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Ionic liquid phase organic synthesis (IoLiPOS) methodology applied to the preparation of new 3,4-dihydropyrimidine-2(1*H*)-ones bearing bioisostere group in N-3 position

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ABSTRACT

The ionic liquid phase organic synthesis (IoLiPOS) methodology has been used for the preparation of new 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs) bearing bioisostere group in N-3 position. For the 3,4-DHPMs substituted with various thiazole rings, the strategy involved a three-component Biginelli condensation in the second step with good yields (93–96%) from ILP bound acetoacetate, aromatic aldehyde (93–97% yield), and *N*-methyl urea followed by N-3 alkylation with chloroacetonitrile on the ILP bound 3,4-DHPM. Quantitative thionation of the nitrile group grafted on the ILP bound 3,4-DHPM was realized in MeOH with a 40–48% solution of ammonium sulfide and subsequent addition of α-bromoketone produced the thiazole ring appended on the 3,4-DHPM core. After cleavage by transesterification, the target compounds were obtained in good overall yields (47–50%). The efficiency of the IoLiPOS methodology was also demonstrated by the preparation of new 3,4-DHPMs with a tetrazole ring in N-3 position in 5 steps (53–61% overall yield) via the ILP bound 3-cyanomethyl 3,4-DHPM as key intermediate.

1. Introduction

Over the years, research interest in multi-functionalized 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs), has surged rapidly, owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core. A number of recent publications has emerged describing structural variations in N-3 functionalized DHPMs as calcium channel modulators, which exhibit similar biological profiles to DHPs.[1] Notably, N-3 functionalized 4-aryl-3,4-dihydropyrimidine-2(1*H*)-ones exhibit a broad range of biological effects[2] and have recently appeared as, e.g., α_{1a} adrenergic receptor (SNAP 6552)[3] and antihypertensive agents (SQ 32926).[4] Due to the fact that the aminopropyl 4-piperidinyl heterocycle attached to DHPM moiety via a N-3 carboxamide linkage has proven to be excellent template for the treatment of benign prostatic hyperplasia,[5] the investigation of new functionalized DHPMs with structural diversity on N-3 position has been advocated. For the present work, the amide function in N-3 position of the DHPM scaffold will be replaced by thiazole and tetrazole rings as bioisostere groups. Bioisostere replacement[6] forms a rational medicinal approach for the discovery of new leads or series, based on existing key ligands. The thiazole heterocycle was used as pyrazole bioisostere in the CB_1 receptor antagonist rimonabant[7] (SR 14176A) and the tetrazole ring was well known as efficient isosteric substitute[8] for the carboxylic group in biologically active molecules, because they both possess comparable acidity and sizes.[9] The tetrazole unit, however, has proved to be superior in resisting metabolic degradation.

Modern drug discovery steadily relies on high-speed organic synthesis and combinatorial chemistry techniques for the rapid generation of compound libraries. In recent years, task-specific ionic liquids (TSILs)[10] and ionic liquid phases[11] (ILPs)—a subclass of TSILs as alternative soluble supports for liquid phase organic synthesis of small molecules[12]—are receiving growing attention due to their tuneable features for various targeted chemical tasks and the advantages as homogeneous supports. This concept was successfully used to a wide range of applications[13] such as a β-lactam library[14] via multistep reactions, oligonucleotide,[15] oligosaccharide,[16] and peptide[17] synthesis to mention, but few recent examples. Undoubtedly, the IL-supported synthesis possesses the advantages common to homogeneous solution-phase synthesis.

In this context, our aim in this study was to develop a novel ionic liquid phase strategy toward new 3,4-dihydropyrimidine-2(1*H*)-ones bearing in N-3 position a thiazole or a tetrazole ring as bioisosteric substitute. Herein, we present a full account of this study

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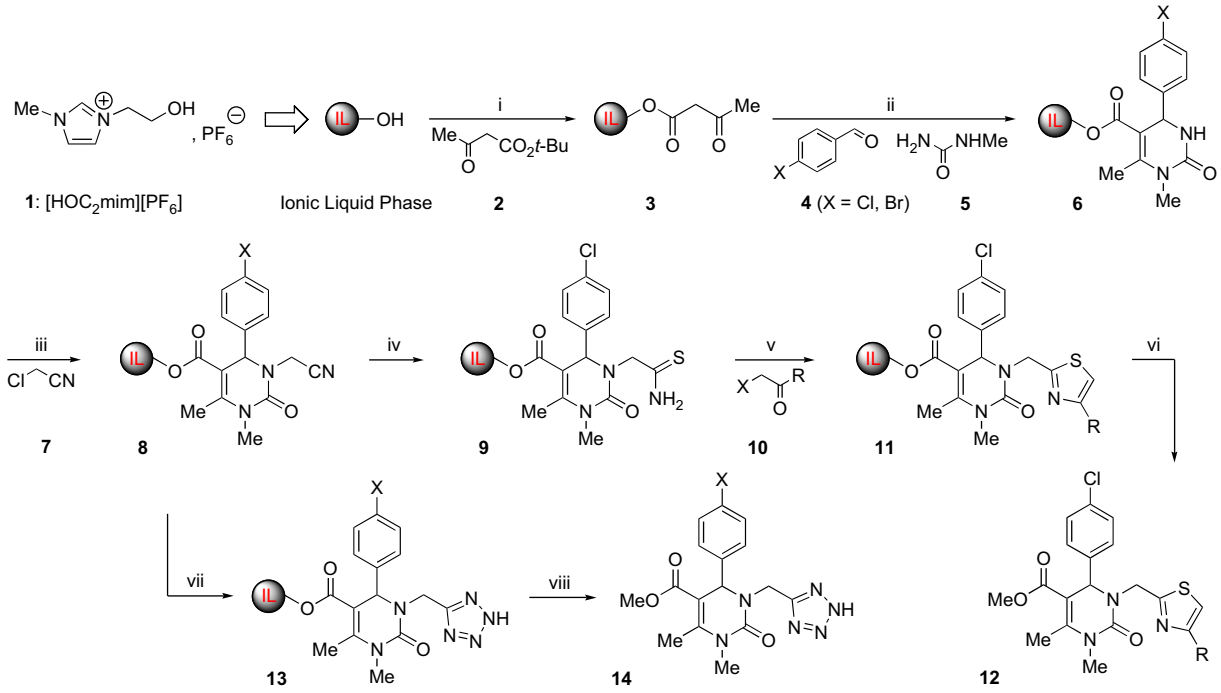


Scheme 1. Preparation of N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones **12** and **14** using IoLiPOS methodology. *Reagents and reaction conditions*: (i) *tert*-butyl acetoacetate **2** (2.5 equiv), 170 °C, μω, 150 W, 10 min. (ii) HCl (0.5 mol %), 4-halogenobenzaldehyde **4** (1 equiv), *N*-methylurea **5** (3 equiv), 100 °C, 1 h. (iii) chloroacetonitrile **7** (2 equiv), NaH (2 equiv), MeCN, 0 °C, 18 h. (iv) $(NH_4)_2S$ (4 equiv), MeOH, 25 °C, 72 h. (v) halogenoketone **10** (1.01 equiv), DMF, 90 °C, 16 h. (vi) MeONa (1 equiv), MeOH, reflux, 15 h. (vii) NaN_3, NH_4Cl, DMF, 100 °C, 24 h. (viii) MeONa (2 equiv), MeOH, reflux, 18 h, then 3 M HCl (pH=2).

according to the 'ionic liquid phase organic synthesis (IoLiPOS)' methodology.

