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Efficient combination of task-specific ionic liquid and microwave dielectric heating applied to one-pot three component synthesis of a small library of 4-thiazolidinones

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Abstract—The first report of the use of task-specific ionic liquid as synthetic equivalent of ionic liquid-phase matrice for the preparation of a small library of 4-thiazolidinones is reported in this paper. The starting (ethyleneglycol)ionic liquid-phase is functionalized in good yields with 4-(formylphenoxy)butyric acid by using usual esterification reaction conditions (DCC/DMAP as catalyst). The synthesis of the ionic liquid-phase bound 4-thiazolidinones was performed by a one-pot three-component condensation under microwave dielectric heating. The final cleavage under microwave/catalysis strategy provides the expected 4-thiazolidinones in high purity after flash-chromatography purification. According to the ionic liquid-phase organic synthesis (IoLiPOS) methodology, it was found that optimized reaction conditions were performed by standard analytical methods (NMR, TLC). The ^{1}H, ^{13}C NMR spectrum of some representative 4-thiazolidinones and ionic liquid-phase bound benzaldehyde are also reported.
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1. Introduction

The use of room temperature ionic liquids[1] (RTILs) as molecular tools for green synthetic chemistry[2] is a fast growing area. The rising number of publications and reviews[3] is indicative of the potential of RTILs as 'neoteric solvents' for a broad range of chemical and industrial processes.[4] RTILs made of organic cations such as alkylpyridinium or dialkyl imidazolium and appropriate anions have attracted much recent attention as solvents for organic chemistry because they have melting points close or near to room temperature.[5] This is also due to a number of intriguing physical and chemical properties[6] of RTILs: they have high thermal and chemical stabilities, negligible vapor pressure, non-flammability and high loading capacity. By a judicious combination of cation and anion, physical properties have been accomplished by altering the length of alkyl chain attached to the cation allowing for fine tuning hydrophobicity, viscosity, polarity and molecular solvatation. Ionic liquids are miscible with polar organic solvents but non-miscible with water on one side and less-polar organic solvents such as aliphatic or aromatic hydrocarbons, diethylether, etc on the other. From this point of view ionic liquids offer the potential of easy separation.[7]

Owing to their high polarity, the RTILs are also suitable for microwave chemistry.[8] Since the first report of microwave assisted synthesis in 1986,[9] this technique has been accepted as a method for reducing reaction time often by several orders of magnitude and for increasing yields of product compared to conventional methods.[10] The combination of modern microwave reactor technology and combinatorial chemistry applications is a logical consequence of the increased speed and effectiveness offered by microwave dielectric heating.[11] The dramatic rate enhancements in the transformations can be mainly attributed to the high temperatures that are rapidly reached by microwave heating.

Several reports have been published on the microwave assisted multi-component synthesis libraries[12] of medicinal compounds using solid phase or soluble polymers such as poly(ethyleneglycol)[13] (PEG).

In connection with our research program on exploitation of microwave-dielectric heating (μω) to room temperature ionic liquid chemistry,[14] we considered that hydrophilic poly(ethyleneglycol)-ionic liquid matrices are potential tools for synthetic applications in liquid-phase combinatorial chemistry.[15]

In a previous paper,[16] we have found that a functionalized PEG-ionic liquid phase (Fig. 1) can be used as a novel matrix in liquid phase organic synthesis (LPOS) potentially compatible with high-throughput production of combinatorial

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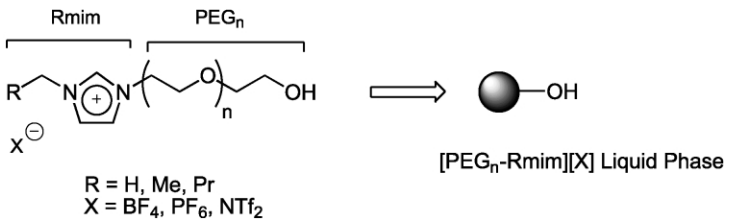


Figure 1. Poly(ethyleneglycol)-ionic liquid matrices used for Ionic Liquid Phase Organic Synthesis (IoLiPOS).

libraries. In order to investigate the PEG-ionic liquid matrices using solventless dielectric heating, we choose to explore the 4-thiazolidinone moiety as a heterocyclic scaffold. 4-Thiazolidinones have been reported to possess a wide range of biological activities (antifungal,[17] antihistaminic or antimicrobial activity[18] or use in the treatment of inflammation,[19] hypertension, renal failure, congestive heart failure, uremia) and are most conveniently made by the three-component condensation of a primary amine, an aldehyde and either a mercaptoacetic acid (Fig. 2). Usually, the reaction proceeds through the intermediate imine and the stepwise assembly of 4-thiazolidinones has also been reported.[20] We wish to report now our efforts on the ionic liquid phase organic synthesis (IoLiPOS) of 4-thiazolidinones using microwave dielectric heating.

2. Results and discussion

For this study (Scheme 1), we have chosen to examine the chemical and physical properties of the 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([PEG_1mim][BF_4]) **3** in IoLiPOS methodology. This PEG_1-ionic liquid phase **3** (PEG-ILP) was prepared in two steps:[21] the first step involves an efficient solventless quaternization using a monomode reactor with focused waves[22] (Prolabo Synthewave® 402)[23] and accurate control of power and temperature (by infrared detection) from an equimolar mixture of 2-chloroethanol and methyl imidazole **1** (98% yield), then followed by a facile anion metathesis with NH_4BF_4 which produces the expected [PEG_1mim][BF_4] liquid phase **3** in 85% yield. This PEG-ILP **3** present a low dynamic viscosity (85 cP at 25°C) and provide a solution like environment for bound molecules, the BF_4^- coordinating ILP **3** would be expected to be thermally stable to decomposition[24] and hence may prove more useful in microwave heating experiments.

There have been reports describing the solid phase synthesis of 4-thiazolidinones[25] and few reports[26] where the nitrogen of this heterocycle originates from an α-aminoacid with the carboxylic function serving as the site of attachment to the support. In our approach, we have examined the imine

