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Sequential synthesis of a new analogue of amlodipine bearing a short amino polyethyleneglycol chain

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Abstract—3-Ethyl 5-methyl 2-[(2-(2-(2-aminoethoxy)ethoxy)ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate as new analogue of amlodipine was prepared in five steps with an overall yield of 22%. The 1,4-dihydropyridine nucleus was built in two steps via Knoevenagel reaction and the amino group of this analogue has been prepared in good yield by Staudinger reduction of the azido 1,4-dihydropyridine precursor in the last step.

1. Introduction

Many 1,4-dihydropyridine (1,4-DHP) derivatives have been studied as a consequence of their pharmacological profile and as the most important calcium channel blockers.[1] The original lead compound in the class of 1,4-DHP is nifedipine[2] (Fig. 1), which is widely used today for the treatment of cardiovascular disease. 1,4-DHPs have undergone several changes to optimize their efficacy and safety. 1,4-DHPs can be classified according to their kinetic properties and/or pharmacodynamic properties. Lacidipine and lercanidipine (Fig. 1) represent the 1,4-DHPs of the fourth generation and these highly lipophilic agents[3] provide a real degree of therapeutic comfort in terms of stable activity in myocardial ischaemia. In the 1990s, progress has been made in the search for new 1,4-DHPs with wider applicability, mainly characterized by a longer duration of action.

Amlodipine[4] (Fig. 1) is comparable from a dynamic point of view to nifedipine[5] and is in late stage clinical evaluation for the once-daily treatment of angina and hypertension.[6] Amlodipine differed from the other 1,4-DHP drugs in possessing a basic side chain[7] linked to the DHP 2-methyl group via an ether oxygen atom and strongly influences the ionization and lipophilicity profiles of the drug. Recent structure relationship of new generation of 1,4-DHPs indicated that the presence of oxypropanolamine moiety on phenyl ring at the 4-position[8] of the DHP nucleus exhibit the β- or α-/β-adrenoceptor blocking activities.[9]

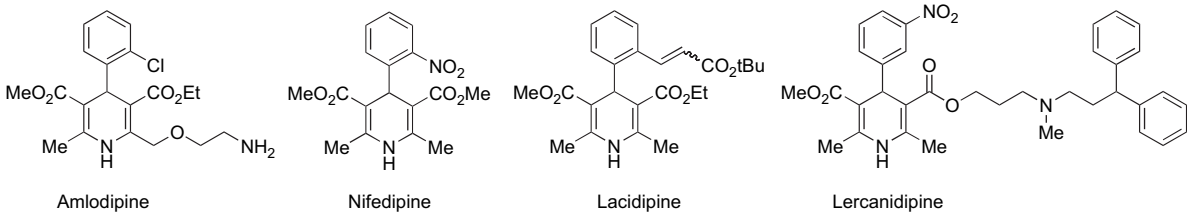

Figure 1. Chemical structures of amlodipine, nifedipine, lacidipine and lercanidipine.

Keywords: Analogue of amlodipine; Knoevenagel reaction; 1,4-Dihydropyridine; Staudinger reduction.
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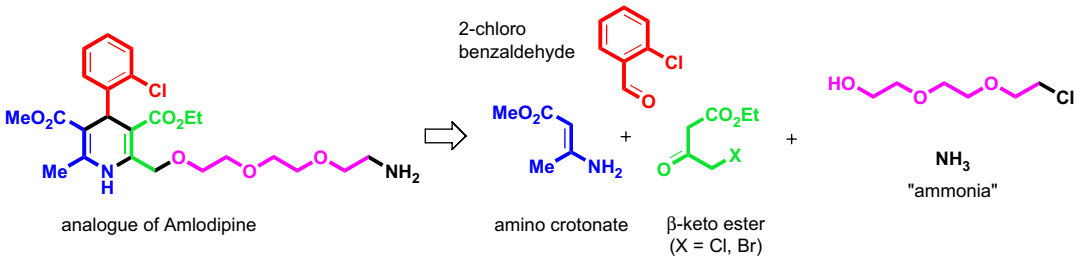


Figure 2. Components used for the synthesis of a new analogue of amlodipine.