2. Results and discussion

The overall strategy for the target N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones bearing a thiazole or tetrazole ring is outlined in Scheme 1.

In this context, we were interested in the preparation of 3,4-DHPMs grafted on the ionic liquid phase (ILP) to introduce diversity on N-3 position via the key intermediate **8**. The nitrile group of the scaffold **8** was expected to be a suitable precursor for the thiazole Hantzsch synthesis. The 3,4-dihydropyrimidine-2(1*H*)-one **8** of interest was assembled via a multicomponent reaction of an aldehyde, urea, and β-ketoester as shown in Figure 1. The construction of an ester linkage between solid- or liquid phase supported hydroxyl functionality with carboxylic acid or ester is one of the most common transformation in solid phase organic synthesis (SPOS) or in liquid phase organic synthesis (LPOS). For this purpose, the starting $[HOC_2mim][PF_6]$ ILP **1** used was prepared according to two-step process in large scale[11] developed previously in our laboratory.

In the first step as shown in Scheme 1, the ionic liquid phase bound β-ketoester **3** was obtained by transesterification (93% yield, Table 1) of *tert*-butyl acetoacetate **2** with $[HOC_2mim][PF_6]$ ILP **1** under solvent-free microwave irradiation[18] after 10 min with a stoichiometry of 1:2.5 of ILP **1**/β-ketoester **2**. The optimal reaction mixture was 170 °C, just below the boiling point of reagent **2** and for safety reasons, a 6-min heating ramp was performed before the temperature[19] was maintained at the selected maximum value of 170 °C (at 150 W in the Synthewave® 402 reactor[20]). For the synthesis of ILP bound 3,4-DHPM **6** in the second step, we have used the one-pot three-component Biginelli[21] formation. A mixture with a stoichiometry of 1:1:3 of IL-phase **3**/4-halogenobenzaldehyde **4**/*N*-methyl urea **5**, respectively, and a catalytic amount of hydrochloric acid (0.5 mol %) was found to react completely without solvent in the three-component Biginelli condensation[22] at 100 °C for 1 h to produce the 3,4-DHPMs **6**(**a**,**b**) (93–96% yield) grafted on ionic liquid phases. The excess of *N*-methyl urea **5** could be removed by simple washings with cold deionized water (1:10 w/v), due to the low miscibility of the IPLs **6** in cold water.

The third step is the preparation of the key intermediate **8** for the elaboration of thiazole and tetrazole moieties. In order to obtain the scaffold intermediate **8**, the corresponding ionic liquid phase bound 3,4-dihydropyrimidine-2(1*H*)-ones **6**(**a**,**b**) were exposed to a $ClCH_2CN$ **7**/NaH/MeCN mixture, which effectively afforded at 0 °C the N-alkylated derivatives of ILP bound 3,4-DHPMs **8**(**a**,**b**). The N-3

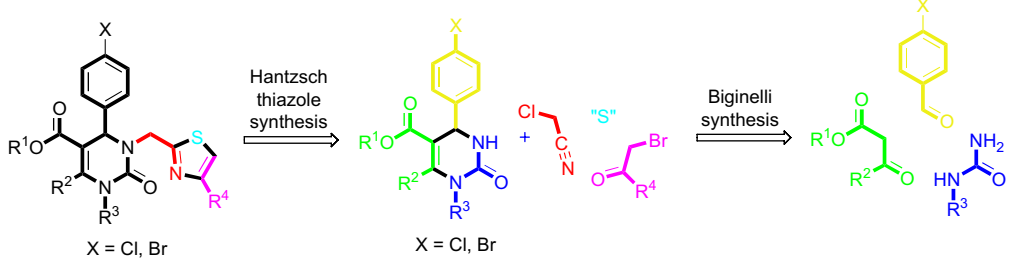
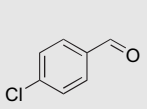
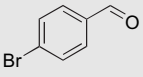


Figure 1. Retrosynthetic strategy toward N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones bearing thiazole moiety as bioisostere group.

Table 1

Product	Starting compounds	X	R	Yield[a] (%)	Overall yield[b] (%)
3	**2**	—	—	90	—
6a	**4a**	Cl	—	96	86
6b	**4b**	Br	—	93	84
8a	**6a**	Cl	—	97	84
8b	**6b**	Br	—	93	78
9	**8a**	Cl	—	96	80
11a	**9**+**10a**	Cl	C_6H_5	85	68
11b	**9**+**10b**	Cl	CH_3	65	52
11c	**9**+**10c**	Cl	*p*-ClC_6H_4	88	71
11d	**9**+**10d**	Cl	*p*-$MeOC_6H_4$	84	68
12a	**11a**	Cl	C_6H_5	73	50
12b	**11b**	Cl	CH_3	71	37
12c	**11c**	Cl	*p*-ClC_6H_4	71	50
12d	**11d**	Cl	*p*-$MeOC_6H_4$	70	47
13a	**8a**	Cl	—	79	66
13b	**8b**	Br	—	71	55
14a	**13a**	Cl	—	92	61
14b	**13b**	Br	—	96	53


4a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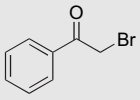
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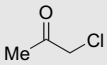
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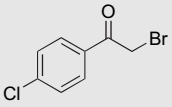
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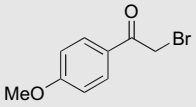
10d

[a] Yield of isolated product.
[b] Overall yield calculated from product **1**.

alkylations[23] are conveniently carried out in acetonitrile solution using a two-fold excess of chloroacetonitrile **7** in the presence of NaH[24] (2 equiv) as a base. Further purification has been performed by washings (1:10 w/v) successively with Et_2O, deionized water, and pentane, and finally were dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h (**8a**: 97%, **8b**: 93%). The scaffold intermediates **8**(**a**,**b**) were synthesized in three linear steps and 78–84% overall yield.

With the N-3 cyanomethyl 3,4-DHPM bound ILP **8** in hand, we have examined the conversion of nitrile group to thioamide. Many different methods have been reported in the literature for the preparation of thioamides. In general, two approaches may be adopted for the preparation of thioamides: (i) the thionation of the corresponding amide with an electrophilic reagent, such as Lawesson's reagent[25] or phosphorus pentasulfide[26] or (ii) reaction with a nucleophilic thionating reagent, by electrophilic activation of an amide[27] or more simply using the corresponding nitrile.[28] The latter conversion requires the use of toxic hydrogen sulfide with a basic catalyst (Et_3N, pyridine) and the alternative reagents (Dowex-SH,[29] $P_4S_{11}Na_2$[30] or sodium trimethylsilanethiolate[31]) require initial preparation. Ammonium sulfide in MeOH has emerged as the less unpleasant-smelling source of hydrogen sulfide for the synthesis of thioamides from nitrile[32] with appreciable yields. On the basis of this work, we have examined the use of ammonium sulfide in MeOH under several reaction conditions for the transformation of **8** into thioamide **9** (Table 2). The best result (entry 3) was encountered by reaction of 4 equiv of ammonium sulfide with 3,4-DHPM **8a** (X=Cl) at 20 °C for 72 h. Pure thioamide bound ILP **9** was obtained at this stage in 96% yield after washings with deionized water (1:10 w/v).

