Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1063–1068

A new approach to N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones with 1,2,4-oxadiazole group as amide isostere via ionic liquid-phase technology

Jean Christophe Legeay,[a] Jean Jacques Vanden Eynde[b] and Jean Pierre Bazureau[a,*]

[a]*Université de Rennes 1, Laboratoire Sciences Chimiques de Rennes, UMR CNRS 6226, Groupe Ingénierie Chimique et Molécules pour le Vivant (ICMV), Bât. 10A, Campus de Beaulieu, Avenue du Général Leclerc, CS 74205, 35042 RENNES Cedex, France*
[b]*Académie Universitaire Wallonie-Bruxelles, University of Mons-Hainaut, Department of Organic Chemistry, Faculty of Sciences, 20 Place du Parc, 7000 MONS, Belgium*

Received 9 November 2006; revised 23 November 2006; accepted 24 November 2006
Available online 22 December 2006

Abstract—New N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones with 1,2,4-oxadiazole group as amide isostere were synthesized in six steps by ionic liquid-phase organic synthesis (IoLiPOS) methodology from ILP bound acetoacetate. The 3,4-dihydropyrimidine-2(1*H*)-one (3,4-DHPM) core was prepared in the first step by one-pot three-component Biginelli condensation followed by N-alkylation with chloroacetonitrile. Then the nitrile group appended on the 3,4-DHPM heterocycle was quantitatively transformed into amidoxime. Addition of aliphatic carboxylic anhydride or aromatic carboxylic acid to the amidoxime produced the expected 1,2,4-oxadiazole via the *O*-acylamidoxime intermediate grafted on the ILP bound 3,4-DHPM using two convergent methods. After cleavage by transesterification under mild conditions, the target compounds were obtained in good overall yields. The structures and the purities of the reaction intermediates in each step were verified easily by routine spectroscopic analysis.

Nifedipine is a well-known 1,4-dihydropyridine (DHP) derivative that is marketed as a drug for the clinical treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias or angina pectoris.[1] Apart from nifidepine and other second-generation DHP analogs, interest has also focused on structurally closely related 3,4-dihydro-2(1*H*)-pyrimidinone analogs (DHPMs), which exhibit similar biological profiles to DHPs.[2]

Of special interest are the N-3 functionalized DHPMs, which are known to be excellent calcium channel modulators, for example, the aryl derivatives **1** (SQ 32926) and **2** (SQ 32547), or α_{1a} adrenergic receptor[3] like **3** (SNAP 6201) that are displayed in Figure 1. Due to the fact that N-3 functionalized DHPM analogs are pharmacologically rather interesting, the investigation of new functionalized DHPMs with potential and similar pharmacological profile to classical DHPs calcium channel modulators has been advocated. The basic idea here was to replace the amide function in N-3 position of DHPM by basic 1,2,4-oxadiazole moiety. The 1,2,4-oxadiazole heterocycle was well known as efficient amide and/or ester bioisostere[4] in peptide mimicry[5] and also increased the pharmacological in vitro and in vivo effects for antiaggregatory and antithrombotic activity essays.[6] It was found to help in the design of compounds with improved physicochemical properties and bioavailability.[7]

The advent of combinatorial chemistry, which has proven particularly useful for multicomponent reactions such as Biginelli[8] and Hantzsch[9] condensations, allows the efficient generation of diverse 3,4-dihydropyrimidin-2-one compound libraries that have been subjected to high throughput screening methods. The use of polymer supported reagents and scavengers is an attractive method due to the facile purification process of removing the excess reagents and side products. On the other hand, the use of polyethylene glycols (PEGs) and

Keywords: Task-specific ionic liquids; Biginelli; 3,4-Dihydropyrimidine-2(1*H*)-one; Three-component reaction; Amidoxime; *O*-Acylamidoxime; 1,2,4-Oxadiazole; Amide isostere; Transesterification; Cleavage.
* Corresponding author. Tel.: +33 2 23 23 66 03; fax: +33 2 23 23 63 74; e-mail: jean-pierre.bazureau@univ-rennes1.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.148