Taking into consideration that nearly all the DHP drugs were essentially neutral molecules with low aqueous solubility and lipophilicity, we chose to focus on a basic DHP derivative with a short amino polyethyleneglycol chain appended to the DHP 2-methyl group. Our aim in this study was to develop a convenient, robust and high yielding reaction protocol for the preparation of this new derivative of amlodipine (Fig. 2).

2. Results and discussion

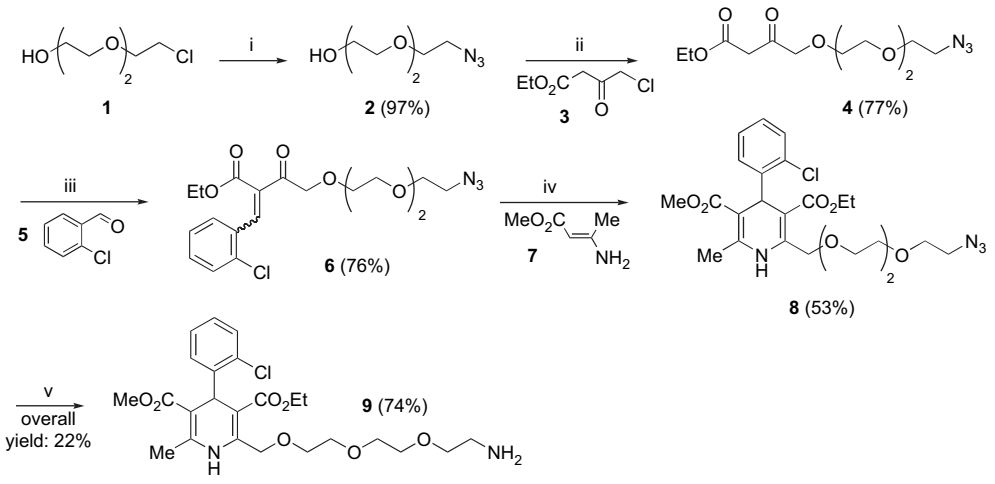
Most of the 1,4-DHPs were prepared by a procedure first described by Hantzsch in 1882. Experimentally, the preparation of the 1,4-DHPs involves a three component, one-step cyclocondensation, because multicomponent reactions (MCRs) constitute an attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step, and the diversity can be simply achieved by varying the reacting components. Owing to their productivity and convergence, the MCRs have attracted considerable attention from the point of view of combinatorial chemistry.[10] For this project, the 1,4-DHP moiety can be built (Fig. 2) from methyl 3-methylaminocrotonate, ethyl 4-halogeno-3-oxo-butanoate as β-keto ester, 2-chlorobenzaldehyde, 2-[2-(2-chloroethoxy)ethoxy)]ethanol as precursor of the short amino polyethyleneglycol side chain of the 1,4-DHP nucleus, ammonia or a synthetic equivalent of ammonia.

In the original synthesis of amlodipine by the Pfizer group,[11] the construction of the 1,4-DHP moiety[12] by a three component Hantzsch condensation[13] from 2-azidoethoxy β-keto ester, 2-chlorobenzaldehyde and methyl 3-methylaminocrotonate as building blocks afforded low yield. To circumvent this drawback, we decided to develop a sequential approach via solution-phase organic synthesis for this new lipophilic derivative of amlodipine. As shown in Scheme 1, the key step of our strategy towards the 1,4-DHP nucleus is based on the product **6** by Knoevenagel reaction.[14]

In the first step, we chose commercially available 2-chloro alcohol **1** as a spacer building block. Complete transformation of the chloro alcohol **1** into azide **2** was accomplished after 38 h in refluxed EtOH with the presence of NaI[15] according to a modified known procedure[16] that gave the desired stable[17] azido compound **2** in 97% yield.

Next, the preparation of the required β-keto ester **4** started with 2-[2-(2-azidoethoxy)ethoxy]ethanol **2**. Initially, our studies started by the reaction of azido compound **2** and ethyl 4-chloro-3-oxobutanoate **3** as β-keto ester at 20 °C using various solvents (MeCN, THF) and various quantities of NaH and NaI (Table 1). Among the conditions studied (entry 4), we found that an equimolecular mixture of compounds **2** and **3** with the presence of NaH[18] (3 equiv) in THF gave good conversion (**4**: 77%) after 24 h.

