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Inhibition of secretory phospholipase A_2. 2-Synthesis and structure–activity relationship studies of 4,5-dihydro-3-(4-tetradecyloxybenzyl)-1,2,4-4*H*-oxadiazol-5-one (PMS1062) derivatives specific for group II enzyme

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Abstract—We have recently reported the discovery of a series of specific inhibitors of human group IIA phospholipase A_2 (hGIIA PLA_2) to display promising in vitro and in vivo properties. Here we describe the influence of different structural modifications on the specificity and potency against hGIIA PLA_2 versus porcine group IB PLA_2. The SAR results, as well as the log *P* and pK_a values of oxadiazolone determined in this work, provide important information towards the comprehension of the mode of action of this kind of compounds.

1. Introduction

The family of phospholipase A_2 (PLA_2) is composed of 12 groups up to date,[1,2] including intracellular PLA_2, such as cytosolic $cPLA_2$ and calcium-independent $iPLA_2$, and secretory $sPLA_2$s. PLA_2 specifically catalyses the hydrolysis of the *sn*-2 ester bond of glycerophospholipids to release free fatty acids and lysophospholipids. In the case of arachidonic acid (AA) and/or lyso-Platelet-Activating Factor (lyso-PAF), inflammatory cascade can be switched on to produce eicosanoids (prostaglandins, leukotrienes and thromboxanes) and/or PAF by variable enzymes such as cyclo-oxygenases (Cox-1 and Cox-2), lipo-oxygenases and PAF-acetyltransferase.

Intracellular PLA_2s are of high molecular weight (60–110 kDa), either submicromolar Ca^{2+}-dependent for translocation rather than for catalysis or Ca^{2+}-independent. The only intracellular PLA_2, which shows a marked preference for AA over other fatty acids is Group IVA PLA_2 (GIVA PLA_2, $cPLA_2\alpha$), and consequently represents a putative inflammation inducer. However, it is only in recent years that this enzyme has received considerable medicinal interest.[3–5]

Secretory PLA_2s ($sPLA_2$s), including Group IB (GIB), GII (A, C, D, E and F), Group III (GIII), Group V (GV), Group X (GX) and Group XII (GXII), are by contrast of low molecular weight (14–18 kDa), except that they contain either an unusually long C-terminal (GIIF) or both N- and C-terminal extensions (GIII). They are all cysteine-rich (5–8 disulfide bridges), structurally globular, millimolar calcium-dependent for catalysis and interfacial enzymes.[1,2,6] GIB $sPLA_2$ is originally named as pancreatic enzyme and considered since its identification to be essential for dietary lipid digestion. Recently it is found to also contribute to other biological

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processes and propagation of inflammation through binding to specific receptors.[7,8] However, other above-mentioned sPLA$_2$s, except for GIIC (pseudogene in human) and GXII sPLA$_2$s,[9] are all reported to be able to induce stimulus-dependent or spontaneous AA release in different cell lines and thus be involved in inflammatory process under certain conditions.[2,9] Although the Ca^{2+}-binding loop (XCGXGG) and the catalytic site (DXCCXXHD) are highly conserved among the AA-releasing sPLA$_2$s and they use exclusively a His/Asp dyad for the catalytic hydrolysis of substrates,[2,8] certain differences are observed between these enzymes in their preference to one or another substrate. The presence of a Trp residue (naturally or introduced by mutation) on the interfacial binding surface (IBS)[10–12] is likely to play an important role in this substrate discrimination. On the other hand, the structure and the size of the active site of each enzyme are critical in the substrate selection, as demonstrated by the crystal structure comparisons of GIB, GIIA and recently GX enzymes, alone or complexed by a substrate analogue or inhibitor.[13–16]

X-ray structure-based drug design,[15] starting from a hit obtained by high through-put screening, enabled Lilly Company to discover in 1996[17–19] a series of highly specific inhibitors of hGIIA sPLA$_2$ versus hGIB, with the leader compound, LY315920, having an IC$_{50}$ of 9 nM to hGIIA sPLA$_2$ and a selectivity (hGIIA/hGIB) of 25-fold.[19] Our laboratory has worked on the development of sPLA$_2$s inhibitors since more than a decade, based on the fact that a natural substrate contains a hydrophilic head and a group of hydrophobic tails, and the early structures of porcine GIB and hGIIA complexed with a substrate analog.[13,14] Different cyclic matrixes, including phenyl and piperazine, have been used to carry a hydrophilic group, such as carboxylic acid, sulfonamide, amide, amidine and a great number of heterocycles, and a linear aliphatic chain of various lengths to mimic the hydrophilic head and the hydrophobic tails, respectively, of a natural substrate.[20–23] This original approach led to the recent discovery of a series of specific GIIA sPLA$_2$ inhibitors with the structure of the leader compound **PMS1062** shown in Figure 1.[23]

In an in vitro enzymatic assay, it exhibited a specific inhibition activity towards GIIA sPLA$_2$s (IC$_{50}$ of about 3 μM) versus GIB enzymes (IC$_{50}$ > 100 μM), and has been shown to be active in the carrageenan-induced oedema model when *ip* administrated, but inactive per os.

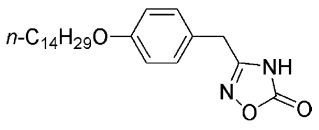


Figure 1. Chemical structure of **PMS1062**.

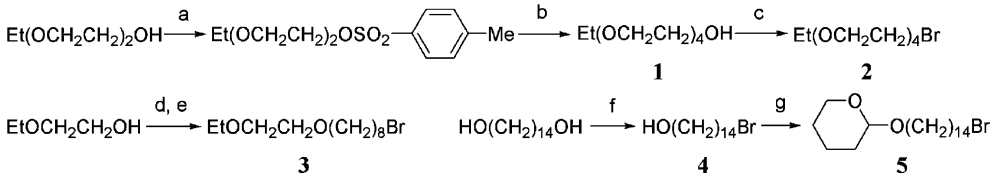
In this work, we have examined the influence of different structural modifications of the above molecule on the specificity and the potency towards porcine GIB and hGIIA sPLA$_2$s. They include aliphatic chain length optimization and insertion of different numbers of oxygens in this chain, replacement of the oxygen atom connecting the alkyl and phenyl groups by other heteroatoms or functions, elongation by adding one more methylene and methylation of the linker between the two rings, utilization of two aliphatic chains instead of one along with some functions, through an amino group or by new substitution of the phenyl group, and N^2 or N^4-methylation of the heterocycle. All of these derivatives have been evaluated in our enzymatic assay for their inhibitory potency against GIB and GIIA sPLA$_2$s. This SAR study, as well as the determination of the log *P* and the pK_a values of oxadiazolone, provides important information towards the comprehension of the mode of action of this kind of compounds.

2. Results and discussion

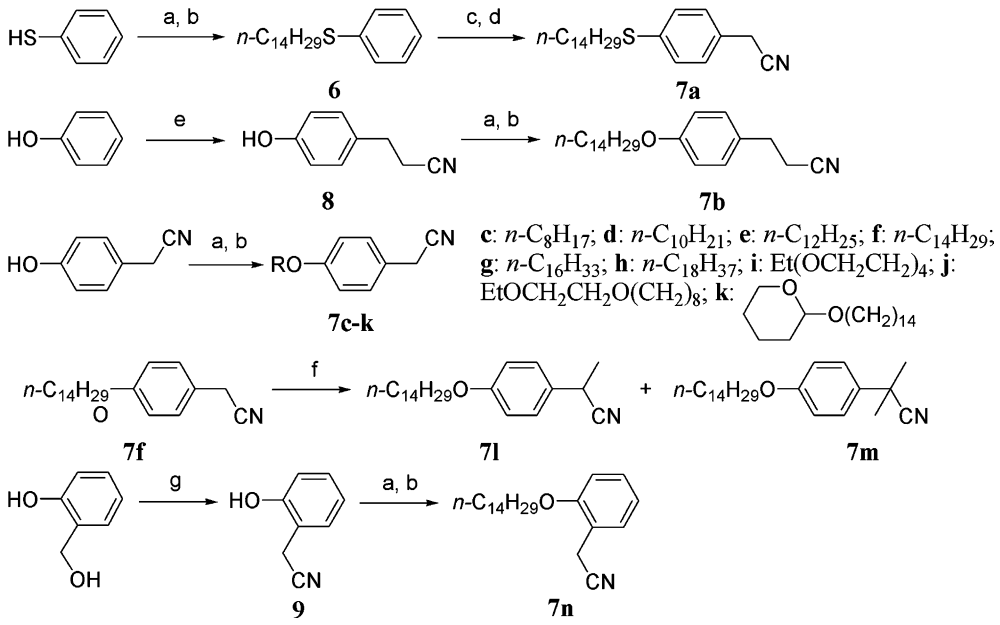
2.1. Chemistry

As outlined in Scheme 1, different alkyl bromides were prepared as key starting materials. Diethyleneglycol monoethyl ether was quantitatively tosylated and the tosylate when treated with diethyleneglycol led to **1**, which was brominated by PBr$_3$ to yield **2**. Starting from commercially available 1,8-dibromooctane and 2-ethoxyethanol, **3** was obtained easily in one step. 1,14-Tetradecanediol was transformed into the monobromide derivative **4** by concentrated aqueous HBr using liquid–liquid extraction and the second hydroxy group was then masked with 3,4-dihydro-2*H*-pyran to provide **5**.

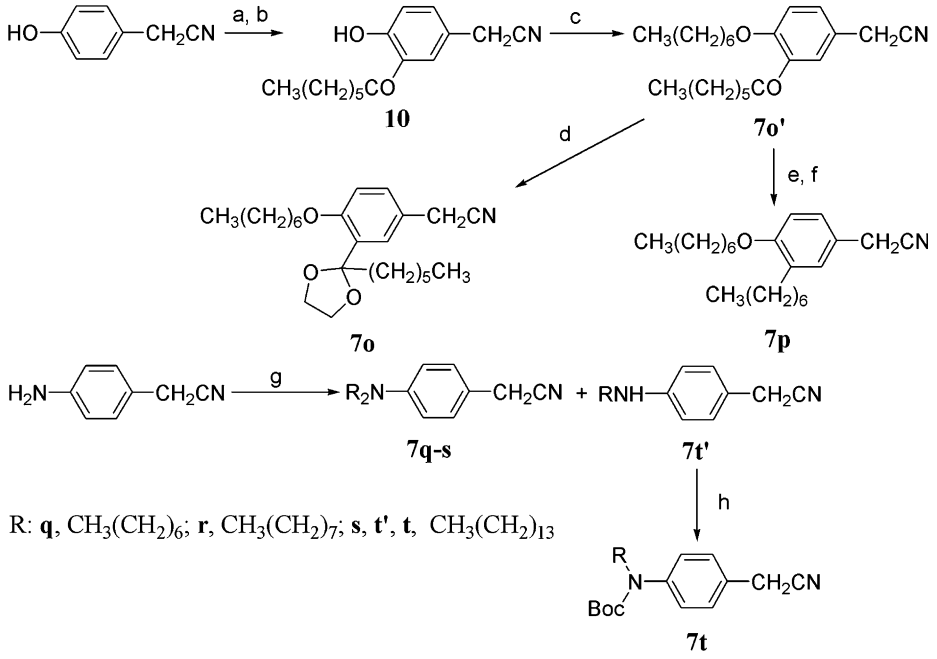
O- or *S*-Alkylation of the phenol or thiophenol derivatives were achieved by condensation of the corresponding alkyl bromides and sodium phenolates or thiophenolate, which were prepared by evaporation of the solvent of a mixture of sodium hydroxide and the phenol derivatives or thiophenol in absolute ethanol prior to use (**6**, **7b**–**k**,**n**, Scheme 2). In the cases where the starting nitriles were not available, the compound **8** was synthesized by cyanoethylation from phenol, while **9** from the corresponding alcohol. The compound **7a** was prepared by bromomethylation of **6**, followed by a nucleophilic substitution with sodium cyanide. α-



Scheme 1. Reagents and conditions: (a) tosyl chloride, Et$_3$N, Et$_2$O; (b) HOCH$_2$CH$_2$OCH$_2$CH$_2$OH, NaH, DMF; (c) PBr$_3$, 100 °C; (d) NaH, DMF; (e) Br(CH$_2$)$_8$Br, DMF; (f) 42% HBr, *n*-heptane, 90 °C; (g) 3,4-dihydro-2*H*-pyran, cat. 37% HCl, anhydrous Et$_2$O.



Scheme 2. Reagents and conditions: (a) NaOH, abs EtOH; (b) n-$C_{14}H_{29}Br$, DMF; (c) $(CH_2O)_n$, 45% HBr; (d) NaCN, DMF; (e) CH_2=CHCN, $AlCl_3$; (f) NaH, CH_3I, DMF; (g) NaCN, DMF, 110–130 °C.

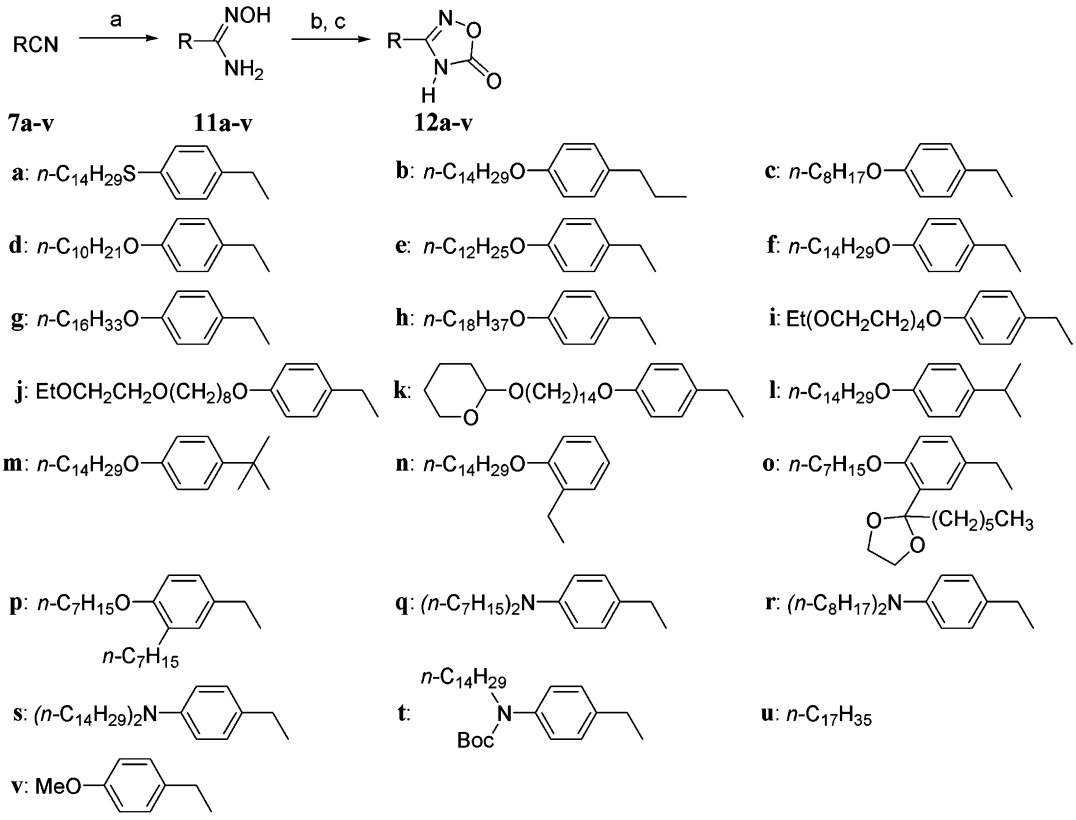


Scheme 3. Reagents and conditions: (a) $CH_3(CH_2)_5COCl$, Et_3N, CH_2Cl_2; (b) $AlCl_3$, $PhNO_2$, 130 °C; (c) $CH_3(CH_2)_6Br$, K_2CO_3, CH_3CN, reflux; (d) $HOCH_2CH_2OH$, PTSA, toluene, reflux; (e) $NaBH_4$, MeOH; (f) Et_3SiH, TFA, 0 °C; (g) RBr, K_2CO_3, CH_3CN; (h) Boc_2O, K_2CO_3, CH_3CN/1,4-dioxane.

