Tetrahedron 66 (2010) 986–994

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using ionic liquid-phase organic synthesis (IoLiPOS) methodology

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ARTICLE INFO

Article history:
Received 13 October 2009
Received in revised form
16 November 2009
Accepted 18 November 2009
Available online 24 November 2009

Keywords:
Ionic liquid
Liquid phase
1,2,4-Oxadiazole
Bioisostere
O-acylamidoxime
Amidoxime

ABSTRACT

New 3,5-disubstituted 1,2,4-oxadiazoles were synthesized in five steps by ionic liquid-phase organic synthesis (IoLiPOS) methodology. The strategy involved the preparation of amidoxime from the ionic liquid-phase bound arylnitrile. Addition of various carboxylic acid to the amidoxime produced the expected 3,5-disubstituted 1,2,4-oxadiazoles via the stable *O*-acyl amidoxime intermediate grafted on the ionic liquid-phase. The 1,2,4-oxadiazoles were easily cleaved by transesterification under mild reaction conditions in high purity with good overall yields. The structures of the intermediates in each step were verified by routine spectroscopic analysis (^{1}H, ^{13}C NMR, and HRMS).

1. Introduction

Nitrogen–oxygen heterocyclic derivatives are of synthetic interest because they represent an important class of natural and non-natural products, many of which exhibit biological activities. The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) relies on from the occurrence of 1,2,4-oxadiazoles in biologically active compounds and natural compounds.[1] This motif is often used as an amide or ester bioisostere.[2] Bioisosteric replacement of the amide moiety represents an area, that is, currently a center of focus because of its implications in peptide chemistry and the development of peptidomimetics.[3] The 1,2,4-oxadiazole scaffold is also found in several drugs and drug leads[4] including the metabrotropic glutamate subtype 5 (mGlu5) receptor antagonist[5] A (Fig. 1) and the potent S1P1 agonist[6] B. Compound D showed a promising profile as a lead compound[7] for the endogenous cannabinoïd CB2 receptor. Furthermore, derivatives C and E containing 1,2,4-oxadiazole ring systems have been identified, respectively, as β-II-tryptase inhibitor[8] and serotoninergic ($5\text{-}HT_3$).[9] Moreover, the 1,2,4-oxadiazole nucleus is the core structural unit of the muscarinic agonist[10] F.

There is a continual need for the development of new technologies that enable the rapid and efficient construction of biologically interesting molecules.[11] The application of automated methods to the synthesis of focused libraries to populate screening collections is an important field of research, particularly for the biopharmaceutical sector. The use of combinatorial chemistry techniques has become common place to generate compounds for the screening and optimization tools for library generation in drug discovery.[12] Liquid-phase combinatorial synthesis[13] offers several advantages: (i) the large excess of reagents typically used in solid-supported synthesis is normally not required, (ii) the purification is possible after each step, (iii) the reactions may be realized in homogeneous solution, (iv) characterization of immobilized intermediates is also straightforward because the soluble polymer support does not interfere with spectroscopic methods. In recent years, task-specific ionic liquids (TSILs)[14] and ionic liquid-phases (ILPs)[15] —a subclass of TSILs as alternative soluble supports for liquid-phase organic synthesis of small molecules[16]— are receiving growing attention due to their tuneable features for various targeted chemical tasks and the advantages as homogeneous supports. This concept initially developed in our laboratory[17] was successfully used to a wide range of applications[18] in solution-phase combinatorial synthesis.[19] In view of the emerging importance of TSILs as alternatives to classical soluble polymeric matrices in combinatorial chemistry, our aim in this study was to develop

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0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.079

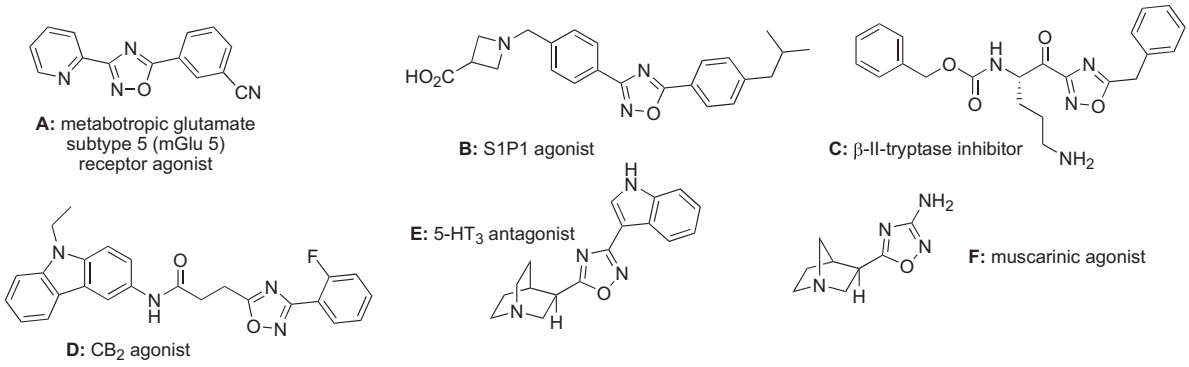


Figure 1. Selected biologically active 1,2,4-oxadiazoles.

a novel ionic liquid-phase strategy toward possible bioactive 3,5-disubstituted 1,2,4-oxadiazoles according to the 'ionic liquid-phase organic synthesis (IoLiPOS)' methodology.

2. Results and discussion

For the preparation of 1,2,4-oxadiazole scaffold, five general synthetic methods are used: (i) cyclization of the *O*-acyl amidoxime[20] formed from reaction of the amidoxime with an acyl chloride or a carboxylic acid, (ii) condensation of *N*-acylamidoximes, (iii) 1,3-dipolar cycloaddition of nitrile oxides to nitriles,[1] (iv) oxidation of 4,5-dihydro-1,2,4-oxadiazoles[21] and (v) electrocyclic ring closure of nitrenoids. For this study, the 1,2,4-oxadiazole can be built from an arylnitrile, hydroxylamine, and a carboxylic acid as building blocks. Thus, arylnitrile and hydroxylamine are converted into amidoxime (Fig. 2) and the *O*-acyl amidoxime is issued from condensation of amidoxime with a carboxylic acid.

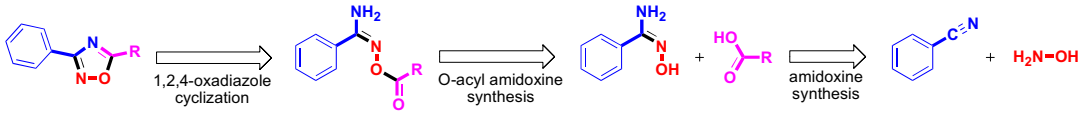
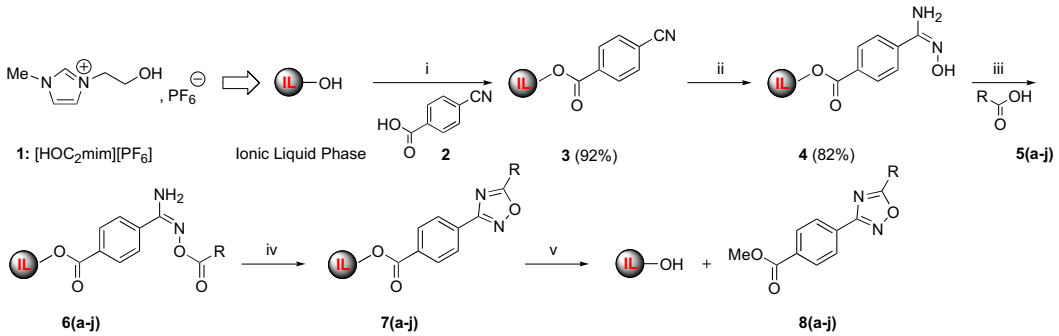


Figure 2. Retrosynthetic strategy toward 3,5-disubstituted 1,2,4-oxadiazole.

One of the common transformations in solid-phase organic synthesis (SPOS), in liquid-phase organic synthesis (LPOS) or in ionic liquid-phase organic synthesis (IoLiPOS) involves the construction of an ester linkage between solid, liquid or ionic liquid supported hydroxy or halogen functionality and carboxylic acid derivative. For this project, the carboxylic function will served as site of attachment to the ionic liquid-phase. As a suitable model reaction for ionic liquid-phase supported organic synthesis, we have chosen to use arylnitrile bound to the ionic liquid moiety (from commercial 4-cyanobenzoic acid) as novel task-specific ionic liquid. In this study, we have examined the chemical and physical properties of the 1-(2-hydroxyethyl)-3-methyl imidazolium hexafluorophosphate ([HOC_2mim][PF_6]) in IoLiPOS methodology. The starting ILP **1** used in Scheme 1, readily available from the reaction of 1-methylimidazole and 2-chloroethanol, presents a dynamic viscosity of 336 cPo at 25 °C and a solution like environment for bound molecules.

For the preparation of the starting ionic liquid-phase bound 4-cyanobenzoic acid **3**, the activation of the carboxylic group by carbodiimide still constitutes the most frequently used method. The esterification of 4-cyanobenzoic acid **2** with the ILP **1** in dry MeCN with 1.1 equiv of dicyclohexyl carbodiimide[22] (DCC) and 2% of 4-dimethylaminopyridine[23] (DMAP) as catalyst produced the functionalized ionic liquid phase **3** in 92% yield (Table 1). During the work-up, insoluble dicyclohexylurea (DCHU) was eliminated first by filtration to ensure the final purity of the new functionalized ionic liquid phase, then on a pad of Celite® to remove the residual traces of DCHU followed by evaporation of the solvent in vacuo. The crude ILP **3** was washed twice with AcOEt (1:5 w/v) and was further dried under high vacuum (10^{-2} Torr) at 25 °C for 24 h. The ILP **3** was characterized by mass spectrometry and proton NMR, confirming that in this esterification the major compound has a molecular ion corresponding to the appropriate product.