With the ethyl 4-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}-3-oxo butanoate **4** in hand, we have examined two experimental protocols for the synthesis of the Knoevenagel building block **6** in step 3. As illustrated in Table 2, the two methods investigated for the preparation of the Knoevenagel product **6** are presented. In the first method[7] (A), the azido β-keto



Scheme 1. Reagents and reaction conditions: (i) NaN_3 (2 equiv), NaI (2 equiv), abs EtOH, reflux, 38 h; (ii) NaH (60% mineral oil), THF, 1.5 h at 0 °C then **3** (1 equiv), 25 °C, 24 h; (iii) **5**, piperidine, Me_2CHOH, 40 °C, 1 h, glacial AcOH, 0 °C then 25 °C, 19 h; (iv) **7** (1 equiv), abs EtOH, reflux, 60 h; (v) Ph_3P (1.3 equiv), THF, 25 °C, 2 h, deionized H_2O (25 equiv), reflux, 48 h.

Table 1. Results of reaction conditions evaluated for the preparation of ethyl 4-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}-3-oxo butanoate **4**

Entry	Solvent	Reaction time (hour)	NaH (equiv)	NaI (equiv)	Yield[a] (%)
1	MeCN	16	2	0	—[b]
2	THF	24	2	0	30
3	THF	24	3	1	68
4	THF	24	3	0	77

[a] Isolated yield.
[b] Decomposition.

Table 2. Results for the preparation of Knoevenagel product **6** according to the methods A and B

Entry	Reaction conditions	Aldehyde **5** (equiv)	Reaction temperature (°C)	Yield[c] (%)
1	Method A[a]	1.05	110	5
2	Method A	2	110	21
3	Method B[b]	1.1	20	76
4	Method B	1.1	90	Decomposition

[a] Method A: piperidinium acetate in C_7H_8, 110 °C, 24 h.
[b] Method B: (i) piperidine 0.5%, Me_2CHOH, 40 °C, 2 h. (ii) AcOH 9%, 0 °C, 1 h. (iii) 25 °C, 19 h.
[c] Isolated yield.

ester **4** was coupled with 2-chlorobenzaldehyde **5** in the presence of piperidinium acetate (10%) in toluene at 110 °C for 24 h. In the second method[18] (B), a mixture constituted by β-keto ester **4**, 1.1 equiv of 2-chlorobenzaldehyde **5** and a catalytic amount of piperidine (4.5%) in isopropanol was heated at 40 °C for 1 h, followed by addition of glacial acetic acid (9%) at 0 °C. Then the reaction mixture is mixed at room temperature over a period of 19 h.

Entries 1 and 2 (method A) show that at a high temperature (110 °C) low yield for **6** is associated to the formation of undesired by-products according to ^{1}H NMR analysis of the crude reaction mixture. It can be observed that the optimal reaction conditions were obtained with the method B at 25 °C (entry 3), to produce the desired product **6** in good yield (76%) as a mixture of stereoisomers *Z*/*E* (1/1).

In the fourth step, we have evaluated the reactivity of the Knoevenagel product **6** and methyl 3-methylaminocrotonate **7** for the preparation of the 1,4-DHP **8** with various quantities of **7** in isopropanol[19] or EtOH at 90 and 79 °C, respectively (Table 3). The reactions were conveniently monitored by ^{1}H NMR or by TLC and among the conditions studied (entry 3), we found that reaction of **6** with 1 equiv of crotonate **7** in EtOH at 79 °C gave good conversion after 60 h. The crude 1,4-DHP was purified by column chromatography on silica gel and was eluted with CH_2Cl_2/AcOEt (9:1, **8**: R_f=0.4) in moderate yield (53%). The structure of the 1,4-DHP **8** was ascertained by high-resolution mass spectrometry, proton and carbon NMR confirming that the major compound is the expected 1,4-DHP.

Table 3. Optimization of reaction conditions used for the preparation of azido 1,4-DHP **8**

Entry	Solvent	Reaction temperature (°C)	Reaction time (hour)	**7** (equiv)	Yield[a] (%)
1	Me_2CHOH	90	48	1	39
2	Me_2CHOH	90	64	1.1	20
3	EtOH	79	60	1	53

[a] Isolated yield.