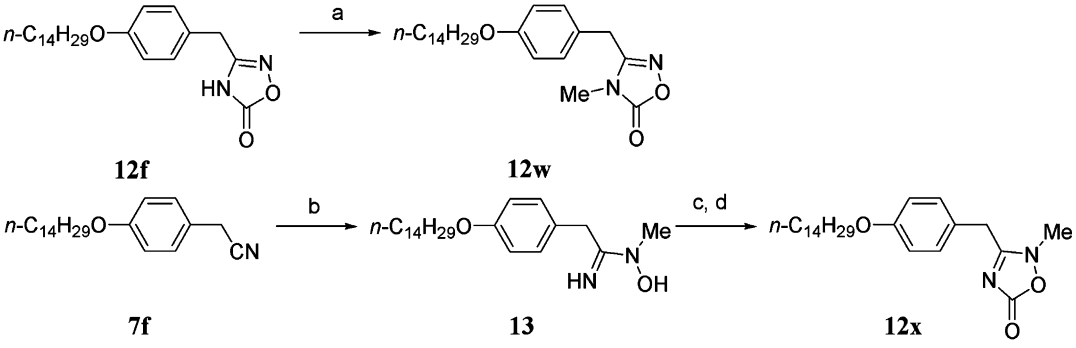
Methylation of the compound **7f** led to the formation of both mono and di-methyl derivatives **7l** and **7m**.

Dialkylated nitrile derivatives were obtained as described in Scheme 3. Esterification of 4-hydroxybenzyl cyanide by heptanoyl chloride, followed by Fries rearrangement provided **10**, which was alkylated as above with 1-bromoheptane to give **7o′**. The latter was either reduced to **7p**, or protected with ethyleneglycol to afford the 1,3-dioxolane derivative **7o**. The dialkylation of 4-aminophenylacetonitrile was more straightforward, using different alkyl bromides and in result, **7q**–**s** were obtained. The secondary amine of **7t′**, which was formed predominantly under the reaction conditions used, was masked with a Boc protecting group to lead to the formation of **7t**.

The nitriles **7a**–**t**, as well as commercially available stearonitrile (**7u**) and 4-methoxybenzyl cyanide (**7v**) were then transformed into amidoxime **11a**–**v** by hydroxylamine, free base released from its HCl salt in situ by potassium carbonate. The oxadiazolones **12a**–**v** were



Scheme 4. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, K_2CO_3, abs EtOH, reflux; (b) PhOCOCl, Et_3N, $CHCl_3$; (c) toluene, reflux.



Scheme 5. Reagents and conditions: (a) CH_2N_2/ether, K_2CO_3, DMF; (b) MeNHOH·HCl, K_2CO_3, abs EtOH; (c) ClCOOEt, Et_3N, CH_2Cl_2; (d) toluene, reflux.

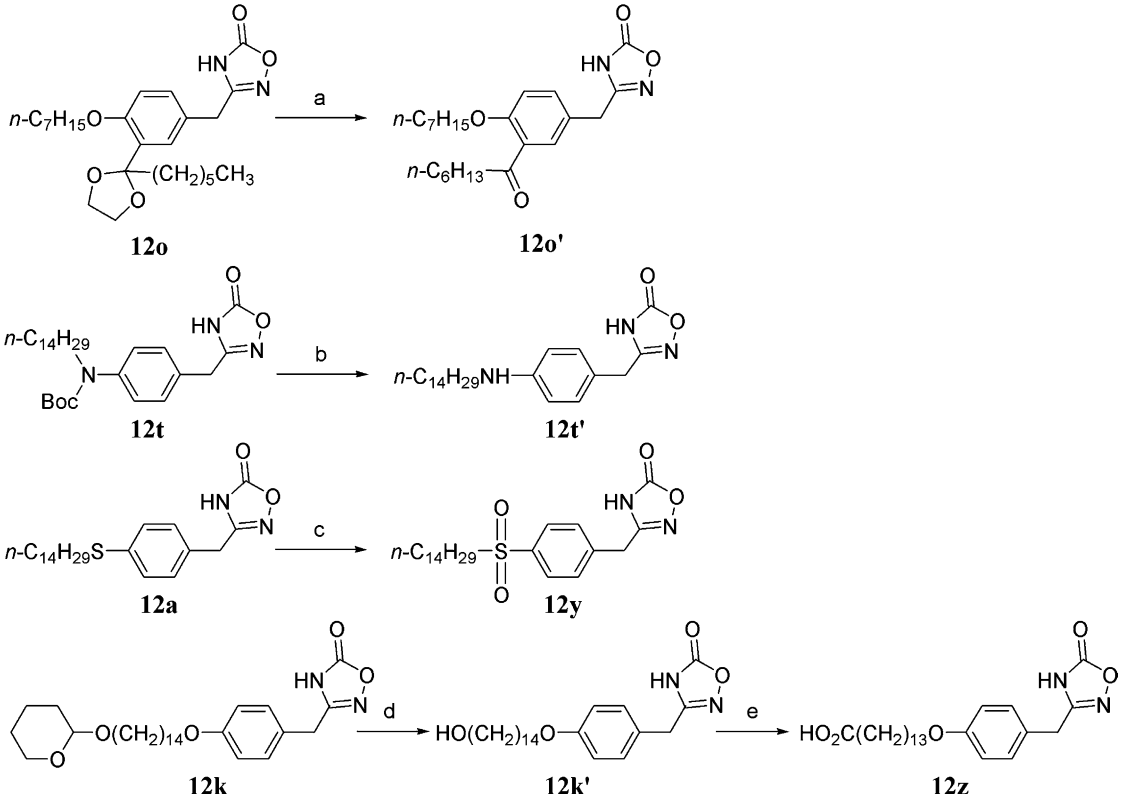
then obtained by cyclization of the crude carbonate intermediates, derived by reaction of the corresponding amidoximes with phenyl chloroformate (Scheme 4).

Direct methylation of the oxadiazolone ring in **12f** (**PMS1062**) with diazomethane has exclusively supplied the N^4-methyloxadiazolone derivative, **12w**, while the N^2-methyl isomer, **12x** was obtained by using *N*-methylhydroxylamine instead of hydroxylamine in the formation of the key intermediate, *N*-methyl-*N*-hydroxylamidine **13** (Scheme 5).

Acid hydrolysis of the protecting groups in **12k**,**o** and **12t** led to the formation of **12k′**,**o′** and **12t′**, respectively (Scheme 6). The alcohol function of **12k′** was then oxidized to carboxylic acid to afford **12z** (Scheme 6). Similarly, oxidization of the thioether **12a** yielded the corresponding sulfone **12y** (Scheme 6).

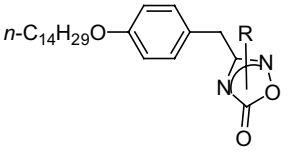
2.2. Biological activity and SAR study

We have demonstrated previously that the specificity has emerged when a basic heterocycle, such as imidazoline, was replaced by oxadiazolone, but unfortunately **PMS1062** was inactive per os in the carrageenan-induced oedema test.[23] This prompted us to determine the pK_a and the partition coefficient of oxadiazolone, two physicochemical parameters important for the comprehension of the activity as well as the specificity of **PMS1062** and the analogues described in this work.



Scheme 6. Reagents and conditions: (a) PPTS, H_2O/acetone, reflux; (b) HCl gas, dry THF, 0 °C; (c) CrO_3/H_2SO_4, acetic acid; (d) PPTS, EtOH, 55 °C; (e) CrO_3/H_2SO_4, acetone/THF, 0 °C.

Table 1. Inhibition of the enzymatic activity of porcine pancreatic PLA_2 (pGIB) and human group IIA PLA_2 (hGIIA) by **PMS1062** derivatives and influence of N^2 or N^4-methylation of oxadiazolone (R)

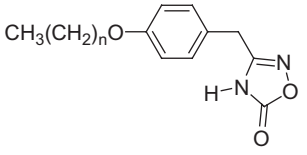


Compound	R	Log P[a]	IC_{50}[b] (μM)	
			pGIB	hGIIA
12f[23]	H	7.08	>100	3.4
12w	4-Me	7.31	>100	>100
12x	2-Me	7.31	>100	>100
LY311727[25]			8.0	0.47

[a] Calculated using the experimental data of **12v** and Rekker's hydrophobic fragmental constants.[24]

[b] Determined with three or more independent sample preparations using the fluorimetric binding assay and given as mean value with SD less than 20% of the mean value.

Table 2. Influence of the chain length (n) and the phenoxy group



Compound	n	Log P[a]	IC_{50}[b] (μM)	
			pGIB	hGIIA
12c	7	3.96	>50	ND
12d	9	5.00	>100	40
12e	11	6.04	>100	ND
12f[23]	13	7.08	>100	3.4
12g	15	8.12	36% at 100 μM	2
12h	17	9.16	44% at 100 μM	0.7
12u[c]	15	6.90	>100	15

[a] Calculated using the experimental data of **12v** and Rekker's hydrophobic fragmental constants.[24]

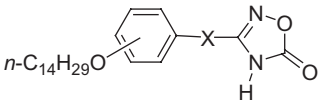
[b] Determined with three or more independent sample preparations using the fluorimetric binding assay and given as mean value with SD less than 20% of the mean value.

[c] Without phenoxy group in its structure.

Thanks to the water-soluble property of **12v**, the pK_a of oxadiazolone has been measured by a classical acid–base titration, being of 5.5 and the partition coefficient (log P) in phosphate buffer (pH 7.4)/n-octanol determined to be of −2.1 units of log P, using the experimental data of **12v** (log P: 0.33) and Rekker's fragmental constants.[24]

All the final compounds were evaluated in our in vitro enzymatic assay for their inhibitory potency against porcine GIB and human GIIA $sPLA_2$s and the results obtained are listed in Tables 1–6 with the corresponding log P values calculated as described above. This method has been demonstrated in our previous publication[23] to be efficient and reliable. Indeed, when **PMS1062** was evaluated in a spectrophotometric assay using a monomeric *sn*-2 thioester as substrate and DTNB as indicator of the enzymatic reaction, similar results were obtained.

Table 3. Influence of the position (*o*, *p*) and the nature of the linker (X) between the two rings

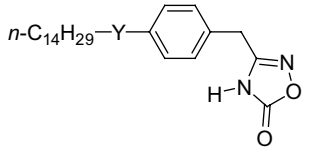


Compound	X		Log *P*[a]	IC_{50}[b] (μM)	
	o, *p*	Nature		pGIB	hGIIA
Ref. 23	*p*	None	6.56	>100	11
12f[23]	*p*	CH_2	7.08	>100	3.4
12b	*p*	CH_2CH_2	7.60	>100	3
12l	*p*	$CHCH_3$	7.60	>100	17
12m	*p*	$C(CH_3)_2$	8.12	>100	34
12n	*o*	CH_2	7.08	>100	33

[a] Calculated using the experimental data of **12v** and Rekker's hydrophobic fragmental constants.[24]

[b] Determined with three or more independent sample preparations using the fluorimetric binding assay and given as mean value with SD less than 20% of the mean value.

Table 4. Influence of the function (Y) branching the alkyl chain

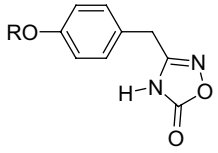


Compound	Y	Log *P*[a]	IC_{50}[b] (μM)	
			pGIB	hGIIA
12f[23]	O	7.08	>100	3.4
12a	S	7.64	>100	1.6
12t′	NH	6.57	73	3.3
12y	SO_2	5.66	49	2

[a] Calculated using the experimental data of **12v** and Rekker's hydrophobic fragmental constants.[24]

[b] Determined with three or more independent sample preparations using the fluorimetric binding assay and given as mean value with SD less than 20% of the mean value.

Table 5. Influence of insertion of oxygens in or incorporation of a functional group at the end of the alkyl chain (R)



Compound	R	Log *P*[a]	IC_{50}[b] (μM)	
			pGIB	hGIIA
12f[23]	$CH_3(CH_2)_{13}$	7.08	>100	3.4
12i	$Et(OCH_2CH_2)_4$	0.93	>100	>100
12j	$EtO(CH_2)_2O(CH_2)_8$	3.42	>100	34
12k′	$HO(CH_2)_{14}$	5.42	>100	17
12z	$HO_2C(CH_2)_{13}$	5.43[c]	26.4	3.8

[a] Calculated using the experimental data of **12v** and Rekker's hydrophobic fragmental constants.[24]

[b] Determined with three or more independent sample preparations using the fluorimetric binding assay and given as mean value with SD less than 20% of the mean value.

[c] 1.37 when taking the carboxylate form.

In the last assay, the enzyme really works in the worst conditions, because it prefers organized substrates. To verify the reliability of this method, one of the specific and active site targeted hGIIA PLA_2 inhibitors of Lilly Company, LY311727,[15] was tested in the same conditions. The IC_{50} value towards hGIIA PLA_2, 0.47 μM obtained is well consistent with its apparent K_B of 0.27 μM against the same enzyme in a tissue-based assay,[15] although its specificity is observed less in our fluorimetric assay conditions than reported previously.[25] This could be due to the difference of the two assay systems and in particular to the side-specific effect of the inhibitor on the substrate vesicles in the case of our fluorimetric assay.

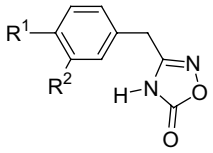
The importance of the acidity of oxadiazolone in **PMS1062** was examined by *N*-methylation. No activity was detected when the N^2 or N^4-methylated derivatives (**12x** and **12w**) were submitted to the in vitro enzymatic assay at the highest concentration of 100 μM tested (Table 1). Nevertheless, any importance in terms of enzyme–inhibitor interactions should not be attributed to this acidic proton, since the enzymatic assay was carried out at neutral pH (7.4) with which oxadiazolone should be apparently in its anionic form. In result, it is this anionic form of oxadiazolone in **PMS1062** that is responsible of the specific recognition between the inhibitor and GIIA $sPLA_2$.

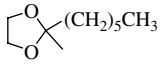
Thanks to the determination of the partition coefficient of **12v**, the log *P* of **PMS1062** has been found to be as high as 7.1 (Table 1), which is certainly unfavourable for its bio-distribution. It is not surprising to find it inactive when tested per os in the carrageenan-induced oedema model.

The choice of the aliphatic chain length in **PMS1062** was based on our previous results of nonspecific inhibitors of $sPLA_2$s.[20] However, it seemed evident that this needed to be re-optimized in this series of specific inhibitors. In consequence, different lengths of alkyl chain from C8 to C18 were introduced and their influence on the IC_{50} and the specificity were studied. As can be seen in Table 2 (**12c**–**h**), longer alkyl chain analogues inhibit better the GIIA $sPLA_2$, while the specificity is less when the carbon number is superior to 14. In result, the optimal chain length is C14 taking into account both inhibition capacity and specificity. It is worthwhile to note that the phenoxy group is important but not absolutely necessary, since **12u**, which does not contain this group remains specific and only 5-fold less active than **PMS1062**.

