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# Marine lipids for prodrugs, soft compounds and other pharmaceutical applications

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In the present review we discuss different approaches to pharmaceutical applications of marine lipids. Investigation of the use of marine lipids as dermal permeation enhancers, the synthesis of triacylglycerols highly enriched in polyunsaturated fatty acids, dermal pro-drugs derivatives of unsaturated fatty acids and diacyl glyceryl derivatives, and the possible synthesis of soft disinfectants from marine fatty acids.

## 1. Introduction

Marine lipids, sold as fish oils, are used for human consumption, and as animal and aquaculture feed. Their main constituents are triacylglycerols comprising a great variety of fatty acids. Marine lipids contain relatively high concentrations of derivatives of unsaturated fatty acids. The long chain n-3 polyunsaturated fatty acids are characteristic of marine lipids of which *cis*-5,8,11,14,17-eicosapentaenoic acid (EPA) and *cis*-4,7,10,13,16,19-docosahexaenoic acid (DHA) are the most abundant. EPA and DHA usually represent 10–25% of the fatty acids found in fish oil triacylglycerols [1] depending on species. Oleic acid is usually the most abundant monounsaturated fatty acid. Commercially available marine oils contain 10–20% oleic acid [2]. Glyceryl ethers of the 1-O-alkyl-2,3-diacyl-sn-glycerols type are major constituents of liver oil of certain species of shark and elasmobranchii fish [3] (Fig. 1).
The nutritional benefits of fish oils are well known. The consumption of polyunsaturated fatty acids from fish oil have been associated with a lowered risk of coronary heart disease [4, 5], improvement in inflammatory disease [4, 6] and better response to infection [6] and are thought to be an important nutrient for neural development [4, 5].
Although there has been a great interest in marine lipids as food supplements and several well known pharmaceutical excipients are obtained form marine lipids, relatively little attention has been paid to marine lipids as starting materials for drug synthesis partly because highly purified single chemical entities of marine lipids are not readily available. Here, different approaches to pharmaceutical applications of marine lipids are discussed.

## 2. Marine lipids as permeation enhancers

Various compounds such as dimethyl sulfoxide, ethanol, propylene glycol, glycerol and dimethyl formamide have been used as permeation enhancers for the percutaneous permeation of drugs. However small molecule weight permeation enhancers can permeate the skin as such and there is concern that some can cause systemic side effects. The fatty acids are relatively large endogenous compounds which, under normal conditions, do not cause any side effects. The fatty acids are also low cost additives available form various sources and have therefore been considered as permeation enhancers for dermal formulations. The saturated fatty acids are relatively well studied. The medium chain length fatty acids such as capric acid (10 : 0), lauric acid (12 : 0) and myristic acid (12 : 0) can all significantly enhance drug permeation [7]. The long chain fatty acids such as palmitic acid (16 : 0) and stearic acid (18 : 0) have much less effect and can in some cases retard permeation of drugs [8]. The fatty acids disturb the barrier function of the stratum cornea layer of the skin, as most other permeation enhancers, but other mechanisms have also been proposed. Unsaturated fatty acids, characteristic of marine lipids, work better as permeation enhancers than their unsaturated counterparts. Several investigators have studied the use of oleic acid and a more than 100-fold increase in permeation of drugs has been reported [7, 9, 10]. The fatty acid appears to have similar effect as other well known high molecular weight permeation enhancers such as Azone [7].
Fatty acids from marine lipids can be obtained as a by-product of the cod-liver oil refining process. This product has been evaluated as a possible permeation enhancer and also measured the contribution of the individual components [10]. Table 1 shows the major components (>3%) of the extract and the effect of the extract and the pure fatty