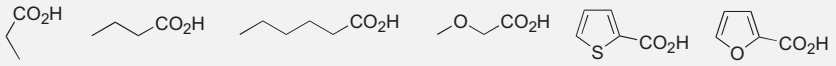
In the second step, the amidoxime **4** was obtained from the ILP bound arylnitrile **3** by treatment with hydroxylamine hydrochloride in the presence of potassium hydroxide in ethanol. As illustrated in Table 2, the reaction conditions investigated for the preparation of the amidoxime **4** are presented. Entry 1 shows with an equivalent mixture of KOH and hydroxylamine (1.5 equiv) gave

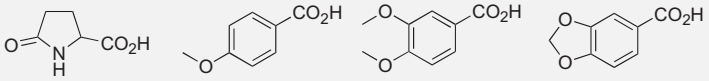


Scheme 1. Reagent and reaction conditions: (i) **2** 1.1 equiv, DCC 1.1 equiv, DMAP 2%, dry MeCN, 25 °C, 24 h. (ii) NH_2OH HCl 1.6 equiv, KOH 1.62 equiv, EtOH abs, 0 °C, 30 min, then **3** 1 equiv, reflux, 18 h. (iii) DCC 1.02 equiv, DMAP 6–8%, **5** 1.1 equiv, dry MeCN, 25 °C, 48 h. (iv) H_2O, reflux, 24 h. (v) MeONa 0.75 equiv, MeOH, reflux, 24 h.

Table 1
Results for the preparation of ionic liquid-phases **3**, **4**, ionic liquid-phase bound acylated aldoximes **6**(**a**–**j**) and ionic liquid-phase bound 1,2,4-oxadiazoles **7**(**a**–**j**)

Product	Starting compounds	R	Yield[a] (%)	Overall yield[b] (%)
3	**1**+**2**	—	92	—
4	**3**	—	82	75
6a	**4**+**5a**	$MeCH_2$	89	67
6b	**4**+**5b**	$Me(CH_2)_2$	84	63
6c	**4**+**5c**	$Me(CH_2)_4$	90	68
6d	**4**+**5d**	$MeOCH_2$	91	68
6e	**4**+**5e**	2-thiophenyl	89	67
6f	**4**+**5f**	2-furanyl	85	64
6g	**4**+**5g**	5-oxo-2-pyrrolidinyl	87	65
6h	**4**+**5h**	*p*-$MeOC_6H_4$	87	65
6i	**4**+**5i**	3,4-$(MeO)_2C_6H_3$	85	64
6j	**4**+**5j**	3,4-$(CH_2O_2)C_6H_3$	87	65
7a	**6a**	$MeCH_2$	90	60
7b	**6b**	$Me(CH_2)_2$	90	60
7c	**6c**	$Me(CH_2)_4$	71	64
7d	**6d**	$MeOCH_2$	98	67
7e	**6e**	2-thiophenyl	93	62
7f	**6f**	2-furanyl	89	57
7g	**6g**	5-oxo-2-pyrrolidinyl	66	43
7h	**6h**	*p*-$MeOC_6H_4$	97	63
7i	**6i**	3,4-$(MeO)_2C_6H_3$	93	60
7j	**6j**	3,4-$(CH_2O_2)C_6H_3$	97	63


5a **5b** **5c** **5d** **5e** **5f**


5g **5h** **5i** **5j**

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

Table 2
Results of reaction conditions evaluated for the preparation of ionic liquid-phase bound amidoxime **4**

Entry	KOH (equiv)	NH_2OH HCl (equiv)	Yield[a] (%)
1	1.5	1.5	86[b]
2	1.7	1.6	82
3	1.7	1.4	78

[a] Isolated yield.
[b] Isolated yield of **4** associated to the amide derivative of **3**.

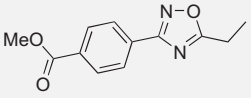
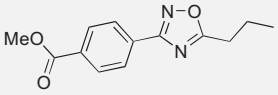
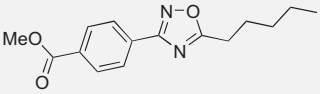
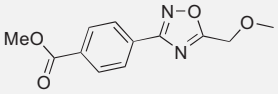
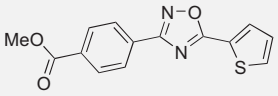
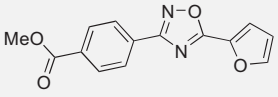
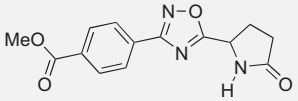
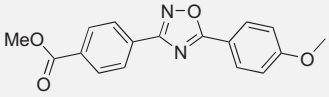
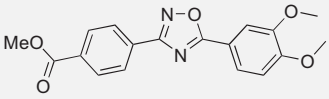
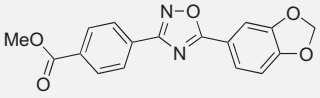
the compound **4** in good yield (86%) associated to the formation of undesired amide derivative of **3** (<5%) as by-product according to ^{1}H NMR analysis of the crude reaction mixture. It can be observed that the optimal reaction conditions for compound **4** were obtained with a stoichiometry of 1:1.7:1.6 of ILP **3**/KOH/hydroxylamine to produce the desired ILP bound amidoxime **4** in good yield (82%). Purification of amidoxime **4** has been performed by washings (1:10 w/v) successively with cold deionized water and Et_2O.

In the third step, our focus was the transformation of the ionic liquid-phase bound arylamidoxime **4** into *O*-acyl amidoxime **6**. Existing methods of synthesizing *O*-acyl amidoxime from carboxylic acid esters require the presence of strong base, such as NaH[24], $MeONa$[25], K_2CO_3[26] or $EtONa$[27] in refluxing THF, MeOH or EtOH, and generally give low yields. Acylation of amidoximes by acid chlorides[28] have some drawbacks. Acid chlorides are toxic and reactive chemicals, and only a few acid chlorides are commercially readily available. Historically, the preferred method of obtaining *O*-acyl amidoximes is the reaction of amidoximes with carboxylic acid in the presence of a coupling reagent, such as DCC, EDCI, CDI, TBTU or HBTU[29] to react with amidoximes.[30] Using simple anhydrides as activated acid derivatives in DMF/pyridine is also a frequently used method.[31]

For the synthesis of the target *O*-acyl amidoxime **6** grafted on the ionic liquid phase, we examined a series of aliphatic carboxylic acids **5**(**a**–**d**), heteroaromatic acids **5**(**e**, **f**), substituted aromatic acids **5**(**h**–**j**) and the heterocyclic acid **5g**. After exploring a few sets of reaction conditions, the one that proved to be the most effective was the addition of carboxylic acid **5** to a diluted solution of ILP bound amidoxime **4** in acetonitrile at room temperature with dicyclohexylcarbodiimide (DCC) and 6–8% of 4-dimethylamino pyridine. After 48 h and elimination of the insoluble diclohexylurea (DCHU), the crude ILP bound *O*-acyl amidoxime **6** was washed with AcOEt (1:10 w/v) to remove excess of the unreacted starting reagents (DCC and carboxylic acid **5**) and ^{1}H NMR showed that *O*-acyl amidoxime **6** was only observed (Table 3).

Cyclodehydratation (step 4) of ILP bound *O*-acyl amidoxime **6** to 1,2,4-oxadiazole **7** was carried out in deionized water for 24 h under reflux. After work-up, it is noteworthy that the products **7**(**a**–**j**) formed were estimated very easily by ^{1}H NMR without detaching the material from the ionic liquid phase and examination of the results in Table 1 showed that the expected 1,2,4-oxadiazoles **7**(**a**–**j**) were prepared in good yields (66–98%). After demonstrating the feasibility of our protocol for the construction of functionalized 1,2,4-oxadiazole grafted on the ILP, we have finally examined the cleavage of 1,2,4-oxadiazole moiety from the ILP. The target compounds **8**(**a**–**j**) were easily released from the ionic liquid-phase bound 1,2,4-oxadiazole **7**(**a**–**j**) by treatment with sodium methoxide (0.75 equiv) in refluxed methanol. Complete cleavage of the compounds **7** was easily monitored by thin-layer chromatography (TLC) or by the observation of a new singlet at δ 3.95 ppm for the methyl ester group of **8** and also the upfield shift of the α-methylene protons of the side chain appended on the imidazolium cation of the ionic liquid-phase [HOC_2mim][PF_6] **1** from δ 4.42 ppm to 4.00 ppm in the ^{1}H NMR of the crude reaction mixture. If the peak

Table 3
Results for the preparation of 1,2,4-oxadiazoles **8**(**a**–**i**) from ionic liquid-phases **7**(**a**–**i**) after cleavage by transesterification

Product		Starting product	Yield[a] (%)	Overall yield[b] (%)
8a		**7a**	89	53
8b		**7b**	82	49
8c		**7c**	73	47
8d		**7d**	83	56
8e		**7e**	82	51
8f		**7f**	84	48
8g		**7g**	75	32
8h		**7h**	83	52
8i		**7i**	70	42
8j		**7j**	87	55

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

of the α-methylene proton was still present after NMR checking, the recovered ILP bound 1,2,4-oxadiazole **7** could be resubmitted to the same reaction conditions until a complete cleavage was achieved. Normally, the cleavage by transesterification was complete using the above reaction conditions (MeONa 0.75 equiv/refluxed MeOH) after 24 h. Owing to the small quantities of the starting ILP bound 1,2,4-oxadiazole **7**, the separation and the purification of **8** from the starting ILP **1** by classical washings with an appropriate solvent are not practicable, but the use of flash-purification on alumina gel using CH_2Cl_2/MeOH (99:1) as eluent afforded the desired 1,2,4-oxadiazole **8** (R_f=0.95) as white solid. Importantly, the purity of the transesterified products **8** cleaved from the ionic liquid-phase was high enough for NMR (^{1}H, ^{13}C) and mass spectrometry (HRMS) characterization and no further purification was necessary. As it can be seen from inspection of the data presented in Table 2, the 1,2,4-oxadiazoles **8**(**a**–**j**) were prepared after cleavage in good yields (70–89%). The target compounds **8**(**a**–**j**) were synthesized in five steps from the starting ILP **1** in moderate to good overall yields (35–55%). Additionally, the ionic liquid-phase [HOC_2mim][PF_6] **1** issued from transesterification cleavage can be eventually reused after elution by MeOH (1/5 w/v).

