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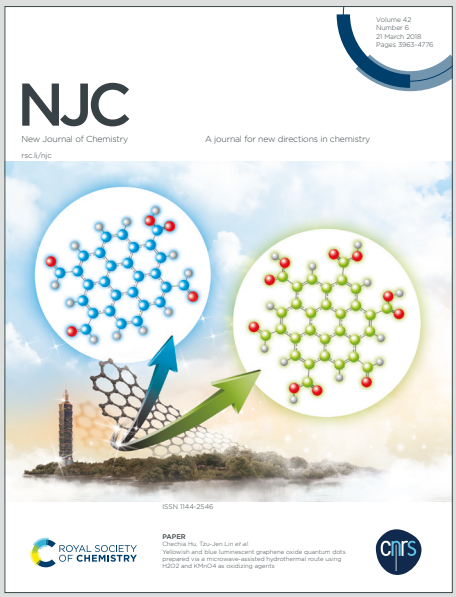

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ARTICLE

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Synthesis of (+/-)-Pregabalin and its novel lipophilic β-alkyl-substituted analogues from fatty chains

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In this work, were synthesized for the first time a series of new lipophilic β-alkyl substituted GABA derivatives from fatty alkyl chains. The synthesis of these GABA analogues was investigated by two different bicomponent approaches as a key step. The results showed low yields in the path from aliphatic nitroolefins and Meldrum's acid, whereas the Knoevenagel condensation between aliphatic aldehydes and Meldrum's acid afforded fatty alkylidenes in good yields (75-97%). These compounds were subsequently subjected to a conjugate addition reaction with nitromethane, resulting in the fatty Michael adducts (in 87-97% yields) which were in turn submitted to a *one pot* domino hydrolysis-decarboxylation, leading to the isolation of β-alkyl-substituted γ-nitro acids in good yields (78-92%). Finally, the reduction of the fatty γ–nitro acids allowed for the access to new lipophilic β-alkyl substituted GABA analogues, which were isolated in high yields (90-98%). The new methodology was also applied to the synthesis of antiepileptic drug (+/-)-Pregabalin, which was obtained after four steps in high overall yield.

Introduction

The γ-aminobutyric acid (GABA, **1**) is the most important inhibitory neurotransmitter of Central Nervous System (CNS).[1] The transmission of electrical signals between nervous cells is mediated by excitation and inhibition processes, regulated by an equilibrating level of GABAergic system.[2] Concentrations below a threshold level of GABA in the brain have been directly associated with epilepsy and also with other important psychiatric disorders such as Alzheimer's, Parkinson's and Huntington's diseases.[3] However, the direct administration of GABA is not considered an effective therapy due to the high hydrophilicity of GABA (Figure 1) which results in poor permeability across lipophilic Blood-Brain Barriers (BBB).

One of the principal methods to raise the GABA level in the CNS is the use of small molecules, also named GABAergic drugs and prodrugs, able to diffuse through the BBB and inhibit the activity of GABA-aminotransferase (GABA-AT). These compounds are mainly β-aryl-[4] or β-alkyl[5,6] substituted, and have been the subject of extensive investigations to produce GABA analogues, described as lipophilic GABA derivatives, such as Pregabalin (**2a**),[7]Phenibut (**3**),[8] Baclofen (**4**),[9] and Gabapentin (**5**)[10] (Figure 1).

In this context, the antiepileptic drug (AED) Pregabalin (**2a**) has been the most effective compound in the treating of epilepsy. However, despite its significant safety and efficacy profile in blocking seizures, the drug presents little effect in preventing or curing epilepsy completely.[11,12] Although anticonvulsant agents have been introduced in clinical practices, up to one-third of patients have developed resistance to recommended doses, emphasizing the need for the development of improved AEDs drugs.[13,14]

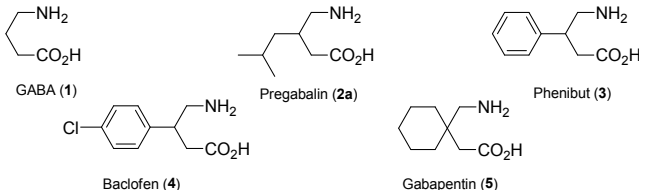

Fig. 1 GABA, β-aryl- and β-alkyl-substituted GABA analogues.

Pregabalin (**2a**) was discovered in 1991 by Silverman *et al.*,[15] and is used to treat epilepsy and neuropathic pain. Pregabalin, marketed by Pfizer under the name Lyrica®, due to the wide spectrum of therapeutic activities, represent profits of about US $ 1 billion annually for the pharmaceutical market.

The industrial production (first-generation manufacturing process) of (*S*)-Pregabalin involves the classical Knoevenagel condensation between diethyl malonate and *iso*-valeraldehyde, resulting in malonyl alkylidene as key intermediate (Scheme 1). In the next step, the cyanide Michael addition is followed by hydrolysis, hydrogenation and decarboxylation reactions to yield racemic Pregabalin (**2a**). Afterwards, the racemate resolution with (*S*)-mandelic acid leads to the biologically active (*S*)-Pregabalin (**2a**). However, in this process toxic CN sources and a large amount of Raney nickel in the reduction step are required. In addition, in some cases, the drug is marketed in is racemic form on the basis of overall

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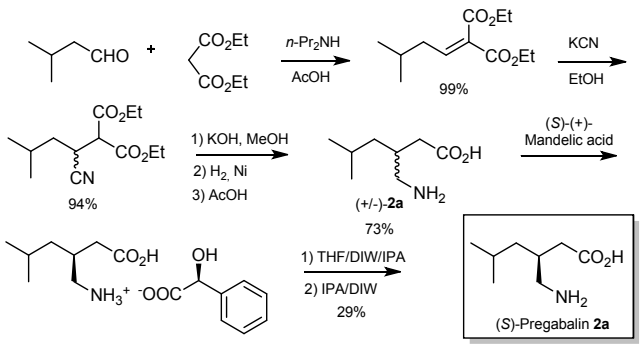
yield, cost, and high throughput. Alternative methods utilizing enzymes and sequential-flow method have also been reported.[16]



Scheme 1. First-generation manufacturing process of the (*S*)-Pregabalin (**2a**).

According to the literature, the BBB is constituted by a vascular endothelium that interacts directly with astrocytes, neurons and pericytes. It protects the brain from molecules of systemic circulation but it has to be overcome for the proper treatment of brain cancer, psychiatric disorders or neurodegenerative diseases, which are dramatically increasing as global population ages.[17]

The capillary endothelial cells present in the BBB are an additional hurdle and the tight intercellular junctions of which are believed to present a more significant permeability hurdle than other membranes such as those of the intestines. Hence, the CNS exposure of a drug relative to its plasma concentration is function of the balance between its plasma protein and CNS tissue binding and its ability to permeate the BBB, all of which are likely to increase with increasing lipophilicity.[18]

The drug design based on medicinal chemistry consists of reversible modifying the physicochemical properties of the drug to generate prodrugs, that after chemical or enzymatic cleavage exerts its biological effect.[17]

The increase in the molecule lipophilicity or reducing the ability to bind hydrogen may be a strategy to improve its permeability across the BBB improving its targeting to the CNS.[19] These chemical modifications, such as increasing their lipophilicity, turn the drug more prone to be internalized in the brain. In addition, others molecular strategies also are described to bind the drugs such as liposomes or nanoparticles that will act as drug deliverers in brain. According Tajes *et al.*, this fusion of the classical pharmacology with nanotechnology has opened a wide field to many different approaches with promising results to hypothesize that BBB will not be a major problem for the new generation of drugs.[17]

In this sense, lipophilic compounds, as fatty acid hybrids or fatty acids derivatives have been described in the literature as a new class of compounds with a broad range of biological activities and significance in the field of medicinal chemistry.[20]

