mTHPC – A Drug on its Way from Second to Third Generation Photosensitizer?†

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Summary
5,10,15,20-Tetrakis(3-hydroxyphenyl)chlorin (mTHPC, Temoporfin) is a widely investigated second generation photosensitizer. Its initial use in solution form (Foscan®) is now complemented by nanoformulations (Fospeg®, Foslip®) and new chemical derivatives related to the basic hydroxyphenylporphyrin framework. Advances in formulation, chemical modifications and targeting strategies open the way for third generation photosensitizers and give an illustrative example for the developmental process of new photoactive drugs.

Abbreviations: ALA – δ-aminolevulinic acid; Gly – glycosyl; HpD – haematoporphyrin derivative; mTHPC – 5,10,15,20-Tetrakis(3-hydroxyphenyl)chlorin; mTHPP –
5,10,15,20-Tetrakis(3-hydroxyphenyl)porphyrin; PD – photodiagnostics; PDT – photodynamic therapy; PS – photosensitizer.

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**Introduction**

Photosensitizers (PS) employed in photodynamic therapy (PDT) are often labeled as first, second, and third generation PS. This relates in part to the historical development and in part to conceptual approaches. Historically, the first (generation) PS was haematoporphyrin derivative (HpD), a mixture of oligomeric haematoporphyrins. Based on groundbreaking work by Dougherty a more active product, dihaematoporphyrindiether or Porfimer Sodium, was approved for clinical use in 1993 under the trade name Photofrin® [1,2,3].

While it is used for an expanding array of modalities is has several limitations. HpD has a rather weak absorption band near 630 nm which means that irradiation on this desirable wavelength does not result in a large optical response from the PS. The low absorption at the irradiation wavelength also results in a requirement of high doses of the drug to inflict enough damage to result in cell destruction. Theoretically, an ideal photosensitizer should have a strong absorption at longer wavelengths (between 650 – 800 nm) which would allow tissue penetration up to 1 cm in depth and whilst the light still carries enough energy into the target to induce a photosensitizing effect. Photofrin, in spite of being purified, still contains a large number of different compounds [4]. Therefore, reproducibility in synthesis and medical or (bio)chemical analysis becomes difficult and this ultimately affects the commercial viability. For an ideal PS, the in vivo concentration ratio of the drug between cancerous and normal cells should be as high as possible. In the case of Photofrin the difference in concentration between the two cell lines is often less than one magnitude, which means damage is almost equally inflicted to the surrounding normal tissue during the PDT process. Photofrin localizes mostly in the skin and remains there for four to six weeks thus keeping patients photosensitive for a rather long time.

In a sense the potential of the PDT concept becomes apparent if it is noticed that HpD and its derivatives are only a success in cancer therapy not because but in spite of their properties. Herein lies the motivation for researchers to develop new photosensitizers or to enhance the properties of the existing ones to develop drugs with the most ideal properties for this light mediated modality for cancer treatment and in photomedicine. As a result, interest in the development of related PS with improved drug properties arose quickly. The latter included optimized spectroscopic characteristics, e.g., bathochromically shifted absorption spectra for increased tissue penetration and the requirement to be a chemically defined single compound. These were termed 2nd generation PS and many well known examples have been developed. These include compounds such as ALA, hypericin, benzoporphyrin derivative, phthalocyanines, many chlorophyll derivatives such as mono-L-aspartyl chlorin e₆, texaphyrins, and many others [5,6,7].

In a conceptional sense many of the requirements for a 2nd generation PS are chemical ones: single compound, good absorption in the visible/near IR, high singlet oxygen quantum yield, etc. Several of these drugs have now reached the clinical practice. Still as good as they may be, there is always room for improvement. This is especially true for pharmacological aspects and tumor selectivity. Thus, current efforts are aimed at so-called 3rd generation PS where additional biological criteria are included
in the design principle. Examples are special drug delivery and formulation techniques, e.g., liposomes and nanomaterials, or bioconjugate PS with appropriate targeting units.

5,10,15,20-Tetrakis(3-hydroxyphenyl)chlorin (mTHPC, 1) with the generic name ‘Temoporfin’ and the proprietary name ‘Foscan®’ is one of the oldest examples for a second generation PS drug and, next to Photofrin, presents one of most widely studied drugs in PDT and photodiagnostics (PD) (Fig. 1) [8]. It is used in an ever expanding array of applications and a significant body of information has been accumulated for this drug and in a recent review we discussed the development of Foscan and the clinical experience with Temoporfin and its nano derivatives [9]. Here, this analysis is extended to chemical advances made in altering the basic mTHPC framework and to 3rd generation PS strategies.