As shown in our previous publication,[23] when the linker methylene between the phenyl and the oxadiazolone rings in **PMS1062** was deleted, the inhibition activity decreased to one fourth (Table 3). This led us to modify the linker in order to appreciate more deeply its contribution to both activity and specificity. The linker was firstly elongated by another methylene (**12b**, Table 3), little variation of both IC_{50} and specificity as compared to **PMS1062**, along with the earlier result[23] suggests that a free rotation, thanks to the presence of at least one methylene as linker, is important for the relative orienta-

Table 6. Influence of double alkyl chains (R^1 and R^2)



Compound	R^1	R^2	Log P[a]	IC_{50}[b] (μM)	
				pGIB	hGIIA
12f[23]	*n*-$C_{14}H_{29}O$	H	7.08	>100	3.4
12o	*n*-$C_7H_{15}O$		6.01	>100	19
12p	*n*-$C_7H_{15}O$	*n*-C_7H_{15}	7.08	>10	7% at 10 μM
12o′	*n*-$C_7H_{15}O$	*n*-$C_6H_{13}CO$	5.78	68	18
12q	(*n*-C_7H_{15})$_2$N	H	6.77	>100	25
12r	(*n*-C_8H_{17})$_2$N	H	7.81	>100	8
12s	(*n*-$C_{14}H_{29}$)$_2$N	H	14.0	>100	1.3
12t	(*n*-$C_{14}H_{29}$)(Boc)N	H	5.13	>100	13

[a] Calculated using the experimental data of **12v** and Rekker's hydrophobic fragmental constants.[24]
[b] Determined with three or more independent sample preparations using the fluorimetric binding assay and given as mean value with SD less than 20% of the mean value.

tion of these two rings and therefore for the inhibitory activity. On the other hand, when the linker methylene in **PMS1062** was methylated once or twice, the inhibitory potency decreased 5- to 10-folds (**12l** and **12m**, Table 3). This is likely due to an unfavourable steric hindrance induced by the methyl group(s). Finally, when the linker was on the *ortho* position of the alkoxy group (**12n**, Table 3), a 10-fold loss in the activity was found, probably due to an unsuitable relative orientation of the rings or a steric hindrance. Nevertheless, what should be underlined is that the specificity is not lost upon these structural modifications.

The enhancement of the inhibitory potency, resulting from the replacement of the oxygen between the hydrophobic tail and the phenyl group (Table 4) of **PMS1062** by a sulfur atom, could be likely explained by the increase of global hydrophobicity of the molecule. Nevertheless, when the thioether was oxidized to sulfone (**12y**), the IC_{50} remained to be as low as that before oxidization, but the specificity was significantly reduced. It suggests that the sulfone group could create new (or reinforce) interactions between the inhibitor and the GIB enzyme, while would not have any influence on those between the inhibitor and the GIIA $sPLA_2$. It seems less probable that the loss of 2 units of log P in **12y**, as compared to **12a** (Table 4) and the electron-withdrawing effects ($-M$) of SO_2 instead of electron-donating effects ($+M$) of O or S could be responsible of this loss of specificity, since the phenyl group is important but not absolutely necessary for the activity (see above) and some compounds which are much less hydrophobic than **PMS1062** remain to be specific (see below). The similar result, obtained when NH is used to replace the oxygen (**12t′**, Table 4), agrees with the argument about the decrease in specificity in the case of the sulfone.

The high lipophilicity of **PMS1062** represents a real obstacle for its biodistribution and consequently prevents it from any oral application. To decrease the hydrophobic character, different numbers of oxygens were inserted into the alkyl chain, while its length was maintained to be 14 atoms. Surprisingly, when four oxygens were dispensed regularly in the C14 chain (**12i**, Table 5), no activity was detected at the highest concentration tested, 100 μM no matter, which $sPLA_2$ was used. This could be because of the loss of global hydrophobicity of the molecule (decrease of log P from 7.08 to 0.93 units), but the turn-over seems too spectacular, especially when taking into account the inhibition and log P data of **12z** (Table 5). Another explanation could be the disruption of Van der Waals interactions between the C14 chain and the hydrophobic well of the enzyme because of the intercalation of these oxygens. One may also speculate that the complexation of calcium in large excess (see enzymatic assay conditions in Experimental section) by the polyoxygenated chain associated with the oxadiazolone, would make the molecule highly structured, in the same manner as a crown ether, for example, and prevent the molecule from the hydrophobic, even also other interactions with the GIIA enzyme, due to the restriction of its spatial flexibility. Along with the second argument is that compound **12j**, in which only two oxygens were incorporated into the left part of the alkyl chain, kept both the specificity and activity, although 10 times less active than **PMS1062**. Here again, the activity diminution results more likely from a partial loss of Van der Waals interactions in the presence of the oxygens than the decrease of global hydrophobicity of the compound (from 7.08 to 3.42 units). Hydroxy and carboxylic acid groups were also attached to the end of the alkyl chain in order to reduce the global log P of the molecule (**12k′** and **12z**, Table 5), especially in the last case. We expected that these hydrophilic groups at the end of the hydrophobic tail would not significantly influence the interactions between the tail and the lipophilic residues of the enzyme. It is interesting to observe that the presence of a hydroxy group has no effect on the discrimination of the molecule towards GIB and GIIA

$sPLA_2$s and reduces only 5-folds the potency of the compound, while incorporation of a carboxylic function induces a diminution of the specificity, but has no effect on the anti-GIIA $sPLA_2$ activity as compared with **PMS1062**. What is worthwhile to note is that the log *P* of **12z** drops down to 1.37 at physiological pH, providing a solid evidence that a reduction of the lipophilicity does not mean a loss of activity in such kind of compounds, while the specificity needs to be optimized.

Glycerophospholipids, the natural substrates of PLA_2, always contain two more or less long alkyl chains. This fact prompted us to split up the C14 chain into two equal fragments, and attach them either through 3,4-disubstitution of the phenyl group or a disubstituted amino group. In parallel, a certain number of functional groups were introduced (Table 6). To our surprise, although the log *P* of **12p** (Table 6) is the same as that of **PMS1062** (Table 2), new substitution on the *ortho* position of the alkoxy group dramatically reduced the inhibition potency of the molecule to GIIA $sPLA_2$. However, when a dioxolane was present on the α-position of this fragment (**12o**, Table 6), the activity was significantly restored. It suggests that a bulky heterocycle as dioxolane at this position has a beneficial effect on the activity as well as on the specificity, while the presence of a heteroatom alone as in a carbonyl function (**12o′**, Table 6) is not sufficient to maintain the specificity. In the series of dialkylamino derivatives (**12q–s**, Table 6), longer chains were in favour of the interactions with the GIIA enzyme, while no gain in activity was observed in parallel towards the GIB enzyme. This is likely dependent on the increase of the hydrophobic character of the molecule. When the *tert*-butyloxycarbonyl was present along with the tetradecyl group (**12t**, Table 6), the IC_{50} is 10 times and 4 times higher than those of **12s** (Table 6) and **12t′** (Table 4), respectively. The bulky *t*-Bu group is probably responsible for this loss of activity.

Taking into account all the above results, one hypothesis can be forwarded to explain the mode of action of **PMS1062** and its analogues. The hydrophilic head of these compounds in anionic form at neutral pH could be involved in the chelation of the calcium at the active site of the enzyme and the occurrence of this chelation is controlled by interactions between the lipophilic tail of the inhibitor and the hydrophobic well near the active site of the enzyme, defined by a great number of hydrophobic residues.[13–16] This will be further studied in the next publication.

3. Conclusions

We have demonstrated in this work that the lipophilic character of the long carbon chain, of which the optimal length is 14 carbons, is important for the Van der Waals interactions between the inhibitors and the hydrophobic residues of the GIIA enzyme. However, reduction of the global hydrophobicity does not necessarily decrease the inhibitory potency. Free rotation around the linker between the two rings is in favour of the binding of the inhibitors to GIIA $sPLA_2$, but steric hindrance at this level decreases the inhibitory potency. Deletion of the labile hydrogen of oxadiazolone abolishes completely the inhibition activity of the molecules, suggesting that the anionic form of the heterocycle issued by its deprotonation plays a crucial role for the specificity as well as the activity. This could be important evidence that the oxadiazolone ring would be close to the active site and the anionic form would play a role of Ca^{2+} ligand. This hypothesis will be explored in the next manuscript and we will enlarge our SAR studies into other structural parameters, such as using other heterocycles or functional groups in the place of oxadiazolone.

4. Experimental section

4.1. Materials and methods

All the chemicals were obtained from Acros, Aldrich Chimie and Fluka (Paris, France) with the adequate purity and used without purification. Porcine pancreatic $sPLA_2$, BSA (fraction V) were purchased from Sigma (Paris, France) and hGIIA $sPLA_2$ was synthesized as previously reported.[25] 1-Hexadecanoyl-2-(10-pyrene-decanoyl)-*sn*-glycero-3-phosphoglycerol, ammonium salt (β-py-C_{10}-PG) was from Molecular Probes (Eugene, OR).

Proton and carbon-13 NMR spectra were run at 200 MHz on a Brücker AC spectrometer and chemical shifts are reported in parts per million (*δ*) downfield from hexamethyldisiloxane (HMDS) as internal standard and coupling constant expressed in Hz. Elemental analyses were performed for C, H and N by the Service Régional de Microanalyse de l'Université PARIS 6 and were within ±0.4% of theoretical values. Silica gel 60 (70–230 mesh) and Kieselgel F_{254} plastic sheets from Merck were used for column chromatography and analytical thin-layer chromatography (TLC), respectively. Melting points (not corrected) were determined in an Electrothermal digital apparatus. Infra-red spectra were recorded on an Ati Mattson Genesis (series FTIR™) apparatus.

4.2. Synthesis of benzyl cyanide derivatives

4.2.1. 2-(2-(2-(2-Ethoxyethoxy)ethoxy)ethoxy)ethanol (1). Tosyl chloride (21.3 g, 0.11 mol) in powder form was added to a solution of 2-(2-ethoxyethoxy)ethanol (15 mL, 0.11 mol) in ether (100 mL) in the presence of triethylamine (23.3 mL, 0.17 mol). The reaction mixture was stirred at room temperature for 18 h and the triethylammonium chloride was filtered, then washed with ether (2 × 100 mL). The organic solution was washed with 1 N HCl (60 mL), H_2O (60 mL), 10% $NaHCO_3$ (60 mL), H_2O (60 mL), brine (60 mL), dried over $MgSO_4$ and evaporated to dryness. The tosylate was used in the next step without further purification.

Diethyleneglycol (19 mL, 0.20 mol) dissolved in *N*,*N*-dimethylformamide (DMF, 200 mL) was treated with NaH (60% in mineral oil, 5.2 g, 0.13 mol) at 0 °C. When

no H_2 escaped any more from the suspension (about 15 min after addition of NaH), the above tosylate dissolved in DMF (100 mL) was added dropwise. The reaction mixture was then stirred at room temperature for 5 days and DMF removed under reduced pressure. The residue was dissolved in water (200 mL), extracted with EtOAc (3×50 mL) and the combined organic phases dried over $MgSO_4$. After filtration, the solution was evaporated to dryness and the residue was distilled under reduced pressure to afford a colourless and unhomogeneous oil (100–142 °C/0.5 mmHg, 11.6 g). It was subjected to a silica gel column chromatography (EtOAc/CH_2Cl_2 = 3/7–1/1) and the title compound **1** was obtained as a colourless oil (5.60 g, 23% yield): ^{1}H NMR ($CDCl_3$): δ 1.14 (t, 3H, J = 7.00, CH_3), 3.21 (t, 1H, J = 5.46, OH), 3.46 (q, 2H, J = 7.00, CH_2CH$_3$), 3.60 (m, 16H, OCH_2).

4.2.2. 2-(2-(2-(2-Ethoxyethoxy)ethoxy)ethoxy)ethyl bromide (2). The alcohol **1** (2.22 g, 10 mmol) and PBr_3 (0.31 mL, 3.3 mmol) were heated at 100 °C for 1 h and then cooled to room temperature. The reaction mixture was partitioned in ether (150 mL) and H_2O (20 mL) and the organic phase was washed with H_2O (2×20 mL), brine, then dried over $MgSO_4$. The residue obtained after filtration and evaporation of the solvent was purified by silica gel column chromatography (ether/petroleum ether = 3/7) to afford **2** as a colourless oil (0.82 g, 29% yield): ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J = 7.00, CH_3), 3.41 (t, 2H, J = 6.48, CH_2Br), 3.45 (q, 2H, J = 7.00, CH_2CH$_3$), 3.61 (m, 12H, CH_2O), 3.75 (t, 2H, J = 6.31, OCH_2CH$_2$Br).

4.2.3. 8-Bromooctyl 2-ethoxyethyl ether (3). NaH (60% in mineral oil, 1.47 g, 36.8 mmol) was added to a solution of 2-ethoxyethanol (3.5 mL, 54.6 mmol) in DMF at 0 °C and the suspension was stirred at 0 °C until the end of H_2 emission (about 30 min). This suspension was then added dropwise to a solution of 1,8-dibromooctane (10 g, 36.8 mmol) in DMF (50 mL) during 3 h and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue dissolved in ether (150 mL) and H_2O (30 mL). The organic phase was washed with H_2O (2×30 mL), brine (30 mL) and dried over $MgSO_4$. The yellow oil obtained after filtration and evaporation of the solvent was chromatographed through a silica gel column (petroleum ether, ether/petroleum ether = 2/98–5/95) to afford **3** as a colourless oil (1.68 g, 16% yield): ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J = 7.00, CH_3), 1.26 (m, 8H, $(CH_2)_{ch}$), 1.49 (dt, 2H, J = 6.70, OCH$_2$CH_2), 1.79 (dt, 2H, J = 7.00, CH_2CH$_2$Br), 3.34 (t, 2H, J = 6.80, CH_2Br), 3.39 (t, 2H, J = 6.70, OCH_2), 3.47 (q, 2H, J = 7.00, CH_2CH$_3$), 3.51 (s, 4H, OCH$_2$CH$_2$O).

4.2.4. 14-Bromotetradecan-1-ol (4). 1,14-Tetradecanediol (10 g, 43.4 mmol) was heated to 90 °C with 42% HBr (240 mL) and heptane (50 mL) in the flask A of a liquid–liquid extraction system for 18 h, while the flask B of the system, containing only heptane (50 mL), was heated in the manner that a regular condensation of heptane into the flask A was observed. All of the organic solution was recovered, diluted with ether (150 mL) and cooled at −20 °C. The crystals (3.4 g of unreacted diol) were removed by filtration and the solution was evaporated to dryness. The residue was then chromatographed through a silica gel column (CH_2Cl_2/petroleum ether = 1/1–4/1) and recrystallized in heptane to afford **4** as white crystals (6.64 g, 52.3% yield): mp 42–43 °C; ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 18H, $(CH_2)_{ch}$), 1.50 (m, 4H, CH_2CH$_2$CH$_2$Br and CH_2CH$_2$O), 1.79 (dt, 2H, J = 7.00, CH_2CH$_2$Br), 3.34 (t, 2H, J = 6.90, CH_2Br), 3.56 (t, 2H, J = 6.50, CH_2O).

4.2.5. 14-Bromotetradecyl tetrahydropyran-2-yl ether (5). HCl (36%, two drops) and 3,4-dihydro-2*H*-pyran (2.2 mL, 24.1 mmol) were added to a solution of **4** (6.00 g, 20.4 mmol) in anhydrous ether (80 mL) at 0 °C and the mixture was heated to reflux for 3 days. The reaction mixture was then diluted with ether (100 mL) and EtOAc (150 mL), washed with 5% $NaHCO_3$ (40 mL), H_2O (40 mL), brine (40 mL) and dried over $MgSO_4$. The residue obtained after removal of the solvent was purified by silica gel column chromatography (ether/petroleum ether = 1/9) to afford **5** as a colourless oil (7.51 g, 97.3% yield): ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 20H, $(CH_2)_{ch}$), 1.49 (m, 6H, CH_2CH$_2$CH$_2$Br and $2 \times$OCH$_2$CH_2), 1.79 (m, 4H, OCHCH_2 and CH_2CH$_2$Br), 3.34 (t, 2H, J = 6.86, CH_2Br), 3.37 (m, 2H, $(OCH_2)_{ch}$), 3.74 (m, 2H, $(OCH_2)_{cycle}$), 4.51 (t, 1H, J = 2.91, OCHO).

4.2.6. Phenyl tetradecyl thioether (6). NaOH (7.64 g, 0.19 mol) was dissolved in absolute ethanol (100 mL) and to this solution was added thiophenol (20.0 g, 0.18 mol). The mixture was stirred at room temperature for 15 min and the solvent removed under reduced pressure. The residue dissolved in DMF (200 mL) was added dropwise to a solution of 1-bromotetradecane (54.2 mL, 0.18 mol) in DMF (300 mL) at 0 °C. The mixture was stirred at room temperature overnight, then diluted with 2 L of water and extracted with ether (500 mL). The organic phase was washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford **6** as a white solid (53.63 g, 97% yield) used without further purification: mp 40–41 °C; ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.40, CH_3), 1.20 (m, 22H, $(CH_2)_{ch}$), 1.58 (dt, 2H, J = 7.27, CH_2CH$_2$S), 2.84 (t, 2H, J = 7.30, CH_2S), 7.23 (m, 5H, H_{ar}).