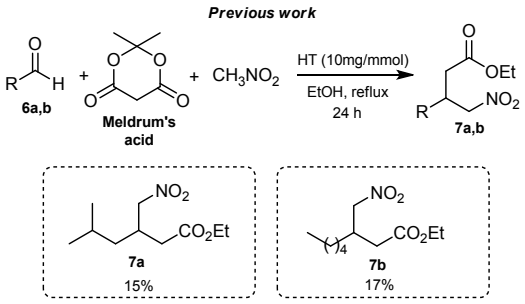
Fatty acids have been used as starting material to produce pharmacologically interesting compounds through simple transformations and their derivatives are promising molecules in the treatment of cancers, for example, breast (MCF7), lung (NCI-H460), glioma (C6 rat and U138-MG human) and CNS (SF-268) cell lines.[21-23] These results also suggest that the fatty derivatives with poor water solubility and high lipophilicity will likely cross the BBB.[17] In another example, a series of fatty acid–amino acid–1-*β*-D-arabinofuranosylcytosine (Ara-C, Cytarabine) analogues were synthesized in order to improve the lipophilicity and bioavailability of Ara-C, used for acute nonlymphocytic leukemia (ANLL).[24] However, the bioavailability of Ara-C is relatively low due to its low lipophilicity. According to the results observed, synthesized Ara-C derivatives were more lipophilic than Ara-C and the *in vitro* cytotoxicity and *in vivo* anti-tumor activity showed that the fatty derivatives were more active than Ara-C in Hela cells, but not in HL-60 cells, whereas *in vivo* results indicated a higher efficiency for some of the derivatives in mice bearing S_{180} tumor, while others showed a decreased activity in comparison with Ara-C.

In addition, fatty acid analogues and fatty acids hybrids molecules have been found to be associated with diverse biological activities such as anti-inflammatory, antioxidant, antimicrobial and neuroprotective.[25,26]

In this work, we synthesized, for the first time, a series of new lipophilic *β*-alkyl substituted *g*-Aminobutyric acid (GABA) using the Michael addition reaction as a key step towards fatty alkylidenes derived from Meldrum's acid. In addition, this methodology was applied to synthesis of (+/-)-Pregabalin.

Results and Discussion

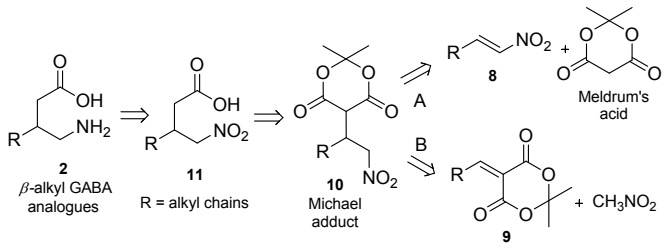
In our previous work, we have demonstrated that the synthesis of (+/-)-Phenibut and (+/-)-Baclofen can be achieved in 63% and 61% overall yield, respectively, by using a multicomponent/domino approach which combines reactions between Meldrum's acid, aromatic aldehydes and nitromethane in methanol.[27] The multicomponent synthetic strategy was promoted by a mixed aluminium-magnesium oxide catalyst derived from hydrotalcite (HT). However, in that same study, the employment of the aliphatic *iso*-valeral and hexanoic aldehydes in the multicomponent/domino reaction afforded the *β*–alkyl substituted *γ*-nitroesters in low yields, equal to 15% and 17%, respectively (Scheme 2). This fact was interpreted as being a consequence of the auto-condensation of aliphatic aldehydes under basic media.



Scheme 2. Multicomponent synthesis of *β*–alkyl substituted γ-nitroesters.

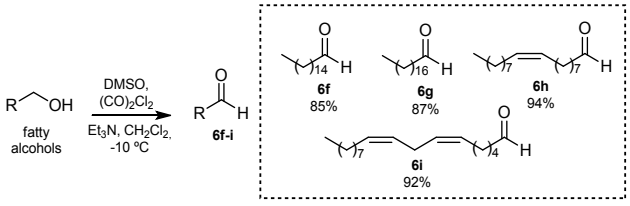
Based on the poor results obtained in the multicomponent/domino approach, in this study, the synthesis of the *β*-alkyl substituted GABA analogues **2** was investigated based on

bicomponent approach by different paths: pathways A or B, from aliphatic nitroolefin **8** and Meldrum's acid or aliphatic alkylidenes **9** and nitro methane, respectively (Scheme 3).



Scheme 3. Retrosynthetic pathway to synthesis of fatty β-alkyl substituted GABA analogues.

To synthesize the aliphatic nitroolefins **8** or alkylidenes **9**, the several aldehydes were used as starting material and in the all cases the procedures were based on the literature.[28,29] The commercially available isovaleric (**6a**), hexanoic (**6b**), octanoic (**6c**), decanoic (**6d**) and dodecanoic (**6e**) aldehydes, were used directly as received. The palmitic (**6f**), stearic (**6g**) and oleic (**6h**) aldehydes were synthesized from the oxidation of the respective commercially available fatty alcohols. The linoleic (**6i**) aldehyde was prepared from the reduction of commercially available linoleic acid, followed by oxidation of the respective fatty alcohol. The reduction of linoleic acid was performed using lithium aluminum hydride under reflux for 24 hours, resulting in the linoleic alcohol in 90% yield (see ^{1}H and ^{13}C NMR spectra, Figure S1) in the crude form which was then subjected to further oxidation without chromatographic purification step. Thus, the commercially available palmitic, stearic and oleic alcohols, plus linoleic alcohol obtained by reduction, were submitted to an adapted Swerns oxidation to give the respective fatty aldehydes **6f-i** (Scheme 4) in high yields and purity.[30]

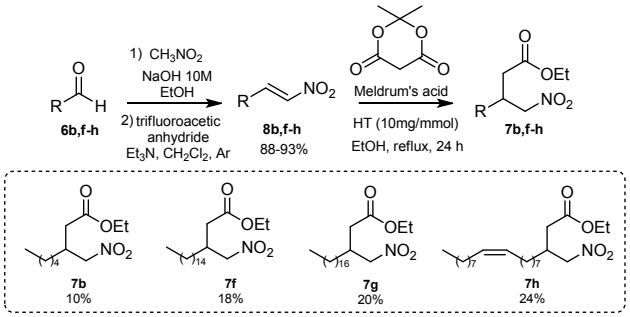


Scheme 4. Synthesis of fatty aldehydes **6f-i** by Swern's oxidation.

With the aliphatic aldehydes in hand, studies towards the synthesis of alkyl nitroolefins were performed according to literature.[31] Initially, some representatives saturated and unsaturated fatty aldehydes were investigated as a model. The Henry condensation[32] reaction with nitromethane under alkaline catalysis, followed subsequent elimination reaction in the presence of trifluoroacetic anhydride give nitroolefins **8b**,**f-h** in good yields (88-93%). The conversion of aldehydes to fatty acid nitroolefins (Scheme 5) was confirmed from the ^{1}H NMR spectrum analysis, where it was possible to observe the presence of characteristic vinylic hydrogen signal at 6.9-7.3 ppm.

