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Ionic liquid phase technology supported the three component synthesis of Hantzsch 1,4-dihydropyridines and Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones under microwave dielectric heating

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Abstract—A microwave dielectric heating assisted liquid phase synthesis of 1,4-dihydropyridines, 3,4-dihydropyrimidin-2(1*H*)-ones, pyridines and polyhydroquinolines using task-specific ionic liquid as a soluble support was described. The efficiency of the ionic liquid phase organic synthesis (IoLiPOS) methodology was demonstrated by using a one-pot three component condensation. The structure of the intermediates in each step was verified routinely by spectroscopic analysis and, after cleavage the target compounds were obtained in good yields and high purities.

1. Introduction

Faced with the increasing demand of novel drug targets, there is considerable current interest to accelerate the technologies associated with combinatorial chemistry and high-throughput synthesis.[1] The initial efforts were focused on the use of automated solid phase organic synthesis (SPOS) based on the original Merrifield method for the preparation of peptides[2] and oligonucleotides, by taking advantage of simple filtration techniques to wash off the excess reagents and by-products from the desired polymer bound product. However, one disadvantage of this methodology compared to standard solution-phase synthesis is the comparatively long reaction times that are usually required owing to the heterogeneous reaction conditions involving insoluble polymer supports and the difficulties to monitor reaction progress. The use of these cross-linked polystyrene based resins[3] is important due to their good stability, high compatibility and good swelling characteristic with non-polar solvents.[4] Nevertheless, these resins fail when polar solvents are needed due to hindered accessibility to the reactive sites.[5] Polystyrene can be modified by grafting poly(ethyleneglycol) to the hydrophobic core to produce a polymer that swells in both non-polar and polar solvents.[6] Among these PEG-grafted polystyrene supports (PS-*g*-PEG), TentaGel has been used extensively in solid phase synthesis because of the mechanical stability of the beads and swelling properties in organic and aqueous media.[7] ArgoGel displays a similar characteristic to TentaGel yet swells more extensively because of a higher PEG content.[8] Liquid phase combinatorial synthesis offers several advantages: the large excess of reagents typically used in solid-supported synthesis is normally not required in liquid-phase organic synthesis (LPOS), reactions may be carried out in homogeneous solution and purification is possible after each step.[9] The chemistry of PS-*g*-PEG and PEG-resins is not limited by the hydroxyl group (sometimes its weak nucleophilicity restricts the resin from wide application), and conversion of the hydroxyl group is possible by using standard methods.[10]

The utility of microwave irradiation (mw) to carry out organic reactions has now become a regular feature. This is evident from the increasing number of reviews and books[11]

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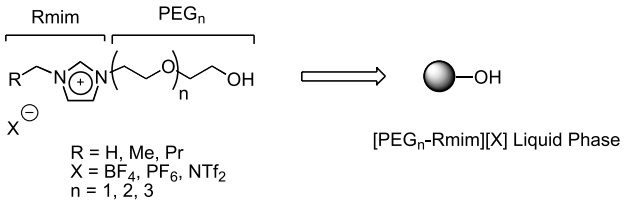


Figure 1. PEG-ionic liquid matrices used for ionic liquid phase organic synthesis (IoLiPOS).

published on the use of microwave technology for carrying out organic reactions. The main benefits of performing reactions under microwave irradiation conditions are the significant rate-enhancements and the higher product yields that can be observed. It is clear that the application of microwave technology to rapid synthesis of potential biological molecules on liquid phases or hybrid polymers and solid phases is a useful tool for the combinatorial and/or medicinal community, for whom reaction speed is of great importance.[12]

Recently, we have shown that the use of task-specific ionic liquids[13] (TSILs) on which poly(ethyleneglycol) units are grafted (Fig. 1), can be used as alternatives to classical soluble polymeric matrices in combinatorial chemistry.[14] This new class of soluble support used in ionic liquid phase organic synthesis (IoLiPOS) methodology was valided by examples in various chemistries.[15] An attracting feature of ionic liquid phases is that their solubilities can be turned readily, so they can phase separate from organic as well as aqueous media, depending on the choice of cation and anions. An illustration of ionic liquid phase supported synthesis is given in Figure 2. After the first reactant is anchored to an ionic liquid phase (ILP), the excess reagents and byproducts in subsequent reactions can be removed easily by simple solvent washing. The advantages offered by the use of PEG-ionic liquid phases (PEG-ILPs) are: (i) the possibility of homogeneous reaction, (ii) the compatibility to standard analytical methods, (iii) the high loading capacity, (iv) the routine product isolation by simple extraction and washings, (v) the high absorption of microwave energy by which the reaction rate is accelerated remarkably. In connection with our research program on exploitation of the PEG-ILPs as tools in liquid phase organic synthesis (LPOS), we choose to explore now the 1,4-dihydropyridines and 1,4-dihydropyrimidines as new heterocyclic scaffolds on PEG-ILPs. Hantzsch 3,4-dihydropyridines[16] and Biginelli 1,4-dihydropyrimidines[17] are a biological, medicinally and synthetically important class of compounds in the field of drugs and pharmaceuticals.

2. Results and discussion

For this study (Scheme 1), we have chosen to examine the

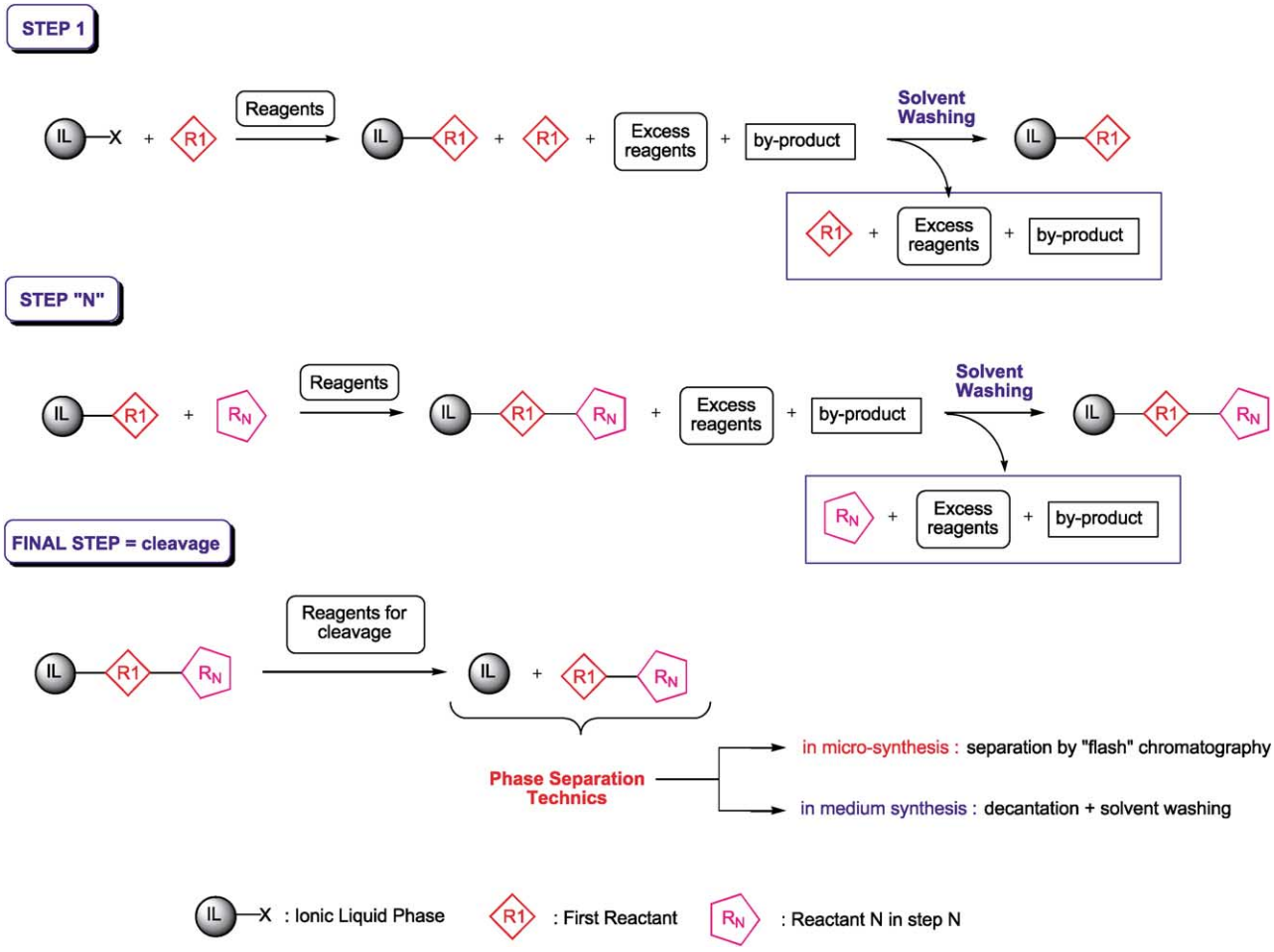
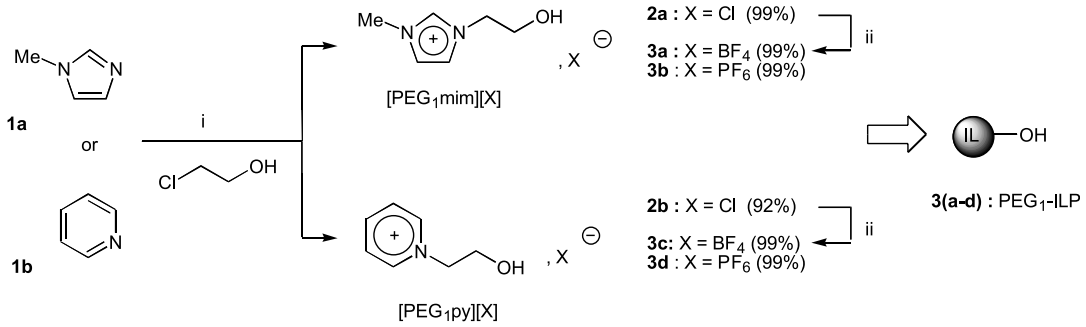


Figure 2. General concept of ionic liquid phase organic synthesis (IoLiPOS).