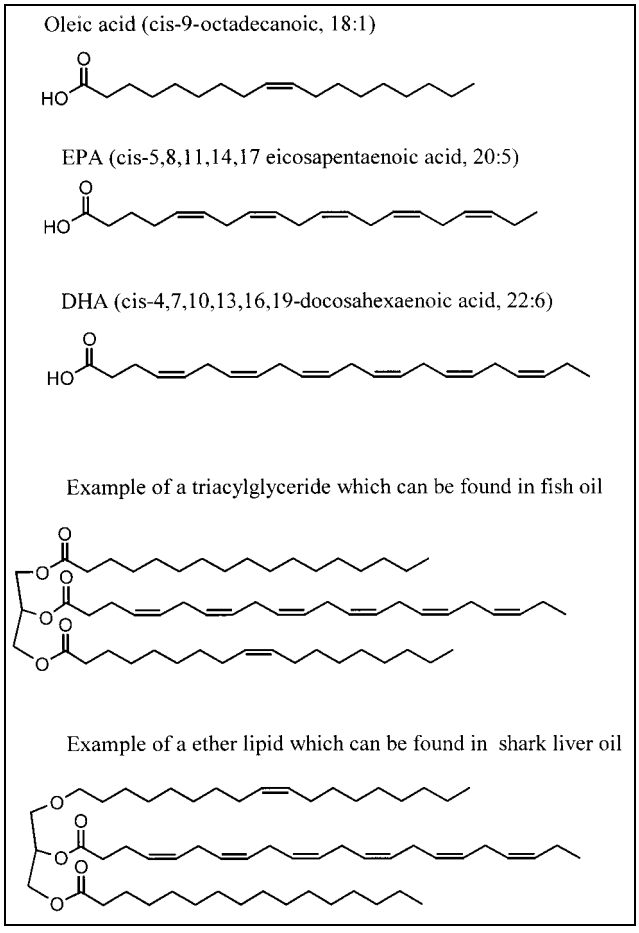



Fig. 1: Structures of typical marine lipids

**Table 1: Fatty acid composition of the cod liver oil extract and the effect on hydrocortisone permeation through hairless mouse skin**

| Fatty acid (carbons: double bounds) | Precentace of total weight | Permeation enhancement |
|---|---|---|
| Non | | 1 |
| The extract | | 25 |
| Unsaturated fatty acids | 83 | |
| Saturated fatty acids | 17 | |
| Myristic acid (14 : 0) | 3.6 | 0.8 |
| Palmitic acid (16 : 0) | 10.4 | 2.6 |
| Stearic acid (18 : 0) | 2.6 | 0.6 |
| Palmitoleic acid (16 : 1) | 6.5 | 640 |
| Cis-Vaccenic acid (18 : 1) | 4.4 | 380 |
| Oleic acid (18 : 1) | 16.3 | 250 |
| Cetoleic acid (22 : 1) | 7.7 | ND |
| EPA (20 : 5) | 9.6 | 440 |
| DHA (22 : 6) | 12.6 | 320 |

Only the major constituents of the extract (>2.5%) are shown. The vehicle for the skin permeation study was propylene glycol containing 1% hydrocortisone and 1% fatty acid (or extract)

acids on *in-vitro* permeation of hydrocortisone through hairless mouse skin. The extract increased the permeation 25-fold. The saturated fatty acids had little or negative effect on the permeation whereas the unsaturated fatty acids increased the permeation more than 200-fold. The polyunsaturated EPA and DHA were even more effective than the monounsaturated fatty acids. The effect of the extract was notably less than the sum of its parts. However the effect of the extract increased with increasing concentration, above 1%, whereas the effect of oleic acid remained constant above this concentration. Therefore an enrichment of the extract in unsaturated fatty acids, characteristic for marine lipids, could possibly improve the permeation enhancement. The permeation of hydrocortisone from an ointment formulation increased with addition of the extract. The permeation of 17β-estradiol through hairless mouse skin, from 1% propylene glycol solutions, was improved 10-fold by adding 3% of the extract to the solution.

1-O-Alkyl-2,3-diacyl-sn-glycerol monoethers were obtained by extraction from the unsaponifiable material of oils from shark and certain species of fish. We have investigated the permeation enhancing properties of the glycerol ether extract form the liver oil of deep-sea shark *(Centroporus squamosus)* [11].

Addition of a small amount of the extract to propylene glycol based vehicle resulted in a significant enhancement of drug delivery through hairless mouse skin (Table 2). The flux of hydrocortisone was increased just over 400-fold and the flux of 17β-estradiol was increased 6 to 7-fold and the nitroglycerine flux was increased 4.5-fold. The ether lipid extract was less effective than oleic acid at similar concentration [9, 10, 12, 13], but still a very powerful permeation enhancer. However the unsaturated fatty acids can cause skin irritation at relatively low concentrations [7, 14] whereas no irritation was observed when drug-free monoglyceride ethers ointment was applied to the skin of human volunteers [14].

