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Full-length paper

Solid-phase total synthesis of (–)-Phenylhistine and (–)-Aurantiamine. Synthesis of a diverse dehydro-2,5-diketopiperazine library. Part II

Elias A. Couladouros*[1,2] & Alexandros D. Magos[1,2]
[1]*Chemistry Laboratories, Agricultural University of Athens, Iera Odos 75, Athens 118 55 (Greece);* [2]*Organic and Bioorganic Chemistry Laboratory, NCSR "DEMOKRITOS", 153 10 Ag. Paraskevi Attikis, POB 60228, Athens (Greece)*
*(*Author for correspondence, E-mail: ecoula@chem.demokritos.gr, Tel.: 30210-529-4245, Fax: 30210-677-7849)*

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Summary

The preparation of solid supported glycine phosphonate and its utilization for the total synthesis of two natural products is presented. The proposed protocol combines diversity with accessibility and speed, which makes this scaffold suitable for automated parallel synthesis and combinatorial chemistry. The preparation of a small library of dehydro-2,5-diketopiperazines, combining several natural amino acids with diverse heterocycles (including thiazoles, pyridines, indoles and imidazoles), is also demonstrated.

Abbreviations: DCC, 1,3-dicyclohexylcarbodiimide; (4)-DMAP, 4-dimethylaminopyridine; DMF, Dimethylformamide; TFA, trifluoroacetic acid; Boc, *t*-butoxycarbonyl; (+)-CSA, (+)-10-camphorosulfonic acid; HOBt, 1-hydroxybenzotriazole; EDC·HCl, *N′*-(3-dimethylaminopropyl)-*N*-ethyl-carbodiimide hydrochloride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.; TBAF, tetrabutylammonium fluoride; Het, Heterocycle; TBS, *t*-butyl dimethyl silyl-; r.t., room temperature; TLC, thin layer chromatography; HRMS, high resolution mass spectroscopy; FAB, fast atom bombardment; MALDI-FTMS, matrix-assisted laser desorption/ionization-fourier transform mass spectroscopy; EI, electron ionization; m.p., melting point; DMSO, dimethyl sulfoxide.

Introduction

The use of polymorphic building blocks as cornerstones for the construction of small-molecule libraries of increased skeletal and functional group diversity has been recently presented [1]. According to this concept, well-established multifunctional key intermediates, which have found wide application in traditional medicinal chemistry for the construction of pharmacologically important compounds (via both skeletal rearrangements and functional group interconversions), may be used as core structures for directed libraries. Ideally, this concept should encompass heterocyclic compounds, which are considered amongst the most promising molecules as lead structures for the design of new drugs.

A polymorphic molecule with this potential is Schmidt's phosphonate **1** [2]. A two-carbon trifunctional building block, **1** is useful as common key intermediate for the preparation of a great variety of pharmacophoric scaffolds (Figure 1) [3–19]. Among the many compounds accessible via **1**, diketopiperazines are quite attractive targets from a medicinal perspective [20–23].

We report the solid-phase total synthesis of two naturally occurring dehydro-diketopiperazine derivatives of impressive biological activity, namely (–)-Phenylhistine (**16**) and (–)-Aurantiamine (**17**) [24, 25]. Furthermore, the efficiency and versatility of our strategy is illustrated by the construction of a dehydro-diketopiperazine library [26, 27].

Results and discussion

Dehydro-(2,5)-diketopiperazines **2** (Figure 2), may be seen as an amino acid moiety, a heterocyclic side chain, and a derivatized glycine backbone. The two former are potential sites of diversification. To secure maximum diversity during library construction, the glycine backbone should be mounted on the resin in such a way to allow functionalization on the amine as well as the α-carbon. Retrosynthetically, this disconnection

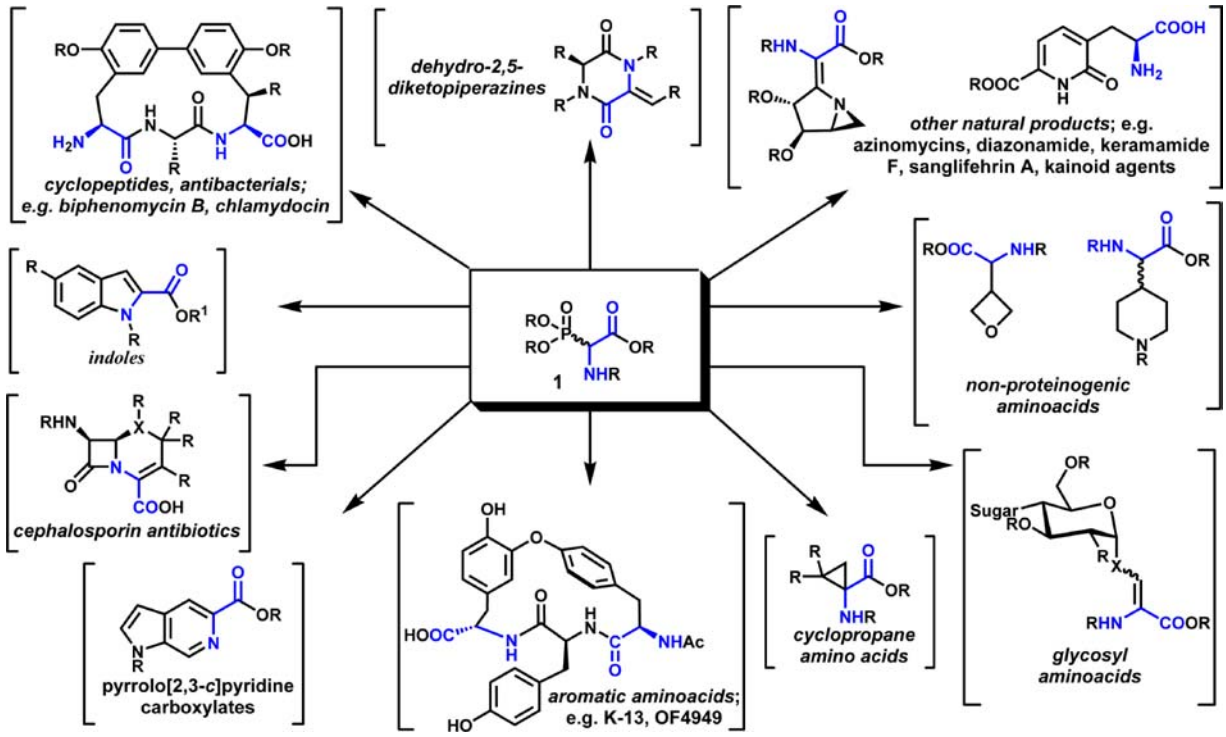


Figure 1. Representative reported derivatizations and applications of Schmidt's phosphinyl glycine ester.