Scheme 1. Reagents and reactions conditions: (i) chloroethanol (1 equiv), mw: 180 °C (power level: 20%, 60 W), 10 min, N_2; (ii) NH_4BF_4 or KPF_6 (1 equiv), MeCN, 80 °C, 24 h.

Table 1. Starting ILPs used and prepared

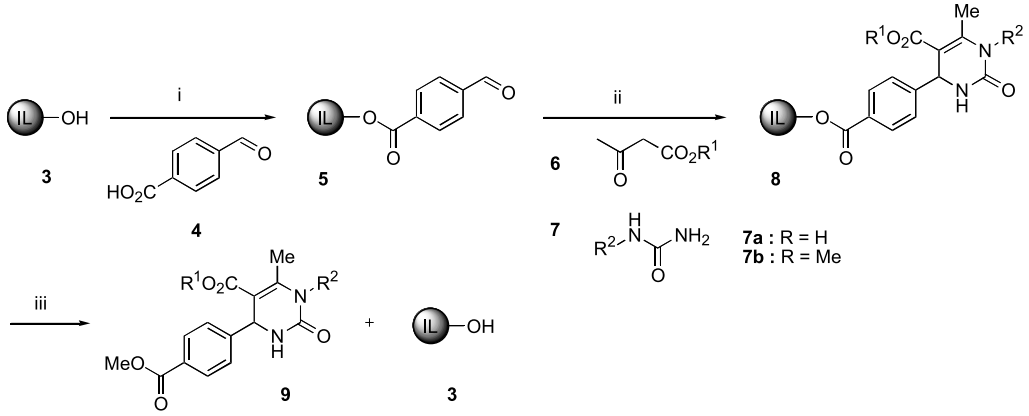
Product	Cation	Anion	Yield (%)[a]
2a	[PEG_1mim]	Cl	99
3a	[PEG_1mim]	BF_4	99
3b	[PEG_1mim]	PF_6	99
2b	[PEG_1py]	Cl	92
3c	[PEG_1py]	BF_4	99
3d	[PEG_1py]	PF_6	99

[a] Yield of isolated product.

chemical properties of the respective 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate **3a** or hexafluoroborate **3b** (**3a**: [PEG_1mim][BF_4], **3b**: [PEG_1mim][PF_6]) and *N*-(2-hydroxyethyl)pyridinium tetrafluoroborate **3c** or hexafluoroborate **3d** (**3c**: [PEG_1py][BF_4], **3d**: [PEG_1py][PF_6]) in IoLiPOS methodology. The starting PEG-ILPs **3**(**a**,**b**) were synthesized according to our previous method[18] (Table 1).

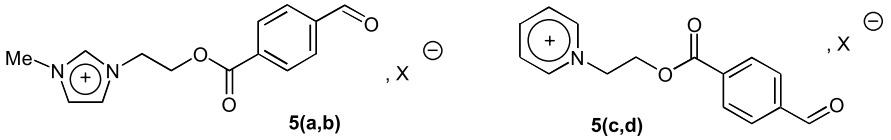
Esterification of PEG-ILPs **3**(**a**–**d**) with 4-formylbenzoic acid **4** were realised in dry MeCN with dicyclohexylcarbodiimide[19] (DCC) and 5% of dimethylamino pyridine[20] (DMAP) as catalyst and afforded the functionalized ILP bound aldehydes **5** in high yields (Scheme 2). During the work-up, insoluble dicyclohexyl urea (DCHU) was easily removed by filtration to ensure the final purity of aldehydes **5** and the resulting ILPs **5** were washed with AcOEt (1:5 w/v). The structure of ILPs **5** was ascertained by mass spectrometry and proton NMR, confirming that the major compound is the expected aldehydes **5** (Table 2).

With the desired ILP bound aldehydes **5** in hand, we have



Scheme 2. Reagents and reactions conditions: (i) DCC (1 equiv), DMAP (5%), dry MeCN, rt, 24 h; (ii) **6** (1 equiv), **7** (3 equiv), concd HCl (0.5%), mw: 120 °C (power level: 50%, 150 W), 10 min; (iii) MeONa (1 equiv), MeOH, reflux, 18 h.

Table 2. Results for the preparation of aldehydes **5**(**a**–**d**) from ILPs **3**(**a**–**d**) and 4-formylbenzoic acid **4**



Product	Anion	Yield (%)[a]
5a	BF_4	96
5b	PF_6	95
5c	BF_4	98
5d	PF_6	98

[a] Yield of isolated product.

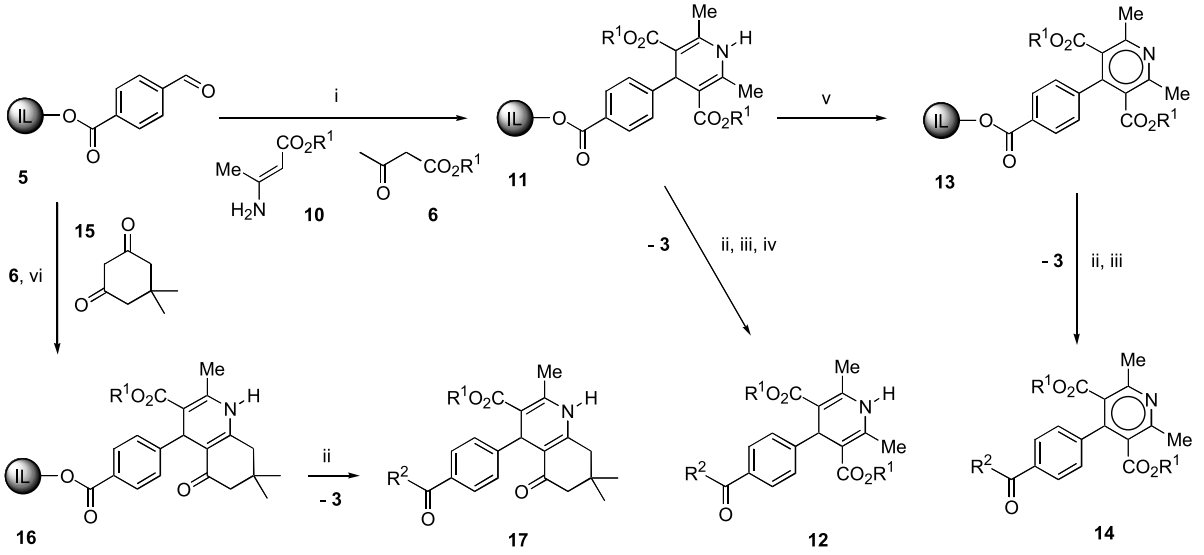
Table 3. Results for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones **8**(**a**–**d**) and **9a** from aldehydes **5**, β-ketoesters **6**(**a**,**b**) and ureas **7**(**a**,**b**)

Compound	Starting products	R^1	R^2	Reaction conditions	Yield (%)[a]
8a	**5d**+**6a**+**7a**	Me	H	120 °C, 10 min, mw[b]	86
8b	**5d**+**6b**+**7a**	Et	H	120 °C, 10 min, mw[b]	80
8c	**5d**+**6a**+**7b**	Me	Me	120 °C, 10 min, mw[b]	83
8c′	**5b**+**6a**+**7b**	Me	Me	110 °C, 1 h.[c]	88
8d	**5b**+**6b**+**7b**	Et	Me	110 °C, 1 h.[c]	87
9a	**8a**	Me	H	MeOH, Δ, 18 h[d]	80

[a] Yield of isolated product after purification.
[b] mw=under microwave irradiation (Power level: 50%, 150W).
[c] Neat conditions.
[d] Catalyst: MeONa (1 equiv).

examined the Biginelli 3,4-dihydropyrimidine (3,4-DHPM) synthesis (Scheme 2). For the 3,4-DHPM preparation, we have used a one-pot three component formation[21] under microwave[22] for a rapid synthesis of ILP bound 3,4-DHPMs **8**. A stoichiometry of 1/1.06/3 of IL-phase **5d**/β-ketoester **6**/ urea **7**, respectively, was found to react completely without solvent in the three component Hantzsch condensation at 120 °C under microwave exposure (120 W, 50% power level) during 10 min with two drops of concentrated HCl as catalyst. In the same manner, the reaction of IL-phase **5b** with β-ketoester **6**(**a**,**b**) and urea **7** produced, respectively, the desired 3,4-DHPMs **8c′** and **8d** using neat conditions (110 °C, 1 h). The excess of urea (**7a**: R=H or **7b**: R=Me) could be removed by simple washings with cold deionized water (1:10 w/v), due to the low miscibility of the ILPs **8** in cold water. Finally, the ILP **8a** was treated with sodium methoxide (1 equiv) in refluxed MeOH for 24 h. On completion of the cleavage step (monitored by TLC or ^{1}H NMR), the solvent was removed in vacuo, and the expected ester **9a** was obtained in good yields (Table 3) by precipitation in cold water. The 3,4-DHPM methyl ester **9a** was characterized by conventional techniques (^{1}H, ^{13}C NMR and HRMS) and the purity was controlled by HPLC.