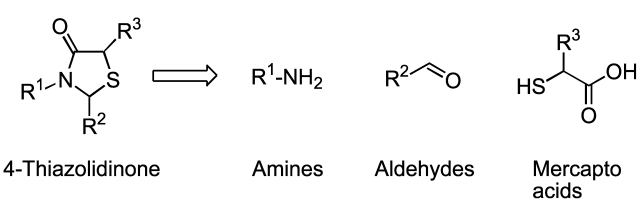
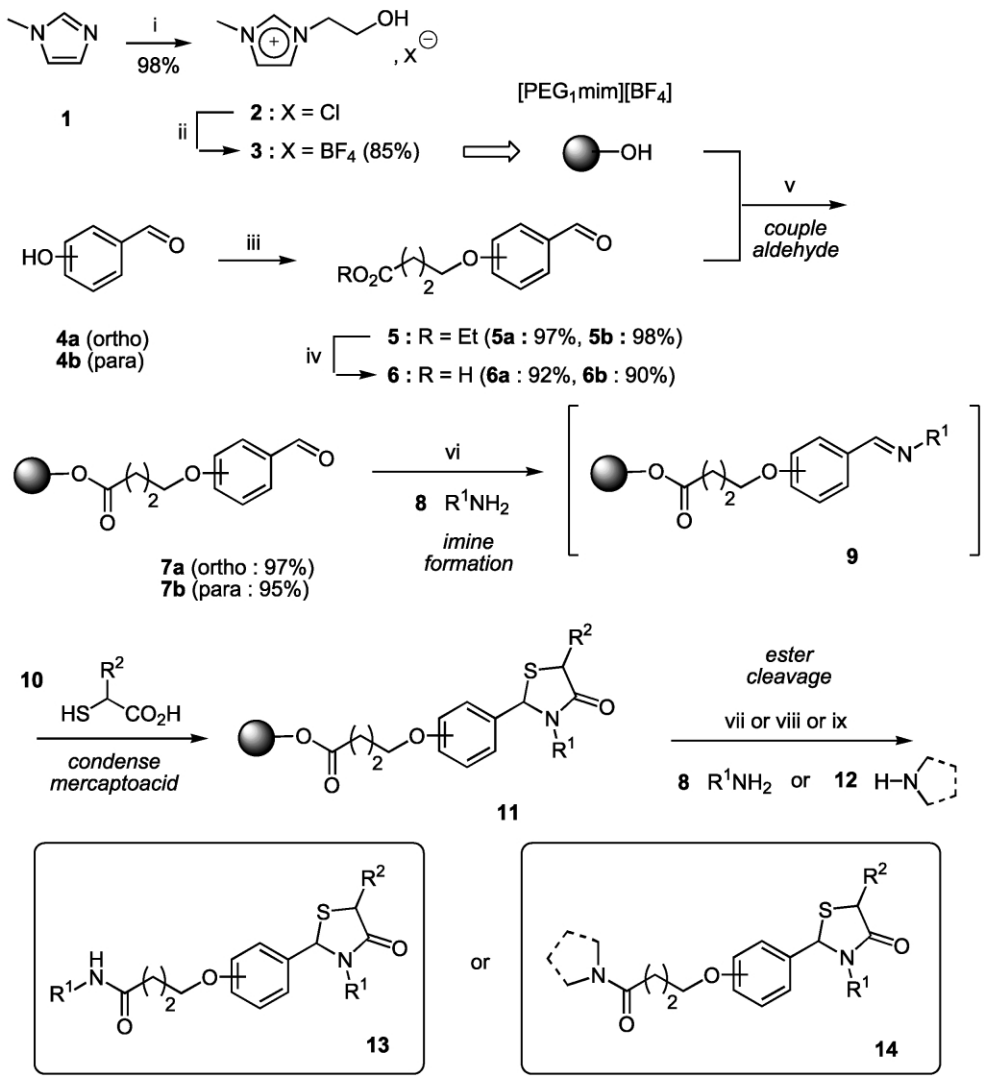


Figure 2. Components for the synthesis of 4-thiazolidinones.

formation on the [PEG_1mim][BF_4] liquid phase **3** with aromatic aldehydes (salicylaldehyde **4a** and 4-hydroxybenzaldehyde **4b**) bound to the ionic liquid moiety. For the preparation of the starting 4-(formylphenoxy)butyric acid **6a**,**b**, salicylaldehyde **4a** and 4-hydroxybenzaldehyde **4b** were reacted in a Williamson ether synthesis with ethyl bromobutyrate (EBB) to give esters **5a**,**b** in quantitative yields (**5a**:[27] 97%, **5b**:[28] 98%) followed by saponification with KOH in refluxing MeOH[29] (**6a**: 92%, **6b**: 90%). The aldehydes **6a**,**b** could be assembled on the [PEG_1mim][BF_4] liquid phase **3**. One of the most common transformations in solid-phase organic synthesis (SPOS) or in liquid phase organic synthesis (LPOS) involves the construction of an ester linkage between a solid or liquid supported hydroxy or halogen functionality and carboxylic acid derivative. The activation of the carboxylic acid by carbodiimide still constitutes the most frequently used method. As shown in Scheme 1, the esterification of esters **6a**,**b** (1.1 equiv.) with the ILP **3** in dry MeCN with dicyclohexyl carbodiimide[30] (DCC) and 5% of 4-dimethylamino pyridine[31] (DMAP) as catalyst produced the functionalized ionic liquid phases[32] **7a**,**b** in high yields (**7a**: 97%, **7b**: 95%). During the work-up, insoluble dicyclohexylurea (DCHU) was removed first by filtration to ensure the final purity of the functionalized ionic liquid phase, then the crude mobile pale yellow ILPs **7a**,**b** were washed successively twice with dry toluene (1:5 w/v), AcOEt (1:5 w/v) and was further dried under high vacuum (10^{-2} Torr) at 60°C for 1 h. The ILPs **7a**,**b** were characterized by mass spectrometry and proton NMR, confirming that in esterification the major compound has a molecular ion corresponding to the appropriate product.

In the second step, we initially examined the formation of imines via condensation of amines **8** with the ILP **3** under microwaves. Reactions were performed in open cylindrical quartz reactor (∅=1 cm) with the Synthewave 402® microwave reactor. This reactor operates with an adjustable power range 0–300 W and may be monitored either in power or in temperature or both. An array of experiments carried out with different reaction temperatures under microwaves irradiations revealed that the optimal results were obtained at 100°C after 20 min at 20% power (60 W) level with continuous mixing (at elevated power levels, it is possible to observe partial decomposition of the ILPs **9** by microwave absorption, which results in lower yields). The successful regioselective addition of amines **8** into the IL-phase **3** will allow diversity introduction at this step.

Then we turned our attention to the scope and limitations of 4-thiazolidinone formation on the Il-phases **7a**,**b** using a one-pot three-component condensation for a rapid synthesis of 4-thiazolidinones under microwaves. A stoichiometry of 1:1:1 of IL-phase **3**: amine **8**: mercaptoacetic acid **10**,



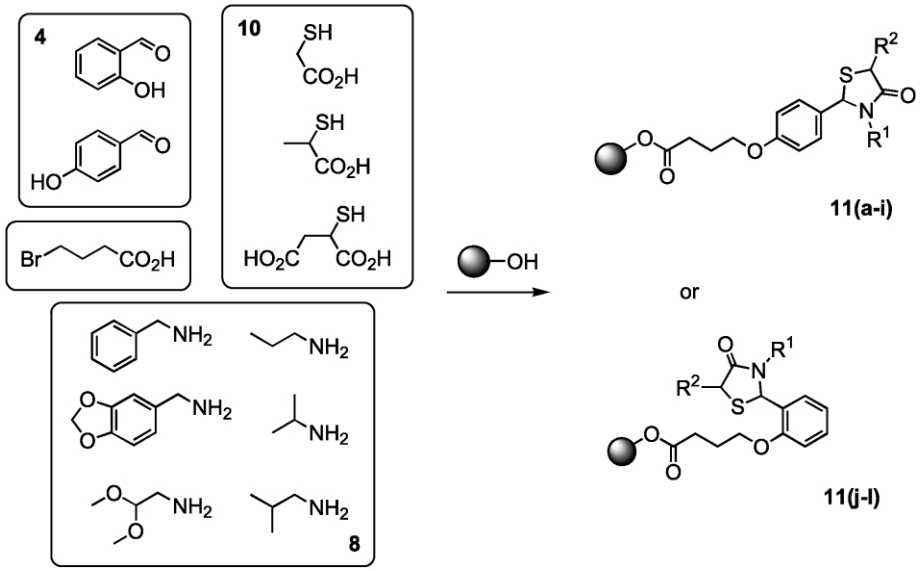
Scheme 1. *Reagents and conditions*: (i) chloroethanol (1 equiv.), μω, 180°C, Power=20%, 10 min, N_2; (ii) NH_4BF_4 (3 equiv.), MeCN, 60°C, 20 h; (iii) EBB (1 equiv.), from **4a**: K_2CO_3 (2 equiv.), MeCN, reflux, 24 h, from **4b**: K_2CO_3 (1.5 equiv.), MeCN, reflux, 96 h,; (iv) KOH 2N, MeOH, from **5a**: reflux, 1.5 h, HCl 5N, from **5b**: reflux, 2 h, HCl 3N; (v) DCC (1 equiv.), DMAP (5%), dry MeCN, rt, 18 h; (vi) **8** (1 equiv.), **10** (1 equiv.), μω, 100°C, Power=20%, 60–120 min; (vii) **8** (3 equiv.), μω, 100°C, 10 min; (viii) **8** (1 equiv.), *t*-BuOK (0.5 equiv.), μω, 100°C, 10–20 min; (ix) **8** or **12** (1 equiv.), *t*-BuOK (0.5 equiv.), μω, 150°C, 10 min.