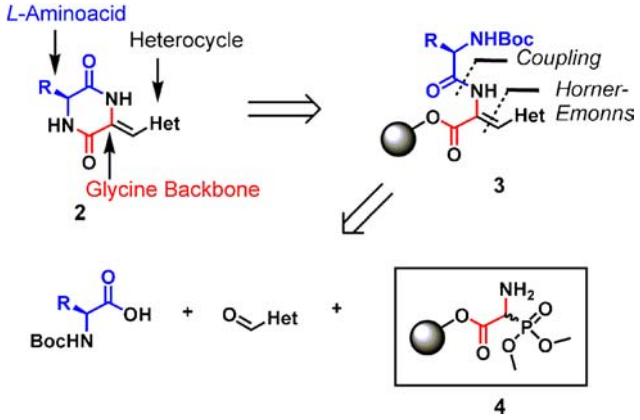


Figure 2. Retrosynthetic strategy for the library construction of dehydro-2,5-diketopiperazines.

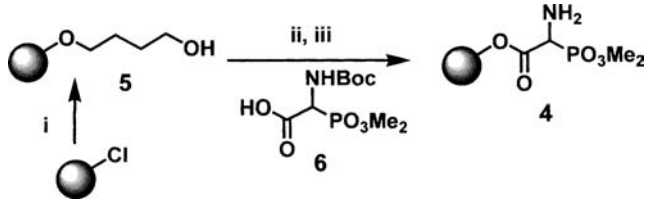


Figure 3. Preparation of the solid supported polymorphic scaffold **4**. Reagents and conditions: i) Merrifield resin (1 eq), 1,4-butanediol (5 eq), NaH (5 eq), imidazole (0.4 eq), Bu_4NI (0.4 eq), DMF 60 °C to 40 °C; ii) **6** (5 eq), DCC (5.5 eq), (4)-DMAP (0.5 eq), CH_2Cl_2/DMF (4:1), 0 °C to r.t.; iii) (+)-CSA (11 eq), CH_2Cl_2, 0 °C to r.t.

leads to supported ester **3**. The additional advantage of this design is traceless cleavage from the resin at the final step, since, after deprotection of the terminal amine, concomitant intramolecular amidation and cleavage are predicted. On the basis of our solution chemistry experience [28], intermediate **3** is further retrosynthetically disconnected into two components, the parent amino acid and heterocyclic aldehyde moieties, leaving solid supported phosphonate **4** as the required starting material.

To validate our design, the synthesis of naturally occurring dehydro-diketopiperazines (–)-Phenylhistine (**16**) and (–)-Aurantiamine (**17**) was initially attempted in a parallel fashion [29]. Extended Merrifield resin (**5**)[1] [30] (Figure 3) was coupled with known acid **6** [2]. Both our previous experience and experimentation on the solid-phase revealed Boc as the optimum *L*-amino acid *N*-protective group. Although the attempted TFA deprotection caused substantial ester cleavage, CSA treatment resulted in successful deprotection affording the target molecule loaded and ready for amide coupling. Loading and deprotection were tested using the ninhydrin test [31, 32] and the yield was found to be more than 90%.

Coupling of **4** was then performed with suitably *N*-protected *L*-amino acids, relevant to the target natural products, Boc-L-Phe-OH (**7**) and Boc-L-Val-OH (**8**) by means of EDC·HCl/HOBt conditions (Figure 4).

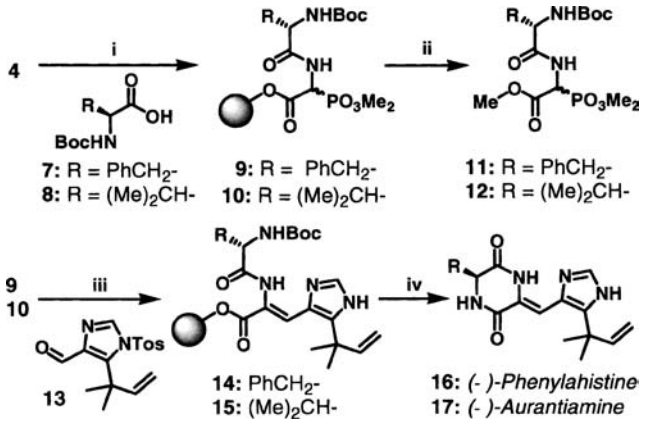


Figure 4. Solid-phase synthesis of the naturally occurring dehydro-2,5-diketopiperazines: (–)-Phenylhistine, (–)-Aurantiamine. Reagents and conditions: (i) **7** or **8** (4.5 eq), HOBt (6eq), EDC·HCl (6 eq), Et_3N (1.3 eq), CH_2Cl_2, r.t. (ii) NaOMe (2.5 eq), MeOH/THF (1:1). (iii) **13** (3 eq), DBU (3 eq), CH_2Cl_2, 0 °C to r.t. (iv) (+)-CSA (11 eq), CH_2Cl_2, r.t. then Et_3N (20 %), CH_2Cl_2, r.t.

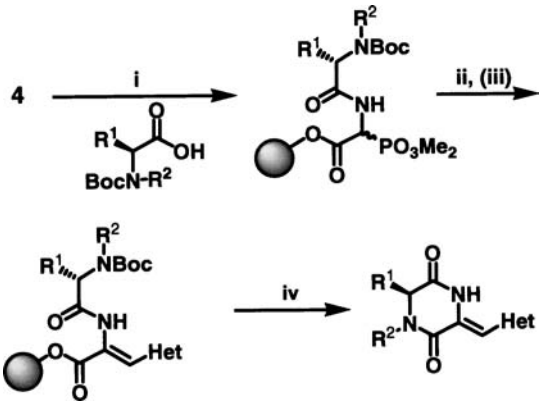


Figure 5. General reaction sequence followed for the preparation of the dehydro-2,5-diketopiperazines' library. Reagents and conditions: i) protected *L*-amino acid (4.5 eq), HOBt (6eq), EDC·HCl (6 eq), Et_3N (1.3 eq), CH_2Cl_2, r.t.. ii) Heterocyclic carboxaldhyde (3 eq), DBU (3 eq), CH_2Cl_2, 0 °C to r.t.. iii) Only for *N*-*p*-toluenesulfonyl indolyl and 4-methyl-imidazolyl entries. Sublibrary A: TBAF (1M in THF; 3 eq), CH_2Cl_2, r.t.; Sublibrary B: TBAF (1M in THF, 4 eq), CH_3CN/toluene (4:1), 60 °C. (iv) (+)-CSA (11 eq), CH_2Cl_2, r.t. then Et_3N (20 %), CH_2Cl_2, r.t.; Wherein For R^1, R^2, Het see entries at Tables 1 and 2.