For the last step, our focus was the transformation of the azido 1,4-DHP **8** into amino derivative **9** of amlodipine. To the best of our knowledge, all the common methods for reduction of azides are based on hydride[20] ($LiAlH_4$ in THF), tin(II) chloride[21] or zinc dust[12] in methanol, or palladium-catalyzed hydrogenolysis.[7,22] This implies that specific tedious synthetic protocol has to be devised for each new compound. In 1919, Staudinger and Meyer reported that azides react smoothly with triaryl phosphanes to form iminophosphoranes.[23,24] If the Staudinger reaction is carried out in aqueous solvent, the readily formed iminophosphorane is hydrolyzed rapidly to generate a primary amine and phosphane(V) oxide. The so-called Staudinger reaction is a frequently used method[25] for the smooth reduction of azides to amines. On the basis of the recent works of the Shibasaki[26] and Cho[27] groups, the reduction of the azido group of **8** was tried under several experimental conditions (Table 4). The best results (entry 3) were encountered by reaction of 1.3 equiv of triphenylphosphine with azido product **8** in tetrahydrofuran, followed by addition of 25 equiv of deionized water and heating under reflux for 48 h. Pure amino 1,4-DHP **9** was obtained at this stage by chromatography on alumina gel with CH_2Cl_2/AcOEt (9:1) as eluent. The final 3-ethyl 5-methyl 2-[(2-(2-(2-aminoethoxy)-ethoxy)ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate **9** was obtained in 74% yield.

Table 4. Reaction conditions used for Staudinger reaction

Entry	Reaction conditions	Reaction time (hour)	PPh_3 (equiv)	Deionized water (equiv)	Yield[c] (%)
1	Method A[a]	48	1.5	25	14
2	Method A[a]	24	2	25	30
3	Method B[b]	48	1.3	25	74

[a] Method A: stirred mixture of **8** with PPh_3 and deionized water at room temperature.
[b] Method B: (i) **8**, PPh_3 (1.3 equiv), THF, 2 h, 25 °C. (ii) deionized water (25 equiv), reflux, 48 h.
[c] Isolated yield.

3. Conclusion

In summary, we developed the synthesis of new analogue of amlodipine in five steps with an overall yield[28] of 22% starting from 2-[2-(2-chloroethoxy)ethoxy]ethanol **1**. The key steps of this sequential solution-phase organic synthesis are the Knoevenagel condensation in step 3 (76%) and transformation of the azido 1,4-DHP **8** into new amino analogue of amlodipine **9** by smooth Staudinger reduction conditions (74%). This useful approach may be used as an alternative route to provide a new 1,4-dihydropyridine bearing a short amino polyethyleneglycol side chain as new analogue amlodipine drug. We are currently exploring the scope of this methodology for the preparation of new 1,4-dihydropyridines derived from amlodipine that will be much more reliable for biological screening.

4. Experimental

4.1. General

Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) or neutral alumina oxide gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative column chromatography, silica gel 60F 254 Merck (230–240 mesh ASTM) and neutral alumina oxide gel 90 (Merck) were used. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) and BRUKER ARX 200 (200 MHz) spectrometers, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J (in hertz). The mass spectra (HRMS) were taken, respectively, on a MS/MS ZABSpec TOF Micromass (EBE TOF geometry) at an ionizing potential of 8 eV or on a VARIAN MAT 311 at an ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3 Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification.

4.2. 2-[2-(2-Azidoethoxy)ethoxy]ethanol (2)