In order to determine the ability of the ILP **5** in ionic liquid-phase combinatorial synthesis, we have also checked the reactivity of the aldehyde covalently grafted on the IL-phase in Hantzsch condensation (Scheme 3). For the synthesis of ILP bound aryl-1,4-dihydropyridine **11** (1,4-DHP) under microwave irradiation, we have studied two experimental procedures: (a) in the first method, the ILP **5** was treated with 1 equiv of β-ketoester **6** (**6a**: R=Me, **6b**: R=Et) and 1 equiv of aminocrotonate **10** (**10a**: R=Me, **10b**: R=Et) to form the Il-phases **11** using solvent-free conditions associated with microwave irradiation (120 °C, 150 W, 50% power level, time exposure: 10 min), (b) in the second method the Il-phase bound 1,4-DHP **11** was prepared by an one-pot three component condensation from β-ketoester **6** (2 equiv) and NH_4AcO (2 equiv) using the same microwave reaction conditions (120 °C, 10 min). Following AcOEt or Et_2O washings (1:10 w/v) of the IL-phase, the bound products **11** were subjected to cleavage by: (a) transesterification with 30% of MeONa in refluxed MeOH during 18 h, (b) saponification with 60% of LiOH in THF at room temperature, followed by controlled acidification with a solution of 3 M HCl or (c) ester aminolysis with propylamine or butylamine (10 equiv) under microwave (80 °C, 15 min). Owing to the small quantities of the starting IL-phase bound 1,4-DHP **11** (~500 mg) used in the cleavage step, the desired compounds **12**(**a**–**c**) were purified by filtration on alumina gel using AcOEt–DCM (1/1) as washing eluent (Table 4). Next, the IL-phase bound 1,4-



Scheme 3. Reagents and reactions conditions: (i) method A: **6** (1 equiv), **10** (1 equiv), mw: 120 °C (power level: 50%, 150 W), 10 min or method B: **6** (2 equiv), NH_4AcO (2 equiv), mw: 120 °C (power level: 50%, 150 W); (ii) MeONa 30%, MeOH, reflux, 18 h; (iii) LiOH 60%, THF, rt, 20 h then 3 M HCl; (iv) $PrNH_2$ or $BuNH_2$ (10 equiv), mw: 80 °C (power level: 50%, 150 W), 15 min; (v) DDQ (1.1 equiv), DCM, reflux, 2 h; (vi) **15** (1 equiv), **6** (1 equiv), NH_4AcO (1 equiv), mw: 120 °C (power level: 50%, 150 W), 10 min.

Table 4. Results for the preparation of various Hantzsch 1,4-dihydropyridines, pyridines and polyhydroquinolines

Compound	Starting products	R^1	R^2	Yield (%)[a]
11a	**5d**+**10a**[b]	Me	—	94
11a	**5d**+**6a**[c]	Me	—	96
11b	**5d**+**10b**[b]	Et	—	95
11b	**5d**+**6b**[c]	Et	—	97
12a	**11a**+MeONa[d]	Me	OMe	86
12b	**11b**+MeONa[d]	Et	OMe	85
12c	**11a**+LiOH, HCl	Me	OH	85
12d	**11a**+$PrNH_2$	Me	$NH(CH_2)_2Me$	45
12e	**11a**+$BuNH_2$	Me	$NH(CH_2)_3Me$	35
13a	**11a**+DDQ	Me	—	90
13b	**11a**+DDQ	Et	—	88
14a	**13a**+MeONa[d]	Me	OMe	94
14b	**13b**+MeONa[d]	Et	OMe	90
14c	**13b**+LiOH, HCl	Et	OH	87
16a	**5d**+**10a**+**15**	Me	—	97
16b	**5d**+**10b**+**15**	Et	—	90
17a	**16a**+MeONa[d]	Me	OMe	85
17b	**16b**+MeONa[d]	Et	OMe	80

[a] Yield of isolated product after purification.
[b] Method A.
[c] Method B.
[d] MeONa as catalyst (1 equiv).

DHP **11** was also submitted to oxidation[23] with DDQ (1.1 equiv) in refluxed DCM for 2 h to afford the corresponding bound pyridines **13**(**a**,**b**) (quantitative conversion by ^1H NMR). After removal solvent in vacuo, the expected pyridines **13**(**a**,**b**) were separated from $DDQH_2$ by filtration on a small pad of alumina gel with DCM-MeOH (95/5) as eluent. Subsequent cleavage (transesterification or saponification–acidification methods) of the pyridines **13** led, respectively, to the esters **14**(**a**,**b**) and the acid **14c** in good yields (87–94%) (Table 4).

Having established the effectiveness of IL-phase **5** in the synthesis of 1,4-DHPs[24] and pyridines,[25] we set out to explore its potential in the preparation of polyhydroquinoline[26] derivatives under microwave conditions. Solvent-free addition of dimedone **15** (1 equiv), β-ketoester **6** (1 equiv) and NH_4AcO (1 equiv) to the IL-phase bound aldehyde **5** at 120 °C (150 W, 50% power level, time exposure: 10 min) provided the desired compounds **16** (Table 4). After washing with Et_2O (1:10 w/v), the ILP intermediates **16** were cleaved under basic conditions (MeONa 30%) in refluxing MeOH (18 h) and the structure of **17**(**a**,**b**) was confirmed by ^1H, ^{13}C NMR and HRMS.

3. Conclusion

In conclusion, we have demonstrated that the combination of IL-phase bound aldehyde and microwave dielectric heating allows a rapid and practical preparation of Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones, Hantzch 1,4-dihydropyridines, pyridines by oxidation and polyhydroquinolines[27] using a one-pot three component methodology. The specific advantages of the IoLiPOS methodology are the following: (i) the reactions under microwave irradiation are performed in homogeneous solution without solvent, (ii) the loading capacity of the ILPs is higher because only a molar equivalent of the low molecular weigh ionic liquid phase is used, (iii) the stable intermediates in the sequence can be purified by simple washings with the appropriate solvent and the structure could be verified easily by routine spectroscopic methods at each step, (iv) the final cleavage is possible by transesterification, saponification/acidification or ester aminolysis. We are currently exploring the scope of IoLiPOS methodology to the synthesis of small library of 3,4-DHPMs and 1,4-DHPs that will be much more reliable for biological screening.[28]

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 60F 254 (Merck). Visualisation 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. IR spectra were recorded on a BIORAD FTS 175C spectrophotometer. ^1H 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 are given 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 for the ILPs and on a VARIAN MAT 311 at an ionizing potential of 70 eV for the other compounds in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Synthewave® 402 apparatus[22] (Merck Eurolab, Div. Prolabo, France) in quartz open reactor vessel prolonged by a condenser. The microwave instrument consists of a continuous focused microwave power output from 0 to 300 W. All the experiments were performed using stirring option. The target temperature was reached with a ramp of 3 min and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time include the ramp period. 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. The starting $[PEG_1\text{-mim}][X]$ ionic liquid phases **2a** and **3**(**a**,**b**) were synthesized according to our previous method[14b] for 1-(2-hydroxy-ethyl)-3-methyl-imidazolium chloride $[PEG_1mim][Cl]$ **2a**, 1-(2-hydroxy-ethyl)-3-methyl-imidazolium tetrafluoroborate $[PEG_1mim][BF_4]$ **3a**, 1-(2-hydroxy-ethyl)-3-methyl-imidazolium hexafluorophosphate $[PEG_1mim][PF_6]$ **3b**.

4.1.1. 1-(2-Hydroxy-ethyl)pyridinium chloride (2b). A mixture of freshly distilled pyridine **1b** (9.81 g, 124 mmol) and commercial 2-chloroethanol (10 g, 124 mmol) was

heated at 120 °C for 24 h under nitrogen with vigorous magnetic stirring. Then the mixture was allowed to cool down and a white solid formed rapidly (~15 min) at 25 °C. The crude solid that had formed was filtered off (under nitrogen), washed with anhydrous ether (3×30 ml), and vacuum dried in a dessicator over $CaCl_2$ for 4 h. The solid salt [PEG_1py][Cl] **2b** was further dried under high vacuum (10^{-2} Torr) at 60 °C for 8 h and was stored (17.62 g, 92% yield) in the dark at 4 °C under nitrogen. Mp=128–130 °C. ^{1}H NMR (D_2O, 300 MHz) δ=4.00 (t, 2H, J=5.1 Hz, OCH_2), 4.86 (t, 2H, J=4.9 Hz, NCH_2), 7.98 (t, 2H, J=6.9 Hz, H-3, H-5), 8.74 (t, 1H, J=8.0 Hz, H-4), 8.77 (d, 2H, J=6.5 Hz, H-2, H-6).

4.1.2. 1-(2-Hydroxy-ethyl)pyridinium tetrafluoroborate (3c). A mixture of 1-(2-hydroxy-ethyl)pyridinium chloride **2b** (2.50 g, 15.7 mmol) and NH_4BF_4 (1.65 g, 15.7 mmol) in dry acetonitrile (100 ml) was stirred vigorously at 25 °C under nitrogen for 24 h. After elimination of the precipitated salt (NH_4Cl) on a filter paper, the resulting filtrate was quickly refiltered through a short column of Celite® to remove some residual salt and finally concentrated by rotary evaporation that gave the expected mobile liquid phase **3c** in 99% yield. The ionic liquid phase **3c** was further dried under high vacuum (10^{-2} Torr) at 60 °C for 6 h. It is recommandle to handle the [PEG_1py][BF_4] ionic liquid phase **3c** in the dark under an inert atmosphere at 4 °C. ^{1}H NMR (D_2O, 200 MHz) δ=4.06 (t, 2H, J=4.8 Hz, CH_2O), 4.71 (t, 2H, J=5.0 Hz, CH_2N), 8.07 (t, 2H, J=7.2 Hz, H-3, H-5), 8.57 (t, 1H, J=7.9 Hz, H-4), 8.84 (d, 2H, J=5.7 Hz, H-2, H-6); ^{13}C NMR (75 MHz, D_2O) δ=60.49 (CH_2O), 63.64 (CH_2N), 128.23 (C-3, C-5), 144.72 (C-2, C-6), 146.07 (C-4). HRMS, *m/z*: 335.1558 found (calculated for $C_{14}H_{20}N_2O_2F_4B$, [$2C^+$, BF_4^-]$^+$ requires 335.1554).

