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Synthesis of imidazolidin-4-one and 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione derivatives of primaquine: scope and limitations

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Abstract—The synthesis of imidazolidin-4-one derivatives of primaquine as potential antimalarial agents is described. The target compounds were synthesized in three steps: (i) condensation of (±)-primaquine with N^{α}-protected amino acids, (ii) removal of the N^{α}-protecting group, and (iii) reaction of the N-acylprimaquine with a carbonyl compound: acetone, three cyclic ketones and veratraldehyde. Using 2-formylbenzoic acid in the third step afforded 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones. All products were isolated in good to excellent yields. Whereas imidazolidin-4-ones were formed as mixtures of all possible diastereomers in equal amounts, 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones were produced in a stereoselective fashion. The compounds hydrolyse very slowly ($t_{1/2}$ 5–30 d) in pH 7.4 buffer to release primaquine. These primaquine derivatives are being submitted to biological assays, and preliminary results of their antimalarial activity are quite encouraging.

1. Introduction

Primaquine, **1**, is the only currently available drug that is active against both the latent liver forms of the relapsing malaria caused by *Plasmodium vivax* and *Plasmodium ovale*[1] and the gametocytes from all species of parasite causing human malaria, including chloroquine-resistant *Plasmodium falciparum*.[2] However, the clinical use of primaquine is impaired as a result of a rapid metabolic inactivation to form carboxyprimaquine **2**,[3–6] and to serious blood toxicity, particularly the ability to induce oxidation of oxyhemoglobin to methemoglobin.[7] Several peptide and amino acid derivatives of primaquine, for example, **3**, have been prepared to reduce toxicity of the parent as well as to reduce the oxidative deamination metabolic pathway leading to **2**.[8–11] Despite the improved activity/toxicity ratio usually displayed by **3**, most of these derivatives are rapidly hydrolysed to primaquine by aminopeptidases and endopeptidases,[11,12] suggesting that they might undergo extensive hydrolysis to the parent drug in the intestinal lumen when given orally. Thus, the design of orally effective and metabolically stable derivatives of the antimalarial agents **3** is of obvious interest.

Replacement of an amide bond with appropriate isosteres is a commonly used lead-optimization strategy for enhancing enzymatic stability of a peptide.[13] Alternatively, the peptide drug can be converted into a prodrug or transport form that

Keywords: Antimalarial; Imidazolidin-4-one; 1*H*-Imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones; Malaria; Primaquine; Stereoselectivity.

Abbreviations: AA, amino acid; HAAPQ, amino acid derivative of primaquine (unprotected); Ala, alanine residue; Boc, *tert*-butyloxycarbonyl (protecting group); BocAAOH, N^{α}-Boc-protected amino acid; BocAAPQ, N^{α}-Boc-protected amino acid derivative of primaquine; bs, broad singlet; Bzl, benzyl; $CDCl_3$, deuterated chloroform; d, doublet; dd, double doublet; dt, double triplet; δ, chemical shift (in ppm); DCCI, N,N′-dicyclohexylcarbodiimide; DCM, dichloromethane; DCU, N,N′-dicyclohexylurea; DHB, 2,5-dihydroxybenzoic acid; DIEA, diisopropylethylamine; DIPCDI, N,N′-diisopropylcarbodiimide; DIU, N,N′-diisopropylurea; Gly, glycine residue; HOBt, N-hydroxybenzotriazole; ^{t}Bu, *iso*butyl; ^{i}Pr, *iso*propyl; Leu, leucine residue; m, unresolved multiplet; MALDI-TOF, matrix-assisted laser desorption ionization—time-of-flight; NOE, nuclear Overhauser effect; PES, potential energy surface; Phe, phenylalanine residue; ppm, parts per million (NMR chemical shift unit); PQ, primaquine; q, quartet; s, singlet; t, triplet; TEA, triethylamine; THF, tetrahydrofuran; TLC, thin layer chromatography; TMS, tetramethylsilane; Val, valine residue.

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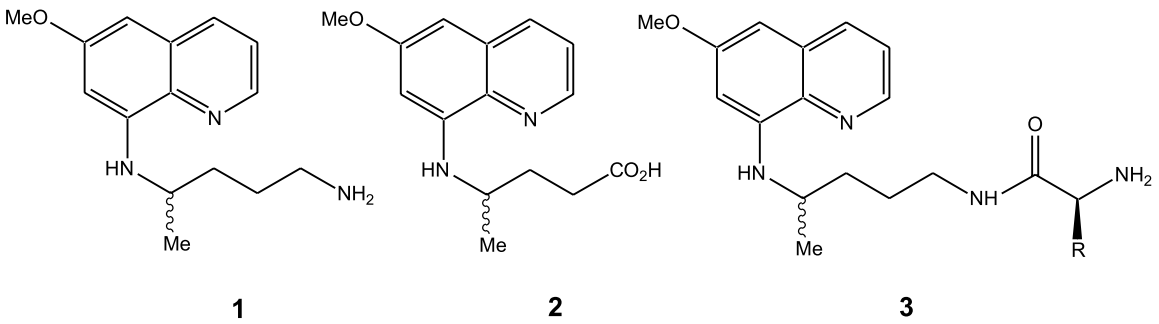
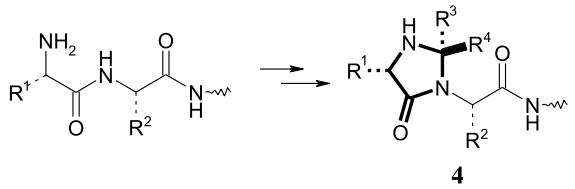


1 **2** **3**



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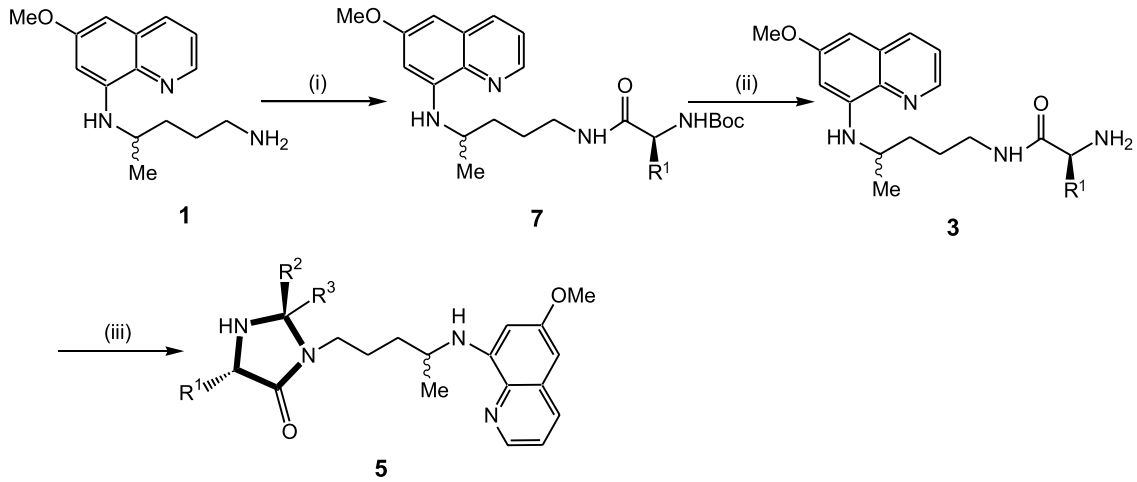
Scheme 1.

protects the parent peptide against proteolytic degradation at the mucosal absorption barrier or in the blood.[14] Such a prodrug must be capable of reverting to the parent peptide drug following oral absorption via an unspecific plasma enzyme-catalysed reaction or a non-enzymatic pathway. Imidazolidin-4-one, **4**, formation was introduced as a useful prodrug approach to protect the *N*-terminal amino acid residue of di-, tri- and pentapeptides against



1 **7** **3**

5

Compound	R^1	R^2	R^3	Yield (%)
5a	H	Me	Me	74
5b	Me	Me	Me	81
5c	$CHMe_2$	Me	Me	76
5d	CH_2CHMe_2	Me	Me	62
5e	CH_2Ph	Me	Me	52
5f	H	$-(CH_2)_4-$		50
5g	Me	$-(CH_2)_4-$		61
5h	$CHMe_2$	$-(CH_2)_4-$		55
5i	CH_2CHMe_2	$-(CH_2)_4-$		54
5j	CH_2Ph	$-(CH_2)_4-$		59
5k	H	$-(CH_2)_5-$		75
5l	Me	$-(CH_2)_5-$		69
5m	$CHMe_2$	$-(CH_2)_5-$		62
5n	CH_2CHMe_2	$-(CH_2)_5-$		66
5o	CH_2Ph	$-(CH_2)_5-$		69
5p	H	$-(CH_2)_6-$		52
5q	Me	$-(CH_2)_6-$		44
5r	$CHMe_2$	$-(CH_2)_6-$		48
5s	CH_2CHMe_2	$-(CH_2)_6-$		55
5t	CH_2Ph	$-(CH_2)_6-$		59
5u	Me	3,4-$(MeO)_2$-C_6H_3	H	78[a]
5w	$CHMe_2$	3,4-$(MeO)_2$-C_6H_3	H	85[a]
5y	CH_2CHMe_2	3,4-$(MeO)_2$-C_6H_3	H	57[a]
5x	CH_2Ph	3,4-$(MeO)_2$-C_6H_3	H	94[a]

[a] Total yield corresponding to the sum of all fractions isolated by column chromatography

Scheme 2. (i) DCCI, HOBt, BocAAOH; (ii) (1) TFA, (2) Na_2CO_3; (iii) Me_2CO or C_5, C_6 or C_7 cyclic ketones or 3,4-$(MeO)_2-C_6H_3CHO$ in refluxing MeOH, TEA, molecular sieves.

aminopeptidase-catalysed hydrolysis (Scheme 1).[15–18] The synthetic approaches for the preparation of imidazolidin-4-ones involve the reaction of the peptide with an aldehyde or ketone followed by intramolecular cyclization. This reaction is catalysed by acids[19] or bases[20] although no catalyst is needed with acetone.[21] Usually, peptide imidazolidin-4-one derivatives, **4**, were quantitatively hydrolysed to the parent peptide in physiological conditions (pH 7.4 buffer at 37 °C) with half-lives ranging from in 1 to 30 h, depending on the *N*-terminal dipeptide sequence and on the R^3, R^4 imidazolidinone substituents (Scheme 1).[15–18] The same imidazolidin-4-one strategy was used to improve the bioavailability of ampicillin, a β-lactam that also contains a peptide backbone.[22] The corresponding imidazolidin-4-one, hetacillin, is also rapidly hydrolysed to ampicillin in physiological conditions.

Here we report the synthesis of compounds **5**, incorporating the imidazolidin-4-one scaffold, as potential peptidase-stable prodrugs of amino acid derivatives of primaquine, **3** (Scheme 2). As the primaquine starting material was a racemate, the cyclization reactions of **3** with ketones or aldehydes yielded compounds **5** as the corresponding diastereomeric mixtures. Reaction of **3** with 2-formylbenzoic acid leads to 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione production, **6**, via a diastereoselective cyclization (Scheme 3).