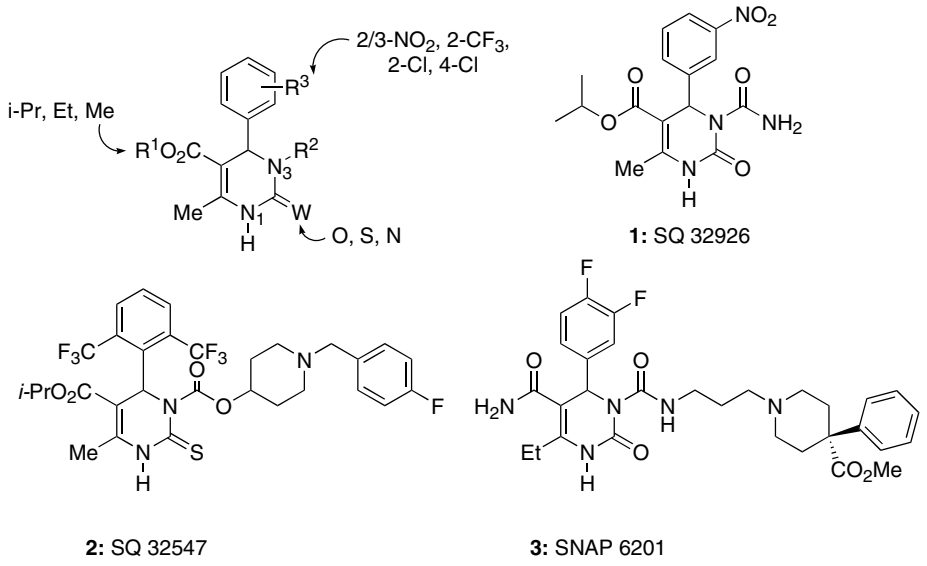


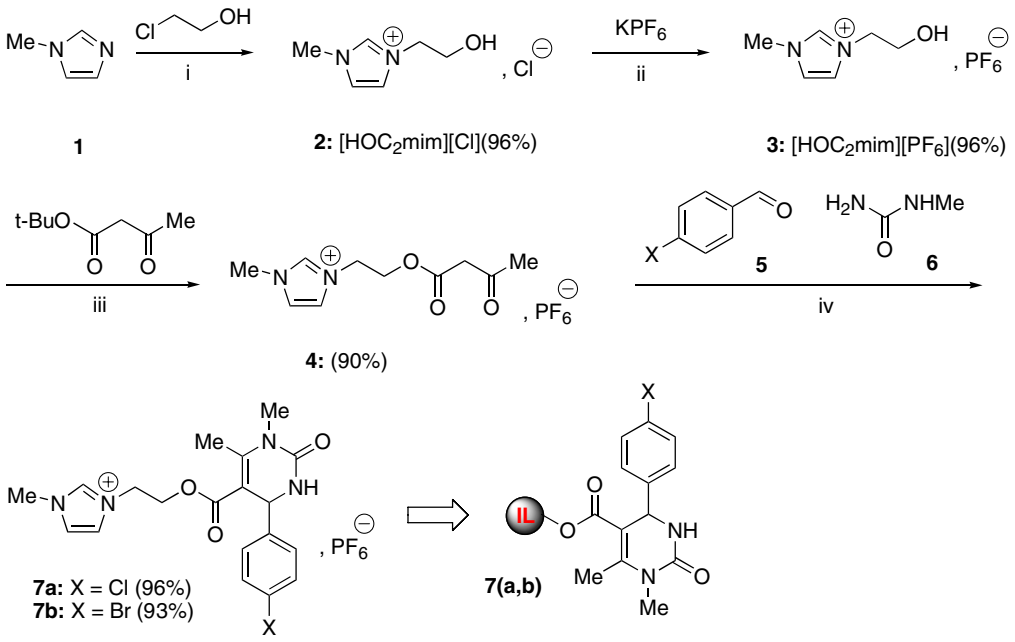
Figure 1. Structure–activity relationship of DHPM calcium channel blockers and biological active DHPM lead compounds.