Transesterification of loaded esters **9** and **10** with sodium methoxide afforded cleaved esters **11** and **12**, allowing a mass balance evaluation of the preparation progress. Finally, the mild Horner–Emmons conditions previously developed and optimized [28] were applied on resins **9** and **10**, to load the heterocyclic moiety and synthesize the fully functionalized intermediates **14** and **15**. Acid and base treatment of the latter resins afforded dehydro-2,5-diketopiperazines **16** and **17**, which were found to be the natural products (–)-Phenylhistine and (–)-Aurantiamine, respectively. Presumably *N*-tosyl-deprotection took place simultaneously with olefin formation [28] allowing the target compounds to be cleanly isolated in their final free form in excellent chemical yields and optical purities. To summarize, the full elaboration of the library required only five operations. Theoretically, the minimum number of steps required for a doubly diversified library is four (i.e., loading, first derivatization, second derivatization, cleavage). This scheme combines diversity with accessibility and speed, which makes this scaffold suitable for automated parallel synthesis and combinatorial chemistry.

In order to test the applicability of this method in preparing dehydro-2,5-diketopiperazines from combinations of various *L*-amino acids with diverse heterocycles, the right choice of protective groups had first to be considered. Regarding aromatic *N*-heterocycles and in the particular cases of methyl-imidazoles and indoles, complications and resistance of *N*-tosyl alkaline deprotection were previously identified in our earlier work [28]. TBAF-mediated cleavage of the sulfonyl amide before removal of the *N*-Boc terminal group and subsequent amidation were found to be the optimum conditions. Consequently, the above-described solid-phase approach had to be modified by inserting an additional deprotection step after the Horner–Emmons coupling. Any additional functionalities present within the *L*-amino acid part of the molecules were equally carefully masked. Histidine's imidazole moiety was Boc-protected, aiming for simultaneous deprotection with the terminal *N*-Boc, whereas *L*-serine's hydroxyl group was silylated before use.

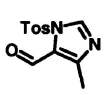
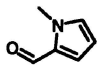
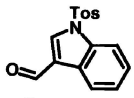
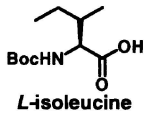
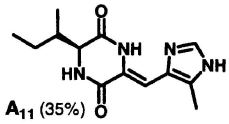
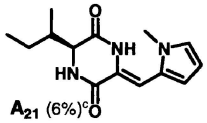
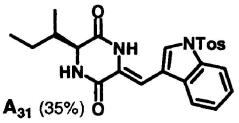
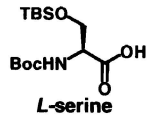
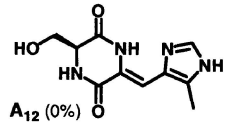
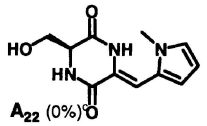
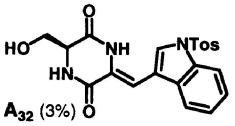
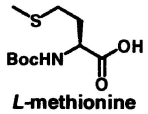
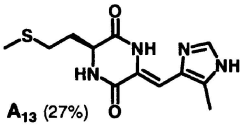
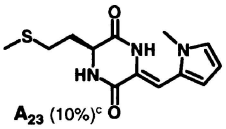
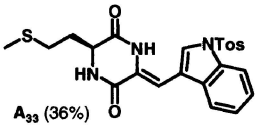
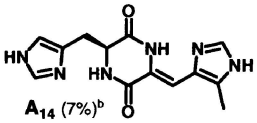
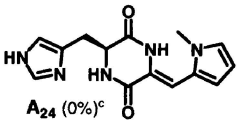
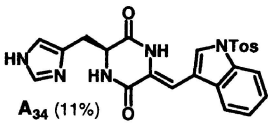
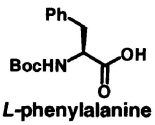
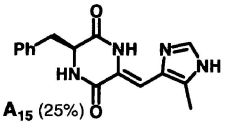
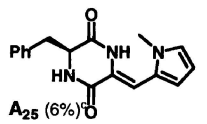
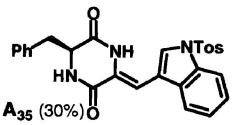
The formation of the library was attempted in two separate runs (Figure 5). As is depicted in Table 1 (Sublibrary A), the final overall yields obtained in the first attempt were relatively high with all *L*-amino acids except for the serine analogues. The observed low yields of *N*-methyl-pyrrole diketopiperazines were attributed to the insufficient basicity of the applied conditions during the final amidation-cleavage step. Indeed, after subsequent treatment of this set of resins with a solution of DBU, additional amount of the related diketopiperazines were derived. Surprisingly, all indole diketopiperazines were derived exclusively in their protected form. In an effort to achieve generally optimum conditions for all entries, in the second run (Table 2, Sublibrary B), harsher conditions were applied in the TBAF step. In this case, indole analogues were derived in free form, apart from the glycine entry, in which all examples gave low yields.

Exclusive formation of the *Z* double bond was observed in all cases except *L*-proline analogues.[2] The purity of the derived compounds was relatively high, requiring only a small column filtration (Table 3). Careful chromatographic purification was needed in the cases of *L*-serine and glycine sets, and for the separation of *L*-proline isomers.

Conclusion

Polymorphic key-intermediate Schmidt's phosphonate **1** has been prepared in solid-supported form. Employing this new building block, we have developed a methodology for the

Table 1. Sublibrary A. Diversity set of Dehydro-2,5-Diketopiperazines

SUBLIBRARY A Compound (yield %)[a]			
 *L*-isoleucine	 A_{11} (35%)	 A_{21} (6%)[c]	 A_{31} (35%)
 *L*-serine	 A_{12} (0%)	 A_{22} (0%)[c]	 A_{32} (3%)
 *L*-methionine	 A_{13} (27%)	 A_{23} (10%)[c]	 A_{33} (36%)
 *L*-histidine	 A_{14} (7%)[b]	 A_{24} (0%)[c]	 A_{34} (11%)
 *L*-phenylalanine	 A_{15} (25%)	 A_{25} (6%)[c]	 A_{35} (30%)

[a]Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.
[b]The tosylated analogue was also isolated in 15% yield.
[c]Product yields before DBU treatment.