2. Results and discussion

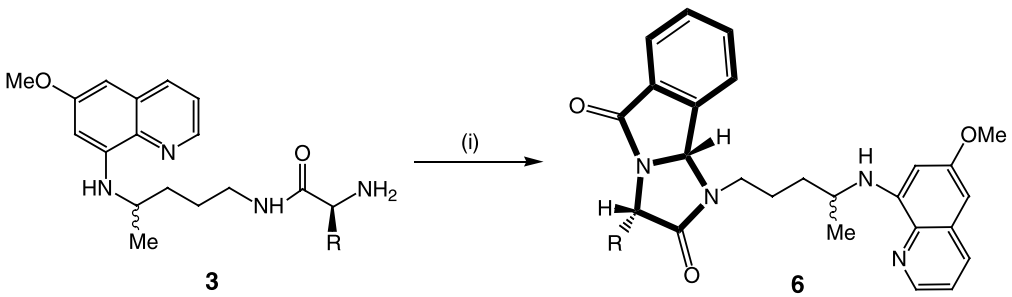
2.1. Synthesis of *N*-α-aminoacylprimaquine derivatives

The target imidazolidin-4-ones **5** were synthesised via the corresponding amino acid derivatives **3** (Scheme 2). The Boc-protected amino acid intermediates **7** were prepared using standard peptide coupling methods[23] that involved N^{α}-Boc protected amino acid (BocAAOH) coupling to (±)-primaquine (PQ), using either dicyclohexylcarbodiimide (DCCI)[24] or diisopropylcarbodiimide (DIPCDI)[25] in combination with the auxiliary nucleophile 1-hydroxybenzotriazole (HOBt).[26] Products **7b–e** were isolated as mixtures of the two possible diastereomers (^{13}C NMR signal duplications were observed), even though they could not be distinguished by the chromatographic techniques employed. The N^{α}-Boc-protected amino acid derivatives of primaquine, **7a–e**, were treated with neat trifluoroacetic acid (TFA) to remove the Boc-protecting group.[27] After neutralization of the resulting trifluoroacetates with aqueous sodium carbonate, the deprotected amino acid derivatives of primaquine (HAAPQ, **3**) were extracted with chloroform and isolated as yellow-orange waxy oils in 83–97% yields. All HAAPQ derivatives, **3a–e**, were characterized by NMR and MALDI-TOF-MS.

2.2. Reaction of the *N*-α-aminoacylprimaquine derivatives with carbonyl compounds

The HAAPQ intermediates, **3a–e**, reacted with acetone, cyclopentanone, cyclohexanone and cycloheptanone, by refluxing both reactants in methanol in the presence of triethylamine (TEA), 4 Å molecular sieves and an excess of the ketone, to form the expected imidazolidin-4-ones, **5**, in good yields (44–81%). When the reaction of **3** with ketones was carried out without TEA or 4 Å molecular sieves (or both) only small amounts of condensation products **5** were isolated. The imidazolidin-4-ones **5**, containing a chiral amino acid residue (e.g., **5b–e**, derived from Ala, Val, Leu and Phe, respectively) were isolated as mixtures of two co-eluting diastereomers, as detected by the duplication of some ^{13}C NMR signals. For example, compound **5c** derived from HValPQ, **3c**, and acetone presented two signals for the following resonances: C-2, C-5 and C-6 in the quinoline ring; C-1′, C-2′, C-3′ and C-4′ in the amine side-chain; C-2 and C-4 in the imidazolidin-4-one ring.

All HAAPQ derivatives, **3**, were also reacted with formaldehyde and ethyl glyoxylate, but, unfortunately,



3 **6**

Compound	R	Yield (%)
6a	H	56
6b	Me	53
6c	$CHMe_2$	59
6d	CH_2CHMe_2	44
6e	CH_2Ph	60

Scheme 3. (i) 2-CHO–$C_6H_4CO_2H$ in refluxing MeOH, TEA, molecular sieves.

only untractable mixtures were obtained. In constrast, reaction of compounds **3b**–**e** with veratraldehyde (3,4-dimethoxybenzaldehyde) as described above, afforded the corresponding imidazolidin-4-ones **5u**–**x** with global yields of 57–94%. The imidazolidin-4-one derived from HGlyPQ, **3a**, was probably formed, since the correct molecular weight was detected by MALDI-TOF-MS analysis of the crude mixture. However, this compound was too unstable to be satisfactorily isolated and characterized by NMR.

The cyclization of **3b**–**e** with aldehydes generates a new chiral centre, so four imidazolidin-4-one diastereomeric pairs are to be expected. In fact, TLC monitoring could distinguish one to four spots in the reaction of veratraldehyde with compounds **3b**–**e**. The closeness between the R_f values for the different diastereomers was obviously high, depending on the amino acid involved. Best chromatographic resolution was found for the Phe-derived product **5x** (all four spots, though close, could be distinguished), whereas for the Leu-derived compound **5y** a single fraction was obtained. Interestingly, the ^{1}H NMR spectra of **5y** presented four well-resolved and equally intense signals at 5.12, 5.20, 5.25 and 5.31 ppm, corresponding to the imidazolidinone NC*H*N resonance, suggesting that equal amounts of all four diastereomers were formed. In contrast, it was possible to isolate two pure diastereomers of **5x**, each one presenting a singlet at ca. 5.1 ppm, corresponding to the imidazolidinone NC*H*N resonance, and three singlets at 3.7–3.9 ppm, corresponding to each of the CH_3O resonances. In addition, a 1:1 mixture of the other two diastereomers of **5x** was also isolated, as indicated by the two equally intense singlets at ca. 5.0 ppm and six singlets in the 3.7–3.9 ppm region. The compounds derived from alanine, **5v**, and valine, **5w**, had an intermediate behaviour: two fractions could be isolated in both cases, each of which corresponded to different combinations of the four diastereomers.

The reactions of compounds **3a**–**e** with 2-formylbenzoic acid afforded the corresponding 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones, **6a**–**e** in good yields (44–60%). Mass spectrometric analysis of crude **6e** exhibited a signal at *m*/*z*=538.6 corresponding to the imidazolidin-4-one intermediate that is formed prior to the cyclization that leads to the formation of the isoindole ring. The structural assignment of compounds **6** is based on spectroscopic data. For the glycine derivative **6a**, two diastereomeric pairs of enantiomers were to be expected, and it was indeed possible to separately isolate two fractions from the reaction of **3a** and 2-formylbenzoic acid. A characteristic feature of the ^{1}H NMR spectrum of each enantiomeric pair of **6a** is the resonance of the NC*H*N group, which appears as a singlet at 5.6–5.8 ppm. Moreover, the glycine CH_2 signal appears as two doublets with typical geminal coupling constants (^2J=11.7 Hz), reflecting the diastereotopic nature of the methylene protons. In contrast, compounds **6b**–**e** were formed as mixtures of non-isolable diastereomers. However, the following ^{1}H and ^{13}C NMR data suggest the formation of only two diastereomers in each case, even though a total of four was anticipated. First, the resonance of the NC*H*N proton (H_{9b}) appears as two 1:1 singlets at 5.7–5.9 ppm. Second, the ^{13}C NMR spectra of **6b**–**e** presented duplication for, among others: the C-5 and C-7 quinoline carbons; the C-1′, C-2′, C-3′ and C-4′ amine side-chain carbons; and the C-2, C-3 and C-5 atoms of the 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione system.

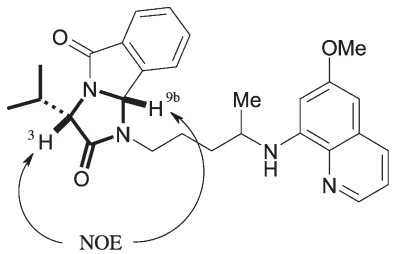


Figure 1. NOE effect of the *cis*-isomer of **6c** as observed in $CDCl_3$ at 300 K.

In order to determine the absolute configuration of the new chiral center in **6b**–**e** we carried out NOE experiments. For compound **6c**, irradiation of C_{9b}–H of each diastereomer led to a clear positive NOE-effect for the C_3–H (Fig. 1) and for one of the methyls in the isopropyl side chain. In contrast, no significant effect was observed for hydrogen $(CH_3)_2CH$ in the same group upon irradiation of C_{9b}–H. Similar results were obtained for **6b** and **6d**: irradiation of C_{9b}–H of each **6b** diastereomer caused a positive NOE for the C_3–H and had no effect on the hydrogen atoms of the CH_3; irradiation of the C_{9b} proton in compound **6d** caused positive NOEs on C_3–H and $(CH_3)_2CHCH_2$, but no effect

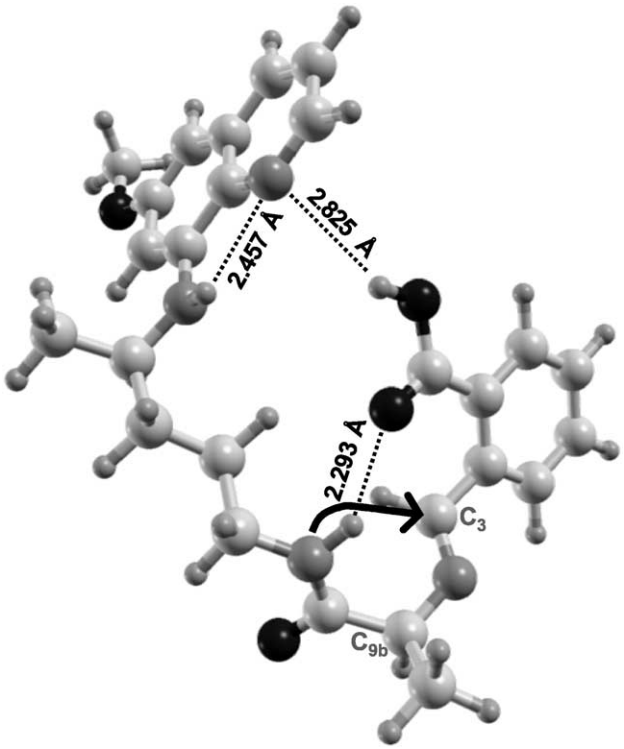


Figure 2. AM1-optimised structure of the imine intermediate formed from 2-formylbenzoic acid and the N-acylprimaquine **3b**. Small spheres=H; black spheres=O; dark grey spheres=N; light grey spheres=C; dotted lines show intramolecular hydrogen bonds and their lengths are also displayed; black arrow depicts the favoured orientation for ring closure leading to a final 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione structure with C_3-H and C_{9b}-H atoms in *cis*-orientation (see text).

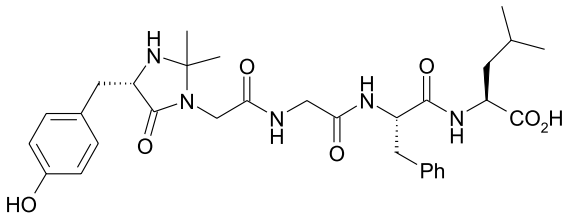
on $(CH_3)_2CHCH_2$. These findings suggest that the C_3-H and $C_{9b}-H$ have a *cis* orientation. This contrasts with results obtained by Katritzky and co-workers, who found that stereoselective syntheses of 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones led to the *trans*-orientation of C_3-H and $C_{9b}-H$.[28] The cause of such difference is not clear. The reaction path leading to 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones is essentially the same as for imidazolidin-4-ones, that is, imine formation followed by intramolecular cyclization to the imidazolidinone structure, including an additional step for the intramolecular amide bond formation that generates the final pyrrolidinone structure. A possible explanation is that the *o*-carboxyl substituent in 2-formylbenzoic acid could establish a hydrogen bond with the amide group, yielding a rigid conformation that would constrain the stereochemistry of the subsequent intramolecular cyclization step. The lack of any such constraint in veratraldehyde would explain its different behaviour. To evaluate the validity of this hypothesis, we have performed semi-empirical calculations at the AM1 level[29] to optimise the geometry of the imine intermediate formed upon reaction with 2-formylbenzoic acid. The simplest chiral amino acid, alanine, was considered, and the calculations yielded the optimised structure depicted in Figure 2. This structure clearly shows three intramolecular hydrogen bonds that stabilize the folding of the imine and favours a stereo-controlled cyclization. This leads to a final 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione structure where atoms C_3-H and $C_{9b}-H$ are *cis*-oriented, which is in agreement with the NOE experiments. A final confirmation of this rationale could be given by X-ray diffraction experiments. Unfortunately, compounds **6** are all oils and all attempts to obtain crystals have been unsuccessful.