**Table 2: Glycerol monoether enhancement of the permeation of drugs through hairless mouse skin**

| Glycerol monoether concentration (% w/v) | Enhancement of hydrocortisone permeation | Enhancement of 17β-estradiol permeation | Enhancement of nitroglycerine permeation |
|---|---|---|---|
| 0 | 1 | 1.0 | 1.0 |
| 0.5 | 140 | 6.7 | 1.6 |
| 1 | 180 | 5.8 | 2.8 |
| 2 | 400 | 3.5 | 4.5 |
| 3 | 440 | ND | ND |
| 5 | 420 | ND | ND |

The monoether and the drug were added to propylen glycol vehicle (donor phase)

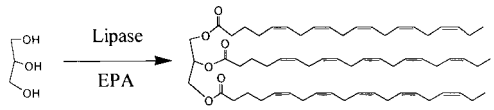
## 3. Synthesis of lipids enriched with polyunsaturated fatty acids

The health benefits of fish oils is different from dietary oils from other sources containing unsaturated fatty acids. These specific beneficial effects are attributed to the n-3 polyunsaturated fatty acids, in particular EPA and DHA [4–6, 15]. Consequently, there is a strong interest among researchers and within the health industry in oils containing lipids which are highly enriched with regard to these fatty acids [5].

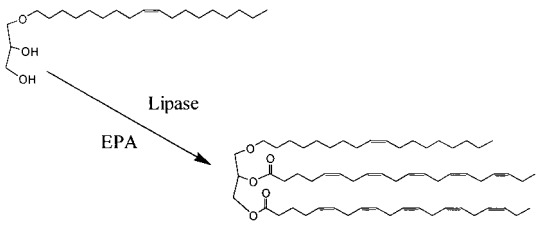
Triacylglycerol oils with concentrations of polyunsaturated fatty acids (EPA and DHA) up to 30% can be prepared directly form fish oils, without splitting of the fat, by various methods such as winterization, molecular distillation and solvent crystallisation [16]. The triacylglycerols, which can contain fatty acids in any combination, have to be cleaved to obtain higher concentrations. Specific methods, which are not suitable for large scale production are required to concentrate EPA and DHA above the 90% level [17].

The use of lipase offers some specific advantages [18]. Most conventional chemical esterification procedures will partly destroy the all-*cis* n-3 framework of EPA and DHA, whereas the lipase reactions can be carried out under very mild con-

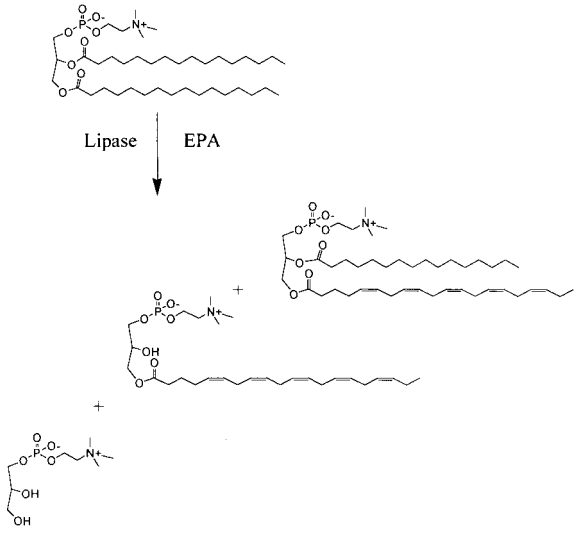
**Scheme 1**




a. Example of the direct esterification of glycerol with EPA




b. Conversion of 1-O-oleyl-sn-glycerol with EPA the presence of Lipase




c. Acidolysis of dipalmitoyl-sn-glycerol-3-phosphatityl choline in the presence of lipase and EPA (the three main products are shown)

ditions. Lipases can also be used to resolve EPA and DHA and their use is compatible with the production of compounds intended for human consumption as food supplements. Here we describe the use of lipase in the production of triacylglycerols, ether lipids and phospholipids enriched with EPA and DHA but we are also investigating the use of lipase to link these fatty acids with drug compounds.