In a 100 mL two-necked round-bottomed flask, provided with a magnetic stirrer and reflux condenser, 2-[2-(2-chloroethoxy)ethoxy]ethanol **1** (4.053 g, 23.07 mmol) and sodium azide (3.030 g, 46.12 mmol, 2 equiv) were dispersed in absolute ethanol (30 mL). To this mixture, sodium iodide NaI (6.920 g, 46.16 mmol) was added portion wise and the reaction mixture was stirred at room temperature. The resulting yellowish solution was heated at 79 °C for 38 h under vigorous magnetic stirring, then cooled down to room temperature. The solvent was evaporated in vacuo. The residue was poured in water (100 mL) and was extracted with methylene chloride (2×100 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was eliminated in a rotary evaporator under reduced pressure. After evaporation, the desired azido alcohol **2** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h and was obtained as a mobile colourless oil in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.32 (br s, 1H, OH); 3.39 (t, 2H, J=5.2 Hz, H-9); 3.60 (t, 2H, J=5 Hz, H-8); 3.67 (m, 6H, H-6, H-5, H-3); 3.73 (t, 2H, J=4.9, 4.1 Hz, H-2). ^{13}C NMR (75 MHz, acetone-d_6) δ: 50.40 (C-9); 61.42 (C-2); 69.78–70.12–70.39–72.35 (C-3, C-5, C-6, C-8). HRMS m/z: found 119.0705 (calculated for $C_5H_{11}O_3$ $[M^{-\bullet}CH_2N_3]^+$ requires 119.0708).

4.3. Ethyl 4-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}-3-oxo butanoate (4)

In a 50 mL two-necked round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, sodium hydride (0.945 g of a 60% suspension in mineral oil, 23.63 mmol) was dispersed in freshly dry tetrahydrofuran (10 mL). To this slurry was added dropwise 2-[2-(2-azidoethoxy)ethoxy]-ethanol **2** (1.375 g, 7.85 mmol, dissolved in 5 mL of tetrahydrofuran) at 0 °C over a period of 60 min. The mixture was stirred for 30 min at 0 °C, after which ethyl 4-chloro-3-oxobutanoate **3** (1.05 mL, 7.85 mmol dissolved in 5 mL of dry tetrahydrofuran) was added dropwise at 0 °C over 30 min. The reaction mixture was stirred at 25 °C over a period of 24 h. After elimination of the solvent in a rotary evaporator under reduced pressure, the residue was poured in water (20 mL) and it was acidified at pH 3 with 1 M hydrochloric acid. The mixture was transferred to a separating funnel and was extracted with dichloromethane (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was eliminated in vacuo. The residue was purified by column chromatography (silica gel 60 F 254 Merck, column dimensions 16.0×2.4 cm, AcOEt/CH_2Cl_2 (1:1) as eluent). The desired product **4** was obtained as a yellowish oil after pooling and evaporation of the appropriate fractions (R_f=0.63) and was further dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h (yield=77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, 3H, J=7.1 Hz, CH_2CH_3); 3.39 (t, 2H, J=4.9 Hz, H-13); 3.54 (s, 2H, H-4); 3.68 (m, 10H, H-6, H-7, H-9, H-10, H-12); 4.19 (m, 4H, J=7.1 Hz, H-2, CH_2CH_3). ^{13}C NMR (75 MHz, acetone-d_6) δ: 13.86 (CH_3CH_2); 45.63 (C-2); 50.41 (C-13); 61.11 (CH_2CH_3); 69.81–70.42–70.88 (C-12, C-7, C-6, C-9, C-10), 76.00 (C-4); 166.83 (C-1); 201.80 (C-3). HRMS m/z: found 303.1330 (calculated for $C_{12}H_{21}N_3O_6$ $[M^{+\bullet}]$ requires 303.1447).