2.3. In vitro assessment of imidazolidin-4-ones 5 as potential prodrugs

The reactivity of several imidazolidin-4-ones **5** derived from ketones in pH 7.4 phosphate buffer at 37 °C was assessed by HPLC. Quite surprisingly, compounds **5** hydrolyse very slowly, though quantitatively, to the corresponding amino acid derivative **3** (Table 1). This behaviour contrasts with the rapid hydrolysis of their counterparts **4** derived from a dipeptide framework. For example the 2,2-dimethylimidazolidin-4-one **5a**, derived from HGlyPQ, **3a**, is hydrolysed ca. 100 times slower than their counterparts **4** derived from Gly-Phe or Gly-Tyr.[16] The same trend is observed when comparing derivatives **5** with imidazolidin-4-ones derived from higher peptides. For example, compound **5e** derived from HPhePQ, **3e**, is hydrolysed 60 times slower than the Leu-enkephalin derivative **8**.[17] The rates of hydrolysis of **5** are largely affected by the substituents at C-2 of the imidazolidin-4-one moiety, with those derived from cyclopentanone, **5h** and **5j**, being significantly more reactive than those derived from acetone or cyclohexanone. Unfortunately, derivatives **5** derived from cycloheptanone displayed very low aqueous solubility precluding their study in the pH 7.4 phosphate buffer. The results presented herein indicate that imidazolidin-4-ones **5** will likewise hydrolyse slowly in vivo and thus can be considered as slow-release systems of the amino acid derivatives of primaquine.

Table 1. Rate of hydrolysis of imidazolidin-4-ones 5 in pH 7.4 phosphate buffer at 37 °C

Compound	$t_{1/2}$ (d)
5a	9.8
5c	12
5e	31
5h	8.8
5j	6.4
5l	12
5m	26



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3. Conclusion

In summary, amino acid derivatives, **3**, of primaquine can be converted to the corresponding imidazolidin-4-ones **5** in good yields by reaction with both cyclic and acyclic ketones and aromatic aldehydes. Cyclization of **3** with an unsymmetrical carbonyl (veratraldehyde) yields mixtures of all four possible stereomers. However, when cyclization was carried out with an *o*-carboxylated aldehyde, diastereoselectivity was encountered, since only two out of four possible stereomers of the corresponding 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6** were formed. The low rates of hydrolysis of imidazolidin-4-ones **5** in physiological conditions suggest that they may be useful as slow-release forms of the parent amino acid derivatives **3**.

4. Experimental

4.1. General details

N^{α}-Protected amino acids were purchased from NovaBiochem (Switzerland). Solvents were of p.a. quality and bought from Merck (Germany). Both thin layer chromatography (TLC) aluminium foil plates covered with silica 60 F_{254} (0.25 mm) and silica-gel 60 (70–230 mesh ASTM) for preparative column chromatography were also purchased from Merck. When required, solvents were previously dried with pre-activated molecular sieves (4 Å) (Merck). Other chemicals were obtained from Sigma-Aldrich.

NMR spectra of compounds dissolved in deuterated chloroform ($CDCl_3$), containing tetramethylsilane (TMS) as internal reference, were acquired on a Bruker AMX-300 spectrometer. Mass spectrometry (MS) was performed by the matrix-assisted laser desorption ionization—time-of-flight (MALDI-TOF) technique on an Applied Biosystems

Voyager STR-DE spectrometer, using either anthracene or 2,5-dihydroxibenzoic acid (DHB) as adjuvant matrices.

4.2. Condensation of PQ with N$^{\alpha}$-Boc protected amino acids—synthesis of compounds 7a–e

Compounds **7a–e** were prepared by condensation of PQ with N$^{\alpha}$-Boc-protected amino acids by the carbodiimide/1-hydroxybenzotriazole (DCCI or DIPCDI/HOBt) method. Briefly, primaquine bis[dihydrogenophosphate] (3.3 mmol) was suspended in dichloromethane (DCM, 30 mL), TEA (14 mmol) was added and the mixture was stirred in an ice-water–NaCl bath for 30 min. After addition of the BocAAOH (3.3 mmol) and HOBt (4.0 mmol), the carbodiimide (DCCI or DIPCDI, 4.0 mmol) was slowly added to the mixture, which was kept at 0 °C for 2 h more. The reaction was allowed to proceed at room temperature for 2 d, with periodic monitoring by TLC. A second stepwise addition of carbodiimide (4.0 mmol) was made, and the reaction prolonged for a further 3 d. The solid phase formed was removed by suction filtration and identified as the carbodiimide-derived urea (DCU or DIU). The filtrate was evaporated to dryness and the residue dissolved in the minimum amount of warm acetone; the resulting solution was stored overnight at 4 °C and the urea precipitated was again removed by suction filtration. The filtrate was evaporated to dryness and the residue submitted to column chromatography on silica-gel, using DCM/acetone mixtures as eluents (in the proportions of 5:1 for compounds **7a–c** and 10:1 for compounds **7d–e**). Products **7a–e** were isolated as yellow-orange oils in 78–93% yields and successfully characterized by high-resolution MS and NMR, as detailed below.

4.2.1. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-2-oxooctyl}carbamic acid *tert*-butyl ester (7a). δ_H ($CDCl_3$, 300 MHz) 8.50 (dd, 1H, J=4.20, 1.47 Hz); 7.90 (dd, 1H, J=8.22, 1.65 Hz); 7.28 (dd, 1H, J=8.22, 4.20 Hz); 6.31 (d, 1H, J=2.56 Hz); 6.24 (d, 1H, J=2.56 Hz); 6.17 (m, 1H); 5.97 (m, 1H); 5.16 (m, 1H); 3.87 (s, 3H); 3.72 (d, 2H, J=5.88 Hz); 3.61 (m, 1H); 3.28 (m, 2H); 1.57 (m, 4H); 1.40 (s, 9H); 1.27 (d, 3H, J=6.24 Hz). δ_C ($CDCl_3$, 300 MHz) 169.3; 159.4; 156.0; 144.9; 144.3; 135.3; 134.8; 129.9; 121.9; 96.8; 91.7; 80.2; 55.2; 50.8; 50.7; 47.8; 44.4; 39.3; 37.5; 34.4; 33.7; 30.9; 28.3; 26.2; 20.5. m/z ($MW_{monoisotopic}$)=416.2107 (Calcd, 416.24).

4.2.2. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-methyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7b). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.22, 1.64 Hz); 7.87 (dd, 1H, J=8.28, 1.60 Hz); 7.30 (dd, 1H, J=8.25, 4.23 Hz); 6.47 (m, 1H); 6.33 (d, 1H, J=2.48 Hz); 6.26 (d, 1H, J=2.48 Hz); 5.98 (d, 1H, J=8.25 Hz); 5.19 (m, 1H); 4.13 (m, 1H); 3.68 (s, 3H); 3.61 (m, 1H); 3.26 (m, 2H); 3.28 (m, 2H); 1.64 (m, 4H); 1.39 (s, 9H); 1.33 (d, 3H, J=6.46 Hz); 1.27 (d, 3H, J=6.24 Hz). δ_C ($CDCl_3$, 300 MHz) 172.6; 159.3; 155.5; 144.8; 144.2; 135.3; 134.8; 129.8; 121.8; 96.7; 91.6; 79.9; 55.1; 50.0; 48.9; 47.7; 39.2; 33.9; 33.6; 28.2; 26.1; 25.6; 24.9; 20.5; 18.5. m/z ($MW_{monoisotopic}$)=430.2658 (Calcd, 430.26).

4.2.3. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-isopropyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7c). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.05, 1.35 Hz); 7.90 (dd, 1H, J=8.25, 1.35 Hz); 7.28 (dd, 1H, J=7.25, 4.95 Hz); 6.53 (m, 1H); 6.33 (d, 1H, J=2.10 Hz); 6.27 (d, 1H, J=2.10 Hz), 5.99 (d, 1H, J=7.20 Hz); 5.30 (dd, 1H, J=8.25, 2.00 Hz); 3.92 (m, 1H); 3.87 (s, 3H); 3.59 (m, 1H); 3.25 (m, 2H); 2.05 (m, 1H); 1.63 (m, 4H); 1.39 (s, 9H); 1.27 (d, 3H, J=6.00 Hz); 0.93 (d, 3H, J=6.90 Hz); 0.90 (d, 3H, J=6.90 Hz). δ_C ($CDCl_3$, 300 MHz) 171.7; 159.4; 156.0; 144.9; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.7; 79.7; 60.0; 55.1; 50.8; 50.7; 47.8; 47.7; 44.4; 39.3; 39.2; 33.9; 33.8; 30.9; 28.3; 26.3; 26.2; 20.5; 19.3; 17.9. m/z ($MW_{monoisotopic}$)=458.1214 (Calcd, 458.29).

4.2.4. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-isobutyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7d). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, J=4.10, 1.70 Hz); 7.92 (dd, 1H, J=7.50, 1.70 Hz); 7.31 (dd, 1H, J=7.50, 4.10 Hz); 6.34 (d, 1H, J=2.00 Hz); 6.31 (m, 1H); 6.27 (d, 1H, J=2.00 Hz); 5.99 (d, 1H, J=8.20 Hz); 4.99 (m, 1H); 4.05 (m, 1H); 3.89 (s, 3H); 3.63 (m, 1H); 3.27 (m, 2H); 2.12 (m, 1H); 1.66 (m, 6H); 1.41 (s, 9H); 1.29 (d, 3H, J=6.00 Hz); 0.92 (d, 3H, J=6.90 Hz); 0.90 (d, 3H, J=6.90 Hz). δ_C ($CDCl_3$, 300 MHz) 172.5; 159.3; 156.0; 144.8; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.6; 80.2; 68.7; 55.2; 49.0; 47.8; 47.7; 33.9; 33.7; 33.6; 30.3; 28.2; 26.2; 26.1; 25.6; 24.9; 24.7; 22.9; 20.5. m/z ($MW_{monoisotopic}$)=472.3163 (Calcd, 472.30).