A 1,3-regiospecific lipase form the fungus *Mucor miehei* was used to produce triacylglycerols highly enriched with EPA and DHA (Scheme 1a). Reaction in the presence of a threefold excess of either free fatty acid or ethyl ester resulted in an oil with 60–65% EPA + DHA content [17, 19]. The enzyme is 1,3-regiospecific and should therefore catalyse the reaction of the primary alcoholic end-positions of the triacylglycerols. Despite the regiospecificity randomization the substitution of EPA and DHA was observed. Further investigations showed that this was due to nonenzymatic intramolecular acyl migration during substitution, of fatty acids in the triacylglycerols [20].

A different lipase, the non-regiospecific yeast lipase from *Candida antartica*, was highly efficient in generating triacylglycerols containing 100% EPA and DHA. This was accomplished by direct esterification of glycerol with stoichiometric amounts of either pure EPA or DHA, without any solvent. The co-produced water was continuously removed by evacuation and thus driving the reaction to completion (Scheme 1a).

Similar methods were used to prepare ether lipids enriched with EPA and DHA. Isolated 1-O-alkyl-sn-glycerols were reacted with concentrates of EPA or DHA as free acids in reaction catalysed by *Candida antarctica* lipase (Scheme1b) or in a transesterification reaction catalysed by *Mucor miehei* lipase [21]. The fatty alcohol composition in the ether moiety was unchanged from the original 1-O-alkyl-sn-glycerol, where palmityl, stearyl and oleyl alcohols were the most abundant components. Interestingly, the 1-O-alkyl-2,3-diacyl-sn-glycerols were less prone to acyl migration than their triacylglycerol analogues.

Phospholids containing EPA and DHA are important components of the cell membranes in fish. These fatty acids presumably play a significant role in maintaining the membrane mobility at low temperature and allows it to function at temperatures typical for the marine environment. These compounds can have academic interest and could be used as new pharmaceutical ingredients for applications such as biodegradable liposomes [22, 23] and penetration enhancers [24].

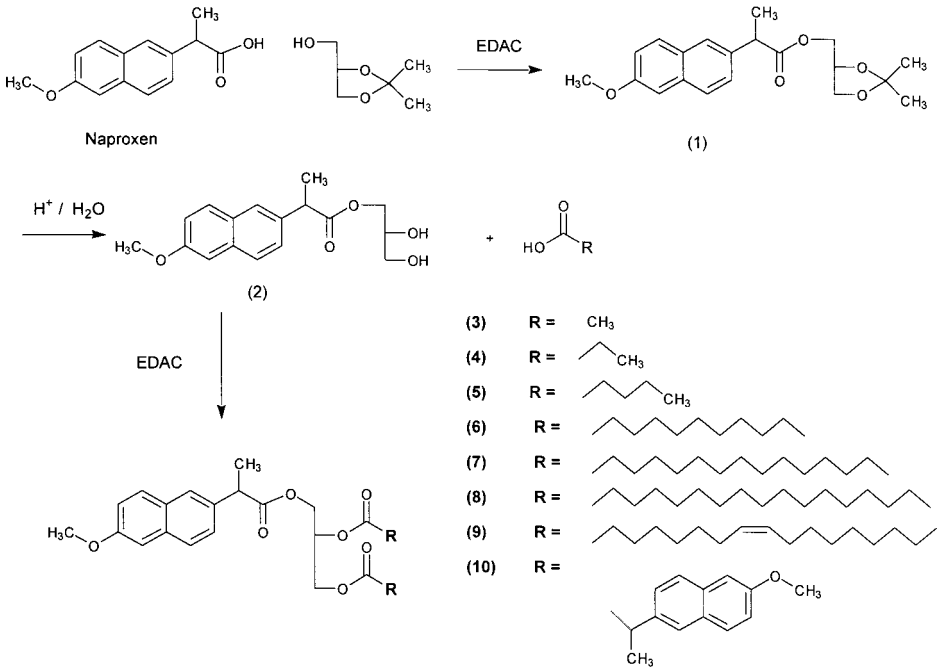
Dipalmitoyl-sn-glycero-3-phosphatidyl choline could be reacted with excess EPA using *Rhizomucor miehei* lipase as a catalyst [25]. Phosphatidyl choline is zwitterionic and a poor substrate for the lipase. Therefore, larger quantities of the enzyme were required. The enzyme contains 5% water and will also catalyse the hydrolysis of the desired phospholipid. The product was therefore partially hydrolysed. The final comprised 39% phosphatitylcholine containing 59% EPA, 44% lysophosphatidylcholine containing 70% EPA, and 17% glycerophosphatidylcholine, on molar basis (Scheme 1c). When 1-lyspalmitoyl-sn-phosphatityl choline was used as a substrate, 60% incorporation of EPA was achieved.