PEG-grafted polystyrene supports has been employed successfully because of their homogeneous phase chemistry strategies. However, some limitations were expressed for the use of solid-phase and soluble polymers such as difficulties to monitor reaction progress, the large excess of reagents typically used in solid-phase supported synthesis, low loading capacity and limited solubility during the reaction progress and the heterogeneous reaction condition with solid-phases.[10] To circumvent these drawbacks, task-specific ionic liquids (TSILs), a subclass of usual room temperature ionic liquids (RTILS), have attracted interest as alternative soluble supports for liquid-phase organic synthesis[11] (LPOS). By introduction of hydroxyl group on the cation of ionic liquid,[12] these ionic liquid-phases (ILPs) have been used as synthetic equivalents of classical polymeric matrices in combinatorial chemistry. These alcohol-functionalized ILPs have been studied initially in our laboratory[13] and by other groups[14] in solution-phase combinatorial synthesis as scavengers. Continuing our work in this area, we have developed the synthesis of N-3 functionalized DHPMs with 1,2,4-oxadiazole group via the three-component Biginelli's condensation without solvent, according to the 'ionic liquid-phases organic synthesis' (IoLiPOS) methodology. In the present letter, we report some preliminary results on this investigation.

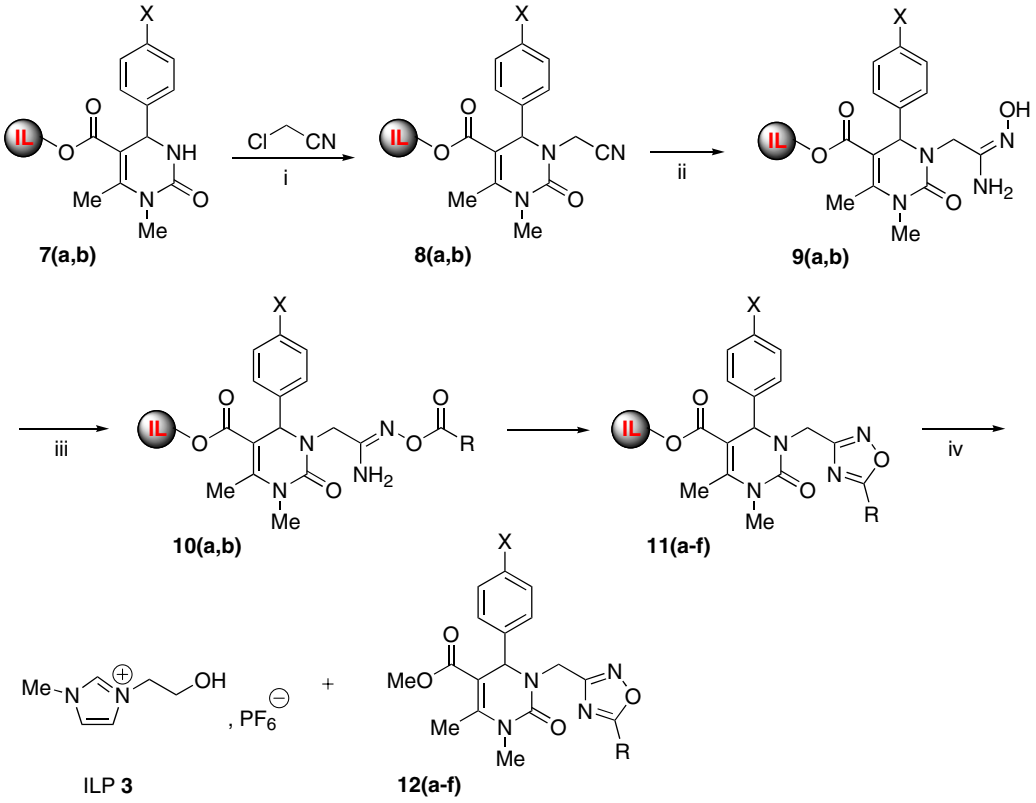
As shown in Scheme 1, the key step of our synthetic strategy toward 3,4-dihydro-2(1*H*)-pyrimidine **7** is based on the three-component Biginelli's reaction with ionic liquid-phase technology.[15] The starting DHPMs **7**(**a**,**b**) were chosen as starting compounds for the present investigation and were conveniently prepared according to the four step process developed in our group. The ionic liquid-phase **3** is readily available by solventless quaternization of methyl imidazole **1** on chloroethanol at 180 °C for 10 min under microwave[16a] dielectric heating (Synthewave® 402 reactor[16b]) followed by anion-metathesis of **2** with KPF_6 salt. In the third step, the reaction of ILP **3** with *tert*-butylacetoacetate produced the transacetoacetyled compound **4** in good yield (90%) using microwave-assisted solvent-free ionic liquid-phase synthesis[17] (170 °C, 10 min) without the need of a catalyst as is often used in the literature. Finally, a mixture constituted by 3 equiv of *N*-methyl urea **6**, *para*-halogenobenzaldehyde **5**(**a**,**b**), ILP bound acetoacetate **4** and a catalytic amount of hydrochloric acid was heated at 100 °C for 1 h to produce the DHPMs **7**(**a**,**b**) (93–96%) grafted on ionic liquid-phases.