4.1.3. 1-(2-Hydroxy-ethyl)pyridinium hexafluorophosphate (3d). The [PEG_1py][PF_6] ionic liquid phase **3d** was prepared according to the method used for the synthesis of **3c** from 1-(2-hydroxy-ethyl)pyridinium chloride **2b** (2.50 g, 15.7 mmol) and KPF_6 (2.89 g, 15.7 mmol) that gave the desired ionic liquid phase **3d** in 99% yield as colourless needles. Mp=28–30 °C. ^{1}H NMR (D_2O, 200 MHz) δ=4.10 (t, 2H, J=4.9 Hz, OCH_2), 4.72 (t, 2H, J=5.0 Hz, NCH_2), 8.10 (t, 2H, J=7.2 Hz, H-3, H-5), 8.56 (t, 1H, J=7.9 Hz, H-4), 8.84 (d, 2H, J=5.9 Hz, H-2, H-6); ^{13}C NMR (75 MHz, D_2O) δ=60.39 (CH_2O), 63.52 (CH_2N), 128.17 (C-3, C-5), 144.63 (C-2, C-6), 146.00 (C-4). HRMS, *m/z*: 393.1158 found (calculated for $C_{14}H_{20}N_2O_2F_6P$, [$2C^+$, PF_6^-]$^+$ requires 393.1167).

4.2. Standard procedure for the synthesis of the aldehydes 5(a–d) from imidazolium or pyridinium ionic liquid phases 3(a–d) and 4-formylbenzoic acid 4

To a mixture of dicyclohexylcarbodiimide (2.97 g, 14.42 mmol) and dimethylaminopyridine 5% (88 mg, 0.7 mmol) in dry acetonitrile (75 ml) were added successively the ionic liquid phase **3** ([PEG_1mim][BF_4] **3a** (3.08 g, 14.42 mmol), or [PEG_1mim][PF_6] **3b** (3.08 g, 14.42 mmol), or [PEG_1py][BF_4] **3c** (3.08 g, 14.42 mmol), or [PEG_1py][PF_6] **3d** (3.08 g, 14.42 mmol)) in one portion, then 4-formylbenzoic acid **4** (3 g, 14.42 mmol). After vigorous stirring at room temperature for 24 h, the insoluble *N*,*N*′-dicyclohexylurea (DCHU) was removed by filtration. The filtrate was concentrated under reduced pressure and the resulting crude reaction mixture was washed three times with AcOEt (20 ml). Removal of the solvent in vacuo lead to a pale yellow viscous oil in yield ranging from 95 to 98%. The desired ionic liquid phase **3** was stored under inert atmosphere at 4 °C. The aldehydes **5(a–d)** were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

4.2.1. 1-[2-(4-Formylbenzoyloxy)ethyl]-3-methylimidazolium tetrafluoroborate (5a). Yield=96%. Mp=85–87 °C. IR (KBr): 1275, 1561, 1574, 1649, 1721, 2852, 3153 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=4.04 (s, 3H), 4.79 (t, 2H, J=5.0 Hz, CH_2N), 4.87 (t, 2H, J=4.9 Hz, CH_2O), 7.72 (s, 1H, Ar, H-4, H-5), 7.91 (s, 1H, H-4, H-5), 8.01 (d, 2H, J=8.2 Hz, H-3′, H-5′), 8.20 (d, 2H, J=8.2 Hz, H-2′, H-6′), 9.19 (s, 1H, H-2), 10.13 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=36.62 (NCH_3), 49.35 (CH_2O), 64.53 (NCH_2), 123.92 (C-4, C-5), 124.85 (C-4, C-5), 130.26 (C-1′), 131.05 (C-3′, C-5′), 134.94 (C-4′), 138.16 (C-2), 140.54 (C-1′), 165.61 (CO), 192.91 (CHO). HRMS, *m/z*: 259.1082 found (calculated for $C_{14}H_{15}N_2O_3$, C^+ requires 259.1082).

4.2.2. 1-[2-(4-Formylbenzoyloxy)ethyl]-3-methylimidazolium hexafluorophosphate (5b). Yield=95%. Mp=95–97 °C. IR (KBr): 1281, 1568, 1574, 1695, 1733, 2852, 3178 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=4.00 (s, 3H), 4.74 (t, 2H, J=3.1 Hz,CH_2N), 4.82 (t, 2H, J=3.9 Hz, CH_2O), 7.65 (d, 1H, J=1.6 Hz, H-4, H-5), 7.84 (d, 1H, J=1.6 Hz, H-4, H-5), 7.95 (d, 2H, J=8.4 Hz, H-3′, H-5′), 8.13 (d, 2H, J=8.4 Hz, H-2′, H-6′), 9.12 (s, 1H, H-2), 10.10 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=36.70 (NCH_3), 49.47 (CH_2O), 64.39 (NCH_2), 123.97 (C-4, C-5), 124.93 (C-4, C-5), 130.26 (C-1′), 131.02 (C-3′, C-5′), 134.96 (C-1′), 137.93 (C-2), 140.61 (C-4′), 165.60 (CO), 192.85 (CHO). HRMS, *m/z*: 259.1082 found (calculated for $C_{14}H_{15}N_2O_3$, C^+ requires 259.1082).

4.2.3. 1-[2-(4-Formylbenzoyloxy)ethyl]pyridinium tetrafluoroborate (5c). Yield=98%. Mp=127–129 °C. IR (KBr): 1272, 1487, 1699, 1722, 2852, 2944, 3088, 3132 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=4.99 (t, 2H, J=5.0 Hz, NCH_2), 5.35 (t, 2H, J=5.0 Hz, OCH_2), 8.01 (d, 2H, J=8.4 Hz, H-3′, H-5′), 8.18 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.32 (t, 2H, J=7.4 Hz, H-3, H-5), 8.77 (t, 1H, J=7.8 Hz, H-4), 9.34 (d, 2H, J=5.6 Hz, H-2, H-6), 10.13 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=61.27 (CH_2O), 64.73 (CH_2N), 129.40 (C-3′, C-5′), 130.25 (C-3, C-5), 130.99 (C-2′,C-6′), 134.68 (C-1′), 140.50 (C-4′), 146.36 (C-2, C-6), 147.37 (C-4), 165.45 (CO), 192.93 (CHO). HRMS, *m/z*: 256.0965 found (calculated for $C_{14}H_{14}NO_3$, C^+ requires 256.0974).

4.2.4. 1-[2-(4-Formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate (5d). Yield=98%. Mp=139–141 °C. IR (KBr): 1272, 1491, 1499, 1690, 1718, 1737, 2879, 3073, 3097, 3141 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=5.02 (t, 2H, J=4.9 Hz, NCH_2), 5.35 (t, 2H, J=5.0 Hz, OCH_2), 8.00 (d, 2H, J=8.2 Hz, H-3′, H-5′), 8.16 (d, 2H, J=8.2 Hz, H-2′, H-6′), 8.32 (t, 2H, J=7.2 Hz, H-3, H-5), 8.78 (t, 1H, J=7.8 Hz, H-4), 9.29 (d, 2H, J=5.6 Hz, H-2, H-6), 10.12 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=61.40

(CH_2O), 64.58 (CH_2N), 129.43 (C-3′, C-5′), 130.23 (C-3, C-5), 130.93 (C-2′, C-6′), 134.67 (C-1′), 140.54 (C-4′), 146.21 (C-2, C-6), 147.42 (C-4), 165.44 (CO); 192.15 (CHO). HRMS, *m/z*: 256.0965 found (calculated for $C_{14}H_{14}NO_3$, C^+ requires 256.0974).

4.3. Standard procedure for the one-pot three component synthesis of 3,4-DHPMs 8(a–c) from aldehydes 5d, β-ketoesters 6(a,b) and ureas 7(a,b) under solventless microwave dielectric heating

In a cylindrical quartz reactor (Ø=1.8 cm) was placed a mixture of 1-[2-(4-formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate **5d** (539.2 mg, 1.34 mmol), methyl acetoacetate **6a** (164.8 mg, 1.42 mmol, 1.06 equiv) or ethyl acetoacetate **6b** (184.6 mg, 1.42 mmol, 1.06 equiv) and commercial urea **7a** (241.2 mg, 4.02 mmol, 3 equiv) or methylurea **7b** (297.5 mg, 4.02 mmol, 3 equiv) followed by addition of three drops of concentrated HCl as catalyst. The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was irradiated at 120 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and deionized water (10 ml) was added in the reactor. The desired insoluble 3,4-DHPM **8** was collected by filtration and was purified by washing with diethylether (2× 10 ml). The expected 3,4-DHPM **8** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **8(a–c)** were characterized by ^{1}H, ^{13}C NMR and HRMS.

4.3.1. 1-[2-[4-[5-(Methoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (8a). Yield=86%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ=2.38 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 4.95 (t, 2H, J=4.6 Hz, NCH_2), 5.32 (t, 2H, J=4.6 Hz, OCH_2), 5.43 (d, 1H, J=3.2 Hz, CH), 7.15 (br s, 1H, NH), 7.46 (d, 2H, J=8.3 Hz, Ar), 7.93 (d, 2H, J=8.3 Hz, Ar), 8.33 (t, 2H, J=7.4 Hz, H-3′,H-5′), 8.64 (br s, 1H, NH), 8.77 (t, 1H, J=7.8 Hz, H-4′), 9.32 (d, 2H, J=6.5 Hz, H-2,H-6′); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=17.95 (CH_3), 50.99 (OCH_3), 53.76 (C-4″), 59.76 (CH_2O), 63.44 (CH_2N), 98.43 (Ar), 126.10 (Ar), 127.95 (Ar), 128.14 (Ar), 129.78 (Ar), 145.50 (C-2, C-6), 146.22 (C-4), 149.32–150.24–152.05 (C-1′, C-4′, C-2″, C-6″), 164.91 (ArCO), 165.75 (CO). HRMS, *m/z*: 396.1561 found (calculated for $C_{21}H_{22}N_3O_5$, C^+ requires 396.1560).