4.2.5. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-benzyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7e). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.17, 1.55 Hz); 7.91 (dd, 1H, J=8.31, 1.59 Hz); 7.32–7.12 (m, 6H); 6.33 (d, 1H, J=2.90 Hz); 6.25 (d, 1H, J=2.90 Hz); 6.03 (m, 1H); 5.58 (m, 1H); 4.27 (m, 1H); 3.87 (s, 3H); 3.52 (m, 1H); 3.17 (m, 2H); 3.15 (d, 2H, J=6.68 Hz); 1.49 (m, 4H); 1.37 (s, 9H); 1.25 (d, 3H, J=6.33 Hz). δ_C ($CDCl_3$, 300 MHz) 173.9; 173.8; 159.3; 156.0; 144.8; 144.1; 136.8; 136.7; 135.2; 134.6; 129.7; 129.5; 128.4; 126.7; 121.7; 96.5; 91.4; 75.9; 58.6; 55.0; 47.8; 47.6; 40.1; 40.0; 36.8; 36.7; 33.9; 33.8; 27.8; 26.2; 26.1; 25.9; 25.8; 20.5. m/z ($MW_{monoisotopic}$)=506.2019 (Calcd, 506.29).

4.3. Acidic removal of the N$^{\alpha}$-Boc protecting group—synthesis of compounds 3a–e

Compounds **7a–e** were dissolved in a small volume of neat trifluoroacetic acid (TFA, ca. 5 mL) and the deprotection reactions allowed to proceed for 1–2 h at room temperature. Excess TFA was neutralized by dropwise addition of aqueous Na_2CO_3 at 30% until pH 10; the supernatant oily phase formed in this process was extracted seven times with 10-mL portions of chloroform and the organic phases pooled, dried over anhydrous $MgSO_4$ and evaporated to dryness. Products **3a–e** were thus isolated as yellow-orange oils in 83–97% yields and successfully characterized by high-resolution MS and NMR, as detailed below.

4.3.1. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-aminoacetamide (3a). δ_H ($CDCl_3$, 300 MHz) 8.48 (dd, 1H, J=4.23, 1.65 Hz); 7.87 (dd, 1H, J=9.51, 1.29 Hz); 7.26 (dd, 1H, J=9.72, 4.23 Hz); 6.30 (d, 1H, J=2.56 Hz); 6.24

(d, 1H, *J*=2.56 Hz); 5.92 (m, 1H); 3.83 (s, 3H); 3.53 (m, 1H); 3.39 (m, 2H); 3.19 (m, 2H); 1.59 (m, 4H); 1.20 (d, 3H, *J*=6.21 Hz). δ_C ($CDCl_3$, 300 MHz) 159.4; 144.9; 144.3; 137.4; 135.3; 134.8; 129.9; 121.9; 96.9; 91.7; 78.1; 77.2; 55.2; 48.2; 47.9; 47.8; 43.7; 43.3; 40.2; 39.7; 39.5; 39.2; 39.1; 26.4; 26.3; 26.1; 20.6; 20.5. *m/z* ($MW_{monoisotopic}$)=316.1992 (Calcd, 316.19).

4.3.2. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-aminopropanamide (3b). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.20, 1.53 Hz); 7.92 (dd, 1H, *J*=8.25, 1.51 Hz); 7.31 (dd, 1H, *J*=8.22, 4.20 Hz); 6.34 (d, 1H, *J*=2.45 Hz); 6.28 (d, 1H, *J*=2.45 Hz); 6.00 (d, 1H, *J*=8.29 Hz); 3.89 (s, 3H); 3.63 (m, 1H); 3.46 (m, 1H); 3.27 (m, 2H); 1.80 (m, 2H); 1.63 (m, 4H); 1.31 (d, 3H, *J*=6.19 Hz); 1.29 (d, 3H, *J*=6.72 Hz). δ_C ($CDCl_3$, 300 MHz) 159.4; 144.9; 144.2; 135.3; 134.8; 129.9; 121.9; 96.8; 91.6; 55.2; 50.7; 47.8; 38.9; 33.8; 26.3; 21.7; 20.5. *m/z* ($MW_{monoisotopic}$)=330.1082 (Calcd, 330.21).

4.3.3. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-amino-3-methylbutanamide (3c). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=3.60, 0.90 Hz); 7.90 (dd, 1H, *J*=8.10, 1.20 Hz); 7.28 (dd, 1H, *J*=7.50, 5.10 Hz); 6.32 (d, 1H, *J*=1.95 Hz); 6.28 (d, 1H, *J*=1.95 Hz), 6.01 (d, 1H, *J*=8.10 Hz); 3.87 (s, 3H); 3.62 (m, 1H); 3.28 (m, 2H); 3.16 (m, 1H); 2.25 (m, 1H); 1.65 (m, 4H); 1.53 (s, 2H); 1.29 (d, 3H, *J*=6.60 Hz); 0.95 (d, 3H, *J*=7.20 Hz); 0.78 (dd, 3H, *J*=6.90, 2.40 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 159.4; 144.9; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.7; 77.3; 63.9; 60.1; 55.2; 47.8; 47.7; 38.9; 38.8; 33.9; 33.8; 30.8; 26.4; 26.3; 20.5; 19.7; 16.0. *m/z* ($MW_{monoisotopic}$)=358.1878 (Calcd, 358.24).

4.3.4. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-amino-4-methylpentanamide (3d). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.90, 1.60 Hz); 7.91 (dd, 1H, *J*=6.80, 1.60 Hz); 7.38 (m, 1H); 7.30 (dd, 1H, *J*=8.20, 4.90 Hz); 6.33 (d, 1H, *J*=2.60 Hz); 6.28 (d, 1H, *J*=2.60 Hz); 6.00 (d, 1H, *J*=8.20 Hz); 3.88 (s, 3H); 3.62 (m, 1H); 3.35 (m, 2H); 3.28 (m, 1H); 1.86 (m, 5H); 1.66 (m, 4H); 1.29 (d, 3H, *J*=6.33 Hz); 0.93 (d, 3H, *J*=6.09 Hz); 0.90 (d, 3H, *J*=5.79 Hz). δ_C ($CDCl_3$, 300 MHz) 172.5; 159.3; 156.0; 144.8; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.6; 80.2; 68.7; 55.2; 49.0; 47.8; 47.7; 33.9; 33.7; 33.6; 30.3; 28.2; 26.2; 26.1; 25.6; 24.9; 24.7; 22.9; 20.5. *m/z* ($MW_{monoisotopic}$)=372.3335 (Calcd, 372.25).

4.3.5. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-amino-3-phenylacetamide (3e). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.22, 1.56 Hz); 7.93 (dd, 1H, *J*=8.36, 1.42 Hz); 7.34–7.16 (m, 6H); 6.33 (d, 1H, *J*=2.51 Hz); 6.27 (d, 1H, *J*=2.51 Hz); 3.88 (s, 3H); 3.57 (m, 2H); 3.28 (m, 2H); 3.21 (m, 1H); 2.66 (dd, 1H, *J*=13.7, 9.31 Hz); 1.62 (m, 6H); 1.30 (d, 3H, *J*=6.35 Hz). δ_C ($CDCl_3$, 300 MHz) 174.0; 159.3; 156.0; 144.8; 144.2; 137.8; 135.2; 134.6; 129.8; 129.2; 128.5; 126.7; 121.8; 96.6; 91.5; 56.3; 55.1; 47.7; 40.9; 38.9; 36.8; 33.7; 26.1; 20.4. *m/z* ($MW_{monoisotopic}$)=406.2477 (Calcd, 406.24).

4.4. Reaction of 3a–e with symmetrical ketones: synthesis of imidazolidin-4-ones 5a–t

Compounds **3a–e** (2 mmol) were mixed with an excess (4 mmol) of the appropriate ketone (acetone, cyclopentanone, cyclohexanone or cycloheptanone) and TEA (2 mmol) in dry methanol (10 mL) and the mixture refluxed for 3 d in the presence of 4 Å molecular sieves (1 g). The reaction was monitored by TLC and ketone was re-added (2 mmol) once per day. The molecular sieves were removed by decantation and the solution evaporated to dryness. The oily residue was submitted to column chromatography on silica-gel, eluted with DCM/THF (varying solvent proportions) or, for compound **5a**, DCM/ethanol 15:1 (v/v). Fractions containing the chromatographically homogeneous product were pooled and evaporated to dryness, yielding **5a–t** as yellow-orange oils (44–81%) that were analyzed by high-resolution MS and NMR, as detailed below.

4.4.1. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2,2-dimethylimidazolidin-4-one (5a). δ_H ($CDCl_3$, 300 MHz) 8.50 (dd, 1H, *J*=4.20, 1.80 Hz); 7.89 (dd, 1H, *J*=8.40, 1.80 Hz); 7.27 (dd, 1H, *J*=8.40, 4.20 Hz); 6.31 (d, 1H, *J*=2.40 Hz); 6.26 (d, 1H, *J*=3.00 Hz); 5.99 (d, 1H, *J*=7.80 Hz); 3.86 (s, 3H); 3.62 (m, 1H); 3.40 (s, 2H); 3.16 (m, 2H); 2.05 (m, 1H); 1.69 (m, 4H); 1.27 (m, 9H). δ_C ($CDCl_3$, 300 MHz) 173.6; 159.3; 144.9; 144.2; 135.2; 134.7; 129.8; 121.8; 96.7; 91.6; 78.1; 55.1; 48.1; 47.8; 40.1; 33.9; 26.3; 26.2; 26.1; 20.5. *m/z* ($MW_{monoisotopic}$)=356.1004 (Calcd, 356.22).

4.4.2. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2,2,5-trimethylimidazolidin-4-one (5b). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.23, 1.66 Hz); 7.92 (dd, 1H, *J*=8.28, 1.66 Hz); 7.30 (dd, 1H, *J*=8.28, 4.23 Hz); 6.33 (d, 1H, *J*=2.50 Hz); 6.28 (d, 1H, *J*=2.50 Hz); 6.00 (d, 1H, *J*=7.16 Hz); 3.88 (s, 3H); 3.64 (m, 1H); 3.50 (q, 1H, *J*=6.87 Hz); 3.32 (m, 1H); 3.04 (m, 1H); 1.93 (m, 1H); 1.72 (m, 4H); 1.32 (m, 12H). δ_C ($CDCl_3$, 300 MHz) 175.6; 159.3; 144.9; 144.2; 135.3; 134.7; 129.8; 121.8; 96.7; 91.6; 75.7; 55.2; 53.6; 47.8; 45.0; 40.3; 33.8; 28.1; 26.2; 25.8; 25.6; 20.5; 17.4. *m/z* ($MW_{monoisotopic}$)=370.2809 (Calcd, 370.24).

4.4.3. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-5-isopropyl-2,2-dimethylimidazolidin-4-one (5c). δ_H ($CDCl_3$, 300 MHz) 8.51 (d, 1H, *J*=3.60 Hz); 7.90 (d, 1H, *J*=7.80 Hz); 7.29 (dd, 1H, *J*=7.80, 3.60 Hz); 6.31 (d, 1H, *J*=2.10 Hz); 6.29 (d, 1H, *J*=2.10 Hz), 6.01 (m, 1H); 3.87 (s, 3H); 3.63 (m, 1H); 3.46 (m, 3H); 2.96 (m, 1H); 2.18 (m, 1H); 1.71 (m, 4H); 1.29 (m, 9H); 1.03 (d, 3H, *J*=6.90 Hz); 0.91 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.2; 166.0; 159.4; 145.5; 145.0; 144.3; 135.4; 134.7; 129.9; 121.8; 96.8; 91.7; 75.7; 65.8; 62.8; 55.2; 48.0; 47.7; 40.2; 40.0; 34.1; 34.0; 30.3; 28.9; 28.3; 26.6; 26.5; 26.2; 26.1; 20.6; 19.3; 16.7; 15.3. *m/z* ($MW_{monoisotopic}$)=398.2293 (Calcd, 398.27).

