Novel bipodal, tripodal, and tetrapodal 1,4-dihydropyridines — Microwave-assisted synthesis and structural confinements

Kancherla Rajesh, Bandapalli Palakshi Reddy, and Vijayaparthasarathi Vijayakumar

Abstract: The one pot, three component reaction of *p*-hydroxy benzaldehyde, β-ketoester, and ammonium acetate afforded the corresponding monopodal 1,4-dihydropyridines as building blocks, which in turn converted into diversified novel bipodal, tripodal, and tetrapodal 1,4-dihydropyridines with different alkylating agents through conventional as well as microwave assisted reactions. The unambiguous structural confinements of the all the synthesized compounds were drawn out with the help of 2D NMR (H-H COSY and C-H COSY).

Key words: bipodal-tripodal-tetrapodal 1,4-dihydropyridines, Hantzsch pyridines, microwave irradiation.

Résumé : La réaction monotope, à trois composants, du *p*-hydroxybenzaldéhyde, d′un β-cétoester et de l′acétate d′ammonium conduit aux 1,4-dihydropyridines correspondantes, des synthons monopodes qui, par le biais de réactions normales ou assistées par des microondes, peuvent être transformées à leur tour en nouvelles 1,4-dihydropyridines bipodes, tripodes et tétrapodes portant divers agents alkylants. Les confinements structuraux non ambiguës de tous les composés synthétisés ont été délimités à l′aide de la RMN 2D (COSY H-H et COSY C-H).

Mots-clés : 1,4-dihydropyridines bipodes, tripodes ou tétrapodes, pyridines de Hantzsch, irradiation microonde.

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Introduction

The synthesis of 1,4-dihydropyridines (1,4-DHPs) via a three-component cyclocondensation reaction of acetoacetic ester, arylaldehyde, and ammonia was first reported by Arthur Hantzsch in 1882.[1] Since then a lot of new variants of the original method have been developed, allowing the synthesis of different substituted 1,4-DHPs, which have now been recognized as vital drugs in the treatment of angina and hypertension. Some of the representatives like nifedipine,[2] felodipine,[3] nicardipine,[4] amlodipine,[5] and manidipine hydrochloride (Fig. 1), have been commercialized and have proven their pharmaceutical action in binding to the voltage dependent L-type calcium channel, thus decreasing the passage of calcium ions into the cell. The result is the relaxation of smooth muscle cells and the lowering of blood pressure.

Studies revealed that 1,4-DHPs exhibit several other medicinal applications, which include neuroprotectant[6] and platelet antiaggregatory activity,[7] in addition to acting as a cerebral anti-ischemic agent in the treatment of Alzheimer's disease[8] and as a chemosensitizer in tumor therapy.[9] The examples clearly demonstrate the potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the compressive medicinal chemistry database found that the DHP framework to be among the most prolific chemo-types. Thus, the synthesis of molecules containing this heterocyclic nucleus with diverse properties and applications has been of continuing interest, which led to the development of novel synthetic strategies. So far the attention has mainly been paid to the synthesis of monopodal 1,4-DHP derivatives, and the highly functional ones are seldom investigated. A series of *bis*-1,4-DHP derivatives was synthesized by Songlei Zhu et al. by the reaction of *p*-phenylenedialdehyde or *m*-phenylenedialdehyde and active methylene compounds.[10] Mohammad Ali Zolfigol et al. synthesized new tripodal 1,4-DHPs under solvent-free conditions by the reaction of a mixture of β-ketoester and tri-aldehydes in the presence of ammonium fluoride.[11] Although the methods described above have been beneficial in the specific examples for which they were developed, they do not show much scope for the synthesis of varyingly substituted bipodal, tripodal, and tetrapodal 1,4-DHPs, where synthesis by the former methods requires bis, tris, and tetra aldehydes, which is a costlier approach and not applicable in some cases. A retro synthetic analysis approach (Scheme 1) for target bipodal 1,4-DHPs has shown that the simple monopodal 1,4-DHPs can serve as building blocks for the construction of the target molecules.

The synthesis of monopodal 1,4-DHP building blocks involves one-pot multicomponent coupling reactions (MCRs), where several organic moieties coupled in one step for carbon–carbon and carbon–heteroatom bond formation, which is an attractive synthetic strategy for the synthesis of small molecule libraries with several degrees of structural diver-

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Fig. 1. Biologically active 1,4-dihydropyridines.

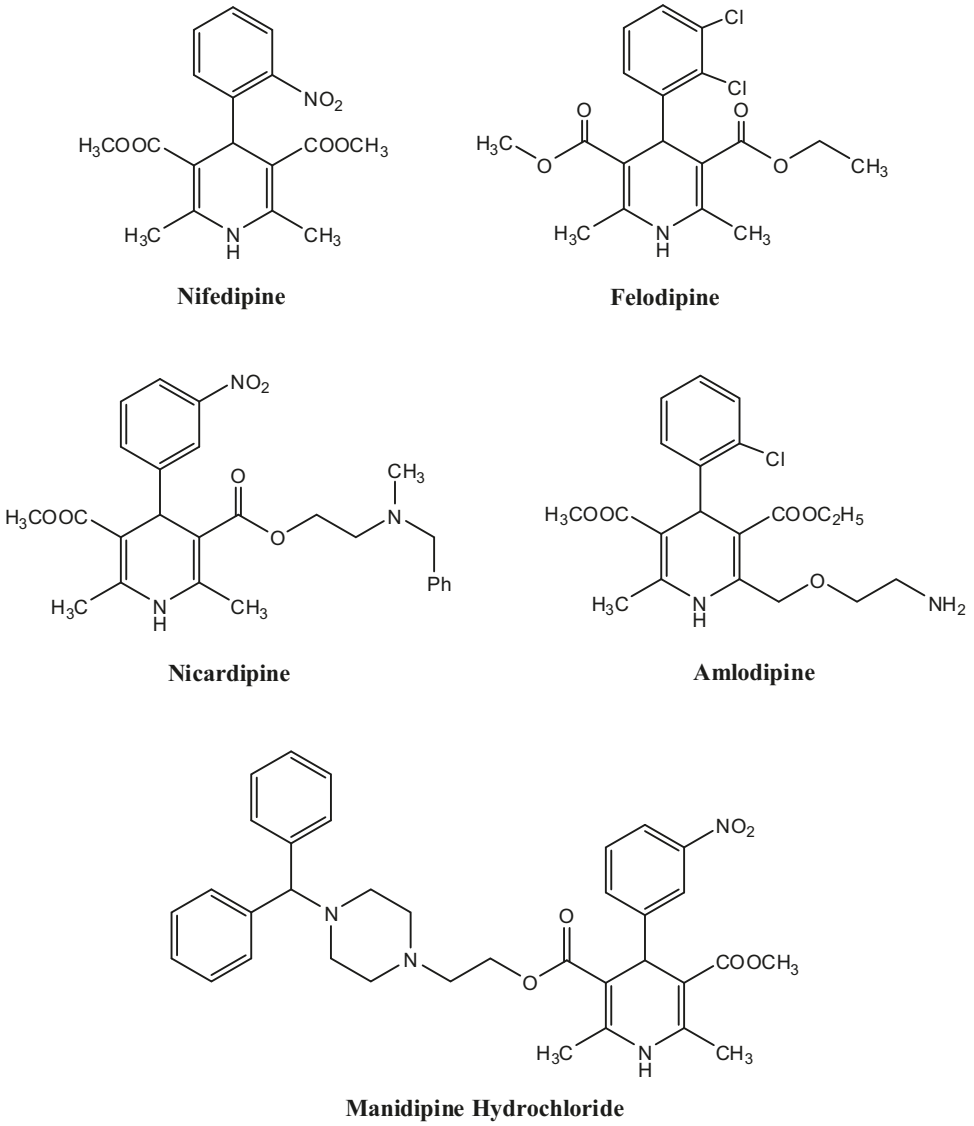
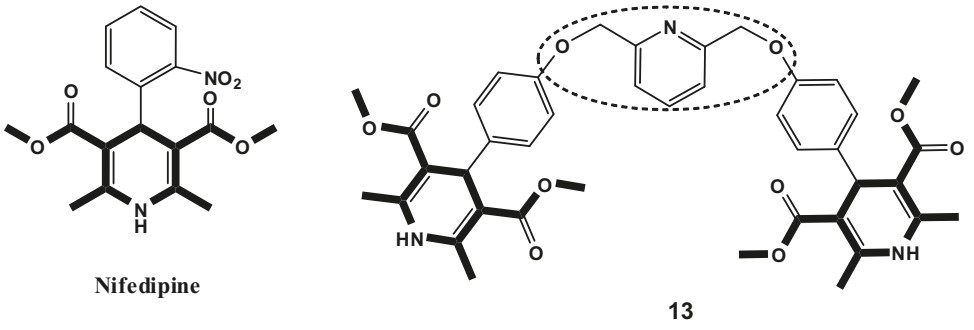