respectively, were found to react completely in the imine/cyclization step at 100°C (Table 1). Progress of one-pot cyclization was easily monitored by proton NMR spectroscopy and showed that optimized reaction conditions for cyclization were achieved with a reaction time ranging from 1 to 2 h under microwave exposure at 20% power level (60 W). Mercaptoacetic acid **10** was used to allow for the incorporation of a third diversity point.

We have found that condensation of α-mercapto carboxylic acid **10** (1 equiv.) with ILPs-bound arylidene imines **9** provides 4-thiazolidinones **11** in yields ranging from 12 to 86% (estimated by ^{1}H NMR spectroscopy in $CDCl_3$). In our approach, it was not necessary to use large excess of α-mercapto carboxylic acid **10** with respect to imines **9** as described in the literature.[26b] During the experiments, we have observed that the best yields for products **11** were obtained from α- and β-substituted primary amines **8** (i.e. benzylamine, piperonylamine and 2,2-dimethoxyethylamine), on the other hand the thiazolidinone formation is not favored with the use of volatile amines **8** (i.e. propylamine, isopropylamine, isobutylamine).

Cleavage of the ILP-bound thiazolidinones **11** was performed by amide formation with primary amines **8** and secondary amines **12**. Ester aminolysis,[33] in general, occurs under harsh conditions that require high temperatures and extended reaction periods or the use of strong alkali metal catalysts. A microwave-specific effect for the synthesis of amides from non-enolizable esters and amines using *t*-BuOK has been reported[34] under microwave irradiation using solventless conditions.[35] With this information in hand, we have conducted a series of experiments at various temperatures using microwave dielectric heating. Our straightforward procedure entails addition of a small amount of solid potassium *tert*-butoxide (5%) to a premixed mixture of ILP **11** and 1 equiv. of amine **8** or **12**, and exposing the reaction mixture to microwave irradiation for the specified reaction time (10 or 20 min) at 100°C for butylamine or at 150°C for β-substituted primary amines **8**.

Table 1. Results of the three component synthesis of 4-thiazolidinones **11a**–**l** grafted on PEG_1-Ionic Liquid Phase from the $[PEG_1mim][BF_4]$ Ionic Liquid Phase **7a**,**b**, amines **8** and α-mercapto carboxylic acid **10** by imine/cyclization under solventless microwave dielectric heating



Product **11**	R^1 from **8**	R^2 from **10**	Reaction time[a] (min)	Conversion[b] (%)
11a	Bn	H	90	86
11b	Bn	Me	90	79
11c	Bn	CH_2CO_2H	90	60
11d	piperonyl	H	120	71
11e	$CH_2CH(OMe)_2$	H	120	84
11f	CH_2-CH=CH_2	H	120	82
11g	Pr	H	80	41
11h	*i*-Pr	H	60	12
11i	*i*-Bu	H	120	42
11j	Bn	H	120	61
11k	Pr	H	120	71
11l	*i*-Bu	H	120	47

[a] Reactions were run in a focused microwave reactor (Synthewave® 402, Merck Eurolab, Div. Prolabo, Fr) at 100°C, Power=20% (60 W).
[b] Conversion of **7a**,**b** into **11** (*ortho*, *para*) estimated from the crude reaction mixture by ^1H NMR ($CDCl_3$, Bruker AC 300P, TMS as internal reference).

On completion of the reaction, as determined by ^1H NMR, the reaction mixture was extracted into chloroforme (1:5 w/v) and subsequent product purification by flash chromatography on silica gel 60 F-254 (Merck) afforded the 4-thiazolidinones **13** or **14** using $CHCl_3$ or AcOEt as eluent. The purified products were characterized by conventional techniques (^1H, ^{13}C NMR and HRMS). The overall yields of isolated 4-thiazolidinones **13** and **14** (Table 2) are quite respectable in their own right, but the main advantage of having assembled the molecules on the ionic liquid phase $[PEG_1mim][BF_4]$ **3** is demonstrated by the purities of the crude material: no further purification is needed. Table 2 outlines 12 representatives examples where initial imine/cyclization step were proceeded efficiently.

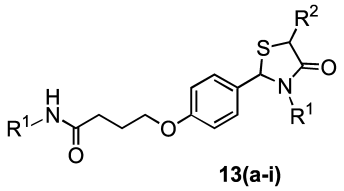
3. Conclusion

In conclusion, we have demonstrated that the combination of task-specific ionic liquid (TSIL) and microwave dielectric heating allow a rapid and practical preparation of a small library of amido 4-thiazolidinones. To our knowledge, this methodology has never been reported and may complement those existing in the literature.

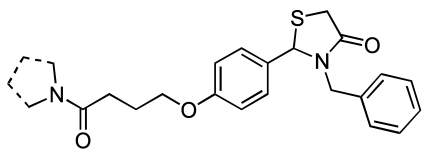
In our approach, we have found that it is possible to perform perfect attachment of aromatic aldehydes to a TSIL-phase via an esterification reaction using conventional protocol. 4-Thiazolidinone formation is typically achieved in 1–2 h in good yields by microwave irradiation with IL-phase bound arylidene imine derivatives. The microwave heating can be safely performed at atmospheric pressure and eliminates the need for specialized pressure vessels for the one-pot three component condensations of α-mercapto carboxylic acids, amines and aldehydes to generate the 4-thiazolidinone moiety on the IL-phase. Cleavage of the IL-phase bound thiazolidinone was realized with various amines and *t*-BuOK as catalyst under microwave heating and allowed for the incorporation of a fourth diversity point. The presented examples indicate that the microwave/catalysis strategy provides a wide scope in the development of pure amides with moderate elevated temperature (150°C) but without large molar excess of reagent.