![Chemical formulas](image.png)

Figure 1. Chemical formulas of compounds related to mTHPC.

The basic Temoporfin drug continues to be used in many studies. For example, it was used to test the utility of a ratiometric imaging method with NIR autofluorescence detection in a skin-fold observation chamber in Fischer rats with implanted mammary adenocarcinoma (R3230AC) to improve in vivo quantification methods [10]. New clinical studies included a case report on the treatment of adenoid cystic carcinoma of the base of the tongue using ultrasound guided transcutaneous interstitial PDT as a salvage treatment. A marked response was obtained using high light power 100 J.cm⁻² [11]. A more detailed study with 21 patients and a mean follow up of 36 months showed the utility of Foscan PDT for this modality. Improvements in breathing (9/11 patients), swallowing (19/21) and speech (11/13) were noted [12].
Simple Modifications and Formulations of mTHPC

mTHPC is derived from mTHPP (2) through reduction and the latter is still used in some studies. Although its utility in standard PDT is limited, it can serve as a suitable test compound for the initial evaluation of new formulation techniques. It also has found use in nonclinical applications, such as sterilization [9,13]. Similarly, the doubly reduced bacteriochlorin mTHPBC (3) has been known for some time [8]. The lower stability of the compound and only minor advantages suggests that the utility of this dye is limited [9].

More significant advances were made through the use of nano strategies for PS development. Initially, this involved the preparation of pegylated derivatives of mTHPC. This alters not only the solubility but also the size and thus results in different tumor:tissue distributions. Pegylated mTHPC derivatives are available with various degree of pegylation (different sizes) and the commercial version is called Fospeg® [14]. A similar strategy utilized the mTHPC compound in chemically unaltered form but incorporates them into vesicles to achieve nanosized formulations. The best known examples here are liposomal formulations, e.g. Foslip® [15]. The relevant in vitro tests have been discussed before [9].

Recent studies in this area focus on release and distribution studies and on further applications of nano derivatives. The rate of mTHPC release from lipid vesicles varies with the composition [16] and thus requires a fine-tuning of the various fluorescence based detection techniques. Photo-induced fluorescence quenching was shown to be the most suitable method for commercial mTHPC liposomal formulations [17]. Another study compared the various lipid vesicle systems (liposomes, invasosome, ethosomes) on the skin penetration of mTHPC. Both vesicular and nonvesicular formulations gave drug accumulation predominantly in the superficial skin layer [18]. A fluorescence quenching study of Fospeg showed two molecular pools; one in the PEG shell and one in the lipid bilayer. The different release kinetics account in part for the faster release of mTHPC from Fospeg compared to Foslip [19] and for the increased bioavailability of mTHPC from liposomal preparations [20]. In the context of new applications, a study investigated the antimicrobial effect of liposome enriched mTHPC for the use of Foscan in periodontal diseases. Enterococcus faecalis could be photo-inactivated with 50 μM mTHPC and 100 J.cm⁻² indicating the possibility of adjuvant treatment of endodontic infections [21]. Related investigations include studies on the mechanism of cell death [22], the suppression of dark toxicity in PLGA nanoparticles [23], invasosomes for skin delivery of temoporfin [24], amongst others.

Chemical Advances

Parallel to the development of new formulations and delivery vehicles for Foscan, several groups have investigated the properties of chemically closely related compounds.

Porphyrrins and Chlorins

An early example from 1998 reported the use of 5,10,15,20-tetrakis(3-carboxymethoxyphenyl)chlorin 7 [25]. It showed no dark toxicity in human
adenocarcinoma and Chinese hamster ovarian cell lines and gave promising initial results but appears to not have been followed up. These and other related $S_4$-symmetric compounds are prepared via simple condensation reactions.