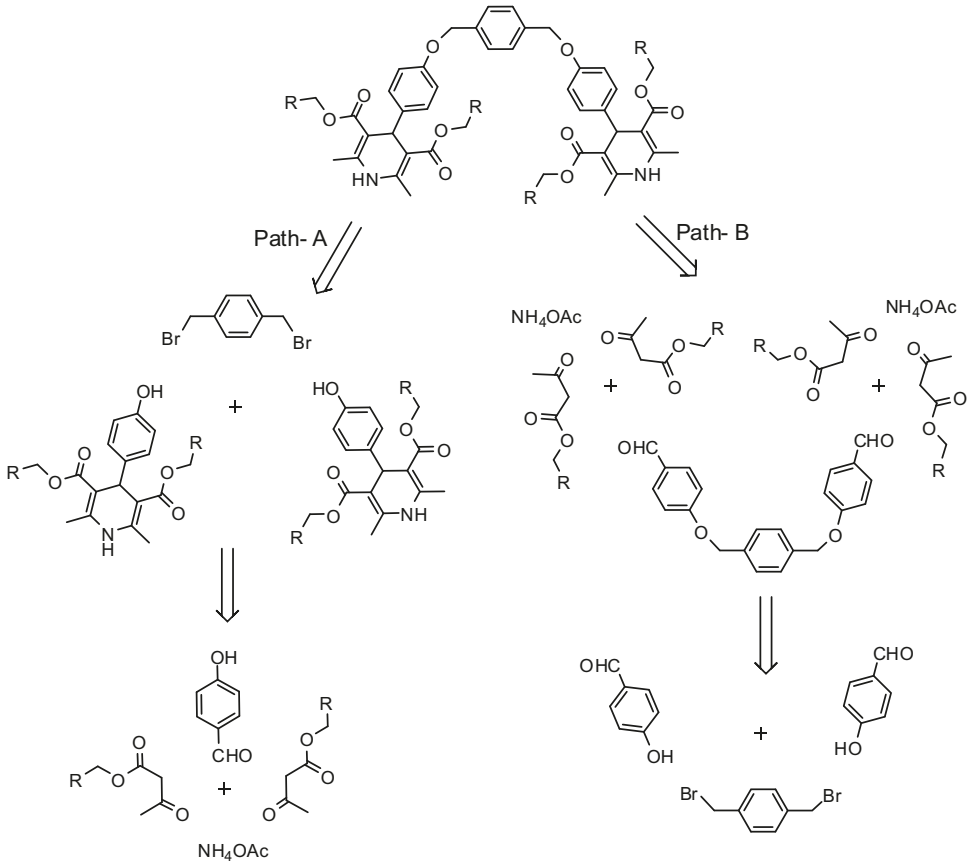
Fig. 2. Structural correlation of the synthesized bipodal 1,4-DHP **13** with the nifedipine.



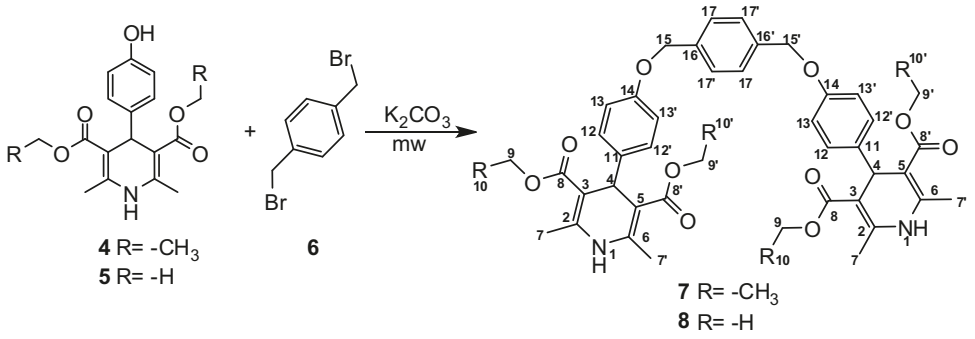
sities.[12–14] The synthesis mainly involves the dehydration of arylaldehydes, β-ketoester or diketone, and ammonium acetate.

The present work describes a direct approach, where the monofunctional 1,4-DHPs, thus synthesized according to the literature,[15,16] serve as building blocks for the construction of novel bipodal, tripodal, and tetrapodal 1,4-DHPs by the conventional methods and by microwave irradiation, which is hitherto unreported in the literature, and all the results were best executed. The structural correlation of the synthesized bipodal 1,4-DHP **13** with nifedipine (vital drug in treatment of angina and hypertension) can be seen in Fig. 2.