Next, the Michael addition reaction from long-chain nitroolefins and Meldrum's acid (see pathway A, Scheme 3) was investigated (Scheme 5).[33,34] In previous works we showed the *one pot* domino reaction for the synthesis of γ-nitroderivatives using hydrotalcite (HT) as catalyst.[33] HTs has shown catalytic applicability as solid catalysts in several organic reactions, including aldol[35] and Knoevenagel condensations.[36] In addition, previously we demonstrated the ability HTs catalyst to promote the conjugated addition reaction of 1,3-diketones, 1,3-ketoesters or malonates and aromatic nitroolefins, leading to the isolation of nitroesters in good yields. This methodology was extended to a series of reactions between Meldrum's acid and several aromatic nitroolefins and γ-nitroesters were isolated through a simple filtration process, to give good yields of the product (85–95%).[32]

Thus, the reaction from Meldrum's acid and fatty nitroolefins **8b**,**f-h** was performed in the presence of calcined HT as catalyst at reflux in ethanol for 24 hours (Scheme 5), under the same experimental conditions employed for aromatic nitroolefins. However, the β-alkyl substituted γ–nitroesters **7b**,**f-h** were isolated in poor yields. This result was attributed to a probable instability of aliphatic nitroolefins under the conditions employed in the reaction.



Scheme 5. Synthesis of fatty nitroolefins and Michael addition reaction in the presence of Meldrum's acid and hydrotalcite (HT).

Based on the poor results obtained in the pathway A for the synthesis of β–alkyl substituted γ-nitroesters from long-chain nitroolefins, the approach based in the Michael addition reaction from aliphatic alkylidenes and nitro methane (see pathway B, Scheme 3) was investigated.

Initially, for synthesis of alkylidenes **9a-i** the Knoevenagel condensation reaction was realized in agreement to literature (Scheme 6).[37] The piperidinium acetate catalyst was easily prepared and isolated by addition of acetic acid to a piperidine solution in dry toluene. The use of this catalyst and molecular sieves in the reaction between aliphatic aldehydes **6a-i** and Meldrum's acid afford the alkylidenes **9a-i** in good yields. Afterwards, the compounds **9a-i** were then submitted to conjugate 1,4-addition of nitromethane, in the presence of DBU, for 8 hours at room temperature. In this way, the aliphatic Michael adducts **10a-i** were isolated in 87-97% yields (Scheme 6).[38] Table 1 show the yields of Knoevenagel condensation and of Michael adducts **10a-i** obtained from aliphatic alkylidenes **9a-i** and nitro methane (see pathway B, Scheme 3).

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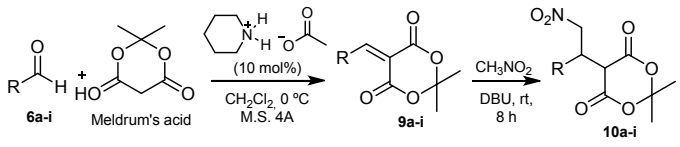
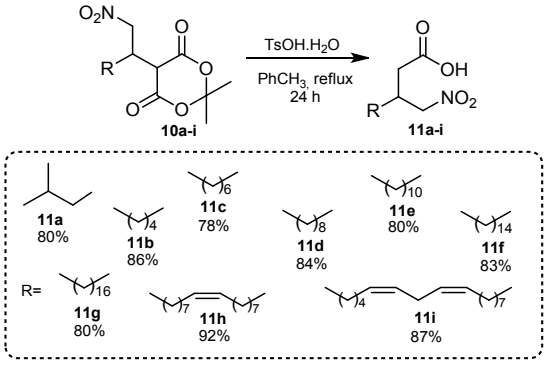


Scheme 6. Knoevenagel condensation and synthesis of Michael adducts from long-chain alkylidenes.

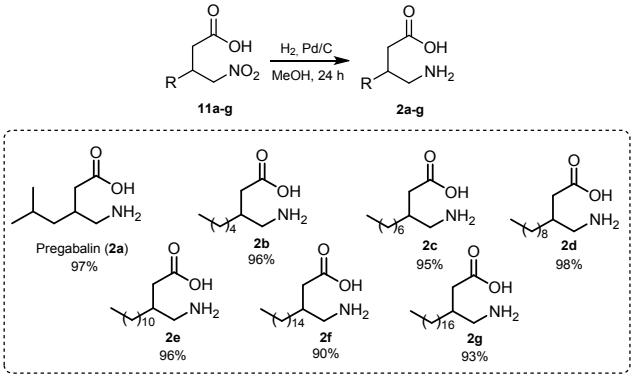
The formation of the Michael adducts was confirmed by ^{1}H NMR analysis, from observation of signals in 4.5-5.0 ppm, as double doublets attributed to diasterotopic α–NO_2 hydrogens; followed by doublet at 3.9 ppm, characteristic of α–carbonyls hydrogen, confirming the nitromethane addition into the alkylidene structure. Several attempts of purification by chromatography columns of the Michael adducts proved to be inefficient, suggesting an instability of compounds. Thus, due to the high purity observed in the ^{1}H NMR spectrum from crude product, the next transformation was carried out from crude adducts **10a-i**. The domino hydrolysis and decarboxylation were successfully performed, in accordance to literature methods, using TsOH.H_2O (PTSA, *p*-toluene sulfonic acid) as catalyst at reflux in toluene for 24 hours.[39] Afterward, the lipophilic β-alkyl substituted γ-nitro acids **11a-i** were isolated in good yields (Scheme 7).



Scheme 7. Syntheses of lipophilic β-alkyl-substituted γ-nitro acids **11a-i**.

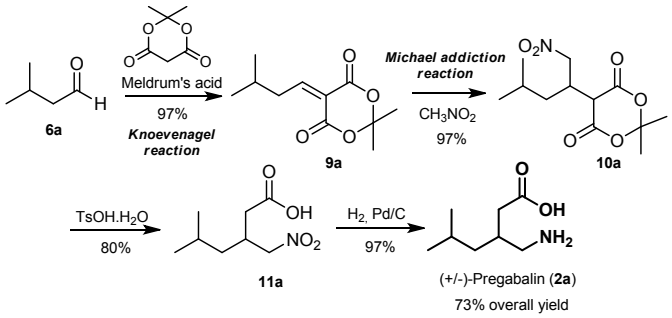
Afterwards, the saturated alkyl nitro acids **11a-g**, derived from saturated fatty alkyl chains, were submitted to the same reduction conditions employed in the synthesis of (+/-)-Pregabalin.[40] The reactions were realized in an appropriate reactor, under hydrogen atmosphere, in MeOH as solvent for 24 hours. After this period, removal of the catalyst by filtration on Celite® gave access to the racemic Pregabalin (**2a**) and new lipophilic β–alkyl substituted GABA derivatives **2b-g**, which were isolated in high yields and characterized by spectroscopic methods (Scheme 8).

Due the incompatibility of the double bond present in alkyl nitro acids **11h** and **11i**, attempts to synthesize unsaturated amino acids were carried out by reduction of β–alkyl-substituted nitro acid **11h** and **11i** in the presence of Indio as catalyst. Initially, the reaction was investigated using nitro acid **11h**. However, even with the consumption of the starting material after 5 hours of reaction, observed by Thin Layer Chromatography (TLC), the product **2h** was isolated in poor yields. Attempts to improve the yields have been unsuccessful, and for this reason the reduction of unsaturated nitro acids was suspended.



Scheme 8. Synthesis of saturated β-alkyl-substituted amino acids **2a-g**.

Our results show that the new lipophilic β-alkyl substituted GABA derivatives **2b-g** can be synthesized in high overall yields from fatty aldehydes. In addition, this new methodology can be applied to the synthesis of (+/-)-Pregabalin (**2a**), used to treat epilepsy and neuropathic pain, through a four-step process (Knoevenagel, Michael addition, hydrolysis, hydrogenation reactions) with a 73% overall yield from *iso*-valeraldehyde (Scheme 9).



Scheme 9. Synthesis of (+/-)-Pregabalin **2a**.