The specific advantages offered by the use of TSILs as new tools in liquid-phase organic synthesis (LPOS) are the following: (1) the routine product isolation is very simple because the side product is removed by washings from the IL-phase with the appropriate solvent/eluent, (2) the cleaved

Table 2. Representative 4-thiazolidinones **13** or **14** and results obtained for conversion of **11** grafted on PEG_1-Ionic Liquid Phase into **13** or **14** by addition of primary amine **8** or secondary amine **12** using solventless microwave dielectric heating (in the Synthewave 402 reactor)



13(a-i)



14(a-c)

Product **13** or **14**	R^1 from **8**	R^2 from **10**	Reaction conditions for cleavage			Yield[a] (%)
			Amine **8** or **12**	Method[b]	Time[c] (min)	
13a	Bn	H	Pr-NH_2	vii	20	44
13b	Bn	H	Bu-NH_2	viii	10	47
13c	Bn	H	Piperonyl-NH_2	ix	10	40
13d	Bn	Me	Pr-NH_2	vii	20	61
13e	Bn	CH_2-CO_2H	Pr-NH_2	vii	20	41
13f	Piperonyl	H	Pr-NH_2	vii	20	40
13g	Piperonyl	H	Bn-NH_2	ix	10	39
13h	CH_2-$CH(OMe)_2$	H	Pr-NH_2	vii	10	47
13i	CH_2-CH=CH_2	H	Bn-NH_2	ix	30	30
14a	Bn	-	Piperidine	ix	10	26
14b	Bn	-	Pyrrolidine	ix	10	30
14c	Bn	-	Morpholine	ix	10	25

[a] Overall yield of isolated product obtained after purification by flash chromatography on silica gel 60 F-254 (Merck).
[b] Reaction conditions used under microwave irradiation: (vii) **8** (3 equiv.), 100°C; (viii) **8** (1 equiv.), *t*-BuOK (0.5 equiv.), 100°C; (ix) **8** or **12** (1 equiv.), *t*-BuOK (0.5 equiv.), 150°C.
[c] Reaction time estimated by conversion of **9** into **13** or **14** in the crude reaction mixture by ^1H NMR ($CDCl_3$, Bruker AC 300P, TMS as internal reference).

product was obtained with high purity after flash chromatography, (3) at each step of the synthesis, the ILPs bound products allow standard analytical methods (^1H NMR, TLC) to be used to monitor reaction progress, (4) the high polarity of IL-phases is suitable for microwave dielectric heating, and the combination of ILP/microwave decreases the viscosity of the reaction medium and gives significant rate enhancements, and (5) the IL-phases are easy to prepare by a judicious combination of cation and anion.

We are currently exploring the scope and potential of microwave dielectric heating assisted ionic liquid phase organic synthesis (IoLiPOS) by extending the methodology described herein[36] to other heterocyclic targets, and the simplicity of the experimental procedures renders this approach particularly attractive.

4. Experimental

4.1. General

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative column chromatography, silica gel 60 F-254 Merck (230–240 mesh ASTM) was used. ^1H NMR spectra were recorded on BRUKER ARX 200 P (200 MHz), BRUKER AC 300 P (300 MHz) spectrometers, ^{13}C NMR spectra on BRUKER ARX 200 P (50 MHz), BRUKER AC 300 P (75 MHz) spectrometers. 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, singulet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants *J* are given in Hertz. The mass spectra (HRMS) were taken on a VARIAN MAT 311 at an ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). For the dynamic viscosity, the measurements were carried out at 25°C on the AR 1000 microviscosimeter (TA Instruments) with a stainless cone plate geometry (diameter: 40 mm, angle: 1°1′). A flow procedure was applied from 0.06 to 200 s^{-1} in 3 min with 20 points by decade. Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3 Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification. 1-Methylimidazole **1** was distilled from CaH_2 prior to use.

4.1.1. 1-(2-Hydroxy-ethyl)-3-methylimidazolium chloride (2). A mixture of freshly distilled 1-methylimidazole **1** (15 g, 182.6 mmol) and 2-chloroethanol (14.70 g, 182.6 mmol) was placed in a cylindrical quartz reactor (∅=4 cm). The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor [2.45 GHz, adjusted power within the range 0–300 W and a wave guide (single mode T_{01}) fitted with a stirring device and an IR temperature detector]. The stirred liquid mixture was irradiated twice at 20% power level for 5 min at 180°C. Then the mixture was allowed to cool down and a white solid formed rapidly (~5 min) at 25°C. The crude solid that had formed was filtered off (under nitrogen), washed successively with anhydrous ether (3×30 mL), dry acetonitrile (2×20 mL), and vacuum dried in a dessicator over $CaCl_2$ for 1 h. The solid salt [PEG_1mim][Cl] **2** was further dried under high vacuum (10^{-2} Torr) at 60°C for 8 h and

was stored (23.44 g, 94% yield) in the dark at 4°C under nitrogen. Recrystallization from dry MeCN gave **2** in 80% yield as colourless needles, mp=86–88°C. ^{1}H NMR (D_2O, 200 MHz) δ 3.82 (s, 3H); 3.84 (t, 2H, J=5.9 Hz); 4.23 (t, 2H, J=5.9 Hz); 7.37 (t, 1H, J=1.2 Hz, H-4, H-5); 7.41 (t, 1H, J=1.2 Hz, H-4, H-5); 8.67 (s, 1H, H-2).

4.1.2. 1-(2-Hydroxy-ethyl)-3-methylimidazolium tetrafluoroborate [PEG$_1$mim][BF$_4$] (3). A mixture of 1-(2-Hydroxy-ethyl)-3-methylimidazolium chloride **2** (10 g, 61.54 mmol) and NH_4BF_4 (6.46 g, 61.54 mmol, 1 equiv.) in dry acetonitrile (160 mL) was stirred vigorously at 25°C under nitrogen for 24 h. After elimination of the precipitated salt (NH_4Cl) on a filter paper, the resulting filtrate was quickly refiltered through a short column of Celite® to remove some residual salt and finally concentrated by rotary evaporation that gave the expected mobile liquid phase **3** in 98% yield (12.91 g). The ionic liquid phase **3** was further dried under high vacuum (10^{-2} Torr) at 60°C for 6 h. It is recommandle to handle the [PEG$_1$mim][BF$_4$] ionic liquid phase **3** in the dark under an inert atmosphere at 4°C. Dynamic viscosity: 86 cP at 25°C (0.01 g cm^{-1} s^{-1}). ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 3.92 (t, 2H, J=4.8 Hz); 4.01 (s, 3H); 4.22 (br. s, 1H, OH); 4.38 (t, 2H, J=5 Hz); 7.63 (t, 1H, J=1.6 Hz, H-4, H-5); 7.68 (t, 1H, J=1.6 Hz, H-4, H-5); 8.85 (s, 1H, H-2).

4.1.3. Acid 4-(2-formyl-phenoxy)-butyric (6a). To a stirred suspension of 2-hydroxybenzaldehyde **4a** (5 g, 40.94 mmol) and potassium carbonate (11.31 g, 58.89 mmol) in acetonitrile (80 mL) was added dropwise over 15 min at room temperature ethyl bromobutyrate (7.62 g, 39.06 mmol), then the mixture was heated for 20 h. The reaction mixture was allowed to cool down to room temperature. After filtration and removal solvent in vacuo, diethyl ether (50 mL) was added to the crude reaction mixture and the resulting solution was filtered though a pad of Celite® to remove the precipitated salt KBr, and the solvent was removed on a Rotovapor. The crude reaction mixture gave the expected ethyl 4-(2-formyl-phenoxy)-butyrate **5a** as a mobile and colourless oil in 97% yield.

To a solution of ethyl 4-(2-formyl-phenoxy)-butyrate **5a** (5 g, 21.16 mmol) in methanol (25 mL) was added dropwise a solution of potassium hydroxyde 2N (2.85 g, 50.79 mmol) over 20 min under vigorous magnetic stirring. The reaction mixture was refluxed during 2 h. After elimination of solvent in a rotary evaporator, the precipitated acid **6a** was obtained at pH 1 by addition of a solution of HCl 3N in the crude residue. The precipitated crude acid **6a** was filtered off, washed with deionized water (3×50 mL) and dried under reduced pressure during 3 h. The expected acid **6a** was obtained in 93% yield as colourless needles, mp=91–92°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.25 (quint, 2H, J=6.8 Hz); 2.65 (t, 2H, J=7 Hz); 4.19 (t, 2H, J=6 Hz); 7.02 (m, 2H, H-3, H-5); 7.57 (ddd, 1H, J=8.2, 1.8 Hz, H-4); 7.85 (dd, 1H, J=7.7, 1.7 Hz, H-6); 10.50 (s, 1H, CHO); 10.81 (br. s, 1H, OH).