Scheme 1. Retrosynthetic analysis approach for bipodal 1,4-DHPs.



Scheme 2. Synthetic scheme for bipodal *p*-substituted 1,4-DHPs **7–8**.

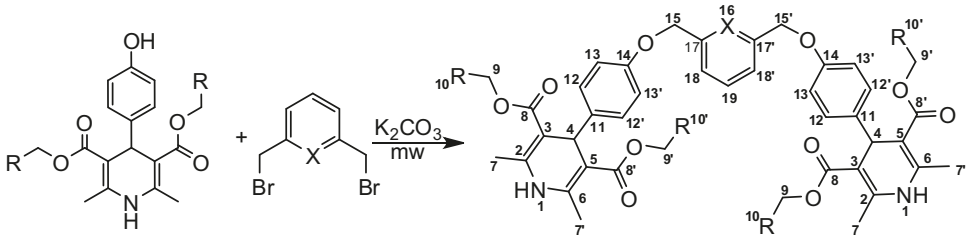


Results and discussion

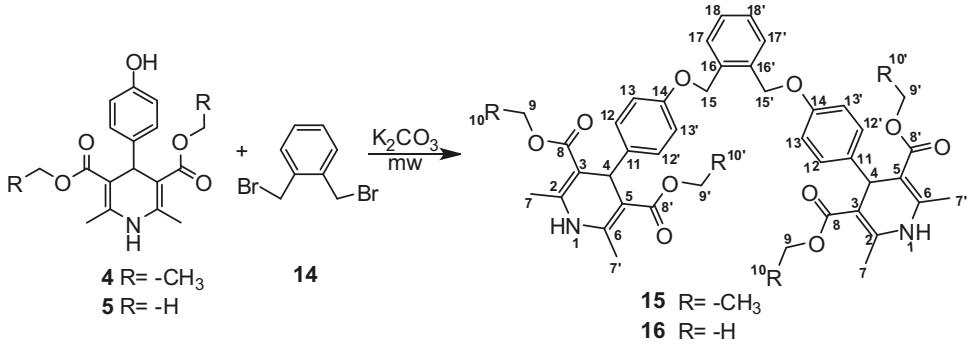
As part of the continuing interest in the synthesis of 1,4-DHP nucleus[17–20] and heterocyclic compounds bearing bipodal and tripodal moieties,[21–23] we synthesized novel bipodal, tripodal, and tetrapodal 1,4-DHPs by the reaction of monofunctional 1,4-DHP (**4, 5**) with different alkylating agents by using powdered K_2CO_3 as mild base (Schemes 2–6).

The two possible retro synthetic analysis approaches, Path-A and Path-B for bipodal 1,4-DHPs, are given in Scheme 1. In case of Path-A, as a part of a first step, the desired 1,4-DHPs (**4, 5**) have to be synthesized, which may then be reacted with di-bromo, tri-bromo, or tetra-bromo benzenes to give the desired polypodals by using a mild base. Alternatively, this can also be achieved via Path-B, where bis, tris, and tetrakis aldehydes have to be synthesized in a first step using di-bromo, tri-bromo, or tetra-bromo benzenes with *p*-hydroxybenzaldehyde, which can further be reacted with β-ketoester and ammonium acetate to give the desired polypodals, but large amounts of di-bromo, tri-bromo, and tetra-bromo benzenes are needed to carry out the first step, which is a costlier approach. So, Path-A was chosen for convenience, where a mixture of *p*-hydroxy benzaldehyde, β-ketoester, and ammonium acetate in ethanol were heated to give the desired 1,4-DHPs (**4, 5**) in a first step (Table 1). The structure of the products **4** and **5** have been characterized using ^{1}H NMR and HRMS data. The melting point, retention factor, R_f (the retention factor value of the synthesized sample was compared with that of the sample commercially sourced from Sigma-Aldrich), and spectral data were found to be in accord with the literature.[15,16]

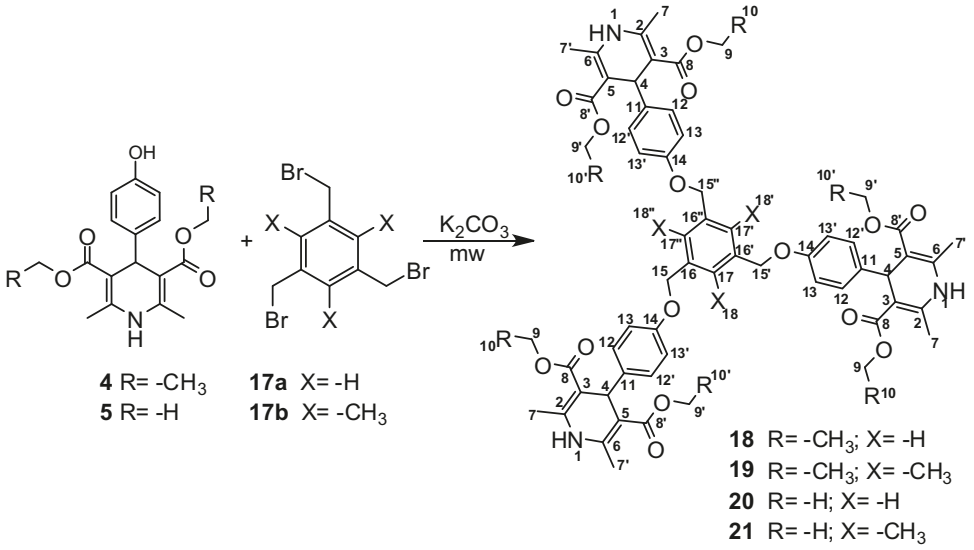
Scheme 3. Synthetic scheme for bipodal *m*-substituted 1,4-DHPs **10–13**.



Scheme 4. Synthetic scheme for bipodal *o*-substituted 1,4-DHPs **15–16**.



Scheme 5. Synthetic scheme for tripodal 1,4-DHPs **18–21**.



The compounds **4, 5** were converted into the desired polypodals by reacting it with di-bromo, tri-bromo, and tetra-bromo benzenes using powdered K_2CO_3/Na_2CO_3 as mild base. Initially the reaction was carried by using sodium hydride/THF, which promoted the reaction but with lowered yields (Method-A). This is because of the strong basic nature of NaH, which allows the maximum reactivity of –OH, –NH, and esters over 1,4-DHP towards **6**, resulting in undesired side products, which in turn effect the yield of the final product. This led us to quantitatively investigate an efficient approach to synthesize **7** and its derivatives. The use of powdered Na_2CO_3 or K_2CO_3 in DMF at controlled temperature (60 °C) lead to the formation of **7** and its subsequent derivatives very smoothly.