4.2.7. 4-Tetradecylthiophenylacetonitrile (7a). To a solution of paraformaldehyde (4.90 g, 163 mmol) in 33% HBr in glacial acetic acid (50 mL) was added compound **6** (5.00 g, 16.3 mmol). The mixture was stirred at room temperature for 30 h and poured onto 300 mL of ice-chilled water. The precipitation was recovered by filtration, dissolved in ether (300 mL) and washed with 10% $NaHCO_3$, water and brine. After being dried over $MgSO_4$, the organic solution was cooled at −20 °C to afford the *para*-bromomethyl derivative of **6** as white crystals (3.10 g). The solvent was then reduced to about 100 mL and the solution was cooled again to −20 °C to yield another portion of the same compound (1.34 g). The total yield was 68%. This compound was not stable in open air at room temperature and was used immediately in the next step: ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H,

J = 6.36, CH_3), 1.19 (m, 22H, $(CH_2)_{ch}$), 1.59 (dt, 2H, J = 7.05, CH_2CH_2S), 2.85 (t, 2H, J = 7.29, CH_2S), 4.40 (s, 2H, CH_2Br), 7.18 (d, 2H, J = 8.75, H_{ar}), 7.23 (d, 2H, J = 8.75, H_{ar}).

The above compound (3.00 g, 7.52 mmol) and sodium cyanide (0.37 g, 7.52 mmol) were mixed in DMF (100 mL) and stirred at room temperature for 48 h. The solvent was then removed under reduced pressure and the residue was partitioned in ether (300 mL) and water (100 mL). The aqueous phase was extracted with ether (100 mL) and the combined organic phases were washed with water, brine and then dried over $MgSO_4$. Compound **7a** was obtained after evaporation of the solvent as a pale yellow solid (2.59 g, quantitative yield) and used without purification: mp 80–82 °C; ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.42, CH_3), 1.18 (m, 22H, $(CH_2)_{ch}$), 1.57 (dt, 2H, J = 7.23, CH_2CH_2S), 2.84 (t, 2H, J = 7.29, CH_2S), 3.63 (s, 2H, CH_2CN), 7.14 (d, 2H, J = 8.67, H_{ar}), 7.23 (d, 2H, J = 8.67, H_{ar}).

4.2.8. 3-(4-Hydroxyphenyl)propionitrile (8). In a three-neck flask equipped with a mechanical stirrer and a refrigerant was dissolved phenol (188 g, 2 mol) in acrylonitrile (131.5 mL, 2 mol). To this well stirred solution was added in small portions $AlCl_3$ (133.5 g, 1 mol) and one half hour later the solution was bubbled with anhydrous HCl gas for 1.5 h. The mixture was then heated at reflux for 2 h and poured onto ice (2 kg). The hydrolysis was carried out for 2 days and the insoluble particles were eliminated by filtration. The filtrate was extracted twice with toluene (2 × 150 mL) and the organic phases were washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue distilled under high vacuum (157–163 °C/1 mmHg) to give the compound **8** as a viscous colourless oil (200 g, 74% yield): ^{1}H NMR ($CDCl_3$): δ 2.50 (t, 2H, J = 7.11, CH_2CN), 2.79 (t, 2H, J = 7.11, CH_2CH_2CN), 6.48 (br s, 1H, OH), 6.70 (d, 2H, J = 8.57, H_{ar}), 6.97 (d, 2H, J = 8.57, H_{ar}).

4.2.9. 3-(4-Tetradecyloxyphenyl)propionitrile (7b). Compound **7b** was prepared using the same procedure as for **6** from 1-bromotetradecane (62.4 mL, 0.21 mol), **8** (29.4 g, 0.20 mol) and isolated after work-up as a white solid (64.23 g, 93.5% yield): mp 59–61 °C; ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.43, CH_3), 1.19 (m, 22H, $(CH_2)_{ch}$), 1.70 (dt, 2H, J = 6.95, CH_2CH_2O), 2.50 (t, 2H, J = 7.26, CH_2CN), 2.82 (t, 2H, J = 7.31, CH_2CH_2CN), 3.86 (t, 2H, J = 6.53, OCH_2), 6.78 (d, 2H, J = 8.66, H_{ar}), 7.06 (d, 2H, J = 8.66, H_{ar}).

4.2.10. 4-*n*-Octyloxyphenylacetonitrile (7c). Compound **7c** was prepared using the same procedure as for **6** from 1-bromooctane (2.6 mL, 15 mmol), 4-hydroxybenzyl cyanide (2.00 g, 15 mmol), and isolated by silica gel column chromatography (ether/petroleum ether) as a pale yellow solid (2.76 g, 75% yield): mp 36–38 °C; IR (KBr, cm^{-1}): 2246 (CN); ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, J = 6.40, CH_3), 1.35 (m, 10H, $(CH_2)_{ch}$), 1.83 (dt, 2H, J = 6.87, CH_2CH_2O), 3.72 (s, 2H, CH_2CN), 3.99 (t, 2H, J = 6.50, CH_2O), 6.93 (d, 2H, J = 8.50, H_{ar}), 7.26 (d, 2H, J = 8.50, H_{ar}).

4.2.11. 4-Decyloxyphenylacetonitrile (7d). Compound **7d** was prepared using the same procedure as for **6** from 1-bromodecane (3.14 mL, 15 mmol), 4-hydroxybenzyl cyanide (2.00 g, 15 mmol), and purified by crystallization in methanol as pale yellow crystals (2.70 g, 66% yield): mp 50–51 °C; IR (KBr, cm^{-1}): 2246 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 5.98, CH_3), 1.20 (m, 14H, $(CH_2)_{ch}$), 1.70 (m, 2H, CH_2CH_2O), 3.60 (s, 2H, CH_2CN), 3.87 (t, 2H, J = 6.31, CH_2O), 6.81 (d, 2H, J = 8.24, H_{ar}), 7.14 (d, 2H, J = 8.24, H_{ar}).

4.2.12. 4-Dodecyloxyphenylacetonitrile (7e). Compound **7e** was prepared using the same procedure as for **6** from 1-bromododecane (9.47 mL, 39.5 mmol), 4-hydroxybenzyl cyanide (5.00 g, 37.6 mmol), and purified by silica gel column chromatography (CH_2Cl_2/petroleum ether) as a pale yellow solid (8.57 g, 76% yield): mp 59–60 °C; IR (KBr, cm^{-1}) 2246 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.44, CH_3), 1.20 (m, 18H, $(CH_2)_{ch}$), 1.70 (dt, 2H, J = 6.92, CH_2CH_2O), 3.60 (s, 2H, CH_2CN), 3.87 (t, 2H, J = 6.53, CH_2O), 6.81 (d, 2H, J = 8.78, H_{ar}), 7.14 (d, 2H, J = 8.78, H_{ar}).

4.2.13. 4-Tetradecyloxyphenylacetonitrile (7f). Compound **7f** was prepared using the same procedure as for **6** from 1-bromotetradecane (65.52 mL, 0.22 mol), 4-hydroxybenzyl cyanide (30 g, 0.22 mol), and purified by silica gel column chromatography as a pale yellow solid (63.41 g, 87.6% yield): mp 68–70 °C; IR (KBr, cm^{-1}): 2246 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.37, CH_3), 1.19 (m, 22H, $(CH_2)_{ch}$), 1.70 (m, 2H, CH_2CH_2O), 3.59 (s, 2H, CH_2CN), 3.86 (t, 2H, J = 6.52, CH_2O), 6.81 (d, 2H, J = 8.70, H_{ar}), 7.14 (d, 2H, J = 8.70, H_{ar}).

4.2.14. 4-Hexadecyloxyphenylacetonitrile (7g). Compound **7g** was prepared using the same procedure as for **6** from 1-bromohexadecane (4.60 mL, 15 mmol), 4-hydroxybenzyl cyanide (2.00 g, 15 mmol), and purified by crystallization in ethanol as pale yellow crystals (3.94 g, 73% yield): mp 77–79 °C; IR (KBr, cm^{-1}): 2246 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.40, CH_3), 1.20 (m, 26H, $(CH_2)_{ch}$), 1.70 (m, 2H, CH_2CH_2O), 3.60 (s, 2H, CH_2CN), 3.87 (t, 2H, J = 6.50, CH_2O), 6.81 (d, 2H, J = 8.70, H_{ar}), 7.14 (d, 2H, J = 8.70, H_{ar}).

4.2.15. 4-Octadecyloxyphenylacetonitrile (7h). Compound **7h** was prepared using the same procedure as for **6** from 1-bromooctadecane (5.15 mL, 15 mmol), 4-hydroxybenzyl cyanide (2.00 g, 15 mmol), and recovered by precipitation in water as a pale yellow solid (5.21 g, 90% yield): mp 78–80 °C; IR (KBr, cm^{-1}): 2246 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 5.98, CH_3), 1.20 (m, 30H, $(CH_2)_{ch}$), 1.70 (m, 2H, CH_2CH_2O), 3.60 (s, 2H, CH_2CN), 3.87 (t, 2H, J = 6.50, CH_2O), 6.81 (d, 2H, J = 8.50, H_{ar}), 7.14 (2H, d, J = 8.50, H_{ar}).

4.2.16. 4-(2-(2-(2-(2-Ethoxyethoxy)ethoxy)ethoxy)ethoxy)-benzyl cyanide (7i). Compound **7i** was prepared using the same procedure as for **6** from **2** (0.7 g, 0.25 mmol), 4-hydroxybenzyl cyanide (0.33 g, 0.25 mmol) and purified by silica gel column chromatography (ether/petroleum ether) as a yellow oil (0.19 g, 23% yield): ^{1}H

NMR ($CDCl_3$): δ 1.14 (t, 3H, $J = 7.01$, CH_3), 3.45 (q, 2H, $J = 7.00$, CH_2CH_3), 3.60 (m, 14H, $(OCH_2CH_2O)_3$ and CH_2CN), 3.79 (dd, 2H, $J = 3.58$, 4.52, CH_2CH_2OPh), 4.06 (dd, 2H, $J = 4.52$, 3.58, CH_2OPh), 6.84 (dd, 2H, $J = 8.77$, 2.16, H_{ar}), 7.15 (dd, 2H, $J = 8.77$, 2.16, H_{ar}).

4.2.17. 4-(8-(2-Ethoxyethoxy)octyloxy)benzyl cyanide (7j). Compound **7j** was prepared using the same procedure as for **6** from **3** (1.5 g, 5.3 mmol), 4-hydroxybenzyl cyanide (0.75 g, 5.6 mmol) and purified by silica gel column chromatography (ether/petroleum ether) as a colourless oil (1.26 g, 71% yield): ^1H NMR ($CDCl_3$): δ 1.15 (t, 3H, $J = 7.00$, CH_3), 1.28 (m, 8H, $(CH_2)_{ch}$), 1.53 (dt, 2H, $J = 6.64$, CH_2CH_2O), 1.71 (dt, 2H, $J = 6.85$, CH_2CH_2OPh), 3.40 (t, 2H, $J = 6.70$, CH_2O), 3.45 (q, 2H, $J = 7.00$, CH_2CH_3), 3.51 (s, 4H, OCH_2CH_2O), 3.61 (s, 2H, CH_2CN), 3.87 (t, 2H, $J = 6.50$, CH_2OPh), 6.81 (dd, 2H, $J = 8.70$, 2.08, H_{ar}), 7.15 (d, 2H, $J = 8.70$, H_{ar}).

4.2.18. 4-(14-(Tetrahydropyran-2-yloxy)tetradecyloxy)-benzyl cyanide (7k). Compound **7k** was prepared using the same procedure as for **6** from **5** (6.00 g, 15.9 mmol), 4-hydroxybenzyl cyanide (2.22 g, 16.7 mmol) and purified by silica gel column chromatography (ether/petroleum ether) as a pale yellow solid (4.15 g, 61% yield). Analytical sample (white crystals) was obtained by recrystallization (ether and petroleum ether): mp 46–47 °C; ^1H NMR ($CDCl_3$): δ 1.20 (m, 20H, $(CH_2)_{ch}$), 1.49 (m, 6H, $CH_2CH_2CH_2OPh$ and OCH_2CH_2), 1.70 (m, 4H, $OCHCH_2$ and CH_2CH_2OPh), 3.35 (m, 2H, $(CH_2O)_{ch}$), 3.60 (s, 2H, CH_2CN), 3.72 (m, 2H, $(CH_2O)_{cycle}$), 3.87 (t, 2H, $J = 6.51$, CH_2OPh), 4.51 (t, 1H, $J = 2.92$, OCHO), 6.81 (d, 2H, $J = 8.75$, H_{ar}), 7.14 (d, 2H, $J = 8.75$, H_{ar}).

4.2.19. 2-(4-Tetradecyloxyphenyl)propionitrile (7l) and 2-methyl-2-(4-tetradecyloxyphenyl)-propionitrile (7m). To a stirred solution of **7f** (3.29 g, 10.0 mmol) in DMF (60 mL) at 0 °C was added NaH (60% in mineral oil, 0.40 g, 10 mmol) and the suspension was warmed to room temperature until no gas was observed. To this suspension well stirred was then added dropwise iodomethane (0.63 mL, 10 mmol). Upon completion of addition, the mixture was stirred for 3 h, diluted with water (50 mL) and extracted with ether (100 and 50 mL). The combined organic phases were washed with aqueous HCl solution (1 N), water and brine then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether) to afford **7l** as a pale yellow solid (0.52 g, 15% yield) and **7m** as a white solid (0.81 g, 23% yield): mp (**7l**) 37–38 °C, mp (**7m**) 41–42 °C; ^1H NMR ($CDCl_3$): (**7l**) δ 0.81 (t, 3H, $J = 6.40$, CH_2CH_3), 1.20 (m, 22H, $(CH_2O)_{ch}$), 1.51 (d, 3H, $J = 7.27$, $CHCH_3$), 1.71 (dt, 2H, $J = 7.10$, CH_2CH_2OPh), 3.77 (q, 1H, $J = 7.30$, $CHCH_3$), 3.87 (t, 2H, $J = 6.52$, CH_2OPh), 6.82 (d, 2H, $J = 8.70$, H_{ar}), 7.18 (d, 2H, $J = 8.70$, H_{ar}); (**7m**) δ 0.81 (t, 3H, $J = 6.40$, CH_2CH_3), 1.20 (m, 22H, $(CH_2O)_{ch}$), 1.63 (s, 6H, $C(CH_3)_2$), 1.71 (dt, 2H, $J = 6.55$, CH_2CH_2OPh), 3,88 (t, 2H, $J = 6.50$, CH_2OPh), 6.83 (d, 2H, $J = 8.85$, H_{ar}), 7.28 (d, 2H, $J = 8.85$, H_{ar}).

4.2.20. 2-Hydroxybenzyl cyanide (9). Compound **9** was obtained according to the procedure as described.[26] 2-Hydroxybenzyl alcohol (50.0 g, 0.403 mol) and NaCN (23.9 g, 0.487 mol) were stirred at 110–130 °C in DMF (650 mL) for 20 h. To the reaction mixture cooled to room temperature was added an aqueous solution of NaOH (20%, 20 mL) and the solvent was removed under reduced pressure. The residue was then dissolved in H_2O and the solution acidified by acetic acid (130 mL). The escaped HCN gas was captured by two successive traps of 20% NaOH and the acidified solution, after stirred in open air in a hood overnight, was then extracted with $CHCl_3$ (3×200 mL). The combined organic phases were washed with H_2O (3×200 mL) and dried over $MgSO_4$. Compound **9** was obtained after silica gel column chromatography purification (CH_2Cl_2/petroleum ether) as a pale yellow solid (33.7 g, 63% yield): mp 116–118 °C; IR (KBr, cm^{-1}) 3218 (OH), 2248 (CN); ^1H NMR ($CDCl_3$): δ 3.58 (s, 2H, CH_2CN), 6.82 (m, 2H, H_{ar}), 7.21 (m, 2H, H_{ar}).