With the selected ILP bound 3,4-DHPMs **7**(**a**,**b**) in hand, we investigated the possibility of building the 1,2,4-oxadiazole group on N-3 position. The common methods reported for the preparation of 1,2,4-oxadiazoles are cyclization of *O*-acylamidoximes obtained from acylation of amidoximes by derivatives of carboxylic acids[18] in the presence of a coupling reagent. The heterocycle is subsequently formed by intramolecular cyclodehydratation. This can be performed either after isolation of the O-acylated amidoxime precursor or immediately following its formation in a one-pot reaction. The starting amidoximes[19] are accessible by the reaction of nitriles with hydroxylamine. Our aim was to quickly develop a convenient, robust and high-yielding reaction protocol for the introduction of 1,2,4-oxadiazole moiety on the 3,4-DHPM structure.

Initially, our studies commenced by the reaction of ILP bound 3,4-DHPM **7** and chloroacetonitrile (Scheme 2) at different reaction temperatures using various bases (Et_3N, Cs_2CO_3, iPr_2NEt) and solvents. The reactions were conveniently monitored by ^1H NMR and among the conditions studied, we found that treatment of **7** with 2 equiv of $ClCH_2CN$ in the presence of NaH[20] (2 equiv) in acetonitrile at 0 °C gave good conversion after 18 h (Table 1). The ionic liquid-phases **8**(**a**,**b**) were purified by washing successively with diethyl ether (1/10 w/v), deionised water (1:10 w/v), pentane (1:10 w/v) and were further dried under high vacuum (10^{-2} Torr) at



Scheme 1. Preparation of ionic liquid-phases **7**(**a**,**b**) bound 3,4-dihydropyrimidine-2(1*H*)-ones. Reagents and reaction conditions: (i) chloroethanol (1 equiv), mw, 180 °C, 60 W, 10 min; (ii) KPF_6 (1 equiv), MeCN, 25 °C, 18 h; (iii) *tert*-butyl acetoacetate (2.6 equiv), μω, 170 °C, 150 W, 10 min; (iv) 100 °C, HCl cat., 60 min.



Scheme 2. Preparation of N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones **12**(**a**–**f**). Reagents and reaction conditions: (i) NaH (2 equiv), 0 °C, MeCN, 18 h; (ii) KOH (1.7 equiv), NH_2OH, HCl (1.6 equiv), EtOH, 0 °C, 1 h then reflux, 18 h; (iii) *Method A*: a. $(RCO)_2O$ (20 equiv), 25 °C, 18 h; b. H_2O, reflux, 18 h.; *Method B*: a. RCO_2H (1.09 equiv), DCC (1.02 equiv), DMAP 5%, MeCN, 25 °C, 48 h; b. H_2O, reflux, 36 h; (iv) MeONa (1 equiv), MeOH, reflux, 18 h.

room temperature for 4 h. Next, the nitrile group of **8** was easily transformed into amidoxime **9** by addition at 0 °C of a solution of hydroxylamine hydrochloride (1.6 equiv) and potassium hydroxide (1.7 equiv) in ethanol followed by moderate reflux for 18 h to achieve complete conversion (80–82%).

