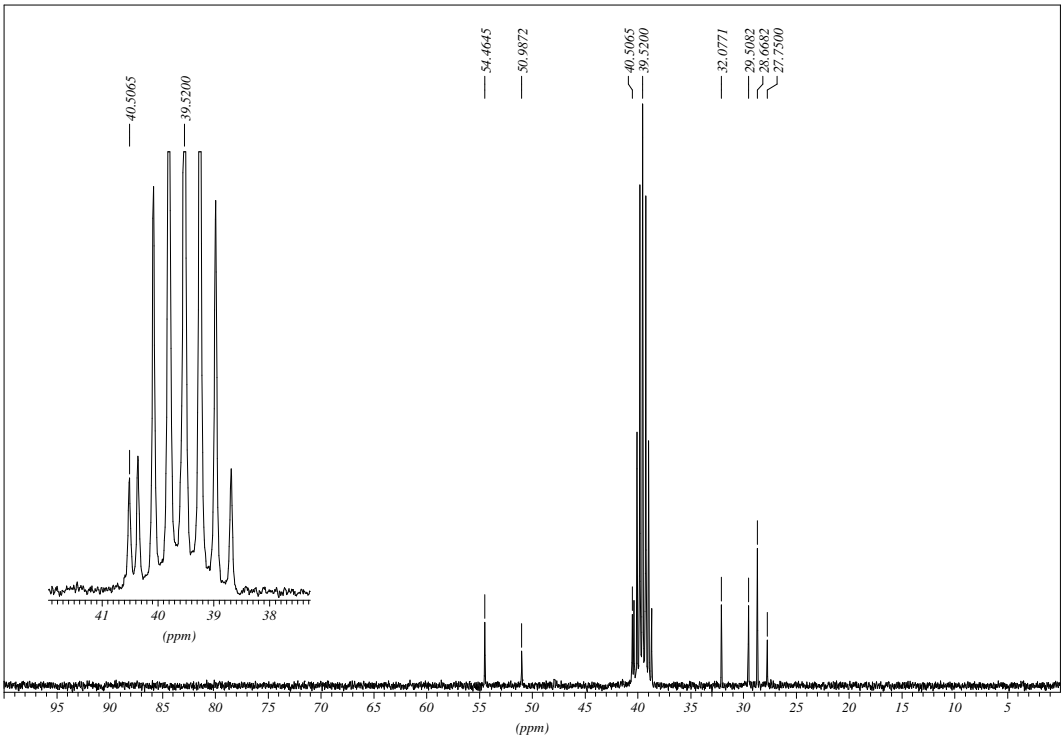
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of diamine **6-Boc**



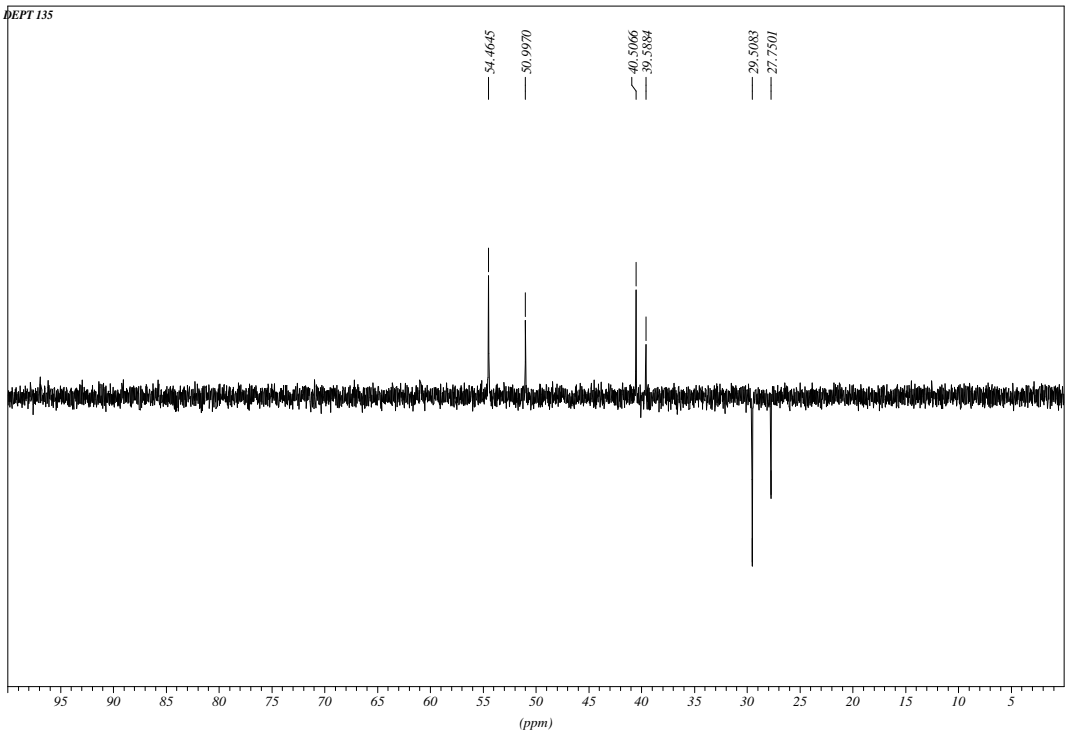


^{1}H NMR spectrum (600 MHz, DMSO-d_6) (top) and ^{13}C NMR (75 MHz, DMSO-d_6) of diamine **3●2HCl**