Table 2
Reaction conditions used for thionation of 3,4-DHPM bound ILP **8**

Entry	Reaction temperature (°C)	Reaction time (h)	Ammonium sulfide (equiv)	Yield[a] of **9** (%)
1	20	24	2	0
2	20	24	4	73
3	20	72	4	96
4	65	24	1	0
5	65	24	2	Decomposition
6	65	24	4	68[b]

[a] Isolated yield.
[b] Reaction conducted in a sealed tube.

In step 5, our focus was the transformation of the thioamide bound ILP **9** into thiazole derivative **11** by Hantzsch reaction. Initially our studies started by the reaction of thioamide **9** and α-bromoketone **10** using various solvents as EtOH,[33] DMF,[34] and DME[35] at various reaction temperature (70–110 °C) in the presence of K_2CO_3. Among the reaction conditions evaluated, we found that reaction of **9** with 1.01 equiv of α-halogenoketone **10** (X=Br, Cl) in DMF (0.6 ml/mmol) at 90 °C gave good thiazole formation after 16 h. As it can be seen from inspection of the data presented in Table 1, the thiazole **11**(**a**–**d**) issued, respectively, from bromoacetophenone **10a**, chloroacetone **10b**, 2-bromo-4′-chloroacetophenone **10c**, 2-bromo-4′-methoxyacetophenone **10d** were obtained in yields ranging from 65 to 88% after successive washings (deionized water, Et_2O, pentane) and drying under reduced pressure. It is worth noting that the Hantzsch thiazole products **12** were estimated easily by ^1H NMR without detaching the material from the ionic liquid phase. In the last step, the thiazole derivatives **12** appended to the 3,4-DHPM moiety were released from the ILP **11** by treatment with sodium methoxide (1 equiv) in refluxing MeOH for 15 h. Cleavage by transesterification led to the starting ILP **1** and thiazole **12**, which could be easily separated by flash filtration[36] on alumina gel using AcOEt (R_f=1.0) as eluent. 3,4-DHPMs **12**(**a**–**d**) functionalized with a thiazole ring were obtained in good yields (70–73%) and the structure of the new DHPMs was ascertained by conventional techniques (^1H, ^{13}C NMR) and the purity was controlled by HRMS. The experiments demonstrate that the ILP bound β-ketoester **3** afforded the target 3,4-DHPMs **12** in moderate to good overall yields (37–50%) in five steps via Biginelli and Hantzsch reactions.

In order to establish the scope of the cyanomethyl chain appended to the 3,4-DHPM moiety, we were interested in the preparation of tetrazole derivatives using simple reaction conditions. Previous approaches to the tetrazole ring formation

presented some problems associated to (i) the need of highly toxic trialkyltin azide[37] in the conversion of arylnitrile intermediate to tetrazole, (ii) the use of hazardous reagents,[38] (iii) the use of expensive metallic species that generate dangerous metallic residues not only harmful to human health but also to the environment. Alternative approaches have been explored by the group of Lukyanov[39] under microwave irradiation from sterically hindered nitriles. Our goal was to minimize the use of expensive and hazardous metals and increase the overall efficiency of the tetrazole synthesis. Initially, our studies started by reaction of nitrile intermediate **8** and various solvents (EtOH, DMF), various quantities of sodium azide and ammonium chloride (Table 3) and different reaction temperature according to known procedures.[40]

Entries 3 and 5 show that the optimal reaction conditions involved a mixture constituted of 2 equiv of NaN_3 and NH_4Cl in DMF at 100 °C that gave after 24 h the desired ILP bound tetrazole **13** in good yields (**13a**: 79% and **13b**: 71%). After purification by washings with deionized water, the ILP bound tetrazole **13** was treated with sodium methoxide (2 equiv) in refluxing MeOH for 24 h followed by controlled acidification with a solution of 3 M HCl at room temperature. Due to the low miscibility of the expected tetrazole **14** in the acidic crude reaction mixture (pH 2), filtration and purification by washings (with cold deionized water) afforded the desired tetrazole methyl ester **14** (92–96% yields). According to this approach the compounds **14**(**a**,**b**) were prepared in 5 steps with good overall yields (**14a**: 61% and **14b**: 53%) and the structure was confirmed by conventional techniques (^1H, ^{13}C NMR, and HRMS).

3. Conclusion

In summary, we have developed a highly versatile and general ionic liquid phase protocol for the synthesis of new functionalized 3,4-dihydropyrimidine-2(1*H*)-ones. This approach is particularly attractive for the preparation of 3,4-DHPMs bearing a thiazole ring as bioisostere group in N-3 position with good overall yields using Biginelli and Hantzsch reactions. By applying this 'ionic liquid phase organic synthesis (IoLiPOS)' methodology we were able to extend this strategy to the synthesis of new 3,4-DHPMs with a tetrazole ring in N-3 position in five steps via the 3-cyanomethyl DHPM **8** as key intermediate. The further use of this scaffold intermediate **8** as a starting point of diversity is ongoing. We are currently exploring the scope and the potential of the 3-cyanomethyl 3,4-DHPM **8** grafted on the ionic liquid phase for the preparation and biological screening of a wider library.

4. Experimental

4.1. General

Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F_{254} (Merck) or neutral alumina oxide gel 60 F_{254} (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. IR spectra were recorded on a BIORAD FTS 175C spectrophotometer. ^1H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer and ^{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* is 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 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 (Merck Eurolab, Div. Prolabo, France) in quartz open reactor vessel fitted with 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 included 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, and Fluka France, and were used without further purification. The starting [HOC_2-mim][PF_6] ionic liquid phase **1**[11] was synthesized according to our previous method.

Table 3
Reaction conditions used for the synthesis of ILP bound tetrazole **13** after 24 h

Entry	X	NaN_3 (equiv)	NH_4Cl (equiv)	Solvent	Reaction temperature (°C)	Yield[a] of **13** (%)
1	Cl	2	2	—[b]	130	0
2	Cl	2	2	EtOH	79	0
3	Cl	2	2	DMF	100	79
4	Cl	1	1	DMF	100	93[c]
5	Br	2	2	DMF	100	71

[a] Isolated yields.
[b] Without solvent.
[c] Conversion of **8a** into **13a** estimated by ^1H NMR until disappearance of the starting product **8a**.