4.3.2. 1-[2-[4-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (8b). Yield=80%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ=1.14 (t, 3H, J=7.1 Hz, CH_3), 2.38 (s, 3H, CH_3), 4.04 (q, 2H, J=7.1 Hz, OCH_2), 4.93 (t, 2H, J=4.8 Hz, NCH_2), 5.34 (t, 2H, J=4.8 Hz, OCH_2), 5.44 (d, 1H, J=2.7 Hz, CH), 7.26 (br s, 1H, NH), 7.46 (d, 2H, J=8.3 Hz, Ar), 7.92 (d, 2H, J=8.3 Hz, Ar), 8.31 (t, 2H, J=7.3 Hz, H-3, H-5), 8.76 (t, 1H, J=7.8 Hz, H-4), 8.82 (br s, 1H, NH), 9.31 (d, 2H, J=5.5 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=14.09 (CH_3), 17.90 (CH_3), 53.91 (CH), 59.39 (CH_2O), 59.78 (OCH_2), 63.39 (CH_2N), 98.63 (C-4″), 126.80 (Ar), 127.91 (C-1′, C-4′), 128.15 (C-5, C-3), 129.74 (Ar), 145.45 (C-2, C-6), 146.26 (C-4′), 149.05–150.46–152.00 (C-1′, C-4′, C-2″, C-6″), 164.92 (ArCO), 165.23 (CO). HRMS, *m/z*: 410.1712 found (calculated for $C_{22}H_{24}N_3O_5$, C^+ requires 410.1716).

4.3.3. 1-[2-[4-[5-(Methoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (8c). Yield=83%. Viscous oil. ^{1}H NMR ($(CD_3)_2SO$, 200 MHz) δ=2.10 (s, 3H, CH_3), 3.11 (s, 3H, NCH_3), 3.59 (s, 3H, OCH_3), 4.79 (t, 2H, J=4.6 Hz, NCH_2), 5.06 (t, 2H, J=4.5 Hz, OCH_2), 5.24 (d, 1H, J=3.8 Hz, CH), 7.37 (d, 2H, J=8.3 Hz, Ar), 7.87 (d, 2H, J=8.4 Hz, Ar), 8.12 (d, 1H, J=3.9 Hz, NH), 8.23 (t, 2H, J=7.4 Hz, H-3, H-5), 8.66 (t, 1H, J=7.7 Hz, H-4), 9.21 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ=16.18 (CH_3), 29.86 (NCH_3), 51.25 (OCH_3), 52.20 (C-4″), 59.82 (CH_2O), 63.45 (CH_2N), 101.51 (C-5″), 126.57 (Ar), 128.03 (C-1′, C-4′), 128.18 (C-5, C-3), 129.84 (Ar), 145.47 (C-2, C-6), 146.27 (C-4), 149.53–151.66–153.00 (C-1′, C-4′, C-2″, C-6″), 164.93 (ArCO), 166.00 (CO). HRMS, *m/z*: 410.1722 found (calculated for $C_{22}H_{24}N_3O_5$, C^+ requires 410.1716).

4.4. Procedure for the one-pot three component synthesis of 3,4-DHPMs 8c′ and 8d from aldehydes 5d, β-ketoesters 6(a,b) and methylurea 7b in oil bath using solvent-free reaction conditions

A mixture of 1-[2-(4-formylbenzoyloxy)ethyl]imidazolium hexafluorophosphate **5b** (845.0 mg, 2.09 mmol), methyl acetoacetate **6a** (248.0 mg, 2.14 mmol, 1.02 equiv) or ethyl acetoacetate **6b** (280.0 mg, 2.13 mmol, 1.02 equiv), commercial methylurea **7b** (485.0 mg, 6.48 mmol, 3.1 equiv) and three drops of concentrated HCl as catalyst was stirred vigorously at 110 °C without solvent for 1 h. After cooling down to room temperature, deionized water (10 ml) was added in the crude reaction mixture. The desired insoluble 3,4-DHPM **8c′** or **8d** was collected by filtration and was purified by washing with diethylether (2×10 ml). The expected 3,4-DHPM **8** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **8c′** or **8d** was characterized by ^{1}H, ^{13}C NMR and HRMS.

4.4.1. 1-[2-[4-[5-(Methoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]3-methylimidazolium hexafluorophosphate (8c′). Yield=88%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ=2.58 (s, 3H, CH_3), 3.20 (s, 3H, $CONCH_3$), 3.62 (s, 3H, OCH_3), 4.07 (s, 3H, NCH_3), 4.76 (t, 2H, J=4.1 Hz, NCH_2), 4.86 (t, 2H, J=4.2 Hz, OCH_2), 5.43 (d, 1H, J=3.5 Hz, H-4″), 7.17 (d, 1H, J=3.2 Hz, NH), 7.44 (d, 2H, J=8.2 Hz, Ar), 7.74 (s, 1H, H-4, H-5), 7.91 (s, 1H, H-4, H-5), 7.95 (d, 2H, J=8.3 Hz, Ar), 9.20 (s, 1H, H-2); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=16.53 (CH_3), 30.30 (NCH_3), 36.65 (NCH_3), 49.55 (CH_2O), 51.43 (OCH_3), 53.78 (C-4″), 63.86 (CH_2N), 103.16 (C-5″), 123.94 (C-4, C-5), 124.84 (C-4, C-5), 127.38 (Ar), 129.34 (C-1′, C-4′), 130.73 (Ar), 137.90 (C-2), 150.46–152.14–154.13 (C-1′, C-4′, C-2″, C-6″), 166.02 (ArCO), 166.86 (CO). HRMS, *m/z*: 413.1823 found (calculated for $C_{21}H_{25}N_4O_5$, C^+ requires 413.1825).

4.4.2. 1-[2-[4-[5-(Ethoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl] 3-methylimidazolium (8d). Yield=87%. Viscous oil. ^{1}H

NMR ($(CD_3)_2CO$, 200 MHz) $\delta=1.17$ (t, 3H, $J=7.1$ Hz, CH_3), 2.58 (s, 3H, CH_3), 3.20 (s, 3H, NCH_3), 4.07 (s, 3H, NCH_3), 4.08 (q, 2H, $J=7.0$ Hz, OCH_2), 4.76 (t, 2H, $J=4.2$ Hz, NCH_2), 4.86 (t, 2H, $J=4.3$ Hz, OCH_2), 5.44 (d, 1H, $J=3.6$ Hz, H-4″), 7.01 (d, 1H, $J=3.5$ Hz, NH), 7.45 (d, 2H, $J=8.3$ Hz, Ar), 7.74 (s, 1H, H-4 or H-5), 7.91 (s, 1H, H-4 or H-5), 7.96 (d, 2H, $J=8.3$ Hz, Ar), 9.19 (s, 1H, H-2); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) $\delta=14.46$ (CH_3), 16.50 (CH_3), 30.27 (NCH_3), 36.64 (NCH_3), 49.56 (CH_2O), 53.98 (C-4″), 60.51 (CH_2O), 63.86 (CH_2N), 103.40 (C-5″), 123.95 (C-4, C-5), 124.86 (C-4, C-5), 127.47 (Ar), 129.34 (C-1′, C-4′), 130.70 (Ar), 137.89 (Ar, C-2), 150.66–151.86–154.06 (C-1′, C-4′, C-2″, C-6″), 166.02 (CO), 166.36 (CO). HRMS, *m/z*: 427.1982 found (calculated for $C_{22}H_{27}N_4O_5$, C^+ requires 427.1982).

4.4.3. Methyl 4-[4-(methoxycarbonyl)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9a). To a solution of 1-[2-[4-[5-(methoxycarbonyl)-6-methyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]-pyridinium hexafluorophosphate **8a** (539 mg, 1 mmol) in anhydrous methanol (10 ml) was added commercial sodium methoxide (54 mg, 1 mmol) in one portion under nitrogen. After vigorous stirring at 78 °C for 18 h, the solvent was eliminated in vacuo. Then 10 ml of deionized water was added to the crude reaction mixture and a crude solid (**9a**) was obtained after 30 min of stirring. The precipitated ester **9a** was filtered, washed with dionized water (2×10 ml) and dried under reduced pressure (10–2 Torr) during 3 h. The expected ester **9a** was obtained in 80% yield (243 mg) as colourless needles (mp=212–214 °C). ^1H NMR ($(CD_3)_2SO$, 200 MHz) $\delta=2.38$ (s, 3H); 3.59 (s, 3H); 3.86 (s, 3H); 5.44 (d, 1H, $J=2.7$ Hz); 7.20 (br s, 1H, NH); 7.47 (d, 2H, $J=8.2$ Hz, Ar); 7.97 (d, 2H, $J=8.2$ Hz, Ar); 8.71 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) $\delta=17.93$; 50.85; 52.10; 53.81; 98.44; 126.66; 128.70; 129.55; 149.21; 149.83; 152.02; 165.72; 166.01. HRMS, *m/z*=304.1054 found (calculated for $C_{15}H_{16}N_2O_5$, M^+ requires 304.1059).