Conclusions

In this study, for the first time, we synthesize a series of new lipophilic β-alkyl GABA's derivatives from fatty alkyl chains. The results showed that the Knoevenagel condensation between aliphatic aldehydes and Meldrum's acid affords long-chain fatty alkylidenes in good yields. Furthermore, the conjugate 1,4-addition of nitromethane resulted in Michael adducts in high yields, which were submitted to a *one pot* domino hydrolysis-decarboxylation process, leading to nitro acids in good yields. Finally, the adducts were reduced to access the new lipophilic β-alkyl substituted GABA's derivatives. This methodology led to the new lipophilic GABA derivatives after four steps with high yields. In addition, this new methodology afforded the synthesis of the antiepileptic drug (+/-)-Pregabalin (**2a**) in a high overall yield (73%) from iso-valeraldehyde. According to the structures of the new lipophilicity fatty β-alkyl GABA's derivatives synthesized suggests their likely ability to permeate through the BBB, representing therefore promising candidates for the treatment of psychiatric disorders.

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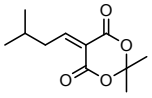
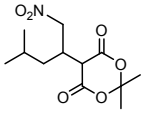
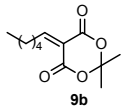
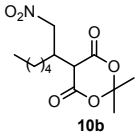
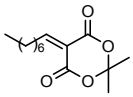
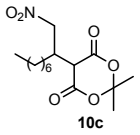
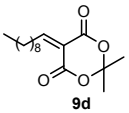
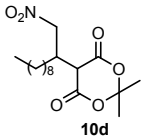
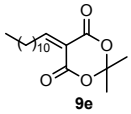
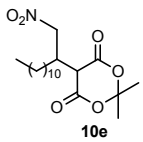
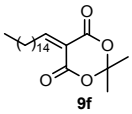
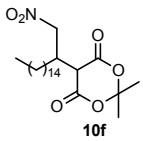
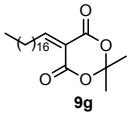
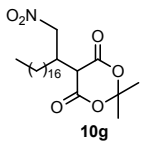
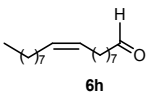
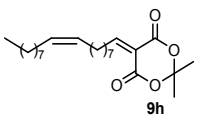
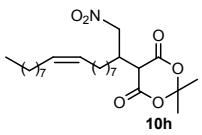
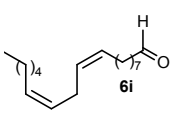
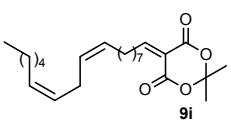
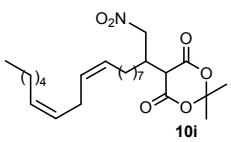
Table 1. Yields of lipophilic alkylidenes and aliphatic Michael adducts after nitro methane addition.

Entry	Aldehydes (**6a-i**)	Alkylidenes (**9a-i**)	Yield[a] (%)	Michael adducts (**10a-i**)	Yield[b] (%)
1	 **6a**	 **9a**	97	 **10a**	97
2	 **6b**	 **9b**	95	 **10b**	95
3	 **6c**	 **9c**	92	 **10c**	90
4	 **6d**	 **9d**	85	 **10d**	87
5	 **6e**	 **9e**	86	 **10e**	92
6	 **6f**	 **9f**	80	 **10f**	90
7	 **6g**	 **9g**	83	 **10g**	95
8	 **6h**	 **9h**	81	 **10h**	92
9	 **6i**	 **9i**	75	 **10i**	92

[a] Yields obtained after chromatographic purification. [b] Crude yields.

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Experimental section

Materials and methods

The reagents were purchased from Aldrich Chemical Co. and used without further purification. All organic solvents used for the synthesis were of analytical grade. Hydrotalcite (HT, Mg/Al ratio 3:1) was synthesized according to previous works.[27,32,41] The piperidinium acetate catalyst was prepared *in situ* and isolated from the addition of acetic acid to a piperidine solution in dry toluene according to literature.[36] Column chromatography was performed using a Silica Gel 60 A (ACROS Organics, 0.035–0.070 mesh). Infrared (IR) spectra were measured on a Schimadzu PRESTIGIE-21 FT-IR spectrophotometer. The NMR spectra were recorded using a Varian VNMRS 300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75.5 MHz) in $CDCl_3$, MeOH-d_4, DMSO-d_6 or D_2O as solvents. The chemical shift data are reported in units of δ (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. The coupling constants (^3J) are reported in Hz and refer to apparent peak multiplicities. The melting points were obtained on a Fisatom 430D apparatus and are uncorrected. High resolution mass spectra (HRMS) were recorded on Waters XEGO G2 Q-TOF Mass Spectrometer.

Synthesis

*General procedure for the synthesis of fatty aldehydes **6f-i**.*

To a round-bottom flask equipped with an addition funnel and magnetic stirring bar under N_2 atmosphere at -10 °C were added dry CH_2Cl_2 (5 mL) and oxalyl chloride ($C_2O_2Cl_2$, 11 mmol). Then, with an addition funnel, DMSO (24 mmol) in 5 mL CH_2Cl_2 was slowly added for 2 minutes at the same temperature. After, 5 mmol of respective fatty alcohol in 5 mL of CH_2Cl_2 were added slowly, maintaining vigorous stirring for 5 minutes at -10 °C. In the next step, Et_3N (25 mmol) was added, with stirring maintained at -10 °C for 15 minutes. Afterwards, the reaction was warmed to room temperature before the addition of 10 mL of H_2O. The mixture was extracted with CH_2Cl_2 (3×10 mL) and washed with the same quantities of brine, 1% HCl, H_2O and 5% Na_2CO_3, respectively. The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to provide fatty aldehydes **6f-i**.

Hexadecanaldehyde (6f). Yield 85%. White solid. Melting point 33-35 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.0 Hz), 1.26 (m, 22H), 1.63 (m, 4H), 2.40 (dt, 2H, *J* = 9.0 and 3.0 Hz), 9.77 (t, 1H, *J* = 3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.0, 22.0, 22.6, 29.1, 29.3, 29.4 (2C), 29.5, 29.6 (3C), 29.7 (2C), 31.9, 43.9, 202.9. IR (ν_{max}, cm^{-1}): 2919, 2848, 2746, 1711, 1474.

Octadecanaldehyde (6g). Yield 87%. White solid. Melting point 42-43 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.0 Hz), 1.25 (m, 26H), 1.63 (m, 4H), 2.42 (dt, 2H, *J* = 9.0 and 3.0 Hz), 9.77 (t, 1H, *J* = 3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.1, 22.1, 22.7, 29.1 (2C), 29.3 (3C), 29.4 (2C), 29.6 (2C), 29.7 (3C), 31.9, 43.9, 203.0. IR (ν_{max}, cm^{-1}): 2922, 2852, 2744, 1710, 1470.

(Z)-Octadec-9-enaldehyde (6h). Yield 94%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* = 6.0 Hz), 1.29-1.33 (m, 20H), 1.65 (m, 2H), 2.03 (m, 4H), 2.44 (dt, 2H, *J* = 6.0 and 3.0 Hz), 5.37 (m, 2H), 9.78 (t, 1H, *J* = 3.0 Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ13.4, 21.4, 22.0, 26.5, 26.6 (2C), 28.4, 28.5, 28.6, 28.7, 28.9, 29.0, 29.1, 31.3, 43.2, 129.0, 129.3, 201.7. IR (ν_{max}, cm^{-1}): 3009, 2928, 2855, 2717, 1722, 1462, 1123, 710.

(9Z,12Z)-Octadeca-9,12-dienaldehyde (6i). Yield 92%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.84 (t, 3H, *J* = 6.0 Hz), 1.31 (m, 14H), 1.63 (m, 2H), 2.05 (q, 4H, *J* = 6.0 Hz), 2.41 (dt, 2H, *J* = 6.0 and 3.0 Hz), 2.77 (t, 2H, *J* = 6.0 Hz), 5.35 (m, 4H), 9.76 (t, 1H, *J* = 3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ13.9, 21.9, 22.4, 25.5, 27.0, 27.1, 28.9, 29.0, 29.1, 29.2, 29.4, 31.4, 43.7, 127.7, 127.9, 129.8, 130.0, 202.6. IR (ν_{max}, cm^{-1}): 3009, 2920, 2855, 2717, 1722, 1462, 718.