4.1.4. Acid 4-(4-formyl-phenoxy)-butyric (6b). Ethyl 4-(4-formyl-phenoxy)-butyrate **5b** was prepared in 98% yield from 4-hydroxybenzaldehyde **4b** (5 g, 40.94 mmol), potassium carbonate (11.31 g, 58.89 mmol) and ethyl bromobutyrate (7.62 g, 39.06 mmol) in refluxed acetonitrile (80 mL) with a reaction time of 4 days. Then, acid 4-(4-formyl-phenoxy)-butyric **6b** was synthetized according to the method described for **6a** which gave the expected acid **6b** in 97% yield as colourless needles, mp=245–246°C. ^{1}H NMR (DMSO d^6, 200 MHz) δ 1.96 (quint, 2H, J=6.9 Hz); 2.39 (t, 2H, J=7.3 Hz); 4.08 (t, 2H, J=6.6 Hz); 7.08–7.83 (d, 2H, J=8.7 Hz, Ar); 9.84 (s, 1H, CHO).

4.1.5. 1-{2-[4-(2-Formyl-phenoxy)-butyryloxy]-ethyl}-3-methyl-imidazolium tetrafluoroborate (7a). To a mixture of dicyclohexylcarbodiimide (2.97 g, 14.42 mmol) and dimethylaminopyridine 5% (88 mg, 0.7 mmol) in dry acetonitrile (75 mL) were added successively the ionic liquid phase [PEG$_1$mim][BF$_4$] **3** (3.08 g, 14.42 mmol) in one portion, then 4-(2-formylphenoxy)butyric acid **6a** (3 g, 14.42 mmol). After vigorous stirring at room temperature for 18 h, the insoluble *N*,*N*′-dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and the resulting crude reaction mixture was washed three times with toluene (20 mL). Removal of the solvent in vacuo lead to a pale yellow viscous oil in 97% yield. The ionic liquid phase **7a** was stored under inert atmosphere at 4°C. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 2.15 (quint., 2H); 2.66 (t, 2H); 4.02 (s, 1H); 4.20 (t, 2H); 4.52 (t, 2H); 4.66 (t, 2H); 7.06 (t, 1H); 7.20 (d, 1H); 7.63 (ddd, 1H); 7.67 (t, 1H); 7.73 (dd, 1H); 7.78 (t, 1H); 9.02 (s, 1H); 10.44 (s, 1H). ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 24.98 (thept, J=129, 2.5 Hz); 30.82 (tt, J=129, 4.5 Hz); 36.60 (q, J=144 Hz); 49.49 (t, J=145 Hz); 63.12 (tt, J=151, 3.2 Hz); 68.32 (tquint, J=146, 4.3 Hz, OCH2); 114.02 (ddt, J=161, 7.6, 1.5 Hz, C-3); 121.46 (dd, J=164, 7.8 Hz, C-5); 123.86 (dm, J=204 Hz, C-4′, C-5′); 124.70 (dm, J=204 Hz, C-4′, C-5′); 125.65 (dm, J=34 Hz, C-1); 128.43 (ddt, J=161, 8.5, 1.9 Hz, C-6); 137.03 (ddd, J=160, 9.1, 1.9 Hz, C-4); 138.05 (dm, J=222 Hz, C-2′); 163.10 (m, C-2); 173.15 (m, CO); 189.76 (ddd, J=180, 4.2, 1.6 Hz, CHO); HRMS, *m*/*z*: 317.1497 found (calcd for $C_{17}H_{21}N_2O_4$, M^+ requires: 317.1501).

4.1.6. 1-{2-[4-(4-Formyl-phenoxy)-butyryloxy]-ethyl}-3-methyl-imidazolium tetrafluoroborate (7b). To a mixture of dicyclohexylcarbodiimide (2.97 g, 14.42 mmol) and dimethylaminopyridine 5% (88 mg, 0.7 mmol) in dry acetone (75 mL) were added successively the ionic liquid phase [PEG$_1$mim][BF$_4$] **3** (3.08 g, 14.42 mmol) in one portion, then 4-(4-formylphenoxy)butyric acid **6b** (3 g, 14.42 mmol). After vigorous stirring at room temperature for 18 h, the insoluble *N*,*N*′-dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and the resulting crude reaction mixture was washed three times with AcOEt (20 mL). Removal of the solvent in vacuo lead to a pale yellow viscous oil in 95% yield. The ionic liquid phase **7b** was stored under an inert atmosphere at 4°C. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 2.10 (quint, 2H, J=6.61 Hz); 2.93 (t, 2H, J=7.3 Hz); 4.02 (s, 3H); 4.15 (t, 2H, J=6.30 Hz); 4.55 (t, 2H, J=5.3 Hz); 4.66 (t, 2H, J=5.3 Hz); 7.10 (d, 1H, J=8.7 Hz, H-3, H-5); 7.66 (t, 1H, J=1.6 Hz, H-4′, H-5′); 7.77 (t, 1H, J=1.6 Hz, H-4′, H-5′); 7.89 (t, 1H, J=8.8 Hz, H-2, H-6); 9.00 (s, 1H, H-2′); 9.91 (s, 1H, CHO). ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 24.85 (tm, J=130 Hz); 30.67 (tt, J=129, 4.4 Hz); 36.48 (q,

J=144 Hz); 49.39 (t, J=146 Hz); 63.09 (t, J=151 Hz); 67.89 (tquint, J=145, 4.6 Hz); 115.59 (dd, J=163, 4.5 Hz, C-3, C-5); 123.70 (dm, J=204 Hz, C-4′, C-5′); 124.56 (dm, J=204 Hz, C-4′, C-5′); 130.80 (dt, J=23.8, 6.9 Hz, C-4); 132.58 (ddd, J=161, 7.2, 2 Hz, C-2, C-6); 137.81 (dm, J=222 Hz, C-2′); 164.60 (tt, J=9.3, 2 Hz, C-1); 173.24 (m, CO); 181.84 (dt, J=174, 4.6 Hz, CHO); HRMS, *m/z*: 317.1499 found (calcd for $C_{17}H_{21}N_2O_4$, M^+ requires: 317.1501).