DEPT 135° NMR spectrum (75 MHz, DMSO-d_6) of diamine **3●2HCl**



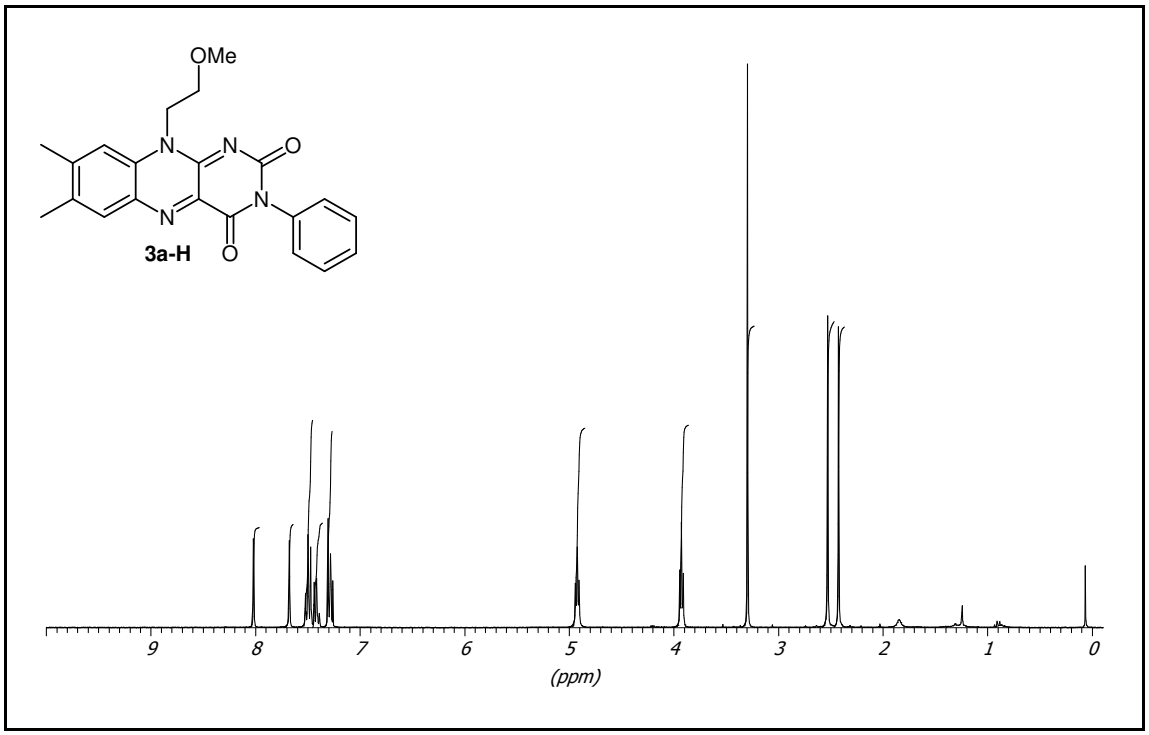
Appendix E

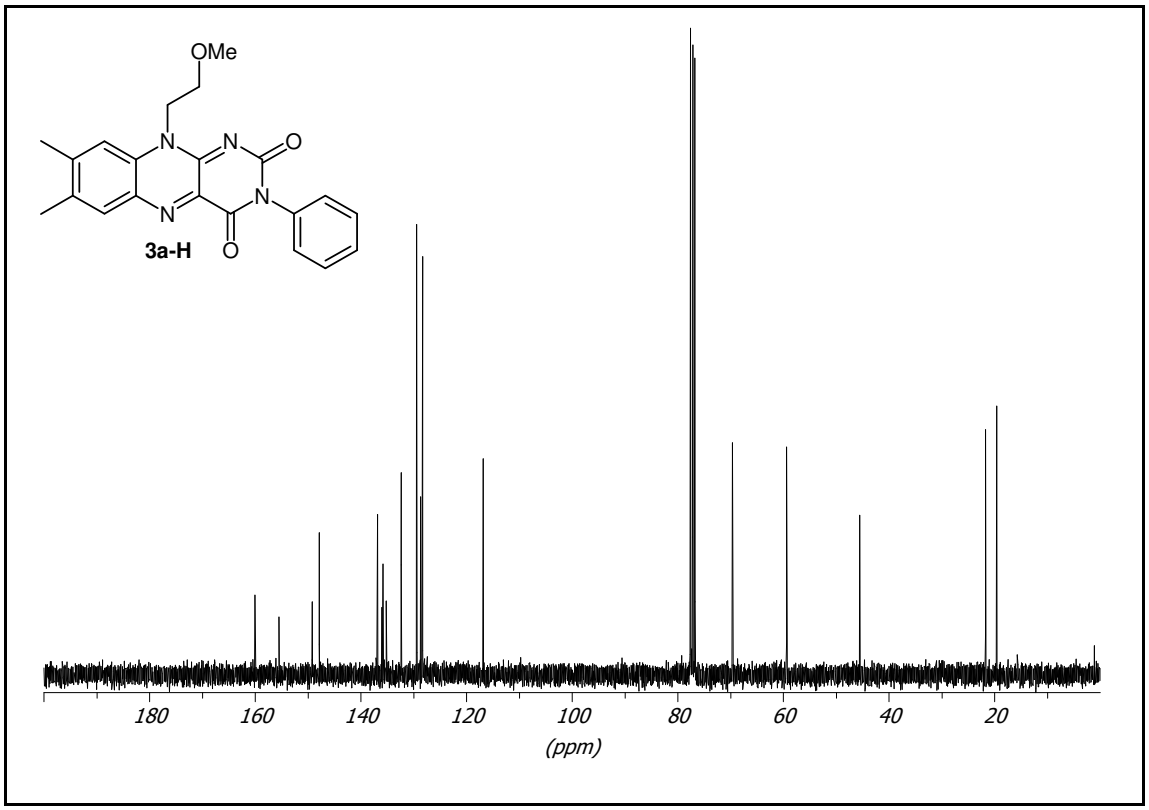
Supporting Information to Chapter 6 – Copper-Mediated 3-N-Arylation of Flavins