*Synthesis of long-chain alkylidenes **9a-i**.*

To a round-bottom flask equipped with a magnetic stirring bar were added Meldrum's acid (1.1 mmol) in CH_2Cl_2 (3 mL) and piperidinium acetate (10 mol%). The mixture was kept under stirring for 5 minutes at room temperature and then cooled to 0 °C. In the next step, the aliphatic aldehyde (**6a-i**, 1 mmol) was added slowly, maintaining stirring for 45 minutes at 0 °C in an ice bath. Finally, activated 4 Å molecular sieves were added to the system, maintaining the stirring for 15 minutes at room temperature. The mixture was extracted with CH_2Cl_2 (3×10 mL) and washed with distilled water (3×10 mL) until a neutral pH. The organic solution was washed with saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and solvent evaporated under reduced pressure, giving long-chain alkylidenes **9a-i**.

2,2-dimethyl-5-(3-methylbutylidene)-1,3-dioxane-4,6-dione (9a).[7] Yield 97%. Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.01 (d, 6H, *J* = 6.0 Hz), 1.75 (s, 6H), 1.96 (sept., 1H, *J* = 7.5 Hz), 2.86 (t, 2H, *J* = 7.5 Hz), 7.96 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ22.5 (2C), 27.6 (2C), 28.6, 39.7, 104.8, 118.6, 159.8, 161.8, 167.9. IR (ν_{max}, cm^{-}

[1]): 3479, 3004, 2956, 2860, 1789, 1733, 1637, 1476, 1286, 1202, 1001, 912, 799.

2,2-Dimethyl-5-(hexylidene)-1,3-dioxane-4,6-dione (9b). Yield 95%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.92 (t, 3H, *J* = 6.0 Hz), 1.38 (m, 4H), 1.62 (m, 2H), 1.76 (s, 6H), 2.96 (q, 2H, *J* = 7.5 Hz), 7.95 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 23.2, 28.3, 29.5, 31.7, 32.3, 105.4, 118.6, 160.4, 162.5, 165.6, 169.6. IR (ν_{max}, cm^{-1}): 3479, 3004, 2956, 2860, 1789, 1733, 1637, 1476, 1286, 1202, 1001, 912, 799.

2,2-Dimethyl-5-(octylidene)-1,3-dioxane-4,6-dione (9c). Yield 92%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.90 (t, 3H, *J* = 6.0 Hz), 1.30 (m, 10H), 1.61 (quint, 2H, *J* = 6.0 Hz), 1.76 (s, 6H), 2.96 (q, 2H, *J* = 6.0 Hz), 7.95 (t, 1H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 23.2, 28.3, 28.8, 29.6, 30.0, 31.8, 32.3, 105.4, 118.7, 160.5, 162.5, 165.6, 169.7. IR (ν_{max}, cm^{-1}): 3446, 3009, 2936, 2855, 1795, 1746, 1624, 1560, 1357, 1301, 1195, 1017, 928, 799.

2,2-Dimethyl-5-(decylidene)-1,3-dioxane-4,6-dione (9d). Yield 85%. Pale yellow paste. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.88 (t, 3H, *J* = 6.0 Hz), 1.26 (m, 10H), 1.59 (m, 2H), 1.74 (s, 6H), 2.94 (q, 2H, *J* = 9.0 Hz), 7.93 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 23.3, 28.3 (2C), 28.8, 28.9, 29.9, 30.0, 30.1, 31.8, 32.5, 105.5, 118.7, 160.5, 162.6, 169.7. IR (ν_{max}, cm^{-1}): 3009, 2928, 2847, 1792, 1752, 1738, 1639, 1467, 1381, 1296, 1201, 1002, 925, 799.

2,2-Dimethyl-5-(dodecylidene)-1,3-dioxane-4,6-dione (9e). Yield 86%. Pale yellow solid. Melting point 67-69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.91 (t, 3H, *J* = 7.5 Hz), 1.28 (m, 16H), 1.62 (m, 2H), 1.76 (s, 6H), 2.96 (q, 2H, *J* = 6.0 Hz), 7.96 (dt, 1H, *J* = 9.0 e 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.7, 23.3, 28.3, 28.8, 29.9(2C), 30.1(2C), 30.2(2C), 31.6, 31.8, 32.5, 105.4, 118.7, 160.5, 162.6, 169.7. IR (ν_{max}, cm^{-1}): 3398, 3009, 2920, 2847, 1802, 1748, 1738, 1641, 1568, 1462, 1381, 1309, 1203, 1009, 912, 807, 718.

2,2-Dimethyl-5-(hexadecylidene)-1,3-dioxane-4,6-dione (9f). Yield 80%. White solid. Melting point 81-83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.88 (t, 3H, *J* = 6.0 Hz), 1.28 (m, 24H), 1.60 (m, 2H), 1.74 (s, 6H), 2.94 (q, 2H, *J* = 6.0 Hz), 7.93 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 27.6(2C), 28.1, 29.2, 29.3(2C), 29.4(2C), 29.5(2C), 29.6(4C), 31.1, 31.9, 104.7, 118.0, 159.8, 161.9, 169.0. IR (ν_{max}, cm^{-1}): 3001, 2920, 2855, 1795, 1746, 1730, 1641, 1462, 1381, 1301, 1195, 1001, 799, 718.

2,2-dimethyl-5-(octadecylidene)-1,3-dioxane-4,6-dione (9g). Yield 83%. White solid. Melting point 78-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.90 (t, 3H, *J* = 7.5 Hz), 1.27 (m, 28H), 1.61 (m, 2H), 1.76 (s, 6H), 2.95 (q, 2H, *J* = 6.0 Hz), 7.95 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 22.4, 27.2(2C), 27.7, 28.8(2C), 28.9(2C), 29.0(2C), 29.1(2C), 29.2(4C), 30.7, 31.4, 104.3, 117.5, 159.3, 161.4, 168.5. IR (ν_{max}, cm^{-1}): 3001, 2920, 2847, 1786, 1738, 1624, 1471, 1390, 1293, 1195, 1009, 799, 718.

2,2-Dimethyl-5-(Z)-(octadec-9-enylidene)-1,3-dioxane-4,6-dione (9h). Yield 81%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.89 (t, 3H, *J* = 6.0 Hz), 1.28 (m, 20H), 1.60 (m, 2H), 1.74 (s, 6H), 2.01 (m, 4H), 2.95 (m, 2H), 5.36 (m, 2H), 7.94 (t, 1H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 27.1(2C), 27.5, 27.6, 28.0, 28.1, 29.1(2C), 29.3, 29.4(2C), 29.6(2C), 29.7, 31.8, 104.8, 105.7, 129.7, 130.0, 159.8, 165.4, 169.0. IR (ν_{max}, cm^{-1}): 3004, 2924, 2844, 1741, 1620, 1467, 1274, 1202, 1017, 792, 719.

2,2-Dimethyl-5-(9Z,12Z)-(octadeca-9,12-dienylidene)-1,3-dioxane-4,6-dione (9i). Yield 76%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.90 (t, 3H, *J* = 6.0 Hz), 1.32 (m, 14H), 1.76 (s, 6H), 2.06 (m, 4H), 2.79 (m, 2H), 2.95 (m, 2H), 5.36 (m, 4H), 7.94 (t, 1H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 25.6, 26.3, 27.2 (2C), 27.9 (2C), 29.7 (2C), 29.8(2C), 29.9(2C), 31.9, 104.6, 125.7, 127.3, 127.7, 130.0, 130.3, 155.7, 162.4, 165.0. IR (ν_{max}, cm^{-1}): 3478, 3017, 2936, 2839, 1730, 1629, 1454, 1381, 1284, 1195, 1025, 912, 710.