Until recently, lipases have mostly been used to incorporate EPA and DHA into glycerols and related compounds, but there is a wide range of possibilities to use lipase. The lipases can for example be used to concentrate EPA or DHA in fish oils through esterification and transesterification reactions [16, 26]. We are currently investigating the use of lipases to acylate drugs with fatty acids.

## 4. Prodrugs for dermal delivery derived from unsaturated fatty acids

Some diacyl glycerol prodrugs intended for oral application have previously been reported [27–29]. Using the diacyl glycerol pro-moiety for dermal prodrugs offers several advantages. The diacyl glycerol component is ubiquitous in the skin and should have little adverse effects after hydrolysis of the parent compound. The inclusion of a fatty acid in the structure could allow the compound to function similarly as the penetration enhancers previously mentioned. The prodrug could thus facilitate its own ab-

**Scheme 2**




Schematic illustration of the synthesis of the diacyl glycerol derivatives of naproxen

sorption. Furthermore, the structural similarity of the prodrug to the membrane lipids should improve binding in the lipophilic layers of the skin.

NSAID have been used in cream formulations to alleviate allergic skin reactions [30]. Naproxen is an NSAID mainly used in the management of arthritis. Topical application of this drug has been suggested to avoid gastric ulcerogenic side effects [31, 32]. We have investigated the synthesis of diacyl glyseryl esters of naproxen and their dermal application *in-vitro* [33].

The general synthesis procedure is shown in Scheme 2. The oleic acid moiety in compound **9** could function as permeation enhancer.

Acid catalysed degradation of the compounds followed pathway 2 and 3 (Scheme 3) whereby the aliphatic moiety was released first. The base catalysed reaction followed pathway 1 where the naproxen moiety was released first. The compounds were rapidly degraded, following pathway 1, by hydrolytic enzymes in biological samples. In both human serum and in hairless mouse skin homogenate the longer alkyl chain derivatives degraded faster than the short chain derivatives, whereas the reverse trend was observed for non-enzymatic hydrolysis. However, the degradation in biological samples of the longest alkyl chain derivatives could not be measured due to their low solubility.

The *in-vitro* penetration of the diacyl derivatives from propylene glycol solutions through hairless mouse skin was studied in Franz diffusion cells. The appearance of both the intact derivative and naproxen was measured in the receptor phase. The diacyl derivatives could not penetrate mouse skin *in-vitro*. However, after the lag period there was a constant release of naproxen into the receptor phase (Fig. 2). The rate of appearance of naproxen was comparable with the oleyl derivative (**9**) as with short and saturated alphatic chain derivatives (**3**, **5** and **6**). The accumulation of naproxen in the mouse skin was also measrued. After 4 h incubation there was about 10 times more dioleoyl derivative in the skin than dihexanoyl derivative and after 24 h there was still a 1.5 fold difference. This indicated a more rapid absorption of the dioleoyl derivative.