The numbering of the molecules in this appendix refers to chapter 6

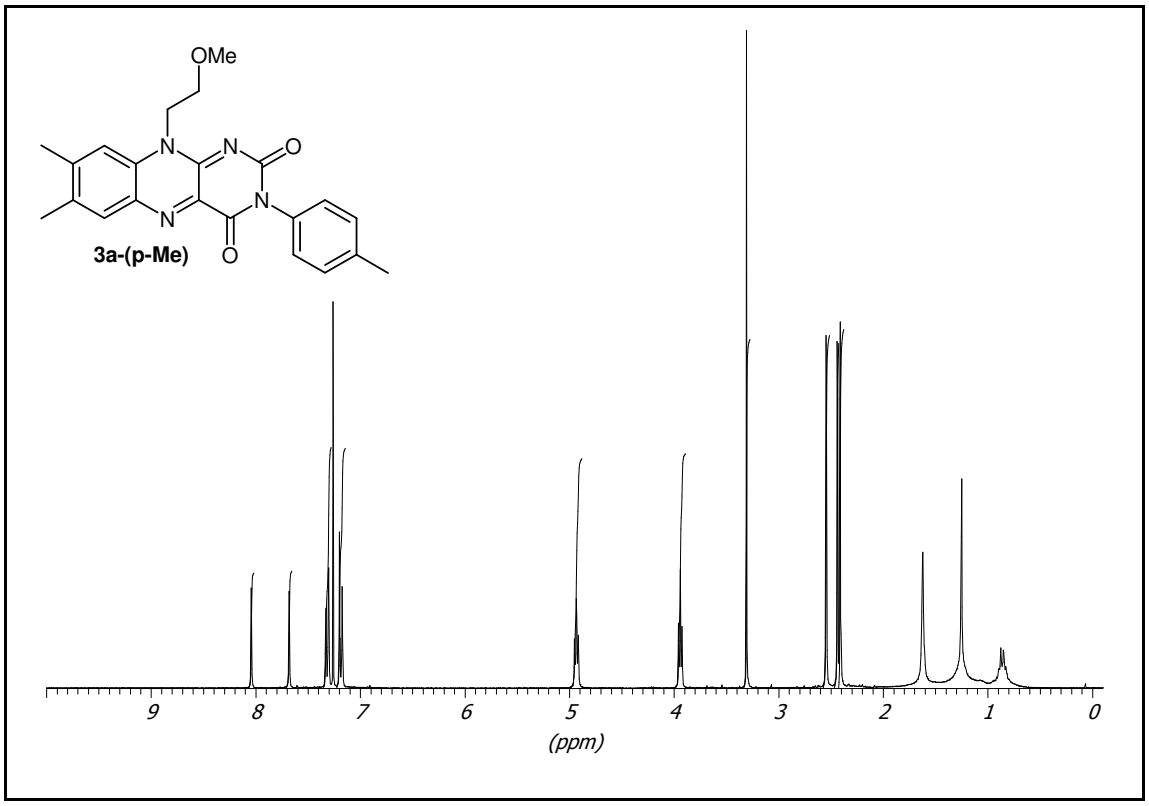
Contents

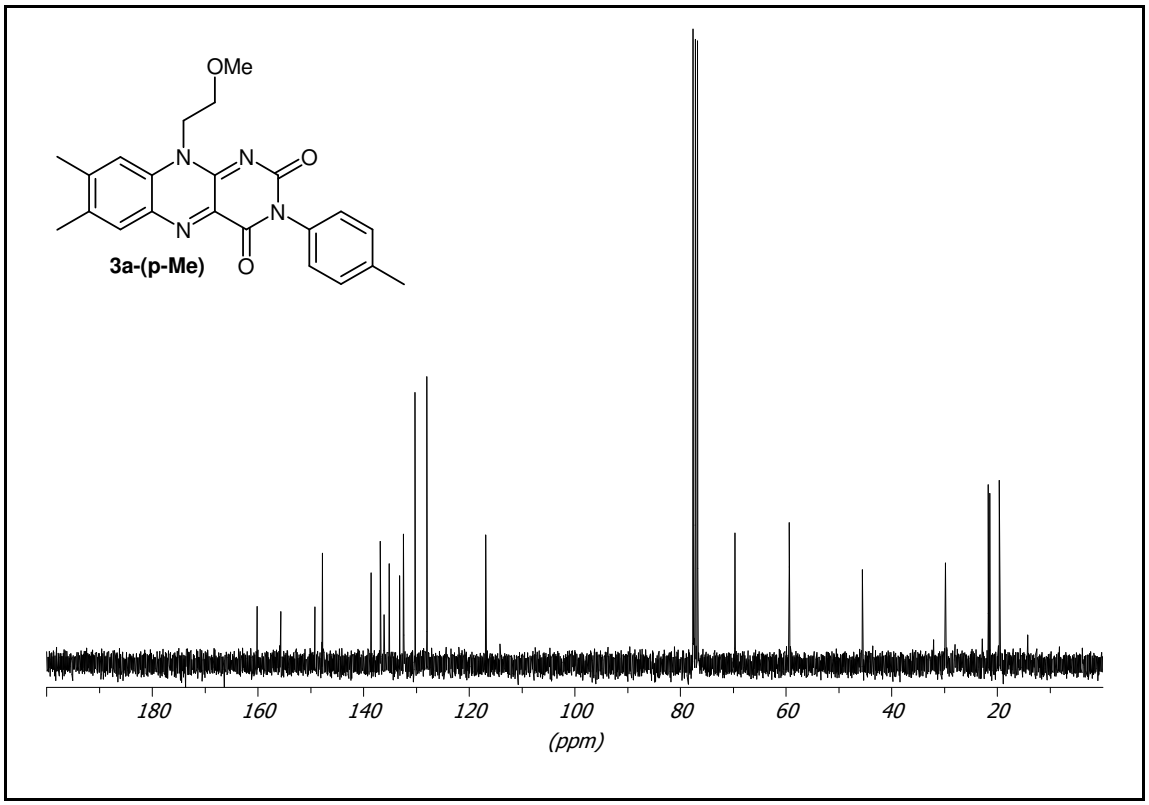
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **3a-H**



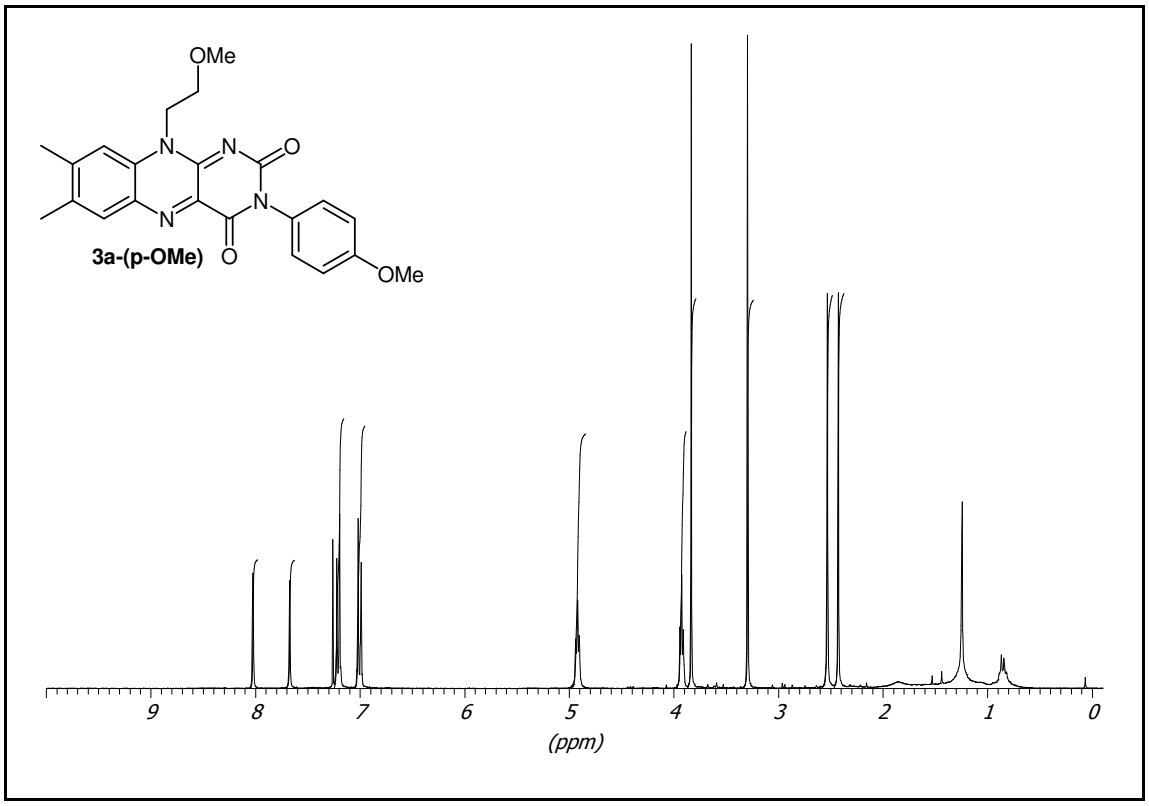


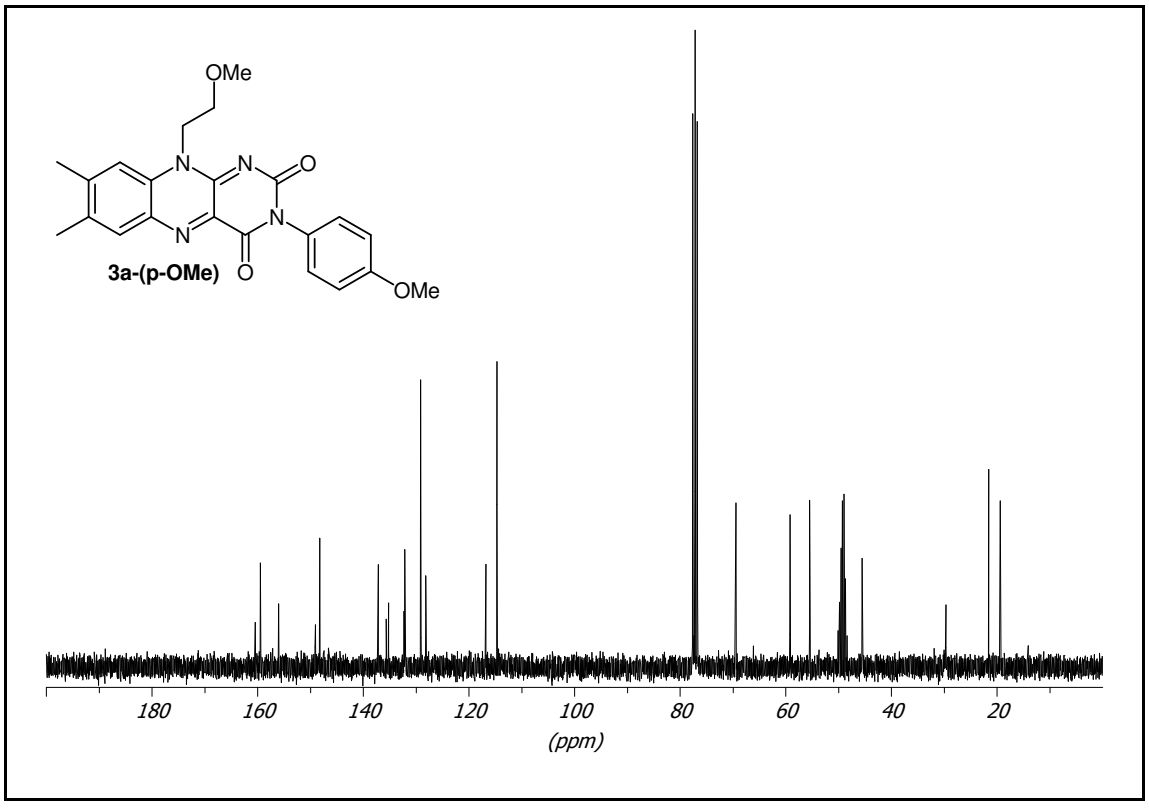
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **3a-(p-Me)**