*Synthesis of Michael adducts **10a-i**.*

To a round-bottom flask equipped with a magnetic stirring bar, the long-chain alkylidene (**9a-i**, 1 mmol) was added. In the next step, CH_3NO_2 (5 mmol) and DBU (1 mmol) were added. The mixture was kept under stirring at room temperature for 8 hours. Afterwards, the excess of nitromethane was evaporated under reduced pressure and the crude was dissolved in 20 mL of CH_2Cl_2 and washed with 1% HCl (3 x 10 mL). The organic solution was dried over $MgSO_4$ and solvent evaporated under reduced pressure, giving long-chain nitro adducts **10a-i**.

2,2-dimethyl-5-(4-methyl-1-nitropentan-2-yl)-1,3-dioxane-4,6-dione (10a).[32] Yield 95%. Pale yellow solid. Melting point 73-75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 3H, *J* = 6.0 Hz), 0.98 (d, 3H, *J* = 6.0 Hz), 1.20 (m, 1H), 1.55 (m, 2H), 1.79 (s, 3H), 1.81 (s, 3H), 3.36 (m, 1H), 3.89 (d, 1H, *J* = 3.0 Hz), 4.53 (dd, 1H, *J* = 12.0 e 6.0 Hz), 4.98 (dd, 1H, *J* = 12.0 e 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ21.4, 23.1, 25.6, 26.8, 28.2, 34.3, 38.1, 47.1, 75.7, 105.4, 163.9, 164.1. IR (ν_{max}, cm^{-1}): 2958, 2873, 1782, 1754, 1549, 1549, 1307, 1195, 980, 631.

2,2-Dimethyl-5-(1-nitroheptan-2-yl)-1,3-dioxane-4,6-dione (10b). Yield 95%. Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.87 (t, 3H, *J* = 7.5 Hz), 1.28-1.58 (m, 8H), 1.77 (s, 3H), 1.79 (s, 3H), 3.25 (m, 1H), 3.89 (d, 1H, *J* = 3 Hz), 4.55 (dd, 1H, *J* = 12.0 e 6.0 Hz), 4.93 (dd, 1H, *J* = 15.0 e 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.8, 23.9, 25.7, 26.8, 26.9, 29.6, 33.2, 49.0, 76.2, 105.4, 164.1, 164.9. IR (ν_{max}, cm^{-1}): 2906, 2863, 1778, 1730, 1560, 1397, 1317, 1203, 1047, 841, 685.

2,2-Dimethyl-5-(1-nitrononan-2-yl)-1,3-dioxane-4,6-dione (10c). Yield 90%. Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.90 (t, 3H, *J* = 7.5 Hz), 1.28-1.42 (m, 12H), 1.81 (s, 3H), 1.83 (s, 3H), 3.30 (m, 1H), 3.92 (m, 1H), 4.58 (dd, 1H, *J* = 15.0 e 6.0 Hz), 5,00 (dd, 1H, *J* = 12.0 e 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.1, 22.8, 23.7, 25.9, 26.9,

27.1, 29.2, 29.4, 29.6, 32.1, 51.0, 77.9, 104.9, 164.2, 164.8. IR (ν_{max}, cm^{-1}): 2964, 2932, 2851, 1781, 1749, 1550, 1306, 1210, 1073.

2,2-Dimethyl-5-(1-nitroundecan-2-yl)-1,3-dioxane-4,6-dione (10d). Yield 87%. Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.88 (t, 3H, *J* = 6.0 Hz), 1.25 (m, 16H), 1.79 (s, 3H), 1.81 (s, 3H), 3.26 (m, 1H), 3.90 (d, 1H, *J* = 3.0 Hz), 4.57 (dd, 1H, *J* = 9.0 e 3.0 Hz), 4.97 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 26.8, 27.4, 28.2, 29.2(2C), 29.3(2C), 29.4(2C), 31.8, 36.4, 46.9, 77.0, 105.4, 164.1. IR (ν_{max}, cm^{-1}): 2930, 2850, 1775, 1735, 1550, 1470, 1390, 1190, 1069, 1013, 973, 884, 845.

2,2-Dimethyl-5-(1-nitrotridecan-2-yl)-1,3-dioxane-4,6-dione (10e). Yield 92%. Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.88 (t, 3H, *J* = 6.0 Hz), 1.25 (m, 20H), 1.79 (s, 3H), 1.81 (s, 3H), 3.27 (m, 1H), 3.89 (d, 1H, *J* = 3.0 Hz), 4.56 (dd, 1H, *J* = 12.0 e 6.0 Hz), 4.96 (dd, 1H, *J* = 12.0 e 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 26.8, 27.3, 28.2, 29.2(2C), 29.3(2C), 29.4(2C), 29.5(2C), 31.8, 36.4, 46.9, 75.8, 105.4, 164.0. IR (ν_{max}, cm^{-1}): 2906, 2858, 1783, 1735, 1550, 1390, 1310, 1205, 981, 877, 716.

2,2-Dimethyl-5-(1-nitrohepdecan-2-yl)-1,3-dioxane-4,6-dione (10f). Yield 90%. Palle yellow paste. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.88 (t, 3H, *J* = 7.5 Hz), 1.25 (m, 28H), 1.79 (s, 3H), 1.81 (s, 3H), 3.26 (m, 1H), 3.90 (d, 1H, *J* = 3.0 Hz), 4.56 (dd, 1H, *J* = 15.0 e 3.0 Hz), 4.95 (dd, 1H, *J* = 15.0 e 9.0). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 26.8, 27.3, 28.2(2C), 29.2, 29.3(2C), 29.4(2C), 29.5, 29.6(4C), 30.9 (2C), 31.9, 46.9, 75.8, 105.4, 164.0. IR (ν_{max}, cm^{-1}): 2911, 2855, 1786, 1738, 1551, 1462, 1374, 1309, 1203, 880, 710.

2,2-Dimethyl-5-(1-nitrononadecan-2-yl)-1,3-dioxane-4,6-dione (10g). Yield 95%. Yellow paste. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.81 (t, 3H, *J* = 6.0 Hz), 1.18 (m, 32H), 1.71 (s, 3H), 1.74 (s, 3H), 3.19 (m, 1H), 3.84 (d, 1H, *J* = 3.0 Hz), 4.48 (dd, 1H, *J* = 15.0 e 6.0 Hz), 4.7 (dd, 1H, *J* = 15.0 e 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.8, 23.3, 27.5, 28.0, 28.9(2C), 29.9(2C), 30.0(2C), 30.1(2C), 30.2(3C), 30.3(4C), 32.5, 37.1, 47.6, 76.5, 106.1, 164.7. IR (ν_{max}, cm^{-1}): 3492, 2920, 2850, 1791, 1735, 1542, 1470, 1310, 1213, 1061, 877.

2,2-dimethyl-5-(Z)-(1-nitrononadec-10-en-2-yl)-1,3-dioxane-4,6-dione (10h). Yield 92%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 6.0 Hz), 1.28 (m, 24H), 1.79 (s, 3H), 1.82 (s, 3H), 2.01 (m, 4H), 3.28 (m, 1H), 3.90 (d, 1H, *J* = 3.0 Hz), 4.57 (dd, 1H, *J* = 9.0 e 3.0 Hz), 4.96 (m, 1H), 5.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.0, 22.6 (2C), 26.7, 27.0, 27.1, 27.3, 28.1, 29.0, 29.1(2C), 29.2, 29.4(2C), 29.6, 29.7, 30.8, 31.8, 36.3, 46.9, 75.8, 105.4, 129.6, 129.9, 164.0. IR (ν_{max}, cm^{-1}): 3004, 2924, 2844, 1741, 1620, 1467, 1274, 1202, 1017, 792, 719.