4.2. Standard procedure for the three-component synthesis of 4-thiazolidinone 13 or 14 from the ionic liquid phase 7 under solventless microwave dielectric heating

In a cylindrical quartz reactor (∅=1.8 cm) were placed an equimolar mixture of 1-{2-[4-(formyl-phenoxy)-butyryloxy]-ethyl}-3-methyl-3*H*-imidazol-1-ium tetrafluoroborate **7b** (0.5 g, 1.5 mmol), freshly distilled or dry amine **8** (1.5 mmol) and commercial α-mercapto carboxylic acid **10** (1.5 mmol). The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred liquid mixture was irradiated at 100°C (20% power level) for a reaction time ranging from 60 to 120 min (see Table 1). After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and was controlled by ^{1}H NMR spectroscopy in $CDCl_3$ or eventually by TLC analysis with 0.2 mm precoated plates of silica gel 60F-254 (Merck), visualization was made with ultraviolet light (254 or 365 nm). The ester aminolysis of the crude product **11** was realized with vigorous stirring under nitrogen using the appropriate method (see Table 2): (vii) addition of dry amine **8** (4.5 mmol) followed by microwave irradiation at 100°C for 10–20 min or, (viii) addition of amine **8** (1.5 mmol) and potassium terbutoxide (0.75 mmol, 84 mg, 0.5 equiv.). The stirred mixture was heated at 100°C for 10 min or, (ix) addition of dry amine **8** or **12** (1.5 mmol) and *t*-BuOK (0.5 equiv.) followed by heating at 150°C with vigorous stirring for 10 min. After ester aminolysis, the reaction mixture was allowed to cool down at 25°C and chloroform (4 mL) was added in the reactor. Then, the solution was half concentrated by rotary evaporation and the crude solution was purified by flash chromatography (column: ∅=1 cm, H=7 cm) on silica gel 60F-254 (Merck) with $CHCl_3$ or AcOEt as eluent. The desired fraction was concentrated in vacuo and gave compound **13** or **14** as a nearly yellowish pure oil. The pure products **13a–i** and **14a–c** were characterized by ^{1}H, ^{13}C NMR and HRMS.

4.2.1. 4-[4-(3-Benzyl-4-oxo-thiazolidin-2-yl)-phenoxy]-*N*-propyl-butyramide (13a).

Yield=46%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J=7.2 Hz); 1.50 (sext., 2H, J=7.20 Hz); 2.09 (quint., 2H, J=7.6 Hz); 2.39 (t, 2H, J=7.2 Hz); 3.17 (q, 2H, J=6.6 Hz); 3.52 (d, 1H, J=14.7 Hz); 3.77 (dd, 2H, J=39.3, 15.6 Hz, SCH_2); 3.99 (t, 2H, J=6.30 Hz); 5.05 (d, 1H, J=14.7 Hz); 5.35 (s, 1H); 6.50 (br t, 1H, J=5.2 Hz, NH); 6.86–7.27 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.44 (qt, J=126, 4.03 Hz); 21.75 (tm, J=126 Hz); 25.25 (tm, J=125 Hz); 32.70 (tm, J=125 Hz); 33.06 (t, J=146 Hz); 41.23 (tm, J=140 Hz); 46.01 (tm, J=140 Hz); 62.52 (d, J=153 Hz); 67.17 (t, J=142 Hz); 114.89 (d, J=159 Hz, C-3, C-5); 127.88 (dt, J=168, 7.4 Hz, C-4′); 128.25 (dm, J=159 Hz, C-2′, C-5′); 128.74 (dd, J=161, 6.6 Hz, C-2, C-6); 128.84 (dm, J=160 Hz, C-3′, C-5′); 130.50 (t, J=7.5 Hz, C-1); 135.28 (m, C-1′); 159.53 (m, C-4); 171.12 (m, C-4, CO); 172.58 (m, CONH); HRMS, *m/z*: 413.1901 found (calcd for $C_{23}H_{29}N_2O_3S$, $[M+H]^+$ requires: 413.1899).

4.2.2. 4-[4-(3-Benzyl-4-oxo-thiazolidin-2-yl)-phenoxy]-*N*-butyl-butyramide (13b).

Yield=47%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, J=7.2 Hz); 1.31 (sext, 2H, J=6.2 Hz); 1.45 (quint, 2H, J=6.5 Hz); 2.15 (quint, 2H, J=6.2 Hz); 2.37 (t, 2H, J=7.3 Hz); 3.27 (q, 2H, J=7 Hz); 3.51 (d, 1H, J=14.7 Hz); 3.80 (dd, 2H, J=37.47, 15.58 Hz, SCH_2); 4.01 (t, 2H, J=6 Hz); 5.11 (d, 1H, J=14.7 Hz); 5.35 (s, 1H, CH); 5.73 (t large, 1H, NH); 6.83–7.32 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.79 (qt, J=125, 2.5 Hz); 20.08 (tm, J=126 Hz); 25.20 (tm, J=122 Hz); 31.70 (tm, J=125 Hz); 32.08 (tm, J=122 Hz); 33.12 (t, J=145 Hz); 39.30 (tm, J=137 Hz); 46.06 (tm, J=141 Hz); 62.49 (d, J=157 Hz); 67.03 (t, J=145 Hz); 114.91 (d, J=160 Hz, C-3, C-5); 127.79, 128.39, 128.72, 128.75, 130.73 (m, C-2, C-6, C-2′, C-3′, C-4′, C-5′, C-6′, C-1); 138.29 (m, C-1′); 159.55 (m, C-4); 171.11 (m); 172.19 (m, CONH); HRMS, *m/z*: 427.2046 found (calcd for $C_{24}H_{31}N_2O_3S$, $[M+H]^+$ requires: 427.2055).

4.2.3. *N*-Benzo[1,3]dioxol-5-yl-methyl-4-[4-(3-benzyl-4-oxo-thiazolidin-2-yl)-phenoy)-butyramide (13c).

Yield=40%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (quint., 2H, J=6.3 Hz); 2.41 (t, 2H, J=7 Hz); 3.50 (d, 1H, J=14.70); 3.75 (dd, 2H, J=38, 15.6 Hz, SCH_2); 3.98 (t, 2H, J=6 Hz); 5.07 (d, 1H, J=14.7 Hz); 5.34 (s, 1H); 5.86 (s, 2H); 6.68–7.30 (m, 1H, NH+Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.16 (tm, J=130 Hz); 32.72 (tm, J=130 Hz); 33.09 (t, J=146 Hz); 43.34 (tm, J=137 Hz); 46.04 (tm, J=137 Hz); 62.52 (d, J=144 Hz); 67.09 (t, J=140 Hz); 101.06 (t, J=174 Hz); 108.24 (d, J=164 Hz, C-2″); 108.45 (dm, J=162 Hz, C-6″); 114.90 (d, J=159 Hz, C-3, C-5); 120.99 (dq, J=161, 6.53 Hz, C-2, C-6); 127.73, 127.93, 128.36, 128.66, 128.74, 128.78 (m, C-2′, C-3′, C-4′, C-5′, C-6′, C-5″); 130.64 (t, J=7.6 Hz, C-1); 132.39 (m, C-1′); 135.32 (m, C-1″); 146.86 (m, C-3″); 147.84 (m, C-4″); 159.50 (C-4); 171.17 (m, C-4, CO); 172.39 (m, CONH); HRMS, *m/z*: 505.1802 found (calcd for $C_{28}H_{29}N_2O_5S$, $[M+H]^+$ requires: 505.1797).

4.2.4. 4-[4-(3-Benzyl-5-methyl-4-oxo-thiazolidin-2-yl)-phenoxy]-*N*-propyl-butyramide (13d).