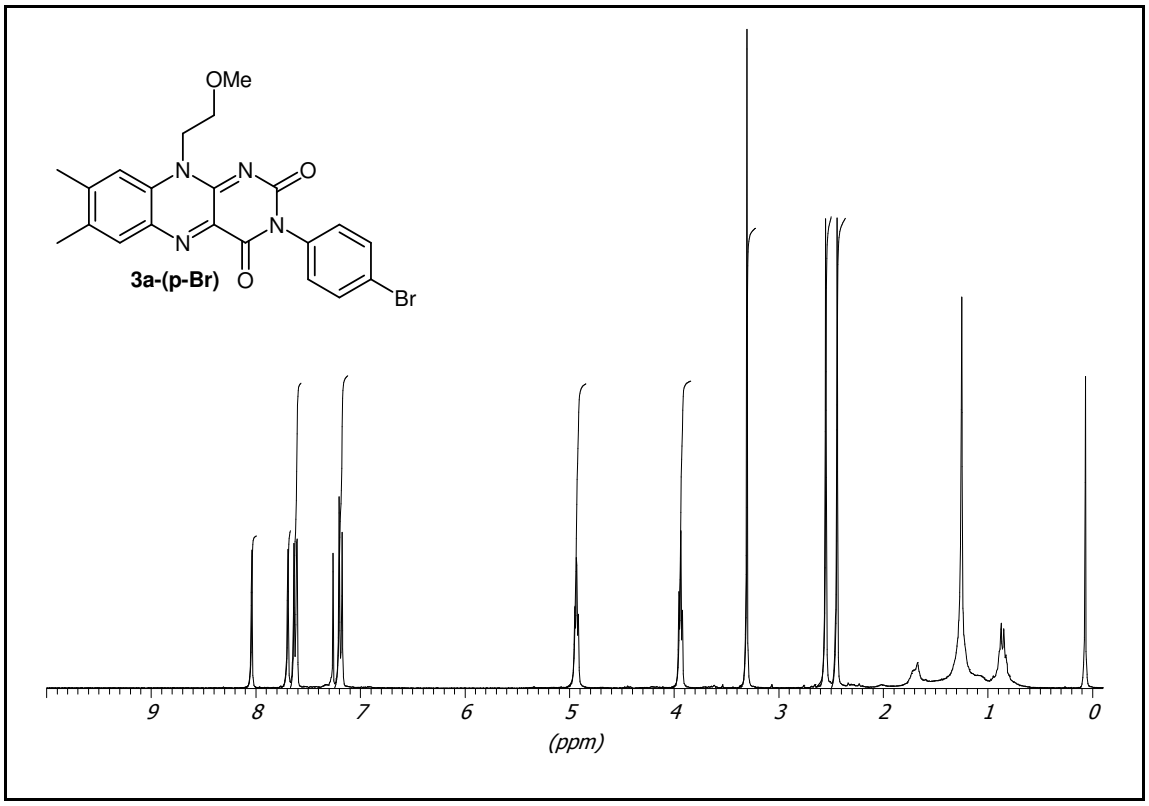


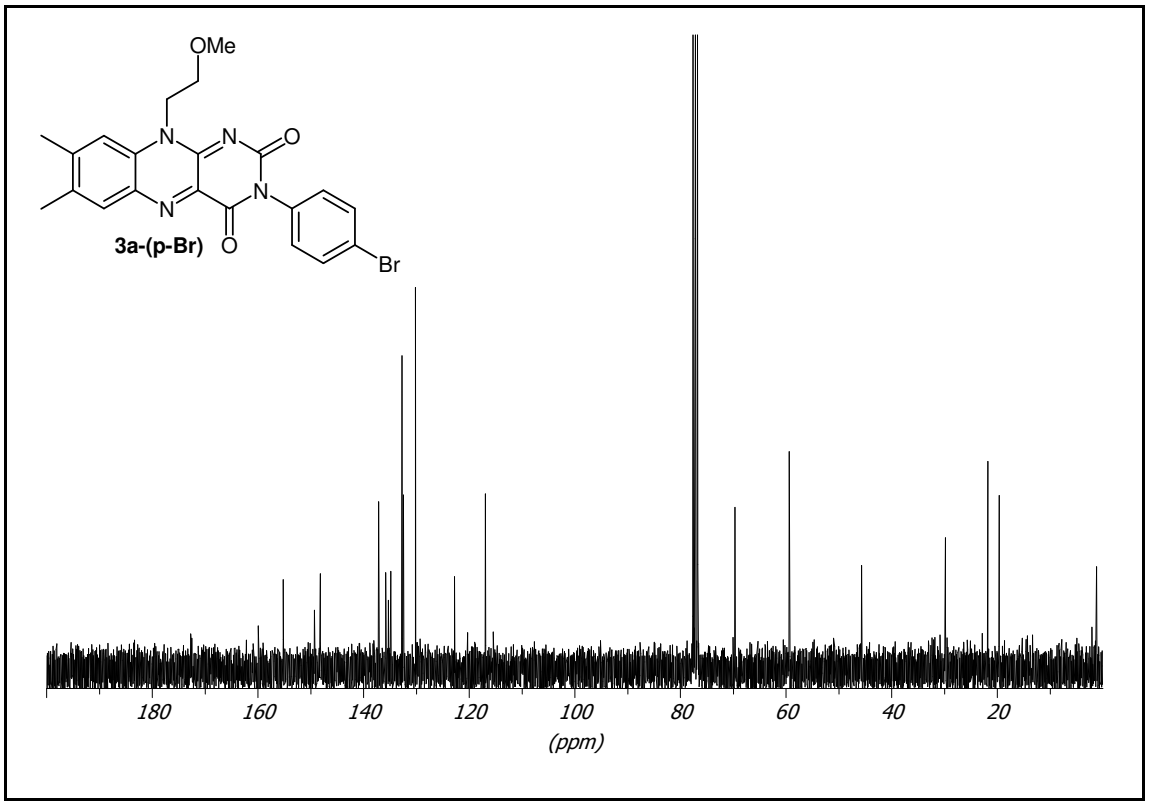
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **3a-(p-OMe)**