4.2. 1-[2-(Acetoacetyloxy) ethyl]-3-methyl-imidazolium hexafluorophosphate (3)

In a cylindrical quartz reactor (∅=1.8 cm) was placed a mixture of 1-(2-hydroxyethyl)-3-methyl-imidazolium hexafluorophosphate **1** (3.4 g, 13 mmol) and *tert*-butyl acetoacetate **2** (5.4 g, 33.8 mmol). The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was irradiated (after a ramp of 6 min from 25 to 170 °C) at 170 °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 product **3** was purified by washings with diethyl ether (2×25 ml) and AcOEt (2×50 ml). The expected product **3** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h and was obtained as white needles (mp=85–87 °C) in 90% yield. IR (KBr): 1712, 1746, 2977, 3168 cm^{-1}. ^1H NMR ($(CD_3)_2CO$, TMS): δ=2.21 (s, 3H); 3.65 (s, 2H); 4.03 (s, 3H); 4.55 (t, 2H, $^3J_{H,H}$=5.1 Hz); 4.64 (t, 2H, $^3J_{H,H}$=5.1 Hz); 7.64 (s, 1H, H-4 or H-5); 7.72 (s, 1H, H-4 or H-5);, 8.87 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2CO$, TMS): δ=30.16 (CH_3); 36.51 (NCH_3); 49.29 (CH_2); 49.82 (CH_2O); 63.32 (NCH_2); 123.57–124.60 (C-4, C-5); 137.97 (C-2); 167.68 (*O*CO); 202.11 (CH_3 *C*O). HRMS, *m*/*z* found: 211.1083 (calculated for $C_{10}H_{15}N_2O_3$, C^+ requires: 211.1082).

4.3. Standard procedure for the solventless three-component synthesis of 3,4-DHPMs 6(a,b)

A mixture of 1-[2-(acetoacetyloxy)ethyl]-3-imidazolium hexafluorophosphate **3** (483.1 mg, 1.35 mmol), commercial 4-chlorobenzaldehyde **4a** or 4-bromobenzaldehyde **4b** (1.35 mmol, 1 equiv), commercial methylurea **5** (300.4 mg, 4.06 mmol, 3 equiv), and 2 drops of concentrated HCl as catalyst was stirred vigorously

at 100 °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 **6** was collected by filtration and was purified by washing with diethyl ether (2×5 ml). The expected 3,4-DHPM **6** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure product **6** was characterized by ^{1}H, ^{13}C NMR, and HRMS.

*4.3.1. 1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**6a**)*

Yield=96%, white needles, mp=170–172 °C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ=2.46 (s, 3H, CH_3); 3.08 (s, 3H, $CONCH_3$); 3.79 (s, 3H, NCH_3); 4.42 (m, 4H, NCH_2CH_2O); 5.07 (d, 1H, J=3.8 Hz, H-4′); 7.12 (d, 2H, J=8.4 Hz, H-2″, H-6″); 7.36 (d, 1H, J=8.4 Hz, H-3″, H-5″); 7.59 (s, 1H, H-4 or H-5); 7.63 (s, 1H, H-4 or H-5); 8.12 (d, 1H, J=3.8 Hz, NH); 9.02 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ=16.14 (CH_3); 29.84 ($CONCH_3$); 35.78 (NCH_3); 47.93 (CH_2O); 51.53 (C-4′); 61.73 (CH_2N); 100.62 (C-5′); 122.38–123.53 (C-4, C-5); 127.97 (C-2″, C-6″); 128.46 (C-3″, C-5″); 131.98 (C-4″); 136.71 (C-2); 142.58 (C-1″); 152.75–152.80 (C-2′, C-6′); 164.97 ($CO_2CH_2CH_2$). HRMS, m/z found: 389.1383 (calculated for $C_{19}H_{22}N_4O_3^{35}Cl$, C^+ requires: 389.1380).

*4.3.2. 1-[2-[4-(4-Bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**6b**)*

Yield=93%, yellow needles, mp=184–186 °C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ=2.46 (s, 3H, CH_3); 3.08 (s, 3H, $CONCH_3$); 3.80 (s, 3H, NCH_3); 4.42 (m, 4H, NCH_2CH_2O); 5.05 (d, 1H, J=3.7 Hz, H-4′); 7.06 (d, 2H, J=8.4 Hz, H-2″, H-6″); 7.49 (d, 1H, J=8.4 Hz, H-3″, H-5″); 7.59 (s, 1H, H-4 or H-5); 7.62 (s, 1H, H-4 or H-5); 8.10 (d, 1H, J=3.8 Hz, NH); 9.00 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ=16.16 (CH_3); 29.85 ($CONCH_3$); 35.82 (NCH_3); 47.94 (CH_2O); 51.58 (C-4′); 61.75 (CH_2N); 100.56 (C-5′); 120.53 (C-4″); 122.39–123.55 (C-4, C-5); 128.34 (C-2″, C-6″); 131.39 (C-3″, C-5″); 136.72 (C-2); 143.00 (C-1″); 152.83–152.75 (C-2′, C-6′); 164.96 ($CO_2CH_2CH_2$). HRMS, m/z found: 433.0878 (calculated for $C_{19}H_{21}N_4O_3^{79}Br$, C^+ requires: 433.0875).

4.4. Typical procedure for the preparation of compounds 8(a,b) by N-3 alkylation of compounds 7(a,b)

In a 100 ml two-necked round bottomed flask, provided with a magnetic stirrer and reflux condenser, the compound **6a** or **6b** (7.5 mmol) was dispersed in dry acetonitrile (30 ml) at 0 °C. To this mixture, sodium hydride (600 mg, 15 mmol, 60% dispersion in mineral oil) was added portionwise under nitrogen and the reaction mixture was stirred for 5 min. After which chloroacetonitrile **7** (970 μl, 1134.06 mg, 15.02 mmol) was added dropwise at 0 °C over 20 min. The reaction mixture was stirred at 0 °C for 10 min then at 25 °C over a period of 18 h. After elimination of solvent in a rotary evaporator under reduced pressure, the crude reaction mixture was washed successively with Et_2O (2×25 ml), deionized water (2×25 ml), and pentane (2×25 ml). The desired product **8** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h. The product **7** was characterized by ^{1}H, ^{13}C NMR, and HRMS.

*4.4.1. 1-[2-[4-(4-Chlorophenyl)-3-(cyanomethyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**8a**)*

Yield=97%, brown powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.44 (s, 3H, CH_3); 3.20 (s, 3H, $CONCH_3$); 3.84 (s, 3H, NCH_3); 4.32–4.42 (m, 6H, NCH_2CH_2O, CH_2CN); 5.34 (s, 1H, H-4′); 7.22 (d, 2H, J=8.3 Hz, H-2″, H-6″); 7.39 (d, 1H, J=8.3 Hz, H-3″, H-5″); 7.67 (s, 1H, H-4 or H-5); 7.69 (s, 1H, H-4, H-5); 9.58 (s, 1H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6) δ=16.17 (CH_3); 30.82 ($CONCH_3$); 35.47 (CH_2CN); 35.84 (NCH_3); 47.94 (CH_2N); 58.77 (C-4′); 62.17 (CH_2O); 102.08 (C-5′); 116.29 (CN); 122.50–123.69 (C-4, C-5); 128.82–128.85 (C-2″, C-6″, C-3″, C-5″); 133.05 (C-4″); 136.81 (C-1″); 138.72 (C-2); 151.30–152.05 (C-2′; C-6′); 164.33 ($CO_2CH_2CH_2$). HRMS, m/z found: 428.1485 (calculated for $C_{21}H_{23}N_5O_3^{35}Cl$, C^+ requires: 428.1489).