4.2.21. 2-Tetradecyloxyphenylacetonitrile (7n). Compound **7n** was prepared using the same procedure as for **6** from 1-bromotetradecane (4.48 mL, 15.0 mmol), **9** (2.00 g, 15.0 mmol) and isolated by silica gel column chromatography purification (ether/petroleum ether) as a white powder (3.24 g, 65% yield): mp 50–52 °C; ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, $J = 6.36$, CH_3), 1.19 (m, 22H, $(CH_2)_{11}CH_3$), 1.73 (dt, 2H, $J = 6.79$, CH_2CH_2O), 3.58 (s, 2H, CH_2CN), 3.90 (t, 2H, $J = 6.42$, CH_2OPh), 6.82 (m, 2H, H_{ar}), 7.21 (m, 2H, H_{ar}).

4.2.22. 3-Heptanoyl-4-hydroxybenzyl cyanide (10). Heptanoyl chloride (6.5 mL, 42 mmol) was added dropwise to a solution of 4-hydroxybenzyl cyanide (5.00 g, 37.6 mmol) in CH_2Cl_2 (50 mL) in the presence of Et_3N (8 mL, 57.5 mmol) at room temperature. The mixture was stirred for 30 min, diluted with CH_2Cl_2, washed with H_2O and dried over $MgSO_4$. The yellow oil (10.1 g) obtained after evaporation of the solvent was used in the next step without further purification.

The above yellow oil and $AlCl_3$ (12.0 g, 90.0 mmol) were heated to 130 °C in nitrobenzene (100 mL) for 18 h. The reaction mixture was then poured onto ice (600 g) and stirred vigorously for 2 h. The product was extracted with CH_2Cl_2 (300 and 100 mL) and the organic phases were washed with H_2O. After being dried over $MgSO_4$, the organic solution was treated with active charcoal and filtered through Celite. The solvent was removed under reduced pressure and the residue chromatographed through a silica gel column (CH_2Cl_2 and petroleum ether) to afford **10** as a white solid (3.80 g, 41.3% yield): mp 54–55 °C; ^1H NMR ($CDCl_3$): δ 0.84 (t, 3H, $J = 6.37$, CH_3), 1.29 (m, 6H, $(CH_2)_{ch}$), 1.68 (dt, 2H, $J = 7.28$, CH_2CH_2CO), 2.93 (t, 2H, $J = 7.28$, CH_2CO), 3.66 (s, 2H, CH_2CN), 6.93 (d, 1H, $J = 8.60$, H_{ar}), 7.33 (dd, 1H, $J = 8.60$, 2.19, H_{ar}), 7.66 (d, 1H, $J = 2.19$, H_{ar}), 12.34 (s, 1H, OH).

4.2.23. 3-Heptanoyl-4-heptyloxybenzyl cyanide (7o′). 1-Bromoheptane (2.12 mL, 13.0 mmol) and **10** (1.30 g, 5.30 mmol) were heated to reflux of CH_3CN (20 mL) in

the presence of K_2CO_3 (1.80 g, 13.0 mmol) for 48 h. The salt was removed by filtration and washed with the same solvent. The filtrate was evaporated to dryness and the residue recovered in a mixture of ether and water. The organic phase was then washed with 1 N HCl, H_2O, brine and dried over $MgSO_4$. The brown oil after evaporation of the solvent was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether) to afford **7o′** as a pale brown solid (0.97 g, 53% yield): mp 43–44 °C; ^{1}H NMR ($CDCl_3$): δ 0.83 (m, 6H, CH_3), 1.25 (m, 14H, $(CH_2)_{ch}$), 1.60 (dt, 2H, J = 7.45, CH_2CH$_2$CO), 1.78 (dt, 2H, J = 6.90, CH_2CH$_2$OPh), 2.92 (t, 2H, J = 7.45, CH_2CO), 3.63 (s, 2H, CH_2CN), 3.98 (t, 2H, J = 6.35, CH_2OPh), 6.88 (d, 1H, J = 8.54, H_{ar}), 7.35 (dd, 1H, J = 8.54, 2.46, H_{ar}), 7.49 (d, 1H, J = 2.46, H_{ar}).

4.2.24. 4-Heptyloxy-3-(2-hexyl-1,3-dioxolan-2-yl)benzyl cyanide (7o). Ethyleneglycol (0.54 mL, 9.8 mmol) and **7o′** (0.57 g, 1.66 mmol) were heated to reflux of toluene (10 mL) with a catalytic amount of *p*-toluenesulfonic acid (PTSA), using a Dean–Stark apparatus, for 24 h. The solvent was removed under reduced pressure and the residue dissolved in ether. This solution was washed with 10% $NaHCO_3$, H_2O, brine and dried over $MgSO_4$. The yellow oil (0.76 g) obtained after evaporation of the solvent was used directly in the next step without further purification.

4.2.25. 3-Heptyl-4-heptyloxybenzyl cyanide (7p). $NaBH_4$ (0.25 g, 6.6 mmol) was added to a solution of **7o′** (0.97 g, 2.8 mmol) in methanol (20 mL) and the reaction mixture was stirred at room temperature for 3 h. Water was then added to decompose excess of $NaBH_4$ and the solvent was removed under reduced pressure. The residue was dissolved in ether (20 mL) and H_2O (20 mL) and the aqueous phase was extracted with ether (20 mL). The combined organic phases were washed with H_2O, brine and dried over $MgSO_4$. The pale yellow oil (0.90 g) obtained after evaporation of the solvent was dissolved in trifluoroacetic acid (TFA, 7.0 mL) at 0 °C and to this solution was added dropwise triethylsilane (2.8 mL, 17.4 mmol). The solution was stirred at 0 °C for further 30 min after addition and the TFA was removed under reduced pressure. The residue was taken up with a mixture of ether (20 mL) and 1 N NaOH (20 mL). The aqueous solution was extracted once with ether (20 mL) and the combined organic phases washed with H_2O, brine and dried over $MgSO_4$. After purification by silica gel column chromatography (CH_2Cl_2/petroleum ether), **7p** was obtained as a pale yellow solid (0.40 g, 43% yield), of which an analytical sample was recovered by recrystallization (*n*-heptane) as white crystals: mp 38–39 °C; ^{1}H NMR ($CDCl_3$): δ 0.82 (m, 6H, CH_3), 1.25 (m, 18H, $(CH_2)_{ch}$), 1.73 (dt, 2H, J = 6.71, CH_2CH$_2$OPh), 2.52 (t, 2H, J = 7.64, CH_2Ph), 3.58 (s, 2H, CH_2CN), 3.87 (t, 2H, J = 6.30, CH_2OPh), 6.72 (d, 1H, J = 8.15, H_{ar}), 7.00 (m, 2H, H_{ar}).

4.2.26. 4-(*N*,*N*-Di-*n*-heptylamino)benzyl cyanide (7q). *p*-Aminobenzyl cyanide (2.00 g, 15.1 mmol) and 1-bromoheptane (7.10 mL, 45.3 mmol) were stirred in CH_3CN (70 mL) at room temperature for 3 months in the presence of K_2CO_3 (6.3 g, 45.3 mmol). After filtration, the solvent was removed under reduced pressure and the residue dissolved in EtOAc and H_2O. The organic phase was then washed with H_2O, brine and dried over $MgSO_4$. Compound **7q** was obtained after silica gel column chromatography purification (CH_2Cl_2/petroleum ether) as a yellow oil (2.20 g, 63% yield) and the hydrochloride salt of **7q** was then prepared by bubbling HCl gas to an anhydrous ether solution of the free amine: mp 95 °C; IR (Nujol, cm^{-1}) 2253 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 6H, J = 6.30, CH_3), 1.22 (m, 16H, $(CH_2)_{ch}$), 1.48 (m, 4H, NCH$_2$CH_2), 3.18 (t, 4H, J = 7.50, NCH_2), 3.55 (s, 2H, CH_2CN), 6.52 (d, 2H, J = 8.69, H_{ar}), 7.03 (d, 2H, J = 8.69, H_{ar}).

4.2.27. 4-(*N*,*N*-Di-*n*-octylamino)benzyl cyanide (7r). Compound **7r** was prepared using the same procedure as for **7q** from 1-bromooctane (26.3 mL, 0.152 mol) and *p*-aminobenzyl cyanide (2.00 g, 15.1 mmol) in the presence of K_2CO_3 (6.30 g, 45.3 mmol), while the reaction mixture was heated to reflux of CH_3CN for 1 month. **7r** was obtained after silica gel column chromatography purification (CH_2Cl_2/petroleum ether) as a red oil (4.30 g, 82% yield): IR (Nujol, cm^{-1}) 2248 (CN); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 6H, J = 6.00, CH_3), 1.22 (m, 20H, $(CH_2)_{ch}$), 1.48 (m, 4H, NCH$_2$CH_2), 3.16 (t, 4H, J = 7.50, NCH_2), 3.52 (s, 2H, CH_2CN), 6.52 (d, 2H, J = 8.72, H_{ar}), 7.03 (d, 2H, J = 8.71, H_{ar}).

4.2.28. 4-(*N*,*N*-Ditetradecylamino)benzyl cyanide (7s) and 4-(*N*-tetradecylamino)benzyl cyanide (7t′). Compounds **7f** and **7t** were prepared using the same procedure as for **7q** from *p*-aminobenzyl cyanide (1.50 g, 11.5 mmol), 1-bromotetradecane (3.43 mL, 11.5 mmol) in the presence of K_2CO_3 (3.2 g, 23.0 mmol), while the reaction mixture was stirred for 1 month. **7s** and **7t′** were obtained after silica gel column chromatography purification (CH_2Cl_2/petroleum ether) as a yellow oil (0.35 g, 5.8% yield) and a yellow solid (1.35 g, 36.5% yield) respectively: mp (**7t′**) 45 °C; IR (Nujol, cm^{-1}) (**7s**) 2248 (CN); (**7t′**) 2249 (CN); ^{1}H NMR ($CDCl_3$): (**7s**) δ 0.81 (t, 6H, J = 6.01, CH_3), 1.19 (m, 44H, $(CH_2)_{ch}$), 1.44 (m, 4H, NCH$_2$CH_2), 3.16 (t, 4H, J = 7.51, NCH_2), 3.54 (s, 2H, CH_2CN), 6.53 (d, 2H, J = 8.64, H_{ar}), 7.03 (d, 2H, J = 8.54, H_{ar}); (**7t′**): δ 0.81 (t, 3H, J = 6.69, CH_3), 1.19 (m, 22H, $(CH_2)_{ch}$), 1.50 (dt, 2H, NCH$_2$CH_2), 3.01 (t, 2H, J = 6.94, NCH_2), 3.53 (s, 2H, CH_2CN), 6.50 (d, 2H, J = 8.49, H_{ar}), 7.02 (d, 2H, J = 8.44, H_{ar}).

4.2.29. 4-(*N*-*tert*-Butyloxycarbonyl-*N*-tetradecylamino)benzyl cyanide (7t). Compound **7t′** (1.20 g, 3.66 mmol) and Boc_2O (0.76 g, 3.48 mmol) were stirred in the presence of K_2CO_3 (1.10 g, 7.96 mmol) in a solvent mixture of CH_3CN and dioxane (5/1, v/v, 50 mL) for 1 week at room temperature and then heated to reflux for 2 weeks. The solvents were removed under reduced pressure and the residue dissolved in ethyl acetate and water. The organic phase was washed with H_2O, brine and dried over $MgSO_4$. Compound **7t** was obtained after purification on silica gel column (CH_2Cl_2 and petroleum ether) as a yellow oil (600 mg, 40% yield): IR (Nujol, cm^{-1}) 2250 (CN), 1697 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.04, CH_3), 1.17 (m, 24H, $(CH_2)_{ch}$), 1.36 (s, 9H, C$(CH_3)_3$), 3.53 (t, 2H, J = 7.60,

NCH_2), 3.66 (s, 2H, CH_2CN), 7.13 (d, 2H, $J = 8.50$, H_{ar}), 7.23 (d, 2H, $J = 8.50$, H_{ar}).

4.3. Synthesis of amidoximes

General procedure: nitrile (1 equiv), hydroxylamine hydrochloride (5 equiv) and K_2CO_3 (5.5 equiv) were mixed in absolute ethanol (10 mL/mmol of nitrile) and heated to reflux for 18 h. The salts were filtered and the filtrate was cooled at room temperature or −20 °C to give the amidoximes as crystals or evaporated under reduced pressure. The residue in the second case was chromatographed to afford the pure amidoximes.

4.3.1. 4-Tetradecylthiophenylacetamidoxime (11a). Compound **11a** was prepared according to the above general procedure from **7a** (2.30 g, 6.70 mmol), hydroxylamine hydrochloride (2.40 g, 34.5 mmol), K_2CO_3 (5.00 g, 36.2 mmol) and isolated as a white solid (1.28 g, 51% yield): mp 99–101 °C; IR (KBr, cm^{-1}) 3490, 3375 (NH_2), 3180 (OH, large), 1655 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.44$, CH_3), 1.19 (m, 22H, $(CH_2)_{ch}$), 1.57 (dt, 2H, $J = 7.12$, CH_2CH_2S), 2.83 (t, 2H, $J = 7.29$, CH_2S), 3.35 (s, 2H, CH_2CN), 4.43 (br s, 2H, NH_2), 7.12 (d, 2H, $J = 8.41$, H_{ar}), 7.22 (d, 2H, $J = 8.41$, H_{ar}).

4.3.2. 3-(4-Tetradecyloxyphenyl)propionamidoxime (11b). Compound **11b** was prepared according to the above general procedure from **7b** (30.0 g, 87.4 mmol), hydroxylamine hydrochloride (30.3 g, 437 mmol), K_2CO_3 (66.4 g, 481 mmol) and isolated as white crystals (21.2 g, 65% yield): mp 106–108 °C; IR (KBr, cm^{-1}) 3456, 3361 (NH_2), 3235 (OH, large), 1666 (C=N); ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 0.81 (t, 3H, $J = 6.60$, CH_3), 1.20 (m, 22H, $(CH_2)_{ch}$), 1.66 (dt, 2H, $J = 6.70$, CH_2CH_2O), 2.22 (t, 2H, $J = 6.07$, CH_2CN), 2.66 (t, 2H, $J = 6.07$, CH_2CH_2CN), 3.84 (t, 2H, $J = 6.40$, OCH_2), 6.72 (d, 2H, $J = 8.50$, H_{ar}), 7.00 (d, 2H, $J = 8.50$, H_{ar}).

4.3.3. 4-*n*-Octyloxyphenylacetamidoxime (11c). Compound **11c** was prepared according to the above general procedure from **7c** (2.00 g, 8.16 mmol), hydroxylamine hydrochloride (2.95 g, 42.4 mmol), K_2CO_3 (6.20 g, 45.0 mmol) and isolated as a beige solid (2.05 g, 90% yield): mp 109–111 °C; IR (KBr, cm^{-1}) 3431, 3329 (NH_2), 3200 (OH, large), 1659 (C=N); ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, $J = 6.80$, CH_3), 1.23 (m, 10H, $(CH_2)_{ch}$), 1.70 (dt, 2H, $J = 6.91$, CH_2CH_2O), 3.33 (s, 2H, CH_2C=N), 3.85 (t, 2H, $J = 6.53$, CH_2O), 4.43 (br s, 2H, NH_2), 6.77 (d, 2H, $J = 8.62$, H_{ar}), 7.11 (d, 2H, $J = 8.62$, H_{ar}), 7.30 (br s, 1H, OH).

4.3.4. 4-Decyloxyphenylacetamidoxime (11d). Compound **11d** was prepared according to the above general procedure from **7d** (2.00 g, 7.32 mmol), hydroxylamine hydrochloride (2.65 g, 38.0 mmol), K_2CO_3 (5.56 g, 40.3 mmol) and isolated as beige crystals (1.42 g, 63% yield): mp 109–111 °C; IR (KBr, cm^{-1}) 3490, 3373 (NH_2), 3200 (OH, large), 1657 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.80$, CH_3), 1.21 (m, 14H, $(CH_2)_{ch}$), 1.69 (dt, 2H, $J = 6.44$, CH_2CH_2O), 3.33 (s, 2H, CH_2C=N), 3.85 (t, 2H, $J = 6.26$, CH_2O), 4.43 (br s, 2H, NH_2), 6.77 (d, 2H, $J = 7.95$, H_{ar}), 7.11 (d, 2H, $J = 7.95$, H_{ar}), 8.80 (br s, 1H, OH).