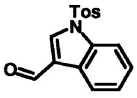
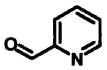
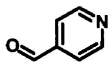
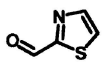
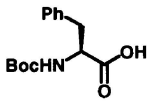
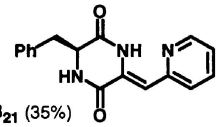
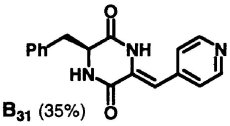
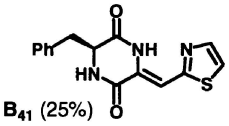
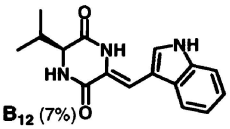
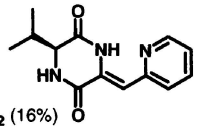
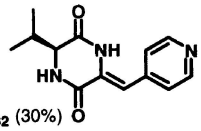
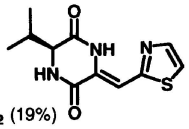
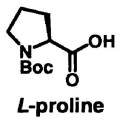
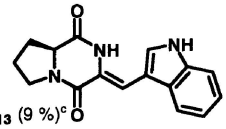
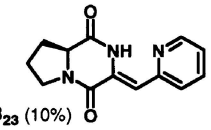
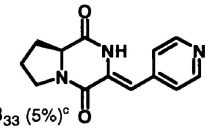
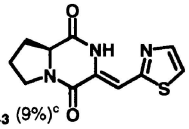
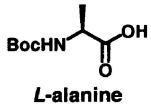
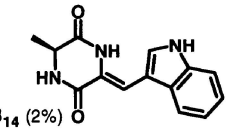
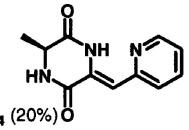
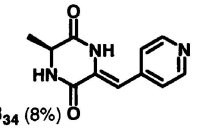
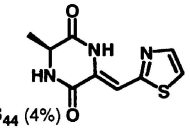
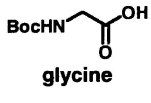
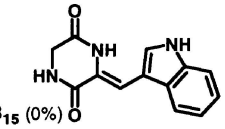
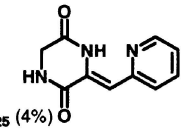
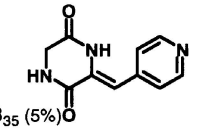
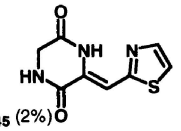
solid-phase synthesis of dehydro-2,5-diketopiperazines, displaying diversity at the two possible positions of the main scaffold. The overall strategy is based on easily available precursors, gives moderate to good chemical purity and yields, and enables rapid parallel synthesis of a large number of diversified structures.

Experimental section

General methods

All reactions were carried out under anhydrous conditions and argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone and dichloromethane (CH_2Cl_2) distilled from CaH_2. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. Merrifield resin was obtained from NovaBiochem (1% DVB crosslinked, 100–200 mesh, 0.57 mmoles/g). All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}), using UV light as visualizing agent and ethanolic phosphomolybdic acid, *p*-anisaldehyde or ninhydrin solution and heat as developing agents. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker AMX-500 or AC-250 instruments. The following abbreviations were used to explain NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, br s = broad singlet. IR spectra were recorded on a Nicolet Magna system 550 FT-IR instruments. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Matrix-assisted (MALDI-FTMS) mass spectra were recorded on a PerSeptive Biosystems Voyager IonSpect mass spectrometer. 70-eV electron ionization (EI) was recorded on Finnigan MAT MS 70 spectrometer. Melting points (m.p.) were recorded on a Gallenkamp melting point apparatus and are uncorrected. An Advanced ChemTech PLS Organic Synthesizer was used for the preparation of the library.

Table 2. Sublibrary B. Diversity set of Dehydro-Diketopiperazines

SUBLIBRARY B Compound (yield %)[a]				
 *L*-phenylalanine	NA[b] B_{11}	 B_{21} (35%)	 B_{31} (35%)	 B_{41} (25%)
 *L*-valine	 B_{12} (7%)	 B_{22} (16%)	 B_{32} (30%)	 B_{42} (19%)
 *L*-proline	 B_{13} (9 %)[c]	 B_{23} (10%)	 B_{33} (5%)[c]	 B_{43} (9%)[c]
 *L*-alanine	 B_{14} (2%)	 B_{24} (20%)	 B_{34} (8%)	 B_{44} (4%)
 glycine	 B_{15} (0%)	 B_{25} (4%)	 B_{35} (5%)	 B_{45} (2%)

[a]Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.
[b]NA = Not Applied.
[c]Isolated as a mixture of E/Z isomers of a ratio ~1:1.

Preparation of the phosphinyl glycine resin 4

To a solution of NaH (684 mg, 28.5 mmoles; 5eq) in anhydrous DMF (100 mL) under argon at 0 °C, a catalytic amount of imidazole (156 mg, 2.27 mmoles; 0.4 eq) and 1,4 butanediol (2.5 mL, 0.0285 moles; 5 eq) were added. The ice-bath was removed and the reaction mixture was heated to 60 °C for 4 h. The reaction mixture was then cooled to room temperature. Subsequently, Merrifield resin (0.57 mmoles/g, 10 g; 1 eq) and *t*-BuNI (831 mg, 2.3 mmoles; 0.4 eq) were added and the mixture was shaken for 30 min. After shaking at 40 °C for 12 h, the resin was filtered and washed sequentially with CH_2Cl_2(2 × 40 mL), MeOH (2 × 40 mL), 1N HCl (50 mL), MeOH (2 × 40 mL), CH_2Cl_2 (2 × 40 mL), MeOH (2 × 20 ml). The alcohol resin was dried under vacuum overnight. FTIR (KBr): $\tilde{V}_{max}$ 3589, 3445, 3090, 3063, 3026, 2933, 2854, 1950, 1880, 1810, 1747, 1680, 1602, 1491, 1360, 1185, 1105, 1030, 910, 844 cm^{-1}.