*4.4.2. 1-[2-[4-(4-Bromophenyl)-3-(cyanomethyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**8b**)*

Yield=93%, brown powder. ^{1}H NMR (300 MHz, acetone-d_6) δ=2.56 (s, 3H, CH_3); 3.29 (s, 3H, $CONCH_3$); 4.05 (s, 3H, NCH_3); 4.22 (d, 1H, J=17.3 Hz, NCH_2CN); 4.51 (d, 1H, J=17.3 Hz, NCH_2CN); 4.60–4.71 (m, 4H, NCH_2CH_2O); 5.50 (s, 1H, H-4′); 7.30 (d, 2H, J=8.3 Hz, H-2″, H-6″); 7.51 (d, 1H, J=8.3 Hz, H-3″, H-5″); 7.67 (s, 1H, H-4 or H-5); 7.69 (s, 1H, H-4 or H-5); 9.07 (s, 1H, H-2). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.63 (CH_3); 31.27 ($CONCH_3$); 35.84 (CH_2CN); 36.69 (NCH_3); 49.38 (CH_2N); 60.13 (C-4′); 62.79 (CH_2O); 103.07 (C-5′); 116.47 (CN); 122.70 (C-4″); 123.55–124.76 (C-4, C-5); 130.11 (C-2″, C-6″); 132.72 (C-3″, C-5″); 137.54 (C-2); 140.15 (C-1″); 152.44–152.75 (C-2′, C-6′); 165.17 ($CO_2CH_2CH_2$). HRMS, m/z found: 472.0988 (calculated for $C_{21}H_{23}N_5O_3^{79}Br$, C^+ requires: 472.0984).

4.5. Preparation of 1-[2-[3-(2-amino-2-thioxoethyl)-4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (9)

In a 50 ml round bottomed flask fitted with a reflux condenser, the compound 1-[2-[4-(4-chlorophenyl)-3-(cyanomethyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate **8a** (3.13 mg, 0.55 mmol) was dissolved in methanol pa (40 ml) under vigorous magnetic stirring. To this solution, an aqueous solution of 40–48% ammonium sulfide $(NH_4)_2S$ (300 μl, 2.2 mmol, 4 equiv) was added and the resulting mixture was stirred at room temperature for 3 days. Excess of ammonium sulfide was eliminated under reduced pressure (10^{-2} Torr) for 3 h and the crude residue was washed with deionized water (2×50 ml). The desired insoluble compound **9** was collected by filtration and was washed again with deionized water (2×10 ml). The expected thioamide **9** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h. Yield=96%, brown foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.44 (s, 3H, CH_3); 3.16 (s, 3H, $CONCH_3$); 3.56 (d, 1H, J=17 Hz, NCH_2CS); 3.85 (s, 3H, NCH_3); 4.31–4.51 (m, 4H, NCH_2CH_2O); 4.54 (d, 1H, J=17 Hz, NCH_2CS); 5.18 (s, 1H, H-4′); 7.16 (d, 2H, J=8.4 Hz, H-2″, H-6″); 7.38 (d, 2H, J=8.3 Hz, H-3″, H-5″); 7.69 (br s, 2H, H-4, H-5); 9.06 (s, 1H, H-2); 9.17 (br s, 1H, NH_2); 9.75 (br s, 1H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ=16.18 (CH_3); 30.85 ($CONCH_3$); 35.85 (NCH_3); 47.81 (CH_2N); 54.96 (NCH_2CS); 57.76 (C-4′); 61.78 (CH_2O); 101.45 (C-5′); 122.69–123.64 (C-4, C-5); 128.37–128.65 (C-2″, C-6″, C-3″, C-5″); 132.49 (C-4″); 136.70 (C-1″); 139.73 (C-2); 151.66–152.49 (C-2′, C-6′); 164.37 ($CO_2CH_2CH_2$); 201.52 (C=S). HRMS, m/z found: 462.1364 (calculated for $C_{21}H_{25}N_5O_3^{35}ClS$, C^+ requires: 462.1367).

4.6. Standard procedure for the synthesis of compounds 11(a–d) functionalized with a thiazole group

In a 50 ml round bottomed flask, provided with a magnetic stirrer and reflux condenser, 1-[2-[3-(2-amino-2-thioxoethyl)-4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate **9** (316 mg, 0.52 mmol) and bromoacetophenone **10a** (103.5 mg, 0.52 mmol) or chloroacetone **10b** (55.76 mg, 48 μl, 0.52 mmol) or 2-bromo-4′-chloroacetophenone **10c** (120 mg, 0.52 mmol) or 2-

bromo-4′-methoxyacetophenone **10d** (119 mg, 0.52 mmol) were dispersed in dry dimethylformamide (0.5 ml). The reaction mixture was heated at 90 °C for 16 h under vigorous magnetic stirring, then cooled down to room temperature. The reaction mixture was successively washed with deionized water (2×5 ml), Et_2O (2×5 ml), and pentane (2×5 ml). The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h. The pure product **11** was characterized by ^1H, ^{13}C NMR, and HRMS.

*4.6.1. 1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-3-[(4-phenyl-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**11a**)*

Yield=85%, brown foam. ^1H NMR (300 MHz, acetone-d_6) δ=2.56 (s, 3H, CH_3); 3.31 (s, 3H, $CONCH_3$); 3.95 (s, 3H, NCH_3); 4.48–4.54 (m, 5H, NCH_2CH_2O, NCH_2C-2‴); 5.20 (d, 1H, J=16 Hz, NCH_2C-2‴); 5.59 (s, 1H, H-4′); 7.32–7.47 (m, 7H, H-2″, H-6″, H-3″, H-5″, H-4‴, H-3‴, H-5‴); 7.55 (br s, 1H, H-4 or H-5); 7.57 (br s, 1H, H-4 or H-5); 7.84 (s, 1H, H-5‴); 7.96 (d, 2H, J=7.2 Hz, H-2‴, H-6‴); 8.95 (s, 1H, H-2). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.74 (CH_3); 31.43 ($CONCH_3$); 36.58 (NCH_3); 48.54 (NCH_2C-2‴); 49.37 (CH_2N); 59.29 (C-4′); 61.75 (CH_2O); 102.98 (C-5′); 114.93 (C-5‴); 123.49–124.54 (C-4, C-5); 126.20 (C-2‴, C-6‴); 128.09–129.49–129.51–129.73 (C-2″, C-6″, C-3″, C-5″, C-5‴, C-6‴, C-4‴); 134.02 (C-1‴); 135.18 (C-4″); 137.43 (C-2); 140.68 (C-1″); 152.73–153.54 (C-2′, C-6′); 155.50 (C-4‴); 165.38 ($CO_2CH_2CH_2$); 167.87 (C-2‴). HRMS, m/z found: 562.1683 (calculated for $C_{29}H_{29}N_5O_3^{35}ClS$, C^+ requires: 562.1680).