4.5. Procedures for the one-pot three component synthesis of 3,4-DHPs 11(a,b) under solventless microwave dielectric heating

Method A. A mixture of 1-[2-(4-formylbenzoyloxy)ethyl]-pyridinium hexafluorophosphate **5d** (1.29 g, 3.2 mmol), methyl 3-aminocrotonate **10a** (0.38 g, 3.2 mmol, 1 equiv) or ethyl 3-aminocrotonate **10b** (0.414 g, 3.2 mmol, 1 equiv) and methyl acetoacetate **6a** (0.376 g, 3.2 mmol, 1 equiv) or ethyl acetoacetate **6b** (0.417 g, 3.2 mmol, 1 equiv) was placed in a cylindrical quartz reactor (Ø=1.8 cm). Then, the reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was stirred mechanically and was irradiated at 120 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and chloroform (10 ml) was added in the cylindrical quartz reactor. The resulting solution was concentrated by rotary evaporation under reduced pressure. The desired 3,4-DHP **11** was purified by washing with diethylether or AcOEt (2×10 ml). The expected 3,4-DHP **11** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **8**(**a–c**) were characterized by ^1H, ^{13}C NMR, IR and HRMS.

Method B. The 3,4-DHPs **11**(**a**,**b**) were prepared according to the general solvent-free reaction conditions of method A under microwave dielectric heating (120 °C, power=150 W, 10 min) with a mixture of 1-[2-(4-formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate **5d** (1.29 g, 3.2 mmol), commercial ammonium acetate (0.247 g, 3.2 mmol, 1 equiv) and methyl acetoacetate **6a** (0.834 g, 6.4 mmol, 2 equiv) or ethyl acetoacetate **6b** (0.834 g, 6.4 mmol, 2 equiv).

4.5.1. 1-[2-[4-[3,5-(Dimethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (11a). Yield=94% (method A), 96% (method B). Viscous oil. IR (KBr): 1117, 1273, 1489, 1694, 1719, 2952, 3093, 3141, 3314 cm^{-1}. ^1H NMR ($(CD_3)_2CO$, 300 MHz) $\delta=2.34$ (s, 6H, CH_3), 3.60 (s, 6H, CO_2CH_3), 4.94 (t, 2H, $J=4.4$ Hz, NCH_2), 5.08 (s, 1H, Ar, H-5″), 5.32 (t, 2H, $J=4.7$ Hz, CH_2O), 7.38 (d, 2H, $J=8.4$ Hz, H-3′, H-5′), 7.83 (d, 2H, $J=8.4$ Hz, H-2′, H-6′), 8.01 (br s, 1H, NH), 8.34 (t, 2H, $J=7.0$ Hz, H-3, H-5), 8.79 (t, 1H, $J=7.7$ Hz, H-4), 9.32 (d, 2H, $J=5.4$ Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) $\delta=18.67$ (CH_3), 18.75 (CH_3), 40.50 (C-5″), 51.00 (OCH_3), 61.67 (OCH_2), 63.87 (NCH_2), 102.70 (C-3″, C-5″), 102.74 (C-3″, C-5″), 127.73 (C-1′), 128.64 (C-3′, C-5′), 129.41 (C-3, C-5), 130.20 (C-2′, C-6′), 146.24 (C-2, C-6), 146.62 (C-2″, C-6″), 146.71 (C-4′), 147.38 (C-4), 154.78 (C-2″, C-6″), 166.11 (ArCO), 168.15 (CO). HRMS, *m/z*: 451.1868 found (calculated for $C_{25}H_{27}N_2O_6$, C^+ requires 451.1869).

4.5.2. 1-[2-[4-[3,5-(Diethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (11b). Yield=95% (method A), 97% (method B). Viscous oil. IR (KBr): 1489, 1684, 1719, 2898, 2984, 3070, 3313 cm^{-1}. ^1H NMR ($(CD_3)_2CO$, 300 MHz) $\delta=1.17$ (t, 6H, $J=7.1$ Hz, CH_3), 2.33 (s, 6H, CH_3), 4.04 (qd, 4H, $J=7.1$, 1.7 Hz, OCH_2), 4.93 (t, 2H, $J=4.7$ Hz, NCH_2), 5.07 (s, 1H, H-5″), 5.30 (t, 2H, $J=4.6$ Hz, CH_2O), 7.40 (d, 2H, $J=8.4$ Hz, H-3′, H-5′), 7.82 (d, 2H, $J=8.3$ Hz, H-2′, H-6′), 7.93 (br s, 1H, NH), 8.32 (t, 2H, $J=6.8$ Hz, H-3, H-5), 8.77 (t, 1H, $J=7.8$ Hz, H-4), 9.29 (d, 2H, $J=5.4$ Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) $\delta=14.60$ (CH_3), 18.81 (OMe), 18.73 (OMe), 40.81 (C-5″), 60.01 (OCH_2), 61.74 (OCH_2), 63.88 (NCH^2), 103.08 (C-3″, C-5″), 127.71 (C-1′), 129.02 (C-3′, C-5′), 129.45 (C-3, C-5), 130.08 (C-2′, C-6′), 146.34 (C-2, C-6), 146.41 (C-4′), 147.44 (C-4), 155.16 (C-2″, C-6″), 166.15 (ArCO), 167.69 (CO). HRMS, *m/z*: 479.2167 found (calculated for $C_{27}H_{31}N_2O_6$, C^+ requires 479.2182).

4.5.3. Dimethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12a). To a solution of 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **11a** (517 mg, 0.87 mmol) in anhydrous methanol (20 ml) was added commercial sodium methoxide (15 mg, 0.28 mmol, 0.32 equiv) in one portion under nitrogen. After vigorous stirring at 78 °C for 18 h, the solvent was eliminated in vacuo. The crude reaction mixture was submitted directly to purification by flash chromatography (column: Ø=1 cm, H=7 cm) on neutral alumina oxide 90 gel (Merck) using CH_2Cl_2–AcOEt (1/1) as eluent. The desired fraction was concentrated in

vacuo and gave the desired compound **12a** in 86% yield as a yellowish nearly pure oil, which crystalized on standing. The pure product **12a** was characterized by ^{1}H, ^{13}C NMR, IR and HRMS. Mp = 238–240 °C. IR (KBr): 1290, 1430, 1492, 1687, 1700, 2946, 3014, 3097, 3301 cm^{-1}. ^{1}H NMR (CD_3Cl_3, 300 MHz) δ = 2.31 (s, 6H, CH_3), 3.63 (s, 6H, CO_2CH_3), 3.87 (s, 3H, $ArCO_2CH_3$), 5.05 (s, 1H, H-4), 5.78 (br s, 1H, NH), 7.33 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.88 (d, 2H, J = 8.4 Hz, H-3′, H-6′); ^{13}C NMR (CD_3Cl_3, 75 MHz) δ = 19.42 (CH_3), 39.76 (C-4), 51.09 (CO_2CH_3), 52.08 ($ArCO_2CH_3$), 103.15 (C-3, C-5), 127.85 (C-2′, C-6′), 127.97 (C-4′), 129.56 (C-3′, C-5′), 145.13 (C-1′), 152.99 (C-2, C-6), 167.46 (ArCO), 167.97 (CO). HRMS, *m*/*z*: 359.1369 found (calculated for $C_{19}H_{21}NO_6$, M^+ requires 359.1369).

4.5.4. Diethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12b). The desired compound **12b** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate **11b** according to the experimental procedure used for the preparation of **12a**. Yield = 85%. Mp = 180–182 °C. IR (KBr): 1289, 1442, 1491, 1650, 1695, 2989, 3336 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 1.17 (t, 6H, J = 7.1 Hz, CH_3), 2.34 (s, 6H, CH_3), 3.83 (s, 3H, $ArCO_2CH_3$), 4.04 (m, 4H, J = 7.1, 3.2 Hz, CH_2O), 5.09 (s, 1H, H-4), 7.42 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.86 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.92 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ = 14.62 ($CO_2CH_2CH_3$), 18.82 (CH_3), 40.72 (C-4), 52.08 ($ArCO_2CH_3$), 59.97 (OCH_2), 103.24 (C-3, C-5), 128.80 (C-4′), 128.94 (C-2′, C-6′), 129.82 (C-3′, C-5′), 146.20 (C-3, C-5), 146.29 (C-3, C-5), 154.59 (C-2, C-6), 167.21 (ArCO), 167.68 (CO). HRMS, *m*/*z*: 387.1685 found (calculated for $C_{21}H_{25}NO_6$, M^+ requires 387.1682).

4.5.5. Dimethyl 4-(4-carboxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12c). To a solution of 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate **11a** (571 mg, 0.96 mmol) in 10 ml of THF–$_2$O (2/1) was added dropwise over 10 min a solution of LiOH (47 mg, 0.63 mmol, 65%) under vigorous magnetic stirring. The reaction mixture was stirred for 20 h at room temperature. After elimination of solvent in a rotary evaporator under reduced pressure and addition of deionized water (10 ml), the precipitated crude acid **12c** was obtained at pH 2 by addition of a solution of 3 M HCl in the crude residue. The precipitated crude acid **12c** was filtered off and washed with deionized water (2×10 ml). The crude acid **12c** was directly purified by flash chromatography (column: Ø = 1 cm, H = 4 cm) on silica gel 60F 254 (Merck) using CH_2Cl_2–MeOH (9/1) as eluent. The desired fraction was concentrated in vacuo and gave the desired compound **12c** in 85% yield as white needles. Mp = 240–242 °C. IR (KBr): 1212, 1484, 1654, 1697, 2524, 2950, 3339 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 2.34 (s, 6H, CH_3), 3.59 (s, 6H, CO_2CH_3), 5.09 (s, 1H, H-4), 7.39 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.89 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 8.01 (br s, 2H, NH, CO_2H); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ = 18.71 (CH_3), 40.42 (C-4), 50.98 (CO_2CH_3), 102.88 (C-3, C-5), 128.50 (C-2′, C-6′), 129.00 (C-4′), 130.28 (C-3′, C-5′), 146.57 (C-3, C-5), 146.66 (C-1′), 154.22 (C-2, C-6), 167.83 (ArCO), 168.20 (CO). HRMS, *m*/*z*: 345.1225 found (calculated for $C_{18}H_{19}NO_6$, M^+ requires 345.1212).