4.4.4. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-5-isobutyl-2,2-dimethylimidazolidin-4-one (5d). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 2.10 Hz); 7.90 (dd, 1H, *J*=8.40, 2.10 Hz); 7.38 (m, 1H); 7.28 (dd, 1H, *J*=8.40, 4.20 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 6.29 (d, 1H, *J*=2.40 Hz); 6.10 (d, 1H, *J*=6.60 Hz); 3.88 (s, 3H); 3.63 (m, 1H); 3.44 (dd, 1H, *J*=9.90, 3.30 Hz); 3.33 (m, 1H); 3.02 (m, 1H); 1.84 (m, 3H); 1.71 (m, 4H); 1.34 (d, 3H, 6.90 Hz), 1.30 (d, 3H, *J*=6.30 Hz); 0.96 (d, 3H, *J*=6.00 Hz); 0.94 (d, 3H,

J=6.00 Hz). δ_C ($CDCl_3$, 300 MHz) 175.7; 165.9; 159.4; 145.0; 144.3; 135.3; 134.7; 129.9; 121.8; 96.7; 91.6; 76.1; 56.3; 55.2; 47.9; 47.8; 41.7; 40.3; 40.2; 33.9; 28.2; 26.2; 26.1; 25.9; 25.3; 23.4; 21.5; 20.6; 20.5. m/z ($MW_{monoisotopic}$)=412.1843 (Calcd, 412.28).

4.4.5. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-5-benzyl-2,2-dimethylimidazolidin-4-one (5e). δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.90 (d, 1H, J=8.18 Hz); 7.22 (m, 6H); 6.32 (d, 1H, J=2.46 Hz); 6.28 (d, 1H, J=2.46 Hz); 6.00 (dd, 1H, J=8.24, 5.66 Hz); 3.87 (s, 3H); 3.75 (t, 1H, J=5.39 Hz); 3.61 (m, 1H); 3.33 (m, 1H); 3.07 (d, 2H, J=5.24 Hz); 2.94 (m, 1H); 1.63 (m, 5H); 1.28 (dd, 3H, J=6.34, 2.12 Hz); 1.20 (d, 3H, J=2.45 Hz); 1.08 (s, 3H). δ_C ($CDCl_3$, 300 MHz) 174.0; 159.4; 156.0; 145.0; 144.3; 136.9; 135.3; 134.7; 129.9; 129.6; 128.5; 126.6; 121.6; 96.7; 91.6; 76.1; 58.8; 55.2; 53.9; 47.9; 47.8; 40.3; 36.9; 34.0; 30.7; 29.3; 28.0; 26.4; 26.3; 26.1; 26.0; 20.6. m/z ($MW_{monoisotopic}$)=446.3802 (Calcd, 446.27).

4.4.6. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,4-diazaspiro[4.4]nonan-2-one (5f). δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.91 (d, 1H, J=8.40 Hz); 7.29 (dd, 1H, J=7.80, 4.20 Hz); 6.33 (m, 1H); 6.28 (m, 1H); 6.01 (d, 1H, J=8.10 Hz); 3.89 (s, 3H); 3.66 (m, 1H); 3.36 (s, 2H); 3.13 (m, 2H); 1.89 (bs, 1H); 1.72 (m, 8H); 1.54 (m, 4H); 1.30 (d, 3H, J=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 159.4; 145.0; 144.3; 135.3; 134.8; 129.9; 121.9; 96.7; 91.6; 88.1; 77.3; 76.8; 55.2; 48.3; 47.8; 40.1; 35.5; 35.4; 33.8; 26.2; 23.0; 20.6; 20.7. m/z ($MW_{monoisotopic}$)=382.2637 (Calcd, 382.24).

4.4.7. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,4-diazaspiro[4.4]nonan-2-one (5g). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.35, 1.65 Hz); 7.92 (dd, 1H, J=8.40, 1.20 Hz); 7.30 (dd, 1H, J=8.10, 4.20 Hz); 6.33 (d, 1H, J=2.40 Hz); 6.28 (d, 1H, J=2.40 Hz); 6.01 (m, 1H); 3.88 (s, 3H); 3.66 (m, 1H); 3.44 (q, 1H, J=10.0 Hz); 3.32 (m, 1H); 2.93 (m, 1H); 1.69 (m, 12H); 1.33 (d, 3H, J=6.30 Hz); 1.30 (d, 3H, J=5.40 Hz). δ_C ($CDCl_3$, 300 MHz) 176.3; 159.4; 145.0; 144.9; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 96.7; 91.6; 85.9; 77.2; 55.2; 53.9; 48.0; 47.7; 40.4; 40.2; 37.5; 33.8; 30.3; 26.2; 23.2; 23.0; 20.7; 20.6; 17.0. m/z ($MW_{monoisotopic}$)=396.3026 (Calcd, 396.25).

4.4.8. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,4-diazaspiro[4.4]nonan-2-one (5h). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.35, 1.35 Hz); 7.91 (dd, 1H, J=8.25, 1.35 Hz); 7.28 (dd, 1H, J=7.95, 4.35 Hz); 6.32 (d, 1H, J=2.70 Hz); 6.29 (d, 1H, J=2.85 Hz), 6.02 (d, 1H, J=8.70 Hz); 3.88 (s, 3H); 3.64 (m, 1H); 3.37 (m, 1H); 3.32 (d, 1H, J=4.2 Hz); 2.87 (m, 1H); 2.15 (m, 1H); 1.80–1.50 (m, 12H); 1.30 (d, 3H, J=6.90 Hz); 1.02 (d, 3H, J=6.75 Hz); 0.90 (d, 3H, J=6.75 Hz). δ_C ($CDCl_3$, 300 MHz) 174.9; 174.8; 159.5; 159.4; 145.0; 144.3; 144.2; 135.4; 134.7; 129.9; 121.8; 96.8; 96.7; 91.6; 85.7; 77.3; 63.0; 55.2; 48.0; 47.6; 40.2; 39.9; 37.7; 35.5; 35.4; 34.1; 33.9; 28.9; 26.2; 26.0; 25.6; 23.1; 22.9; 20.7; 20.6; 19.3; 19.2; 17.1; 17.0. m/z ($MW_{monoisotopic}$)=424.1883 (Calcd, 424.28).

4.4.9. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,4-diazaspiro[4.4]nonan-2-one (5i). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.20, 1.50 Hz); 7.92 (dd, 1H, J=8.40, 1.50 Hz); 7.29 (dd, 1H, J=8.40, 4.20 Hz); 6.32 (d, 1H, J=2.40 Hz); 6.28 (m, 1H); 6.02 (m, 1H); 3.88 (s, 3H); 3.64 (m, 1H); 3.37 (dd, 1H, J=9.90, 3.90 Hz); 3.32 (m, 1H); 2.93 (m, 1H); 2.00–1.50 (m, 16H); 1.30 (d, 3H, J=6.30 Hz), 0.94 (m, 6H). δ_C ($CDCl_3$, 300 MHz) 176.4; 159.6; 145.1; 144.4; 135.4; 134.9; 130.0; 121.9; 96.9; 93.8; 91.8; 86.2; 56.6; 55.3; 48.1; 47.9; 41.4; 40.4; 40.3; 37.7; 35.2; 35.0; 34.1; 34.0; 26.3; 26.2; 25.3; 23.5; 23.4; 23.3; 21.9; 20.8; 20.7. m/z ($MW_{monoisotopic}$)=438.3199 (Calcd, 438.30).

4.4.10. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,4-diazaspiro[4.4]nonan-2-one (5j). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.36, 2.85 Hz); 7.92 (dd, 1H, J=8.26, 1.62 Hz); 7.32–7.17 (m, 6H); 6.33 (d, 1H, J=2.39 Hz); 6.28 (d, 1H, J=2.88 Hz); 6.00 (t, 1H, J=8.24 Hz); 3.88 (s, 3H); 3.68 (t, 1H, J=5.28 Hz); 3.61 (m, 1H); 3.36 (m, 1H); 3.12 (dd, 1H, J=14.3, 5.64 Hz); 3.07 (dd, 1H, J=14.3, 4.84 Hz); 2.86 (m, 1H); 1.79–1.48 (m, 12H); 1.29 (dd, 3H, J=6.35, 2.39 Hz). δ_C ($CDCl_3$, 300 MHz) 174.6; 174.5; 159.4; 159.3; 144.9; 144.2; 144.1; 136.8; 136.7; 135.3; 135.2; 134.7; 129.8; 129.6; 128.5; 126.8; 121.8; 96.6; 96.5; 91.5; 85.9; 77.2; 58.9; 58.8; 55.1; 47.9; 47.6; 40.2; 40.1; 37.3; 36.4; 36.3; 35.1; 34.9; 33.9; 33.8; 30.9; 26.1; 25.9; 20.6.; 20.5 m/z ($MW_{monoisotopic}$)=472.3531 (Calcd, 472.28).

4.4.11. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,4-diazaspiro[4.5]decan-2-one (5k). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.20, 1.50 Hz); 7.92 (dd, 1H, J=8.10, 2.70 Hz); 7.30 (dd, 1H, J=8.10, 4.20 Hz); 6.33 (d, 1H, J=2.70 Hz); 6.29 (d, 1H, J=2.70 Hz); 6.01 (d, 1H, J=8.40 Hz); 3.89 (s, 3H); 3.64 (m, 1H); 3.37 (s, 2H); 3.14 (m, 2H); 1.80 (bs, 1H); 1.74–1.48 (m, 14H); 1.30 (d, 3H, J=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 173.9; 159.4; 145.0; 144.2; 135.3; 134.7; 129.9; 121.8; 96.6; 91.5; 80.1; 77.2; 55.2; 48.0; 47.8; 39.8; 34.9; 34.8; 33.8; 30.3; 26.4; 25.6; 24.7; 22.5; 20.7. m/z ($MW_{monoisotopic}$)=396.0727 (Calcd, 396.25).

4.4.12. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,4-diazaspiro[4.5]decan-2-one (5l). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.31, 1.68 Hz); 7.92 (dd, 1H, J=8.24, 1.61 Hz); 7.30 (dd, 1H, J=8.28, 4.26 Hz); 6.33 (d, 1H, J=2.51 Hz); 6.28 (d, 1H, J=2.51 Hz); 6.01 (d, 1H, J=8.22 Hz); 3.88 (s, 3H); 3.63 (m, 1H); 3.44 (q, J=7.05 Hz+q, J=6.84 Hz, 1H); 3.32 (m, 1H); 2.96 (m, 1H); 1.76–1.40 (m, 14H); 1.32 (d, 3H, J=4.70 Hz); 1.30 (d, 3H, J=4.23 Hz). δ_C ($CDCl_3$, 300 MHz) 175.9; 159.3; 145.0; 144.9; 144.2; 135.3; 134.7; 129.8; 121.8; 96.7; 96.6; 91.5; 78.0; 77.4; 55.1; 53.4; 47.9; 47.6; 40.0; 39.8; 37.8; 37.7; 33.7; 33.6; 33.3; 33.2; 30.2; 26.4; 24.8; 22.9; 22.2; 20.7; 17.7; 15.2. m/z ($MW_{monoisotopic}$)=410.3247 (Calcd, 410.27).