Figure 2. Chemical formulas of simple porphyrins.
Despite problems with regard to their absorption a range of 5,15-disubstituted or 5,10,15,20-tetrasubstituted hydroxyphenylporphyrins such as 5 and -chlorins closely related to mTHPC have been prepared and initial testing underlines their potential as photosensitizers (Fig. 2) [26,27,28,29,30]. An example for a simple symmetric system is 5,10,15,20-tetraakis(4-carboxyphenyl)porphyrin 6 which was incorporated into NPs. Tests with SW480 cells showed that rapid internalization occurs via a clathrin-mediated endocytosis pathway and indicated significant photocytotoxicity [31]. Simple modifications of the mTHPP framework have been used to prepare a variety of related derivatives. For example, introduction of naphthyl residues gave compound 8, which showed better photostability and lower dark cytotoxicity in HT29 cells compared to mTHPP [32].

A first approach towards OSAR analyses of simple tetrapyrrrole systems was given by Banfi et al. [33]. Introduction of nitro groups in meso arylporphyrins lowered the PDT activity, e.g. in 9, while the presence of a nitrophenyl residue in 10 increased the activity. An earlier study had already identified that compound 5 had a lower IC50 for HCT116 cells than mTHPC [29]. A more detailed QSAR analysis of 34 different tetrapyrrroles compared the PDT activity of meso tetra-, di- and monoarylporphyrins and chlorins [34]. Surprisingly, 5,15-diarylsubstituted porphyrins were found to exhibit a much higher PDT activity against human colon adenocarcinoma cells than mTHPC or related 5,10,15,20-tetraarylporphyrins. Not too surprisingly, hydroxyaryl compounds were more active than methoxyaryl derivatives. For example, the IC50 of porphyrin 11 was 1.06 nM compared to 7.60 nM for Temoporfin (note, that an earlier study reported an IC50 of 36 nM [29]). Indeed, even the meso monosubstituted porphyrin 12 exhibited an IC50 of 1.85 nM, significantly lower than mTHPC. If confirmed, these results raise the question whether elaborate chemical manipulations of complex porphyrins are necessary for PDT? A related study from 2009 addressed the utility of various 5,15-diaryl substituted porphyrins. Studies with the human colon carcinoma cell line HCT116 identified several potent compounds, e.g., (5-phenyl-15-(3-methoxyphenyl)porphyrin, 5-phenyl-15-(3-hydroxyphenyl)porphyrin, 5,15-diphenylporphyrin, all of which were more active in vitro than mTHPC. All compounds tested exhibited similar singlet oxygen quantum yields and differences in phototoxicity were attributed to differential intracellular accumulation. Flow cytometric analysis showed that all candidates induce apoptosis, although other cytotoxic processes appear to be active as well [35]. A number of arylhalogenated derivatives of 5,15-bis(3-hydroxyphenyl)porphyrin were tested as well. Although the compounds showed higher in vitro activity than Photofrin, halogenation resulted in a lower uptake [36].

Fluorescence spectroscopy is the standard method to detect tetrapyrrolic photosensitizers in vivo. However, while being a sensitive technique, it has the one disadvantage that it is to some extent limited to surface analysis. The development of additional analytical and diagnostic tools would be desirable. As fluorine substitution delivers both an excellent NMR nucleus and access to radiodiagnostic applications, fluorine substituted derivatives of mTHPP (e.g., 13) have been prepared through condensation methods (Fig. 3) [37,38]. The PDT response from these fluorinated derivatives are reported to be at least as effective as mTHPC, although the compounds are relatively hydrophobic [39]. Likewise, a number of 2,3-dihydroxy-1-
propyloxyphenylporphyrins were prepared to decrease the hydrophobicity of the Temoporfin system [40].

![Chemical formulas of simple porphyrins and chlorins.](image)

Figure 3. Chemical formulas of simple porphyrins and chlorins.

5,15-Bis(3,5-dihydroxyphenyl)chlorin 14 is another example for a chemically simple hydroporphyrin. It was prepared through condensation of dipyrromethane with 3,5-dimethoxybenzaldehyde, followed by protecting group transformations and reduction [26,27]. In vitro tests showed similar effects to mTHPC. However, an animal model showed a higher tumor/tissue ratio and notably a much more rapid clearance of this PS. In vitro and animal tests showed that the uptake is much faster, e.g., optimum drug-light interval for treatment was 12 h. An in vivo study using an orthotopic C6 tumor model in rats showed that the mean survival time was significantly improved compared with controls, HPD-, or mTHPC-treated groups [41]. Roughly speaking the efficacy of this PS is similar to that of Foscan but has more favorable pharmacokinetics. Animal tests with mice bearing HT29 human adenocarcinoma showed a better uptake for the dimyristoyl phosphatidylcholine liposomal formulation of the chlorin. Maximum tumor concentration for both the native drug and its liposomal formulation was 12 h post injection. A 2 mg.kg\(^{-1}\) dose of PS resulted in 26 % tumor growth reduction for the chlorin and 35 % for the chlorin incorporated into liposomes [28].