In the case of ethoxy substituent, a maximum yield of 67% was achieved for the bipodal para isomer **7**, and the other two meta substituted bipodal molecules **10** and **11** showed closely adjusted yields of 19% and 67%, respectively (Table 2). A yield of 10% was achieved for bipodal ortho isomer **15**, whereas the tripodal **18** and **19** showed yields of 67% and 50%, respectively. A yield of 49% was achieved for tetrapodal **23**. In the case of methoxy substituent, a maximum yield of 72% was achieved for the bipodal para isomer **8**, and the other two meta substituted bipodal molecules **12** and **13**

Scheme 6. Synthetic scheme for tetrapodal 1,4-DHPs **23–24**.

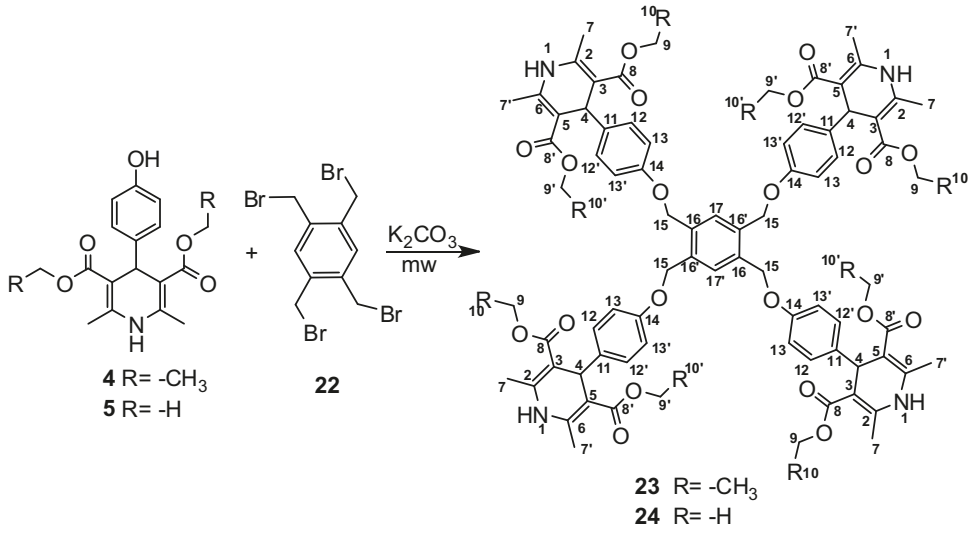
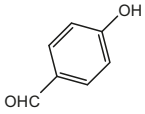
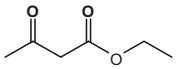
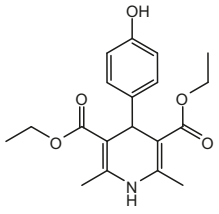
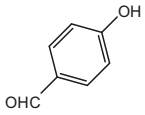
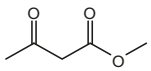
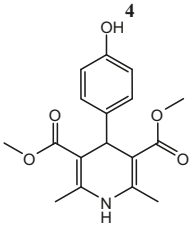


Table 1. Reaction of *p*-hydroxybenzaldehyde, ammonium acetate and β-ketoester leading to monopodal 1,4-DHPs.

				Mp (°C)	
Entry	Aldehyde	Ester	Product	Found	Reported
1			 **4**	228–230	230–232[17]
2			 **5**	230–232	231–233[18]

showed closely adjusted yields of 64% and 59%, respectively. A yield of 52% was achieved for the bipodal ortho isomer **16**, whereas tripodal **20** and **21** showed 69% and 63% yield, respectively. A yield of 54% was achieved for tetrapodal **24**. The marked differentiation in yields was expected because of a high steric hindrance over the molecule, especially for **10** and **15**. Better results were observed in powdered Na_2CO_3 or K_2CO_3 over the granular forms because of the larger surface area, which allows maximum reactivity of the alkylating agent towards hetero atoms.

The reaction was expected to proceed via a S_N2 mechanism. The use of elevated temperatures may produce higher impurity levels, which is consistent with the carbocation mechanism. The stronger activation may result in faster generation of carbocation and has a propensity to undergo side reactions. Thus, we are confined to carry the reactions under controlled temperatures, typically at 60 °C using K_2CO_3 as mild base. Rather than changing the base and reaction temperature, we thought to change the methodology. Microwave-assisted synthesis of bipodal, tripodal, and tetrapodal 1,4-DHPs were also carried out to produce the reaction with better yield. Microwave irradiation of a mixture of diethyl or dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, alkylating agent, powdered K_2CO_3, and 5 to 6 drops of DMF, at 30% power, was applied for 12 min (six pulses each of 2 min), resulting in product formation with good purity and yield (Table 2). The synthesized compounds were subjected to LC-MS as crude to find the presence of mono-substituted products instead of bis, tris, and tetrakis substitutions. But it was very clear that the mono-substituted compounds were not found, and the unambiguous structural confinements for the synthesized compounds were drawn out with the help of 2D NMR (H-H COSY and C-H COSY).

Conclusion

In conclusion, the mono functional 1,4-DHPs served as building blocks for the construction of novel bipodal, tripodal, and tetrapodal 1,4-DHPs by conventional method and by

Table 2. Reaction of 1,4-DHP with alkylating agents in the presence of K_2CO_3 under conventional and solvent free microwave Irradiation.

				Yield (%)[a]	
Entry	Alkylating agent	1,4-DHP	Product	Conv.[b]	Mw[c]
1	α,α′-Dibromo-*p*-xylene **6**	**4**	**7**	67	81
2	α,α′-Dibromo-*p*-xylene **6**	**5**	**8**	72	87
3	α,α′-Dibromo-*m*-xylene **9a**	**4**	**10**	19	39
4	2,6-Bis(bromomethyl)pyridine **9b**	**4**	**11**	67	83
5	α,α′-Dibromo-*m*-xylene **9a**	**5**	**12**	64	80
6	2,6-Bis(bromomethyl)pyridine **9b**	**5**	**13**	59	78
7	α,α′-Dibromo-*o*-xylene **14**	**4**	**15**	10	31
8	α,α′-Dibromo-*o*-xylene **14**	**5**	**16**	52	71
9	1,3,5-Tris(bromomethyl)benzene **17a**	**4**	**18**	67	82
10	2,4,6-Tris(bromomethyl)mesitylene **17b**	**4**	**19**	50	77
11	1,3,5-Tris(bromomethyl)benzene **17a**	**5**	**20**	69	85
12	2,4,6-Tris(bromomethyl)mesitylene **17b**	**5**	**21**	63	79
13	1,2,4,5-Tetrakis(bromomethyl)benzene **22**	**4**	**23**	49	72
14	1,2,4,5-Tetrakis(bromomethyl)benzene **22**	**5**	**24**	54	80

[a]The yields refer to the isolated pure products.
[b]Reaction carried under conventional heating.
[c]Reaction carried under microwave irradiation.

microwave irradiation. The microwave mehtod exhibited several advantages over conventional heating by significantly reducing the reaction time and improving the reaction yield, owing to a specific non-thermal microwave effect. The methodology employed for this synthesis shows much scope not only for the synthesis of bipodal and tripodal 1,4-DHPs but also for tetrapodal moieties, which is not possible to do by the methods in the literature.