Alcohol resin (0.54 mmoles/g, 9.316 g) was suspended in a 4:1 mixture of CH_2Cl_2/DMF (251 mL) under argon and shaken for 20 min at 25 °C. *t*-Butoxycarbonyl-amino-2-dimethoxyphosphinyl-acetic acid (**7**) (7.12 g, 25.1 mmoles; 5 eq) was added and the solution was cooled at 0 °C. DCC (5.71 g, 27.6 mmoles; 5.5 eq) and a catalytic amount of (4)-DMAP (307.1 mg, 2.5 mmoles; 0.5 eq) were successively added to the suspension. The mixture was shaken at 0 °C for 2 days, then filtered, and washed sequentially with CH_2Cl_2 (2 × 50 mL), MeOH (2 × 50 mL), hot H_2O (2 × 50 mL), CH_2Cl_2 (2 × 50 mL), MeOH (2 × 50 mL), CH_2Cl_2 (2 × 50 mL), MeOH (2 × 50 mL). The phosphinyl resin was dried under vacuum for 24 h. FTIR: (KBr): $\tilde{V}_{max}$ 3653, 3446, 3069, 3032, 2928, 2848, 1948, 1872, 1811, 1755, 1722, 1608, 1500, 1457, 1373, 1269, 1156, 1029, 845, 817, 751 cm^{-1}.

The phosphinyl-glycine resin (theoretical loading: 0.46 mmoles/g) was suspended in anhydrous CH_2Cl_2. An excess of (+)-CSA (11 eq) was added and the suspension was shaken at 25 °C for 2 days under argon atmosphere. The resin was filtered and washed sequentially with CH_2Cl_2 (2 × 40 ml), MeOH (40 ml), CH_2Cl_2 (2 × 40 ml) to afford the sensitive resin **4**, which was used immediately to the next step.

Table 3. Chemical yields, optical rotation and unit masses of the components of libraries A and B

Entry	Yield[a]	$[\alpha]_D^{25}$ (c; solv.)	Mass (calcd.)	Entry	Yield[a]	$[\alpha]_D^{25}$ (c; solvent)	Mass (calcd.)
A_{11}	35%	−34.5 (0.19; $CHCl_3$)	263.1499 (263.1502)[b]	B_{14}	2%	–	256.10 (256.10)[b]
A_{12}	0%	–	–	B_{15}	0%	–	–
A_{13}	27%	−9.8 (0.15; $CHCl_3$)	281.1066 (281.1067)[b]	B_{21}	35%	−83.0 (0.28; $CHCl_3$)	316.11 (316.11)[c]
A_{14}	15%	–	441.1331 (441.1339)[b]	B_{22}	16%	−94.6 (0.82; $CHCl_3$)	246.1243 (246.1244)[b]
A_{15}	25%	– 168.1 (0.21; DMSO)	319.1163 (319.1165)[c]	B_{23}	10%	+ 2.1 (0.24; $CHCl_3$)	244.1086 (244.1088)[b]
A_{21}	6%	[d]	284 (284)[c]	B_{24}	20%	−3.1 (0.87; $CHCl_3$)	218.0927 (218.0931)[b]
A_{22}	0%	–	–	B_{25}	9%	–	
A_{23}	10%	–	280.1113 (280.1114)[b]	B_{31}	40%	−127.7 (0.13; MeOH)	300.08 (300.08)[b]
A_{24}	0%	–	–	B_{32}	39%	−402.9 (0.37; MeOH)	246.12 (246.12)[b]
A_{25}	6%	−11.6 (0.11; $CHCl_3$)	296.1389 (296.1393)[b]	B_{33}	5%	[d]	244.1087 (244.1088)[b]
A_{31}	69%	−190.0 (0.55; DMSO)	474.1460 (474.1458)[c]	B_{34}	8%	–	
A_{32}	3%	–	448 (448)[c]	B_{35}	5%	–	
A_{33}	36%	−29.3 (0.45; DMSO)	492.1023 (492.1022)[c]	B_{41}	25%	−16.3 (0.43; $CHCl_3$)	300.08 (300.08)[b]
A_{34}	11%	+ 7.5 (0.19; $CHCl_3$)	476.1394 (476.1387)[b]	B_{42}	19%	−55.8 (1.0; $CHCl_3$)	252.08 (252.08)[b]
A_{35}	30%	−107.2 (0.25; DMSO)	508.1298 (508.1301)[c]	B_{43}	9%	[d]	–
B_{12}	7%	−4.7 (0.38; DMSO)	283.1319 (283.1321)[e]	B_{44}	4%	+ 20 (0.14; $CHCl_3$)	246.03 (246.03)[c]
B_{13}	9%	[d]	–	B_{45}	2%	–	

[a] The overall yield refers to chromatographically and spectroscopically (^{1}H NMR) pure materials.
[b] Mass calculated for $[M+H]^+$.
[c] Mass calculated for $[M+Na]^+$.
[d] Isolated as a mixture of E/Z isomers at a ratio ∼1:1.
[e] Mass calculated for $[M]^+$.

General procedure for L-amino acids loading on the resin

Resin **4** was suspended in anhydrous CH_2Cl_2 under an argon atmosphere and the *N*-Boc protected *L*-amino acid (**8** or **9**; 4.5 eq) was added. An excess of HOBT (6 eq), EDC HCl (6 eq) and Et_3N (1.3 eq) were added and the suspension was shaken for 36 h at 25 °C. The resin (**10** or **11**) was filtered, washed sequentially with CH_2Cl_2 (2 × 30 mL), MeOH (2 × 30 mL), CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), and dried under vacuum for 24 h. The loading was estimated from the isolated yields of esters, **12** and **13**, after cleavage with MeONa (2.5 eq) in MeOH/THF 1:2. The resin was removed by filtration and washed sequentially with MeOH/THF (1:1), THF, MeOH, CH_2Cl_2, MeOH. The organic filtrate was evaporated *in vacuo* to provide **12** and **13** in 90% yield (based on loaded phosphonate **7**). Analysis of the product by ^{1}H NMR indicated that the products had a purity >90%.

General procedure for the Horner-Emmons reaction

The phosphinyl resin (**10** or **11**) was suspended in anhydrous CH_2Cl_2 (9 mL) under argon atmosphere. Aldehyde **14** (3 eq) was added and the suspension was cooled at 0 °C. An excess of DBU (124.9 μL, 0.836 mmoles; 3 eq) was added and the suspension was shaken at 25 °C for 36 h. The resin (**15** or **16**) was filtered, washed sequentially with CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), and dried under vacuum overnight.