More significant synthetic advances of Temoporfin related compounds are a consequence of general progress in the synthesis of unsymmetrical porphyrins and (bacterio)chlorins [42,43,44,45,46,47,48,49]. These advances have made it possible to prepare porphyrins with different substituent pattern, e.g., different hydrophobic and hydrophilic groups. By now the chemical synthesis of porphyrins with meso substituents has progressed to a point where the synthesis of almost any meso substituted porphyrin
is possible (Fig. 4). This includes unsymmetrical systems of the ABCD-type porphyrins and the Aₓ-type porphyrins with one to four meso residues [46,50,51]. For example, the use of both condensation and substitution reactions allowed the rapid generation of a large library of amphiphilic derivatives of mTHPC with both aryl and alkyl residues [52]. A typical example is compound 15. Photophysical studies showed that substituent variation, e.g., a mixing of alkyl and aryl substituents results in moderate changes in singlet oxygen quantum yield and related properties [53]. The degree of hydrophobicity clearly impacted the liposomal binding and cellular uptake [54]. Thus, the synthetic advances made allow a modulation of the pharmacological properties without drastic changes in the basic photochemistry. Biological tests for several of these compounds prepared in our laboratory are currently in progress. Water soluble 5,15-AB porphyrins are easily available, too [55], as are the related hydroporphyrins [56]. The latter showed high phototoxicity in the nM range in HeLa cells and have a long wavelength absorption between 717 and 780 nm. Most compounds were of the type shown for formula 16 with R being water soluble groups.

Figure 4. Selected members of the Aₓ and ABCD-type porphyrin series.

Without resorting to a comprehensive review of the relevant chemical papers many other synthetic advances have been made in recent years that are of relevance. These include fused systems with π-extended systems, dimeric and oligomeric porphyrin arrays, two-photon absorbers for PDT, and many more.

**Glycoporphyrins**

Carbohydrate appended porphyrins are gaining more and more attention. This is related to their potentially better solubility and uptake, localization in different cell compartments and, down the line, perhaps direct interaction with cellular glycoproteins. Excellent reviews on the chemistry of carbohydrate modified PS were given by Pandey and coworkers [7,57]. Initial studies on related systems were reported in the middle of the nineties and were based on the condensation of appropriate carbohydrate-aldehydes to yield the respective glycoporphyrins [58]. In these compounds the carbohydrate unit was formally
attached to meso phenyl rings in the 4-position. Later Blais’s group prepared Temoporfin related 3-hydroxyphenyl carbohydrate derivatives and reduced these to the respective chlorins [59]. The most interesting set of compounds from these studies relates to the porphyrin 17 and chlorin 18 (Fig. 5).

![Chemical structures of 17, 18, 19, 20, and 21](image)

**Figure 5.** Glycoporphyrins and other compounds related to Temoporfin.

Recently, an improved synthesis containing a zinc-ion-templated condensation was reported to give these interesting derivatives in higher yields and cellular uptake and phototoxicity were found to be promising [60,61]. Nevertheless, cellular uptake does not necessarily correlate with the phototoxicity for these compounds. Non-aqueous capillary electrophoresis and HPLC have been shown to be valuable tools for
analysis of glycoconjugated and hydroxylated porphyrins [62,63,64] and for the quantitative determination of mTHPC in biological samples [65].

With the advent of glycoconjugated derivatives of mTHPC (e.g., 17 and 18) a PS class was introduced which showed superior interaction with blood proteins and enhanced mitochondrial localization in comparison to mTHPC with high phototoxicity for the unsymmetrical derivatives [59,66,67]. The singlet oxygen yield is similar to the one of the nonglycosylated derivatives (0.41-0.58) [68]. The stability of these compounds within adenocarcinoma cells (HT29) and putative decomposition products have been reported [67]. The compounds successively lose the carbohydrate moiety and are slowly oxidized to the respective porphyrins. The final metabolites are those related to mTHPP. An initial pharmacokinetic study in healthy rats showed that mTHPP(glu)3 17 is taken up more rapidly than Foscan. The maximum concentration was reached after 14 h, with concentration in lung, liver and spleen. Clearance is also much more rapid, after 48 h all PS was eliminated from all organs. This indicates significant potential compared to Foscan [69].