Table 1.

Compound	Starting products	X	R	Yield[a] (%)	Overall yield[b] (%)
7a	**5a**	Cl	—	96	—
7b	**5b**	Br	—	93	—
8a	**7a**	Cl	—	97	—
8b	**7b**	Br	—	93	—
9a	**8a**	Cl	—	82	79
9b	**8b**	Br	—	80	74
10a	**9a** + $(RCO)_2O$	Cl	Me	91[c]	72
10b	**9b** + $(RCO)_2O$	Br	Me	98[c]	73
11a	**10a**	Cl	Me	80	58
11b	**10b**	Br	Me	82	60
11c	**9a** + $(RCO)_2O$	Cl	Et	86[d]	68
11d	**9b** + $(RCO)_2O$	Br	Et	80[d]	60
11e	**9a** + RCO_2H	Cl	*p*-$MeOC_6H_4$	68[d]	54
11f	**9b** + RCO_2H	Cl	3,4-$(CH_2O_2)C_6H_3$	56[d]	44
12a	**11a**	Cl	Me	77	45
12b	**11b**	Br	Me	75	45
12c	**11c**	Cl	Et	70	48
12d	**11d**	Br	Et	75	45
12e	**11e**	Cl	*p*-$MeOC_6H_4$	80	43
12f	**11f**	Cl	3,4-$(CH_2O_2)C_6H_3$	81	36

[a] Yield of isolated product.
[b] Overall yield calculated from product **7**.
[c] Prepared according to method A.
[d] Prepared according to method B.

For the preparation of 1,2,4-oxadiazole **11** grafted on the ionic liquid-phase, we have studied two experimental procedures. In the first approach (method A), the reactions were carried out by mixing at room temperature the ILP bound amidoxime **9**(**a**,**b**) with excess of aliphatic anhydride. After 18 h with acetic anhydride as an example, these conditions led to the expected O-acylated amidoximes **10**(**a**,**b**) without contamination. The O-acylated amidoxime derivative **10a** (91%), characterized by mass spectrometry and ^{1}H NMR analyses, was the major product after purification by diethyl ether washings (1:10 w/v) to remove acetic acid and excess of anhydride. For the transformation of O-acylated amidoxime **10**(**a**,**b**) into the corresponding 1,2,4-oxadiazole **11**(**a**,**b**), the cyclization took place when the reaction mixture was heated to reflux in water. It's noteworthy that there was no need of a base as a catalyst[21] (pyridine, AcONa) as described in the literature, because the cyclic dehydration was found to proceed cleanly in good yield (**11a**: 80% and **11b**: 82%) and no cleavage was observed after analysis of the crude reaction mixture by ^{1}H NMR. Interestingly, under reaction conditions of method A, the solventless treatment of ILP bound amidoxime **9**(**a**,**b**) with propionic anhydride afforded directly the cyclized 1,2,4-oxadiazole **11(c,d)**: after 15 h at 25 °C, the crude *O*-acylamidoxime intermediate was mixed in refluxed deionised water to give after work-up the desired 1,2,4-oxadiazole heterocycle, respectively, in 86% yield for **11c** and 80% for **11d**.

In the second method (B), we investigated the use of aromatic carboxylic acid for the in situ preparation of *O*-acylamidoxime **10**. Acylation of the ILP bound amidoxime **9** with carboxylic acid was realized in dry acetonitrile at 25 °C with dicyclohexyl carbodiimide[22] (DCC) and 5% of dimethylaminopyridine[23] (DMAP) as catalyst. After 48 h, the insoluble dicyclohexyl urea (DCHU) was easily removed by filtration and the resulting filtrate was quickly refiltered through a short column of Celite®. Then, the crude reaction mixture was washed (1:10 w/v) with AcOEt/Et_2O (8/2) to remove excess of the starting reagents (DCC and carboxylic acid) and ^{1}H NMR analysis showed that *O*-acylamidoxime **10** and 1,2,4-oxadiazole **11** were both observed. Initial attempts to improve selective preparation of *O*-acylamidoxime **10** by exploring lower temperature, others solvents, short reaction times uniformly failed. To achieve complete cyclization, the resulting crude reaction mixture was submitted to heating in refluxed deionised water for 36 h. After work-up, the expected ILP bound 1,2,4-oxadiazoles **11(e,f)** were obtained in moderate yields (56–68%).