*General procedure for deprotection and lactamidation/ cleavage. Preparation of: (–)-Phenylhistine **16** and (–)-Aurantiamine **17***

Resin **15** or **16** (theoretical: 0.209 mmoles) was suspended in anhydrous CH_2Cl_2 (10 mL) under an argon atmosphere. (+)-CSA (480 mg, 2.06 mmoles; 11 eq) was added at 25 °C and the mixture was shaken for 48 hours. The amine resin was filtered and washed sequentially with CH_2Cl_2 (2 × 20 mL), MeOH (20 mL), Et_3N (5% in CH_2Cl_2; 2 × 15 mL), CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL).

The above resin was suspended in anhydrous CH_2Cl_2 (7.2 mL) and an excess of Et_3N (1.8 mL; 20% in CH_2Cl_2) was added. The suspension was shaken for 36 h, filtered, and washed with CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), $CHCl_3$ (2 × 20 mL). The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (15 ml). The crude mixture was extracted with NH_4Cl (15 ml), brine (15 ml), dried over anhydrous Na_2SO_4, and concentrated under vacuum.

(–)-Phenylhistine (24 mg; 34%): $R_f = 0.39$ ($CHCl_3$/MeOH 9:1); m.p. 228–229 °C; $[\alpha]_D^{25} = -273$ (c = 0.1 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 12.00 (br s, 1H; CON*H*C=), 9.14 (br s, 1H; NH_{imid}), 7.55 (s, 1H; CH_{imid}), 7.42–7.19 (m, 5H, *Ph*), 6.88 (s, 1H; C=C*H*-Imid), 6.02 (dd, ^3J(H,H) = 17.5, 10.8 Hz, 1H; C*H*=CH_2), 5.76 (br s, 1H; CHN*H*CO), 5.20 (d, ^3J(H,H) = 10.8 Hz, 1H; CH=C*H*H), 5.15 (d, ^3J(H,H) = 17.5 Hz, 1H; CH=CH*H*), 4.34 (ddd, ^3J(H,H) = 10.1, 3.4, 2.3 Hz, 1H; C*H*CH_2Ph), 3.50

(dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 3.4 Hz, 1H; C*H*HPh), 2.95 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 10.1 Hz, 1H; CH*H*Ph), 1.50 (s, 6H; *Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 164.7, 159.9, 144.6, 136.6, 135.5, 132.4, 132.2, 129.5, 129.1, 127.5, 123.8, 113.5, 105.4, 57.2, 41.3, 37.6, 27.9 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3434, 2961, 2928, 1651, 1452, 1391, 1277 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{20}H_{22}N_4O_2$ ($[M+H]^+$): m/z 351.1815; found 351.1825.

(–)-Aurantiamine (22 mg; 35%): R_f = 0.39 ($CHCl_3$/MeOH 9:1); m.p. 236–237 °C; $[\alpha]_D^{25} = -95$ (c = 0.1 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 12.05 (br s, 1H; CONHC=), 9.37 (br s, 1H; N*H*$_{imid}$), 7.55 (s, 1H; C*H*$_{imid}$), 6.94 (s, 1H; C=C*H*-Imid), 6.19 (br s, 1H; CHN*H*CO), 6.04 (dd, ^3J(H,H) = 10.6, 17.7Hz, 1H; C*H*=CH_2), 5.19 (d, ^3J(H,H) = 10.5 Hz, 1H; CH=C*H*H), 5.16 (d, ^3J(H,H) = 17.4 Hz, 1H; CH=CH*H*), 4.06 (t, ^3J(H,H) = 2.3 Hz, 1H; C*H*CHMe$_2$), 2.57–2.38 (m, 1H; C*H*Me$_2$), 1.51 (s, 6H; C(*Me*)$_2$), 1.06 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*), 0.96 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 165.1, 160.7, 144.7, 136.7, 132.5, 132.3, 123.7, 113.3, 105.2, 61.2, 37.6, 32.9, 27.9, 18.7, 15.7 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3405, 2958, 2921, 2866, 1738, 1674, 1641, 1443 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{16}H_{17}N_3O_2$ ($[M+H]^+$): m/z 303.1815; found 303.1813.

General procedure for the preparation of dehydro-2, 5-diketopiperazine libraries

Dehydro-2,5-diketopiperazine libraries were synthesized on an Advanced ChemTech PLS organic synthesizer. *N*-Boc protected phosphinyl-glycine resin **4** (400–450 mg) was placed in each reactor and the synthesis was performed as described above. An additional deprotection step was applied after the Horner–Emmons reaction. The exact conditions for this step are described below.

General deprotection of the N-p-Toluenesulfonyl-group for Sublibrary A

To a suspension of the *N*-Tosyl protected resin in CH_2Cl_2 (9 mL) at 25 °C, TBAF (1M in THF; 0.62 mL, 0.826 mmoles; 3 eq) was added. The reaction was shaken for 12 h. The resin was filtered, washed sequentially with CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), and dried under vacuum overnight. Indole derivatives were unreactive under the above conditions.

General deprotection of the N-p-Toluenesulfonyl-group for Sublibrary B

To a suspension of the *N*-Tosyl protected resin in a 4:1 mixture of CH_3CN/toluene (9 mL) at 25 °C, TBAF (1M in THF; 0.83 mL, 0.835 mmoles; 4 eq) was added. The reaction was heated at 60 °C and shaken for 24 h. The resin was filtered, washed sequentially with CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), and dried under vacuum overnight.

Selected data of the synthesized dehydro-2, 5-diketopiperazines

A$_{11}$: R_f = 0.35 ($CHCl_3$/MeOH 9:1); m.p. 156–158 °C; ^{1}H NMR (250 MHz, CD_3OD, 25 °C): δ 7.64 (s, 1H; C*H*$_{imid}$), 6.68 (s, 1H; C=C*H*-Imid), 4.09 (d, ^3J(H,H) = 2.7 Hz, 1H; C*H*CH(CH$_3$)CH$_2$CH$_3$), 2.33 (s, 3H; *Me*$_{Imid}$), 2.07–1.89 (m, 1H; C*H*(CH$_3$)CH$_2$CH$_3$), 1.60–1.44 (m, 1H; C*H*HCH$_3$), 1.37–1.19 (m, 1H; CH*H*CH$_3$), 1.02 (d, ^3J(H,H) = 7.2 Hz, 3H; CHC*H*$_3$), 0.94 (d, ^3J(H,H) = 7.2 Hz, 3H; CH$_2$C*H*$_3$) ppm; ^{13}C NMR (62.9 MHz, CD_3OD, 25 °C): δ 167.2, 162.6, 135.7, 134.0, 129.9, 123.9, 105.9, 61.4, 42.2, 25.4 15.3, 12.1, 9.1 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3190, 3129, 3073, 2961, 2919, 2878, 1664, 1637, 1450, 1386, 1359, 1268, 1245, 1199, 952, 872, 815, 754 cm^{-1}.