Yield=61%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J=7.4 Hz); 1.50 (sext., 2H, J=7.3 Hz); 1.61–1.67 (d, 3H, J=7 Hz); 2.12 (quint., 2H, J=6.4 Hz); 2.39 (t, 2H, J=7.1 Hz); 3.20 (q, 2H, J=6.7 Hz); 3.50–3.53 (d, 1H, J=14.8 Hz); 3.99 (t, 2H, J=7 Hz); 3.99–4.11 (qd, J=7.1, 1.05 Hz); 5.07–5.12 (d, 1H, J=12.9 Hz); 5.29 (d, 1H, J=1.7 Hz); 5.31 (s, 1H); 6.00 (br t, 1H, J=5.2 Hz, NH); 6.87–7.27 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.38 (qt, J=126, 4.2 Hz); 20.26 (q, J=131 Hz); 22.86 (tm, J=131 Hz); 25.22 (tm, J=125 Hz); 32.84 (tm, J=125 Hz); 41.26 (tm, J=137 Hz); 42.39 (dq, J=142, 4.7 Hz); 46.31 (tm, J=141 Hz); 60.84 (dm, J=157 Hz); 67.12 (t, J=145 Hz); 114.91 (dd, J=156, 5.5 Hz, C-3, C-5); 127.87, 127.96, 128.52, 129.24, 130.07 (m, C-2, C-6, C-2′, C-3′, C-4′, C-5′, C-6′, C-1); 135.49 (m, C-1′); 159.55 (m, C-4); 172.31 (m, C-4, CO); 173.90 (CO); HRMS, *m/z*: 427.2052 found (calcd for $C_{24}H_{31}N_2O_3S$, $[M+H]^+$ requires: 427.2055).

4.2.5. Acide [3-benzyl-4-oxo-2-[4-(3-propylcarbamoyl-propoxy)-phenyl]-thiazolidin-5-yl]-acetique (13e). Yield=41%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J=7.4 Hz); 1.48 (sext., 2H, J=7.2 Hz); 2.08 (quint.; 2H, J=5.7 Hz); 2.37 (t, 2H, J=7 Hz); 2.75 (m, 2H); 3.17 (m, 2H); 3.48 (d, 1H, J=14.7 Hz); 3.97 (t, 2H, J=6.9 Hz); 4.29 (dd, 1H, J=9.1, 4.2 Hz); 5.03 (d, 1H, J=14.5 Hz); 5.25 (d, 1H, J=1.5 Hz); 5.27 (s, 1H,); 5.97–6.03 (br t, 1H, NH); 6.80–7.25 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.40 (qt, J=126, 4.03 Hz); 22.82 (tm, J=130 Hz); 25.23 (tm, J=125 Hz); 32.87 (tm, J=125 Hz); 41.27 (tm, J=135 Hz); 44.44 (tm, J=145 Hz); 46.20 (tm, J=141 Hz); 61.01 (dm, J=157 Hz); 67.07 (t, J=145 Hz); 114.79 (dd, J=156, 5.4 Hz, C-3, C-5); 127.83, 128.11, 129.03, 130.18 (m, C-2, C-6, C-2′, C-3′, C-4′, C-5′, C-6′, C-1); 135.28 (m, C-1′); 159.47 (m, C-4); 172.44 (m, C-4, CO); 173.05 (m, CONH); HRMS, *m/z*: 471.1953 found (calcd for $C_{25}H_{31}N_2O_5S$, $[M+H]^+$ requires: 471.1954).

4.2.6. 4-[4-(3-Benzo[1,3]dioxol-5-ylmethyl-4-oxo-thiazolidin-2-yl)-phenoxy]-*N*-propyl-butyramide (13f). Yield=40%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, J=7.4 Hz); 1.51 (sext, 2H, J=7.2 Hz); 2.14 (quint, 2H, J=6.9 Hz); 2.40 (t, 2H, J=7.3 Hz); 3.21 (q, 2H, J=7 Hz); 3.42 (d, 1H, J=14.6 Hz); 3.77 (dd, 2H, J=24.5, 15.5 Hz, SCH_2); 4.10 (t, 2H, J=6 Hz); 4.90 (d, 1H, J=14.6 Hz); 5.36 (s, 1H); 5.93 (s, 2H); 6.20 (broad t, 1H, J=4.8 Hz, NH); 6.50–7.10 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.50 (qt, J=126, 4.1 Hz); 22.90 (tm, J=126 Hz); 25.25 (tm, J=126 Hz); 32.70 (tm, J=125 Hz); 33.10 (t, J=146 Hz, CH_2S); 41.30 (tm, J=140 Hz); 45.80 (tm, J=140 Hz); 62.42 (d, J=156 Hz); 67.19 (t, J=144 Hz); 101.20 (t, J=173 Hz); 108.20 (d, J=165 Hz, C-2′); 108.72 (dm, J=163 Hz, C-6′); 114.87 (d, J=160 Hz, C-3, C-5); 121.88 (dq, J=161, 5.63 Hz, C-2, C-6); 128.78 (dm, J=158 Hz, C-5′); 129.09 (m, C-1′); 130.63 (t, J=7.4 Hz, C-1); 147.26 (m, C-3′); 147.96 (m, C-4′); 159.53 (m, C-4); 171.02 (m); 172.29 (m, CONH); HRMS, *m/z*: 457.1787 found (calcd for $C_{24}H_{29}N_2O_5S$, $[M+H]^+$ requires: 457.1797).

4.2.7. 4-[4-(3-Benzo[1,3]dioxol-5-ylmethyl-4-oxo-thiazolidin-2-yl)-phenoxy]-*N*-benzyl-butyramide (13g). Yield=39%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (quint, 2H, J=6.8 Hz); 2.43 (t, 2H, J=7 Hz); 3.41 (d, 1H, J=14.5 Hz); 3.76 (dd, 2H, J=38.6, 15.6 Hz, SCH_2); 4.02 (t, 2H, J=6 Hz); 4.98 (d, 1H, J=14.6 Hz); 5.36 (d, 1H, J=1.2 Hz); 5.93 (s, 2H); 6.22 (br t, 1H, J=5.6 Hz, NH); 6.48–7.30 (m, 12H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.08 (tm, J=130 Hz); 32.74 (tm, J=125 Hz); 32.10 (t, J=146 Hz, CH_2S); 43.56 (tm, J=137 Hz, CH_2Ar); 45.78 (tm, J=137 Hz, CH_2Ar); 62.36 (d, J=144 Hz); 66.97 (t, J=145 Hz); 101.11 (t, J=173 Hz); 108.19 (d, J=164 Hz, C-2″); 108.74 (dm, J=162 Hz, C-6″); 114.84 (d, J=159 Hz, C-3, C-5); 121.90 (dq, J=161, 6.5 Hz, C-2, C-6); 127.46, 127.60, 128.66, 128.69 (m, C-2′, C-3′, C-4′, C-5′, C-6′, C-5″);129.07 (m, C-1′); 130.67 (t, J=7.6 Hz, C-1); 138.24 (m, C-1″); 147.24 (m, C-3″); 147.94 (m, C-4″); 159.44 (m, C-4); 171.00 (m); 172.11 (m, CONH); HRMS, *m/z*: 505.1802 found (calcd for $C_{28}H_{29}N_2O_5S$, $[M+H]^+$ requires: 505.1797).

