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Synthesis and antioxidant activity of new lipophilic dihydropyridines

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ABSTRACT

Dihydropyridines (DHPs) obtained from Hantzsch multicomponent reactions are an important pharmaceutical class of compounds marketed as antihypertensive (e.g., nifedipine, nitrendipine, and amlodipine) drugs. This study synthesized new symmetrical and unsymmetrical long-chain fatty DHPs using multicomponent reactions under metal-free conditions with sulfamic acid as a catalyst. The DHPs were tested for antioxidant activity using three different methods. The insertion of a long chain into the DHP core contributed to antioxidant potential, and compounds derived from nitro aldehydes have better antioxidant potential than the antihypertensive drug nifedipine. In addition, fatty analogs to nifedipine derived from palmitic and oleic chains showed similar antioxidant activity to the common standards butylated hydroxytoluene and vitamin E. These results showed that our new synthesized products may find novel applications as antioxidant additives or for tools for use in drug discovery.

1. Introduction

Multicomponent reactions (MCRs) entail reactions among three or more reactants at the same time in a single step [1]. They satisfy several principles of green chemistry in that most atoms in each reactant are incorporated into the final product and the one-step reaction decreases the consumption of reagents and solvent used in purification [2]. The first MCR was reported in 1850 by Adolph Strecker, who used this type of reaction to synthesize α-cyano amines [3]. However, arguably the most important MCR ever conducted, in terms of its transformation of the pharmaceutical industry, was performed by Arthur Rudolf Hantzsch in 1881 to synthesize 1,4-dihydropyridines (DHPs) [4]. Today, MCRs are considered very important components of sustainable pharmaceutical production processes [5].

The 1,4-DHPs are one of the most important chemicals ever introduced in the field of medicine [6]. They have revolutionized the pharmaceutical industry with unprecedented biological properties, and have included drugs such as nifedipine (1st generation); nisoldipine, nimodipine, and nitrendipine (2nd generation); and recently pranidipine, lercanidipine, and amlodipine (3rd generation) [7]. Nifedipine was initially developed as a prototype of a calcium antagonist [8], and its introduction to the pharmaceutical market drastically improved the therapeutic standard in the treatment of heart disease. It also served as an excellent tool for researching the primary structure of the calcium channel [6]. Many studies have been conducted on DHPs, not only to understand their mechanisms of action but also to identify their structure–biological activity relationships [9]. Some properties that have reported include anti-inflammatory [10], antitubercular [11], antidyslipidemic [12], antimicrobial, and antioxidant [13] activities.

Antioxidants protect against free radical damage by preventing and reducing the oxidation of macromolecules [14]. DPHs have a structure analogous to nicotinamide adenine dinucleotide (NAD) coenzyme, which is involved in reduction reactions in biological systems [15]; thus, DHPs may be antioxidants. Vijesh et al. [13] synthesized DHPs derived from pyrazole and demonstrated significant antioxidant potential. Kumar et al. [12] reported potent antioxidant activity in synthesized *N*-aryl-1,4-DHPs. In another study triaryl-1,4-DHPs showed better antioxidant activity than nicardipine [16]. DHPs have also been used with reducing agents to synthesize gold nanoparticles [17], reduce olefins [18], and hydrogenate isoindolinones [19], and study also suggest that cationic long chain DHP derivatives may find use as DNA delivery system [20].

As shown in previous studies, increasing lipophilicity and hybridizing molecules [21] may alter the properties of compounds. In

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addition, compounds with optimal lipophilicity have higher chances of success in drug development, based on their preclinical absorption, distribution, metabolism, elimination, and toxicology (ADMET) properties [22]. Hydroxytyrosol and tyrosol saturated fatty esters (C4:0 to C18:0), called hydroxytyrosol esters (HTYEs), were able to scavenge DPPH (1,1-diphenyl-2-picrylhydrazyl) radical, similar to the antioxidant trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) [23]. HTYEs have also been shown to have antioxidant activity in membrane models, demonstrating their efficacy against lipid oxidation [24].

Lipophilic esters (C3:0 to C22:6) from resveratrol have been demonstrated to have antioxidant potential in food and biological systems, in particular those derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [25]. Recently, tocopherol derivatives were synthesized by MCRs and showed antiproliferative activity [26]. Venepally et al. [27] recently reported the importance of heterocyclic–fatty acid hybrid compounds for the development of new bioactive compounds with a broad range of biological activities and significance in the field of medicinal chemistry.

Our laboratory has been studying the synthesis and biological activities of new fatty compounds, such as compounds produced via Hantzsch [28] and Biginelli [29] reactions.

In previous work we investigated the effects of the calcium channel blocker nifedipine and its fatty hybrid derived dipalmitoyl-nifedipine (**16a**) during the process of inducing ischemia and reperfusion in cardiomyoblast H9c2 heart cells [30]. In *in vitro* assays, 3,5-dipalmitoyl-nifedipine by **16a** showed more antioxidant activity than nifedipine. This result demonstrates that the hybridization procedure of two chains of palmitic acid to a nifedipine molecule assigns a greater cardioprotective effect to the molecule, probably due to an enhanced power scavenger and ferric ion reduction capability, thereby reducing the oxidative damage caused by ischemia and reperfusion in a cardiomyoblast culture. In addition, according with literature, the dynamic cellular internalization of lipophilic fatty small-molecules is expected to be better, capable of easily transposing the cell-membrane at low temperatures [31]. Thus, the fatty nifedipine is expected to internalize faster, hence its availability in the intracellular media is higher than nifedipine.

In this study, we synthesized new series of symmetrical and unsymmetrical long-chain fatty DHPs using MCRs and verified the antioxidant activities of the resultant compounds using three different methods, namely, the 2,20-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), ferric ion reducing antioxidant power (FRAP), and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assays.

2. Results and discussion

Fatty β-ketoester precursors **1a, 1b,** and **1c** were synthesized via transesterification of palmitic (C16:0), stearic (C18:0), and oleic (C18:1) fatty alcohols, respectively, in accordance with previous work [29]. Next, the compounds were employed as fatty 1,3-dicarbonnyl compounds in the synthesis of symmetrical and unsymmetrical long-chain fatty DHPs following a Hantzsch multicomponent protocol using furfural along with different substituted benzaldehydes with electron-releasing groups (ERGs) and electron-withdrawing groups (EWGs). The reaction was carried under metal-free conditions using sulfamic acid (SA, $H_3N^+SO_3^-$) as a catalyst [30]. Sulfamic acid was chosen as the catalyst because it is inexpensive, highly stable, and nontoxic [32], in addition to being conducive to excellent results in the synthesis of compounds via Hantzsch synthesis [28,30,33,34].

2.1. Synthesis of symmetrical lipophilic DHPs

The synthesis of symmetrical long-chain DHPs **15-25a-c** was performed using fatty β-ketoesters **1a-c**, aldehydes **3–13**, and ammonium acetate (**2**) in the presence of 30 mol% sulfamic acid (Scheme 1). The reactions were monitored by thin-layer chromatography (TLC). The lowest yields (47–59%) were observed for compounds **15a-c** derived from benzaldehyde. Moderate yields were observed for compounds **22-23a-c** (71–92%) and **16-18a-c** (55–90%) with deactivator groups such as chloride and nitro, respectively, in the aromatic moiety. The highest yields (83–92%) were for compounds **19a-c** derived from furfural (Table 1). In general, high yields were observed for compounds with *para*-substituted groups in the aromatic moiety. Although there is no consensus in the literature on the contribution of substitutions in aromatic rings (electron donor or electron acceptor) to the synthesis of Hantzsch compounds, several papers have reported that *para*-substituted groups prevent steric hindrance and provide higher yields [35–37]. All compounds in this study were purified using column chromatography and characterized by the usual spectroscopic methods, including infrared (IR) spectroscopy and proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance methods.

2.2. Synthesis of unsymmetrical lipophilic DHPs

Aiming to decrease the lipophilicity of the symmetrical fatty DHPs, we synthesized unsymmetrical hybrid fatty DHPs derived from methyl acetoacetate (**1d**). Products **26-35bd** were obtained following the same protocol used to synthesize symmetrical long-chain DHPs **15-25a-c**, except employing one equivalent of non-fatty β-ketoester methyl acetoacetate (**1d**) and fatty β-ketoester **1b** according to Scheme 2.

The unsymmetrical compounds were obtained at moderated yields (Table 2). Minority products (symmetrical fatty and non-fatty DHPs) were observed during purification. In tetracomponent reactions, lower yields were observed for phenyl derivatives **26bd** (35%) and compounds **27-28bd** with a nitro group (51% and 55%) in the aromatic moiety. The best yields were from compounds with chloride in the aromatic moiety (**32-33bd**; 66–78%) and those derived from furfural **29bd** (65%).

However, after several experiments using 2-nitrobenzaldehyde (**4**), the product of a reaction carried out in the presence of β-ketoester **1b**, methyl acetoacetate (**1d**), and ammonium acetate (**2**) was not obtained. High reactivity between methyl acetoacetate (**1d**) and 2-nitrobenzaldehyde (**4**) may have promoted parallel reactions, difficult the obtention of main product.

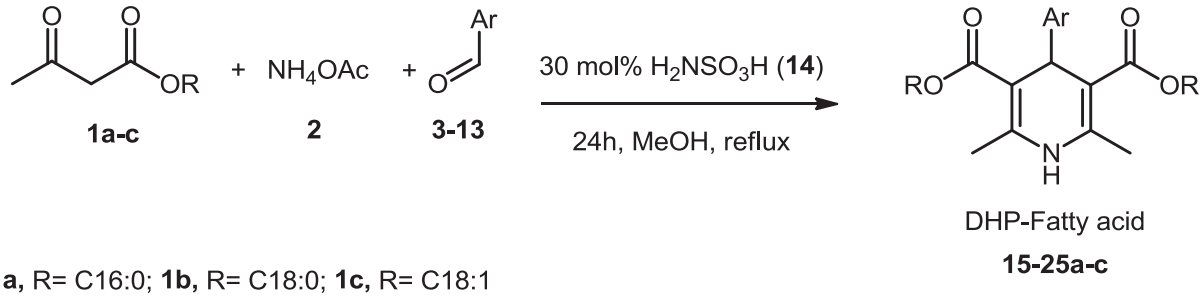
Next, log *P* values (Table 3) of the symmetrical **15-25a-c** and unsymmetrical **26-35bd** fatty DHPs were calculated to provide an estimate of their lipophilicity. The log *P* values for unsymmetrical fatty DHPs were similar to those of the standard antioxidant vitamin E.

2.3. Antioxidant assays

The antioxidant activities of all DHPs were evaluated using three different methods *in vitro*, the 2,20-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) ($ABTS^+$) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and ferric ion reducing antioxidant power (FRAP) assays. Butylated hydroxytoluene (BHT) and vitamin E were used as standards of antioxidant activity, and nifedipine was used as a reference for DHP.

2.4. $ABTS^+$ radical scavenging

All DHPs were tested for free radical scavenging by $ABTS^+$ [38] (Tables 3 and 4). The results are reported as minimal concentrations required to reduce the initial ABTS radical count by 50% (EC50, μM) [39]. All fatty DHPs showed higher antioxidant activity than nifedipine, however, fatty DHPs with hydroxyl or methoxyl groups in aromatic rings and furfural derivatives showed less activity than other DHPs. The best radical scavenging activities were observed for unsymmetrical fatty DHPs **29bd** and **33bd** (Table 4), derived from furfural and 4-chlorobenzaldehyde. Compound **16c** derived from oleic acid and 2-nitrobenzaldehyde (**4**) showed similar activity as sample **16a** derived from palmitic acid and antioxidant standards BHT and vitamin E.