*4.6.2. 1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-3-[(4-methyl-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**11b**)*

Yield=65%, brown foam. ^1H NMR (300 MHz, acetone-d_6) δ=2.34 (s, 3H, C-4‴CH_3); 2.55 (s, 3H, CH_3); 3.29 (s, 3H, $CONCH_3$); 4.04 (s, 3H, NCH_3); 4.36 (d, 1H, J=16.8 Hz, NCH_2C-2‴); 4.48–4.67 (m, 4H, NCH_2CH_2O); 5.06 (d, 1H, J=16 Hz, NCH_2C-2‴); 5.47 (s, 1H, H-4′); 7.06 (s, 1H, H-5‴); 7.29 (m, 4H, H-2″, H-6″, H-3″, H-5″); 7.61 (sl, 1H, H-4 or H-5); 7.69 (br s, 1H, H-4 or H-5); 8.97 (s, 1H, H-2). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.70–16.92 (CH_3, CH_3C-4‴); 31.39 ($CONCH_3$); 36.66 (NCH_3); 48.16 (NCH_2C-2‴); 49.44 (CH_2N); 59.17 (C-4′); 62.69 (CH_2O); 102.91 (C-5′); 115.34 (C-5‴); 123.59–124.69 (C-4, C-5); 129.44–129.63 (C-2″, C-6″, C-3″, C-5″); 133.96 (C-4″); 137.51 (C-2); 140.71 (C-1″); 152.69–153.10–153.47 (C-2′, C-6′, C-4‴); 165.32 ($CO_2CH_2CH_2$); 166.75 (C-2‴). HRMS, m/z found: 500.1531 (calculated for $C_{24}H_{27}N_5O_3^{35}ClS$, C^+ requires: 500.1523).

*4.6.3. 1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-3-[(4-(4-chlorophenyl)-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**11c**)*

Yield=88%, brown foam. ^1H NMR (300 MHz, acetone-d_6) δ=2.57 (s, 3H, CH_3); 3.31 (s, 3H, $CONCH_3$); 3.98 (s, 3H, NCH_3); 4.53–4.67 (m, 5H, NCH_2CH_2O, NCH_2C-2‴); 5.15 (d, 1H, J=16.0 Hz, NCH_2C-2‴); 5.61 (s, 1H, H-4′); 7.31 (m, 4H, H-2″, H-6″, H-3″, H-5″); 7.46 (d, 2H, J=8.5 Hz, H-3‴, H-5‴); 7.57 (sl, 1H, H-4 or H-5); 7.62 (sl, 1H, H-4 or H-5); 7.89 (s, 1H, H-5‴); 7.96 (d, 2H, J=8.5 Hz, H-2‴, H-6‴); 9.13 (s, 1H, H-2). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.76 (CH_3); 31.44 ($CONCH_3$); 36.65 (NCH_3); 48.74 (NCH_2C-2‴); 49.43 (CH_2N); 59.52 (C-4′); 62.80 (CH_2O); 103.03 (C-5′); 115.57 (C-5‴); 123.57–124.61 (C-4, C-5); 128.54 (C-2‴, C-6‴); 129.48 (C-5‴, C-3‴); 129.57–129.76 (C-2″, C-6″, C-3″, C-5″); 133.92–133.97–134.02 (C-1‴, C-4″, C-4‴); 137.55 (C-2); 140.79 (C-1″); 152.72–155.54 (C-2′, C-6′); 154.17 (C-4‴); 165.42 ($CO_2CH_2CH_2$); 168.30 (C-2‴). HRMS, m/z found: 596.1299 (calculated for $C_{29}H_{28}N_5O_3^{35}Cl_2S$, C^+ requires: 596.1290).

*4.6.4. 1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-3-[(4-(4-methoxyphenyl)-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**11d**)*

Yield=84%, brown foam. ^1H NMR (300 MHz, acetone-d_6) δ=2.56 (s, 3H, CH_3); 3.31 (s, 3H, $CONCH_3$); 3.84 (s, 3H, NCH_3); 3.95 (s, 3H, OCH_3); 4.48 (d, 1H, J=16 Hz, NCH_2C-2‴); 4.54–4.65 (m, 4H, NCH_2CH_2O); 5.20 (d, 1H, J=16 Hz, NCH_2C-2‴); 5.59 (s, 1H, H-4′); 7.00 (d, 2H, J=8.8 Hz, H-3‴, H-5‴); 7.32 (br s, 4H, H-2″, H-6″, H-3″, H-5″); 7.54 (br s, 1H, H-4 or H-5); 7.58 (sl, 1H, H-4 or H-5); 7.68 (s, 1H, H-5‴); 7.90 (d, 2H, J=8.8 Hz, H-2‴, H-6‴); 9.02 (s, 1H, H-2). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.75 (CH_3); 31.44 ($CONCH_3$); 36.62 (NCH_3); 48.45 (NCH_2CS); 49.38 (CH_2N); 55.60 (OCH_3); 59.17 (C-4′); 62.83 (CH_2O); 102.98 (C-5′); 112.90 (C-5‴); 114.83 (C-5‴, C-3‴); 123.52–124.56 (C-4, C-5); 128.04 (C-1‴); 128.29 (C-6‴, C-2‴); 129.51–129.73 (C-2″, C-6″, C-3″, C-5″); 134.01 (C-4″); 137.56 (C-2); 140.71 (C-1″); 152.79–153.54 (C- 2′, C-6′); 155.49 (C-4‴); 160.54 (C-4‴); 165.40 ($CO_2CH_2CH_2$); 167.65 (C-2‴). HRMS, m/z found: 592.1790 (calculated for $C_{30}H_{31}N_5O_4^{35}ClS$, C^+ requires: 592.1785).

4.7. Standard procedure for the preparation of compounds 12(a–c) by transesterification of ionic liquid phase bound 3,4-DHPMs 11(a–c)

To a solution of ionic liquid phase bound 3,4-DHPM **11** (740 mmol) in anhydrous methanol (15 ml), in a 50 ml round bottomed flask fitted with a reflux condenser, was added commercial sodium methoxide (40 mg, 740 mmol) in one portion under nitrogen. After vigorous stirring at 78 °C for 18 h, the crude reaction mixture was half concentrated in vacuo. Then, the resulting reaction mixture was submitted to purification by flash chromatography (column: ∅=1 cm, H=4 cm) on neutral alumina oxide 90 gel (Merck) using AcOEt as eluent. The solvent of the desired fraction (R_f=0.9) was eliminated by rotary evaporation with reduced pressure and the crude reaction mixture was further dried at 25 °C for 3 h under high vacuum (10^{-2} Torr), which gave the expected product **12**. The pure product **12** was characterized by ^1H, ^{13}C NMR, and HRMS.

*4.7.1. Methyl 4-(4-chlorophenyl)-1,6-dimethyl-3-[(4-phenyl-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**12a**)*

Yield=73%, white needles, mp=220–222 °C. IR (KBr): 1277, 1490, 1669, 1707, 2950, 3010, 3277 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=2.56 (s, 3H, CH_3); 3.32 (s, 3H, $CONCH_3$); 3.60 (s, 3H, OCH_3); 4.43 (d, 1H, J=16 Hz, NCH_2C-2″); 5.26 (d, 1H, J=15.9 Hz, NCH_2C-2″); 5.65 (s, 1H, H-4); 7.29–7.47 (m, 7H, H-2′, H-6′, H-3′, H-5′, H-4‴, H-3‴, H-5‴); 7.82 (s, 1H, H-5″); 8.00 (d, 2H, J=7.2 Hz, H-2‴, H-6‴). ^{13}C NMR (75 MHz, $CDCl_3$) δ=16.45 (CH_3); 31.11 ($CONCH_3$); 47.33 (NCH_2C-2″); 51.18 (OCH_3); 58.07 (C-4); 103.81 (C-5); 113.51 (C-5″); 126.11 (C-2‴, C-6‴); 127.92–128.16–128.52–128.64 (C-2′, C-6′, C-3′, C-5′, C-5‴, C-6‴, C-4‴); 133.62 (C-1‴); 134.09 (C-4′); 139.01 (C-1′); 149.33 (C-6); 153.27 (C-2); 155.07 (C-4″); 165.70 (CO_2CH_3); 166.15 (C-2″). HRMS, m/z found: 293.0703 (calculated for $C_{14}H_{14}N_2O_3^{35}Cl$, $[M-C_{10}H_8NS]^+$ requires: 293.0693).