4.4. Ethyl 4-{[2-[2-(2-azidoethoxy)ethoxy]ethoxy]-acetyl}-3-(2-chlorophenyl)acrylate (6)

In a 25 mL round-bottomed flask, provided with a magnetic stirrer, ethyl 4-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}-3-oxo butanoate **4** (428 mg, 1.41 mmol) and 2-chlorobenzaldehyde **5** (175 μL, 1.54 mmol) were mixed in isopropanol p.a. (5 mL). To this solution was added dropwise a solution of piperidine (15 μL, 13 mg, 0.15 mmol) in 5 mL of isopropanol p.a. over a period of 2 h. A reflux condenser was then fitted and the reaction mixture was heated at 40 °C for 1 h. After cooling down to 0 °C, glacial acetic acid (17 μL, 17.7 mg, 0.3 mmol) was added in one portion. After stirring at room temperature for 19 h, the crude reaction mixture was submitted to purification by column chromatography on silica gel with CH_2Cl_2/AcOEt (9:1) as eluent. Pooling and evaporation of the solvent in vacuo afforded the expected product **6** as a yellowish oil. The mixture of the stereoisomers Z/E[29] (1:1) was dried under high vacuum (10^{-2} Torr) for 4 h at 25 °C. Yield=76%. E-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, J=7.1 Hz, CH_2CH_3); 3.36 (t, 2H, J=4.9 Hz, H-13″); 3.61 (m, 10H, H-6″, H-7″, H-9″, H-10″, H-12″); 4.18 (s, 2H, H-4″); 4.31 (q, 2H, J=7.1 Hz, CH_2CH_3); 7.22–7.44 (m, 4H, H-6′, H-5′, H-4′, H-3′); 8.05 (s, 1H, H-3). ^{13}C NMR (75 MHz, acetone-d_6) δ: 13.75 (CH_3CH_2); 50.25 (C-13″); 61.39 (CH_2CH_3); 69.61–70.14–70.21–70.50 (C-12′, C-7′, C-6′, C-9′, C-10′); 76.00 (C-4″); 126.75–129.53–129.85–131.01 (C-6′, C-5′, C-4′, C-3′); 131.27 (C-1′); 133.39 (C-2′); 134.11 (C-2); 139.40 (C-3); 163.40 (C-1); 201.54 (C-3″). Z-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, J=7.1 Hz, CH_2CH_3); 3.36 (t, 2H, J=4.9 Hz, H-13″); 3.58 (m, 10H, H-6″, H-7″,

H-9″, H-10″, H-12″); 4.13 (q, 2H, J=7.2 Hz, CH_2CH_3); 4.45 (s, 2H, H-4″); 7.14–7.37 (m, 4H, H-6′, H-5′, H-4′, H-3′); 7.90 (s, 1H, H-3). ^{13}C NMR (75 MHz, acetone-d_6) δ: 13.63 (CH_3CH_2); 50.56 (C-13″); 61.47 (CH_2CH_3); 69.92–70.57–70.98 (C-12′, C-7′, C-6′, C-9′, C-10′); 74.88 (C-4″); 126.56–129.47–129.67–131.15 (C-6′, C-5′, C-4′, C-3′); 132.26 (C-1′); 133.69 (C-2′); 134.53 (C-2); 139.90 (C-3); 166.07 (C-1); 194.44 (C-3″).

4.5. 3-Ethyl 5-methyl 2-[(2-(2-(2-azidoethoxy)ethoxy)-ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (8)

In a 50 mL round-bottomed flask fitted with a reflux condenser, a solution of ethyl 4-{[2-[2-(2-azidoethoxy)ethoxy]ethoxy]acetyl}-3-(2-chlorophenyl)acrylate **6** (392 mg, 0.92 mmol) and methyl 3-methylaminocrotonate **7** (110 mg, 0.92 mmol) in absolute ethanol (10 mL) was refluxed under vigorous magnetic stirring for 60 h. The solvent was eliminated in a rotary evaporator under reduced pressure and the crude residue was purified by column chromatography on silica gel with CH_2Cl_2/AcOEt (9:1) as eluent. Pooling of the appropriate fractions (R_f=0.4) and evaporation in vacuo afforded a residue in 53% yield containing the desired compound **8** as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (t, 3H, J=7.1 Hz, OCH_2CH_3); 2.28 (s, 3H, CH_3); 3.32 (t, 2H, J=4.9 Hz, H-16); 3.55 (s, 3H, OCH_3); 3.58–3.67 (m, 10H, H-9, H-10, H-12, H-13, H-15); 3.97 (dq, 2H, J=7.2, 1.4 Hz, OCH_2CH_3); 4.64 (d, 1H, J=16.8 Hz, H-7); 4.73 (d, 1H, J=16.8 Hz, H-7); 5.36 (s, 1H, H-4); 6.97 (dt, 1H, J=7.7, 1.7 Hz, H-4′); 7.06 (dt, 1H, J=7.6, 1.3 Hz, H-5′); 7.16 (dd, 1H, J=7.8, 1.3 Hz, H-3′); 7.30 (dd, 1H, J=7.7, 1.7 Hz, H-6′); 7.36 (br s, 1H, NH). ^{13}C NMR (75 MHz, acetone-d_6) δ: 14.07 (OCH_2CH_3); 19.11 (CH_3); 37.04 (C-4); 50.42 (C-16); 50.53 (OCH_3); 59.51 (OCH_2CH_3); 67.76 (C-7); 69.84–70.06–70.42–70.57 (C-9, C-10, C-12, C-13, C-15); 101.07 (C-5); 103.60 (C-3); 126.64–127.10–128.97–131.30 (C-6′, C-5′, C-4′, C-3′); 132.07 (C-2′); 144.11 (C-2); 145.59 (C-6); 145.65 (C-1′); 166.97 (CO_2CH_3); 167.86 (CO_2Et). HRMS m/z: found 521.1801 (calculated for $C_{24}H_{30}N_4O_7{}^{35}Cl$ $[M-H]^+$ requires 521.1803).