3. Conclusion

In summary, we have developed the use of hydroxyl ionic liquid [HOC_2mim][PF_6] as soluble support in the liquid-phase organic synthesis of 3,5-disubstituted 1,2,4-oxadiazole. The ionic liquid-phase organic synthesis (IoLiPOS) methodology exemplifies the importance of functionalized ionic liquid-phase combinatorial approach for lead optimization and offers easy access to compound collections containing the 1,2,4-oxadiazole moiety. This protocol involves a facile route to arylnitrile and arylamidoxime grafted on the ILP. From the ionic liquid-phase bound amidoxime **4** as key intermediate, O-acylation and cyclodehydration afforded the 1,2,4-oxadiazoles in high yields and the purity of each intermediate could be controlled by standard spectroscopic methods (^{1}H, ^{13}C NMR and HRMS). We are currently exploring the scope and the potential of the ILP bound amidoxine for the preparation and biological screening of a wider library.

4. Experimental section

4.1. General remarks

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 60F 254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{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 the other compounds in the Center Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3 Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, and Fluka France and were used without further purification. The starting [HOC_2mim][PF_6] ionic liquid phase **1** was synthesized according to our previous method.[14]

4.2. 1-[2-(4-Cyanobenzoyloxy)ethyl]-3-methylimidazolium hexafluorophosphate (3)

In a 250 ml two-necked round-bottomed flask provided with a magnetic stirrer and reflux condenser, 1-(2-hydroxyethyl)-3-methyl-imidazolium hexafluorophosphate **1** (2.97 g, 10.94 mmol) was mixed in acetonitrile p.a. (150 ml). To this solution was added successively *N*,*N*′-dicyclohexylcarbodiimide DCC (2.46 g, 11.9 mmol, 1.1 equiv) portionwise and dimethylaminopyridine DMAP (26.6 g, 0.21 mmol, 0.2 equiv) in one portion; then, the reaction mixture was stirred vigorously for 5 min. After, which 4-cyanobenzoic acid **2** (1.77 g, 11.92 mmol, 1.1 equiv) was added over a period of 20 min. The reaction mixture was stirred at room temperature for 24 h and the insoluble *N*,*N*′-dicyclohexylurea (DCHU) was removed by filtration. The resulting filtrate was refiltered through a short column of Celite®

to remove some residual DCHU and finally concentrated by rotary evaporation that gave the expected ionic liquid-phase bound arylnitrile **3**. Product **3** was further washed with AcOEt (2×50 ml) and was dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h.

Yield=92%, white needles, mp=147–149 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.85 (s, 3H, NCH_3); 4.65 (m, 4H, OCH_2, NCH_2); 7.70 (br s, 1H, H-4); 7.85 (br s, 1H, H-5); 8.00 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-3′, H-5′); 8.10 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-2′, H-6′); 9.20 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.77 (NCH_3); 47.84 (CH_2N); 63.72 (OCH_2); 115.68 (C-4′); 117.94 (*C*N); 122.73 (C-5); 123.63 (C-4); 129.96 (C-3′, C-5′); 132.73 (C-2′, C-6′); 132.95 (C-1′); 137.02 (C-2); 164.09 (*C*=O). HRMS, *m*/*z* found: 256.1095 (calculated for $C_{14}H_{14}N_3O_2$, C^+ requires: 256.1086).

4.3. 1-[2-[3-[2-Amino-2-(hydroxyimino)methyl]-5-carbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (4)

To a solution of potassium hydroxide (1.19 g, 21.2 mmol, 1.62 equiv) in anhydrous ethanol (20 ml), in a 250 ml round-bottomed flask fitted with a reflux condenser, was added portionwise commercial hydroxylamine hydrochloride (1.45 g, 20.9 mmol, 1.6 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then, at 25 °C 1-[2-(4-cyanobenzoyloxy)ethyl]-3-methylimidazolium hexafluorophosphate **3** (5.25 g, 13 mmol, 1 equiv) was dispersed vigorously by magnetic stirring over a period of 20 min. The reaction mixture was heated at 80 °C for 18 h. To the reaction media was added cooled deionized water (30 ml) and the desired unsoluble compound **4** was collected by filtration, then washed with diethylether (10 ml). The amidoxime **4** was dried under high vacuum (10–2 Torr) at 25 °C for 4 h.

Yield=82%, white needles, mp=180–182 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.86 (s, 3H, NCH_3); 4.62–4.64 (m, 4H, OCH_2, NCH_2); 5.96 (br s, 2H, NH_2); 7.69 (m, 1H, H-4); 7.82 (d, 2H, $^3J_{H,H}$=8.5 Hz, H-3′, H-5′); 7.84 (m, 1H, H-5); 7.95 (d, 2H, $^3J_{H,H}$=8.5 Hz, H-2′, H-6′); 9.21 (s, 1H, H-2); 9.95 (br s, 1H, O*H*). ^{13}C NMR ($(CD_3)_2SO$): δ=35.80 (NCH_3); 48.00 (CH_2N); 63.15 (OCH_2); 122.78 (C-5); 123.66 (C-4); 125.54 (C-3′, C-5′); 129.07 (C-1′); 129.23 (C-2′, C-6′); 137.04 (C-2); 138.01 (C-4′); 150.01 (N=*C*–NH_2); 165.01 (*C*=O). HRMS, *m*/*z* found: 289.1301 (calculated for $C_{14}H_{17}N_4O_3$, C^+ requires: 289.1300).

4.4. Standard procedure for the synthesis of ionic liquid-phase bound *O*-acyl amidoxime 6(a–j)

To a solution of amidoxime **4** (1 equiv), *N*,*N*′-dicyclohexylcarbodiimide DCC (1.02 equiv) and dimethylaminopyridine DMAP (0.06–0.08 equiv) in dry acetonitrile (1/8 w/v), was added portionwise carboxylic acid **5** (1.1 equiv) under vigorous magnetic stirring. The reaction mixture was stirred at 25 °C for 48 h. The insoluble diclohexylurea (DCHU) was eliminated by filtration on a filter paper. The resulting filtrate was refiltered though a short column of Celite® and concentrated by rotary evaporation. Then the crude residue was further washed with AcOEt (2×50 ml) to remove some residual DCC and eventually unreacted carboxylic acid **5**. The desired *O*-acyl amidoxime **6** was dried under high vacuum (10–2 Torr) at 25 °C for 3 h. and led to the desired product **6** in 84–91% yield, which was controlled by ^{1}H and ^{13}C NMR spectroscopy. The *O*-acyl amidoxime **6** were stored under inert atmosphere at 4 °C.

*4.4.1. 1-{3-(4-[(Propyloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6a**).* The product **6a** was prepared from 216.2 mg of amidoxime **4** (0.49 mmol, 1 equiv), 96.92 mg of DCC (0.469 mmol), 4.5 mg of DMAP (0.036 mmol) and 39.89 mg of propanoic acid **5a** (0.539 mmol) according to the standard procedure.

Yield=89%, white needles, mp=165–169 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=1.09 (t, 3H, $^3J_{H,H}$=7.5 Hz, CH_3CH_2); 2.48 (q, 2H, $^3J_{H,H}$=7.5 Hz, CH_3CH_2); 3.86 (s, 3H, NCH_3); 4.63–4.65 (m, 4H, OCH_2, NCH_2); 6.96 (br s, 2H, NH_2); 7.71 (m, 1H, H-4); 7.85–7.88 (m, 3H, H-5, H-3′, H-5′); 8.01 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-2′, H-6′); 9.24 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=8.87 (CH_3CH_2); 25.52 (CH_3CH_2); 35.61 (NCH_3); 47.62 (CH_2N); 63.11 (OCH_2); 122.60 (C-5); 123.47 (C-4); 126.91 (C-3′, C-5′); 129.16 (C-2′, C-6′); 130.43 (C-1′); 136.21 (C-4′); 136.87 (C-2); 155.34 (N=*C*–NH_2); 164.46 (*C*=O, C-1′); 164.46 (NO–*C*=O). HRMS, *m*/*z* found: 345.1562 (calculated for $C_{17}H_{21}N_4O_4$, C^+ requires: 345.1562).

*4.4.2. 1-{3-(4-[(Butyloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6b**).* The product **6b** was prepared from 200 mg of amidoxime **4** (0.46 mmol, 1 equiv), 95.02 mg of DCC (0.46 mmol), 4.5 mg of DMAP (0.036 mmol) and 44.63 mg of butanoic acid **5b** (0.506 mmol) according to the standard procedure.

Yield=84%, white needles, mp=166–168 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=0.92 (t, 3H, $^3J_{H,H}$=7.3 Hz, CH_3CH_2); 1.61 (sext, 2H, $^3J_{H,H}$=7.3 Hz, CH_3CH_2); 2.45 (t, 2H, $^3J_{H,H}$=7.3 Hz, CH_2CO); 3.86 (s, 3H, NCH_3); 4.63–4.65 (m, 4H, OCH_2, NCH_2); 6.95 (br s, 2H, NH_2); 7.71 (m, 1H, H-4); 7.85–7.88 (m, 3H, H-5, H-3′, H-5′); 8.01 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-2′, H-6′); 9.21 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=13.46 (CH_3CH_2); 17.90 (CH_3CH_2); 34.12 (CH_2CO); 35.76 (NCH_3); 47.90 (CH_2N); 63.24 (OCH_2); 122.75 (C-5); 123.62 (C-4); 127.04 (C-3′, C-5′); 129.28 (C-2′, C-6′); 130.53 (C-1′); 136.36 (C-4′); 137.00 (C-2), 155.49 (N=*C*–NH_2); 164.74 (*C*=O, C-1′); 170.58 (NO-*C*=O). HRMS, *m*/*z* found: 359.1715 (calculated for $C_{18}H_{23}N_4O_4$, C^+ requires: 359.1719).