4.4.13. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,4-diazaspiro[4.5]decan-2-one (5m). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.14, 1.50 Hz); 7.92 (dd, 1H, J=8.24, 1.59 Hz); 7.30 (dd, 1H, J=8.21, 4.20 Hz); 6.33 (d, 1H, J=2.50 Hz); 6.28 (d, 1H, J=2.50 Hz), 6.01 (d, 1H, J=8.38 Hz); 3.89 (s, 3H); 3.63 (m, 1H); 3.36 (d, 1H, J=3.99 Hz); 3.32 (m, 1H); 3.00 (m, 1H); 2.10 (m, 1H); 1.75–1.37 (m, 15H); 1.30 (d, 3H, J=6.36 Hz); 1.01 (d, 3H, J=6.94 Hz); 0.88 (d, 3H, J=6.80 Hz). δ_C ($CDCl_3$,

300 MHz) 174.3; 159.4; 145.0; 144.2; 135.3; 129.9; 121.8; 96.7; 91.5; 77.2; 62.5; 55.2; 48.0; 47.6; 39.8; 39.6; 37.6; 34.5; 34.0; 33.9; 29.3; 26.5; 24.8; 23.1; 22.9; 22.2; 20.7; 20.6; 19.2; 17.0; 16.9. *m/z* ($MW_{monoisotopic}$)=438.4114 (Calcd, 438.30).

4.4.14. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,4-diazaspiro[4.5]decan-2-one (5n). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 1.50 Hz); 7.92 (dd, 1H, *J*=8.40, 1.50 Hz); 7.30 (dd, 1H, *J*=8.40, 4.20 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 6.29 (d, 1H, *J*=1.80 Hz); 6.02 (m, 1H); 3.88 (s, 3H); 3.64 (m, 1H); 3.38 (m, 1H); 3.30 (m, 1H); 2.98 (m, 1H); 1.98–1.29 (m, 18H); 1.30 (d, 3H, *J*=6.30 Hz), 0.94 (m, 6H). δ_C ($CDCl_3$, 300 MHz) 176.0; 159.4; 145.0; 144.2; 135.3; 134.8; 129.9; 121.8; 96.8; 96.7; 91.6; 78.2; 56.1; 55.2; 48.0; 47.7; 42.0; 41.9; 40.0; 39.8; 37.8; 37.7; 33.9; 33.8; 33.7; 26.5; 25.4; 25.3; 24.8; 23.2; 22.9; 22.2; 21.8; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=452.3154 (Calcd, 452.32).

4.4.15. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,4-diazaspiro[4.5]decan-2-one (5o). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 1.83 Hz); 7.92 (dd, 1H, *J*=8.22, 1.47 Hz); 7.32–7.15 (m, 6H); 6.33 (m, 1H); 6.28 (m, 1H); 6.00 (m, 1H); 3.88 (s, 3H); 3.71 (m, 1H); 3.60 (m, 1H); 3.31 (m, 1H); 3.05 (dd, 2H, *J*=5.3, 2.75 Hz); 1.75–1.40 (m, 14H); 1.29 (dd, 3H, *J*=6.39, 1.83 Hz). δ_C ($CDCl_3$, 300 MHz) 175.4; 173.9; 159.2; 144.8; 144.7; 144.0; 137.1; 137.0; 135.0; 134.9; 134.5; 129.6; 129.5; 128.2; 126.5; 121.7; 96.4; 96.3; 91.4; 72.5; 58.5; 58.4; 55.0; 47.7; 47.6; 40.2; 40.1; 37.4; 37.3; 37.2; 37.1; 34.4; 34.2; 33.7; 33.6; 26.1; 24.4; 22.5; 22.0; 21.9; 20.5; 20.4 *m/z* ($MW_{monoisotopic}$)=486.7263 (Calcd, 486.30).

4.4.16. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,4-diazaspiro[4.6]undecan-2-one (5p). δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.91 (d, 1H, *J*=8.40 Hz); 7.29 (dd, 1H, *J*=7.80, 4.20 Hz); 6.33 (m, 1H); 6.28 (m, 1H); 6.01 (d, 1H, *J*=8.10 Hz); 3.89 (s, 3H); 3.66 (m, 1H); 3.36 (s, 2H); 3.13 (m, 2H); 1.89 (bs, 1H); 1.72–1.40 (m, 14H); 1.30 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 159.4; 145.0; 144.3; 135.3; 134.8; 129.9; 121.9; 102.2; 96.7; 91.6; 88.1; 77.3; 76.8; 55.2; 48.3; 47.8; 40.1; 35.5; 35.4; 33.8; 26.2; 23.0; 20.6; 20.7. *m/z* ($MW_{monoisotopic}$)=410.3558 (Calcd, 410.27).

4.4.17. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,4-diazaspiro[4.6]undecan-2-one (5q). δ_H ($CDCl_3$, 300 MHz) 8.49 (m, 1H); 7.89 (m, 1H); 7.28 (m, 1H); 6.30 (m, 1H); 6.26 (m, 1H); 6.01 (m, 1H); 3.86 (s, 3H); 3.65 (m, 1H); 3.43–3.23 (m, 2H); 3.03 (m, 1H); 1.68 (m, 6H); 1.51 (m, 5H); 1.40–1.17 (m, 9H). δ_C ($CDCl_3$, 300 MHz) 175.5; 175.4; 159.3; 144.9; 144.8; 144.1; 135.2; 134.8; 129.8; 121.7; 96.7; 96.6; 91.6; 91.5; 81.2; 55.1; 53.1; 47.7; 47.6; 47.5; 40.9; 40.8; 40.3; 40.2; 36.9; 36.8; 33.7; 33.6; 29.6; 29.5; 29.1; 26.0; 22.4; 22.1; 22.0; 20.6; 20.5; 20.4; 17.2. *m/z* ($MW_{monoisotopic}$)=424.2835 (Calcd, 424.28).

4.4.18. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,4-diazaspiro[4.6]undecan-2-one (5r). δ_H ($CDCl_3$, 300 MHz) 8.51 (dd, 1H, *J*=3.90, 1.35 Hz); 7.91 (dd, 1H, *J*=8.25, 1.35 Hz); 7.29 (dd, 1H, *J*=8.25, 3.90 Hz); 6.32 (d, 1H, *J*=2.70 Hz); 6.29+6.28 (d+d, 1H, *J*=2.70 Hz), 6.01 (dd, 1H, *J*=7.95, 3.15 Hz); 3.88 (s, 3H); 3.64 (m, 1H); 3.41 (m, 1H); 3.32 (d, 1H, *J*=4.50 Hz); 3.01 (m, 1H); 2.12 (m, 1H); 1.89 (m, 1H); 1.71–1.34 (m, 16H); 1.30 (d, 3H, *J*=6.60 Hz); 1.01 (d, 3H, *J*=6.90 Hz); 0.89 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 174.2; 159.5; 159.4; 145.1; 145.0; 144.3; 144.2; 135.4; 134.7; 129.9; 121.8; 96.8; 96.7; 91.6; 80.9; 80.8; 77.3; 62.3; 55.2; 47.9; 47.5; 41.0; 40.9; 40.2; 40.1; 38.2; 38.1; 34.0; 30.3; 29.5; 29.4; 29.3; 29.2; 26.2; 26.1; 25.6; 22.5; 22.4; 22.1; 21.9; 20.7; 20.6; 19.3; 19.2; 17.1; 17.0. *m/z* ($MW_{monoisotopic}$)=452.3847 (Calcd, 452.32).

4.4.19. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,4-diazaspiro[4.6]undecan-2-one (5s). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 1.80 Hz); 7.91 (dd, 1H, *J*=8.40, 1.80 Hz); 7.29 (dd, 1H, *J*=8.40, 4.20 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 6.28 (m, 1H); 6.02 (m, 1H); 3.88 (s, 3H); 3.64 (m, 1H); 3.36 (m, 2H); 3.05 (m, 1H); 1.93–1.24 (m, 20H); 1.30 (d, 3H, *J*=6.60 Hz), 0.94 (m, 6H). δ_C ($CDCl_3$, 300 MHz) 175.6; 159.5; 145.0; 144.2; 144.1; 135.3; 135.2; 134.8; 134.7; 130.0; 129.9; 121.8; 96.8; 96.7; 918; 81.5; 55.9; 55.2; 47.8; 47.6; 41.7; 41.6; 41.0; 40.4; 40.3; 37.4; 37.2; 33.9; 33.8; 33.7; 29.6; 29.5; 29.3; 29.2; 26.1; 25.4; 25.3; 23.2; 22.5; 22.4; 22.2; 22.0; 21.8; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=466.3315 (Calcd, 466.33).

4.4.20. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,4-diazaspiro[4.6]undecan-2-one (5t). δ_H ($CDCl_3$, 300 MHz) 8.52 (dq, 1H, *J*=50, 1.80 Hz); 7.91 (dt, 1H, *J*=8.40, 1.80 Hz); 7.32–7.14 (m, 6H); 6.32 (m, 1H); 6.27 (m, 1H); 5.99 (t, 1H, *J*=8.70 Hz); 3.88 (s, 3H); 3.67 (t, 1H, *J*=5.40 Hz); 3.61 (m, 1H); 3.37 (m, 1H); 3.11 (m, 3H); 1.64–1.18 (m, 20H); 1.29 (dd, 3H, *J*=6.36, 3.38 Hz). δ_C ($CDCl_3$, 300 MHz) 173.9; 173.8; 159.4; 145.0; 144.9; 144.2; 144.1; 136.9; 136.8; 135.3; 134.7; 129.8; 129.7; 128.4; 126.8; 121.8; 96.6; 96.5; 91.5; 81.3; 77.2; 58.3; 58.2; 55.1; 47.8; 47.5; 40.6; 40.4; 40.3; 37.9; 37.7; 36.6; 36.5; 33.9; 33.8; 29.5; 29.2; 26.1; 25.8; 25.6; 22.3; 22.0; 20.7;20.6 *m/z* ($MW_{monoisotopic}$)=500.3246 (Calcd, 500.32).

4.5. Reaction of compounds 3a–e with veratraldehyde—synthesis of imidazolidin-4-ones 5u–x

Compounds **3a–e** (2 mmol) were mixed with a small excess (2.2 mmol) of veratraldehyde and TEA (2 mmol) in dry methanol (10 mL). The mixture was refluxed for 3 d in the presence of 4 Å molecular sieves (1 g) with periodic monitoring by TLC. One to four new TLC spots could be detected in the different reaction mixtures. The molecular sieves were removed by decantation and the solution evaporated to dryness. The oily residue was submitted to column chromatography on silica-gel, eluted with DCM/THF (varying solvent proportions). Chromatographically homogeneous fractions were pooled and evaporated to dryness, yielding different combinations of the four possible diastereomers for each one of the imidazolidin-4-ones **5u–x**. Global yields ranged from 57 to 95%. The different fractions of **5u–x** were analyzed by MALDI-TOF MS and NMR, and spectral data are detailed below. The product derived from glycine could not be isolated and further characterized by NMR, but the expected molecular weight

(464.24) could be detected in the reaction mixture by MALDI-TOF MS (*m/z* 464.2755).