*4.7.2. Methyl 4-(4-chlorophenyl)-1,6-dimethyl-3-[(4-methyl-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**12b**)*

Yield=71%, brown foam. IR (KBr): 1210, 1457, 1674, 1705, 2853, 2952, 3274 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ=2.33 (s, 3H, C-4″CH_3); 2.55 (s, 3H, CH_3); 3.30 (s, 3H, $CONCH_3$); 3.60 (s, 3H, OCH_3); 4.30 (d, 1H, J=16 Hz, NCH_2C-2″); 5.14 (d, 1H, J=16 Hz, NCH_2C-2″); 5.50 (s, 1H, H-4); 7.03 (s, 1H, H-5″); 7.32 (br s, 4H, H-2′, H-6′, H-3′, H-5′). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.63–16.95 (CH_3, CH_3C-

4″); 31.32 ($CONCH_3$); 47.98 (NCH_2C-2″); 51.45 (OCH_3); 59.21 (C-4); 104.15 (C-5); 115.19 (C-5″); 129.43–129.67 (C-2′, C-6′, C-3′, C-5′); 133.94 (C-4′); 141.11 (C-1′); 150.99 (C-6); 153.23–153.77 (C-2; C-4″); 166.40 (CO_2CH_3); 166.82 (C-2″). HRMS, *m*/*z* found: 293.0703 (calculated for $C_{14}H_{14}N_2O_3^{35}Cl$, $[M-C_{10}H_8NS]^+$ requires: 293.0693).

4.7.3. Methyl 4-(4-chlorophenyl)-1,6-dimethyl-3-[(4-(4-chlorophenyl)-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (**12c**)

Yield=71%, brown foam. IR (KBr): 1277, 1490, 1669, 1705, 2948, 3097, 3301 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ=2.56 (s, 3H, CH_3); 3.32 (s, 3H, $CONCH_3$); 3.60 (s, 3H, OCH_3); 4.48 (d, 1H, *J*=16 Hz, NCH_2C-2″); 5.21 (d, 1H, *J*=16 Hz, NCH_2C-2″); 5.64 (s, 1H, H-4); 7.33 (m, 4H, H-2′, H-6′, H-3′, H-5′); 7.46 (d, 2H, *J*=8.6 Hz, H-3‴, H-5‴); 7.87 (s, 1H, H-5″); 7.97 (d, 2H, *J*=8.6 Hz, H-2‴, H-6‴). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.61 (CH_3); 31.34 ($CONCH_3$); 48.31 (NCH_2C-2″); 51.47 (OCH_3); 59.40 (C-4); 104.15 (C-5); 115.46 (C-5″); 128.48 (C-2‴, C-6‴); 129.54 (C-5‴, C-3‴); 129.47–129.55 (C-2′, C-6′, C-3′, C-5′); 133.90–133.92–133.95 (C-1‴, C-4′, C-4‴); 140.95 (C-1′); 150.87 (C-2); 153.76 (C-6); 154.23 (C-4″); 166.30 (CO_2CH_3); 167.98 (C-2″). HRMS, *m*/*z* found: 293.0675 (calculated for $C_{14}H_{14}N_2O_3^{35}Cl$, $[M-C_{10}H_7NSCl]^+$ requires: 293.0693), found: 470.0504 (calculated for $C_{23}H_{18}N_3O_2^{35}Cl_2S$, $[M-OMe]^+$ requires: 470.0497).

4.7.4. Methyl 4-(4-chlorophenyl)-1,6-dimethyl-3-[(4-(4-methoxyphenyl)-1,3-thiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**12d**)

Yield=70%, brown foam. IR (KBr): 1249, 1490, 1670, 1702, 2948, 3101, 3304 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ=2.56 (s, 3H, CH_3); 3.31 (s, 3H, $CONCH_3$); 3.60 (s, 3H, OCH_3); 3.83 (s, 3H, C-4‴OCH_3); 4.40 (d, 1H, *J*=16 Hz, NCH_2C-2″); 5.25 (d, 1H, *J*=16 Hz, NCH_2C-2″); 5.65 (s, 1H, H-4); 6.98 (d, 2H, *J*=8.9 Hz, H-3‴, H-5‴); 7.34 (q, 4H, *J*=7.5 Hz, H-2′, H-6′, H-3′, H-5′); 7.64 (s, 1H, H-5″); 7.90 (d, 2H, *J*=8.9 Hz, H-2‴, H-6‴). ^{13}C NMR (75 MHz, acetone-d_6) δ=16.62 (CH_3); 31.35 ($CONCH_3$); 48.10 (NCH_2C-2″); 51.48 (OCH_3); 55.59 (C-4‴OCH_3); 59.22 (C-4); 104.24 (C-5); 112.77 (C-5″); 114.83 (C-5‴, C-3‴); 128.21 (C-1‴); 128.35 (C-6‴, C-2‴); 129.48–129.68 (C-2′, C-6′, C-3′, C-5′); 134.00 (C-4′); 141.06 (C-1′); 151.04 (C-6); 153.85 (C-2); 155.71 (C-4″); 160.61 (C-4‴); 166.43 (CO_2CH_3); 167.47 (C-2″). HRMS, *m*/*z* found: 293.0692 (calculated for $C_{14}H_{14}N_2O_3^{35}Cl$, $[M-C_{11}H_{10}NOS]^+$ requires: 293.0693), found: 205.0546 (calculated for $C_{11}H_{11}N_3OS$, $[M+H]^+$ requires: 205.0561).

4.8. Typical procedure for the preparation 1-[2-[4-(4-halogenophenyl)-1,6-dimethyl-2-oxo-3-(2*H*-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate 13(a,b)

In a 50 ml round bottomed flask, provided with a magnetic stirrer and reflux condenser, 1-[2-[4-(4-halogenophenyl)-3-(cyanomethyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate **8** (0.63 mmol), sodium azide (83 mg, 1.26 mmol, 2 equiv), and ammonium chloride (68 mg, 1.26 mmol, 2 equiv) were dispersed in dry dimethylformamide (0.5 ml). The reaction mixture was heated at 110 °C for 24 h under vigorous magnetic stirring, then cooled down to room temperature. To the crude reaction mixture was added deionized water (2×5 ml) and the desired insoluble ionic liquid phase **13** was collected by filtration, then washed with deionized water (5 ml). The compound **13** was dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure product **13** was characterized by ^1H, ^{13}C NMR, and HRMS.