*4.4.3. 1-{3-(4-[(Hexyloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6c**).* The product **6c** was prepared from 200 mg of amidoxime **4** (0.46 mmol, 1 equiv), 95.02 mg of DCC (0.46 mmol), 4.5 mg of DMAP (0.036 mmol) and 63.4 mg of hexanoic acid **5c** (0.506 mmol) according to the standard procedure.

Yield=90%, white needles, mp=172–174 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=0.86–0.88 (m, 3H, H-5″); 1.29–1.31 (m, 4H, H-3″, H-4″); 1.58–1.60 (m, 2H, H-2″); 2.45–2.47 (m, 2H, H-1″); 3.86 (s, 3H, NCH_3); 4.63–4.65 (m, 4H, OCH_2, NCH_2); 6.95 (br s, 2H, NH_2); 7.71 (br s, 1H, H-4); 7.85–7.88 (m, 3H, H-5, H-3′, H-5′); 8.01 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-2′, H-6′); 9.21 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=13.77 (C-5″); 21.76 (C-4″); 24.12 (C-2″); 30.73 (C-3″); 32.21 (C-1″); 35.79 (NCH_3); 47.94 (CH_2N); 63.27 (OCH_2); 122.77 (C-5); 123.65 (C-4); 127.07 (C-3′, C-5′); 129.32 (C-2′, C-6′); 130.57 (C-1′); 136.38 (C-4′); 137.02 (C-2); 155.56 (N=*C*–NH_2); 164.78 (*C*=O, C-1′); 170.79 (NO–*C*=O). HRMS, *m*/*z* found: 387.2030 (calculated for $C_{20}H_{27}N_4O_4$, C^+ requires: 387.2032).

*4.4.4. 1-{3-(4-[(Methoxyethyloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6d**).* The product **6d** was prepared from 500 mg of amidoxime **4** (1.15 mmol, 1 equiv), 261.3 mg of DCC (1.26 mmol), 8.4 mg of DMAP (0.069 mmol) and 114 mg of methoxyacetic acid **5d** (1.26 mmol) according to the standard procedure.

Yield=91%, white needles, mp=146–148 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.32 (br s, 3H, OCH_3); 3.87 (s, 3H, NCH_3); 4.26 (s, 2H, $COCH_2O$); 4.63–4.65 (m, 4H, OCH_2, NCH_2); 7,07 (br s, 2H, NH_2); 7.71 (br s, 1H, H-4); 7.85–7.88 (m, 3H, H-5, H-3′, H-5′); 8.02 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-2′, H-6′); 9.22 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.78 (NCH_3); 47.91 (CH_2N); 58.44 (OCH_3); 63.30 (OCH_2); 68.26 (CH_2O); 122.77 (C-5); 123.64 (C-4); 127.13 (C-3′, C-5′); 129.35 (C-2′, C-6′); 130.71 (C-1′); 136.04 (C-4′); 137.02 (C-2), 156.19 (N=*C*–NH_2); 164.73 (*C*=O, C-1′); 168.33 (NO–*C*=O). HRMS, *m*/*z* found: 361.1520 (calculated for $C_{17}H_{21}N_4O_5$, C^+ requires: 361.1512).

*4.4.5. 1-{3-(4-[(Thiophen-2-yloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6e**).* The product **6e** was

prepared from 500 mg of amidoxime **4** (1.15 mmol, 1 equiv), 261.3 mg of DCC (1.26 mmol), 8.4 mg of DMAP (0.069 mmol) and 161.5 mg of thiophene-2-carboxylic acid **5e** (1.26 mmol) according to the standard procedure.

Yield=89%, yellow needles, mp=199–201 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.87 (s, 3H, NCH_3); 4.63–4.65 (m, 4H, OCH_2, NCH_2); 7.14 (br s, 2H, NH_2); 7.25–7.27 (m, 1H, H-4″); 7.71 (br s, 1H, H-4); 7.87 (br s, 1H, H-5); 7.91 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-3′, H-5′); 7.98–7.99 (m, 1H, H-3″); 8.04 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-2′, H-6′); 8.17–8.19 (m, 1H, H-5″); 9.22 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.77 (NCH_3); 47.91 (CH_2N); 63.27 (OCH_2); 122.76 (C-5); 123.63 (C-4); 127.26 (C-3′, C-5′); 128.28 (C-4″); 129.35 (C-2′, C-6′); 130.69 (C-1′); 132.38 (C-2″); 133.84 (C-3″); 133.94 (C-5″); 136.22 (C-4′); 137.01 (C-2); 156.10 (N=*C*–NH_2); 159.53 (NO–*C*=O); 164.74 (*C*=O, C-1′). HRMS, *m*/*z* found: 399.1133 (calculated for $C_{19}H_{19}N_4O_4S$, C^+ requires: 399.1127).

*4.4.6. 1-{3-(4-[(Furanyloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6f**).* The product **6f** was prepared from 200 mg of amidoxime **4** (0.46 mmol, 1 equiv), 95.02 mg of DCC (0.46 mmol), 4.5 mg of DMAP (0.036 mmol) and 62.4 mg of furane-2-carboxylic acid **5f** (0.506 mmol) according to the standard procedure.

Yield=85%, yellow needles, mp=83–85 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.87 (s, 3H, NCH_3); 4.64–4.66 (m, 4H, OCH_2, NCH_2); 6.74 (dd, 1H, $J_{H,H}$=3.4, 1.6 Hz, H-4″); 7.14 (br s, 2H, NH_2); 7.71 (br s, 1H, H-4); 7.74 (d, 1H, $^3J_{H,H}$=3.4 Hz, H-3″); 7.86 (br s, 1H, H-5); 7.91 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-3′, H-5′); 8.00–8.02 (m, 1H, H-5″); 8.04 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-2′, H-6′); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.78 (NCH_3); 47.92 (CH_2N); 63.27 (OCH_2); 112.12 (C-4″); 118.59 (C-3″); 122.77 (C-5); 123.63 (C-4); 127.25 (C-3′, C-5′); 129.36 (C-2′, C-6′); 130.71 (C-1′); 136.18 (C-4′); 137.03 (C-2); 142.85 (C-2″); 147.66 (C-5″); 155.91 (NO–*C*=O); 156.10 (N=*C*–NH_2); 164.75 (*C*=O, C-1′). HRMS, *m*/*z* found: 383.1348 (calculated for $C_{19}H_{19}N_4O_5$, C^+ requires: 383.1355).

*4.4.7. 1-{3-(4-[(5-Oxo-pyrrolidin-3-yloxy)carbamimidoyl]benzoate)-ethyl}-3-methylimidazolium hexafluorophosphate (**6g**).* The product **6g** was prepared from 500 mg of amidoxime **4** (1.15 mmol, 1 equiv), 261.3 mg of DCC (1.26 mmol), 8.4 mg of DMAP (0.069 mmol) and 163.4 mg of 3-oxo-pyrrolidin-carboxylic acid **5g** (1.26 mmol) according to the standard procedure.

Yield=87%, white needles, mp=179–181 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=1.90–2.41 (m, 4H, H-4″, H-5″); 3.86 (s, 3H, NCH_3); 4.41 (d, 1H, H-2″); 4.63–4.65 (m, 4H, OCH_2, NCH_2); 7.13 (br s, 2H, NH_2); 7.70 (br s, 1H, H-4); 7.85–7.88 (m, 3H, H-5, H-3′, H-5′); 8.03 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-2′, H-6′); 8.22 (br s, 1H, N*H*); 9.22 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=24.23 (C-4″); 28.98 (C-5″); 35.79 (NCH_3); 47.93 (CH_2N); 54.16 (C-2″); 63.31 (OCH_2); 122.78 (C-5); 123.65 (C-4); 127.17 (C-3′, C-5′); 129.40 (C-2′, C-6′); 130.77 (C-1′); 136.05 (C-4′); 137.04 (C-2); 156.25 (N=*C*–NH_2); 164.74 (*C*=O, C-1′); 169.94 (NO–*C*=O); 176.99 (C-3″). HRMS, *m*/*z* found: 400.1622 (calculated for $C_{19}H_{22}N_5O_5$, C^+ requires: 400.1620).

*4.4.8. 1-{3-(4-[(4-Methoxy-benzoyloxy)carbamimidoyl]benzoate)-ethyl}-3-methylimidazolium hexafluorophosphate (**6h**).* The product **6h** was prepared from 1 g of amidoxime **4** (2.3 mmol, 1 equiv), 475.1 mg of DCC (2.3 mmol), 16.8 mg of DMAP (0.138 mmol) and 384.9 mg of 4-methoxybenzoic acid **5h** (2.53 mmol) according to the standard procedure.

Yield=87%, white needles, mp=203–205 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.86 (s, 3H, OCH_3); 3.87 (s, 3H, NCH_3); 4.64–4.66 (m, 4H, OCH_2, NCH_2); 7.06 (d, 2H, $^3J_{H,H}$=8.8 Hz, H-2″, H-6″); 7.10 (br s, 2H, NH_2); 7.72 (br s, 1H, H-4); 7.87 (br s, 1H, H-5); 7.92 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-3′, H-5′); 8.04 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-2′, H-6′); 8.16 (d, 2H, $^3J_{H,H}$=8.8 Hz, H-3″, H-5″); 9.22 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.77 (NCH_3); 47.90 (CH_2N); 55.43 (OCH_3); 63.25 (OCH_2); 113.77 (C-2″, C-6″); 121.30 (C-1″); 122.76 (C-5); 123.63 (C-4); 127.20 (C-3′, C-5′); 129.30 (C-2′, C-6′); 130.55 (C-1′); 131.62 (C-3″, C-5″); 136.52 (C-4′); 137.04 (C-2); 155.63 (N=*C*–NH_2); 163.00 (*C*=O, C-1′); 163.12 (C-4″); 164.74 (NO–*C*=O). HRMS, *m*/*z* found: 423.1666 (calculated for $C_{22}H_{23}N_4O_5$, C^+ requires: 423.1668).