A$_{13}$: R_f = 0.25 ($CHCl_3$/MeOH 9:1); m.p. 207–209 °C; ^{1}H NMR (250 MHz, MeOD, 25 °C): δ 7.65 (s, 1H; C*H*$_{imid}$), 6.70 (s, 1H; C=C*H*-Imid), 4.34 (t, ^3J(H,H) = 5.3 Hz, 1H; C*H*CH$_2$CH$_2$SCH$_3$), 2.65–2.55 (m, 2H; C*H*$_2$SCH$_3$), 2.34 (s, 3H; *Me*$_{Imid}$), 2.25–2.12 (m, 2H; C*H*$_2$CH$_2$SCH$_3$), 2.09 (s, 3H; SC*H*$_3$) ppm; ^{13}C NMR (62.9 MHz, CD_3OD, 25 °C): δ 169.2, 167.4, 135.7, 133.5, 132.3, 129.8, 106.1, 59.4, 34.7, 29.6, 20.6, 9.1 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3180, 3066, 2960, 2925, 2858, 1735, 1684, 1637, 1460, 1381, 1349, 1286, 1204, 1081, 956, 826 cm^{-1}.

A$_{14}$: R_f = 0.45 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (250 MHz, CD_3OD 25 °C): δ 8.05 (br s, 1H; CONHC=), 7.81 (d, ^3J(H,H) = 8.4 Hz, 2H; C*H*$_{Tos}$), 7.64 (s, 1H; CH$_{imid}$), 7.37–7.28 (m, 3H; C*H*$_{Tos}$, CH$_{imid}$), 6.49 (s, 1H; C=C*H*-Imid), 4.45 (t, ^3J(H,H) = 4.8 Hz, 1H; C*H*CH$_2$), 3.38 (dd, ^2J(H,H) = 14.9 Hz, ^3J(H,H) = 4.9 Hz, 1H; CHC*H*H) 3.03 (dd, ^2J(H,H) =14.9 Hz, ^3J(H,H) = 4.6 Hz, 1H; CHCH*H*), 2.36 (s, 3H; *Me*$_{imid}$), 2.31 (s, 3H; *Me*$_{Tos}$) ppm; FTIR (KBr): $\tilde{V}_{max}$ 2960, 2925, 2876, 2856, 1732, 1669, 1449, 1384, 1287, 1180, 1124, 1078, 677 cm^{-1}.

A$_{15}$: R_f = 0.28 ($CHCl_3$/MeOH 9:1); m.p. 283–284 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ 11.48 (br s, 1H; CON*H*C=), 8.32 (br s, 1H; N*H*$_{imid}$), 7.74 (s, 1H; C*H*$_{imid}$), 7.24–7.14 (m, 5H; *Ph*), 6.21 (s, 1H; C=C*H*-Imid), 4.49–4.45 (m, 1H; C*H*CH$_2$Ph), 3.33 (br s, 1H; CHN*H*CO), 3.20 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 4.2 Hz, 1H; C*H*HPh), 2.94 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 4.8 Hz, 1H; CH*H*Ph), 2.19 (s, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, 25 °C): δ 164.2, 158.9, 135.6, 134.6, 132.5, 130.1, 130.0, 128.0, 127.8, 127.5, 126.6, 123.4, 101.6, 55.9, 38.7, 9.1 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3397, 3180, 2961, 2931, 2880, 2859, 1736, 1680, 1446, 1287 cm^{-1}.

A$_{23}$: R_f = 0.45 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (250 MHz, CD_3OD, 25 °C): δ 7.00–6.95 (m, 2H; C=C*H*-

Pyrrole, CH_{pyrrol}), 6.74–6.68 (m, 1H; CH_{pyrrol}), 6.36–6.30 (m, 1H; CH_{pyrrol}), 4.40 (t, ^3J(H,H) = 5.5 Hz, 1H; CHCH$_2$), 3.80 (s, 3H; NCH_3), 2.73 (t, ^3J(H,H) = 7.0 Hz, 2H; CH$_2$CH_2S), 2.38–2.19 (m, 2H; CHCH_2CH$_2$S), 2.19 (s, 3H; SCH_3) ppm.

A$_{25}$: R_f = 0.20 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 7.92 (br s, 1H; CONHC=), 7.37–7.26 (m, 5H; *Ph*), 6.77 (br m, 1H; CH_{pyrrol}), 6.75 (s, 1H; C = CH-Pyrrole), 6.40 (br m, 1H; CH_{pyrrol}), 6.28 (br m, 1H; CH_{pyrrol}), 5.75 (br s, 1H; CHNHCO), 4.46–4.38 (m, 1H; CHCH$_2$Ph), 3.66 (s, 3H; NCH_3), 3.44 (dd, ^2J(H,H) = 14.1 Hz, ^3J(H,H) = 3.2 Hz, 1H; CHHPh), 3.02 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 9.1 Hz, 1H; CHHPh) ppm.

A$_{31}$: R_f = 0.45 (CHCl$_3$/MeOH 9:1); m.p. 228–230 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 10.21 (br s, 1H; CONHC=), 8.54 (s, 1H; CONHCH), 8.34 (s, 1H; C = CHN(Tos)$_{\text{indole}}$), 7.97 (d, ^3J(H,H) = 7.5 Hz, 2H; CH_{Tos}), 7.90 (d, ^3J(H,H) = 8.0 Hz, 1H; CH_{indole}), 7.66 (d, ^3J(H,H) = 7.5 Hz, 1H; CH_{indole}), 7.39 (d, ^3J(H,H) = 8.0 Hz, 2H; CH_{Tos}), 7.40–7.27 (m, 2H; CH_{indole}), 6.81 (s, 1H; C = CH-Indole), 3.95 (br s, 1H; CHCH(Me)CH$_2$CH$_3$), 2.31 (s, 3H; *Me*$_{\text{Tos}}$), 1.90–1.80 (m, 1H; CH(Me)CH$_2$CH$_3$), 1.54–1.43 (m, 1H; CHHCH$_3$), 1.28–1.15 (m, 1H; CHHCH$_3$), 0.93 (d, ^3J(H,H) = 5.7 Hz, 3H; CHCH_3), 0.87 (t, ^3J(H,H) = 6.8 Hz, 3H; CH$_2$CH_3) ppm; ^{13}C NMR (125.8 MHz, [D$_6$]DMSO, 25 °C): δ 167.4, 160.8, 146.5, 134.8, 134.4, 131.1, 130.7, 128.1, 127.9, 126.5, 126.2, 124.7, 120.3, 115.1, 113.9, 103.8, 60.6, 41.1, 25.1, 21.9, 15.7, 12.5 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3199, 3065, 2963, 2927, 2880, 1672, 1636, 1446, 1383, 1176, 1126, 1099, 980, 810, 746, 680 cm^{-1}.