As illustrated in Table 1, the versatility of the two methods[24] was demonstrated through the preparation of a small library of six 1,2,4-oxadiazoles[25] **11**(**a**–**f**) grafted on the ionic liquid phase from aliphatic anhydride or aromatic carboxylic acid and the products formed were estimated easily by ^{1}H NMR without detaching the material from the ionic liquid-phase. These two methods gave yields ranging from 56% to 86% and overall yields from 44% to 68%.

In the last step, the target compounds **12** were released from the ILP bound 1,2,4-oxadiazole **11** by treatment with 1 equiv of sodium methoxide in refluxed MeOH for 18 h and again the reaction was easily monitored by ^{1}H NMR or TLC. After completion of the cleavage, the solvent was removed in vacuo. Owing to the small quantities of the starting ionic ILP bound 1,2,4-oxadiazole **11** (5 mmol), the purification and separation of **12** from the starting ILP **3** by the classical washings with an appropriate solvent are not practicable, but flash-filtration on alumina gel using AcOEt ($R_f = 1.0$) as eluent

followed by recrystallization from EtOH afforded the desired N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones **12**(**a**–**f**) in good yields (70–81%). The structure of the new 3,4-DHPMs **12** was ascertained by conventional techniques (^{1}H, ^{13}C NMR, IR) and the purity was controlled by HRMS. As can be seen in the results of Table 1, the target 3,4-DHPMs **12** were synthesized in five steps from the starting ILP bound Biginelli 3,4-DHPMs **7**(**a**,**b**) in moderate to good overall yield (33–48%).

In summary, new N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones with 1,2,4-oxadiazole as amide isostere using ionic liquid-phase organic synthesis (IoLiPOS) methodology has been developed. To our knowledge, this new approach has never been reported either in classical solution-phase reaction or with solid- or liquid-phase supported organic synthesis. This protocol involved the attachment of the 3,4-DHPM heterocycle on the ILP bound acetoacetate by solventless one-pot three-component condensation. Then, the 3,4-DHPM intermediates were easily functionalized with 1,2,4-oxadiazole using two convergent methods from aliphatic carboxylic anhydrides or from aromatic carboxylic acids. Detachment by transesterification afforded the new N-3 functionalized 3,4-DHPMs in good overall yields. On the basis of this example, the advantages of the ILP technology[26] are that the structure and the purity of each intermediate could be controlled by standard spectroscopic methods (^{1}H, ^{13}C NMR, HRMS and IR) after purification by washings with an appropriate solvent. Owing to the high loading capacity of ILP, in many cases the use of a large excess of reagents can be avoided in contrast to the usual solid-phase synthesis methods. Although a limited number of different and representative substituents of the 1,2,4-oxadiazole grafted on the 3,4-DHPM cores are presented here, it is obvious that a much larger diversity can be easily achieved. We are currently exploring the scope and potential of this ILP protocol for the preparation of new N-3 functionalized 3,4-DHPMs that will be much more reliable for biological screening.

Acknowledgments

One of us (J.C.L.) thanks the 'Ministère de la Recherche et de l'Enseignement Supérieur' for a research fellowship. We also thank Dr Pierre Guénot (CRMPO) for the mass spectrometry measurements and Merck Eurolab Prolabo (Fr.) for providing the Synthewave 402® apparatus.