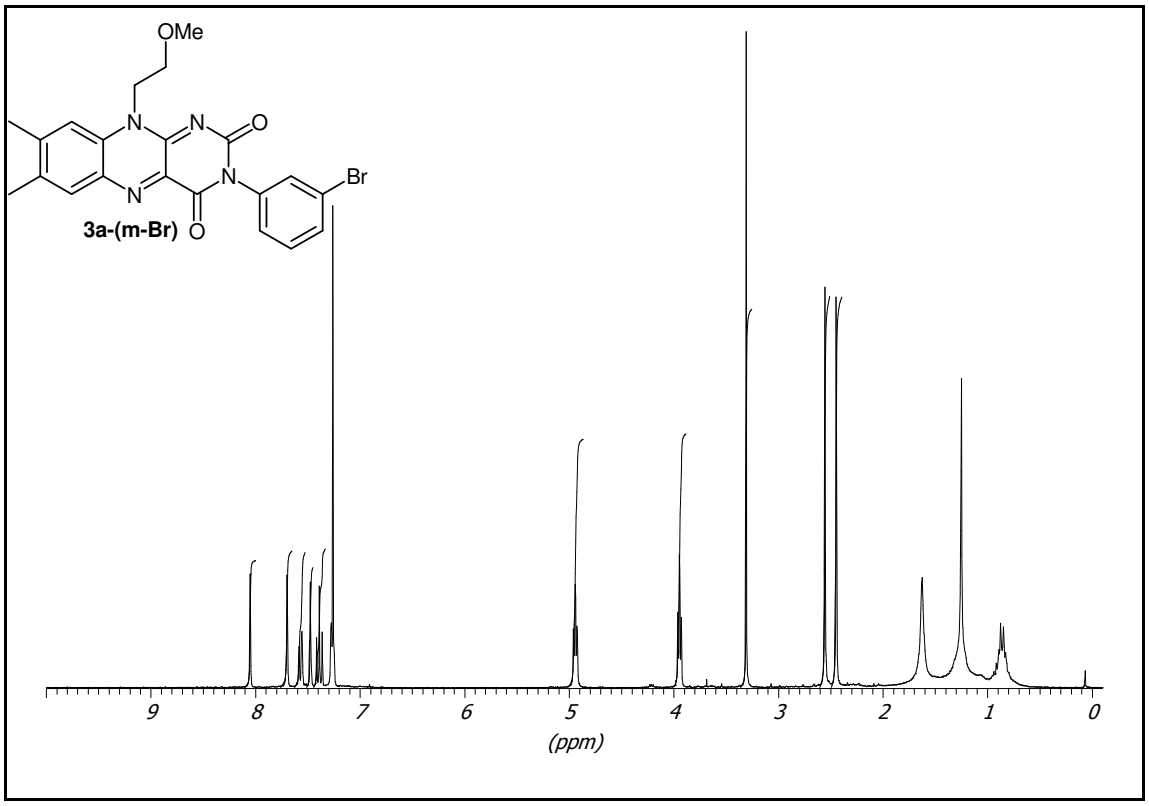


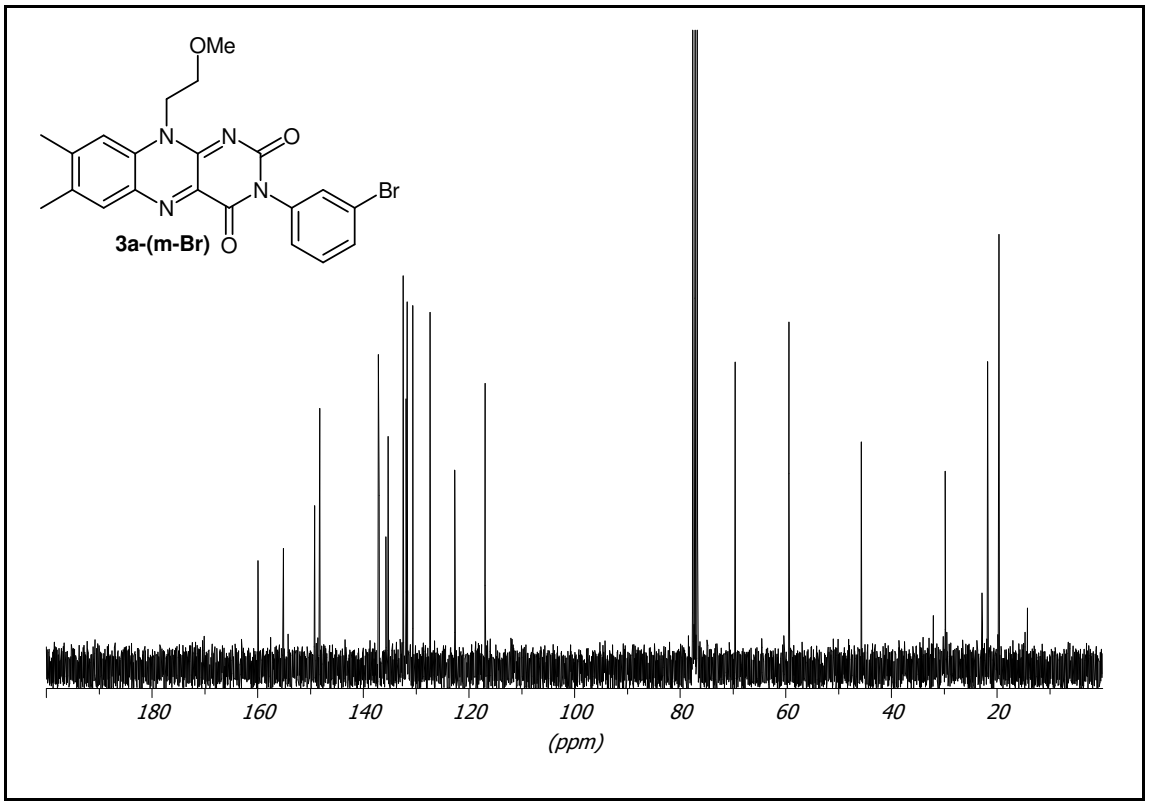
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **3a-(p-Br)**