4.3.5. 4-Dodecyloxyphenylacetamidoxime (11e). Compound **11e** was prepared according to the above general procedure from **7e** (4.00 g, 13.3 mmol), hydroxylamine hydrochloride (4.80 g, 69.1 mmol), K_2CO_3 (9.63 g, 69.7 mmol) and isolated as beige crystals (2.40 g, 54% yield): mp 95–97 °C; IR (KBr, cm^{-1}) 3490, 3372 (NH_2), 3191 (OH), 1656 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.36$, CH_3), 1.20 (m, 18H, $(CH_2)_{ch}$), 1.71 (dt, 2H, $J = 6.96$, CH_2CH_2O), 3.33 (s, 2H, CH_2C=N), 3.85 (t, 2H, $J = 6.52$, CH_2O), 4.42 (br s, 2H, NH_2), 6.78 (d, 2H, $J = 8.55$, H_{ar}), 7.10 (d, 2H, $J = 8.55$, H_{ar}).

4.3.6. 4-Tetradecyloxyphenylacetamidoxime (11f). Compound **11f** was prepared according to the above general procedure from **7f** (19.60 g, 59.57 mmol), hydroxylamine hydrochloride (20.60 g, 300 mmol), K_2CO_3 (45.23 g, 330 mmol) and isolated as beige crystals (17.52 g, 81% yield): mp 102 °C; IR (KBr, cm^{-1}) 3490, 3373 (NH_2), 3200 (OH, large), 1657 (C=N); ^1H NMR ($CDCl_3$): δ 0.81(t, 3H, $J = 6.44$, CH_3), 1.19 (m, 22H, $(CH_2)_{ch}$), 1.70 (dt, 2H, $J = 6.30$, CH_2CH_2O), 3.33 (s, 2H, CH_2C=N), 3.86 (t, 2H, $J = 6.38$, CH_2O), 4.40 (br s, 2H, NH_2), 6.78 (d, 2H, $J = 8.28$, H_{ar}), 7.11 (d, 2H, $J = 8.28$, H_{ar}).

4.3.7. 4-Hexadecyloxyphenylacetamidoxime (11g). Compound **11g** was prepared according to the above general procedure from **7g** (2.00 g, 5.60 mmol), hydroxylamine hydrochloride (2.02 g, 29.12 mmol), K_2CO_3 (4.25 g, 30.8 mmol) and isolated as beige crystals (1.56 g, 72% yield): mp 109–110 °C; IR (KBr, cm^{-1}) 3490, 3375 (NH_2), 3165 (OH, large), 1655 (C=N); ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 0.81 (t, 3H, $J = 6.40$, CH_3), 1.19 (m, 26H, $(CH_2)_{ch}$), 1.70 (dt, 2H, $J = 7.13$, CH_2CH_2O), 3.33 (s, 2H, CH_2C=N), 3.86 (t, 2H, $J = 6.53$, CH_2O), 4.40 (br s, 2H, NH_2), 6.78 (d, 2H, $J = 8.63$, H_{ar}), 7.10 (d, 2H, $J = 8.63$, H_{ar}).

4.3.8. 4-Octadecyloxyphenylacetamidoxime (11h). Compound **11h** was prepared according to the above general procedure from **7h** (2.00 g, 5.19 mmol), hydroxylamine hydrochloride (1.88 g, 27.45 mmol), K_2CO_3 (3.94 g, 28.54 mmol) and isolated as beige crystals (1.56 g, 75% yield): mp 109–111 °C; IR (KBr, cm^{-1}) 3490, 3375 (NH_2), 3180 (OH, large), 1655 (C=N); ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 0.81 (t, 3H, $J = 6.50$, CH_3), 1.19 (m, 30H, $(CH_2)_{ch}$), 1.70 (dt, 2H, $J = 6.85$, CH_2CH_2O), 3.31 (s, 2H, CH_2C=N), 3.86 (t, 2H, $J = 6.34$, CH_2O), 4.40 (br s, 2H, NH_2), 6.78 (d, 2H, $J = 8.25$, H_{ar}), 7.10 (d, 2H, $J = 8.25$, H_{ar}).

4.3.9. 4-(2-(2-(2-(2-Ethoxyethoxy)ethoxy)ethoxy)ethoxy)phenylacetamidoxime (11i). Compound **11i** was prepared according to the above general procedure from **7i** (200 mg, 0.59 mmol), hydroxylamine hydrochloride (206.3 mg, 2.95 mmol), K_2CO_3 (0.45 g, 3.24 mmol) and isolated as a viscous yellow oil (161.5 mg, 73% yield): ^1H NMR ($CDCl_3$): δ 1.14 (t, 3H, $J = 7.00$, CH_3), 3.33

(s, 2H, CH_2CN), 3.42 (q, 2H, $J = 7.00$, CH_2CH_3), 3.59 (m, 12H, OCH_2), 3.78 (t, 2H, $J = 4.83$, CH_2CH_2OPh), 4.04 (t, 2H, $J = 4.83$, CH_2OPh), 4.43 (s, 2H, NH_2), 6.80 (d, 2H, $J = 8.46$, H_{ar}), 7.11 (d, 2H, $J = 8.46$, H_{ar}).

4.3.10. 4-(8-(2-Ethoxyethoxy)octyloxy)phenylacetamidoxime (11j). Compound **11j** was prepared according to the above general procedure from **7j** (1.13 g, 3.30 mmol), hydroxylamine hydrochloride (1.20 g, 17.3 mmol), K_2CO_3 (2.60 g, 18.8 mmol) and isolated as a pale yellow solid (0.84 g, 68% yield): mp 55–57 °C; ^1H NMR ($CDCl_3$): δ 1.14 (t, 3H, $J = 7.00$, CH_3), 1.27 (m, 8H, $(CH_2)_{ch}$), 1.52 (dt, 2H, $J = 6.43$, CH_2CH_2O), 1.69 (dt, 2H, $J = 6.81$, CH_2CH_2OPh), 3.33 (s, 2H, $CH_2C{=}N$), 3.39 (t, 2H, $J = 6.71$, CH_2O), 3.46 (q, 2H, $J = 7.00$, CH_2CH_3), 3.51 (s, 4H, OCH_2CH_2O), 3.84 (t, 2H, $J = 6.44$, CH_2OPh), 4.45 (s, 2H, NH_2), 6.76 (d, 2H, $J = 8.47$, H_{ar}), 7.10 (d, 2H, $J = 8.47$, H_{ar}), 8.10 (br s, 1H, OH).

4.3.11. 4-(14-(Tetrahydropyran-2-yloxy)tetradecyloxy)-phenylacetamidoxime (11k). Compound **11k** was prepared according to the above general procedure from **7k** (2.80 g, 6.52 mmol), hydroxylamine hydrochloride (2.30 g, 33.0 mmol), K_2CO_3 (5.00 g, 36.2 mmol) and isolated as a pale yellow solid (1.71 g, 57% yield). An analytical sample was obtained by recrystallization (CH_2Cl_2 and petroleum ether): mp 89–90 °C; ^1H NMR ($CDCl_3$): δ 1.20 (m, 18H, $(CH_2)_{ch}$), 1.52 (m, 6H, CH_2CH_2-CH_2OPh and OCH_2CH_2), 1.70 (m, 6H, $OCHCH_2$ and CH_2CH_2OPh), 3.33 (s, 2H, $CH_2C{=}N$), 3.46 (m, 2H, $(CH_2O)_{ch}$), 3.66 (m, 2H, $(CH_2O)_{cycle}$), 3.85 (t, 2H, $J = 6.49$, CH_2OPh), 4.43 (s, 2H, NH_2), 4.51 (t, 1H, $J = 2.92$, OCHO), 6.77 (d, 2H, $J = 8.61$, H_{ar}), 7.11 (d, 2H, $J = 8.61$, H_{ar}).

4.3.12. 2-(4-Tetradecyloxyphenyl)propionamidoxime (11l). Compound **11l** was prepared according to the above general procedure from **7l** (0.41 g, 1.2 mmol), hydroxylamine hydrochloride (0.43 g, 6.2 mmol), K_2CO_3 (0.91 g, 6.6 mmol) and isolated as a white solid (203 mg, 45.2% yield): mp 85–87 °C; IR (KBr, cm^{-1}) 3490, 3375 (NH_2), 3180 (OH, large), 1655 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.50$, CH_2CH_3), 1.19 (m, 25H, $(CH_2O)_{ch}$ and $CHCH_3$), 1.70 (dt, 2H, $J = 6.65$, CH_2CH_2OPh), 3.49 (q, 1H, $J = 6.75$, $CHCH_3$), 3.86 (t, 2H, $J = 6.20$, CH_2OPh), 4.30 (br s, 2H, NH_2), 4.90 (br s, 1H, OH), 6.79 (d, 2H, $J = 8.10$, H_{ar}), 7.14 (d, 2H, $J = 8.10$, H_{ar}).

4.3.13. 2-Methyl-2-(4-tetradecyloxyphenyl)propionamidoxime (11m). Compound **11m** was prepared according to the above general procedure from **7m** (0.50 g, 1.4 mmol), hydroxylamine hydrochloride (0.50 g, 7.2 mmol), K_2CO_3 (1.06 g, 7.7 mmol) and isolated as a white solid (0.48 g, 87% yield): mp 63–65 °C; IR (KBr, cm^{-1}) 3490, 3375 (NH_2), 3180 (OH, large), 1655 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.41$, CH_2CH_3), 1.20 (m, 22H, $(CH_2O)_{ch}$), 1.46 (s, 6H, $C(CH_3)_2$), 1.70 (dt, 2H, $J = 7.07$, CH_2CH_2OPh), 3.87 (t, 2H, $J = 6.50$, CH_2OPh), 4.23 (br s, 2H, NH_2), 6.79 (d, 2H, $J = 8.82$, H_{ar}), 7.22 (d, 2H, $J = 8.82$, H_{ar}), 8.44 (br s, 1H, OH).

4.3.14. 2-Tetradecyloxyphenylacetamidoxime (11n). Compound **11n** was prepared according to the above general procedure from **7n** (2.00 g, 6.04 mmol), hydroxylamine hydrochloride (2.20 g, 31.7 mmol), K_2CO_3 (4.60 g, 33.3 mmol) and isolated as beige crystals (1.32 g, 60% yield): mp 74–76 °C; IR (KBr, cm^{-1}) 3456, 3361 (NH_2), 3235 (OH, large), 1666 (C=N); ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, $J = 6.36$, CH_3), 1.18 (m, 22H, $(CH_2)_{11}CH_3$), 1.73 (dt, 2H, $J = 6.79$, CH_2CH_2O), 3.40 (s, 2H, CH_2CN), 3.92 (t, 2H, $J = 6.44$, CH_2OPh), 4.80 (s, 2H, NH_2), 6.79 (m, 2H, H_{ar}), 7.13 (m, 2H, H_{ar}).

4.3.15. 4-*n*-Heptyloxy-3-(2-*n*-hexyl-1,3-dioxolan-2-yl)-phenylacetamidoxime (11o). Compound **11o** was prepared according to the above general procedure from crude **7o** (1.66 mmol), hydroxylamine hydrochloride (0.60 g, 8.63 mmol), K_2CO_3 (1.30 g, 9.42 mmol) and isolated as a pale yellow oil (0.34 g, 49% yield): ^1H NMR ($CDCl_3$): δ 0.80 (m, 6H, CH_3), 1.20 (m, 16H, $(CH_2)_{ch}$ and $CH_2CH_2CO_2$), 1.75 (dt, 2H, $J = 6.96$, CH_2CH_2OPh), 2.07 (m, 2H, CH_2CO_2), 3.35 (s, 2H, $CH_2C{=}N$), 3.77 (m, 2H, CH_2OPh), 3.92 (m, 4H, OCH_2-CH_2O), 4.44 (s, 2H, NH_2), 6.77 (d, 1H, $J = 8.32$, H_{ar}), 7.00 (br s, 1H, OH), 7.20 (dd, 1H, $J = 2.26$, 8.32, H_{ar}), 7.29 (d, 1H, $J = 2.26$, H_{ar}).

4.3.16. 3-*n*-Heptyl-4-*n*-heptyloxyphenylacetamidoxime (11p). Compound **11p** was prepared according to the above general procedure from **7p** (0.29 g, 0.88 mmol), hydroxylamine hydrochloride (0.33 g, 4.75 mmol), K_2CO_3 (0.70 g, 5.07 mmol) and isolated as a pale yellow solid (0.19 g, 59% yield). An analytical sample (white crystals) was obtained by recrystallization (abs EtOH): mp 78–79 °C; ^1H NMR ($CDCl_3$): δ 0.82 (m, 6H, CH_3), 1.24 (m, 18H, $(CH_2)_{ch}$), 1.72 (dt, 2H, $J = 6.81$, CH_2CH_2OPh), 2.50 (t, 2H, $J = 7.65$, CH_2Ph), 3.32 (s, 2H, $CH_2C{=}N$), 3.86 (t, 2H, $J = 6.28$, CH_2OPh), 4.43 (s, 2H, NH_2), 6.69 (d, 1H, $J = 8.94$, H_{ar}), 6.96 (m, 2H, H_{ar}).

4.3.17. 4-(*N*,*N*-Di-*n*-heptylamino)phenylacetamidoxime (11q). Compound **11q** was prepared according to the above general procedure from **7q** (1.00 g, 3.04 mmol), hydroxylamine hydrochloride (1.06 g, 15.2 mmol), K_2CO_3 (2.31 g, 16.7 mmol) and isolated as a red oil (0.88 g, 80% yield): IR (Nujol, cm^{-1}) 3506, 3400 (NH_2), 3225 (OH), 1665 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 6H, $J = 6.35$, CH_3), 1.23 (m, 16H, $(CH_2)_{ch}$), 1.48 (m, 4H, NCH_2CH_2), 3.13 (t, 4H, $J = 7{,}36$, NCH_2), 3.28 (s, 2H, $CH_2C{=}N$), 4.41 (s, 2H, NH_2), 5.22 (br s, 1H, OH), 6.51 (d, 2H, $J = 8.69$, H_{ar}), 7.00 (d, 2H, $J = 8.59$, H_{ar}).

4.3.18. 4-(*N*,*N*-Di-*n*-octylamino)phenylacetamidoxime (11r). Compound **11r** was prepared according to the above general procedure from **7r** (1.00 g, 2.80 mmol), hydroxylamine hydrochloride (0.97 g, 14.0 mmol), K_2CO_3 (2.13 g, 15.4 mmol) and isolated as a brown oil (0.71 g, 65% yield): IR (Nujol, cm^{-1}) 3495, 3376 (NH_2), 3180 (OH), 1664 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 6H, $J = 6.72$, CH_3), 1.22 (m, 20H, $(CH_2)_{ch}$), 1.48 (m, 4H, NCH_2CH_2), 2.88 (t, 4H, $J = 7.25$,

NCH_2), 3.26 (s, 2H, $CH_2C{=}N$), 4.44 (s, 2H, NH_2), 6.49 (d, 2H, $J = 8.65$, H_{ar}), 7.01 (d, 2H, $J = 8.56$, H_{ar}).

4.3.19. 4-(*N*,*N*-Ditetradecylamino)phenylacetamidoxime (11s). Compound **11s** was prepared according to the above general procedure from **7s** (0.35 g, 0.67 mmol), hydroxylamine hydrochloride (233 mg, 3.35 mmol), K_2CO_3 (0.51 g, 3.70 mmol) and isolated as a beige solid (0.23 g, 62% yield): mp 53 °C; IR (Nujol, cm^{-1}) 3482, 3311 (NH_2), 3156 (OH), 1664 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 6H, $J = 6.93$, CH_3), 1.19 (m, 44H, $(CH_2)_{ch}$), 1.47 (m, 4H, NCH_2CH_2), 3.15 (t, 4H, $J = 7.50$, NCH_2), 3.27 (s, 2H, $CH_2C{=}N$), 4.41 (s, 2H, NH_2), 5.41 (br s, 1H, OH), 6.52 (d, 2H, $J = 8.10$, H_{ar}), 7.01 (d, 2H, $J = 7.93$ Hz, H_{ar}).