4.6. 3-Ethyl 5-methyl 2-[(2-(2-(2-aminoethoxy)-ethoxy)ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (9)

In a 50 mL two-necked round-bottomed flask fitted with a reflux condenser, provided with a magnetic stirrer, 3-ethyl 5-methyl 2-[(2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate **8** (228 mg, 0.44 mmol) and triphenylphosphine (150 mg, 0.56 mmol) were dissolved in freshly distilled tetrahydrofuran (5 mL). The homogeneous solution was mixed at room temperature for 2 h, after which deionized water (200 μL, 11.1 mmol) was added in one portion. The reaction mixture was refluxed for 48 h and cooled down to room temperature. The mixture was concentrated in a rotary evaporator and the crude residue was submitted to purification by chromatography on a column of neutral alumina gel using CH_2Cl_2/AcOEt (9:1) as eluent. Pooling and evaporation of the appropriate fraction (R_f=0.58) gave the expected 3-ethyl 5-methyl 2-[(2-(2-(2-aminoethoxy)ethoxy)ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate **9** in 74% yield as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (t, 3H, J=7.1 Hz, OCH_2CH_3); 2.07 (br s, 2H, NH_2); 2.29 (s, 3H, CH_3); 2.84 (br s, 2H, H-16); 3.48 (br s, 2H, H-15); 3.54 (s, 3H, OCH_3); 3.61–3.64 (m, 8H, H-9, H-10, H-12, H-13); 3.97 (dq, 2H, J=7.2, 1.3 Hz, OCH_2CH_3); 4.62 (d, 1H, J=16.4 Hz, H-7); 4.73 (d, 1H, J=16.5 Hz, H-7); 5.34 (s, 1H, H-4); 6.97 (dt, 1H, J=7.7, 1.6 Hz, H-4′); 7.06 (dt, 1H, J=7.4, 1.2 Hz, H-5′); 7.16 (dd, 1H, J=7.9, 1 Hz, H-3′); 7.31 (dd, 1H, J=7.7, 1.5 Hz, H-6′); 7.51 (br s, 1H, NH). ^{13}C NMR (75 MHz, acetone-d_6) δ: 14.10 (OCH_2CH_3); 18.96 (CH_3); 37.07 (C-4); 41.42 (C-16); 50.55 (OCH_3); 59.55 (OCH_2CH_3); 67.72 (C-7); 69.99–70.44–70.46 (C-9, C-10, C-12, C-13); 72.82 (C-15); 101.35 (C-5); 103.53 (C-3); 126.66–127.11–129.00–131.32 (C-6′, C-5′, C-4′, C-3′); 132.10 (C-2′); 144.30 (C-2); 145.53 (C-6); 145.70 (C-1′); 167.04 (CO_2CH_3); 167.89 (CO_2Et). HRMS m/z: found 497.2054 (calculated for $C_{24}H_{34}N_2O_7{}^{35}Cl$ $[M+H]^+$ requires 497.2055).

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28. The overall yield by Pfizer Company is 8.8%, see Ref. 7 and by Kim's group (via Diels–Alder reaction) is 8%, see Ref. 12.
29. Differentiation between (*Z*)- and (*E*)- form of the new compound **6** is possible on the basis of chemical shifts. The shift of H-3 has been found at low field ($\delta_{H\text{-}3}$=8.05 ppm) for the *E*-isomer, see also Ref. 19a for comparison.