4.8.1. 1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-2-oxo-3-(2H-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**13a**)

Yield=79%, brown foam. ^1H NMR (300 MHz, DMSO-d_6) δ=2.42 (s, 3H, CH_3); 3.18 (s, 3H, $CONCH_3$); 3.92 (s, 3H, NCH_3); 4.10 (d, 1H, *J*=15 Hz, NCH_2C-5‴); 4.25–4.43 (m, 4H, NCH_2CH_2O); 5.14 (d, 1H, *J*=15 Hz, NCH_2C-5‴); 5.38 (s, 1H, H-4′); 7.17 (d, 2H, *J*=8.3 Hz, H-2″, H-6″); 7.38 (d, 1H, *J*=8.3 Hz, H-3″, H-5″); 7.69 (s, 1H, H-4 or H-5); 7.71 (s, 1H, H-4 or H-5); 9.11 (s, 1H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6) δ=16.10 (CH_3); 30.89 ($CONCH_3$); 35.88 (NCH_3); 38.66 (NCH_2C-5‴); 48.01 (CH_2N); 56.38 (C-4′); 61.97 (CH_2O); 101.52 (C-5′); 122.47–123.88 (C-4, C-5); 128.66–128.74 (C-2″, C-6″, C-3″, C-5″); 132.63 (C-4″); 136.86 (C-1″); 139.35 (C-2); 151.58–152.41 (C-2′, C-6′); 154.68 (C-5‴); 164.37 ($CO_2CH_2CH_2$). ^{31}P NMR (121 MHz, DMSO-d_6) δ=−144.07 (hept, J_{P-F}=711 Hz, PF_6^-). HRMS, *m*/*z* found: 493.1477 (calculated for $C_{21}H_{23}N_8O_3^{35}ClNa$, $[C-H+Na]^+$ requires: 493.1479), found: 509.1216 (calculated for $C_{21}H_{23}N_3O_3^{35}ClK$, $[C-H+K]^+$ requires: 509.1219).

4.8.2. 1-[2-[4-(4-Bromophenyl)-1,6-dimethyl-2-oxo-3-(2H-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (**13b**)

Yield=71%, brown foam. ^1H NMR (300 MHz, DMSO-d_6) δ=2.42 (s, 3H, CH_3); 3.18 (s, 3H, $CONCH_3$); 3.92 (s, 3H, NCH_3); 4.10 (d, 1H, *J*=15 Hz, NCH_2C-5‴); 4.22–4.43 (m, 4H, NCH_2CH_2O); 5.14 (d, 1H, *J*=15 Hz, NCH_2C-5‴); 5.37 (s, 1H, H-4′); 7.10 (d, 2H, *J*=8.3 Hz, H-2″, H-6″); 7.52 (d, 1H, *J*=8.3 Hz, H-3″, H-5″); 7.69 (s, 1H, H-4 or H-5); 7.72 (s, 1H, H-4 or H-5); 9.12 (s, 1H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6) δ=16.10 (CH_3); 30.89 ($CONCH_3$); 35.89 (NCH_3); 39.18 (NCH_2C-5‴); 47.99 (CH_2N); 56.41 (C-4′); 61.95 (CH_2O); 101.46 (C-5′); 121.21 (C-4″); 122.47–123.86 (C-4, C-5); 128.96 (C-2″, C-6″); 131.67 (C-3″, C-5″); 136.85 (C-1″); 139.74 (C-2); 151.57–152.39 (C-2′; C-6′); 154.64 (C-5‴); 164.35 ($CO_2CH_2CH_2$). ^{31}P NMR (121 MHz, DMSO-d_6) δ=−143.07 (hept, J_{P-F}=711 Hz, PF_6^-). HRMS, *m*/*z* found: 515.1164 (calculated for $C_{21}H_{24}N_8O_3^{79}Br$, C^+ requires: 515.1158), found: 537.0990 (calculated for $C_{21}H_{23}N_8O_3^{79}BrNa$, $[C-H+Na]^+$ requires: 537.0974).

4.9. Standard procedure for the preparation of compounds 14(a,b) by transesterification of ionic liquid phase bound 3,4-DHPMs 13(a,b)

In a 50 ml round bottomed flask, provided with a magnetic stirrer and reflux condenser, a mixture of ionic liquid phase **13** (370 mmol, 1 equiv) and commercial sodium methoxide (40 mg, 740 mmol, 2 equiv) in anhydrous methanol (15 ml) was heated at 78 °C for 18 h under vigorous magnetic stirring. After cooling down to room temperature, the crude reaction mixture was concentrated in vacuo. To the crude residue was added deionized water (5 ml) and it was acidified at pH 2 with 3 M hydrochloric acid. The desired insoluble N-3 functionalized 3,4-DHPM **14** was collected by filtration and was purified by washings with deionized water (2×5 ml) and was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure product **14** was characterized by ^1H, ^{13}C NMR, and HRMS.

4.9.1. Methyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3-(2H-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**14a**)

Yield=92%, brown foam. IR (KBr): 1211, 1655, 1699, 2947, 3284, 3522 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ=2.48 (s, 3H, CH_3); 3.20 (s, 3H, $CONCH_3$); 3.57 (s, 3H, OCH_3); 4.36 (d, 1H, *J*=16 Hz, NCH_2C-5″); 5.02 (d, 1H, *J*=16 Hz, NCH_2C-5″); 5.42 (s, 1H, H-4); 7.29 (d, 2H, *J*=8.1 Hz, H-2′, H-6′); 7.40 (d, 1H, *J*=8.1 Hz, H-3′, H-5′). ^{13}C NMR

(75 MHz, DMSO-d_6) δ=16.58 (CH_3); 31.21 ($CONCH_3$); 39.98 (NCH_2C-5″); 51.63 (OCH_3); 58.38 (C-4); 103.02 (C-5); 129.09–129.14 (C-2′, C-6′, C-3′, C-5′); 133.05 (C-4′); 140.00 (C-1′); 150.49–153.05 (C-2, C-6); 154.09 (C-5″); 165.86 (CO_2CH_3). HRMS, *m*/*z* found: 295.0653 (calculated for $C_{14}H_{14}N_2O_3^{35}Cl$, $[M-CH_2CN_3NH]^+$ requires: 295.0664).

4.9.2. Methyl 4-(4-bromophenyl)-1,6-dimethyl-2-oxo-3-(2H-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**14b**)

Yield=96%, brown foam. IR (KBr): 1211, 1459, 1629, 1668, 1702, 2952, 3265, 3635 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ=2.46 (s, 3H, CH_3); 3.19 (s, 3H, $CONCH_3$); 3.57 (s, 3H, OCH_3); 4.38 (d, 1H, *J*=16 Hz, NCH_2C-5″); 5.03 (d, 1H, *J*=16 Hz, NCH_2C-5″); 5.41 (s, 1H, H-4); 7.22 (d, 2H, *J*=8.1 Hz, H-2′, H-6′); 7.53 (d, 2H, *J*=8.1 Hz, H-3′, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6) δ=16.56 (CH_3); 31.19 ($CONCH_3$); 39.97 (NCH_2C-5″); 51.62 (OCH_3); 58.54 (C-4); 102.96 (C-5); 121.63 (C-4′); 129.37 (C-2′, C-6′); 132.04 (C-3′, C-5′); 140.36 (C-1′); 150.46–153.02 (C-2, C-6); 153.85 (C-5″); 165.81 (CO_2CH_3). HRMS, *m*/*z* found: 337.0174 (calculated for $C_{14}H_{14}N_2O_3^{79}Br$, $[M-C_2H_3N_4]^+$ requires: 337.0188).

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