4.5.1. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-methylimidazolidin-4-one (5u). *Fraction* 1. δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.20, 1.50 Hz); 7.93 (dd, 1H, *J*=8.40, 1.50 Hz); 7.32 (dd, 1H, *J*=8.40, 4.20 Hz); 6.80–6.65 (m, 3H); 6.34 (m, 1H); 6.25 (m, 1H); 5.95 (m, 1H); 5.39+5.00 (s+s, 1H); 3.88 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H); 3.61 (m, 3H); 2.67 (m, 1H); 1.68–1.60 (m, 5H); 1.38–1.27 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 175.7; 175.6; 159.2; 149.6; 149.5; 149.4; 144.7; 144.6; 144.1; 135.1; 134.6; 134.5; 131.3; 131.2; 129.7; 128.0; 121.7; 119.1; 119.0; 111.0; 110.9; 108.9; 108.8; 96.8; 96.6; 91.6; 91.5; 74.8; 74.7; 55.7; 55.6; 54.9; 54.3; 54.1; 47.4; 47.3; 40.0; 34.0; 33.4; 32.5; 23.4; 22.8; 21.0; 20.5; 20.2; 18.1; 17.8. *m/z* ($MW_{monoisotopic}$)=478.3069 (Calcd, 478.26).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.53 (m, 1H); 7.92 (dd, 1H, *J*=8.40, 1.50 Hz); 7.32 (m, 1H); 6.81–6.74 (m, 3H); 6.33 (d, 1H, *J*=2.40 Hz); 6.25 (d, 1H, *J*=2.70 Hz); 5.94 (m, 1H); 5.18+5.17 (m+ms, 1H); 3.88 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H); 3.59 (m, 3H); 2.70 (m, 1H); 1.66–1.58 (m, 5H); 1.32–1.23 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 175.6; 175.5; 168.1; 159.3; 159.0; 149.8; 149.7; 149.4; 144.8; 144.7; 144.1; 135.2; 134.6; 134.5; 130.8; 130.7; 129.7; 128.1; 121.7; 119.9; 119.8; 119.7; 111.0; 110.9; 109.4; 109.3; 96.7; 96.5; 91.5; 91.4; 75.1; 75.0; 55.7; 55.6; 55.0; 54.9; 47.5; 47.4; 40.3; 40.1; 34.1; 33.6; 33.2; 32.5; 23.5; 23.3; 21.0; 20.5; 20.3; 18.0; 17.9. *m/z* ($MW_{monoisotopic}$)=478.3083 (Calcd, 478.26).

4.5.2. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-isopropylimidazolidin-4-one (5v). *Fraction* 1. δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.92 (d, 1H, *J*=7.80 Hz); 7.30 (dd, 1H, *J*=7.80, 4.20 Hz); 6.82–6.71 (m, 3H); 6.32 (d, 1H, *J*=2.40 Hz); 6.24 (d, 1H, *J*=2.10 Hz); 5.96 (m, 1H); 5.34+5.24+5.12 (d, *J*=1.20 Hz+d, *J*=1.20 Hz+d, *J*=1.50 Hz; 1H); 3.84–3.49 (m, 11H); 2.67 (m, 1H); 2.18 (m, 1H); 2.02 (bs, 1H); 1.68–1.42 (m, 5H); 1.24 (d, 3H, *J*=2.10 Hz); 1.05–0.92 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 174.3; 174.2; 159.4; 159.3; 149.7; 149.5; 145.0; 144.9; 144.8; 144.2; 135.3; 134.8; 134.7; 132.4; 132.3; 129.9; 121.9; 121.8; 119.6; 119.5; 119.4; 111.2; 111.1; 111.0; 109.0; 108.9; 97.0; 96.9; 96.8; 91.7; 91.6; 91.5; 76.6; 76.6; 63.9; 63.8; 55.9; 55.8; 55.2; 47.8; 47.6; 47.5; 40.3; 40.2; 40.1; 40.0; 33.9; 33.8; 33.1; 31.2; 31.1; 25.6; 23.7; 23.5; 20.7; 20.5; 19.5; 16.7; 16.6. *m/z* ($MW_{monoisotopic}$)=506.2897 (Calcd, 506.29).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.20, 2.10 Hz); 7.92 (dd, 1H, *J*=8.40, 1.50 Hz); 7.30 (dd, 1H, *J*=8.40, 4.20 Hz); 6.86–6.70 (m, 3H); 6.33 (d, 1H, *J*=2.10 Hz); 6.24 (m, 1H); 5.96 (m, 1H); 5.34+5.31+5.24+5.13 (d, *J*=2.10 Hz+d, *J*=1.50 Hz+d, *J*=1.80 Hz+d, *J*=1.50 Hz; 1H); 3.88–3.74 (m, 10H); 3.71–3.49 (m, 3H); 2.66 (m, 1H); 2.25 (m, 1H); 1.96 (bs, 2H); 1.68–1.44 (m, 4H); 1.24 (m, 3H); 1.07–0.92 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 174.4; 174.3; 174.2; 174.1; 159.5; 159.4; 149.9; 149.8; 149.7; 149.6; 149.5; 145.1; 145.0; 144.9; 144.8; 144.3; 135.4; 134.8; 134.7; 132.4; 131.6; 131.5; 129.9; 130.0; 121.9; 121.8; 120.2; 120.1; 119.6; 119.5; 119.4; 111.3; 111.2; 111.1; 111.0; 109.8; 109.7; 109.0; 108.9; 97.0; 96.9; 96.8; 96.7; 91.8; 91.7; 91.6; 91.5; 76.6; 76.5; 74.8; 74.7; 68.0; 64.2; 64.1; 64.0; 63.8; 56.0; 55.9; 55.8; 55.7; 55.2; 47.8; 47.7; 47.6; 47.5; 40.2; 40.1; 40.0; 33.9; 33.8; 31.2; 30.3; 29.3; 29.2; 25.6; 25.5; 23.8; 23.7; 23.6; 23.3; 22.7; 20.7; 20.6; 20.5; 20.4; 19.5; 19.4; 16.8; 16.7; 16.6. *m/z* ($MW_{monoisotopic}$)=506.2887 (Calcd, 506.29).

4.5.3. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-isobutylimidazolidin-4-one (5w). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.25, 1.40 Hz); 7.92 (dd, 1H, *J*=8.24, 1.41 Hz); 7.31 (dd, 1H, *J*=8.22, 4.23 Hz); 6.82–6.68 (m, 3H); 6.34 (m, 1H); 6.24 (m, 1H); 5.96 (m, 1H); 5.37+5.30+5.22+5.15 (d, *J*=1.12 Hz+d, *J*=1.01 Hz+d, *J*=0.98 Hz+d, *J*=1.00 Hz; 1H); 3.97–3.72 (m, 11H); 3.59 (m, 2H); 2.66 (m, 1H); 1.94 (m, 2H); 1.58–1.50 (m, 5H); 1.25 (m, 3H); 0.94 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 175.8; 175.7; 175.6; 165.7; 165.5; 159.3; 149.8; 149.6; 149.5; 149.4; 144.9; 144.8; 144.7; 144.2; 135.2; 134.7; 131.6; 130.8; 129.8; 121.8; 119.9; 119.8; 119.4; 119.3; 111.1; 111.0; 110.3; 109.5; 109.4; 108.9; 108.8; 96.8; 96.6; 96.5; 91.6; 91.5; 91.4; 75.4; 75.3; 75.2; 75.1; 57.7; 57.2; 57.1; 55.8; 55.7; 55.1; 47.6; 47.5; 42.0; 41.6; 40.3; 40.2; 40.1; 39.9; 33.7; 33.6; 33.1; 33.0; 30.2; 25.5; 25.2; 25.1; 23.5; 23.4; 23.2; 23.1; 21.4; 20.6; 20.5; 20.4. *m/z* ($MW_{monoisotopic}$)=520.4108 (Calcd, 520.30).

4.5.4. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-benzylimidazolidin-4-one (5x). *Fraction* 1. δ_H ($CDCl_3$, 300 MHz) 8.50 (m, 1H); 7.92 (dd, 1H, *J*=8.30, 0.90 Hz); 7.34–7.12 (m, 6H); 6.78–6.64 (m, 3H); 6.33 (d, 1H, *J*=2.80 Hz); 6.23 (d, 1H, *J*=2.80 Hz); 5.93 (m, 1H); 5.05+4.97 (m+m, 1H); 4.05 (m, 1H); 3.87+3.85 (s+s, 3H); 3.84+3.82 (s+s, 3H), 3.80+3.75 (s+s, 3H); 3.55 (m, 2H); 3.10 (m, 1H); 2.97 (m, 1H); 2.56 (m, 1H); 2.15 (bs, 1H); 1.58–1.43 (m, 4H); 1.22 (d, 3H, *J*=6.70 Hz). δ_C ($CDCl_3$, 75 MHz) 173.9; 173.8; 159.4; 149.7; 149.6; 145.0; 144.9; 144.3; 137.5; 137.4; 135.3; 134.8; 134.7; 131.7; 129.9; 129.8; 128.5; 128.4; 126.8; 126.7; 121.9; 119.5; 111.1; 111.0; 109.1; 109.0; 96.8; 96.6; 91.6; 91.5; 75.5; 75.4; 60.1; 56.0; 55.9; 55.8; 55.2; 47.7; 47.6; 40.2; 40.0; 38.5; 33.6; 33.4; 30.3; 23.4; 23.3; 20.6; 20.4. *m/z* ($MW_{monoisotopic}$)=554.6603 (Calcd, 554.29).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=3.90, 1.80 Hz); 7.91 (dd, 1H, *J*=8.40, 1.80 Hz); 7.32–7.16 (m, 6H); 6.68 (d, 1H, *J*=8.40 Hz); 6.42 (dd, 1H, *J*=8.40, 2.10 Hz); 6.32 (m, 2H); 6.24 (d, 1H, *J*=2.40 Hz); 5.94 (m, 1H); 5.06 (d, 1H, *J*=0.90 Hz); 3.87 (s, 3H); 3.81 (s, 3H); 3.80 (m, 1H); 3.63 (s, 3H); 3.58 (m, 1H); 3.42 (dt, 1H, *J*=14.1, 7.10 Hz); 3.26 (dd, 1H, *J*=14.1, 5.70 Hz); 3.10 (dd, 1H, *J*=13.9, 4.50 Hz); 2.71 (dt, 1H, *J*=13.8, 6.90 Hz); 1.86 (bs, 1H); 1.58–1.43 (m, 4H); 1.24 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 75 MHz) 174.4; 166.1; 149.9; 149.4; 144.9; 144.2; 136.9; 135.3; 134.8; 130.6; 129.9; 129.8; 126.9; 121.8; 120.2; 111.0; 109.2; 96.9; 91.6; 75.6; 60.2; 55.9; 55.8; 55.2; 47.6; 40.6; 36.6; 34.2; 33.4; 30.3; 23.5; 20.6; 20.4. *m/z* ($MW_{monoisotopic}$)=554.6391 (Calcd, 554.29).