References and notes

1. (a) Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775–785; (b) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956–965.
2. (a) Atwal, K. S.; Swanson, B. M.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806–811; (b) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. M.; Gougoutas, J. Z.; Schwartz, J.; Smille, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629–2635.
3. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.
4. (a) Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, 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.
5. Burell, G.; Evans, J. M.; Hadley, M. S.; Hicks, F.; Stemp, G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1285–1290.
6. Bethge, K.; Pertz, H. H.; Rehse, K. *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 78–96.
7. Naka, T.; Kubo, K. *Curr. Pharm. Dis.* **1999**, *5*, 543–572.
8. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–413.
9. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1–82.
10. Toy, P. M.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554.
11. Lee, S. *J. Chem. Soc., Chem. Commun.* **2006**, 1049–1063.
12. Fraga-Dubreuil, J.; Famelart, M. H.; Bazureau, J. P. *Org. Proc. Res. Dev.* **2002**, *6*, 374–378.
13. (a) Debdab, M.; Mongin, F.; Bazureau, J. P. *Synthesis* **2006**, 4046–4052; (b) Legeay, J. C.; Vanden Eynde, J. J.; Bazureau, J. P. *Tetrahedron* **2005**, *61*, 12386–12397; (c) Hakkou, H.; Vanden Eynde, J. J.; Hamelin, J.; Bazureau, J. P. *Tetrahedron* **2004**, *60*, 3745–3753; (d) Hakkou, H.; Vanden Eynde, J. J.; Hamelin, J.; Bazureau, J. P. *Synthesis* **2004**, 1793–1798; (e) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron Lett.* **2001**, *42*, 6097–6100.
14. (a) Cai, Y.; Zhang, Y.; Peng, Y.; Lu, F.; Huang, X.; Song, G. *J. Comb. Chem.* **2006**, *8*, 636–638; (b) Huang, J. Y.; Lei, M.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 3047–3050; (c) Sang, G.; Cai, Y.; Peng, Y. *J. Comb. Chem.* **2005**, *7*, 561–566; (d) Miao, W.; Chan, T. H. *J. Org. Chem.* **2005**, *70*, 3251–3255; (e) Yi, F.; Peng, Y.; Song, G. *Tetrahedron Lett.* **2005**, *46*, 3931–3933; (f) de Kort, M.; Tuin, A.; Kuiper, S.; Overkleeft, H. S.; Vander Marel, G. A.; Buijsman, R. C. *Tetrahedron Lett.* **2004**, *45*, 2171–2175; (g) Anjaiah, S.; Chandrasekkar, S.; Gree, R. *Tetrahedron Lett.* **2004**, *45*, 569–571; (h) Handy, S. T.; Okello, T. L. *Tetrahedron Lett.* **2003**, *44*, 8399–8402; (i) Miao, W.; Chan, T. H. *Org. Lett.* **2003**, *5*, 5003–5005.
15. Legeay, J. C.; Toupet, L.; Vanden Eynde, J. J.; Bazureau, J. P. *Arkivoc* **2007**, 13–28.
16. (a) Bazureau, J. P.; Mongin, F.; Hamelin, J.; Texier-Boullet, F. *Microwave in Organic Synthesis*, In *Microwave in Heterocyclic Chemistry*; 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 10, pp 426–523; (b) Besson, T.; Brain, C. *Microwave Assisted Organic Synthesis*. In *Heterocyclic Chemistry Using Microwave Assisted Approaches*; Tierney, J. P., Lidström, P., Eds.; Blackwell Publishing, 2004; Chapter 3; (c) Commarmot, R.; Didenot, R.; Gardais, J. F. *Fr Demande* **1985**, *25*, 560 529; *Chem. Abstr.* **1986**, *105*, 17442.
17. Legeay, J. C.; Goujon, J. Y.; Toupet, L.; Vanden Eynde, J. J.; Bazureau, J. P. *J. Comb. Chem.* **2006**, *8*, 829–833.
18. (a) Wang, Y.; Miller, R. L.; Sauer, D. R.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 925–928; (b) Santagada, V.; Frecentese, F.; Perissutti, E.; Cirillo, D.; Terraciano, S.; Caliendo, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4491–4493.
19. Eloy, F. R. L. *Chem. Rev.* **1962**, *62*, 155–183.
20. Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Hommick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagaratham, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703–2718.
21. (a) Hamzé, A.; Hernadez, J. F.; Fulerand, P.; Martinez, J. *J. Org. Chem.* **2003**, *68*, 7316–7321; (b) Borg, S.; Vollinga,