*4.4.9. 1-{3-(4-[(3,4-Dimethoxy-benzoyloxy)carbamimidoyl]benzoate)-ethyl}-3-methylimidazolium hexafluorophosphate (**6i**).* The product **6i** was prepared from 200 mg of amidoxime **4** (0.46 mmol, 1 equiv), 95.2 mg of DCC (0.46 mmol), 4.5 mg of DMAP (0.036 mmol) and 92.3 mg of 3,4-dimethoxybenzoic acid **5i** (0.506 mmol) according to the standard procedure.

Yield=85%, white needles, mp=197–199 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.86 (d, 6H, 2×OCH_3); 3.87 (s, 3H, NCH_3); 4.64–4.66 (m, 4H, OCH_2, NCH_2); 7.07 (d, 1H, $^3J_{H,H}$=8.7 Hz, H-5″); 7.11 (br s, 2H, NH_2); 7.60 (d, 1H, $^3J_{H,H}$=1.8 Hz, H-2″); 7.71 (br s, 1H, H-4); 7.84 (d, 1H, *J*=8.7, 1.8 Hz, H-6″); 7.87 (br s, 1H, H-5); 7.92 (d, 2H, $^3J_{H,H}$=8,4 Hz, H-3′, H-5′); 8.05 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-2′, H-6′); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.78 (NCH_3); 47.93 (CH_2N); 55.65 (2×OCH3); 63.27 (OCH_2); 110.96 (C-2″); 112.17 (C-5″); 121.28 (C-1″); 122.78 (C-5); 123.64 (C-4, C-6″); 127.26 (C-3′, C-5′); 129.33 (C-2′, C-6′); 130.59 (C-1′); 136.55 (C-4′); 137.03 (C-2); 148.33 (C-3″); 152.89 (C-4″); 155.79 (N=*C*–NH_2); 163.31 (*C*=O, C-1′); 164.77 (NO–*C*=O). HRMS, *m*/*z* found: 453.1773 (calculated for $C_{22}H_{25}N_4O_6$, C^+ requires: 453.1773).

*4.4.10. 1-{3-(4-[(3,4-Methylenedioxy-benzoyloxy)carbamimidoyl]benzoate)ethyl}-3-methylimidazolium hexafluorophosphate (**6j**).* The product **6j** was prepared from 1 g of amidoxime **4** (2.3 mmol, 1 equiv), 475.1 mg of DCC (2.3 mmol), 16.8 mg of DMAP (0.138 mmol) and 420.5 mg of 3,4-methylenedioxybenzoic acid **5j** (2.53 mmol) according to the standard procedure.

Yield=87%, white needles, mp=206–208 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.87 (s, 3H, NCH_3); 4.64–4.66 (m, 4H, OCH_2, NCH_2); 6.15 (s, 2H, OCH_2O); 7.05 (d, 1H, $^3J_{H,H}$=7.9 Hz, H-5″); 7.13 (br s, 2H, NH_2); 7.74–7.76 (m, 3H, H-4, H-2″, H-6″); 7.87 (br s, 1H, H-5); 7.92 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-3′, H-5′); 8.04 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-2′, H-6′); 9.22 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.78 (NCH_3); 47.93 (CH_2N); 63.26 (OCH_2); 101.97 (OCH_2O); 108.10 (C-5″); 109.20 (C-2″); 122.77 (C-5); 122.83 (C-1″); 123.63 (C-4); 125.44 (C-6″); 127.23 (C-3′, C-5′); 129.33 (C-2′, C-6′); 130.60 (C-1′); 136.51 (C-4′); 137.02 (C-2); 147.48 (C-3″); 151.32 (C-4″); 155.65 (N=*C*–NH_2); 162.80 (*C*=O, C-1′); 164.76 (NO–*C*=O). HRMS, *m*/*z* found: 437.1461 (calculated for $C_{22}H_{21}N_4O_6$, C^+ requires: 437.1461).

4.5. Standard procedure for the synthesis of ionic liquid-phase bound 1,2,4-oxadiazole 7(a–j)

In a 50 ml round-bottomed flask fitted with a reflux condenser and provided with a magnetic stirrer, the *O*-acyl amidoxime **6** (1.89 mmol) was dispersed in deionized water (10 ml). The reaction mixture was heated at 100 °C for 24 h under vigorous stirring. After cooling down to room temperature over a period of 30 min, the unsoluble ionic liquid-phase bound 1,2,4-oxadiazole **7** was submitted to filtration under reduced pressure. The desired compound **7** was further dried under high vacuum at 25 °C for 4 h and was obtained as white or yellowish needles (excepted for **7g**).

*4.5.1. 1-{3-[4-(Ethyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7a**).* Yield=90%, white needles, mp=116–118 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=1.34 (t, 3H, $^3J_{H,H}$=7.3 Hz, CH_3CH$_2$); 3.03 (q, 2H, $^3J_{H,H}$=7.3 Hz, CH$_3$CH_2); 3.87 (s, 3H, NCH_3); 4.64–4.66 (m, 4H, OCH_2, NCH_2); 7.71 (br s, 1H, H-4); 7.86 (br s, 1H, H-5); 8.11–8.13 (m, 4H, H-2′, H-3′, H-5′, H-6′, Ar); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=10.29 (CH_3CH$_2$); 19.54 (CH$_3$CH_2); 35.78 (NCH_3); 47.94 (CH_2N); 63.36 (OCH_2); 122.75 (C-5); 123.68 (C-4); 127.23 (C-3′, C-5′); 130.16 (C-2′, C-6′); 130.70 (C-4′); 131.36 (C-1′); 137.03 (C-2);

164.61 (*C*=O); 166.72 (C-3″); 181.66 (C-5″). HRMS, *m*/*z* found: 327.1455 (calculated for $C_{17}H_{19}N_4O_3$, C^+ requires: 327.1457).

*4.5.2. 1-{3-[4-(Propyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7b**).* Yield=90%, white needles, mp=103–105 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=0.98 (t, 3H, $^3J_{H,H}$=7.3 Hz, C*H*$_3$CH$_2$); 1.81 (sext, 2H, $^3J_{H,H}$=7.3 Hz, CH$_3$C*H*$_2$); 2.98 (t, 2H, $^3J_{H,H}$=7.3 Hz, CH$_3$C*H*$_2$CH$_2$); 3.89 (s, 3H, NC*H*$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 7.72 (br s, 1H, H-4); 7.87 (s, 1H, H-5); 8.11–8.13 (m, 4H, H-2′, H-3′, H-5′, H-6′); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=13.23 (*C*H$_3$CH$_2$); 19.41 (CH$_3$*C*H$_2$); 27.51 (CH$_3$*C*H$_2$CH$_2$); 35.78 (NCH$_3$); 47.95 (*C*H$_2$N); 63.36 (OCH$_2$); 122.76 (C-5); 123.68 (C-4); 127.24 (C-3′, C-5′); 130.16 (C-2′, C-6′); 130.70 (C-4′); 131.37 (C-1′); 137.04 (C-2); 164.62 (*C*=O); 166.75 (C-3″); 180.70 (C-5″). HRMS, *m*/*z* found: 341.1624 (calculated for $C_{18}H_{21}N_4O_3$, C^+ requires: 341.1613).

*4.5.3. 1-{3-[4-(Pentyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7c**).* Yield=71%, yellowish needles, mp=84–86 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=0.87 (t, $^3J_{H,H}$=7.3 Hz, 3H, C*H*$_3$CH$_2$); 1.37 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$); 1.79 (quint, 2H, $^3J_{H,H}$=7.3 Hz, CH$_3$CH$_2$CH$_2$C*H*$_2$); 3.01 (t, 2H, $^3J_{H,H}$=7.3 Hz, CH$_3$CH$_2$CH$_2$CH$_2$C*H*$_2$); 3.87 (s, 3H, NC*H*$_3$); 4.64–4.66 (m, 4H, OC*H*$_2$, NC*H*$_2$); 7.72 (br s, 1H, H-4); 7.87 (br s, 1H, H-5); 8.10–8.17 (m, 4H, Ar, H-2′, H-3′, H-5′, H-6′, Ar); 9.22 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=13.69 (*C*H$_3$CH$_2$); 21.58 (CH$_3$*C*H$_2$); 25.53 (CH$_3$CH$_2$CH$_2$*C*H$_2$); 25.66 (CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$); 30.45 (CH$_3$CH$_2$CH$_2$); 35.80 (NCH$_3$); 47.93 (*C*H$_2$N); 63.37 (OCH$_2$); 122.76 (C-5); 123.69 (C-4); 127.28 (C-3′, C-5′); 130.19 (C-2′, C-6′); 130.70 (C-4′); 131.40 (C-1′); 137.02 (C-2); 164.61 (*C*=O); 166.74 (C-3″); 180.91 (C-5″). HRMS, *m*/*z* found: 369.1930 (calculated for $C_{20}H_{25}N_4O_3$, C^+ requires: 369.1926).