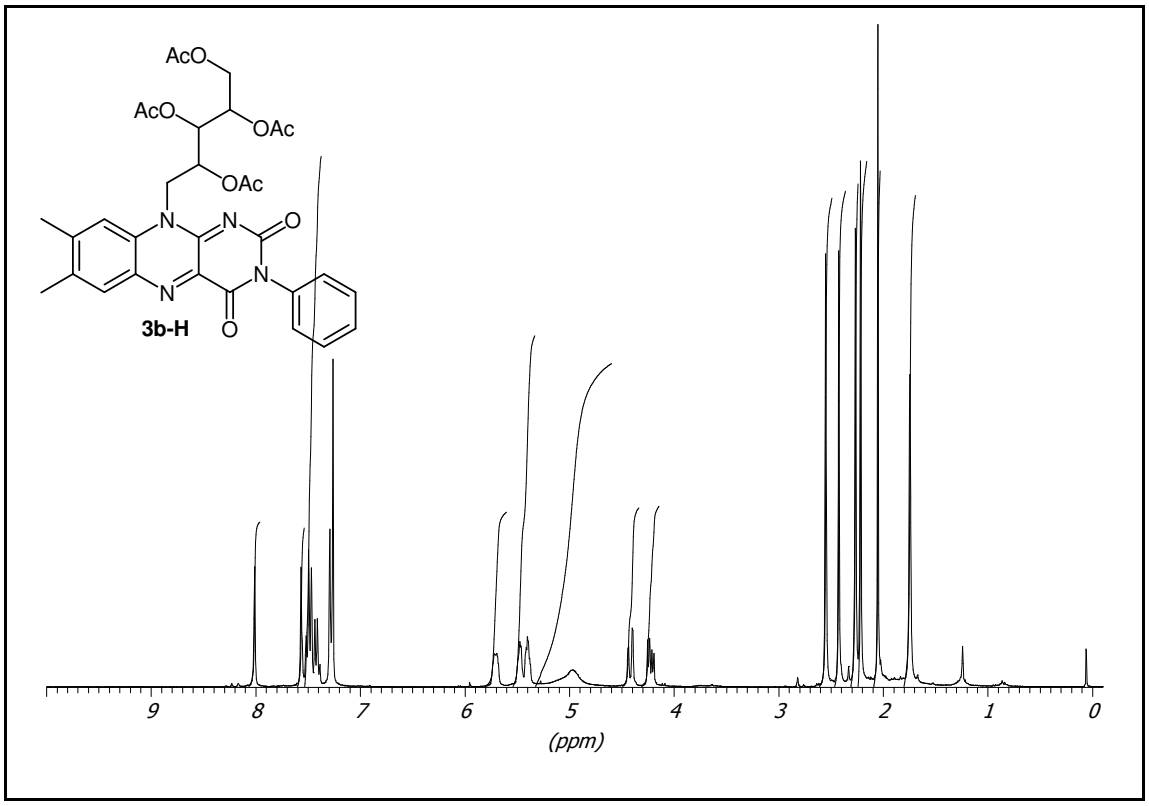


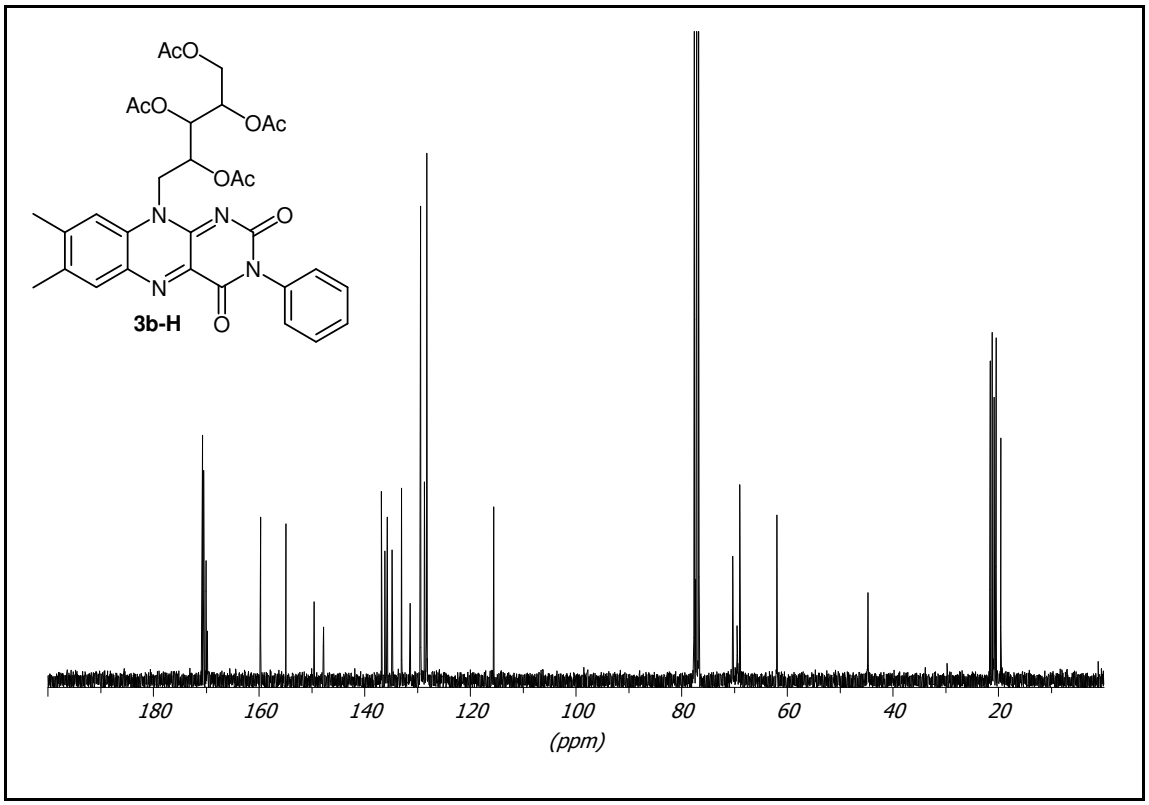
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **3a-(m-Br)**