Experimental section

General

Solvents and reagents were commercially sourced and used without further purification, with the exception of THF, which was freshly distilled over sodium. Melting points were taken with a Elchem microprocessor-based DT apparatus in open capillary tubes and are corrected with benzoic acid. IR spectra were obtained on an Avatar-330 FTIR spectrophotometer (Thermo Nicolet) using KBr pellets, and only noteworthy absorption levels (reciprocal centimetres) are listed. The NMR spectra were recorded on a Bruker 300 and 500 MHz spectrometer, using TMS as internal standard (chemical shifts δ in ppm). Mass spectra were recorded on HRMS and LCMS by an Agilent 1200 series LC and Micromass zQ spectrometer. Microwave oven used is of synthetic microwave, CATA R with the maximum power of 700 W at 100% power level. All reactions were carried at 30% power level, which produces power of 210 W. Thin-layered chromatography (TLC) was performed on preparative plates of silica gel (s.d. fine). Visualization was made with an iodine chamber. Column chromatography was performed by using silica gel (60–120 mesh).

General procedure for synthesis of 1,4-DHPs (4, 5)

A mixture of *p*-hydroxybenzaldehyde (10 mmol, 1.0 equiv.), β-ketoester (20 mmol, 2.0 equiv.) and ammonium acetate (12 mmol, 1.2 equiv.) were heated for 15 min in the presence of ethanol (10 mL). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was left aside for the formation of product, filtered to remove the insoluble solids and then the filter cake was washed with diethyl ether. The solid was recrystallized from absolute ethanol to yield respective 1,4-dihydropyridine derivatives as a yellow solid.

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4)

Yellow solid (recrystallized from ethanol). R_f (pet. ether/EtOAc, 6:4) = 0.83. Mp 228–230 °C (Lit. 230–232 °C).[15] IR (KBr, cm^{-1}): 3345, 2981, 1662, 1486. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.5 Hz, 6H), 2.77 (s, 6H), 3.66–3.76 (q, J = 6.0 Hz, 4H), 4.49 (s, 1H), 6.30 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 7.60 (s, -NH, 1H), 8.27 (s, -OH, 1H). HRMS: *m/z* 345.1582 (M^+).

Dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5)

Yellow solid (recrystallized from ethanol). R_f (pet. ether/EtOAc, 6:4) = 0.8. Mp 230–232 °C (Lit. 231–233 °C).[16] IR (KBr, cm^{-1}): 3339, 3003, 2950, 1680, 1647, 1611. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.86 (s, 6H), 3.28 (s, 6H), 4.51 (s, 1H), 6.31 (d, J = 8.0 Hz, 2H), 6.70 (d, J = 8.0 Hz, 2H), 7.73 (s, -NH, 1H), 8.35 (s, -OH, 1H). HRMS: *m/z* 317.1270 (M^+).

Representative procedure for preparation of bipodal, tripodal, and tetrapodal 1,4-DHP derivatives

Method A (Classical method using NaH)

To a slurry of 22 mmol of NaH in 20 mL of dry THF in a three-necked round bottom flask under an N_2 atmosphere, 2 mmol of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4**) dissolved in 30 mL of dry THF was added dropwise and the mixture was refluxed for 1 h. α,α′-Dibromo-*p*-xylene (**6**) (1.1 mmol) was dissolved in 100 mL of THF and added to the above reaction mixture

with stirring for 12 h and then at reflux for a further 12 h. The reaction mixture quenched with aq NH_4Cl solution to remove excess NaH, and THF was removed under reduced pressure. The residue was extracted with $CHCl_3$ and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel, using pet. ether/EtOAc (8:2) as eluent to give tetraethyl 4,4′-(4,4′-(1,4-phenylenebis (methylene)) bis(oxy)bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (**7**) in 32% yield.

Method B (Classical method using powdered K_2CO_3)

To a suspension of 1.05 equiv. of diethyl or dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4** or **5**) in 10 volumes of dry DMF, 3.0 equiv. of powdered K_2CO_3 was added, stirred well for 15 min at just above room temperature (40 °C). To that, alkylating agent (0.5 equiv. in case of **6**, **9a**, **9b**, and **14**; 0.333 equiv. in case of **17a** and **17b;**; 0.25 equiv. in case of **22**) dissolved in minimum amount of DMF was added drop wise for 1 h with stirring at 50 °C. After the complete addition, the reaction mixture heated at 60 °C with stirring for 48 h. The completion of reaction was monitored by TLC. Then the reaction mixture was allowed cool to room temperature, filtered to remove the insoluble solids, and then the filter cake was washed with DMF. Excess solvents were removed under reduced pressure and then quenched with ice-cold water; the obtained crude products were purified by column chromatography (60–120 mesh), which produced the products in good to moderate yields.

Method C (Microwave irradiation)

A mixture of 1.05 equiv. of diethyl or dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4** or **5**), alkylating agent (0.5 equiv. in the case of **6**, **9a**, **9b**, and **14**; 0.333 equiv. in case of **17a** and **17b;**; 0.25 equiv. in case of **22**), 3.0 equiv. of powdered K_2CO_3, and 5 to 6 drops of DMF, which acts as homogenizer were finely ground. Microwave irradiation at 30% power was applied for 12 min (six pulses each of 2 min). The progress of the reaction was followed by TLC. After the completion of reaction, the reaction mixture poured into ice-cold water; the obtained solid was filtered, washed with water, and air dried to afford the desired product. The obtained crude products were purified by column chromatography on silica gel (60–120 mesh), which obtained the products in good to moderate yields.