Subsequently, a QSAR study of glycosylated derivatives was reported using human adenocarcinoma HT29 and retinoblastoma cell lines. As before the unsymmetrical derivatives with three glucose residues showed the highest phototoxicity and no cytotoxicity. The need for real QSAR studies was indicated by the fact that linker groups between the meso phenyl and sugar residue (here diethyleneglycol spacers) and the anomeric configuration significantly improved the IC50 values by about one order of magnitude [70]. Overall, compounds derived from the 5,10,15-tri(hydroxyphenyl)-20-phenyl frameworks (19 and 20) gave the best results. Interestingly, the p-derivative 21 is more active then the m-derivative 18. Both their photoactivities are similar to Foscan and better than the related β-glycosylated compounds. In this set of experiments introduction of carbohydrate units only gave results superior to Foscan when α-galactose units where connected through longer linkers in the p-position (e.g., 21). However, its cytotoxicity is higher than that of the other compounds mentioned. Thus, the carbohydrate porphyrins and chlorins exhibit an intricate interplay of substituent pattern, regiochemistry and linker dependence and require quite detailed QSAR analyses. The porphyrins used in these studies were subsequently used for binding studies with DMPC liposomes and albumin [71]. Only limited aggregation in polar media and rapid binding to DMPC liposomes was found for the more polar compounds. Hydroxylated compounds with intermediate lipophilicity exhibited the highest affinity for liposomes while the highest affinity for liposomes was observed for hydroxylated derivatives.

Generally speaking, the tetraglycosylated derivate was internalized poorly and showed only weak photoactivity. The unsymmetric and more amphiphilic compound 18 was a better PS than mTHPC. Drug concentration, temperature and sodium azide effects indicated it is taken up via an active receptor-mediated endocytosis mechanism. The uptake is a saturable process and was 30% lower than for mTHPC. Yet, the maximum phototoxicity in HT29 cells was reached at a 4fold lower concentration (2 mM) than with Temoporfin [59]. Similarly, mTHPP and the triglyco derivative 17 were shown to incorporate into phospholipid monolayers, while the tetraglycosylated compound showed only weak interactions. This indicates the potential to facilitate membrane passage through asymmetric glycosylation [72]. Note, that a 23Na MRI analysis of
retinoblastoma xenografts with a triglycosylated PS (mannosyl derivative) showed potential for developing new analytical techniques based on such materials [73,74]. A potential problem might be the susceptibility of the O-linked conjugates through hydrolysis. Here, thioester linkages have recently been used to prepare more stable derivatives [75].

Like many other areas porphyrin carbohydrate conjugates are now accessible via Cu(I) mediated Huisgen click reaction. These reactions require an alkynyl and an azido precursor compound and typically give excellent yields. Here, Scanlan and coworkers prepared a variety of mono- (22) and disubstituted porphyrins (23) using 4-azidophenylporphyrins and propargyl glucose derivatives (Fig. 6) [76]. Maillard's group described the synthesis of a range of compounds starting from compound 20 [77]. The trihydroxyphenylporphyrin was converted into –O-alkylazido compounds or the respective O-propargyl derivatives. Reaction with propargyl glycosyl compounds then gave compounds of the type 24-26. Photocytotoxicity studies with colorectal adenocarcinoma cells (HT29) and human retionoblastoma cells (Y79) showed better PDT effects in the latter. IC50 values ranged from 0.4–15 μM. Notably, the type of glycosyl units did not influence the photocytotoxicity.

![Figure 6. Glycoporphyrins prepared via click reaction.](image)

**Other Tetrapyrroles**
An interesting compound, aptly named temocene was prepared by Garcia-Diaz et al. [78]. Temocene is the porphycene analog of mTHPC. Porphycenes are porphyrin isomers which exhibit larger absorption coefficients but similar photophysical properties compared to porphyrins [79]. Compound 27 exhibited lower PDT activity with HeLa cells compared to mTHPC but showed better photostability and lower dark toxicity (Fig. 7). Thus, compounds of this type appear to be intriguing candidates for further development.