4.3.20. 4-(*N*-Boc-*N*-tetradecylamino)phenylacetamidoxime (11t). Compound **11t** was prepared according to the above general procedure from **7t** (0.80 g, 1.87 mmol), hydroxylamine hydrochloride (0.65 g, 9.35 mmol), K_2CO_3 (1.42 g, 10.3 mmol) and isolated as a yellow oil (0.47 g, 55% yield): IR (Nujol, cm^{-1}) 3497, 3344 (NH_2), 3254 (OH), 1678 (C=O), 1587 ($C{=}C_{ar}$); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.67$, CH_3), 1.18 (m, 24H, $(CH_2)_{ch}$), 1.37 (s, 9H, $C(CH_3)_3$), 3.38 (s, 2H, $CH_2C{=}N$), 3.51 (t, 2H, $J = 7.21$, NCH_2), 4.44 (br s, 2H, NH_2), 7.07 (d, 2H, $J = 8.50$, H_{ar}), 7.18 (d, 2H, $J = 8.50$, H_{ar}).

4.3.21. Octadecylamidoxime (11u). Compound **11u** was prepared according to the above general procedure from stearonitrile (10.0 g, 37.7 mmol), hydroxylamine hydrochloride (13.1 g, 189 mmol), K_2CO_3 (28.6 g, 207 mmol) and isolated as white crystals (7.50 g, 67% yield): mp 100–102 °C; ^1H NMR ($CDCl_3$ + 10% CD_3OD at 35 °C): δ 0.81 (t, 3H, $J = 6.44$, CH_3), 1.19 (m, 28H, $(CH_2)_{ch}$), 1.48 (dt, 2H, $J = 7.23$, $CH_2CH_2C{=}N$), 2.04 (t, 2H, $J = 7.63$, $CH_2C{=}N$), 3.67 (br s, 3H, NH_2 and OH).

4.3.22. 4-Methoxyphenylacetamidoxime (11v). Compound **11v** was prepared according to the above general procedure from commercially available 4-methoxybenzyl cyanide (6.00 g, 40.8 mmol), hydroxylamine hydrochloride (14.2 g, 204 mmol), K_2CO_3 (31.0 g, 224 mmol) and isolated by crystallization (CH_2Cl_2) of the residue issued from evaporation of the solvent as white crystals (4.37 g, 60% yield): mp 110–112 °C; IR (KBr, cm^{-1}) 3375 (NH), 3200 (OH, large), 1661 (C=N); ^1H NMR ($CDCl_3$): δ 3.31 (s, 2H, CH_2–C=N), 3.74 (s, 3H, CH_3), 6.84 (d, 2H, $J = 8.00$, H_{ar}), 7.20 (d, 2H, $J = 8.00$, H_{ar}).

4.4. Synthesis of oxadiazolone by cyclization

General procedure: To a solution of amidoxime (1 equiv) in $CHCl_3$ (5–25 mL/mmol of amidoxime) in the presence of triethylamine (1.5 equiv) at 0 °C was added phenyl chloroformate (1.1 equiv). Upon completion, the solution was stirred for 1 h, then washed with water to neutral pH and dried over $MgSO_4$. The solvent was removed under reduced pressure and the carbonate, dissolved in toluene, was heated to reflux for 18 h. After evaporation of the solvent, the residue was chromatographed to yield pure oxadiazolone derivatives.

4.4.1. 4,5-Dihydro-3-(4-tetradecylthiobenzyl)-4*H*-1,2,4-oxadiazol-5-one (12a). Compound **12a** was prepared following the above general procedure from **11a** (1.10 g, 2.91 mmol) and phenyl chloroformate (0.44 mL, 3.50 mmol) and isolated by silica gel column chromatography as a white solid (0.71 g, 70% yield): mp 139–140 °C; ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.33$), 1.19 (m, 22H), 1.57 (dt, 2H, $J = 7.41$), 2.84 (t, 2H, $J = 7.26$), 3.74 (s, 2H), 7.12 (d, 2H, $J = 8.24$), 7.23 (d, 2H, $J = 8.24$). Anal. ($C_{23}H_{36}N_2O_2S$) C, H, N.

4.4.2. 4,5-Dihydro-3-(4-tetradecyloxyphenethyl)-4*H*-1,2,4-oxadiazol-5-one (12b). Compound **12b** was prepared following the above general procedure from **11b** (3.76 g, 10.0 mmol) and phenyl chloroformate (1.26 mL, 10.0 mmol) and isolated by silica gel column chromatography as a pale pink solid (2.0 g, 50% yield): mp 102–103 °C; ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, $J = 6.39$), 1.20 (m, 22H), 1.70 (dt, 2H, $J = 6.95$), 2.82 (m, 4H), 3.86 (t, 2H, $J = 6.53$), 6.77 (d, 2H, $J = 8.57$), 7.03 (d, 2H, $J = 8.57$). Anal. ($C_{24}H_{38}N_2O_3$) C, H, N.

4.4.3. 4,5-Dihydro-3-(4-*n*-octyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12c). Compound **12c** was prepared following the above general procedure from **11c** (0.80 g, 2.87 mmol) and phenyl chloroformate (0.39 mL, 3.16 mmol) and isolated as white crystals (0.42 g, 48% yield): mp 118–120 °C; IR (KBr, cm^{-1}) 3121 (NH), 1839 (C=O), 1728 (C=N); ^1H NMR ($CDCl_3$): δ 0.81(t, 3H, $J = 6.50$), 1.22 (m, 10H), 1.69 (dt, 2H, $J = 6.92$), 3.71 (s, 2H), 3.85 (t, 2H, $J = 6.52$), 6.78 (d, 2H, $J = 8.64$), 7.09 (d, 2H, $J = 8.64$), 10.22 (s, 1H). Anal. ($C_{17}H_{24}N_2O_3$) C, H, N.

4.4.4. 3-(4-Decyloxybenzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12d). Compound **12d** was prepared following the above general procedure from **11d** (1.23 g, 4.0 mmol) and phenyl chloroformate (0.80 mL, 6.4 mmol) and isolated as white crystals (0.73 g, 55% yield): mp 120–122 °C; IR (KBr, cm^{-1}) 3118 (NH), 1838 (C=O), 1727 (C=N); ^1H NMR ($CDCl_3$): δ 0.81(t, 3H, $J = 6.40$), 1.20 (m, 14H), 1.69 (dt, 2H, $J = 6.84$), 3.71 (s, 2H), 3.85 (t, 2H, $J = 6.52$), 6.78 (d, 2H, $J = 8.62$), 7.09 (d, 2H, $J = 8.62$). Anal. ($C_{19}H_{28}N_2O_3 \cdot 1/6H_2O$) C, H, N.

4.4.5. 3-(4-Dodecyloxybenzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12e). Compound **12e** was prepared according to the general procedure from **11e** (0.50 g, 1.5 mmol) and phenyl chloroformate (0.23 mL, 1.8 mmol) and isolated by silica gel column chromatography (MeOH/CH_2Cl_2) followed by crystallization (EtOAc/*n*-hexane), as white crystals (172 mg, 32% yield): mp 117–119 °C; IR (KBr, cm^{-1}) 3121 (NH), 1842 (C=O), 1730 (C=N) ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.44$), 1.20 (m, 18H), 1.70 (dt, 2H, $J = 6.87$), 3.72 (s, 2H), 3.85 (t, 2H, $J = 6.53$), 6.79 (d, 2H, $J = 8.68$), 7.10 (d, 2H, $J = 8.68$). Anal. ($C_{21}H_{32}N_2O_3$) C, H, N.

4.4.6. 4,5-Dihydro-3-(4-tetradecyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12f, PMS1062). Compound **12f** was prepared following the above general procedure from **11f** (19.0 g, 52.5 mmol) and phenyl chloroformate

(7.9 mL, 63 mmol) and isolated by crystallization (EtOAc/petroleum ether) as beige crystals (12.5 g, 61% yield): mp 123–124 °C; IR (KBr, cm^{-1}) 3116 (NH), 1728 (C=O), 1517 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.44$), 1.20 (m, 22H), 1.70 (dt, 2H, $J = 6.87$), 3.72 (s, 2H), 3.85 (t, 2H, $J = 6.53$), 6.79 (d, 2H, $J = 8.68$), 7.10 (d, 2H, $J = 8.68$). Anal. ($C_{23}H_{36}N_2O_3$) C, H, N.

4.4.7. 3-(4-Hexadecyloxybenzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12g). Compound **12g** was prepared following the above general procedure from **11g** (1.38 g, 3.54 mmol) and phenyl chloroformate (0.49 mL, 3.89 mmol) and isolated as beige crystals (0.58 g, 40% yield): mp 121–123 °C; IR (KBr, cm^{-1}) 3116 (NH), 1840 (C=O), 1728 (C=N); ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 0.81, (t, 3H, $J = 6.43$), 1.19 (m, 26H), 1.70 (dt, 2H, $J = 6.97$), 3.71 (s, 2H), 3.86 (t, 2H, $J = 6.54$), 6.80 (d, 2H, $J = 8.68$), 7.10 (d, 2H, $J = 8.68$). Anal. ($C_{25}H_{40}N_2O_3$) C, H, N.

4.4.8. 4,5-Dihydro-3-(4-octadecyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12h). Compound **12h** was prepared following the above general procedure from **11h** (1.33 g, 3.18 mmol) and phenyl chloroformate (0.44 mL, 3.50 mmol) and isolated as beige crystals (0.70 g, 50% yield): mp 122–124 °C; IR (KBr, cm^{-1}) 3116 (NH), 1839 (C=O), 1728 (C=N); ^1H NMR (DMSO-d_6 at 50 °C): δ 0.81 (t, 3H, $J = 6.43$), 1.25 (m, 30H), 1.70 (dt, 2H, $J = 6.97$), 3.78 (s, 2H), 3.94 (t, 2H, $J = 6.19$), 6.88 (d, 2H, $J = 8.21$), 7.20 (d, 2H, $J = 8.21$). Anal. ($C_{27}H_{44}N_2O_3$) C, H, N.

4.4.9. 3-(4-(2-(2-(2-(2-Ethoxyethoxy)ethoxy)ethoxy)ethoxy)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12i). Compound **12i** was prepared following the above general procedure from **11i** (130 mg, 0.35 mmol) and phenyl chloroformate (53 μL, 0.42 mmol) and isolated as a yellow oil (100 mg, 70% yield): ^1H NMR ($CDCl_3$): δ 1.10 (t, 3H, $J = 7.01$), 3.45 (q, 2H, $J = 7.00$), 3.54 (m, 12H), 3.72 (s, 2H), 3.75 (dd, 2H, $J = 3.18, 4.27$), 4.00 (dd, 2H, $J = 4.27, 3.18$), 6.76 (d, 2H, $J = 8.66$), 6.90 (br s, 1H), 7.08 (d, 2H, $J = 8.66$). Anal. ($C_{19}H_{28}N_2O_7$) C, H, N.

4.4.10. 3-(4-(8-(2-Ethoxyethoxy)octyloxy)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12j). Compound **12j** was prepared following the above general procedure from **11j** (0.72 g, 1.97 mmol) and phenyl chloroformate (0.30 mL, 2.39 mmol) and isolated as white crystals (0.60 g, 78% yield): mp 71–72 °C; ^1H NMR ($CDCl_3$): δ 1.11 (t, 3H, $J = 7.00$), 1.24 (m, 10H), 1.74 (t, 2H, $J = 6.84$), 3.36 (t, 2H, $J = 6.70$), 3.45 (q, 2H, $J = 7.00$), 3.50 (s, 4H), 3.72 (s, 2H), 3.86 (t, 2H, $J = 6.40$), 6.79 (d, 2H, $J = 8.47$), 7.10 (d, 2H, $J = 8.47$), 9.60 (br s, 1H). Anal. ($C_{21}H_{32}N_2O_5$) C, H, N.

4.4.11. 4,5-Dihydro-3-(4-(14-(tetrahydropyran-2-yloxy)-tetradecyloxy)benzyl)-4*H*-1,2,4-oxadiazol-5-one (12k). Compound **12k** was prepared following the above general procedure from **11k** (1.40 g, 3.03 mmol) and phenyl chloroformate (0.42 mL, 3.35 mmol), while the cyclization was done in 4 h, and isolated as a yellow solid (1.80 g, quantitative yield). It was used directly in the next step without further purification.

4.4.12. 4,5-Dihydro-3-(4-(14-hydroxytetradecyloxy)benzyl)-4*H*-1,2,4-oxadiazol-5-one (12k′). The crude product **12k** (1.80 g) and pyridinium *p*-toluenesulfonate (PPTS, 76 mg, 0.30 mmol) were heated at 55 °C in EtOH (30 mL) overnight. Water (about 40 mL) was added into the mixture, while it was maintained to reflux. The clear yellow solution was then kept at room temperature and the insoluble brown oil was separated from the supernatant by decantation. After drying under reduced pressure, the brown oil was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$) and then recrystallized ($CHCl_3$) to afford **12k′** as white crystals (0.80 g, 66% yield): mp 129–130 °C; ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 1.21 (m, 22H), 1.71 (dt, 2H, $J = 6.93$), 3.49 (t, 2H, $J = 6.69$), 3.72 (s, 2H), 3.89 (t, 2H, $J = 6.50$), 6.82 (d, 2H, $J = 8.73$), 7.12 (d, 2H, $J = 8.73$). Anal. ($C_{23}H_{36}N_2O_4$) C, H, N.

4.4.13. 4,5-Dihydro-3-(α-methyl-4-tetradecyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12l). Compound **12l** was prepared according to the general procedure from **11l** (147 mg, 0.39 mmol) and phenyl chloroformate (59 μL, 0.47 mmol) and isolated by silica gel column chromatography followed by crystallization as white crystals (69 mg, 44% yield): mp 93–95 °C; IR (KBr, cm^{-1}) 3116 (NH), 1728 (C=O), 1517 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.39$), 1.20 (m, 22H), 1.55 (d, 3H, $J = 7.22$), 1.70 (dt, 2H, $J = 6.82$), 3.87 (m, 3H), 6.80 (d, 2H, $J = 8.70$), 7.11 (d, 2H, $J = 8.70$). Anal. ($C_{24}H_{38}N_2O_3$) C, H, N.

4.4.14. 4,5-Dihydro-3-(α,α-dimethyl-4-tetradecyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12m). Compound **12m** was prepared according to the general procedure from **11m** (0.39 g, 1.00 mmol) and phenyl chloroformate (130 μL, 1.04 mmol) and isolated by silica gel column chromatography followed by crystallization as white crystals (0.24 g, 58% yield): mp 86–87 °C; IR (KBr, cm^{-1}) 3116 (NH), 1728 (C=O), 1517 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.44$), 1.20 (m, 22H), 1.59 (s, 6H), 1.70 (dt, 2H, $J = 6.88$), 3.86 (t, 2H, $J = 6.50$), 6.79 (d, 2H, $J = 8.85$), 7.16 (d, 2H, $J = 8.85$). Anal. ($C_{25}H_{40}N_2O_3 \cdot 1/3H_2O$) C, H, N.

4.4.15. 4,5-Dihydro-3-(2-tetradecyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12n). Compound **12n** was prepared following the above general procedure from **11n** (1.00 g, 2.76 mmol) and phenyl chloroformate (0.36 mL, 2.85 mmol) and isolated as a pale yellow solid (0.43 g, 40% yield): mp 80–82 °C; IR (Nujol, cm^{-1}) 3227 (NH), 1171 (C=O), 1729 (C=N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.36$), 1.19 (m, 22H), 1.75 (dt, 2H, $J = 6.79$), 3.79 (s, 2H), 4.00 (t, 2H, $J = 6.64$), 6.88 (m, 2H), 7.19 (m, 2H). Anal. ($C_{23}H_{36}N_2O_3$) C, H, N.