Tetraethyl 4,4′-(4,4′-(1,4-phenylenebis(methylene))bis(oxy) bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (7)

Pale yellow solid (recrystallized from pet. ether/EtOAc, 8:2). Mp 102–104 °C. IR (KBr, cm^{-1}): 3337, 3097, 2979, 2929, 1678, 1505. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (t, J = 6 Hz, 12 protons at H-10, 10′), 2.32 (s, 12 protons at H-7, 7′), 4.09 (q, 8 protons at H-9, 9′), 4.92 (s, 2 protons at H-4), 5.00 (s, 4 protons at H-15, 15′), 5.61 (bs, 2protons at -NH), 6.81 (d, J = 9 Hz, 4 arom. protons at H-13, 13′), 7.19 (d, J = 6 Hz, 4 arom. protons at H-12, 12′), 7.41 (s, 4 arom. protons at H-17, 17′). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 14.28 (C-10, 10′), 19.50 (C-7, 7′), 38.72 (C-4), 59.72 (C-9, 9′), 69.66 (C-15, 15′), 104.17 (C-3, 5), 114.09 (C-13, 13′), 127.69 (C-17, 17′), 128.98 (C-12, 12′), 136.93 (C-16, 16′), 140.67 (C-11), 143.85 (C-2, 6), 157.10 (C-14), 167.79 (C-8, 8′). LC-MS: m/z 793.2 (M+1). Anal. calcd. for $C_{46}H_{52}N_2O_{10}$: C, 69.68; H, 6.61; N, 3.53. Found: C, 69.50; H, 6.81; N, 3.45.

Tetramethyl 4,4′-(4,4′-(1,4-phenylenebis(methylene))bis (oxy)bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (8)

White solid (recrystallized from diethyl ether/methanol, 5:5). Mp 282–284 °C; IR (KBr, cm^{-1}): 3344, 2947, 1701, 1650. ^{1}H-NMR (500 MHz, DMSO-d6) δ_H: 2.25 (s, 12 protons at H-7, 7′), 3.32 (s, 12 protons at H-9, 9′), 4.82 (s, 2 protons at H-4), 5.02 (s, 4 protons at H-15, 15′), 6.84 (d, J = 10 Hz, 4 arom.protons at H-13, 13′), 7.03 (d, J = 8.5 Hz, 4 arom. protons at H-12, 12′), 7.42 (s, 4 arom. protons at H-17, 17′), 8.82 (s, 2protons at -NH). LC-MS: m/z 735.4 (M–1), 759.4 (M+Na). Anal. calcd. for $C_{42}H_{44}N_2O_{10}$: C, 68.46; H, 6.02; N, 3.80. Found: C, 69.16; H, 5.91; N, 3.77.

Tetraethyl 4,4′-(4,4′-(1,3-phenylenebis(methylene))bis(oxy) bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (10)

Pale yellow solid (recrystallized from pet. ether/EtOAc, 8:2). Mp 106–108 °C. IR (KBr, cm^{-1}): 3341, 3091, 2982, 1697, 1647. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (t, J = 7.05 Hz, 12 protons at H-10, 10′), 2.32 (s, 12 protons at H-7, 7′), 4.09 (q, 8 protons at H-9, 9′), 4.93 (s, 2 protons at H-4), 5.00 (s, 4 protons at H-15, 15′), 5.64 (bs, 2 protons at -NH), 6.81 (d, J = 8.4 Hz, 4 arom. protons at H-13, 13′), 7.14–7.45 (m, 8 arom. protons at H-12, 12′, 16, 18, 18′, 19). LC-MS: m/z 793.3 (M+1). Anal. calcd. for $C_{46}H_{52}N_2O_{10}$: C, 69.68; H, 6.61; N, 3.53. Found: C, 70.24; H, 6.24; N, 3.40.

Tetraethyl 4,4′-(4,4′-(pyridine-2,6-diylbis(methylene))bis (oxy)bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (11)

White solid (recrystallized from pet ether/EtOAc, 7.5:2.5). Mp 100–102 °C. IR (KBr, cm^{-1}): 3337, 3096, 2979, 1693, 1608. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.21 (t, J = 7.05 Hz, 12 protons at H-10, 10′), 2.32 (s, 12 protons at H-7, 7′), 4.08 (q, 8 protons at H-9, 9′), 4.93 (s, 2 protons at H-4), 5.14 (s, 4 protons at H-15, 15′), 5.69 (bs, 2protons at -NH), 6.82 (d, J = 8.7 Hz, 4 arom. protons at H-13, 13′), 7.20 (d, J = 8.4 Hz, 4 arom. protons at H-12, 12′), 7.43 (d, J = 7.8 Hz, 2 arom. protons at H-18, 18′), 7.71 (t, J = 7.5 Hz, 1 arom. proton at H-19). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 14.23 (C-10, 10′), 19.56 (C-7, 7′), 38.72 (C-4), 59.67 (C-9, 9′), 70.43 (C-15, 15′), 104.27 (C-3, 5), 114.04 (C-13, 13′), 119.99 (C-18, 18′), 129.03 (C-12, 12′), 140.17 (C-19), 140.79 (C-11), 143.58 (C-2, 6), 156.67 (C-17, 17′), 156.95 (C-14) 167.65 (C-8, 8′). LC-MS: m/z 792.5 (M–1), 816.4 (M+Na). Anal. calcd. for $C_{45}H_{51}N_3O_{10}$: C, 68.08; H, 6.47; N, 5.29. Found: C, 68.64; H, 6.90; N, 5.18.

Tetramethyl 4,4′-(4,4′-(1,3-phenylenebis(methylene))bis (oxy)bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (12)

White solid (recrystallized from pet. ether/EtOAc, 8:2). Mp 116–118 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.30 (s, 12 protons at H-7, 7′), 3.63 (s, 12 protons at H-9, 9′), 4.93 (s, 2 protons at H-4), 4.98 (s, 4 protons at H-15, 15′), 5.84

(bs, 2protons at -NH), 6.80 (d, J = 6.9 Hz, 4 arom. protons at H-13, 13′), 7.16 (d, J = 8.4 Hz, 4 arom. protons at H-12, 12′), 7.25–7.47 (m, 4 arom. protons at H-16, 18, 18′, 19). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 19.52 (C-7, 7′), 38.35 (C-4), 50.98 (C-9, 9′), 69.77 (C-15, 15′, 103.94 (C-3, 5), 114.28 (C-13, 13′), 126.49 (C-16), 126.96 (C-18, 18′),128.59 (C-12, 12′), 128.77 (C-19), 137.57 (C-11), 140.20 (C-17, 17′), 144.07 (C-2, 6), 157.16 (C-14), 168.11 (C-8, 8′). LC-MS: m/z 735.5 (M–1). Anal. calcd. for $C_{42}H_{44}N_2O_{10}$: C, 68.46; H, 6.02; N, 3.80. Found: C, 69.47; H, 5.70; N, 4.05.