*4.5.4. 1-{3-[5-(Methoxymethyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7d**).* Yield=98%, yellowish needles, mp=160–162 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.44 (br s, 3H, OC*H*$_3$); 3.88 (s, 3H, NC*H*$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 4.85 (s, 2H, C-5"-C*H*$_2$O); 7.72 (br s, 1H, H-4); 7.87 (br s, 1H, H-5); 8.15 (q, 4H, $^3J_{H,H}$=8.6 Hz, H-2′, H-3′, H-5′, H-6′, Ar); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=37.79 (NCH$_3$); 47.93 (*C*H$_2$N); 58.76 (OCH$_3$); 63.41 (OCH$_2$); 64.39 (C-5″-*C*H$_2$O); 122.76 (C-5); 123.68 (C-4); 127.37 (C-3′, C-5′); 130.23 (C-2′, C-6′); 130.31 (C-4′); 131.57 (C-1′); 137.03 (C-2), 164.58 (*C*=O); 166.83 (C-3″); 177.25 (C-5″). HRMS, *m*/*z* found: 343.1405 (calculated for $C_{17}H_{19}N_4O_4$, C^+ requires: 343.1406).

*4.5.5. 1-{3-[5-(Thiophen-2-yl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7e**).* Yield=93%, yellowish needles, mp=209–211 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.89 (s, 3H, NC*H*$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 7.36 (t, 1H, $^3J_{H,H}$=8.4 Hz, H-4&tprime, Ar); 7.73 (br s, 1H, H-4); 7.87 (br s, 1H, H-5); 8.05–8.20 (m, 6H, H-3′, H-5′, H-3&tprime, H-2′, H-6′, H-5″, Ar); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.80 (NCH$_3$); 47.93 (*C*H$_2$N); 63.37 (OCH$_2$); 122.77 (C-5); 123.69 (C-4); 124.21 (C-2‴) 127.40 (C-3′, C-5′); 129.26 (C-4‴) 130.15 (C-2′, C-6′); 130.24 (C-4′); 131.54 (C-1′); 133.01 (C-3‴) 134.30 (C-5‴) 137.03 (C-2); 164.56 (C-5″); 167.30 (*C*=O); 171,39 (C-3″). HRMS, *m*/*z* found: 381.1021 (calculated for $C_{19}H_{17}N_4O_3S$, C^+ requires: 381.1021).

*4.5.6. 1-{3-[4-(Furan-2-yl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7f**).* Yield=89%, orange needles, mp=91–93 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.88 (s, 3H, NC*H*$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 6.86–6.88 (m, 1H, H-4‴) 7.64 (d, $^3J_{H,H}$=3.1 Hz, 1H, H-3‴) 7.72 (br s, 1H, H-4); 7.87 (br s, 1H, H-5); 8.11–8.19 (m, 5H, H-2′, H-3′, H-5′, H-6′, H-5‴, Ar); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.79 (NCH$_3$); 47.92 (*C*H$_2$N); 63.38 (OCH$_2$); 113.14 (C-4‴) 117.96 (C-3‴) 122.75 (C-5); 123.68 (C-4); 127.41 (C-3′, C-5′); 130.16 (C-2′, C-6′, C-1′); 131.58 (C-4′); 137.03 (C-2); 138.77 (C-2‴) 148.52 (C-5‴) 164.55 (C-5″); 167.19 (*C*=O); 167.55 (C-3″). HRMS, *m*/*z* found: 365.1246 (calculated for $C_{19}H_{17}N_4O_4$, C^+ requires: 365.1249).

*4.5.7. 1-{3-[4-(3-Oxo-pyrrolidin-2-yl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7g**).* Yield=66%, viscous oil. ^{1}H NMR ($(CD_3)_2SO$): δ=2.07–2.62 (m, 4H, H-4&tprime, H-5‴) 3.88 (s, 3H, NCH$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 5.14 (m, 1H, H-2‴) 7.72 (br s, 1H, H-4); 7.84 (br s, 1H, H-5); 8.15 (m, 4H, H-3′, H-5′, H-2′, H-6′, Ar); 8.42 (s, 1H, N*H*); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=25.80 (C-4‴) 28.77 (C-5‴) 35.81 (NCH$_3$); 47.94 (*C*H$_2$N); 49.49 (C-2‴) 63.42 (OCH$_2$); 122.77 (C-5); 123.69 (C-4); 127.40 (C-3′, C-5′); 130.27 (C-2′, C-6′); 131.63 (C-1′); 137.05 (C-2, C-4′); 164.59 (*C*=O); 166.97 (C-5″); 176.96 (C-3‴); 181.01 (C-3&tprime). HRMS, *m*/*z* found: 382.1514 (calculated for $C_{19}H_{20}N_5O_4$, C^+ requires: 382.1515).

*4.5.8. 1-{3-[4-(4-Methoxyphenyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7h**).* Yield=99%, white needles, mp=208–210 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.86 (s, 3H, OC*H*$_3$); 3.89 (s, 3H, NC*H*$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 7.16 (d, 2H, $^3J_{H,H}$=8.8 Hz, H-2&tprime, H-6‴) 7.73 (sl, 1H, H-4); 7.88 (br s, 1H, H-5); 8.07–8.09 (m, 6H, H-3′, H-5′, H-2′, H-6′, H-3&tprime, H-5&tprime, Ar); 9.24 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.80 (NCH$_3$); 47.93 (*C*H$_2$N); 55.57 (OCH3); 63.38 (OCH$_2$); 114.92 (C-2&tprime, C-6‴) 115.38 (C-1‴) 122.77 (C-5); 123.69 (C-4); 127.31 (C-3′, C-5′); 129.92 (C-5&tprime, C-3‴) 130.13 (C-2′, C-6′); 130.65 (C-4′); 131.38 (C-1′); 137.03 (C-2); 163.16 (C-4‴) 164.59 (*C*=O); 167.28 (C-3″); 175.56 (C-5″). HRMS, *m*/*z* found: 405.1580 (calculated for $C_{22}H_{21}N_4O_4$, C^+ requires: 405.1562).

*4.5.9. 1-{3-[4-(3,4-Dimethoxyphenyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7i**).* Yield=93%, yellowish needles, mp=195–197 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.86–3.90 (3×s, 9H, 2×OC*H*$_3$, NC*H*$_3$); 4.66 (br s, 4H, OC*H*$_2$, NC*H*$_2$); 7.19 (d, 1H, $^3J_{H,H}$=8.5 Hz, H-5‴) 7.60 (d, 1H, $^3J_{H,H}$=1.9 Hz, H-2‴) 7.73 (br s, 1H, H-4); 7.78 (dd, 1H, *J*=8.5, 1.9 Hz, H-6‴) 7.88 (br s, 1H, H-5); 8.12 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-3′, H-5′); 8.20 (d, 2H, $^3J_{H,H}$=8.4 Hz, H-2′, H-6′); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.80 (NCH$_3$); 47.92 (*C*H$_2$N); 55.63 (OCH$_3$); 55.75 (OCH$_3$); 63.37 (OCH$_2$); 110.10 (C-2‴) 111.94 (C-5‴) 115.22 (C-1‴) 121.92 (C-6‴) 122.77 (C-5); 123.69 (C-4); 127.36 (C-2′, C-6′); 130.14 (C-3′, C-5′); 130.63 (C-4′); 131.41 (C-1′); 137.02 (C-2); 149.02 (C-4‴) 153.05 (C-3‴) 164.59 (*C*=O); 167.32 (C-3″); 175.68 (C-5″). HRMS, *m*/*z* found: 435.1661 (calculated for $C_{23}H_{23}N_4O_5$, C^+ requires: 435.1668).

*4.5.10. 1-{3-[4-(3,4-Methylenedioxy-phenyl-1,2,4-oxadiazol-3-yl)benzoate]ethyl}-3-methylimidazolium hexafluorophosphate (**7j**).* Yield =97%, yellow needles, mp=203–205 °C. ^{1}H NMR ($(CD_3)_2SO$): δ=3.88 (s, 3H, NC*H*$_3$); 4.65–4.67 (m, 4H, OC*H*$_2$, NC*H*$_2$); 6.20 (s, 2H, OC*H*$_2$O); 7.17 (d, 1H, $^3J_{H,H}$=8.2 Hz, H-5‴); 7.61 (d, 1H, *J*=1.6 Hz, H-2‴); 7.73 (br s, 1H, H-4); 7.76 (dd, 1H, *J*=8.2, 1.6 Hz, H-6‴); 7.88 (br s, 1H, H-5); 8.13 (d, 2H, $^3J_{H,H}$=8.5 Hz, H-3′, H-5′); 8.19 (d, 2H, $^3J_{H,H}$=8.5 Hz, H-2′, H-6′); 9.23 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$): δ=35.78 (NCH$_3$); 47.90 (*C*H$_2$N); 63.37 (OCH$_2$); 102.37 (OCH$_2$O); 107.24 (C-2‴); 109.19 (C-5‴); 116.68 (C-1‴); 122.75 (C-5); 123.67 (C-4); 123.83 (C-6‴); 127.32 (C-3′, C-5′); 130.13 (C-2′, C-6′); 130.55 (C-4′); 131.44 (C-1′); 137.01 (C-2); 148.17 (C-4‴); 151.66 (C-3‴); 164.57 (*C*=O); 167.30 (C-3″); 175.39 (C-5″). HRMS, *m*/*z* found: 419.1361 (calculated for $C_{22}H_{19}N_4O_5$, C^+ requires: 419.1355).

4.6. Standard procedure for the preparation of compounds 8(a–j) by transesterification of ionic liquid-phase bound 1,2,4-oxadiazole 7(a–j)

To a solution of compound **7** (600 mmol) in anhydrous methanol (10 ml), in a 50 ml round-bottomed flask fitted with a reflux condenser, was added commercial sodium methoxide (24.3 mg,

450 μmol, 0.75 equiv) in one portion under nitrogen. After vigorous stirring at 78 °C for 24 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 CH_2Cl_2/MeOH (99:1) as eluent. The solvent of the desired fraction (R_f=0.9) was eliminated by rotary evaporation under reduced pressure. The 1,2,4-oxadiazole **8** was dried at 25 °C for 3 h under high vacuum (10^{-2} Torr) and was characterized by ^{1}H, ^{13}C NMR and HRMS.