R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J. Med. Chem.* **1999**, *42*, 4331–4342.
22. Mathias, L. J. *Synthesis* **1979**, 561–576.
23. Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129–161.
24. General procedure for the preparation of 1,2,4-oxadiazole **11** grafted on ionic liquid-phase bound 3,4-DHPM:
Method A: A mixture of amidoxime **9** (1.04 mmol) and aliphatic carboxylic anhydride (2 mL) was stirred vigorously at 25 °C for 18 h. Diethyl ether (5 mL) was added to the reaction mixture and the crude insoluble *O*-acylamidoxine was collected by filtration and was purified by washing with Et_2O (1:10 w/v). The purity of *O*-acylamidoxime intermediate **10** was controlled by ^1H NMR. Compound **10** was mixed in refluxed deionised water (1:10 w/v) for 18 h. After removal of solvent in vacuo, the desired 1,2,4-oxadiazole **11** was further dried under high vacuum (10^{-2} Torr) at room temperature for 4 h. Products **11** were characterized by ^1H, ^{13}C NMR, and HRMS.
Method B: To a mixture of dicyclohexylcarbodiimide (1.02 equiv) and dimethylaminopyridine 5% in dry acetonitrile (15 mL) were added successively amidoxime **9** (0.9 mmol, 1 equiv) in one portion, then aromatic carboxylic acid (1.09 equiv). After vigorous stirring at 25 °C for 48 h, 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 *O*-acylamidoxime intermediate **10**. Product **10** was further washed (1:10 w/v) with a mixture of Et_2O/AcOEt (4:1). To product **10** was added deionised water (1:15 w/v) and the resulting mixture was heated at 100 °C for 36 h. After removal of solvent in vacuo, the desired 1,2,4-oxadiazole **11** was further dried under high vacuum (10^{-2} Torr) at room temperature for 4 h. Products **11** were characterized by ^1H, ^{13}C NMR, and HRMS.
25. *Selected data of methyl 4-(4-chlorophenyl)-1,6-dimethyl-3-[(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**12e**): Yield = 81%. White needles, mp = 80–82 °C from EtOH. IR (KBr): 1260, 1492, 1670, 1700, 2838, 2951 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.43 (s, 3H, Me), 3.25 (s, 3H, NMe), 3.56 (s, 3H, OMe), 3.82 (s, 3H, Ar–OMe), 4.02 (d, 1H, $J = 16$ Hz, N–CH_2), 5.18 (d, 1H, $J = 16$ Hz, N-CH_2), 5.38 (s, 1H, H-4), 6.93 (d, 2H, $J = 8.9$ Hz, H-3‴, H-5‴), 7.16 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.98 (d, 2H, $J = 8.9$ Hz, H-2‴, H-6‴). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 16.59 (Me), 31.20 (CONCH_3), 40.96 (NCH_2), 51.21 (OCH_3), 55.37 (ArOCH_3), 57.96 (C-4), 103.61 (C-5), 114.36 (C-3‴, C-5‴), 116.32 (C-1‴), 128.34–128.72 (C-2′, C-3′, C-5′, C-6′), 129.96 (C-2‴, C-6‴), 133.77 (C-4′), 139.04 (C-1′), 149.30–153.23 (C-2, C-6), 163.12 (C-4‴), 165.83 (CO_2Me), 166.98 (C-3‴), 175.96 (C-5‴). HRMS, *m*/*z*: 481.1251 found (calculated for $C_{24}H_{22}N_4O_5{}^{35}Cl$, $[M-H]^+$ requires 481.1279).
26. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121–6130, 'Tetrahedron Top-50 Most cited Paper 2003-2006 Award', 232nd ACS Full National Meeting 'Cycle of Excellence', San Francisco (USA), September 10, 2006.