Scheme 1. Synthesis of symmetrical fatty DHPs **15-25a-c**.

2.5. DPPH radical scavenging

All DHPs were tested for free radical scavenging by DPPH [40] (Tables 3 and 4). The scavenging abilities of DHPs **16a** derived from palmitic acid, 2-nitrobenzaldehyde (**4**) and **25c** derived from oleic acid and 4-metoxybenzaldehyde, **16b** (a 2-nitrobenzaldehyde derivative), and **17c** (a 3-nitrobenzaldehyde derivative) were the highest, being nearly identical to that of BHT. Compounds **16c** (2-nitrobenzaldehyde derivative) and **20a** (3-hidroxybenzaldehyde derivative) derived from oleic and the palmitic chain also demonstrated good antioxidant activity, similar to that of vitamin E.

In sum, symmetrical fatty DHPs **16a-c** derived from 2-nitro benzaldehyde, which are analogous to nifedipine, had the best DPPH test results. In this assay Nifedipine presents lower antioxidant activity compared to your fatty analogues, EC50 33.64 ± 1.53 μM as previously observed also in the ABTS test. In general, antioxidant activity results by via radical methods DPPH and ABTS are similar, but EC50 values are lower for the DPPH test.

In contrast, DHPs derived from furfural (**19a-d**) showed poor results, with the worst performance observed for chlorinated and 4-methoxy fatty DHP derivatives **22-23a-c** and **24-25a-c**.

2.6. FRAP assay

The FRAP assay is used to assess the reduction reaction of iron ions, with the assumption that antioxidant activity may be correlated with the reducing power of a compound [41]. All DHPs were again tested using this assay (Tables 3 and 4). Symmetrical DHPs showed values statistically equal to samples **17c** derived from 3-nitrobenzaldehyde and the oleic chain and **16a** derived form 2-nitrobenzaldehyde and the palmitic chain. Their EC50 values (Table 3) were higher than those observed for antioxidant standards BHT and vitamin E and DHP analog nifedipine.

Interestingly, the less lipophilic unsymmetrical **27bd** (derived from 3-nitrobenzaldehyde) and **28bd** (derived from 4-nitrobenzaldehyde) obtained from the stearic chain showed the best results, again better than the reference antioxidants and nifedipine (Table 4). Compounds **20-21a-c** and **30-31bd** with hydroxyl groups in the aromatic ring, which did not have good results in the DPPH and ABTS assessments, had similar EC50 values to BHT and vitamin E in the FRAP assay.

In general, more lipophilic symmetrical fatty DHPs showed better antioxidant activities than unsymmetrical derivatives. This shows that the insertion of two fatty chains in the DHP core with an NO_2 group in the aromatic ring contributed to the antioxidant activity. This finding is also supported by the fact that all DHPs exhibited higher antioxidant activity than nifedipine.

However, in all tests, nifedipine showed lower antioxidant activity than vitamin E and BHT. In the literature, the antioxidant potential of nifedipine is compared with other calcium blockers and nifedipine presents the best result than Propranolol, Verapamil and Diltiazem [42]. Compared with ascorbic acid (antioxidant standard) and DHPs derivative from amino acid, nifedipine shows lower antioxidant potential by DPPH test [43].

The aromatization of Hantzsch compounds results in the oxidation of the DHP ring generated pyridine rings. In this process, DHPs are reducing agents, and derivatives of furfural tend to have low yields and long reaction times [44,45]. This behavior may explain the lowest antioxidant activity observed for compounds **19a-c** derived from furfural (Table 4).

According to polar paradox theory, lipophilic antioxidants tend to be more effective in polar media; the reverse is usually true for more polar antioxidants [46]. Thus, this theory can explain the results obtained in this work where lipophilic fatty DHPs had more effective antioxidant activity in polar media. However, there are limitations to this theory [47], as in the case of antioxidant activities of long-chain chlorogenic acid esters [48].

According to the results of all assays, the insertion of a long chain into DHP compounds contributed to antioxidant potential. To explain these results, a principal component analysis (PCA) was conducted. Compounds **16a** and **16c**, derived from 2-nitrobenzaldehyde and substituted with palmitic and oleic chains, presented 93.8% of the variance, showing similar antioxidant activities as the references vitamin E and BHT, and had better antioxidant activity than the antihypertensive drug nifedipine (Fig. 1). These results are in agreement with those observed for fatty DHP **16a** in a previous work [30], demonstrating that the presence of two chains of palmitic acid in the nifedipine core assigns a greater cardioprotective effect to the molecule, probably due to an enhanced power scavenger and ferric ion reduction.

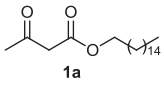
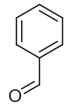
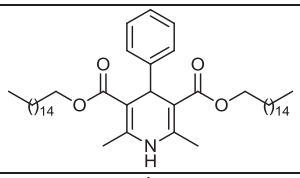
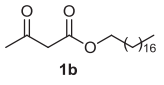
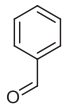
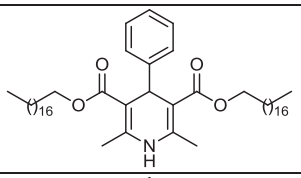
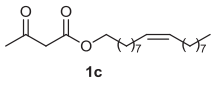
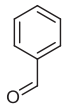
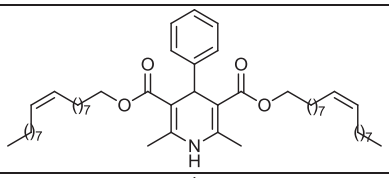
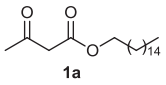
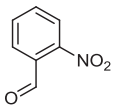
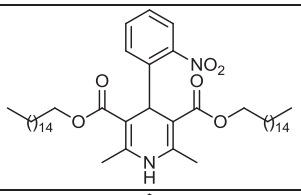
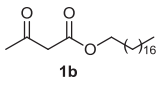
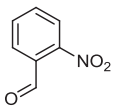
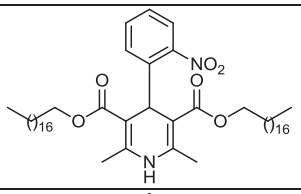
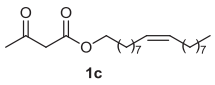
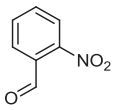
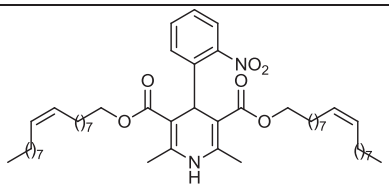
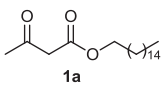
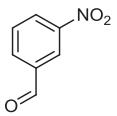
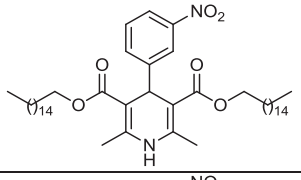
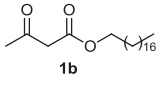
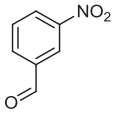
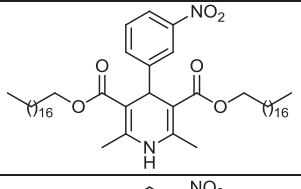
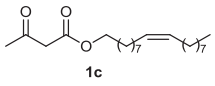
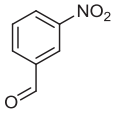
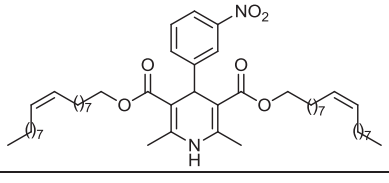
In addition, as shown in Fig. 2, the benzylic hydrogen for compounds derived from 2-nitrobenzaldehydes exhibit a chemical shift of 5.84 ppm, and are more deshielded than other H-benzylic fatty DHP derivatives (range 4.95–5.22 ppm). This may explain the better antioxidant activity of fatty DHP 2-nitrobenzaldehyde derivatives, correlates with the aromatization of the pyridine ring and collaborates with antioxidant activity of these compounds (see Scheme 3).

Thus, according to our experimental results, fatty DHPs derived from nifedipine could have therapeutic benefits, combating reactive oxygen species (ROS) and conferring advantages over other drugs [30,14].

3. Conclusion

Several fatty DHPs, symmetrical **15-25a-c** and unsymmetrical **26-35bd**, were synthesized at good yields using Hantzsch MCRs. The compounds were characterized and tested for antioxidant activity using three different methods. In general, compounds derived from palmitic and oleic acid showed good results, demonstrating that the insertion of a long chain into DHP compounds contributes to antioxidant potential.

Table 1
Yields of symmetrical lipophilic DHPs **15-25a-c**.

Comp. No.	Fatty acetoacetate	Aldehyde	Symmetrical lipophilic DHPs	Yield[a] (%)
15a	 **1a**			59
15b	 **1b**			56
15c	 **1c**			47
16a	 **1a**			75
16b	 **1b**			60
16c	 **1c**			55
17a	 **1a**			75
17b	 **1b**			80
17c	 **1c**			63

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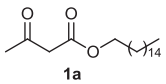
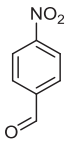
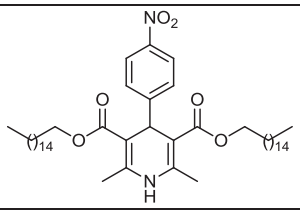
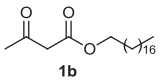
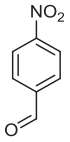
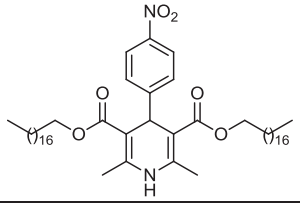
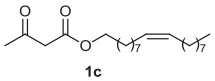
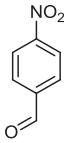
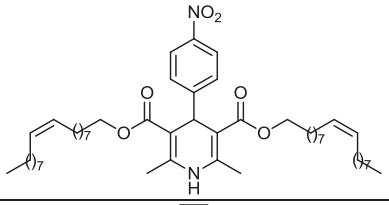
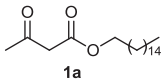
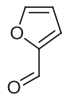
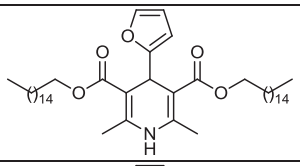
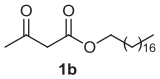
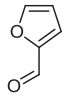
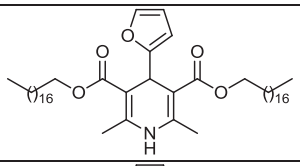
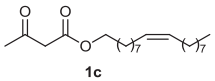
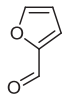
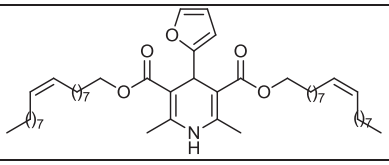
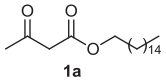
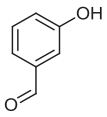
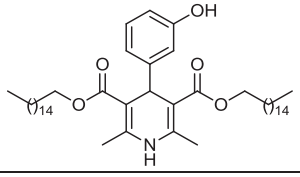
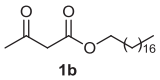
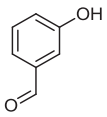
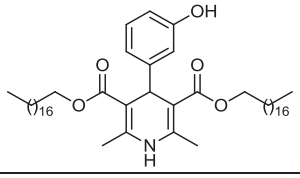
18a				89
18b				90
18c				62
19a				90
19b				92
19c				83
20a				66
20b				64