*4.6.1. Methyl 4-(5-ethyl-1,2,4-oxadiazol-3-yl) benzoate (**8a**).* Yield =89%, white needles, mp=83–85 °C. ^{1}H NMR ($CDCl_3$): δ=1.46 (t, 3H, $^3J_{H,H}$=7.6 Hz, C*H*$_3$CH$_2$); 2.99 (q, 2H, $^3J_{H,H}$=7.6 Hz, CH$_3$C*H*$_2$); 3.94 (s, 3H, OC*H*$_3$); 8.14 (br s, 4H, H-2, H-3, H-5, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=10.55 (*C*H$_3$CH$_2$); 20.08 (CH$_3$*C*H$_2$); 52.09 (O*C*H$_3$); 127.10 (C-3, C-5, Ar); 129.78 (C-2, C-6, Ar); 130.77 (C-4, Ar); 132.05 (C-1, Ar); 166.16 (*C*=O); 167.33 (C-3′); 180.87 (C-5′). HRMS, *m*/*z* found: 232.0851 (calculated for $C_{12}H_{12}N_2O_3$, $M^{+\bullet}$ requires: 232.0847).

*4.6.2. Methyl 4-(5-propyl-1,2,4-oxadiazol-3-yl) benzoate (**8b**).* Yield =82%, white needles, mp=67–69 °C. ^{1}H NMR ($CDCl_3$): δ=1.05 (t, 3H, $^3J_{H,H}$=7.4 Hz, C*H*$_3$CH$_2$); 1.90 (sext, 2H, $^3J_{H,H}$=7.4 Hz, CH$_3$C*H*$_2$); 2.93 (t, 2H, $^3J_{H,H}$=7.4 Hz, CH$_3$CH$_2$C*H*$_2$); 3.93 (s, 3H, OC*H*$_3$); 8.13 (br s, 4H, H-2, H-3, H-5, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=13.39 (*C*H$_3$CH$_2$); 19.95 (CH$_3$*C*H$_2$); 28.23 (CH$_3$CH$_2$*C*H$_2$); 52.10 (O*C*H$_3$); 127.12 (C-3, C-5); 129.80 (C-2, C-6); 130.81 (C-4); 132.06 (C-1); 166.18 (*C*=O); 167.33 (C-3′); 180.05 (C-5′). HRMS, *m*/*z* found: 246.1007 (calculated for $C_{13}H_{14}N_2O_3$, $M^{+\bullet}$ requires: 246.1004).

*4.6.3. Methyl 4-(5-pentyl-1,2,4-oxadiazol-3-yl) benzoate (**8c**).* Yield =73%, white needles, mp=83–85 °C. ^{1}H NMR ($CDCl_3$): δ=0.92 (t, 3H, $^3J_{H,H}$=6.9 Hz, C*H*$_3$–CH$_2$–); 1.33–1.46 (m, 4H, CH$_3$-*CH*$_2$*CH*$_2$); 1.87 (quint, 2H, $^3J_{H,H}$=7.5 Hz, CH$_3$CH$_2$CH$_2$–*CH*$_2$); 2.94 (t, 2H, $^3J_{H,H}$=7.5 Hz, CH$_3$–CH$_2$–CH$_2$–CH$_2$–C*H*$_2$); 3.93 (s, 3H, OC*H*$_3$); 8.13 (br s, 4H, H-2, H-3, H-5, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=1.60 (*C*H$_3$–CH$_2$–); 21.93 (CH$_3$–*C*H$_2$–); 26.08 (CH$_3$–CH$_2$–*C*H$_2$); 26.36 (CH$_3$–CH$_2$–*C*H$_2$); 30.92 (CH$_3$–CH$_2$–CH$_2$–CH$_2$–*C*H$_2$); 52.09 (O*C*H$_3$); 127.12 (C-3, C-5, Ar); 129.79 (C-2, C-6, Ar); 130.82 (C-4, Ar); 132.06 (C-1, Ar); 166.17 (*C*=O); 167.33 (C-3′, Ar); 180.24 (C-5′, Ar). HRMS, *m*/*z* found: 274.1319 (calculated for $C_{15}H_{18}N_2O_3$, $M^{+\bullet}$ requires: 274.1319).

*4.6.4. Methyl 4-(5-methoxymethyl-1,2,4-oxadiazol-3-yl) benzoate (**8d**).* Yield=83%, white needles, mp=109–111 °C. ^{1}H NMR ($CDCl_3$): δ=3.56 (br s, 3H, CH$_2$OC*H*$_3$); 3.94 (s, 3H, OC*H*$_3$); 4.75 (s, 2H, C*H*$_2$O); 8.15 (m, 4H, H-2, H-3, H-5, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=53.13 (O*C*H$_3$); 59.45 (CH$_2$O*C*H$_3$); 64.90 (C-5′, *C*H$_2$O); 127.25 (C-3, C-5, Ar); 129.84 (C-2, C-6, Ar); 130.23 (C-4, Ar); 132.33 (C-1, Ar); 166.10 (*C*=O); 167.49 (C-3′, Ar); 176.07 (C-5′, Ar). HRMS, *m*/*z* found: 248.0786 (calculated for $C_{12}H_{12}N_2O_4$, $M^{+\bullet}$ requires: 248.0797).

*4.6.5. Methyl 4-(5-thiophen-2-yl-1,2,4-oxadiazol-3-yl) benzoate (**8e**).* Yield=82%, white needles, mp=130–132 °C. ^{1}H NMR ($CDCl_3$): δ=3.96 (s, 3H, OC*H*$_3$); 7.22–7.24 (m, 1H, H-4″, Ar); 7.68 (d, 1H, $^3J_{H,H}$=4.8 Hz, H-3″, Ar); 7.97 (d, $^3J_{H,H}$=3.5 Hz, 1H, H-5″, Ar); 8.16 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-3, H-5, Ar); 8.23 (d, $^3J_{H,H}$=8.3 Hz, H-2, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=52.14 (O*C*H$_3$); 125.37 (C-4″, Ar); 127.31 (C-3, C-5, Ar); 128.36 (C-5″, Ar); 129.81 (C-2, C-6, Ar); 130.53 (C-4, Ar); 131.87 (C-1, Ar); 132.03 (C-3″, Ar); 132.24 (C-2″, Ar); 166.18 (C-5′, Ar); 167.92 (*C*=O); 171.44 (C-3′, Ar). HRMS, *m*/*z* found: 286.0430 (calculated for $C_{14}H_{10}N_2O_3S$, $M^{+\bullet}$ requires: 286.0412).

*4.6.6. Methyl 4-(5-furan-2-yl-1,2,4-oxadiazol-3-yl) benzoate (**8f**).* Yield =84%, white needles, mp=136–138 °C. ^{1}H NMR ($CDCl_3$): δ=3.94 (s, 3H, OC*H*$_3$); 6.65 (s, 1H, H-4″, Ar); 7.38 (d, 1H, $^3J_{H,H}$=2.3 Hz, H-3″, Ar); 7.72 (s, 1H, H-5″, Ar); 8.15 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-3, H-5, Ar); 8.22 (d, 2H, $^3J_{H,H}$=8.1 Hz, H-2, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=52.13 (O*C*H$_3$); 112.36 (C-4″, Ar); 116.69 (C-3″, Ar); 127.33 (C-3, C-5, Ar); 129.82 (C-2, C-6, Ar); 130.29 (C-4, Ar); 132.32 (C-1); 139.69 (C-2″, Ar); 146.69 (C-5″, Ar); 166.12 (C-5′, Ar); 167.62 (*C*=O); 167.76 (C-3′, Ar). HRMS, *m*/*z* found: 270.0637 (calculated for $C_{14}H_{10}N_2O_4$, $M^{+\bullet}$ requires: 270.0640).

*4.6.7. Methyl 4-[5-(3-oxo-pyrrolidin-2-yl)-1,2,4-oxadiazol-3-yl] benzoate (**8g**).* Yield=75%, white needles, mp=166–168 °C. ^{1}H NMR ($CDCl_3$): δ=2.22–2.65 (m, 4H, H-4″, H-5″); 3.89 (s, 3H, OC*H*$_3$); 5.13 (m, 1H, H-2″); 8.14 (q, 4H, $^3J_{H,H}$=8.5 Hz, H-3, H-5, H-2, H-6, Ar); 8.40 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ=25.75 (C-4″); 28.71 (C-5″); 49.43 (O*C*H$_3$); 52.36 (C-2″); 127.35 (C-3, C-5, Ar); 129.98 (C-2, C-6, Ar); 132.10 (C-4, Ar); 137.52 (C-1, Ar); 165.44 (*C*=O); 166.95 (C-5′); 176.82 (C-3′); 180.91 (C-4", *C*=O). HRMS, *m*/*z* found: 287.0913 (calculated for $C_{14}H_{13}N_3O_4$, $M^{+\bullet}$ requires: 287.0906).

*4.6.8. Methyl 4-[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl] benzoate (**8h**).* Yield=83%, white needles, mp=163–165 °C. ^{1}H NMR ($CDCl_3$): δ=3.88 (s, 3H, OC*H*$_3$); 3.94 (s, 3H, CO–OC*H*$_3$); 7.02 (d, 2H, $^3J_{H,H}$=8.8 Hz, H-2″, H-6″, Ar); 8.11–8.17 (m, 4H, H-3, H-5, H-3″, H-5″, Ar); 8.22 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-2, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=52.08 (O*C*H$_3$); 55.28 (O*C*H$_3$); 114.31 (C-2″, C-6″, Ar); 116.36 (C-1″, Ar); 127.20 (C-3, C-5, Ar); 129.77 (C-5″, C-3″, Ar); 129.86 (C-2, C-6, Ar); 131.01 (C-4, Ar); 132.05 (C-1, Ar); 163.07 (C-4″, Ar); 166.21 (*C*=O); 167.86 (C-3′, Ar); 175.67 (C-5′, Ar). HRMS, *m*/*z* found: 310.0944 (calculated for $C_{17}H_{14}N_2O_4$, $M^{+\bullet}$ requires: 310.0953).