2,2-dimethyl-5-(10Z,13Z)-(1-nitrononadeca-10,13-dien-2-yl)-1,3-dioxane-4,6-dione (10i). Yield 92%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.91 (t, 3H, *J* = 7.5 Hz), 1.31 (m, 20H), 1.80 (s, 3H), 1.83 (s, 3H), 2.06 (m, 4H), 2.79 (m, 2H), 3.29 (m, 1H), 3.91 (d, 1H, *J* = 3.0 Hz), 4.58 (m, 1H), 4.97 (dd, 1H, *J* = 15.0 e 9.0 Hz), 5.37 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.0, 22.5 (2C), 25.5, 26.8, 27.1(2C), 27.3, 28.2, 29.0(2C), 29.1, 29.3(2C), 29.5, 31.4, 36.4, 46.9, 75.8, 105.4, 127.8, 128.0, 129.9, 130.2, 164.0. IR (ν_{max}, cm^{-1}): 3009, 2920, 2847, 1778, 1722, 1560, 1454, 1211.

*Synthesis of lipophilic β-alkyl-substituted nitro acids **11a-i**.*

To a round bottom flask, the long-chain nitro adduct (**10a-i**,1 mmol) and 5 ml of toluene were added. After complete dissolution of the starting material *p*-toluenesulfonic acid (0.5 mmol) and 2.5 mmol of H_2O were added to the solution at room temperature. The reaction mixture was kept under reflux with continuous magnetic stirring for 24 hours. Afterwards, the solvents were evaporated under reduced pressure and the residue obtained was purified by flash column chromatography on silica gel using hexane:ethyl acetate (90:10) mixture as eluent, giving long-chain nitro acids **11a-i**.

5-Methyl-3-(nitromethyl)-hexanoic acid (11a).[37] Yield 80%. Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.93 (t, 6H, *J* = 6.0 Hz), 1.29 (m, 2H), 1.67 (non, 1H, *J* = 6.0 Hz), 2.51 (d, 2H, *J* = 3.0 Hz), 2.69 (hept, 1H, *J* = 6.0 Hz), 4.44 (dd, 1H, *J* = 9.0 e 3.0 Hz), 4.48 (dd, 1H, *J* = 9.0 e 3.0 Hz), 10.4 (sl, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ22.1, 22.3, 24.9, 31.7, 35.6, 40.3, 78.4, 177.7. IR (ν_{max}, cm^{-1}): 3179, 2952, 2863, 1714, 1551, 1381, 1211, 944.

3-(Nitromethyl)-octanoic acid (11b). Yield 86%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.90 (t, 3H, *J* = 7.5 Hz), 1.31-1.44 (m, 8H), 2.53 (d, 2H, *J* = 9.0 Hz), 2.64 (hept, 1H, *J* = 6.0 Hz), 4.50 (m, 2H), 9.62 (sl, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ13.8, 22.3, 25.9, 31.1, 31.4, 33.8, 35.5, 78.2, 177.9. IR (ν_{max}, cm^{-1}): 3163, 2928, 2855, 1705, 1551, 1381, 1220, 928.

3-(Nitromethyl)-decanoic acid (11c). Yield 78%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 0.90 (t, 3H, *J* = 6.0 Hz), 1.29 (m, 10H), 1.45 (m, 2H), 2.54 (d, 2H, *J* = 6.0 Hz), 2.64 (hept, 1H, *J* = 6.0 Hz), 4.51 (m, 2H), 8.52 (sl, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.4, 22.9, 26.7, 29.4, 29.6, 31.6, 32.0, 34.2, 35.9, 78.6, 178.2. IR (ν_{max}, cm^{-1}): 3155, 2928, 2855, 1714, 1551, 1374, 1288, 936, 718.

3-(Nitromethyl)-dodecanoic acid (11d). Yield 84%. Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.88 (t, 3H, *J* = 6.0 Hz), 1.26 (m, 14H), 1.43 (m, 2H), 2.52 (d, 2H, *J* = 6.0 Hz), 2.63 (hept, 1H, *J* = 7.5 Hz), 4.49 (m, 2H), 8.66 (sl, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5 (2C), 26.3, 29.2, 29.3, 29.4, 31.2, 31.7, 33.8, 35.5, 78.2, 177.7. IR (ν_{max}, cm^{-1}): 3203, 2920, 2847, 1714, 1551, 1381, 1211, 936, 718.

3-(Nitromethyl)-tetradecanoic acid (11e). Yield 80%. Pale yellow paste. ^{1}H NMR (300 MHz, $CDCl_3$): δ0.81 (t, 3H, *J* = 6.0 Hz), 1.19 (m, 16H), 1.36 (m, 2H), 2.44 (d, 2H, *J* = 6.0 Hz), 2.55 (hept, 1H, *J* = 6.0 Hz), 4.42 (m, 2H), 8.46 (sl, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ14.1, 22.6, 26.3, 29.3(2C), 29.4(2C), 29.5(2C), 31.2, 31.8, 33.9, 35.4, 78.2, 177.6. IR (ν_{max}, cm^{-1}): 3195, 2920, 2847, 1705, 1551, 1228.

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3-(Nitromethyl)-octadecanoic acid (11f). Yield 83%. Yellow paste. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.5 Hz), 1.29 (m, 26H), 1.47 (m, 2H), 2.56 (d, 2H, *J* = 6.0 Hz), 2.66 (hept, 1H, *J* = 6.0 Hz), 4.53 (m, 2H), 8.58 (sl, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 26.4, 29.3(3C), 29.5(2C), 29.6(4C), 31.3(2C), 31.9, 33.9, 35.5, 78.3, 177.6. IR (ν_{max}, cm^{-1}): 2920, 2845, 1726, 1548, 1465, 1251, 924, 728.

3-(Nitromethyl)-icosanoic acid (11g). Yield 80%. Pale yellow solid. Melting point 58-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* = 7.5 Hz), 1.28 (m, 30H), 1.45 (m, 2H), 2.54 (d, 2H, *J* = 6.0 Hz), 2.65 (hept, 1H, *J* = 7.5 Hz), 4.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 26.4, 29.3(2C), 29.4(3C), 29.5, 29.6(3C), 29.7(2C), 31.3(2C), 31.9, 33.9, 35.5, 78.3, 177.4. IR (ν_{max}, cm^{-1}): 3452, 2922, 2850, 1783, 1711, 1550, 1470, 1222, 1077, 716.

(Z)-3-(Nitromethyl)-icos-11-enoic acid (11h). Yield 92%. Pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, 3H, *J* = 7,5 Hz), 1.19 (m, 22H), 1.56 (m, 2H), 1.89 (m, 4H), 2.37 (d, 2H, *J* = 6.0 Hz), 2.55 (m, 1H), 4.41 (m, 2H), 5.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.8, 26.4, 27.1, 28.5, 29.1(2C), 29.3, 29.4, 29.5(2C), 29.7, 31.3, 31.8, 34.2, 35.8, 78.5, 130.0, 130.4, 171.6. IR (ν_{max}, cm^{-1}): 3452, 2922, 2850, 1783, 1711, 1550, 1470, 1222, 1077, 716.

(11Z,14Z)-3-(Nitromethyl)-icosa-11,14-dienoic acid (11i). Yield 87%. Palle yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, *J* = 6.0 Hz), 1.32 (m, 16H), 2.03 (q, 4H, *J* = 6.0 Hz), 2.80 (t, 3H, *J* = 6.0 Hz), 4.52 (dd, 1H, *J* = 9.0 e 3.0 Hz), 4.61 (dd, 1H, *J* = 9.0 e 6.0 Hz), 5.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 25.6, 26.2, 27.1, 28.9, 29.1, 29.2, 29.3, 29.6, 31.5, 33.6, 35.9, 38.5, 41.4, 75.9, 127.8, 128.1, 129.9, 130.2, 181.4.