4.4.16. 3-(4-*n*-Heptyloxy-3-(2-*n*-hexyl-1,3-dioxolan-2-yl)-benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12o). Compound **12o** was prepared following the above general procedure from **11o** (0.30 g, 0.71 mmol) and phenyl chloroformate (100 μL, 0.80 mmol) and isolated as

white crystals (0.25 g, 78% yield): mp 97–98 °C; ^{1}H NMR ($CDCl_3$): δ 0.80 (m, 6H), 1.20 (m, 16H), 1.74 (dt, 2H, J = 6.63), 2.05 (m, 2H), 3.73 (m, 4H), 3.92 (m, 4H), 6.80 (d, 1H, J = 8.23), 7.03 (dd, 1H, J = 1.63, 8.23), 7.30 (d, 1H, J = 1.63), 10.18 (s, 1H). Anal. ($C_{25}H_{38}N_2O_5$) C, H, N.

4.4.17. 3-(3-*n*-Heptanoyl-4-*n*-heptyloxybenzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12o′). Compound **12o** (51 mg, 0.14 mmol) was heated to reflux of acetone (10 mL) with H_2O (1 mL) in the presence of PPTS (6.0 mg) for 14 h. The solvent was removed under reduced pressure and the white residue taken up with EtOAc (45 mL), was washed with H_2O (3 × 10 mL), brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, **12o′** was obtained quantitatively without further purification as a white powder (46 mg): mp 100–101 °C; IR (Nujol, cm^{-1}) 3149 (br, NH), 1789 (C=O), 1727 (C=N), 1698 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.82 (m, 6H), 1.23 (m, 14H), 1.55 (dt, 2H, J = 7.11), 1.77 (dt, 2H, J = 6.80), 2.92 (t, 2H, J = 7.48), 3.76 (s, 2H), 3.97 (t, 2H, J = 6.36), 6.86 (d, 1H, J = 8.56), 7.31 (dd, 1H, J = 2.40, 8.56), 7.51 (d, 1H, J = 2.40), 10.32 (br s, 1H). Anal. ($C_{23}H_{34}N_2O_4$) C, H, N.

4.4.18. 3-(3-*n*-Heptyl-4-*n*-heptyloxybenzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12p). Compound **12p** was prepared following the above general procedure from **11p** (168 mg, 0.46 mmol) and phenyl chloroformate (70 μL, 0.56 mmol) and isolated as white crystals (121 mg, 67% yield): mp 101–102 °C; ^{1}H NMR ($CDCl_3$): δ 0.82 (m, 6H), 1.23 (m, 18H), 1.73 (dt, 2H, J = 6.97), 2.50 (t, 2H, J = 7.66), 3.69 (s, 2H), 3.85 (t, 2H, J = 6.26), 6.70 (d, 1H, J = 8.85), 6.95 (m, 2H), 9.98 (s, 1H). Anal. ($C_{23}H_{36}N_2O_3$) C, H, N.

4.4.19. 3-(4-(*N*,*N*-Di-*n*-heptylamino)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12q). Compound **12q** was prepared following the above general procedure from **11q** (1.00 g, 2.77 mmol) and phenyl chloroformate (0.36 mL, 2.91 mmol), while the cyclization was done in 5 h, and isolated as a green oil (0.50 g, 47% yield). The hydrochloride salt was obtained by bubbling HCl gas into an anhydrous solution of **12q** in ether and the analyses were performed on recrystallized samples of the salt (pink crystals): IR (Nujol, cm^{-1}) 3000 (NH), 1771 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.74 (6H, t, J = 6.00), 1.07 (m, 16H), 1.73 (m, 4H), 3.19 (m, 2H), 3.43 (m, 2H), 3.97 (s, 2H), 7.62 (m, 2H), 7.70 (m, 2H), 11.86 (br s, 1H). Anal. ($C_{23}H_{37}N_3O_2$·HCl·1/4H_2O) C, H, N.

4.4.20. 3-(4-(*N*,*N*-Di-*n*-octylamino)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12r). Compound **12r** was prepared following the above general procedure from **11r** (1.00 g, 2.57 mmol) and phenyl chloroformate (0.36 mL, 2.91 mmol), while the cyclization was done in 2 h, and isolated as a brown oil (0.27 g, 25% yield). The hydrochloride salt (red oil) was obtained by bubbling HCl gas into an anhydrous solution of **12r** in ether: IR (Nujol, cm^{-1}) 3400 (NH), 1776 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.76 (t, 6H, J = 6.86), 1.09 (m, 20H), 1.73 (m, 4H), 3.39 (m, 4H), 3.99 (s, 2H), 7.59 (m, 2H), 7.68 (m, 2H), 11.90 (br s, 1H). Anal. ($C_{25}H_{41}N_3O_2$·HCl·H_2O) C, H, N.

4.4.21. 3-(4-(*N*,*N*-Ditetradecylamino)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12s). Compound **12s** was prepared following the above general procedure from **11s** (0.23 g, 0.41 mmol) and phenyl chloroformate (55 μL, 0.44 mmol), while the cyclization was done in 2 h, and isolated as a brown oil (82 mg, 34% yield): IR (Nujol, cm^{-1}) 3168 (NH), 1790 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 6H, J = 6.86), 1.19 (m, 44H), 1.47 (m, 4H), 3.15 (m, 4H), 3.66 (s, 2H), 6.51 (d, 2H, J = 8.50), 6.98 (d, 2H, J = 8.32). Anal. ($C_{37}H_{65}N_3O_2$·2/3EtOH) C, H, N.

4.4.22. 3-(4-(*N*-Boc-*N*-tetradecylamino)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12t). Compound **12t** was prepared following the above general procedure from **11t** (0.45 g, 0.98 mmol) and phenyl chloroformate (127 μL, 1.03 mmol), while the cyclization was done in 5 h, and isolated as a yellow oil (0.40 g, 64% yield): IR (Nujol, cm^{-1}) 3200 (NH), 1787 (C=O), 1699 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.71), 1.17 (m, 24H), 1.39 (s, 9H), 3.49 (t, 2H, J = 7.01), 3.66 (s, 2H), 7.07 (d, 2H, J = 8.70), 7.13 (d, 2H, J = 8.70). Anal. ($C_{28}H_{45}N_3O_4$) C, H, N.

4.4.23. 4,5-Dihydro-3-(4-(*N*-tetradecylamino)benzyl)-4*H*-1,2,4-oxadiazol-5-one (12t′). A solution of HCl in anhydrous ether (1.83 M, 3.0 mL) was added to a solution of **12t** (50 mg, 0.10 mmol) in anhydrous THF (4.0 mL) at 0 °C under N_2 atmosphere and the mixture was stirred firstly at 0 °C for 2 h, then at room temperature for 1 h. The solvent was removed under reduced pressure and the residue recovered in CH_2Cl_2 (40 mL), washed with 10% $NaHCO_3$, H_2O and dried over $MgSO_4$. Compound **12t′** was obtained after silica gel column chromatography purification (MeOH/CH_2Cl_2) as a brown powder (16.6 mg, 44% yield): mp 80–82 °C; IR (Nujol, cm^{-1}) 3200 (NH), 1787 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.37), 1.19 (m, 22H), 1.49 (dt, 2H, J = 6.64), 2.99 (t, 2H, J = 7.01), 3.64 (s, 2H), 6.47 (d, 2H, J = 8.42), 6.96 (d, 2H, J = 8.42). Anal. ($C_{23}H_{37}N_3O_2$·1/4MeOH) C, H, N.

4.4.24. 3-Heptadecyl-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12u). Compound **12u** was prepared according to the general procedure from **11u** (1.51 g, 5.0 mmol) and phenyl chloroformate (0.66 mL, 5.26 mmol) and isolated by silica gel column chromatography as a white solid (0.61 g, 38% yield): mp 96–97 °C; ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 6.44), 1.19 (m, 28H), 1.62 (dt, 2H, J = 7.22), 2.51 (t, 2H, J = 7.59). Anal. ($C_{19}H_{36}N_2O_2$) C, H, N.

4.4.25. 4,5-Dihydro-3-(4-methoxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12v). Compound **12v** was prepared according to the general procedure from **11v** (2.00 g, 11.0 mmol) and phenyl chloroformate (1.40 mL, 13.2 mmol) and isolated by silica gel column chromatography as a white solid (1.46 g, 65% yield): mp 137 °C; IR (KBr, cm^{-1}) 3116 (NH), 1728 (C=O); 1517 (C=N); ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ 3.71 (s, 3H), 3.73 (s,

2H), 6.80 (d, 2H, $J = 8.00$), 7.10 (d, 2H, $J = 8.00$). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

4.4.26. 4,5-Dihydro-4-methyl-3-(4-tetradecyloxybenzyl)-4*H*-1,2,4-oxadiazol-5-one (12w). A solution of diazomethane in ether prepared prior to use was added dropwise into a solution of **12f** (1.00 g, 2.58 mmol) in DMF (30 mL) until the pale yellow colour persist during 30 min. Several drops of acetic acid were added into the reaction mixture and the solvent evaporated to dryness. After dried over KOH in a desiccator, the residue was recrystallized (EtOAc/CH_2Cl_2) to afford **12w** as white crystals (0,76 g, 73% yield): mp 93 °C; IR(KBr, cm^{-1}) 1779 (C═O); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.50$), 1.20 (m, 22H), 1.74 (dt, 2H, $J = 6.95$), 2.93 (s, 3H), 3.83 (s, 2H), 3.90 (t, 2H, $J = 6.50$), 6.81 (d, 2H, $J = 8.50$), 7.10 (d, 2H, $J = 8.50$). Anal. ($C_{24}H_{38}N_2O_3$) C, H, N.

4.4.27. *N*-Hydroxy-*N*-methyl-4-tetradecyloxybenzylamidine (13). Compound **13** was prepared according to the general procedure to synthesize amidoximes, from **7f** (3.00 g, 9.20 mmol), *N*-methylhydroxylamine hydrochloride (3.18 g, 38.1 mmol) and K_2CO_3 (6.96 g, 50.4 mmol). It was isolated as white crystals (1,7 g, 52% yield): mp 102 °C; IR (KBr, cm^{-1}) 3395, 3323 (NH_2), 3278 (OH), 1662 (C═N); ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 6.50$, CH_3), 1.18–1.36 (m, 22H, $(CH_2)_{ch}$), 1.69 (dt, 2H, OCH_2CH_2), 3.45 (s, 3H, NCH_3), 3.61 (s, 2H, $CH_2C{=}N$), 3.87 (t, 2H, $J = 6.50$, OCH_2), 6.81 (d, 2H, $J = 8.64$, H_{ar}), 7.03 (d, 2H, $J = 8.61$, H_{ar}).

4.4.28. 4,5-Dihydro-2-methyl-3-(4-tetradecyloxybenzyl)-2*H*-1,2,4-oxadiazol-5-one (12x). Compound **12x** was prepared according to the general procedure to synthesize oxadiazolones, from **13** (0.50 g, 1.52 mmol) and ethyl chloroformate (0.15 mL, 1.52 mmol), while the cyclization was done in 1 h, and isolated by silica gel column chromatography (MeOH/CH_2Cl_2), then crystallized (CH_2Cl_2/petroleum ether) as white crystals (50 mg, 12% yield): mp 98 °C; IR (KBr, cm^{-1}) 1760 (C═O); ^1H NMR ($CDCl_3$/CD_3OD): δ 0.81 (t, 3H, $J = 6.50$), 1.18–1.36 (m, 22H), 1.68 (m, 2H), 3.47 (s, 3H), 3.82 (s, 2H), 3.86 (t, 2H, $J = 6.17$), 6.80 (d, 2H, $J = 8.32$), 7.10 (d, 2H, $J = 7.98$). Anal. ($C_{24}H_{38}N_2O_3$) C, H, N.

4.4.29. 4,5-Dihydro-3-(4-tetradecylsulfonylbenzyl)-4*H*-1,2,4-oxadiazol-5-one (12y). Compound **12a** (100 mg, 0.24 mmol) was heated in acetic acid (20 mL) at 50 °C for 30 min to a clear solution, to which Jones' reagent (CrO_3/H_2SO_4) was added dropwise until a pale yellow colour persisted. The mixture was diluted with H_2O (400 mL) and extracted with EtOAc (3×150 mL). The organic phase was washed with H_2O up to neutral pH, dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was recrystallized (MeOH) to provide **12y** as white crystals (40 mg, 38% yield): mp 132 °C; IR (Nujol, cm^{-1}) 3114 (NH), 1822 (C═O), 1733 (C═N), 1323, 1145 (SO_2); ^1H NMR ($CDCl_3$/CD_3OD): δ 0.81 (t, 3H, $J = 6.41$), 1.75 (m, 22H), 1.61 (dt, 2H), 3.03 (m, 2H), 3.89 (s, 2H), 7.49 (d, 2H, $J = 8.24$), 7.82 (d, 2H, $J = 8.27$). Anal. ($C_{23}H_{36}N_2O_4S$) C, H, N.

4.4.30. 3-(4-(13-Carboxytridecyloxy)benzyl)-4,5-dihydro-4*H*-1,2,4-oxadiazol-5-one (12z). To a solution of **12k′** (150 mg, 0.370 mmol) in THF (15 mL) and acetone (35 mL) at 0 °C was added Jones' reagent until the yellow colour of this reagent in the reaction mixture persisted during 1 h. The excess of Jones' reagent was then decomposed by isopropanol and the solvents reduced to dryness. The dark green residue was stirred with EtOAc (100 mL) and H_2O (30 mL), and the aqueous phase was extracted with 5% isopropanol in $CHCl_3$ (60 mL). Insoluble particles were filtered, washed with water, ether and dried in open air. They were dissolved in DMSO, then precipitated by water and the precipitate was collected by filtration, washed with water, ether, and dried in open air (85 mg, 55% yield): mp 134–136 °C; IR (Nujol, cm^{-1}) 3064 (br, OH, NH), 1776 (C═O), 1715 (C═O), 1655 (C═N); ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 1.20 (m, 18H), 1.54 (dt, 2H, $J = 7.00$), 1.70 (dt, 2H, $J = 6.62$), 2.22 (t, 2H, $J = 7.45$), 3.71 (s, 2H), 3.87 (t, 2H, $J = 6.49$), 6.80 (d, 2H, $J = 8.53$), 7.10 (d, 2H, $J = 8.53$). Anal. ($C_{23}H_{34}N_2O_5 \cdot 1/2CH_3CH(OH)CH_3$) C, H, N.

4.5. Determination of the log *P* of oxadiazol-5-one

The partition coefficient (log *P*) of the compound **12v** in *n*-octanol and a phosphate buffer (40 mM, pH 7.4) containing 15 mM NaCl was measured and the result was found to be 0.33 ± 0.04 unit of log *P*. The contribution of oxadiazolone was deduced from this value, using the hydrophobic fragmental constants published by Rekker and De Kort,[24] and we found that it represented −2.1 units of log *P*.

4.6. Determination of the pK_a of oxadiazol-5-one

Titration of an aqueous solution of the compound **12v** in sodium salt (20 mM) with hydrochloric acid (12 mM) was performed classically using a burette and a pH meter. The pK_a of oxadiazolone was thus determined to be 5.5.

4.7. Fluorimetric binding assay

In a polystyrene cuvette containing 970 μL of the assay solution: 50 mM Tris–HCl (pH 7.5), 0.5 M NaCl, 1 mM EGTA, 0.1% BSA (fatty acid free), and 2 μM 1-hexadecanoyl-2-(10-pyrenedecanoyl)-*sn*-glycero-3-phosphoglycerol, ammonium salt (β-py-C_{10}-PG), were added to the final products at different concentrations (10 μL of stock solutions in DMSO or EtOH), hGIIA (1 ng in 10 μL) or porcine pancreatic PLA_2 (60 ng in 10 μL) and 10 μL of an aqueous solution of calcium chloride (1 M) successively. The variation of the fluorescence ($\lambda_{ex} = 342$ nm and $\lambda_{em} = 398$ nm) was recorded and the initial slope of the curve was used to calculate velocity of the enzymatic reaction. The IC_{50} values were determined with three or more independent sample preparations in two different solvents (DMSO and EtOH) by plotting inhibition percentage obtained from the ratio of the velocities of two assays with or without the inhibitor, versus log concentration, until the standard error was less than 20% of the mean value.

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