Fraction 3. δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=3.90,

1.50 Hz); 7.92 (dd, 1H, *J*=8.40, 1.20 Hz); 7.32–7.19 (m, 6H); 6.60 (d, 1H, *J*=8.40 Hz); 6.44 (dd, 1H, *J*=7.80, 1.80 Hz); 6.32 (m, 2H); 6.21 (d, 1H, *J*=2.40 Hz); 5.94 (m, 1H); 5.20 (d, 1H, *J*=1.50 Hz); 3.87 (s, 3H); 3.84 (m, 1H); 3.80 (s, 3H); 3.57 (s, 3H); 3.48 (m, 2H); 3.28 (dd, 1H, *J*=14.1, 5.40 Hz); 3.12 (dd, 1H, *J*=13.8, 4.50 Hz); 2.66 (m, 1H); 1.86 (bs, 1H); 1.64–1.43 (m, 4H); 1.22 (d, 3H, *J*=6.60 Hz). δ_C ($CDCl_3$, 75 MHz) 174.4; 166.1; 149.9; 149.4; 144.9; 144.2; 136.9; 135.3; 134.8; 130.6; 129.9; 129.8; 126.9; 121.8; 120.2; 111.0; 109.2; 96.9; 91.6; 75.6; 60.2; 55.9; 55.8; 55.2; 47.6; 40.6; 36.6; 34.2; 33.4; 30.3; 23.5; 20.6; 20.4. *m/z* ($MW_{monoisotopic}$)=554.7268 (Calcd, 554.29).

4.6. Reaction of compounds 3a–e with 2-formylbenzoic acid—synthesis of 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*, 9b*H*)-diones 6a–e

Compounds **3a–e** (2 mmol) were mixed with a small excess of 2-formylbenzoic acid (2.2 mmol) and TEA (2 mmol) in dry methanol (10 mL). The mixture was refluxed for 3 d in the presence of 4 Å molecular sieves (1 g) with periodic monitoring by TLC. In the syntheses of compounds **6b–d** only one new spot could be detected in the reaction mixtures, whereas two spots could be distinguished in the reaction mixtures for the syntheses of **6a** and **6e**. Molecular sieves were removed by decantation and the solution evaporated to dryness. The oily residue was submitted to column chromatography on silica-gel, eluted with DCM/THF (varying solvent proportions). Chromatographically homogeneous fractions were pooled, evaporated to dryness and analyzed by NMR and MALDI-TOF MS. Global yields ranged from 44 to 60% and compounds **6b–e** were found to be mixtures of two diastereomers (NMR), whereas it was possible to isolate each of the two diastereomers of **6a**. In the purification of compound **6e**, a second fraction of impure product was collected and analyzed by MALDI-TOF MS, showing the presence of an *m/z* peak (538.34) compatible with the imidazolidin-4-one structure (Calcd, 538.26).

4.6.1. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6a).

Fraction 1. δ_H ($CDCl_3$, 300 MHz) 8.50 (dd, 1H, *J*=4.20, 1.20 Hz); 7.92 (dd, 1H, *J*=8.40, 1.20 Hz); 7.83 (d, 1H, *J*=7.80 Hz); 7.50–7.24 (m, 4H); 6.36 (d, 1H, *J*=2.40 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 5.95 (m, 1H); 5.69 (s, 1H); 4.42 (d, 1H, *J*=16.2 Hz); 3.88 (s, 4H), 3.74 (d, 1H, *J*=16.2 Hz), 3.60 (m, 1H); 3.40 (m, 1H); 1.92-1.65 (m, 4H); 1.27 (d, 3H, *J*=6.60 Hz). δ_C ($CDCl_3$, 75 MHz) 173.1; 170.5; 159.2; 144.6; 144.2; 142.0; 135.1; 134.7; 132.7; 130.4; 129.8; 124.9; 123.6; 121.7; 96.8; 91.7; 74.7; 55.1; 47.7; 47.2; 40.5; 34.0; 33.1; 24.0; 20.4. *m/z* ($MW_{monoisotopic}$)=430.2296 (Calcd, 430.20).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.49 (dd, 1H, *J*=4.50, 1.50 Hz); 7.90 (dd, 1H, *J*=8.10, 1.50 Hz); 7.80 (d, 1H, *J*=7.80 Hz); 7.50–7.24 (m, 4H); 6.34 (d, 1H, *J*=2.10 Hz); 6.27 (d, 1H, *J*=2.10 Hz); 6.01 (m, 1H); 5.80 (s, 1H); 4.44 (d, 1H, *J*=16.2 Hz); 3.86 (s, 4H), 3.78 (d, 1H, *J*=16.2 Hz), 3.64 (m, 1H); 3.28 (m, 1H); 1.90-1.60 (m, 4H); 1.26 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 75 MHz) 173.1; 170.4; 159.2; 144.6; 144.2; 141.9; 135.1; 134.6; 132.6; 130.3; 129.8; 124.9; 123.6; 121.8; 96.8; 91.8; 74.6; 55.0; 47.7; 47.1; 40.1; 34.0; 33.4; 23.9; 20.5. *m/z* ($MW_{monoisotopic}$)=430.2315 (Calcd, 430.20).

4.6.2. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6b).

δ_H ($CDCl_3$, 300 MHz) 8.50 (m, 1H); 7.88 (m, 1H); 7.78 (m, 1H); 7.48–7.24 (m, 4H); 6.32 (m, 2H); 6.04 (m, 1H); 5.76 (s, 0.7H); 5.59 (s, 0.3H); 4.52 (m, 1H); 3.85 (s, 3H), 3.65 (m, 2H), 3.30 (m, 1H); 1.79-1.60 (m, 4H); 1.50-1.42 (m, 3H); 1.27-1.24 (m, 3H). δ_C ($CDCl_3$, 75 MHz) 173.1; 173.0; 172.7; 172.6; 159.1; 159.0; 144.4; 143.9; 141.7; 141.6; 135.1; 134.9; 134.4; 132.3; 132.0; 130.5; 130.0; 129.5; 129.4; 124.5; 123.5; 123.4; 121.5; 96.7; 96.6; 91.5; 91.4; 72.7; 72.6; 54.1; 54.0; 46.9; 46.8; 40.1; 39.7; 38.2; 33.8; 33.0; 32.6; 23.6; 20.3; 20.1; 16.7; 16.6. *m/z* ($MW_{monoisotopic}$)=444.2428 (Calcd, 444.22).

4.6.3. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6c).

δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.94 (m, 1H); 7.86 (m, 1H); 7.52–7.23 (m, 4H); 6.37 (m, 1H); 6.32 (m, 1H); 6.01 (m, 1H); 5.80+5.71 (s+s, 1H); 4.28 (m, 1H); 3.90 (s, 3H), 3.70 (m, 2H), 3.30 (m, 1H); 2.34 (m, 1H); 1.80-1.62 (m, 4H); 1.31 (m, 3H); 1.19 (m, 3H); 0.99 (m, 3H). δ_C ($CDCl_3$, 75 MHz) 173.1; 171.5; 171.4; 158.8; 144.1; 143.6; 142.1; 142.0; 134.6; 134.1; 132.0; 131.9; 131.7; 129.6; 129.3; 129.2; 124.0; 123.2; 123.1; 121.2; 96.3; 91.2; 91.1; 74.1; 73.9; 64.1; 54.4; 46.8; 46.3; 39.9; 39.4; 32.9; 32.8; 23.6; 23.2; 20.0; 19.9; 19.0; 17.0. *m/z* ($MW_{monoisotopic}$)=472.3159 (Calcd, 472.25).

4.6.4. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6d).

δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.94 (m, 1H); 7.85 (m, 1H); 7.51–7.24 (m, 4H); 6.38-6.30 (m, 2H); 6.01 (t, 1H, *J*=8.70 Hz); 5.82+5.70 (s+s, 1H); 4.48 (dt, 1H, *J*=11.4, 3.30 Hz); 3.89 (s, 3H), 3.87 (m, 1H); 3.69 (m, 2H), 3.40 (m, 1H); 1.92 (m, 2H); 1.80–1.67 (m, 4H); 1.31+1.29 (d, *J*=1.80 Hz+d, *J*=1.80 Hz; 3H); 1.12 (d, *J*=6.60 Hz, 3H); 1.02+0.99 (d, *J*=1.80 Hz+d, *J*=1.80 Hz; 3H). δ_C ($CDCl_3$, 75 MHz) 173.4; 173.3; 173.2; 159.4; 159.3; 144.8; 144.7; 144.3; 144.2; 142.1; 142.0; 135.2; 134.7; 134.3; 132.6; 130.8; 130.4; 129.9; 129.8; 125.3; 124.9; 123.8; 123.7; 123.3; 121.9; 121.8; 96.9; 96.8; 91.8; 91.7; 73.3; 73.1; 58.0; 57.9; 55.1; 47.4; 47.1; 40.5; 40.0; 39.8; 39.1; 33.4; 33.2; 24.1; 23.9; 23.2; 23.1; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=486.2896 (Calcd, 486.26).

4.6.5. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6e).

δ_H ($CDCl_3$, 300 MHz) 8.54+8.52 (dd, *J*=4.20, 1.20 Hz+dd, *J*=4.20, 1.50 Hz; 1H); 7.95 (dd, 1H, *J*=8.40, 1.90 Hz); 7.84 (m, 1H); 7.45 (m, 1H); 7.34-7.14 (m, 9H); 6.37+6.35 (d+d, 1H, *J*=2.40 Hz); 6.29+6.26 (d+d, 1H, *J*=2.40 Hz); 5.95 (m, 1H); 4.84+4.80 (s+s, 1H); 4.77 (t, 1H, *J*=4.50 Hz); 3.90 (s, 3H), 3.62-2.96 (m, 5H); 1.61-1.31 (m, 4H); 1.26 (m, 3H). δ_C ($CDCl_3$, 75 MHz) 173.6; 173.5; 172.0; 171.8; 159.5; 144.9; 144.8; 144.4; 144.3; 134.8; 132.7; 132.6; 130.4; 130.3; 130.2; 130.1; 127.2; 125.1; 125.0; 123.8; 123.7; 122.0; 121.9; 96.9; 96.8; 91.9; 91.8; 74.3; 74.1; 60.2; 60.1; 55.2; 47.7; 47.1; 40.7; 40.2; 37.4; 37.3; 33.6; 33.5; 23.9; 23.4; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=520.3128 (Calcd, 520.258).

4.7. Kinetics of hydrolysis

The kinetics of hydrolysis of imidazolidin-4-ones were studied by HPLC using a Waters® assembly equipped with a model 600 controlled pump and a model 991 photodiode-array detector set at 265 nm. The separation was performed on a Purospher®, 250×4.0-mm i.d. 5 μm analytical column. The mobile phase consisted of a mixture of acetonitrile and sodium acetate buffer (pH 4.75; 0.05 M) containing 10^{-3} M triethylamine. Two gradients were developed: one for the imidazolidin-4-one derivatives of phenylalanine and the other for the derivatives of valine. A gradient method using 50–90% (v/v) acetonitrile over 20 min was used for compounds **5a**, **5e**, **5j** and **5l**, while a gradient using 60–90% (v/v) acetonitrile over 20 min was used for compounds **5c**, **5h** and **5m**. Usually, a 10 μL aliquot of a 10^{-2} M stock solution of substrate in acetonitrile was added to 10 mL of the appropriate thermostatted buffer solution. At regular intervals, samples of the reaction mixture were analysed by HPLC. All reactions followed first-order kinetics over four half-lives.

4.8. Computational details

The geometry of the imine intermediate has been optimised by the semi-empirical AM1 method as included in the GAMESS-US suite of programs.[29] Several different starting geometries were considered to ensure that a minimum on the PES was reached. Harmonic vibrational frequencies were calculated through construction and diagonalisation of the Hessian matrices at the obtained optimised molecular geometries. The absence of negative wavenumbers allowed us to characterize the equilibrium geometries as true minima.

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