4.2.8. 4-{4-[3-(2,2-Dimethoxy-ethyl)-4-oxo-thiazolidin-2-yl]-phenoxy}-*N*-propyl-butyramide (13h). Yield=47%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, J=7.4 Hz); 1.50 (sext, 2H, J=7.3 Hz); 2.11 (quint, 2H, J=6.5 Hz); 2.38 (t, 2H, J=7.3 Hz); 2.68 (dd, 1H, J=14.2, 6.8 Hz); 3.20 (q, 2H, J=6.3 Hz); 3.31 (s, 3H); 3.36 (s, 3H); 3.74 (dd, 2H, J=21.8, 15.3 Hz, SCH_2); 4.01 (t, 2H, J=6 Hz); 4.49 (m, 2H); 5.79 (s, 1H); 6.27(br. t, 1H, NH); 6.87 (d, 1H, J=8.7 Hz, Ar); 7.21 (d, 1H, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.38 (qt, J=125, 4.2 Hz); 22.78 (tm, J=125 Hz); 25.17 (tm, J=127 Hz); 32.68 (tm, J=125 Hz); 32.72 (t, J=145 Hz, CH_2S); 41.18 (tm, J=132 Hz); 43.92 (t, J=140 Hz); 54.01 (qd, J=147, 4.9 Hz); 54.88 (qd, J=147, 4.9 Hz); 63.18 (dm, J=157 Hz); 67.06 (t, J=142 Hz); 102.04 (dm, J=161 Hz); 114.78 (dd, J=159, 4.8 Hz, C-3, C-5); 128.73 (ddd, J=158, 7.3, 4.5 Hz, C-2, C-6); 130.88 (t, J=7.3 Hz, C-1); 159.42 (m, C-4); 171.39 (m); 172.54 (m, CONH); HRMS, *m/z*: 411.1953 found (calcd for $C_{20}H_{31}N_2O_5S$, $[M+H]^+$ requires: 411.1954).

4.2.9. 4-[4-(3-Allyl-4-oxo-thiazolidin-2-yl)-phenoxy]-*N*-benzyl-butyramide (13i). Yield=30%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.10 (quint, 2H, J=6.5 Hz); 2.40 (t, 2H, J=7.4 Hz); 3.08 (dd, 1H, J=15.3, 7.8 Hz); 3.69 (dd, 2H, J=35.6, 15.5 Hz, SCH_2); 3.95 (t, 2H, J=6 Hz); 4.37 (d, 2H, J=5.6 Hz); 4.99 (dd, 1H, J=17, 0.6 Hz, H_{allyl}); 5.12 (m, 1H); 5.36 (d, 1H, J=1.2 Hz); 5.15 (d, 1H, J=9.1 Hz, H_{allyl}); 5.55 (s, 1H); 5.60 (m, 1H, H_{allyl}); 6.78 (s large, 1H, NH); 6.83 (d, 2H, J=8.6 Hz, H-3, H-5); 7.16–7.28 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.15 (tm, J=130 Hz); 32.65 (tm, J=129 Hz); 32.98 (t, J=146 Hz, CH_2S); 43.46 (t, J=138 Hz); 45.02 (tm, J=139 Hz); 62.77 (dm, J=156 Hz); 67.07 (t, J=144 Hz); 114.85 (dd, J=160, 4.8 Hz, C-3, C-5); 118.86 (tt, J=154 Hz, CH_2=); 127.36, 127.68, 128.62, 128.65 (m, C-2′, C-3′, C-4′, C-5′, C-6′, C-2, C-6);130.78 (t, J=7.43 Hz, C-1); 131.07 (dm, J=160 Hz, CH=); 138.46 (m, C-1′); 159.50 (m, C-4); 170.84 (m); 172.42 (m, CONH); HRMS, *m/z*: 411.1744 found (calcd for $C_{23}H_{27}N_2O_3S$, $[M+H]^+$ requires: 411.1742).

4.2.10. 3-Benzyl-2-[4-(4-oxo-4-piperidin-1-yl-butoxy)-phenyl]-thiazolidin-4-one (14a). Yield=26%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45–1.65 (m, 6H); 2.11 (quint., 2H, J=6.9 Hz); 2.44 (t, 2H, J=7.1 Hz); 3.38–3.53 (m, 5H); 3.76 (dd, 2H, J=38.7, 15.6 Hz, SCH_2); 4.02 (t, 2H, J=6 Hz); 5.08 (d, 1H, J=15.6 Hz); 5.34 (s, 1H); 6.52–7.33 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.50, 24.89, 25.57, 26.44, 29.39 (tm, J=130 Hz); 33.09 (t, J=145 Hz); 42.71 (tm, J=137 Hz); 46.03 (tm, J=139 Hz); 62.51 (dm, J=159 Hz); 67.27 (tm, J=145 Hz); 114.91 (dd, J=162, 4.7 Hz, C-3, C-5); 127.72, 127.91, 128.40, 128.84, 130.50 (m, C-2, C-6, C-2′, C-4′, C-5′, C-6′, C-1); 135.51 (m, C-1′); 159.59 (m, C-4); 170.46 (m, C-4, CO); 171.10 (m, CONH); HRMS, *m/z*: 439.2053 found (calcd for $C_{25}H_{31}N_2O_3S$, $[M+H]^+$ requires: 439.2055).

4.2.11. 3-Benzyl-2-[4-(4-oxo-4-pyrrolidin-1-yl-butoxy)-phenyl]-thiazolidin-4-one (14b). Yield=30%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83–1.91 (sext., 4H, J=6.5 Hz); 2.13 (quint., 2H, J=6.6 Hz); 2.45 (t, 2H, J=7 Hz); 3.40–3.44 (t, 4H, J=6.7 Hz); 3.52 (d, 1H, J=14.7 Hz); 3.78 (dd, 2H, J=35.5, 14.6 Hz, SCH_2); 4.04 (t, 2H, J=6.0 Hz); 5.10 (d, 1H, J=14.7 Hz); 5.35 (s, 1H); 6.90–7.35 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.38 (tm, J=129 Hz); 26.05 (tm, J=129 Hz); 30.73 (tm, J=125 Hz); 33.08 (t, J=145 Hz);

45.68 (tm, J=140 Hz); 46.55 (tm, J=139 Hz); 62.48 (dm, J=155 Hz); 62.70 (tm, J=144 Hz); 114.89 (dd, J=163 Hz, C-3, C-5); 127.70, 127.86, 128.35, 128.73 (m, C-2, C-6, C-2′, C-3′, C-4′, C-5′, C-6′); 130.50 (m, C-1); 135.36 (m, C-1′); 159.58 (m, C-4); 170.76 (m, C-4, CO); 171.06 (CONH); HRMS, *m/z*: 425.1905 found (calcd for $C_{24}H_{29}N_2O_3S$, $[M+H]^+$ requires: 425.1899).

4.2.12. 3-Benzyl-2-[4-(4-oxo-4-morpholin-1-yl-butoxy)-phenyl]-thiazolidin-4-one (14c). Yield=25%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13 (quint., 2H, J=6.1 Hz); 2.43–2.50 (t, 2H, J=7.2 Hz); 3.41–3.65 (m, 9H); 3.75 (dd, 2H, J=38.8, 15.6 Hz, SCH_2); 3.98–4.02 (t, 2H, J=6 Hz); 5.08 (d, 1H, J=14.7 Hz); 5.33 (s, 1H); 6.87 (d, 2H, J=8.6 Hz, H-3, H-5); 7.05–7.30 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.16 (tm, J=127 Hz); 32.63 (tm, J=127 Hz); 33.06 (t, J=145 Hz); 43.44 (tm, J=140 Hz); 46.02 (t, J=140 Hz); 62.47 (dm, J=156 Hz); 66.80 (tm, J=144 Hz); 67.11 (tt, J=145, 4.4 Hz); 114.88 (dd, J=163, 4.4 Hz, C-3, C-5); 127.32, 127.69, 127.89, 128.34 (m, C-2, C-6, C-2′, C-3′, C-4′, C-5′, C-6′); 130.66 (m, C-1); 138.56 (m, C-1′); 159.51 (m, C-4); 170.91 (m, C-4, CO); 172.38 (CONH); HRMS, *m/z*: 441.1850 found (calcd for $C_{24}H_{29}N_2O_4S$, $[M+H]^+$ requires: 441.1848).

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