Synthesis of saturated β-alkyl-substituted γ-aminobutyric acids ***2a-g***.

In an appropriate flask, after two nitrogen cycles to replace air inside the reaction flask, were added the long-chain nitro acid (**11a-g**, 0.5 mmol) and 10 mL of methanol. Then, 20 mg of 10% Pd/C was added to the system. The reaction mixture was vigorously stirred at 25 ºC under 1 atm of hydrogen for 24 hours. After the reaction, the mixture was filtered under Celite® using methanol as the solvent. The solvent was evaporated under reduced pressure, giving long-chain γ-aminobutyric acids **2a-g**.

3-(Aminomethyl)-5-methyl hexanoic acid, (+/-)-Pregabalin (2a).[42] Yield 97%. White solid. Melting point 169-171 °C. ^{1}H NMR (300 MHz, D_2O): δ 0.73 (d, 3H, *J* = 3.0 Hz), 0.75 (d, 3H, *J* = 3.0 Hz), 1.08 (t, 2H, *J* = 7.5 Hz), 1.51 (hept, 1H, *J* = 7.5 Hz), 2.02 (m, 1H), 2.15 (m, 2H), 2.81 (dd, 1H, *J* = 12.0 e 6.0 Hz), 2.88 (dd, 1H, *J* = 12.0 e 6.0 Hz). ^{13}C NMR (75 MHz, D_2O): δ 21.6, 22.0, 24.4, 31.7, 40.6, 40.7, 43.7, 181.0. IR (ν_{max}, cm^{-1}): 3389, 2952, 2602, 1641, 1551, 1398, 1333, 1276.

3-(Aminomethyl) octanoic acid (2b). Yield 96%. White solid. Melting point 153-155 °C. ^{1}H NMR (300 MHz, MeOH-d_4): δ 0.92 (t, 3H, *J* = 7.5 Hz), 1.33 (m, 8H), 2.00 (m, 1H), 2.27 (dd, 1H, *J* = 15.0 e 9.0 Hz), 2.43 (dd, 1H, *J* = 15.0 e 3.0 Hz), 2.85 (dd, 1H, *J* = 12.0 e 6.0 Hz), 2.97 (dd, 1H, *J* = 12.0 e 3.0 Hz). ^{13}C NMR (75 MHz, MeOH-d_4): δ 14.5, 23.7, 27.6, 33.2, 33.9, 35.7, 42.8, 45.5, 180.5. IR (ν_{max}, cm^{-1}): 2972, 2915, 2851, 2152, 1572, 1403, 993, 703. Elemental Analysis: calcd. for $C_9H_{19}NO_2$, C, 62.39; H, 11.05; N, 8.08; O, 18.47; found: C, 62.30; H, 10.94; N, 8.06; O, 18.38.

3-(Aminomethyl) decanoic acid (2c). Yield 95%. White solid. Melting point 140-144 °C. ^{1}H NMR (300 MHz, MeOH-d_4): δ 0.92 (t, 3H, *J* = 6.0 Hz), 1.33 (m, 12H), 2.04 (m, 1H), 2.29-2.49 (m, 2H), 2.87-3.03 (m, 2H). ^{13}C NMR (75 MHz, MeOH-d_4): δ 14.6, 23.8, 27.9, 30.5, 30.9, 33.1, 33.8, 35.5, 41.9, 45.3, 179.9. IR (ν_{max}, cm^{-1}): 3292, 2928, 2847, 2596, 2175, 1705, 1544, 1398, 645. Elemental Analysis: calcd. for $C_{11}H_{23}NO_2$, C, 65.63; H, 11.52; N, 6.96; O, 15.89; found: C, 65.59; H, 11.34; N, 6.72; O, 15.71.

3-(Aminomethyl) dodecanoic acid (2d). Yield 98%. White solid. Melting point 167-170 °C. ^{1}H NMR (300 MHz, MeOH-d_4): δ 0.90 (t, 3H, *J* = 6.0 Hz), 1.30 (m, 16H), 1.98 (m, 1H), 2.26 (dd, 1H, *J* = 15.0 e 9.0 Hz), 2.43 (dd, 1H, *J* = 15.0 e 6.0 Hz), 2.84 (dd, 1H, *J* = 12.0 e 6.0 Hz), 2.96 (dd, 1H, *J* = 12.0 e 6.0 Hz). ^{13}C NMR (75 MHz, MeOH-d_4): δ 14.6, 23.9, 28.0, 30.6, 30.8, 30.9, 33.2 (2C), 34.0, 35.7, 43.2, 45.6, 180.7. IR (ν_{max}, cm^{-1}): 3302, 2915, 2851, 2610, 2173, 1668, 1540, 1403, 647. Elemental Analysis: calcd. for $C_{13}H_{27}NO_2$, C, 68.08; H, 11.87; N, 6.11; O, 13.95; found: C, 67.26; H, 10.96; N, 5.93; O, 13.90.

3-(Aminomethyl) tetradecanoic acid (2e). Yield 96%. White solid. Melting point 145-149 °C. ^{1}H NMR (300 MHz, MeOH-d_4): δ 0.90 (t, 3H, *J* = 6.0 Hz), 1.29 (m, 20H), 2.00 (m, 1H), 2.26-2.48 (m, 2H), 2.81-3.00 (m, 2H). ^{13}C NMR (75 MHz, MeOH-d_4): δ 13.0, 22.3, 26.4, 29.1, 29.2, 29.3(3C), 29.4(2C), 31.7, 32.3, 34.0, 43.9, 178.5. IR (ν_{max}, cm^{-1}): 3422, 2920, 2855, 2173, 1632, 1527, 1454, 1381, 701. Elemental Analysis: calcd. for $C_{15}H_{31}NO_2$, C, 69.99; H, 12.14; N, 5.44; O, 12.43; found: C, 69.94; H, 12.09; N, 5.38; O, 12.35.

3-(Aminomethyl) octadecanoic acid (2f). Yield 90%. White paste. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H, *J* = 6.0 Hz), 1.26-1.32 (m, 28H), 2.05 (m, 1H), 2.10-2.30 (m, 2H), 2.50-2.70 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.0, 22.7, 26.8, 29.2, 29.5 (2C), 29.6(6C), 29.4, 31.6, 32.0, 34.0, 39.0, 45.0, 178.8. IR (ν_{max}, cm^{-1}): 3438, 2911, 2847, 1641, 1527, 1454, 1390, 855. Elemental Analysis: calcd. for $C_{19}H_{39}NO_2$, C, 72.79; H, 12.54; N, 4.47; O, 10.21; found: C, 72.47; H, 12.28; N, 4.43; O, 10.19.

3-(Aminomethyl) icosanoic acid (2g). Yield 93%. Pale yellow solid. Melting point 59-62 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, *J* = 6.0 Hz), 1.23 (m, 32H), 1.68 (m, 1H), 2.23-2.38 (m, 2H), 2.73-2.74 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 22.1, 25.8, 28.7(3C), 28.8(2C), 28.9(3C), 29.0(3C), 30.3, 30.7(2C), 31.34(2C), 36.4, 175.3. IR (ν_{max}, cm^{-1}): 3446, 2911, 2847, 1714, 1471, 1220, 726. Elemental Analysis: calcd. for $C_{21}H_{43}NO_2$, C, 73.84; H, 12.69; N, 4.10; O, 9.37; found: C, 73.57; H, 12.65; N, 4.12; O, 9.35.

Conflicts of interest

The authors declare no conflict of interest.

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Graphical Abstract

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