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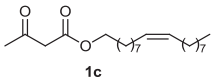
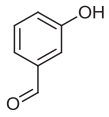
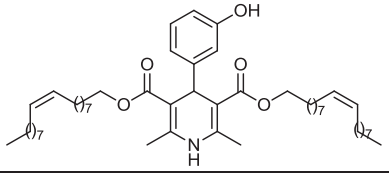
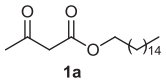
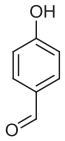
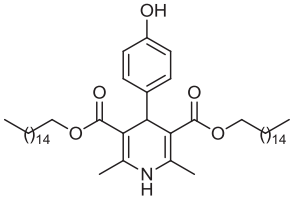
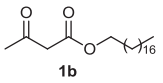
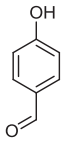
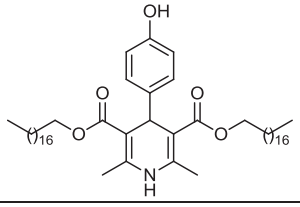
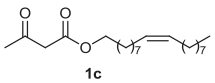
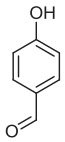
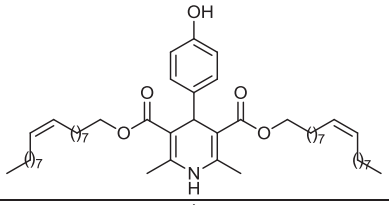
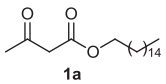
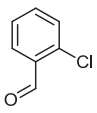
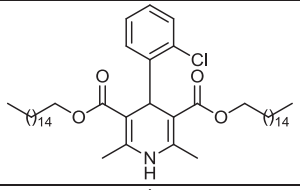
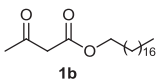
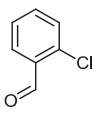
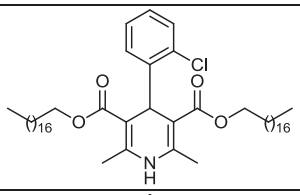
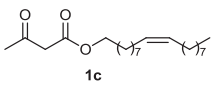
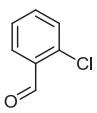
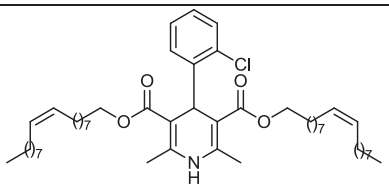
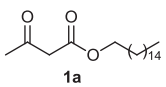
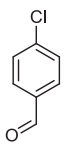
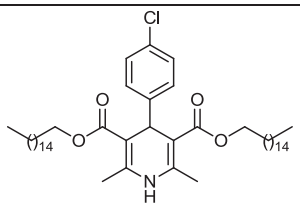
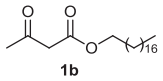
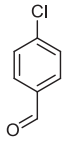
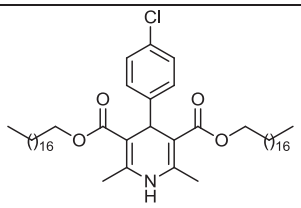
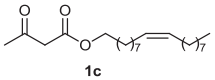
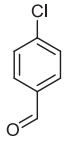
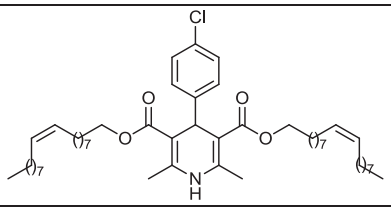
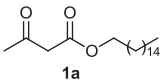
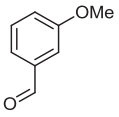
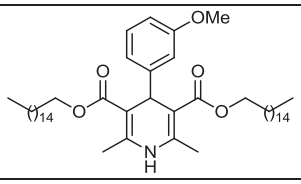
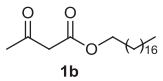
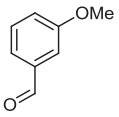
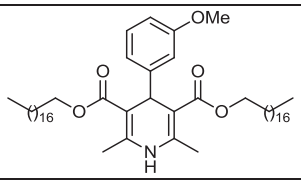
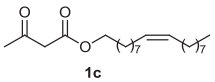
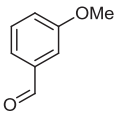
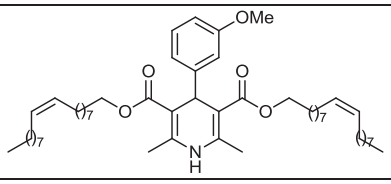
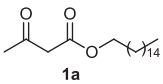
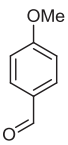
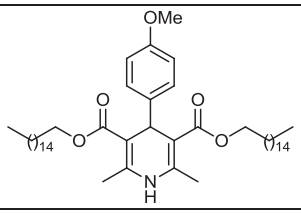
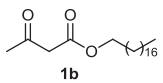
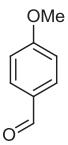
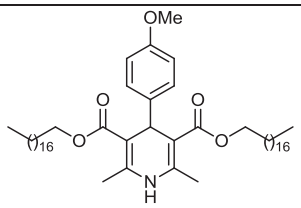
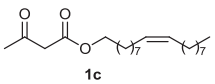
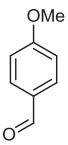
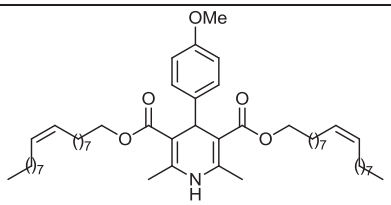
20c				55
21a				77
21b				72
21c				70
22a				79
22b				81
22c				71
23a				89

(*continued on next page*)

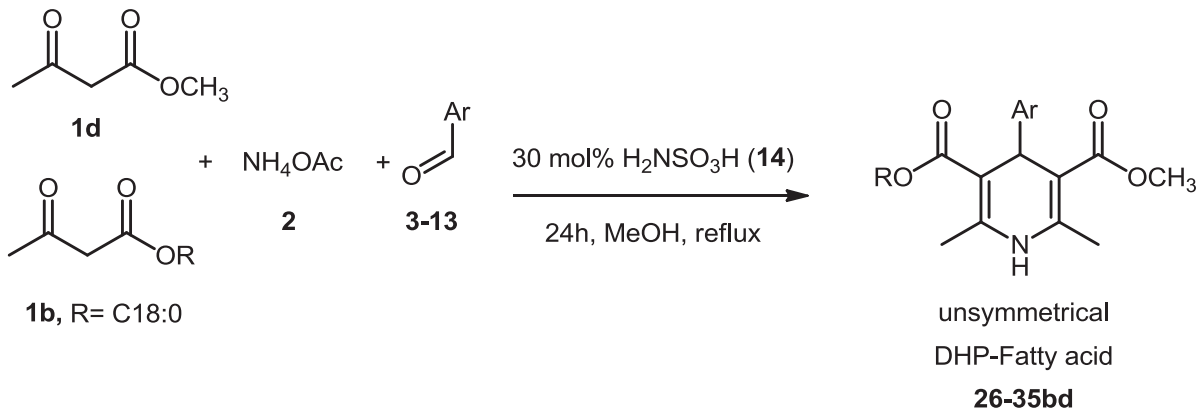
Table 1 (*continued*)

23b	 **1b**			92
23c	 **1c**			80
24a	 **1a**			76
24b	 **1b**			73
24c	 **1c**			62
25a	 **1a**			78
25b	 **1b**			79
25c	 **1c**			70

Conditions: 1 mmol aromatic aldehyde (**3**–**13**), 2 mmol fatty acetoacetate **1a**, **1b**, or **1c**, 3 mmol ammonium acetate (**2**), 30 mol% sulfamic acid (**14**), 4 mL methanol, 24 h at reflux.
[a]Product isolated by column chromatography.

However, fatty DHPs **16c**, **16a**, and **27bd** derived from the nitro group showed the best antioxidant activity in the ABTS, DPPH, and FRAP analyses, respectively.

In principal component analysis (PCA), compounds **16a** and **16c**, analogous to nifedipine, showed the best antioxidant activities, similar to those of vitamin E and BHT. This result adds new applications to compounds, for example, as drug candidates. This strong antioxidant activity may be one possible mechanism responsible for the organ-



Ar = Phenyl, 3-Nitrophenyl, 4-Nitrophenyl, 2-Furyl, 3-Hydroxyphenyl, 4-Hydroxyphenyl, 2-Chlorophenyl, 4-Chlorophenyl, 3-Methoxyphenyl, 4-Methoxyphenyl

Scheme 2. Synthesis of unsymmetrical fatty DHPs **26-35bd**.

Table 2
Yields of unsymmetrical lipophilic DHPs **26-35bd**.

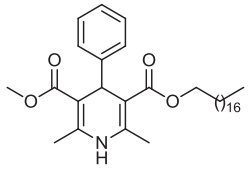
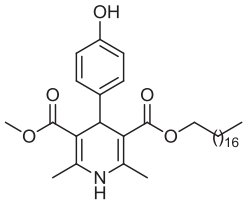
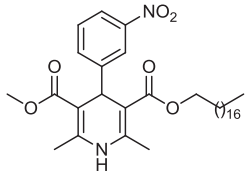
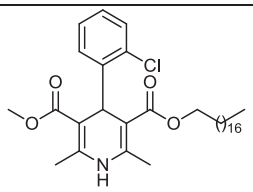
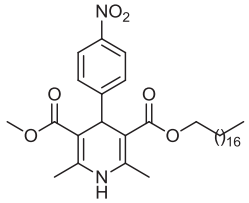
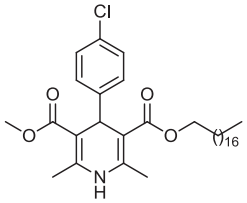
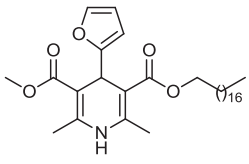
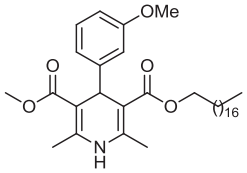
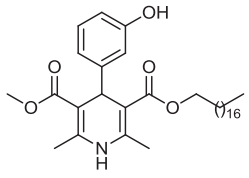
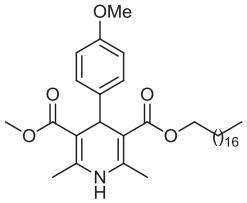
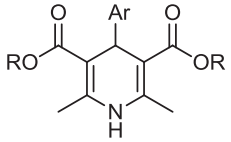
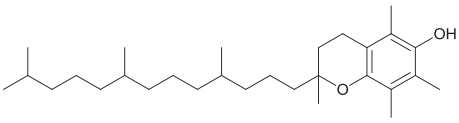
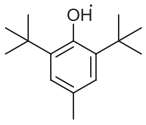
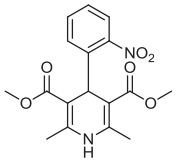
Comp. No.	Unsymmetrical lipophilic DHPs	Yield[a] (%)	Comp. No.	Unsymmetrical lipophilic DHPs	Yield[a] (%)
26bd		35	**31bd**		52
27bd		51	**32bd**		66
28bd		55	**33bd**		78
29bd		65	**34bd**		48
30bd		43	**35bd**		57

Table 3
Antioxidant activity and calculated Log *P* of synthesized symmetrical lipophilic DHPs **15-25a-c**.