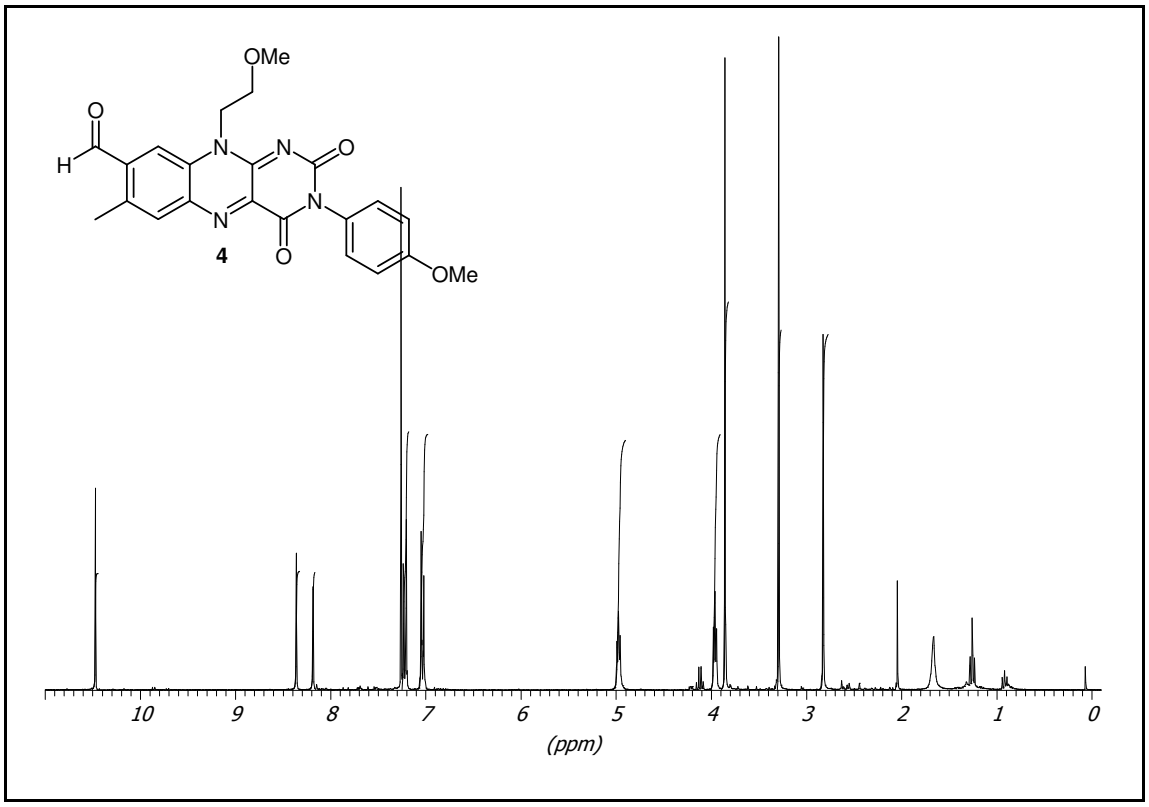


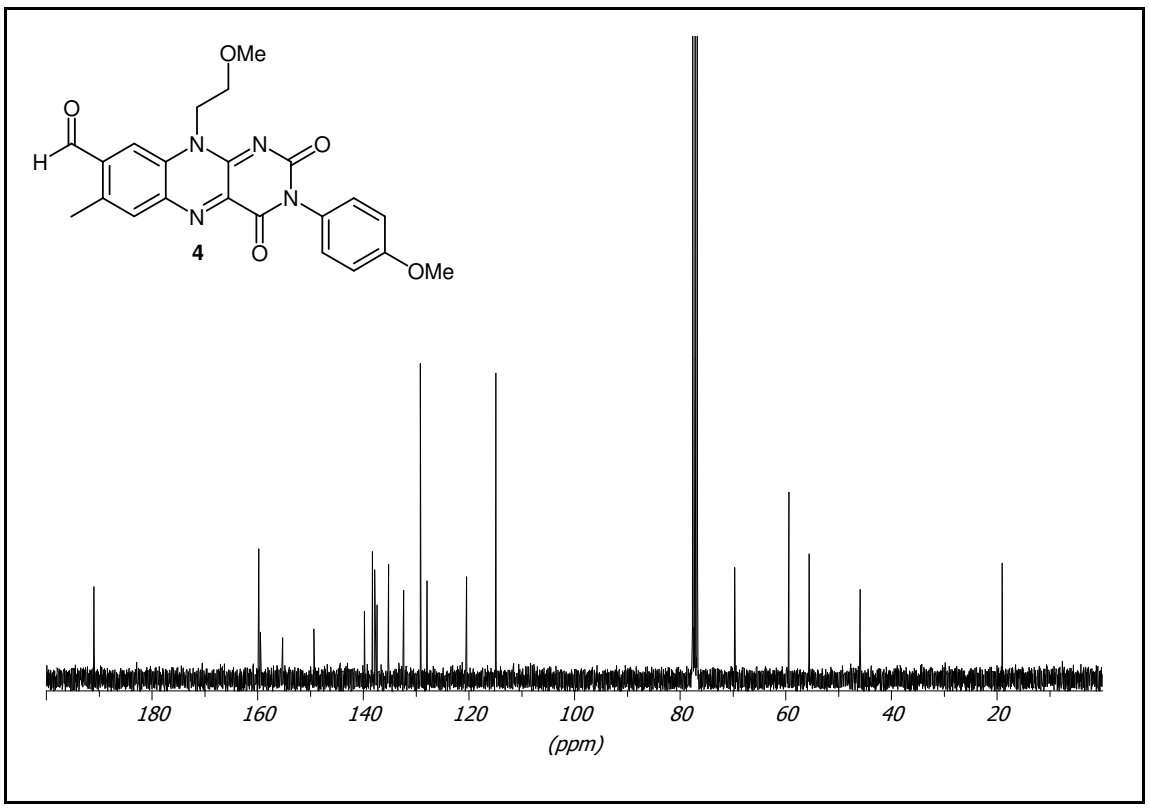
^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **3b-H**