Figure 7. Structural formula of temocene.

Targeting and Bioconjugates

Clearly targeting [80] and combination therapies [81] are main area where we need PS improvement. Esp. the short lifetime of singlet oxygen makes this mandatory [82]. Many possibilities exist, mainly through "nano" modification or the formation of bioconjugates. In chemical terms, this necessitates access to unsymmetrical tetrapyrrroles that allow the selective connection with a targeting or biologically active group. Many reviews have addressed this question and also indicated the need for better intracellular targeting [83]. Specific subcellular targeting has been possible for PS for over a decade and specific targeting signals have been known for much longer. Especially for chlorin e₆ derivatives many targeted bioconjugates were prepared early on and nuclear targeting alone resulted in an increase in PDT effects by a factor of 10³ compared to the free drug [83].

One of the most intriguing approached for the targeting of PS is the use of selective monoclonal antibody conjugates [84]. An initial study using a H&N SCC selective chimeric MAb U36 mTHPC conjugate showed increased tumor selectivity, although the blood clearance rate was accelerated [85]. However, a detailed study with five different SCC cell lines showed that the three studied monoclonal antibody conjugates of mTHPC were ineffective, quite in contrast to chloro(phthalocyaninato tetrasulfonate)aluminum(III), which showed potential [86]. Similarly, the use of signaling peptides offers potential. Vicente’s group reported on a series of simple tetraphenylporphyrin derivatives bearing signaling peptides attached to an aminophenyl group. Cell tests with human prostate cells showed promising results for a porphyrin bearing a cell penetrating peptide, its dark cytotoxicity and its phototoxicity were higher than those of mTHPC [87]. Animal models showed significantly better uptake of this compound compared to HPD.

The attachment of folate receptors to porphyrins has also found to be useful [88]. Folic acid is of interest in oncology as the folate receptor is overexpressed on the cell
surface of many tumor types, as such it presents a natural target for use in bioconjugate drugs [89]. Folic acid can be chemically linked with carboxy acid porphyrins such as 28 (Fig. 7). Conjugates such as 29 have been shown to interact with the phospholipid head groups in DPPC films [88]. A comparison of a mouse xenograft model with (KB) and without (HT29) folate receptor showed enhanced accumulation of the folate drug in the KB case. The tumor to tissue ratio was 5:1 [90].

Figure 8. Folate appended chlorins.

Chemically there are still problems in preparing porphyrin bioconjugates. Suitable and general synthetic methods for the "linker" chemistry remain to be optimized [91]. Likewise the development of photocleavable porphyrin bioconjugates, which would offer the potential of an in vivo pro-drug activation, are still in a developmental stage [92]. It must also be asked if it worthwhile to prepare complex PS carrier systems. Most multicomponent PS-carrier conjugates are chemically complex and require laborious and expensive procedures. One suggestion has been to develop recombinant chimeric vehicles for PS with specific targeting modules [83].

Conclusions

Studies with Temoporfin and its formulations have clearly established the utility of \( m \)-hydroxyphenylporphyrins in PDT. Compared to the simple solution of \( m \)THPC
(Foscan) liposomal preparations such as Fospeg, Foslip or Foslipos give better bioavailability of the photoactive drug and can result in higher tumor:tissue ratios. These various nanodrug modifications have now reached the stage were initial \textit{in vivo} animal tests have been performed and clinical studies will be undertaken. In order to develop true third generation PS based on the results obtained with \textit{m}THPC tissue and intracellular targeting need to be improved. Peptide and protein bioconjugates of porphyrins present the most logical route towards this end. Significant advances have been made with various peptide appended porphyrin systems and Boyle and coworkers have covered this field in a recent review [93]. Glycoporphyrins complement this approach and open new possibilities through lectin targeting. In parallel, advances in porphyrin chemistry have made the construction of bioconjugates much easier and now allow the preparation of selected regioisomers and more unsymmetrical derivatives. Computational approaches for the prediction of suitable candidate molecules are still in its infancy and might never reach practical use [94]. However, the picture evolving for \textit{m}THPC analogs has reached a point where comparative QSAR studies are possible and able to identify suitable compounds for use in more advanced bioconjugate targeting systems.

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