Compound	R	Ar	Calc LogP	ABTS EC50(μM)*	DPPH	FRAP
 **Vitamin E**			11.90	0.98 ± 0.01a	1.93 ± 0.28ab	7.16 ± 0.85e
 **BHT**			5.32	0.97 ± 0.01a	1.01 ± 0.32a	4.55 ± 0.66a
 **Nifedipine**			2.97	94.70 ± 1.98	33.64 ± 1.53h	29.10 ± 1.46
15a	C16:0	Phenyl	19.18	3.87 ± 0.59b	12.56 ± 1.10e	8.96 ± 0.95b
15b	C18:0	Phenyl	21.30	32.16 ± 1.5e	16.49 ± 1.22g	16.60 ± 1.22
15c	C18:1	Phenyl	20.27	5.30 ± 0.72b	14.41 ± 1.16b	11.21 ± 1.05g
16a	C16:0	2-Nitrophenyl	18.91	1.11 ± 0.05a	1.01 ± 0.01a	3.61 ± 0.56ac
16b	C18:0	2-Nitrophenyl	21.03	8.68 ± 0.94c	1.34 ± 0.13a	13.21 ± 1.12f
16c	C18:1	2-Nitrophenyl	20.00	1.00 ± 0.01a	1.91 ± 0.28ab	5.25 ± 0.72a
17a	C16:0	3-Nitrophenyl	18.91	13.39 ± 1.13d	3.08 ± 0.49b	5.52 ± 0.74a
17b	C18:0	3-Nitrophenyl	21.03	8.54 ± 0.87bc	6.21 ± 0.79c	4.03 ± 0.61a
17c	C18:1	3-Nitrophenyl	20.00	7.67 ± 0.88bc	1.34 ± 0.13a	2.94 ± 0.47c
18a	C16:0	4-Nitrophenyl	18.91	8.36 ± 0.92bc	9.50 ± 0.98d	4.97 ± 0.70a
18b	C18:0	4-Nitrophenyl	21.03	12.31 ± 1.09cd	13.07 ± 1.12e	8.42 ± 0.93b
18c	C18:1	4-Nitrophenyl	20.00	31.74 ± 1.50e	12.92 ± 1.11e	8.31 ± 0.92b
19a	C16:0	2-Furyl	18.34	23.45 ± 1.37f	18.15 ± 1.26g	40.23 ± 1.61
19b	C18:0	2-Furyl	20.46	11.00 ± 1.04cd	6.86 ± 0.84c	17.74 ± 1.25d
19c	C18:1	2-Furyl	19.43	13.28 ± 1.12d	22.90 ± 1.36	18.01 ± 1.26d
20a	C16:0	3-Hydroxyphenyl	18.44	24.24 ± 1.39f	2.51 ± 0.40a	6.61 ± 0.82e
20b	C18:0	3-Hydroxyphenyl	20.57	99.02 ± 3.00	17.01 ± 2.23g	6.61 ± 0.82e
20c	C18:1	3-Hydroxyphenyl	19.53	25.16 ± 1.40f	4.37 ± 0.64c	3.99 ± 0.60a
21a	C16:0	4-Hidroxyphenyl	18.44	20.64 ± 1.10h	6.33 ± 0.80c	6.62 ± 0.82e
21b	C18:0	4-Hidroxyphenyl	20.57	28.48 ± 1.46g	6.82 ± 0.83c	6.61 ± 0.82e
21c	C18:1	4-Hidroxyphenyl	19.53	28.12 ± 1.45g	6.64 ± 0.82c	4.37 ± 0.64a
22a	C16:0	2-Chlorophenyl	19.77	9.13 ± 0.96c	32.69 ± 1.51h	12.50 ± 1.10f
22b	C18:0	2-Chlorophenyl	21.90	9.58 ± 0.98c	39.36 ± 1.60	6.67 ± 0.82e
22c	C18:1	2-Chlorophenyl	20.86	4.59 ± 0.66b	30.99 ± 1.49	8.21 ± 0.91eb
23a	C16:0	4-Chlorophenyl	19.77	9.09 ± 0.96c	15.37 ± 1.19bg	7.06 ± 0.85e
23b	C18:0	4-Chlorophenyl	21.90	4.59 ± 0.66b	16.54 ± 1.22g	10.09 ± 1.00g
23c	C18:1	4-Chlorophenyl	20.86	3.46 ± 0.54b	18.76 ± 1.27g	9.59 ± 0.98bg
24a	C16:0	3-Methoxyphenyl	19.09	28.30 ± 1.45g	4.39 ± 0.64c	6.61 ± 0.82e
24b	C18:0	3-Methoxyphenyl	21.22	26.09 ± 1.22f	4.39 ± 0.64c	6.61 ± 0.82e
24c	C18:1	3-Methoxyphenyl	20.18	27.86 ± 1.45g	6.30 ± 0.80c	6.61 ± 0.82e
25a	C16:0	4-Methoxyphenyl	19.09	27.58 ± 1.44g	6.39 ± 0.81c	4.53 ± 0.66a
25b	C18:0	4-Methoxyphenyl	21.22	31.38 ± 1.50e	12.00 ± 1.08e	6.60 ± 0.82e
25c	C18:1	4-Methoxyphenyl	20.18	12.51 ± 1.10d	1.08 ± 0.03a	4.99 ± 0.70a

* Based on mean concentration, values followed by the same letter within each column are not significantly different according to the Tukey test (significance level of 5%).

protective effects of 1,4-DHP calcium channel blockers.

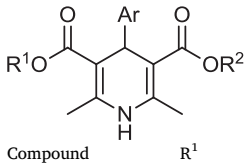
According to results observed in previous work [30], demonstrating that the hybridization procedure of fatty chains assigns a greater cardioprotective effect to the DHP, ischemia and reperfusion induction tests on cardioblasts are currently being conducted to verify other possible activities of the new series of fatty DHPs with the best antioxidant potential.

4. Experimental section

4.1. ABTS radical scavenging

The determination of the radical scavenging effect of hybrid fatty dihydropyridine on ABTS - 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) radicals was performed according to the method of Re et al. [49], with some modifications. Briefly, ABTS radical was added to a

Table 4
Antioxidant activity and calculated Log *P* of synthesized unsymmetrical lipophilic DHPs **26-35bd**.



Compound	R^1	R^2	Ar	Calc LogP	ABTS EC50(μM)*	DPPH	FRAP
Vitamin E				11.90	0.98 ± 0.01a	1.93 ± 0.28ab	7.16 ± 0.85e
BHT				5.32	0.97 ± 0.01a	1.01 ± 0.32a	4.55 ± 0.66a
Nifedipine				2.97	94.70 ± 1.98	33.64 ± 1.53h	29.10 ± 1.46
26bd	C18:0	CH_3	Phenyl	12.57	6.51 ± 0.81b	14.94 ± 1.17b	8.76 ± 0.94b
27bd	C18:0	CH_3	3-Nitrophenyl	12.00	9.85 ± 0.99c	8.72 ± 0.94d	2.29 ± 0.36c
28bd	C18:0	CH_3	4-Nitrophenyl	12.00	9.23 ± 0.97c	9.91 ± 1.00d	2.46 ± 0.39c
29bd	C18:0	CH_3	2-Furyl	11.43	3.86 ± 0.59b	21.91 ± 1.34f	5.19 ± 0.72a
30bd	C18:0	CH_3	3-Hydroxyphenyl	11.53	28.71 ± 1.06g	6.93 ± 0.84c	4.63 ± 0.67a
31bd	C18:0	CH_3	4-Hydroxyphenyl	11.53	28.29 ± 1.15g	6.73 ± 0.83	4.51 ± 0.65a
32bd	C18:0	CH_3	2-Chlorophenyl	12.86	6.24 ± 0.98b	33.05 ± 1.52h	6.50 ± 0.81ea
33bd	C18:0	CH_3	4-Chlorophenyl	12.86	3.95 ± 0.60b	21.84 ± 1.34f	10.22 ± 1.01g
34bd	C18:0	CH_3	3-Methoxyphenyl	12.18	19.91 ± 1.30h	11.21 ± 1.05e	6.61 ± 0.82e
35bd	C18:0	CH_3	4-Methoxyphenyl	12.18	26.62 ± 1.03fg	5.37 ± 0.73c	3.83 ± 0.58a

* Based on mean concentration, values followed by the same letter within each column are not significantly different according to the Tukey test (significance level of 5%).

medium containing DHPs sample (0.1 μM, 1 μM, 10 μM and 100 μM). The media were incubated for 30 min at 25 °C. The decrease in absorbance was measured at 734 nm, depicting the scavenging activity of compounds against the ABTS radical. The radical scavenging activity express in EC50 (Half maximal effective concentration), calculated by non-linear regression [41].

4.2. DPPH photometric assay

The effect of hybrid fatty dihydropyridine on DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals was measured using the modified method of Sharma and Bhat [40]. The compounds were diluted to final concentrations of 0.1μM 1 μM, 10 μM and 100 μM. The reaction mixture was shaken thoroughly and incubated for 30 min at 30 °C in the dark, and the absorbance was measured at 517 nm against a blank. The antioxidant activity (AA) radical scavenging activity was express in EC50 [39].

4.3. Ferric ion reducing antioxidant power (FRAP) assay

The FRAP assay was carried out as described by Benzie et al. [41], with slight modifications. The FRAP reagent was prepared by mixing 38 mM sodium acetate (anhydrous) in milli Q water pH 3.6, 20 mM $FeCl_3{\cdot}6H_2O$ in milli Q water and 10 mM 2,4,6-tri(2-pyridyl)-s-triazine (TPTZ) in 40 mM HCl in proportions of 10:1:1. This reagent was freshly prepared before each experiment. The FRAP reagent was added to DHPs sample (0.1 μM, 1 μM, 10 μM and 100 μM), and the mixture was incubated at 37 °C for 40 min in the dark. The absorbance of the resulting solution was measured at 593 nm by a spectrophotometer. FRAP values were expressed in EC50 [39].

4.4. Statistical analysis

One-way analysis of variance (ANOVA) was used to determine

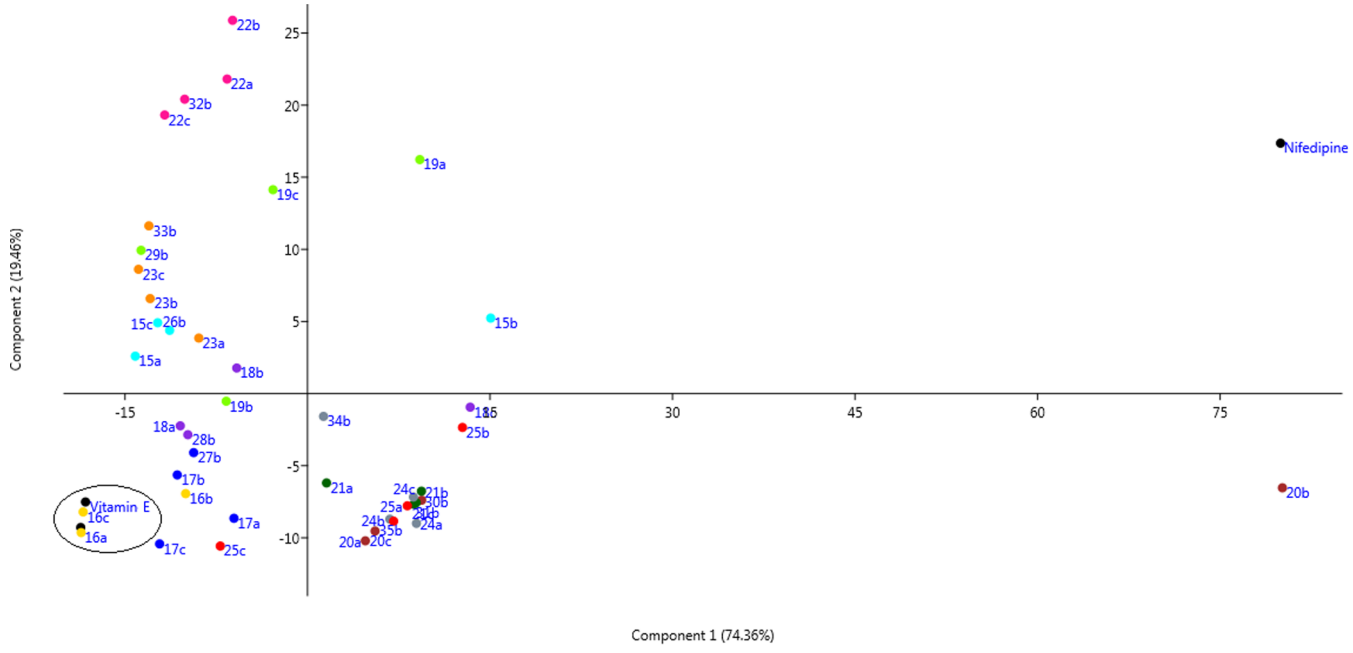


Fig. 1. Principal component analysis (PCA) of the antioxidant activity of lipophilic DHPs.