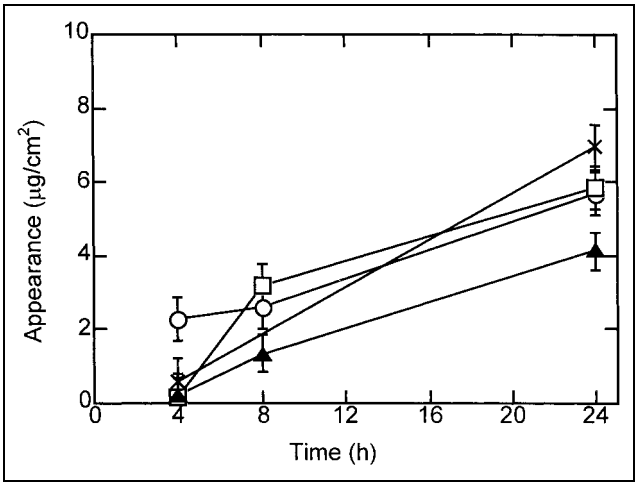


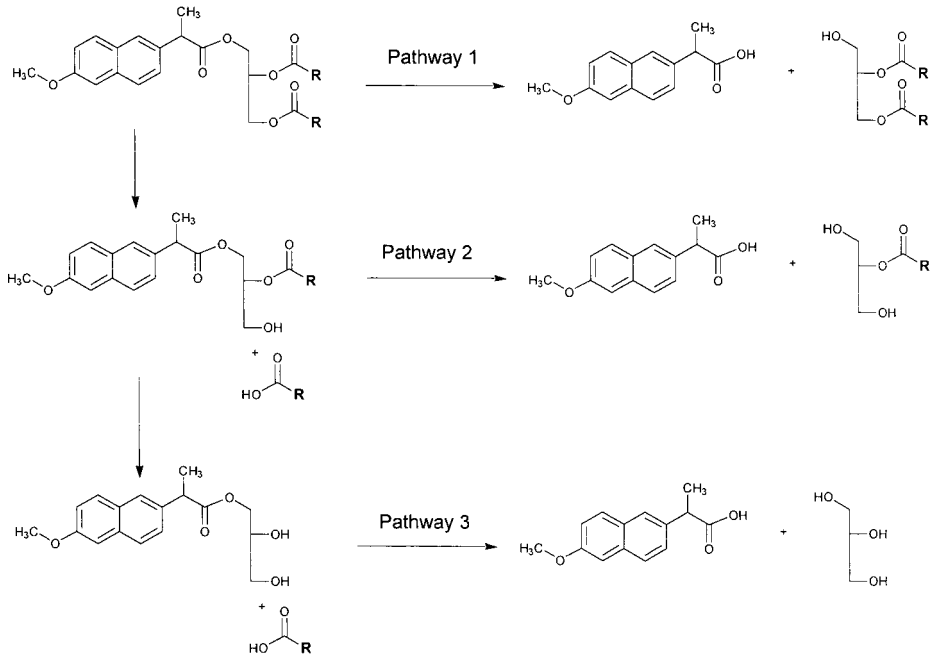

Fig. 2: Appearance of naproxen in the donor phase with 10 mg/ml compound (**3**) (×), (**5**) (▲), (**6**) (□) or (**9**) (○) in the donor phase

Dermal prodrugs containing fatty acids and an antibiotic drug moiety hold special interest because the fatty acid moiety could serve a double purpose. The fatty acid could enhance the permeation of the drug into the skin where the drug would be slowly released. Secondly the free fatty acid itself can have considerable antibacterial activity [34] and could thus enhance the efficacy of the drug.

The antimicrobial drug metronidazole has been used for topical application in the treatment of acne rosacea and acne vulgaris [35, 36]. This compound is very hydrophilic, which limits its dermal absorption. Application of this drug in the form of a more lipophilic prodrug could therefore be advantageous, especially if the drug was released at a significant rate within the skin.

We have synthesised, by carbodiimid coupling, some aliphatic esters of metronidazole with the aliphatic side chains containing 1 to 17 carbon atoms [37]. The structure of metronidazole laurate is shown in Fig. 3.

**Scheme 3**




Degradation pathways for the naproxen derivatives

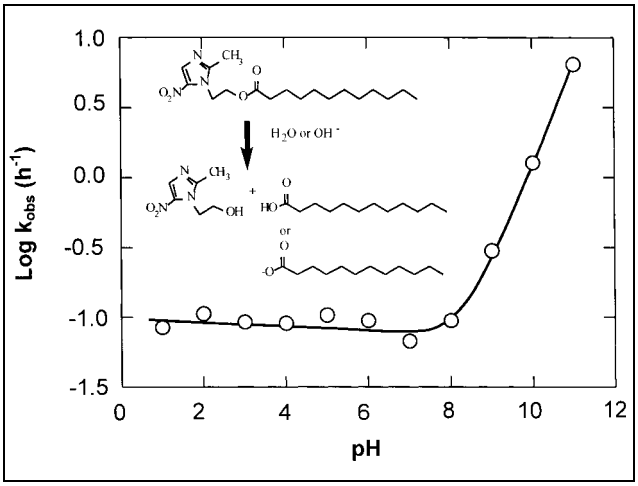



Fig. 3: pH-Degradation rate profile for metronitrazole lautate in KCl/HCl (pH 1) and citrate-phosphate-borate/HCl buffer (pH 2 to 11) at 60 °C. The hydrolysis reaction is shown