4.6. Standard procedure for the synthesis of 3,4-DHPs 12(d,e) by ester aminolysis of ILPs-bound 3,4-DHP 11a using solvent-free reaction conditions under microwave dielectric heating.

A mixture of 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **11a** (310 mg, 0.52 mmol) and commercial butylamine (385 mg, 5.26 mmol, 10 equiv) or propylamine (645 mg, 10.91 mmol, 21 equiv) was placed in a cylindrical quartz reactor (Ø = 1.8 cm). Then, the reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was stirred mechanically and was irradiated at 80 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and acetone (20 ml) was added in the cylindrical quartz reactor. The resulting solution was concentrated by rotary evaporation under reduced pressure. The crude mixture was purified by distillation with a Büchi B-585 microdistillator (to remove excess of volatile amine), followed by flash chromatography (column: Ø = 1 cm, H = 4 cm) on neutral alumina oxide 90 gel (Merck) using CH_2Cl_2 as first eluent then CH_2Cl_2–MeOH (4/1) as second eluent. The desired fraction was controlled by TLC analysis with 0.2 mm precoated plates of neutral alumina oxide gel 60F 254 (Merck) and visualization was made with UV light at 254 or 365 nm. The second fraction was concentrated in vacuo and further dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h, which gave the desired amide **12** as a nearly yellowish pure oil. The pure products **12**(**d**,**e**) were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

4.6.1. Dimethyl 2,6-dimethyl-4-(4-propylcarbamoylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (12d). Yield = 45%. R_f = 0.5 from CH_2Cl_2–MeOH (4/1) as eluent. Viscous oil. IR (KBr): 1214, 1433, 1499, 1548, 1686, 1707, 2946, 3085, 3278 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 0.91 (t, 3H, J = 7.4 Hz, CH_3), 1.58 (m, 2H, J = 7.4, 7.2 Hz, CH_2), 2.32 (s, 6H, CH_3), 3.31 (q, 2H, J = 7.1 Hz, CH_2), 3.58 (s, 6H, CO_2CH_3), 5.05 (br s, 1H, H-4), 7.31 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.58 (br s, 1H, NH), 7.70 (d, 2H, J = 8.3 Hz, H-3, H-5), 8.06 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ = 11.76 (CH_3), 18.69 (CH_3), 18.77 (CH_3), 23.61 (CH_2), 40.24 (C-4), 42.10 (NCH_2), 50.93 (OCH_3), 103.16 (C-3, C-5), 103.20 (C-3, C-5), 127.68 (C-3′, C-5′), 128.25 (C-2′, C-6′), 134.05 (C-4′), 146.32, 146.41 (C-1′), 152.05 (C-2, C-6), 167.50 (ArCO), 168.24 (CO). HRMS, *m*/*z*: 386.1831 found (calculated for $C_{21}H_{26}N_2O_5$, M^+ requires 386.1841).

4.6.2. Dimethyl 2,6-dimethyl-4-(4-butylcarbamoylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (12e). Yield = 35%. R_f = 0.62 from CH_2Cl_2–MeOH (4/1) as eluent. Viscous oil. IR (KBr): 1216, 1433, 1498, 1541, 1650, 1697, 2930, 3346, 3628 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 0.91 (t, 3H, J = 7.3 Hz, CH_3), 1.36–1.56 (m, 2H, CH_2), 2.33 (s, 6H, CH_3), 2.84 (m, 2H, CH_2), 3.36 (s, 6H, CO_2CH_3), 5.06 (br s, 1H, H-4), 7.31 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.59 (br s, 1H, NH), 7.70 (d, 2H, J = 8.3 Hz, H-3′, H-5′),

8.10 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=13.12 (CH_3), 17.77 (CH_3), 19.88 (CH_2), 31.60 (CH_2), 39.00 (NCH_2), 39.23 (C-4), 49.92 (OMe), 102.30 (C-3, C-5), 126.70 (C-3′, C-5′), 127.25 (C-2′, C-6′), 133.06 (C-4′), 145.43 (C-1′), 151.05 (C-2, C-6), 166.44 (ArCO), 167.25 (CO). HRMS, *m/z*: 400.1989 found (calculated for $C_{22}H_{28}N_2O_5$, M^+ requires 400.111998).

4.6.3. 1-[2-[4-[3,5-(Dimethoxycarbonyl)-2,6-dimethylpyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (13a). The compound **13a** was prepared in 90% yield from 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **11a** (715 mg, 1.2 mmol) and commercial 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (306 mg, 1.32 mmol, 1.1 equiv) in refluxed CH_2Cl_2 (40 ml) for 2 h with vigorous magnetic stirring. After cooling down to room temperature, the solvent was eliminated in a rotary evaporator under reduced pressure. Then, the crude reaction mixture was submitted to purification by flash chromatography (column: Ø=1 cm H=4 cm) on neutral alumina oxide 90 gel (Merck) with CH_2Cl_2–MeOH (95/5) as eluent. Removal of solvent in vacuo gave the desired compound **13e** as a viscous oil. IR (KBr): 1246, 1273, 1492, 1557, 1723, 2855, 3098, 3372, 3628 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=2.54 (s, 6H, CH_3), 3.55 (s, 6H, CO_2CH_3), 4.99 (t, 2H, J=4.7 Hz, NCH_2), 5.36 (t, 2H, J=4.6 Hz, OCH_2), 7.35 (d, 2H, J=8.3 Hz, H-3′, H-5′), 8.07 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.32 (t, 2H, J=6.8 Hz, H-3, H-5), 8.77 (t, 1H, J=7.8 Hz, H-4), 9.35 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=23.09 (CH_3), 52.63 (OCH_3), 61.50 (OCH_2), 64.39 (NCH_2), 127.18 (C-1′), 129.13 (C-3′, C-5′), 129.44 (C-3, C-5), 130.18 (C-3″, C-5″), 130.26 (C-2′, C-6′), 142.46 (C-4″), 145.58 (C-4′), 146.36 (C-2, C-6), 147.44 (C-4), 156.46 (C-2″, C-6″), 165.70 (ArCO), 168.32 (CO). HRMS, *m/z*: 449.1712 found (calculated for $C_{25}H_{25}N_2O_6$, C^+ requires 449.1713).

4.6.4. 1-[2-[4-[3,5-(Diethoxycarbonyl)-2,6-dimethylpyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (13b). The desired compound **13b** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate **11b** according to the experimental procedure used for the preparation of **13a**. Yield=88%. Viscous oil. IR (KBr): 1239, 1271, 1490, 1557, 1716, 2981, 3097, 3648 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=0.93 (t, 6H, J=6.8 Hz, CH_3), 2.56 (s, 6H, CH_3), 4.04 (q, 4H, J=6.8 Hz, OCH_2), 5.00 (br s, 2H, NCH_2), 5.33 (br s, 2H, OCH_2), 7.39 (d, 2H, J=8.2 Hz, H-3′, H-5′), 8.09 (d, 2H, J=8.1 Hz, H-2′, H-6′), 8.30 (t, 2H, J=6.8 Hz, H-3, H-5), 8.76 (t, 1H, J=7.7 Hz, H-4), 9.29 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=13.81 (CH_3), 23.02 (CH_3), 61.33 (OCH_2), 62.03 (OCH_2), 64.26 (NCH_2), 127.16 (C-1′), 129.29 (C-3, C-5), 129.33 (C-3′, C-5′), 130.00 (C-3″, C-5″), 130.08 (C-2′, C-6′), 142.39 (C-4″), 145.42 (C-4′), 146.12 (C-2, C-6), 147.31 (C-4), 156.20 (C-2″, C-6″), 165.67 (ArCO), 167.69 (CO). HRMS, *m/z*: 477.2029 found (calculated for $C_{27}H_{29}N_2O_6$, C^+ requires 477.2026).

4.6.5. Dimethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethylpyridine-3,5-dicarboxylate (14a). The product **14a** was prepared from 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate **13a** according to the experimental procedure used for the preparation of **12a**. Yield=94%. White needles. Mp=110–112 °C. IR (KBr): 1234, 1289, 1436, 1557, 1725, 2950 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=2.56 (s, 6H, CH_3), 3.55 (s, 6H, CO_2CH_3), 3.80 (s, 3H, $ArCO_2CH_3$), 7.39 (d, 2H, J=8.4 Hz, H-2′, H-6′), 8.08 (d, 2H, J=8.4 Hz, H-3′, H-5′); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=23.11 (CH_3), 52.49 (OCH_3), 52.55 ($ArCO_2CH_3$), 52.55 (CO_2CH_3), 127.10 (C-4′), 128.97 (C-2′, C-6′), 129.99 (C-3′, C-5′), 131.05 (C-3, C-5), 142.06 (C-4), 145.72 (C-1′), 156.46 (C-2, C-6), 166.63 (ArCO), 168.30 (CO). HRMS, *m/z*: 357.1231 found (calculated for $C_{19}H_{19}NO_6$, M^+ requires 357.1212).

4.6.6. Diethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethylpyridine-3,5-dicarboxylate (14b). The product **14b** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate **13b** according to the experimental procedure used for the preparation of **12a**. Yield=90%. White needles. Mp=120–122 °C. IR (KBr): 1228, 1289, 1437, 1556, 1715, 1726, 2973 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=0.92 (t, 6H, J=7.1 Hz, CH_3), 2.56 (s, 6H, CH_3), 3.91 (s, 3H, $ArCO_2CH_3$), 4.02 (q, 4H, J=7.1 Hz, OCH_2), 7.38 (d, 2H, J=8.4 Hz, H-2′, H-6′), 8.07 (d, 2H, J=8.4 Hz, H-3′, H-5′); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=13.90 (CH_3), 23.06 (CH_3), 52.53 ($ArCO_2CH_3$), 62.00 (OCH_2), 127.37 (C-4′), 129.36 (C-2′, C-6′), 129.94 (C-3′, C-5′), 131.13 (C-3, C-5), 142.13 (C-4), 145.65 (C-1′), 156.29 (C-2, C-6), 166.73 (ArCO), 167.80 (CO). HRMS, *m/z*: 385.1536 found (calculated for $C_{21}H_{23}NO_6$, M^+ requires 385.1525).