*4.6.9. Methyl 4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl] benzoate (**8i**).* Yield=70%, white needles, mp=135–137 °C. ^{1}H NMR ($CDCl_3$): δ=3.94–3.96 (m, 6H, 2×OCH$_3$); 3.99 (s, 3H, OC*H*$_3$); 6.97 (d, 1H, $^3J_{H,H}$=8.4 Hz, H-5″, Ar); 7.65 (d, 1H, $^3J_{H,H}$=1.6 Hz, H-2″, Ar); 7.81 (dd, 1H, *J*=8.4, 1.6 Hz, H-6″, Ar); 8.14 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-3, H-5, Ar); 8.22 (d, 2H, $^3J_{H,H}$=8.3 Hz, H-2, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=52.08 (*C*H$_3$OCO); 55.84 (OCH$_3$); 55.91 (O*C*H$_3$); 110.19 (C-2″, Ar); 110.87 (C-5″, Ar); 116.36 (C-1″, Ar); 121.89 (C-6″, Ar); 127.20 (C-2, C-6, Ar); 129.75 (C-3, C-5, Ar); 130.92 (C-4, Ar); 132.07 (C-1, Ar); 149.07 (C-4″, Ar); 152.76 (C-3″, Ar); 166.18 (*C*=O); 167.88 (C-3′, Ar); 175.67 (C-5′, Ar). HRMS, *m*/*z* found: 340.1053 (calculated for $C_{18}H_{16}N_2O_5$, $M^{+\bullet}$ requires: 340.1059).

*4.6.10. Methyl 4-[5-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazol-3-yl] benzoate (**8j**).* Yield=87%, white needles, mp=206–208 °C. ^{1}H NMR ($CDCl_3$): δ=3.89 (s, 3H, OC*H*$_3$); 6.20 (s, 2H, OC*H*$_2$O); 7.17 (d, 1H, $^3J_{H,H}$=8,0 Hz, H-5″, Ar); 7.62 (s, 1H, H-2″, Ar); 7.77 (d, 1H, $^3J_{H,H}$=8.1 Hz, H-6″, Ar); 8.16 (q, 4H, $^3J_{H,H}$=7.8 Hz, H-3, H-5, H-2, H-6, Ar). ^{13}C NMR ($CDCl_3$): δ=52.08 (O*C*H$_3$); 102.06 (O*C*H$_2$O); 108.19 (C-5″, Ar); 109.29 (C-2″, Ar); 122.92 (C-1″, Ar); 125.53 (C-6″, Ar); 127.32 (C-3, C-5, Ar); 129.42 (C-2, C-6, Ar); 130.69 (C-1, Ar); 136.60 (C-4, Ar); 147.57 (C-3″, Ar); 151.41 (C-4″, Ar); 162.89 (*C*=O). HRMS, *m*/*z* found: 324.0764 (calculated for $C_{17}H_{12}N_2O_5$, $M^{+\bullet}$ requires: 324.0746).

Acknowledgements

Two of us (L.D. and J.C.L.) wishes to thank the 'Ministère de la Recherche et de l'Enseignement Supérieur' for research fellowships.

References and notes

1. Jochims, J. C. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon: London, 1996; Vol. 4; Chapter 4 and references cited therein, pp 179–228.
2. (a) Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescia, N.; Aldous, S.; Pevear, D. C.; Dutkof, F. J. *J. Med. Chem.* **1994**, *37*, 2421–2436; (b) Borg, S.;

Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J. Med. Chem.* **1999**, *42*, 4331–4342.
3. Vu, C. B.; Corpuz, E. G.; Merry, T. J.; Pradeepan, S. G.; Bartlett, C.; Bohacek, R. S.; Botfield, M. C.; Lynch, B. A.; Mc Neil, I. A.; Ram, M. K.; Van Schravendijk, M. R.; Violette, S.; Sawyer, T. K. *J. Med. Chem.* **1999**, *42*, 4088–4098.
4. Zhang, H. Z.; Kasibhtala, S.; Kuemmerle, J.; Kemnitzer, W.; Ollis-Mason, K.; Qui, L.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2005**, *48*, 5215–5223.
5. Rappe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Andersan, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Vanney, M. A.; Prasit, P.; Cosford, N. D. P. *J. Med. Chem.* **2004**, *47*, 4645–4648.
6. Li, Z.; Chen, W.; Hale, J. J.; Lynch, C. L.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G. J.; Chrebet, G.; Parent, S. A.; Bergstrom, J.; Card, D.; Forrest, M.; Quackenbush, E. J.; Wickham, L. A.; Vargas, H.; Evans, R. M.; Rosen, H.; Mandala, S. J. *J. Med. Chem.* **2005**, *48*, 6169–6173.
7. Chen, Y.; Albrecht, B. K.; Brown, J.; Buchanan, J. L.; Buckner, W. H.; Di Mauro, E. F.; Emkey, R.; Fiemeau, R. T.; Harmange, J. C.; Hoffman, B. J.; Huang, L.; Huang, M.; Han Lee, J.; Lin, F. H.; Martin, M. W.; Nguyen, H. Q.; Patel, V. F.; Tomlinson, S. A.; White, R. D.; Xia, X.; Hitchcock, S. A. *J. Med. Chem.* **2008**, *51*, 5019–5034.
8. Sperando, D.; Tai, V. W. F.; Lohman, J.; Hirschbein, B.; Mendonca, R.; Lee, C. S.; Spencer, J. R.; Jane, J.; Nguyen, M.; Beltmann, J.; Sprengeler, P.; Scheerens, H.; Lin, T.; Liu, L.; Kellog, A.; Green, M. J.; Mc Grath, M. E. *Bioorg. Med. Chem. Lett.* **2006**, *6*, 4085–4087.
9. Swain, C. J.; Baker, R.; Keen, C.; Mosely, J.; Seward, E. M.; Stevenjan, G.; Beer, M.; Stanton, J.; Watling, K. J. *J. Med. Chem.* **1991**, *34*, 140–145.
10. Diana, G. D.; Volkors, D. L.; Hitz, T. J.; Bailey, T. R.; Lang, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutka, F. J. *J. Med. Chem.* **1994**, *37*, 2421–2436.
11. Chighine, A.; Sechi, G.; Bradley, M. *Drug Discov. Today* **2007**, *12*, 459–464.
12. Ann, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311–3340.
13. (a) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693–3716; (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554; (c) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174–1196.
14. Lee, S. *Chem. Commun.* **2006**, 1049–1063.
15. Fraga-Dubreuil, J.; Famelart, M. H.; Bazureau, J. P. *Org. Process Res. Dev.* **2002**, *6*, 374–378.
16. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron Lett.* **2001**, *42*, 6097–6100.
17. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121–6130.
18. For a recent review, see: Mia, W.; Chan, T. H. *Acc. Chem. Res.* **2006**, *39*, 897–908.
19. (a) Cai, Y.; Liu, Y. *Monatsh. Chem.* **2009**, *140*, 39–44; (b) Li, M.; Sun, E.; Wen, L.; Sun, J.; Li, Y.; Yang, H. *J. Comb. Chem.* **2007**, *9*, 903–905; (c) Cai, Y.; Zhang, Y.; Peng, Y.; Lu, F.; Huang, X.; Song, G. *J. Comb. Chem.* **2006**, *8*, 636–638; (d) Huang, J. Y.; Lei, M.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 3047–3050; (e) Sang, G.; Cai, Y.; Peng, Y. *J. Comb. Chem.* **2005**, *7*, 561–566; (f) Miao, W.; Chan, T. H. *J. Org. Chem.* **2005**, *70*, 3251–3255; (g) Yi, F.; Peng, Y.; Song, G. *Tetrahedron Lett.* **2005**, *46*, 3931–3933; (h) de Kort, M.; Tuin, A.; Kuiper, S.; Overkleeft, H. S.; Vander Marel, G. A.; Buijsman, R. C. *Tetrahedron Lett.* **2004**, *45*, 2171–2175; (i) Anjaiah, S.; Chandrasekkar, S.; Gree, R. *Tetrahedron Lett.* **2004**, *45*, 569–571; (j) Handy, S. T.; Okello, T. L. *Tetrahedron Lett.* **2003**, *44*, 8399–8402; (k) Miao, W.; Chan, T. H. *Org. Lett.* **2003**, *5*, 5003–5005.
20. Katritzky, A. R.; Shestopolov, A. A.; Suzuki, K. *Arkivoc* **2005**, *vii*, 36–45 and references cited therein.
21. Swinbourne, J. F.; Hunt, H.; Klinkert, G. *Adv. Heterocycl. Chem.* **1987**, *23*, 103–108.
22. Stradler, A.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 3915–3920.
23. Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129–135.
24. Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem.* **1991**, *34*, 140–152.
25. Sauerberg, P.; Kindtler, J. W.; Nielsen, L.; Sheardown, M. J.; Honore, T. *J. Med. Chem.* **1991**, *34*, 687–692.
26. Amarasinghe, K. K. U.; Maier, M. B.; Srivastava, A.; Gray, J. L. *Tetrahedron Lett.* **2006**, *47*, 3629–3632.
27. Chiou, S.; Shine, H. J. *J. Heterocycl. Chem.* **1989**, *26*, 125–128.
28. Gangloff, A. R.; Litvak, J.; Shelton, E. J.; Sperandio, J.; Wang, V. R.; Rice, K. D. *Tetrahedron Lett.* **2001**, *42*, 1441–1443.
29. DCC: dicyclohexylcarbodiimide, EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, CDI: carbonyldiimidazole, TBTU: O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate, HOBt: 1,2,3-benzotriazol-1-hydroxyde, HBTU: O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluoroborate.
30. Eloy, F.; Lenears, R. *Chem. Rev.* **1962**, *62*, 155–183.
31. Srivastava, R. M.; Seabra, G. M. *J. Braz. Chem. Soc.* **1997**, *8*, 397–405.