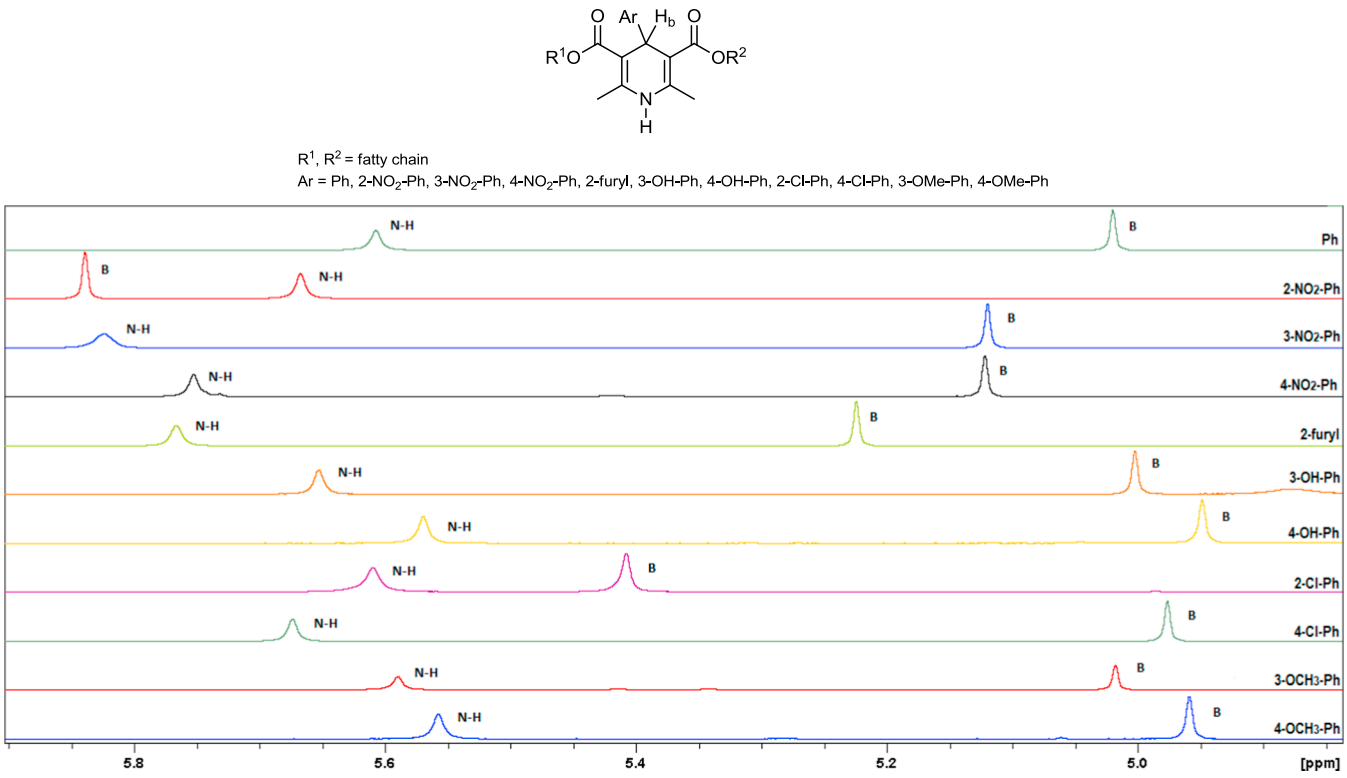


Fig. 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 4.85–5.95 ppm) of fatty DHPs (B = benzylic hydrogen).

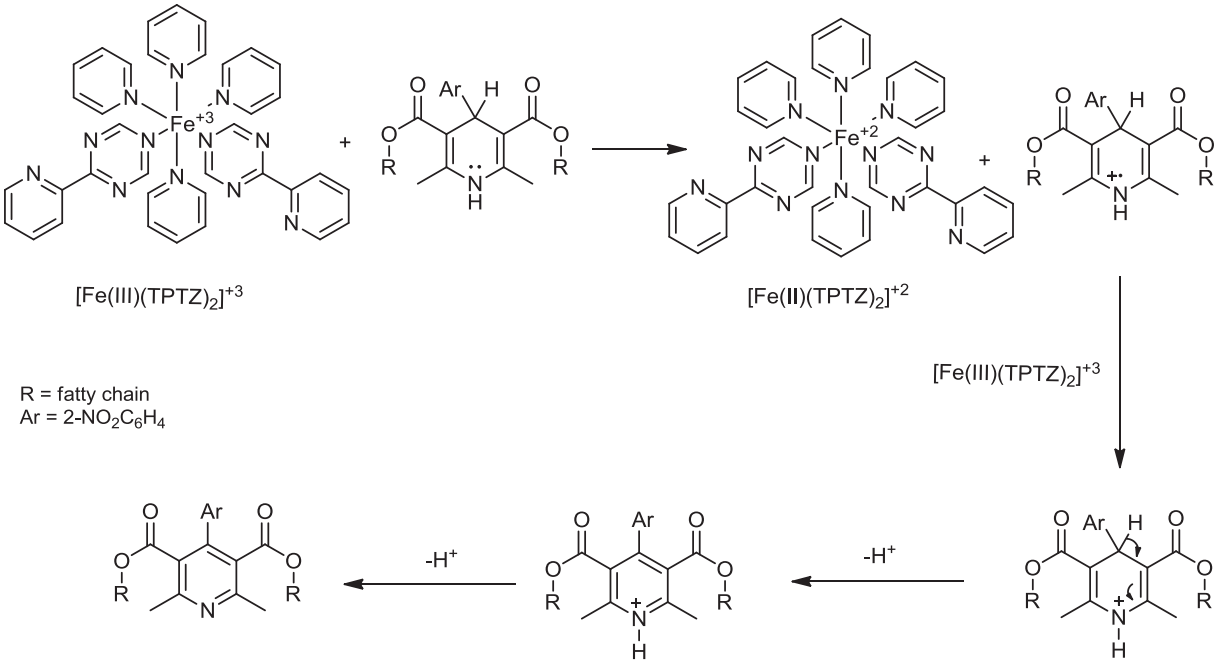
significant between-group differences, followed by Tukey s HSD post hoc test, level significance was set at 5%, using software Origin 8. To multivariate statistical analysis, principal components analysis (PCA), was used software PAST3.17 [50].

4.5. Lipophilicity calculations

The physicochemical parameter, C log *P* (the logarithm of *n*-octanol/water partition coefficient *P* based on established chemical interactions) was calculated using ACD/ChemSketch (Freeware) 2017.1.2: Advanced Chemistry Development, Inc.

4.6. Apparatus and chemistry

The sulfamic acid, methyl acetoacetate, ammonium acetate and aromatic aldehydes, were purchased from Sigma-Aldrich Chemical Co. and were used without purification. All organic solvents used for the synthesis were of analytical grade. The chromatography column was



Scheme 3. Oxidation mechanism of the fatty DHP 2-nitrobenzaldehyde derivatives from FRAP assay.

performed using silica gel 60 Å (ACROS Organics, 0.035–0.070 mesh). The reactions were monitored by thin-layer chromatography (TLC) performed on glass plates coated with silica gel (Merck 60GF245), a mixture of hexane: ethyl acetate was used as the eluent, and the products were visualized using iodine vapor. The melting points were obtained using a Fisatom 430D apparatus and are reported as uncorrected values. ^{1}H and ^{13}C NMR spectra were recorded in deuteron chloroform ($CDCl_3$) as solvent on a Bruker Ascend 400 MHz operating at 400 MHz and 100 MHz, respectively. The chemical shift data are reported in units of δ (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Infrared spectra were measured using potassium bromide (KBr) pellets or sodium chloride (NaCl) disks on a Schimadzu-IR PRESTIGIE-21 spectrometer.

4.7. Synthesis

4.7.1. General procedure for the synthesis of hybrid fatty dihydropyridines

*Synthesis of symmetrical fatty dihydropyridines **15-25a-c:*** In a round bottom flask equipped with a reflux condenser were added two equivalents of respectively fatty *β*-ketoester **1a-c** (2 mmol), aromatic aldehyde (**3–13**, 1 mmol), ammonium acetate (**2**, 3 mmol), and sulfamic acid (**14**, 0.30 mmol) as catalyst in the presence of methanol (5 mL). The reaction mixture was stirred constantly at reflux. After 24 h, the crude mixture was cooled to ambient temperature, concentrated in vacuo and purified by column chromatography with gradient elution of hexane:ethyl acetate to afford the symmetrical fatty DHP in a good yields.

*Synthesis of unsymmetrical hybrid fatty dihydropyridine **26-35bd:*** In a round bottom flask equipped equipped with a reflux condenser were added fatty *β*-ketoester **1b** (1 mmol), methylacetoacetate (**1d**, 1mmol), aromatic aldehyde (**3–13**, 1 mmol), ammonium acetate (**2**, 3 mmol), and sulphamic acid (**14**, 30 mol%) as catalyst in the presence of methanol (5 mL). The reaction mixture was stirred constantly at reflux for 24 h. After, the crude mixture was cooled to ambient temperature, concentrated under vacuum and purified by chromatography column with gradient elution of hexane:ethyl acetate to afford the unsymmetrical fatty DHP in a good yields.

*Dihexadecyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**15a**):* Yield 59%; M.W. 721.6 $gmol^{-1}$; solid; m.p. 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.91 (t, 6H, *J* = 6.5 Hz); 1.29 (m, 52H); 1.61 (m, 4H); 2.36 (s, 6H); 4.05 (m, 4H); 5.02 (s, 1H); 5.63 (s, 1H); 7.13 (t, 1H, *J* = 7.4 Hz); 7.22 (t, 2H, *J* = 7.4 Hz); 7.30 (d, H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.4; 29.7; 31.9; 39.5; 63.9; 104.3; 126.1; 127.8; 127.9; 143.8; 147.7; 167.7; IR (film, ν_{max} cm^{-1}): 752, 1221, 1472, 1683, 2851, 2931, 3010, 3333.

*Dioctadecyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**15b**):* Yield 56%; M.W. 777.7 $gmol^{-1}$; solid; m.p. 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.91 (t, 6H, *J* = 6.8 Hz); 1.28 (m, 60H); 1.61 (m, 4H); 2.36 (s, 6H); 4.04 (m, 4H); 5.02 (s, 1H); 5.61 (s, 1H); 7.13 (t, 1H, *J* = 7.4 Hz); 7.22 (t, 2H, *J* = 7.4 Hz); 7.30 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.7; 31.9; 39.5; 63.9; 104.3; 126.1; 127.8; 127.9; 143.8; 147.7; 167.7; IR (film, ν_{max} cm^{-1}): 765, 1108, 1472, 1676, 2851, 2924, 3010, 3333.