Tetramethyl 4,4′-(4,4′-(pyridine-2,6-diylbis(methylene))bis (oxy)bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (13)

White solid (recrystallized from pet. ether/EtOAc, 8:2). Mp 118–120 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.31 (s, 12 protons at H-7, 7′), 3.63 (s, 12 protons at H-9, 9′), 4.93 (s, 2 protons at H-4), 5.13 (s, 4 protons at H-15, 15′), 5.75 (bs, 2protons at -NH), 6.81 (d, J = 8.4 Hz, 4 arom. protons at H-13, 13′), 7.16 (d, J = 8.1 Hz, 4 arom. protons at H-12, 12′), 7.42 (d, J = 7.8 Hz, 2 arom. protons at H-18, 18′), 7.70 (t, J = 7.5 Hz, 1 arom. proton at H-19). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 19.55 (C-7, 7′), 38.35 (C-4), 50.97 (C-9, 9′), 70.42 (C-15, 15′), 103.93 (C-3, 5), 114.23 (C-13, 13′), 119.99 (C-18, 18′), 128.65 (C-12, 12′), 133.99 (C-11, 11′), 135.73 (C-19), 143.99 (C-2, 6), 154.85 (C-17, 17′), 156.75 (C-14), 168.06 (C-8, 8′). LC-MS: m/z 736.5 (M–1); Anal. calcd. for $C_{41}H_{43}N_3O_{10}$: C, 66.72; H, 5.87; N, 5.70. Found: C, 66.61; H, 5.58; N, 5.46.

Tetraethyl 4,4′-(4,4′-(1,2-phenylenebis(methylene))bis(oxy) bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (15)

Yellow solid (recrystallized from pet. ether/EtOAc, 8:2). Mp 112–114 °C. IR (KBr, cm^{-1}): 3347, 2986, 1661, 1635. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (t, J = 6.9 Hz, 12 protons at H-10, 10′), 2.33 (s, 12 protons at H-7, 7′), 4.09 (q, 8 protons at H-9, 9′), 4.84 (s, 2 protons at H-4), 4.92 (s, 4 protons at H-15, 15′), 5.54 (bs, 2 protons at -NH), 6.66 (d, J = 8.4 Hz, 4 arom. protons at H-13, 13′), 7.14 (d, J = 8.4 Hz, 4 arom. protons at H-12, 12′), 7.26–7.28 (m, 4 arom. protons at H-17, 17′, 18, 18′). HRMS: m/z 792.3620 (M$^+$); Anal. calcd. for $C_{46}H_{52}N_2O_{10}$: C, 69.68; H, 6.61; N, 3.53. Found: C, 69.26; H, 6.46; N, 3.47.

Tetramethyl 4,4′-(4,4′-(1,2-phenylenebis(methylene))bis (oxy)bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (16)

Yellow solid (recrystallized from pet. ether/EtOAc, 8:2). Mp 134–136 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.31 (s, 12 protons at H-7, 7′), 3.64 (s, 12 protons at H-9, 9′), 4.94 (s, 2 protons at H-4), 5.08 (s, 4 protons at H-15, 15′), 5.97 (bs, 2 protons at -NH), 6.81 (d, J = 8.4 Hz, 4 arom. protons at H-13, 13′), 7.17 (d, J = 8.4 Hz, 4 arom. protons at H-12, 12′), 7.34–7.49 (m, 4 arom. protons at H-17, 17′, 18, 18′). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 19.48 (C-7, 7′), 38.30 (C-4), 50.99 (C-9, 9′), 67.72 (C-15, 15′), 103.86 (C-3, 5), 114.26 (C-13, 13′), 128.27 (C-18, 18′), 128.57 (C-12, 12′), 128.78 (C-17, 17′), 135.24 (C-16, 16′), 140.28 (C-11, 11′), 144.20 (C-2, 6), 157.03 (C-14), 168.14 (C-8, 8′). LC-MS: m/z 735.1 (M–1). Anal. calcd. for $C_{42}H_{44}N_2O_{10}$: C, 68.46; H, 6.02; N, 3.80. Found: C, 69.47; H, 5.67; N, 3.66.

Hexaethyl 4,4′,4″-(4,4′,4″-(benzene-1,3,5-triyltris (methylene))tris(oxy)tris(benzene-4,1-diyl))tris(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (18)

White solid (recrystallized from pet. ether/EtOAc, 7:3). Mp 124–126 °C. IR (KBr, cm^{-1}): 3336, 3096, 2978, 2932, 1677. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.23 (18 protons at H-10, 10′), 2.31 (s, 18 protons at H-7, 7′), 4.09 (12 protons at H-9, 9′), 4.99 (s, 9 protons at H-4, 15, 15′, 15″), 6.34 (bs, 3 protons at -NH), 6.82–7.41 (m, 15 arom. protons at H-12, 12′, 13, 13′, 17, 17′, 17″). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 14.28 (C-10, 10′), 19.42 (C-7, 7′), 38.69 (C-4), 59.72 (C-9, 9′), 69.67 (C-15, 15′, 15″), 104.04 (C-3, 5), 114.13 (C-13, 13′), 125.98 (C-17, 17′, 17″), 128.94 (C-12, 12′), 137.95 (C-11), 140.72 (C-16, 16′, 16″), 144.00 (C-2, 6), 157.03 (C-14), 167.82 (C-8, 8′). HRMS: m/z 1149.5192 (M$^+$). Anal. calcd. for $C_{66}H_{75}N_3O_{15}$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.43; H, 6.86; N, 3.58.

Hexaethyl 4,4′,4″-(4,4′,4″-(2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene)tris(oxy)tris (benzene-4,1-diyl))tris (2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (19)

White solid (recrystallized from pet. ether/EtOAc, 6.5:4.5). Mp 120–122 °C. IR (KBr, cm^{-1}): 3338, 3096, 2979, 1678, 1607. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (t, J = 9.4 Hz, 18 protons at H-10, 10′), 2.30 (s, 18 protons at H-7, 7′), 2.35 (s, 9 protons at H-18, 18′, 18″), 4.08 (bs,12 protons at H-9, 9′), 4.93 (s, 3 protons at H-4), 4.98 (s, 6 protons at H-15, 15′, 15″), 5.94 (bs, 3 protons at -NH), 6.83 (d, J = 6.8 Hz, 6 arom. protons at H-13, 13′), 7.20 (d, J = 6.8 Hz, 6 arom. protons at H-12, 12′). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 15.62 (C-10, 10′), 15.99 (C-18, 18′, 18″), 19.27 (C-7, 7′), 38.60 (C-4), 59.63 (C-9, 9′), 64.67 (C-15, 15′, 15″), 103.96 (C-3, 5), 113.79 (C-13, 13′), 128.78 (C-12, 12′), 131.37 (C-17, 17′, 17″), 139.04 (C-16, 16′, 16″), 140.52 (C-11),143.96 (C-2, 6), 157.34 (C-14), 167.76 (C-8, 8′). MS: m/z 1190.54 (M–1). Anal. calcd. for $C_{69}H_{81}N_3O_{15}$: C, 69.50; H, 6.85; N, 3.52. Found: C, 68.89; H, 7.00; N, 3.44.