The fatty acid derivatives were hydrolysed to the parent compounds by specific base catalysis above pH 8.0. The degradation rate in serum was much faster, showing that under such conditions the reaction was mainly enzymatic. As in the case of the naproxen derivatives, the enzymatic conversion was faster for the longer alkyl chain derivatives. The penetration of the metronidazole derivatives through hairless mouse skin was measured in Franz diffusion cells. Metronidazole acetate (MN-acetate) was more lipophilic than metronidazole and penetrated hairless mouse skin approximately 10 times faster (Table 3). However the more lipophilic MN-butyrate could only penetrate hairless mouse skin with difficulty and most of the derivative was converted into free metronidazole before it appeared in the receptor phase. Only metronidazole appeared in the receptor phase when longer alkyl chain derivatives were applied. The calculated permeation was highest for MN-laurate and MN-oleate.

The oleate derivatives were well absorbed both in the case of the diacyl naproxen derivatives and in the case of the metronidazole derivative. Both compounds were present as oils and could be directly applied to the skin without any co-solvents. Further investigation of dermal prodrugs derived form monounsaturated and polyunsaturated fatty acids, characteristic of marine lipids, are therefore warranted. Recent investigations have shown that N-alcoxymethyl theophylline esters of EPA and DHA are rapidly hydrolysed by porcine liver esterase [38].

## 5. Soft antimicrobial compounds and antimicrobial activity of marine fatty acids

The spread of resistance to antibacterial agents in microorganisms is an increasing problem in modern society. By limiting unnecessary prescription of antimicrobial drugs and by avoiding their use in agriculture the viability of resistant microbial strains in the environment can be reduced [39–41]. However, requirements for good hygiene in workplaces such as in the food processing industry and the clinical setting has led to an increased use of antimicrobial disinfectants [42]. The only way to limit the exposure of microorganisms to disinfectants is to use materials that are not persistent in the environment. This can be achieved by the use of volatile disinfectants such as propylene alcohol and formaldehyde, but such compounds can be harmful to human health. Another approach would be designing soft antibacterial agents, which would rapidly be degraded into natural and biologically inactive compounds.

A first systematic approach to design and synthesise soft pharmaceuticals was introduced by Bodor and his coworkers two decades ago [43]. Since then soft anticholinergics [44], β-blockers [45], steroids [46] and antimicrobials [47] have been introduced and various other types of soft compounds have been synthesised.

The structure and the synthesis of one original soft quaternary ammonium antibacterial compound (**11**) [47] is shown in Scheme 5. Enzymatic hydrolysis led to a complete loss of activity. Compounds **12** [48] and **13** [49] have also been introduced as soft antimicrobial agents. Recently we have synthesised series of 1-pyridinium acetyl esters of fatty acid alcohols with the same general structure as **14** [50]. All these compounds were analogues of quaternary surface-active agents, such as hexadecyl pyrdinium chloride (**15**), which are commonly used disinfectants. The soft analogues contain an ester linkage which can be hydrolysed. The soft compounds are generally somewhat less effective against microbes than the traditional antimicrobial agents. However, the *in vivo* toxicity of **11** was 40 times lower than that of **15**, which more than compensated for lower activity [47].

We are presently investigating soft quaternary antimicrobials derived from fatty acids of marine origin. Inclusion of unsaturated fatty acids in the antimicrobial structure may bring additional benefits. The unsaturated fatty acids can inactivate viruses and bacteria at relatively low concentrations [34, 51, 52]. Thus, beneficial effects of the free fatty acids would be observed after degradation of the soft antimicrobial compound into products which would have no adverse effects on the environment.