*Di-(Z)-octadec-9-en-1-yl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**15c**):* Yield 47%; M.W. 773.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, 6H, *J* = 6.6 Hz); 1.29 (m, 44H); 1.61 (m, 4H); 2.04 (m, 8H); 2.36 (s, 6H); 4.04 (m, 4H); 5.02 (s, 1H); 5.37 (m, 4H); 5.62 (s, 1H); 7.13 (t, 1H, *J* = 7.4 Hz); 7.21 (t, 2H, *J* = 7.4 Hz); 7.30 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 27.2; 28.7; 29.3; 29.8; 31.9; 39.5; 63.9; 104.3; 126.1; 127.8; 127.9; 129.8; 129.9; 143.8; 147.7; 167.7; IR (film, ν_{max} cm^{-1}): 712, 1201, 1485, 1703, 2858, 2918, 3016, 3340.

*Dihexadecyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**16a**):* Yield 75%; M.W. 767.6 $gmol^{-1}$; paste; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.89 (t, 6H, *J* = 6.6 Hz); 1.27 (m, 52H); 1.55 (m, 4H); 2.33 (s, 6H); 4.03 (m, 4H); 5.78 (s, 1H); 5.83 (s, 1H); 7.25 (t, 1H, *J* = 7.9 Hz); 7.46 (t, 1H, *J* = 7.9 Hz); 7.54 (d, 1H, *J* = 7.9 Hz); 7.72 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 25.9; 28.5; 29.4; 29.7; 31.9; 34.8; 63.9; 103.9; 124.0; 126.9; 131.3; 132.6; 142.5; 144.4; 147.9; 167.3; IR (film, ν_{max} cm^{-1}): 756, 1217, 1528, 1698, 2851, 2923, 3332.

*Dioctadecyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**16b**):* Yield 60%; M.W. 822.6 $gmol^{-1}$; paste; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, 6H, *J* = 6.6 Hz); 1.28 (m, 60H); 1.55 (m, 4H); 2.34 (s, 6H); 4.02 (m, 4H); 5.67 (s, 1H); 5.84 (s, 1H); 7.26 (t, 1H, *J* = 8.0 Hz); 7.46 (t, 1H, *J* = 8.0 Hz); 7.58 (d, 1H, *J* = 8.0 Hz); 7.73 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 227; 25.9; 28.6; 29.4; 29.7; 31.9; 34.8; 64.3; 104.0; 124.0; 126.9; 131.3; 132.6; 142.5; 144.4; 147.9; 167.3; IV (film, ν_{max} cm^{-1}): 752, 1208, 1472, 1683, 2845, 2918, 3346.

*Di-(Z)-octadec-9-en-1-yl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**16c**):* Yield 55%; M.W. 818.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.89 (t, 6H, *J* = 6.6 Hz); 1.28 (m, 44H); 1.55 (m, 4H); 2.03 (m, 8H); 2.34 (s, 6H); 4.01 (m, 4H); 5.36 (m, 4H); 5.72 (s, 1H); 5.84 (s, 1H); 7.25 (t, 1H, *J* = 8.0 Hz); 7.47 (t, 1H, *J* = 8.0 Hz); 7.54 (d, 1H, *J* = 8.0 Hz); 7.73 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 25.9; 27.2; 28.5; 29.3; 29.3; 29.8; 31.9; 34.8; 64.3; 104.0; 124.0; 126.9; 129.8; 129.9; 131.3; 132.6; 142.5; 144.4; 147.9; 167.3. IR (film, ν_{max} cm^{-1}): 772, 1214, 1524, 1696, 2845, 2924, 3010, 3360.

*Dihexadecyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**17a**):* Yield 75%; M.W. 767.6 $gmol^{-1}$; m.p. 90–92 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, 6H, *J* = 6.5 Hz); 1.28(m, 52H); 1.60 (m, 4H); 2.38 (s, 6H); 4.05 (m, 4H); 5.11 (s, 1H); 5.84 (s, 1H); 7.38 (t, 1H, *J* = 7.9 Hz); 7.65 (d, 1H, *J* = 7.9 Hz); 8.01 (d, 1H, *J* = 7.9 Hz); 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.6; 29.7; 31.9; 39.9; 64.3; 103.4; 121.3; 123.0; 128.6; 134.4; 144.7; 148.2; 149.9; 167.3; IR (film, ν_{max} cm^{-1}): 752, 1201, 1531, 1703, 2852, 2924, 2964, 3380.

*Dioctadecyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**17b**):* Yield 80%; M.W. 822.6 $gmol^{-1}$; m.p. 94–95 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, 6H, *J* = 7.1 Hz); 1.28 (m, 60H); 1.60 (m, 4H); 2.38 (s, 6H); 4.05(m, 4H); 5.12 (s, 1H); 5.82 (s, 1H); 7.38 (t, 1H, *J* = 7.9 Hz); 7.66 (d, 1H, *J* = 7.9 Hz); 8.02 (d, 1H, *J* = 7.9 Hz); 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.3; 29.4; 29.5; 29.6; 31.9; 39.9; 64.3; 103.4; 121.3; 123.0; 128.6; 134.4; 144.7; 148.2; 149.9; 167.2; IR (film, ν_{max} cm^{-1}): 719, 1198, 1524, 1704, 2842, 2915, 2955, 3321.

*Di-(Z)-octadec-9-en-1-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**17c**):* Yield 63%; M.W. 818.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.89 (t, 6H, *J* = 6.4 Hz); 1.28 (m, 44H); 1.60 (m, 4H); 2.04 (m, 8H); 2.34 (s, 6H); 4.05 (m, 4H); 5.12 (s, 1H); 5.37 (m, 4H); 5.83 (s, 1H); 7.38 (t, 1H, *J* = 7.9 Hz); 7.65 (d, 1H, *J* = 7.9 Hz); 8.01 (d, 1H, *J* = 7.9 Hz); 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 26.0; 27.2; 28.7; 29.5; 29.5; 29.8; 29.8; 31.9; 39.9; 64.2; 103.4; 121.3; 123.0; 128.5; 129.8; 129.9; 134.4; 144.4; 148.2; 149.9; 167.1; IR (film, ν_{max} cm^{-1}): 765, 1208, 1531, 1683, 2851, 2924, 3016, 3334.

*Dihexadecyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**18a**):* Yield 89%; M.W. 767.6 $gmol^{-1}$; m.p. 77–79 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, 6H, *J* = 6.6 Hz); 1.28 (m, 52H); 1.60 (m, 4H); 2.38 (s, 6H); 4.05 (m, 4H); 5.12 (s, 1H); 5.76 (s, 1H); 7.45 (d, 2H, *J* = 8.8 Hz); 8.09 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.6; 29.7; 31.9; 40.1; 64.3; 103.3; 123.3; 128.8; 144.7; 146.4; 155.0; 167.3; IR (film, ν_{max} cm^{-1}): 752, 1208, 1531, 1683, 2845, 2924, 3016, 3346.

*Dioctadecyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**18b**):* Yield 90%; M.W. 822.6 $gmol^{-1}$; m.p. 80–81 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, 6H, *J* = 6.7 Hz); 1.28 (m,60H); 1.60(m, 4H); 2.38 (s, 6H); 4.05 (m, 4H); 5.12 (s, 1H); 5.75 (s, 1H); 7.46 (d, 2H, *J* = 8.8 Hz); 8.09 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 26.1; 28.7; 29.3; 29.6; 29.6; 31.9; 40.1; 64.3;

103.3; 123.3; 128.8; 144.6; 146.4; 155.0; 167.1; IR (film, ν_{max} cm^{-1}): 725, 1201, 1518, 1696, 2845, 2924, 3340.

*Di-(Z)-octadec-9-en-1-yl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**18c**):* Yield 62%; M.W. 818.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 44H); 1.60 (m, 4H); 2.04 (m, 8H); 2.34 (s, 6H); 4.05 (m, 4H); 5.12 (s, 1H); 5.37 (m, 4H); 5.73 (s, 1H); 7.46 (d, 2H, J = 8.8 Hz); 8.09 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 26.1; 27.2; 28.7; 29.3; 29.5; 29.8; 31.9; 40.1; 64.2; 103.3; 123.3; 128.8; 129.8; 130.0; 144.7; 146.4; 155.0; 167.1; IR (film, ν_{max} cm^{-1}): 752, 1214, 1518, 1696, 2858, 2924, 3003, 3353.

*Dihexadecyl 4-(fur-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**19a**):* Yield 90%; M.W. 711.6 $gmol^{-1}$; m.p. 70–72 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 7.1 Hz); 1.28 (m, 52H); 1.65 (m, 4H); 2.36 (s, 6H); 4.11 (m, 4H); 5.22 (s, 1H); 5.79 (s, 1H); 5.94 (d, 1H, J = 3.1 Hz); 6.22 (m, 1H); 7.22 (d, 1H, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.5; 22.7; 26.1; 28.8; 29.3; 29.4; 29.6; 29.7; 31.9; 33.4; 64.0; 100.8; 104.4; 110.0; 140.8; 145.0; 158.7; 167.5; IR (film, ν_{max} cm^{-1}): 759, 1208, 1472, 1689, 2851, 2924, 3023, 3334.

*Dioctadecyl 4-(fur-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**19b**):* Yield 92%; M.W. 767.6 $gmol^{-1}$; m.p. 74–76 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 60H); 1.64 (m, 4H); 2.36 (s, 6H); 4.11 (m, 4H); 5.22 (s, 1H); 5.76 (s, 1H); 5.95 (d, 1H, J = 3.2 Hz); 6.22 (m, 1H); 7.22 (d, 1H, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.5; 22.7; 26.1; 28.8; 29.3; 29.4; 29.6; 31.9; 33.4; 64.0; 100.8; 104.4; 110.0; 140.8; 145.0; 158.7; 167.5; IR (film, ν_{max} cm^{-1}): 752, 1214, 1472, 1690, 2845, 2918, 3029, 3327.

*Di-(Z)-octadec-9-en-1-yl 4-(fur-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**19c**):* Yield 83%; M.W. 763.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.4 Hz); 1.28 (m, 44H); 1.64 (m, 4H); 2.04 (m, 8H); 2.36 (s, 6H); 4.11 (m, 4H); 5.22 (s, 1H); 5.37 (m, 4H); 5.76 (s, 1H); 5.95 (d, 1H, J = 3.2 Hz); 6.22 (m, 1H); 7.22 (d, 1H, 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.5; 22.7; 26.1; 28.8; 29.3; 29.3; 29.5; 29.8; 31.9; 32.6; 33.4; 64.0; 100.8; 104.4; 110.0; 129.8; 130.0; 140.8; 145.0; 158.7; 167.5, IR (film, ν_{max} cm^{-1}): 725, 1194, 1472, 1689, 2851, 2931, 3023, 3353.

*Dihexadecyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**20a**):* Yield 66%; M.W. 737.6 $gmol^{-1}$; m.p. 95–98 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 52H); 1.64 (m, 4H); 2.33 (s, 6H); 4.06 (m, 4H); 5.00 (s, 1H); 5.02 (s, 1H); 5.69 (s, 1H); 6.62 (d, 1H, J = 7.8 Hz); 6.78 (s, 1H); 6.87 (d, 1H, J = 7.8 Hz); 7.07 (t, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.7; 29.7; 29.7; 31.9; 39.4; 64.1; 104.0; 113.2; 114.8; 120.4; 128.9; 144.0; 149.4; 155.4; 167.7; IR (film, ν_{max} cm^{-1}): 778, 1201, 1485, 1689, 2851, 2924, 3029, 3333.

*Dioctadecyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**20b**):* Yield 64%; M.W. 793.7 $gmol^{-1}$; m.p. 98–100 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.6 Hz); 1.28 (m, 60H); 1.62 (m, 4H); 2.34 (s, 6H); 4.06 (m, 4H); 4.88 (s, 1H); 5.00 (s, 1H); 5.65 (s, 1H); 6.61 (d, 1H, J = 7.8 Hz); 6.78 (s, 1H); 6.87 (d, 1H, J = 7.8 Hz); 7.07 (t, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.8; 29.3; 29.4; 29.6; 29.7; 29.7; 31.9; 39.4; 64.1; 104.0; 113.1; 114.8; 120.4; 128.9; 144.0; 149.4; 155.4; 167.7; IR (film, ν_{max} cm^{-1}): 732, 1201, 1492, 1703, 2838, 2924, 2996, 3340.

*Di-(Z)-octadec-9-en-1-yl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**20c**):* Yield 55%; M.W. 789.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.29 (m, 44H); 1.62 (m, 4H); 2.04 (m, 8H); 2.34 (s, 6H); 4.06 (m, 4H); 4.86 (s, 1H); 5.00 (s, 1H); 5.37 (m, 4H); 5.65 (s, 1H); 6.61 (d, 1H, J = 7.8 Hz); 6.78 (s, 1H); 6.87 (d, 1H, J = 7.8 Hz); 7.07 (t, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 27.2; 28.7; 29.2; 29.3; 29.3; 29.5; 29.5; 29.7; 29.7; 29.8; 31.9; 32.6; 39.4; 64.0; 104.0; 113.1; 114.8; 120.4; 128.9; 129.8; 130.0; 143.9; 149.4; 155.4; 167.7; IR (film, ν_{max} cm^{-1}): 758, 1221, 1465, 1683, 2845, 2924, 3016, 3333.

*Dihexadecyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**21a**):* Yield 77%; M.W. 737.6 $gmol^{-1}$; m.p. 90–92 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 52H); 1.61 (m, 4H); 2.34 (s, 6H); 4.05 (m, 4H); 4.95 (s, 1H); 5.55 (s, 1H); 6.67 (d, 2H, J = 8.5 Hz); 7.15 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.4; 29.4; 29.6; 29.7; 29.7; 31.9; 38.7; 64.0; 104.5; 114.7;129.1; 140.3; 143.5; 153.9; 167.8; IR (film, ν_{max} cm^{-1}): 752, 1208, 1498, 1696, 2845, 2911, 2996, 3340.

*Dioctadecyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**21b**):* Yield 72%; M.W. 793.7 $gmol^{-1}$; m.p. 95–97 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.5 Hz); 1.28 (m, 60H); 1.61 (m, 4H); 2.34 (s, 6H); 4.05 (m, 4H); 4.95 (s, 1H); 5.59 (s, 1H); 6.67 (d, 2H, J = 8.5 Hz); 7.14 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.7; 29.7; 31.9; 38.7; 64.0; 104.5; 114.7; 129.1; 140.2; 143.5; 153.9; 167.8; IR (film, ν_{max} cm^{-1}): 758, 1214, 1459, 1689, 2858, 2918, 3016, 3366.

*Di-(Z)-octadec-9-en-1-yl) 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**21c**):* Yield 70%; M.W. 789.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.6 Hz); 1.29 (m, 44H); 1.61 (m, 4H); 2.04 (m, 8H); 2.34 (s, 6H); 4.05 (m, 4H); 4.95 (s, 1H); 5.11 (s, 1H); 5.37 (m, 4H); 5.62 (s, 1H); 6.64 (d, 2H, J = 8.5 Hz); 7.13 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 27.2; 28.7; 29.3; 29.3; 29.5; 29.7; 29.7; 31.9; 32.6; 38.7; 64.0; 104.5; 114.7; 129.0; 129.8; 129.9; 140.1; 143.6; 154.0; 167.9; IR (film, ν_{max} cm^{-1}): 745, 121, 1472, 1689, 2851, 2924, 3023, 3346.

*Dihexadecyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**22a**):* Yield 79%; M.W. 755.6 $gmol^{-1}$; m.p. 45–46 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 52H); 1.61 (m, 4H); 2.33 (s, 6H); 4.03 (t, 4H, J = 6.8 Hz); 5.40 (s, 1H); 5.62 (s, 1H); 7.05 (t, 1H, J = 7.6 Hz); 7.13 (t, 1H, J = 7.6 Hz); 7.24 (d, 1H, J = 7.6 Hz); 7.40 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.0; 28.7; 29.4; 29.4; 29.6; 29.6; 31.9; 37.6; 64.1; 103.9; 126.6; 127.2; 129.4; 131.5; 132.6; 143.7; 145.5; 167.7; IR (film, ν_{max} cm^{-1}): 765, 1214, 1479, 1696, 2852, 2931, 3030, 3333.

*Dioctadecyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**22b**):* Yield 81%; M.W. 811.6 $gmol^{-1}$; m.p. 51–53 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.4 Hz); 1.28 (m, 60H); 1.60(m, 4H); 2.33 (s, 6H); 4.04 (t, 4H, J = 6.7 Hz); 5.41 (s, 1H); 5.61 (s, 1H); 7.05 (t, 1H, J = 7.4 Hz); 7.14 (t, 1H, J = 7.4 Hz); 7.24 (d, 1H, J = 7.4 Hz); 7.40 (d, 1H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 26.0; 28.7; 29.4; 29.6; 31.9; 37.6; 64.1; 103.9; 126.6; 127.2; 129.4; 131.5; 132.6; 143.7; 145.5; 167.7; IR (film, ν_{max} cm^{-1}): 745, 1201, 1459, 1683, 2852, 2931, 3017, 3340.

*Di-(Z)-octadec-9-en-1-yl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**22c**):* Yield: 71%; M.W. 807.6 $gmol^{-1}$; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.5 Hz); 1.29 (m, 44H); 1.60 (m, 4H); 2.05 (m, 8H); 2.33 (s, 6H); 4.04 (t, 4H, J = 6.5 Hz); 5.37 (m, 4H); 5.40 (s, 1H); 5.66 (s, 1H); 7.05 (t, 1H, J = 7.7 Hz); 7.13 (t, 1H, J = 7.7 Hz); 7.24 (d, 1H, J = 7.7 Hz); 7.40 (d, 1H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.0; 27.2; 28.7; 29.2; 29.4; 29.5; 29.6; 29.8; 31.9; 32.6; 37.6; 64.1; 103.9; 126.6; 127.2; 129.4; 129.8; 129.9; 131.5; 132.6; 143.8; 145.5; 167.7; IV (film, ν_{max} cm^{-1}): 796, 1115, 1465, 1676, 2845, 2918, 3003, 3333.

*Dihexadecyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**23a**):* Yield 89%; M.W. 755.6 $gmol^{-1}$; m.p. 57–58 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 52H); 1.60 (m, 4H); 2.35 (s, 6H); 4.04 (m, 4H); 4.97 (s, 1H); 5.67 (s, 1H); 7.18 (d, 2H, J = 8.5 Hz); 7.23 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.0; 28.7; 29.4; 29.4; 29.6; 29.7; 29;7; 29.7; 31.9; 39.2; 64.1; 103.9; 127.9; 129.4; 131.7; 144.0; 146.2; 167.5; IR (film, ν_{max} cm^{-1}): 745, 1267, 1465, 1696, 2851, 2918, 3069, 3340.

*Dioctadecyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**23b**):* Yield 81%; M.W. 811.6 $gmol^{-1}$; m.p. 78–80 °C; solid; ^{1}H NMR (400 MHz $CDCl_3$): δ 0.90 (t, 6H, J = 6.5 Hz); 1.28 (m, 60H); 1.60 (m, 4H); 2.35 (s, 6H); 4.04 (m, 4H); 4.97 (s, 1H); 5.67 (s, 1H); 7.18 (d, 2H, J = 8.5 Hz); 7.23 (d, 2H, J = 8.5 Hz); ^{13}C NMR

(100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.4; 29.4; 29.6; 29.7; 31.9; 39.2; 64.1; 103.9; 128.0; 129.3; 131.7; 144.0; 146.3; 167.5; IR (film, ν_{max} cm^{-1}): 752, 1260, 1465, 1683, 2845, 2924, 3043, 3333.

*Di-(Z)-octadec-9-en-1-yl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**23c**):* Yield 80%; M.W. 807.6 $gmol^{-1}$; oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.6 Hz); 1.28 (m, 44H); 1.60 (m, 4H); 2.04 (m, 8H); 2.35 (s, 6H); 4.04 (m, 4H); 4.97 (s, 1H); 5.37 (m, 4H); 5.66 (s, 1H); 7.18 (d, 2H, J = 8.5 Hz); 7.23 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 27.2; 28.7; 29.3; 29.3; 29.5; 29.6; 29.7; 29.7; 29.8; 31.9; 32.6; 39.2; 64.1; 104.0; 128.0; 129.3; 129.8; 130.0; 131.7; 144.0; 146.3; 167.5; IR (film, ν_{max} cm^{-1}): 732, 1260, 1459, 1703, 2845, 2931, 3063, 3340.

*Dihexadecyl 4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**24a**):* Yield 76%; M.W. 751.6 $gmol^{-1}$; m.p. 46–47 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.5 Hz); 1.28 (m, 52H); 1.62 (m, 4H); 2.35 (s, 6H); 3.78 (s, 3H); 4.06 (m, 4H); 5.01 (s, 1H); 5.69 (s, 1H); 6.69 (d, 1H, J = 7.8 Hz); 6.89 (s, 1H); 6.90 (d,1H, J = 7.8 Hz); 7.14 (t, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.8; 29.4; 29.4; 29.6; 29.7; 29.7; 31.9; 39.4; 55.0; 64.0; 104.1; 110.8; 114.2; 120.5; 128.7; 143.9; 149.3; 159.3; 167.7; IR (film, ν_{max} cm^{-1}): 759, 1208, 1452, 1683, 2851, 2938, 3023, 3333.

*Dioctadecyl 4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**24b**):* Yield 73%; M.W. 807.7 $gmol^{-1}$; m.p. 47–48 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.7 Hz); 1.28 (m, 60H); 1.62 (m, 4H); 2.35 (s, 6H); 3.78 (s, 3H); 4.06 (m, 4H); 5.02 (s, 1H); 5.59 (s, 1H); 6.69 (d, 1H, J = 7.6 Hz); 6.86 (s, 1H); 6.90 (d,1H, J = 7.6 Hz); 7.14 (t, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.8; 29.4; 29.4; 29.6; 29.7; 29.7; 31.9; 39.4; 55.0; 64.0; 104.1; 110.9; 114.2; 120.5; 128.7; 143.9; 149.3; 159.3; 167.6; IR (film, ν_{max} cm^{-1}): 752, 1214, 1459, 1683, 2805, 2865, 2977, 3287.

*Di-(Z)-octadec-9-en-1-yl 4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**24c**):* Yield 62%; M.W. 803.6 $gmol^{-1}$; oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.5 Hz); 1.28 (m, 44H); 1.62 (m, 4H); 2.04 (m, 8H); 2.35 (s, 6H); 3.78 (s, 3H); 4.06 (m, 4H); 5.02 (s, 1H); 5.37 (m, 4H); 5.61 (s, 1H); 6.69 (d, 1H, J = 7.9 Hz); 6.86 (s, 1H); 6.90 (d,1H, J = 7.9 Hz); 7.14 (t, 1H, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 27.2; 28.8; 29.2; 29.3; 29.3; 29.5; 29.5; 29.7; 29.7; 29.8; 31.9; 32.6; 39.5; 55.0; 64.0; 104.1; 110.8; 114.2; 120.5; 128.7; 129.8; 129.9; 143.9; 149.3; 159.3; 167.6; IR (film, ν_{max} cm^{-1}): 759, 1208, 1459, 1696, 2851, 2931, 3029, 3353.

*Dihexadecyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**25a**):* Yield 78%; M.W. 751.6 $gmol^{-1}$; m.p. 56–57 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.6 Hz); 1.28 (m, 52H); 1.61 (m, 4H); 2.35 (s, 6H); 3.77 (s, 3H); 4.04 (m, 4H); 4.96 (s, 1H); 5.58 (s, 1H); 6.76 (d, 2H, J = 8.7 Hz); 7.21 (d, 2H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.8; 29.4; 29.7; 29.7; 31.9; 38.7; 55.1; 63.9; 104.1; 113.2; 128.8; 140.2; 143.5; 157.9; 167.7; IR (film, ν_{max} cm^{-1}): 778, 1214, 1465, 1683, 2851, 2931, 3023, 3293.

*Dioctadecyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**25b**):* Yield 79%; M.W. 807.7 $gmol^{-1}$; m.p. 61–62 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.6 Hz); 1.28 (m, 60H); 1.61 (m, 4H); 2.35 (s, 6H); 3.77 (s, 3H); 4.04 (m, 4H); 4.96 (s, 1H); 5.56 (s, 1H); 6.76 (d, 2H, J = 8.7 Hz); 7.21 (d, 2H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.8; 29.4; 29.6; 29.7; 29.7; 31.9; 38.7; 55.1; 63.9; 104.5; 113.2; 128.9; 140.2; 143.5; 157.9; 167.7; IR (film, ν_{max} cm^{-1}): 791, 1233, 1478, 1683, 2851, 2918, 3340.

*Di-(Z)-octadec-9-en-1-yl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**25c**):* Yield 70%; M.W. 803.6 $gmol^{-1}$; oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 6.6 Hz); 1.29 (m, 44H); 1.61 (m, 4H); 2.04 (m, 8H); 2.35 (s, 6H); 3.77 (s, 3H); 4.04 (m, 4H); 4.96 (s, 1H); 5.37 (m, 4H); 5.60 (s, 1H); 6.76 (d, 2H, J = 8.7 Hz); 7.21 (d, 2H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 27.2; 28.8; 29.2; 29.2; 29.3; 29.5; 29.5; 29.5; 29.6; 29.7; 29.7; 29.8; 31.9; 32.6; 38.7; 55.1; 63.9; 104.5; 113.2; 128.9; 129.8; 129.9; 140.2; 143.5; 157.9; 167.7; IR (film, ν_{max} cm^{-1}): 765, 1221, 1452, 1689, 2865, 2918, 3016, 3320.

*3-methyl 5-octadecyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**26bd**):* Yield 35%; M.W. 539.40 $gmol^{-1}$; m.p. 86–88 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.6 Hz); 1.28 (m,30H); 1.60 (m, 2H); 2.35 (s, 3H); 2.37 (s, 3H); 3.66 (s, 3H); 4.05 (m, 2H); 5.00 (s, 1H); 5.65 (s, 1H); 7.15 (t, 1H, J = 7.2 Hz); 7.23 (t, 2H, J = 7.2 Hz); 7.30 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 19.7; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.6; 29.7; 29.7; 31.9; 39.4; 51.0; 64.0; 103.9; 104.2; 126.2; 127.8; 127.9; 143.9; 144.0; 147.6; 167.7; 168.1; IR (film, ν_{max} cm^{-1}): 759, 1116, 1499, 1703, 2852, 2924, 3003, 3340.

*3-methyl 5-octadecyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**27bd**):* Yield 51%; M.W. 584.4 $gmol^{-1}$; m.p. 86–88 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.6 Hz); 1.28 (m,30H); 1.60 (m, 2H); 2.38 (s, 3H); 2.39 (s, 3H); 3.67 (s, 3H); 4.05 (m, 2H); 5.12 (s, 1H); 5.87 (s, 1H); 7.39 (t, 1H, J = 8.0 Hz); 7.65 (d, 1H, J = 8.0 Hz); 8.02 (d, 1H, J = 8.0 Hz); 8.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 19.7; 22.7; 26.0; 28.7; 29.3; 29.4; 29.5; 29.6; 29.7; 29.7; 31.9; 39.8; 51.1; 64.3; 103.1; 103.4; 121.3; 122.9; 128.6; 134.3; 144.7; 144.9; 148.3; 149.7; 167.1; 167.6; IR (film, ν_{max} cm^{-1}): 719, 1233, 1524, 1703, 2851, 2924, 3340.

*3-methyl 5-octadecyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**28bd**):* Yield 55%; M.W. 584.4 $gmol^{-1}$; m.p. 90–91 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.0 Hz); 1.28 (m,30H); 1.61 (m, 2H); 2.37 (s, 3H); 2.39 (s, 3H); 3.67 (s, 3H); 4.05 (m, 2H); 5.12 (s, 1H); 5.74 (s, 1H); 7.46 (d, 2H, J = 7.8 Hz); 8.10 (d, 2H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 19.7; 22.7; 26.1; 28.7; 29.3; 29.4; 29.6; 29.6; 29.7; 29.7; 31.9; 40.0; 51.1; 64.3; 103.0; 103.3; 123.4; 128.7; 144.6; 144.8; 146.4; 154.9; 167.1; 167.5; IR (film, ν_{max} cm^{-1}): 705, 1208, 1537, 1689, 2845, 2924, 2990, 3333.

*3-methyl 5-octadecyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**29bd**):* Yield 65%; M.W. 529.4 $gmol^{-1}$; m.p. 103–105 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.6 Hz); 1.27 (m,30H); 1.65 (m, 2H); 2.36 (s, 6H); 3.73 (s, 3H); 4.12 (m, 2H); 5.21 (s, 1H); 5.81 (s, 1H); 5.95 (d, 1H, J = 3.1 Hz); 6.23 (m, 1H); 7.23 (d, 1H, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.8; 29.3; 29.4; 29.6; 29.7; 29.7; 31.9; 33.3; 51.4; 64.1; 100.5; 100.9; 104.3; 110.0; 140.9; 145.0; 145.4; 158.5; 167.5; 167.9; IR (film, ν_{max} cm^{-1}): 759, 1201, 1465, 1697, 2859, 2925, 3023, 3320.

*3-methyl 5-octadecyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**30bd**):* Yield 43%; M.W. 555.4 $gmol^{-1}$; m.p. 98–100 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.6 Hz); 1.28 (m,30H); 1.60 (m, 2H); 2.35 (s, 3H); 2.36 (s, 3H); 3.67 (s, 3H); 4.05 (m, 2H); 4.74 (s, 1H); 5.00 (s, 1H); 5.61 (s, 1H); 6.62 (d, 1H, J = 7.7 Hz); 6.77 (s, 1H); 6.87 (d, 1H, J = 7.7 Hz); 7.09 (t, 1H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 26.0; 28.7; 29.4; 29.6; 29.7; 31.9; 39.3; 51.0; 64.1; 103.7; 104.0; 113.1; 114.7; 120.3; 129.0; 143.9; 144.1; 149.3; 155.3; 167.7; 168.0; IR (film, ν_{max} cm^{-1}): 745, 1221, 1485, 1683, 2838, 2924, 2996, 3327.

*3-methyl 5-octadecyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**31bd**):* Yield 52%; M.W. 555.4 $gmol^{-1}$; m.p. 90–91 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.9 Hz); 1.28 (m,30H); 1.60 (m, 2H); 2.33 (s, 3H); 2.34 (s, 3H); 3.67 (s, 3H); 4.05 (m, 2H); 4.94 (s, 1H); 5.68 (s, 1H); 5.61 (s, 1H); 6.65 (d, 2H, J = 8.6 Hz); 7.13 (d, 2H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 22.7; 26.1; 28.7; 29.4; 29.6; 29.7; 31.9; 38.6; 51.0; 64.1; 104.2; 104.5; 114.8; 128.9; 139.9; 143.7; 143.8; 154.1; 167.9; 168.4; IR (film, ν_{max} cm^{-1}): 745, 1221, 1452, 1676, 2851, 2938, 3353.

*3-methyl 5-octadecyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**32bd**):* Yield 66%; M.W. 573.4 $gmol^{-1}$; m.p. 81–82 °C; solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.6 Hz); 1.28 (m,30H); 1.59 (t, 2H, J = 7.0 Hz); 2.32 (s, 3H); 2.34 (s, 3H); 3.64 (s, 3H); 4.03 (m, 2H); 5.41 (s, 1H); 5.65 (s, 1H); 7.05 (t, 1H, J = 7.4 Hz); 7.14 (t, 1H, J = 7.4 Hz); 7.24 (d, 1H, J = 7.4 Hz); 7.39 (d, 1H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.5; 19.6; 22.7; 26.0; 28.7; 29.4; 29.7; 31.9; 37.4; 50.8; 64.1; 103.8; 104.1; 126.8; 127.3; 129.3; 131.3; 132.5; 143.8; 143.9; 145.7; 167.6; 168.0; IR (film,

ν_{max} cm^{-1}): 739, 1265, 1472, 1689, 2845, 2918, 3056, 3340.

*3-methyl 5-octadecyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**33bd**):* Yield 78%; M.W. 573.4 $gmol^{-1}$; m.p. 84–86 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.6 Hz); 1.28 (m,30H); 1.59 (m, 2H); 2.35 (s, 3H); 2.36 (s, 3H); 3.66 (s, 3H); 4.04 (m, 2H); 4.97 (s, 1H); 5.65 (s, 1H); 7.18 (d, 2H, J = 8.6 Hz); 7.22 (d, 2H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 19.7; 22.7; 26.1; 28.7; 29.4; 29.7; 31.9; 39.1; 51.0; 64.1; 103.7; 104.0; 128.0; 129.2; 131.8; 144.0; 144.1; 146.1; 167.5; 167.9; IR (film, ν_{max} cm^{-1}): 745, 1247, 1419, 1683, 2818, 2904, 3049, 3380.

*3-methyl 5-octadecyl 4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**34bd**):* Yield 48%; M.W. 569.4 $gmol^{-1}$; m.p. 106–108 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.8 Hz); 1.28 (m,30H); 1.63 (m, 2H); 2.35 (s, 3H); 2.36 (s, 3H); 3.68 (s, 3H); 3.78 (s, 3H); 4.06 (m, 2H); 5.01 (s, 1H); 5.63 (s, 1H); 6.69 (d, 1H, J = 8.1 Hz); 6.86 (s, 1H); 6.90 (d,1H, J = 8.1 Hz); 7.15 (t, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.7; 22.7; 26.0; 28.8; 29.4; 29.7; 31.9; 39.4; 51.0; 55.0; 64.1; 103.8; 104.1; 110.9; 114.0; 120.3; 128.8; 143.9; 144.1; 149.1; 159.3; 167.6; 168.0; IR (film, ν_{max} cm^{-1}): 759, 1221, 1465, 1683, 2859, 2918, 3029, 3346.

*3-methyl 5-octadecyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**35bd**):* Yield 57%; M.W. 569.4 $gmol^{-1}$; m.p. 67–68 °C; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.7 Hz); 1.28 (m,30H); 1.61(m, 2H); 2.34 (s, 3H); 2.35 (s, 3H); 3.67 (s, 3H); 3.77 (s, 3H); 4.05 (m, 2H); 4.96 (s, 1H); 5.65 (s, 1H); 6.79 (d, 2H, J = 8.5 Hz); 7.20 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1; 19.6; 19.7; 22.7; 26.1; 28.8; 29.3; 29.4; 29.7; 31.9; 35.6; 51.0; 55.1; 64.0; 104.2; 104.5; 113.3; 128.8; 140.1; 143.6; 143.8; 157.9; 167.7; 168.1; IR (film, ν_{max} cm^{-1}): 745, 1208, 1472, 1689, 2845, 2918, 3023, 3346.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2018.11.009.

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