Hexamethyl 4,4′,4″-(4,4′,4″-(benzene-1,3,5-triyltris (methylene))tris(oxy)tris(benzene-4,1-diyl))tris(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (20)

Yellow solid (recrystallized from pet. ether/EtOAc, 6:4). Mp 140–142 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.31 (s, 18 protons at H-7, 7′), 3.63 (s, 18 protons at H-9, 9′), 4.94 (s, 3 protons at H-4), 4.98 (s, 6 protons at H-15, 15′, 15″), 6.01 (bs, 3 protons at -NH), 6.79 (d, J = 8.4 Hz, 6 arom. protons at H-13, 13′), 7.17 (d, J = 8.1 Hz, 6 arom. protons at H-12, 12′), 7.38 (s, 3 arom. protons at H-17, 17′, 17″). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 19.46 (C-7, 7′), 38.31 (C-4), 50.98 (C-9, 9′), 69.64 (C-15, 15′, 15″), 103.82 (C-3, 5), 114.32 (C-13, 13′), 125.90 (C-17, 17′, 17″), 128.57 (C-12, 12′), 137.96 (C-11), 140.25 (C-16, 16′, 16″), 144.21 (C-2, 6), 157.08 (C-14), 168.15 (C-8, 8′). HRMS: m/z 1065.4260

(M^+). Anal. calcd. for $C_{60}H_{63}N_3O_{15}$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.71; H, 6.05; N, 3.86.

Hexamethyl 4,4′,4″-(4,4′,4″-(2,4,6-trimethylbenzene-1,3,5triyl)tris(methylene)tris(oxy)tris(benzene-4,1-diyl))tris (2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate)(21)

Yellow solid (recrystallized from pet. ether/EtOAc, 6:4). Mp 138–140 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.32 (s, 18 protons at H-7,7′), 2.37 (s, 9 protons at H-18, 18′, 18″), 3.65 (s, 18 protons at H-9, 9′), 4.96 (s, 3 protons at H-4), 5.00 (s, 6 protons at H-15, 15′, 15″), 5.91 (bs, 3 protons at -NH), 6.86 (d, J = 7.5 Hz, 6 arom. protons at H-13, 13′), 7.21 (d, J = 6.9 Hz, 6 arom. protons at H-12, 12′). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 15.79 (C-18, 18′, 18″), 19.50 (C-7, 7′), 38.36 (C-4), 51.00 (C-9, 9′), 64.67 (C-15, 15′, 15″), 103.94 (C-3, 5), 114.00 (C-13, 13′), 128.55 (C-12, 12′), 131.76 (C-17, 17′, 17″), 139.16 (C-16, 16′, 16″), 140.12 (C-11), 144.12 (C-2, 6), 157.46 (C-14), 168.13 (C-8, 8′). HRMS: *m/z* 1107.4721 (M^+). Anal. calcd. for $C_{63}H_{69}N_3O_{15}$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.88; H, 6.12; N, 3.68.

Octaethyl 4,4′,4″,4‴-(4,4′,4″,4‴-(benzene-1,2,4,5-tetrayltetrakis(methylene))tetrakis(oxy) tetrakis(benzene-4,1-diyl))tetrakis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (23)

White solid (recrystallized from pet. ether/EtOAc, 6:4). Mp 174–176 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 1.21 (t, J = 6 Hz, 24 protons at H-10, 10′), 2.31 (s, 24 protons at H-7, 7′), 4.08 (q, 16 protons at H-9, 9′), 4.92 (s, 4 protons at H-4), 5.07 (s, 8 protons at H-15, 15′, 15″, 15‴), 5.90 (bs, 4 protons at -NH), 6.79 (d, J = 6 Hz, 8 arom. protons at H-13, 13′), 7.18 (d, J = 7.2 Hz, 8 arom. protons at H-12, 12′), 7.61 (s, 2 arom. protons at H-17, 17′). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 14.25 (C-10, 10′), 19.50 (C-7, 7′), 38.60 (C-4), 59.69 (C-9, 9′), 67.52 (C-15, 15′, 15″, 15‴), 104.14 (C-3, 5), 114.12 (C-13, 13′), 127.51 (C-17, 17′), 128.91 (C-12, 12′), 136.92 (C-11), 140.68 (C-16, 16′, 16″, 16‴), 143.81 (C-2, 6), 156.89 (C-14), 167.70 (C-8, 8′). MS: *m/z* 1505.60 (M–1). Anal. calcd. for $C_{86}H_{98}N_4O_{20}$: C, 68.51; H, 6.55; N, 3.72. Found: C, 69.32; H, 6.70; N, 3.64.

Octamethyl 4,4′,4″,4‴-(4,4′,4″,4‴-(benzene-1,2,4,5-tetrayltetrakis(methylene))tetrakis(oxy) tetrakis(benzene-4,1-diyl))tetrakis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (24)

White solid (recrystallized from pet. ether/EtOAc, 6:4). Mp 160–162 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.30 (s, 24 protons at H-7, 7′), 3.62 (s, 24 protons at H-9, 9′), 4.93 (s, 4 protons at H-4), 5.05 (s, 8 protons at H-15, 15′, 15″, 15‴), 6.11 (bs, 4 protons at -NH), 6.77 (d, J = 8.1 Hz, 8 arom. protons at H-13, 13′), 7.14 (d, J = 8.1 Hz, 8 arom. protons at H-12, 12′), 7.58 (s, 2 arom. protons at H-17, 17′). ^{13}C-NMR (75MHz, $CDCl_3$) δ_C: 19.45 (C-7, 7′), 38.27 (C-4), 51.00 (C-9, 9′), 67.51 (C-15, 15′, 15″, 15‴), 103.77 (C-3, 5), 114.33 (C-13, 13′), 124.92 (C-17, 17′, 17″, 17‴), 128.55 (C-12, 12′), 135.26 (C-11), 140.32 (C-16, 16′, 16″, 16‴), 144.32 (C-2, 6), 156.94 (C-14), 168.17 (C-8, 8′). MS: *m/z* 1393.53 (M–1). Anal. calcd. for $C_{78}H_{82}N_4O_{20}$: C, 67.13; H, 5.92; N, 4.01. Found: C, 67.86; H, 5.65; N, 3.94.

Supplementary data

Supplementary data for this article are available on the journal Web site (www.nrcresearchpres.com/cjc).

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