## 6. Conclusion

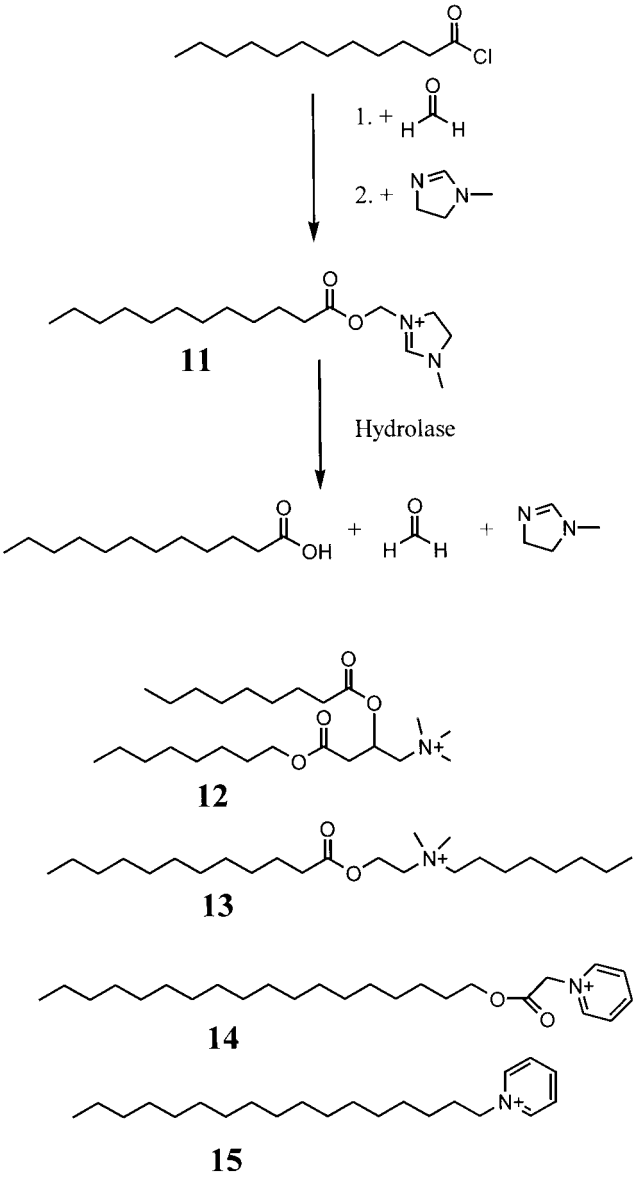
Benefits of marine lipids for human consumption are linked to the presence of unsaturated fatty acids. The lack of saturation also confers additional benefits as these compounds can be used as percutaneous penetration enhancers. Many of the naturally occurring derivatives can be selectively synthesised under mild conditions, in reactions catalysed by lipases. The marine lipids are non-toxic and

**Table 3: Flux and permeation of metronidazole and metronidazole derivatives through hairless mouse skin**

| Compound | Flux of compound $\mu g/(h \times cm^2) \pm SD$ | Appearance of metronidazole $\mu g/(h \times cm^2) \pm SD$ | Total flux of compounds $nmol/(h \times cm^2) \pm SD$ | Permeation of compounds* $(cm/h \pm SD) \times 10^6$ |
|---|---|---|---|---|
| Metronidazole (MN) | 0.17 ± 0.03 | 0.17 ± 0.03 | 1.0 ± 0.2 | 0.17 ± 0.03 |
| MN-acetate | 1.83 ± 1.46 | 1.63 ± 0.90 | 18.2 ± 12.2 | 3.9 ± 2.6 |
| MN-butyrate | 0.17 | 4.10 ± 0.93 | 24.8 ± 5.4 | 6.0 ± 1.3 |
| MN-laurate | 0 | 6.65 ± 6.13 | 39.1 ± 36.1 | 13.8 ± 12.7 |
| MN-palmitate | 0 | 1.58 ± 1.79 | 9.3 ± 10.5 | 3.8 ± 4.3 |
| MN-oleate | 0 | 3.80 ± 0.41 | 22.3 ± 2.4 | 9.7 ± 1.0 |

* Permeation of the compounds was calculated as the total flux of compounds ($nmol \cdot h^{-1} \cdot cm^{-2}$) divided by the concentration of the prodrug in the donor phase ($nmol \cdot ml^{-1}$)

**Scheme 4**




Soft antibacterials based on fatty acids and fatty alcohols

readily metabolised in humans and by other organisms. In our ongoing research we are investigating how these attractive properties of readily available starting materials can be utilised in prodrug and soft drug development.

This research paper was presented during the 2nd Conference on Retrometabolism based Drug Design and Targeting, May 11–14, 1999, Amelia Island, Florida, USA

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