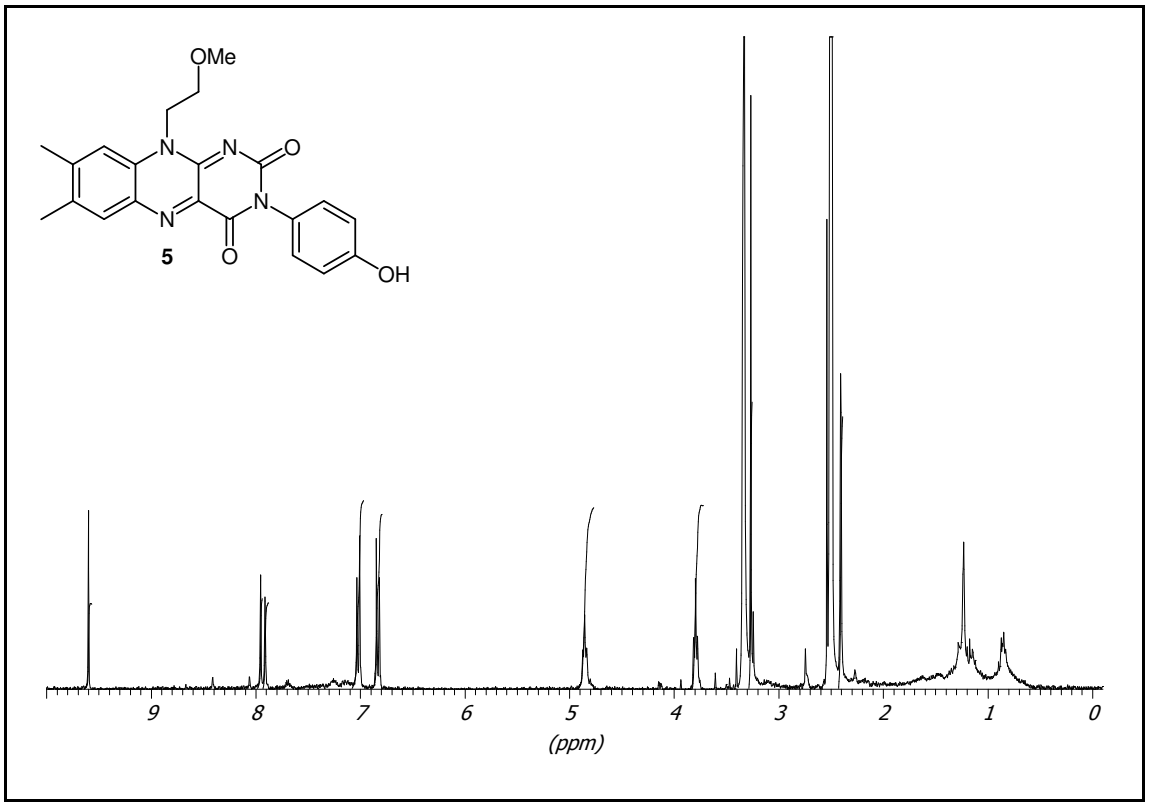


^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **4**

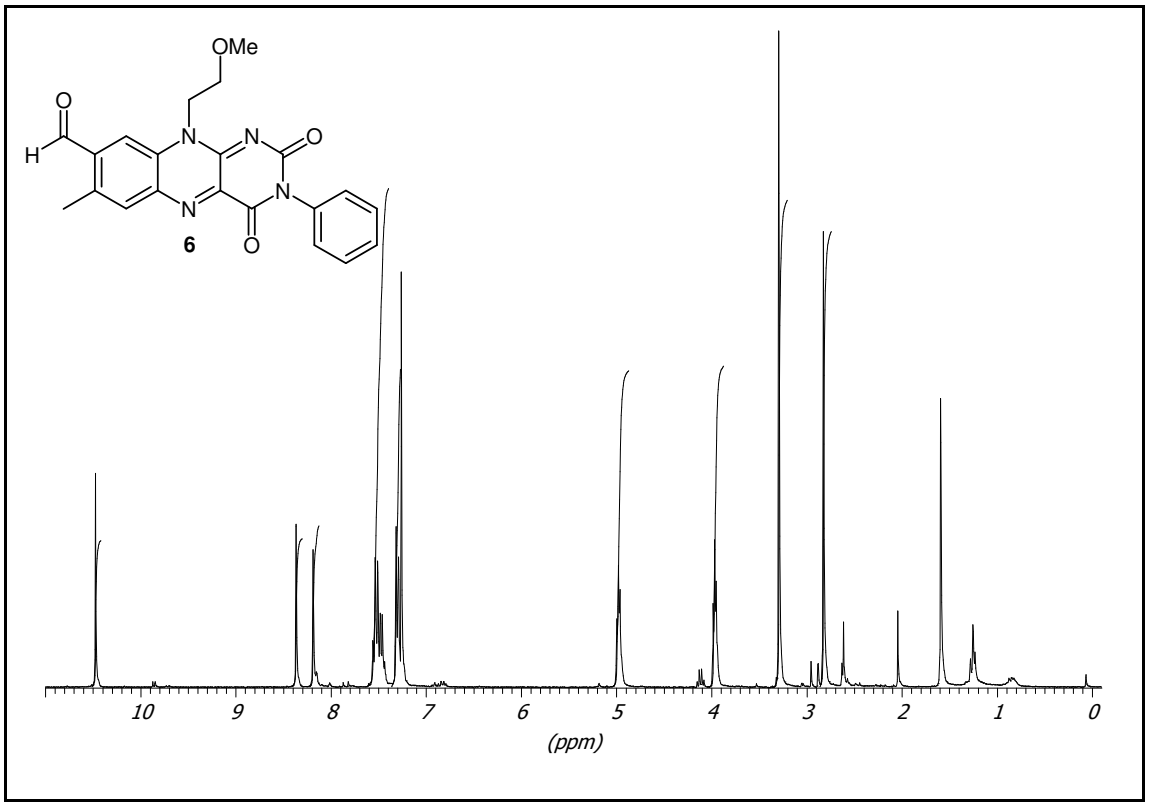


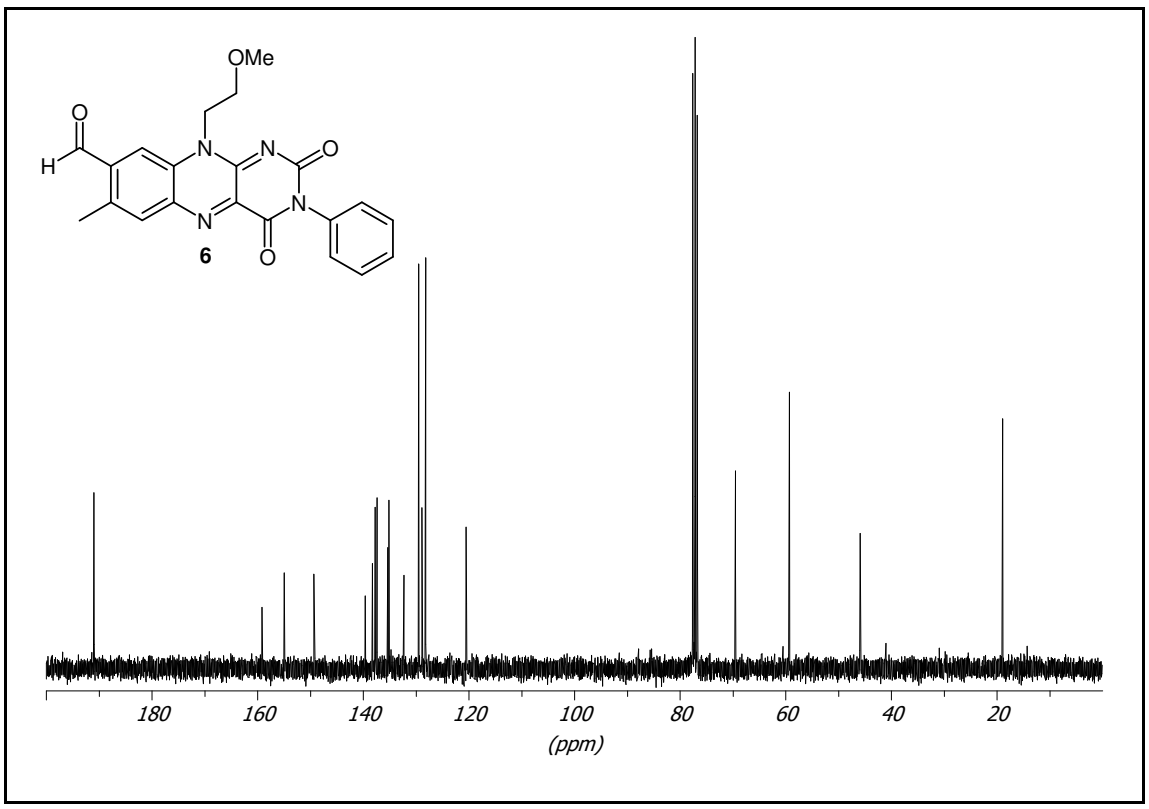


^{1}H NMR spectrum (300 MHz, DMSO-d_6) of **5**



^{1}H NMR spectrum (300 MHz, $CDCl_3$) (top) and ^{13}C NMR (75 MHz, $CDCl_3$) of **6**





List of publications

1
03/2009
"Flavin Photocatalysts with Substrate Binding Sites"
In: Activating Unreactive Substrates: The Role of Secondary Interactions (Ed.: C. Bolm, E. Hahn), Wiley-VCH, Weinheim, **2009**.
ISBN-13: 978-3527318230

2
2009
Synthetic Communications **2009**, *accepted*
"Synthesis of a Bicyclic Diamine Derived from Kemp´s Acid"

3
01/2009
Advanced Synthesis and Catalysis **2009**, *351*, 163–174
"Photooxidation of Benzyl Alcohols with Immobilized Flavins"

4
03/2008
Synthesis **2008**, *11*, 1767–1774
"Copper-Mediated 3-N-Arylation of Flavins"

5
01/2008
Chemistry – A European Journal **2008**, *14*, 1854–1865
"Thiourea-Enhanced Flavin Photooxidation of Benzyl Alcohol"

6
04/2006
European Journal of Organic Chemistry **2006**, *8*, 1899–1903
"Influence of the Number and Geometry of Binding Sites on Host-Guest Affinity: Imidazolium-Substituted Receptor Molecules for Small Inorganic Anions"

Curriculum vitae

Personal data

Name:	Harald Schmaderer
Date of birth:	24. January 1980
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Family status:	Married
Nationality:	German
Address:	Bertolt-Brecht-Weg 21
	D-93051 Regensburg
Email:	harald.schmaderer@web.de

Dissertation

11/2005 – 03/2009	New Flavins and Their Application to Chemical Photocatalysis Chair: Prof. Dr. König, Institute of Organic Chemistry, University of Regensburg

Studies

09/2005	Diploma in chemistry
09/2002	Intermediate diploma
10/2000 – 09/2005	Chemistry studies at University of Ulm
Major Subject:	Organic chemistry and energy management
Diploma Thesis:	Spectroscopic charaterization of the intercalation behaviour of planary aromatic heterocycles into calf thymus DNA
10/2003 – 09/2004	Elected member of the Chemistry Faculty Council
10/2003 – 09/2004	Member of the Chemistry Studies Committee
10/2002 – 09/2005	Advisory member of the Chemistry Examination Board
06/2002 – 06/2003	Elected member of the University Students´ Council

School

06/1999	Leaving certificate
09/1989 – 06/1999	Grammar school Joseph-von-Fraunhofer, Cham
09/1997 – 09/1998	Speaker of the Students´ Council

Teaching and work experience

11/2005 – 03/2009	Supervision of lab courses and final theses
02/2004 – 07/2005	Lecturer at the „Bildungszentrum Umweltschutz", Lauingen (eight weeks overall)
03/2002 – 08/2005	Teaching assistant in chemistry courses for chemists, biologists and physicians

Awards and scholarships

10/2006 – 03/2009	PhD-Scholarship in the DFG graduate college „Sensory photoreceptors in natural and artificial systems"
05/2006	Award of the Dr. Barbara Mez-Starck-Foundation, Freiburg
06/1999	Award of the grammar school Joseph-von-Fraunhofer, Cham

Regensburg, 23. February 2009