4.6.7. Diethyl 4-[4-(carboxyphenyl)]-2,6-dimethylpyridine-3,5-dicarboxylate (14c). The product **14c** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **13b** according to the experimental procedure used for the preparation of **12c**. Yield=87%. Brown needles. Mp=220–222 °C. IR (KBr): 1238, 1557, 1574, 1654, 1731, 2600, 2979 cm^{-1}. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ=0.84 (t, 6H, J=6.9 Hz, CH_3), 2.54 (s, 6H, CH_3), 3.99 (q, 4H, J=6.9 Hz, OCH_2), 7.32 (d, 2H, J=7.8 Hz, H-2′, H-6′), 8.02 (d, 2H, J=7.8 Hz, H-3′, H-5′); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ=13.31 (CH_3), 22.57 (CH_3), 61.30 (OCH_2), 126.10 (C-4′), 128.17 (C-2′, C-6′), 129.23 (C-3′, C-5′), 131.02 (C-3, C-5), 140.29 (C-4), 144.74 (C-1′), 155.61 (C-2, C-6), 166.74 (CO), 166.91 (ArCO). HRMS, *m/z*: 371.1383 found (calculated for $C_{20}H_{21}NO_6$, M^+ requires 371.1369).

4.7. Standard procedure for the one pot three component synthesis of ILP bound polyhydroquinolines 16(a,b) using solvent-free reaction conditions under microwave dielectric heating

A mixture of 1-[2-(4-formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate **5d** (580 mg, 1.45 mmol), methyl 3-aminocrotonate **10a** (173 mg, 1.45 mmol, 1 equiv) or

ethyl 3-aminocrotonate **10b** (188 mg, 1.45 mmol, 1 equiv) and 5,5-dimethyl-1,3-cyclohexanedione **15** (204 mg, 1.45 mmol, 1 equiv) was placed in a cylindrical quartz reactor (Ø=1.8 cm). Then, the reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was stirred mechanically and was irradiated at 120 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and acetone (10 ml) was added in the cylindrical quartz reactor. The resulting solution was concentrated by rotary evaporation under reduced pressure. The desired 3,4-DHP **11** was purified by washing with diethylether (2×10 ml) or flash chromatography (column: Ø=1 cm, H=4 cm) on neutral alumina oxide 90 gel (Merck) with CH_2Cl_2–MeOH (9/1) as eluent. The expected compounds **16**(**a**,**b**) were further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **16**(**a**,**b**) were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

4.7.1. 1-[2-[4-[(3-(Methoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate (16a). Yield= 97%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ= 0.86 (s, 3H, *gem*-CH_3), 1.05 (s, 3H, *gem*-CH_3), 2.09–2.53 (m, 4H, H-8″, H-6″), 2.38 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 4.92 (m, 2H, NCH_2), 5.07 (s, 1H, H-4″), 5.31 (t, 2H, J= 4.9 Hz, OCH_2), 7.38 (d, 2H, J=8.3 Hz, H-3′, H-5′), 7.79 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.21 (br s, 1H, NH), 8.32 (t, 2H, J=7.0 Hz, H-3, H-5), 8.78 (t, 1H, J=7.8 Hz, H-4), 9.32 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=19.89 (CH_3), 26.95 (*gem*-CH_3), 29.60 (*gem*-CH_3), 32.99 (C-7″), 37.73 (C-4″), 40.69 (C-8″), 51.02 (OCH_3), 51.24 (C-6″), 61.72 (OCH_2), 63.88 (NCH_2), 104.35 (C-3″), 111.15 (C-4a″), 127.57 (C-1′), 128.98 (C-3′, C-6′), 129.47 (C-3, C-5), 130.05 (C-2′, C-6′), 146.34 (C-4), 146.50 (C-4′), 147.43 (C-2, C-6), 150.26 (C-2″), 154.45 (C-8a″), 166.13 (ArCO), 168.07 (CO), 195.03 (CO, C-5″). HRMS, *m*/*z*: 475.2227 found (calculated for $C_{28}H_{31}N_2O_5$, C^+ requires 475.2223).

4.7.2. 1-[2-[4-[3-(Ethoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate (16b). Yield= 90%. Viscous oil. IR (KBr): 1220, 1273, 1488, 1717, 2872, 2958, 3069, 3285 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=0.87 (s, 3H, *gem*-CH_3), 1.05 (s, 3H, *gem*-CH_3), 1.15 (t, 3H, J=7.0 Hz, CH_3), 2.09–2.53 (m, 4H, H-8″, H-6″), 2.38 (s, 3H, CH_3), 4.01 (q, 2H, J=7.0 Hz, OCH_2), 4.91 (m, 2H, NCH_2), 5.07 (s, 1H, H-4″), 5.31 (t, 2H, J=4.9 Hz, OCH_2), 7.40 (d, 2H, J=8.3 Hz, H-3′, H-5′), 7.80 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.22 (br s, 1H, NH), 8.32 (t, 2H, J=7.2 Hz, H-3, H-5), 8.78 (t, 1H, J=7.8 Hz, H-4), 9.32 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=14.45 (CH_3), 18.88 (CH_3), 26.85–29.48 (*gem*-CH_3), 32.83 (C-7″), 37.76 (C-4″), 40.64 (C-8″), 51.04 (C-6″), 60.06 (OCH_2), 61.34 (OCH_2), 63.76 (NCH_2), 104.55 (C-3″), 110.75 (C-4a″), 127.32 (C-1′), 128.99 (C-3′, C-5′), 129.18 (C-3, C-5), 129.87 (C-2′, C-6′), 145.95 (C-4), 146.46 (C-4′), 147.17 (C-2, C-6), 150.85 (C-2″), 154.38 (C-8a″), 166.00 (ArCO), 167.70 (CO), 195.54 (CO, C-5″). HRMS, *m*/*z*: 489.2386 found (calculated for $C_{29}H_{33}N_2O_5$, C^+ requires 489.2390).

4.7.3. Methyl 4-[4-(methoxycarbonyl)phenyl]-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-3-carboxylate (17a). The product **17a** was prepared from 1-[2-[4-[3-(methoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (**16a**) according to the experimental procedure used for the preparation of **12a**. Yield=85%. Yellow needles. Mp=228–230 °C. IR (KBr): 1227, 1282, 1489, 1600, 1647, 1687, 1719, 2952, 3078, 3204 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.83 (s, 3H, *gem*-CH3), 1.00 (s, 3H, *gem*-CH3), 2.06–2.27 (m, 4H, H-8, H-6), 2.32 (s, 3H, CH_3), 3.58 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3), 5.10 (s, 1H, H-4), 7.37 (d, 2H, J=8.2 Hz, H-2′, H-6′), 7.54 (br s, 1H, NH), 7.87 (d, 2H, J=8.2 Hz, H-3′, H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=19.18 (CH_3), 26.91–29.57 (*gem*-CH3), 32.65 (C-7), 36.91 (C-4), 40.66 (C-8), 50.78 (C-6), 51.09 (OCH_3), 52.08 (OCH_3), 104.84 (C-3), 111.08 (C-4a), 127.82 (C-4′), 128.02 (C-2′, C-6′), 129.49 (C-3′, C-6′), 145.03 (C-1′), 149.82 (C-2), 152.51 (C-8a), 167.46 (ArCO), 167.77 (CO), 195.83 (CO, C-5). HRMS, *m*/*z*: 383.1744 found (calculated for $C_{22}H_{25}NO_5$, M^+ requires 383.1733).

4.7.4. Ethyl 4-[4-(methoxycarbonyl)phenyl]-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-3-carboxylate (17b). The product **17a** was prepared from 1-[2-[4-[3-(ethoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (**16b**) according to the experimental procedure used for the preparation of **12a**. Yield=80%. Yellow viscous oil. IR (KBr): 1220, 1280, 1487, 1605, 1648, 1700, 1721, 2954, 3074, 3194, 3294 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.83 (s, 3H, *gem*-CH3), 1.00 (s, 3H, *gem*-CH3), 1.15 (t, 3H, J=7.1 Hz, CH_3), 2.04–2.26 (m, 4H, H-8, H-6), 2.31 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.02 (q, 2H, J=7.1 Hz, OCH_2), 5.08 (s, 1H, H-4), 7.37 (d, 2H, J= 8.2 Hz, H-2′, H-6′), 7.50 (br s, 1H, NH), 7.86 (d, 2H, J= 8.2 Hz, H-3′, H-5′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.26 (CH_3), 19.12 (CH_3), 26.91–29.55 (*gem*-CH3), 32.62 (C-7), 37.10 (C-4), 40.65 (C-8), 50.75 (C-6), 51.04 (OCH_3), 59.90 (OCH_2), 105.10 (C-3), 111.12 (C-4a), 127.74 (C-4′), 128.20 (C-2′, C-6′), 129.37 (C-3′, C-5′), 144.73 (C-1′), 149.74 (C-2), 152.68 (C-8a), 167.31 (CO), 167.46 (ArCO), 195.77 (CO, C-5). HRMS, *m*/*z*: 397.1880 found (calculated for $C_{23}H_{27}NO_5$, M^+ requires 397.1889).

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27. This work was presented at the XIII^{eme} Conferences Européennes du Groupement des Pharmacochimistes de l'Arc Atlantique, Université de Rennes 1, France, September 16–17, 2004, *Book of Abstracts* O5/P4.
28. The new 3,4-DHPMs and 1,4-DHPs will be evaluated in a drug discovery program (protein kinase C inhibition activities) at the 'Station Biologique de Roscoff, BP 74, 29682 - Roscoff Cedex, France.'