A$_{32}$: R_f = 0.15 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, [D$_3$]CD$_3$CN, 25 °C): δ 7.98 (d, ^3J(H,H) = 8.6 Hz, 1H; CH_{indole}), 7.87 (s, 1H; C = CHN(Tos)$_{\text{indole}}$), 7.86 (d, ^3J(H,H) = 8.0 Hz, 2H; CH_{Tos}), 7.61 (d, ^3J(H,H) = 8.0 Hz, 1H; CH_{indole}), 7.43–7.29 (m, 5H; CH_{indole}, CH_{Tos}, NH), 6.82 (s, 1H; C = CH-Indole), 6.47 (br s, 1H; CHNHCO), 4.12 (q, 1H; CHCH$_2$OH), 3.92 (dd, ^3J(H,H) = 2.9 Hz, ^2J(H,H) = 11.5 Hz, 1H; CHHOH), 3.74 (dd, ^3J(H,H) = 2.9 Hz, ^2J(H,H) = 11.5 Hz, 1H; CHHOH), 2.34 (s, 3H; *Me*$_{\text{Tos}}$) ppm.

A$_{33}$: R_f = 0.55 (CHCl$_3$/MeOH 9:1); m.p. 237–239 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 10.22 (br s, 1H; CONHC=), 8.59 (s, 1H; CONHCH), 8.35 (s, 1H; C = CHN(Tos)$_{\text{indole}}$), 7.97 (d, ^3J(H,H) = 7.5 Hz, 2H; CH_{Tos}), 7.66 (d, ^3J(H,H) = 8.0 Hz, 1H; CH_{indole}), 7.40 (d, ^3J(H,H) = 8.0 Hz, 2H; CH_{Tos}), 7.40–7.35 (m, 1H; CH_{indole}), 7.31 (t, ^3J(H,H) = 7.5 Hz, 1H; CH_{indole}), 6.80 (s, 1H; C = CH-Indole), 4.22 (br t, ^3J(H,H) = 5.7 Hz, 1H; CHCH$_2$CH$_2$S), 2.64–2.53 (m, 2H; CH$_2$CH_2S), 2.32 (s, 3H; *Me*$_{\text{Tos}}$), 2.06–1.98 (m, 2H; CHCH_2CH$_2$S), 2.05 (s, 3H; S*Me*) ppm; ^{13}C NMR (125.8 MHz, [D$_6$]DMSO, 25 °C): δ 167.0, 159.9, 145.7, 134.0, 133.6, 130.3, 129.9, 127.2, 127.1, 125.9, 125.3, 123.8, 119.5, 114.2, 113.1, 103.3, 53.9, 33.1, 28.5, 21.1, 14.5 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3190, 3057, 2924, 2880, 1666, 1628, 1442, 1404, 1370, 1285, 1175, 1140, 1095, 975, 809, 761 cm^{-1}.

A$_{34}$: R_f = 0.55 (CHCl$_3$/MeOH 9:1); m.p. 146–149 °C; ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 8.09 (br s, 1H; CONHC=), 8.03 (d, ^3J(H,H) = 8.0 Hz, 1H; CH_{indole}), 7.97 (s, 1H; C = CHN(Tos)$_{\text{indole}}$), 7.83 (d, ^3J(H,H) = 8.0 Hz, 2H; CH_{Tos}), 7.77 (s, 1H; NCHN), 7.57 (d, ^3J(H,H) = 7.5 Hz, 1H; CH_{indole}), 7.44–7.19 (m, 7H; CH_{ar}, NH), 6.94 (s, 1H; C = CH-Indole), 4.52 (d, ^3J(H,H) = 8.6 Hz, 1H; CHCH$_2$), 3.34 (d, ^2J(H,H) = 14.9 Hz, 1H; CHCHH), 3.00 (dd, ^2J(H,H) = 14.9 Hz, ^3J(H,H) = 9.2 Hz, 1H; CHCHH), 2.36 (s, 3H; *Me*$_{\text{indole}}$) ppm; ^{13}C NMR (125.8 MHz, CDCl$_3$, 25 °C): δ 165.1, 158.9, 146.5, 145.5, 139.5, 136.6, 134.8, 130.5, 130.1, 128.3, 127.4, 126.9, 125.8, 124.3, 123.9, 119.9, 115.2, 113.7, 106.0, 55.2, 31.8, 21.6 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3219, 3130, 2929, 2856, 1692, 1645, 1602, 1453, 1380, 1179, 1145, 1100, 978, 914, 819, 734, 678, 588 cm^{-1}.

A$_{35}$: R_f = 0.36 (CHCl$_3$/MeOH 9:1); m.p. 225–227 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 10.03 (br s, 1H; CONHC=), 8.52 (br s, 1H; CONHCH), 8.02 (s, 1H; C = CHN(Tos)$_{\text{indole}}$), 7.93 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_{Tos}), 7.86 (d, ^3J(H,H) = 8.0 Hz, 1H; CH_{indole}), 7.45–7.38 (m, 3H; CH_{indole}, CH_{Tos}), 7.36 (dd, ^3J(H,H) = 8.0, 6.9 Hz, 1H; CH_{indole}), 7.27 (dd, ^3J(H,H) = 8.0, 7.5 Hz, 1H; CH_{indole}), 7.21–7.16 (m, 5H; *Ph*), 6.45 (s, 1H; C = CH-Indole), 4.43 (m, 1H; CHCH$_2$Ph), 3.18 (dd, ^3J(H,H) = 4.0 Hz, ^2J(H,H) = 13.8 Hz, 1H; CHHPh), 2.98 (dd, ^3J(H,H) = 4.6 Hz, ^2J(H,H) = 13.8 Hz, 1H; CHHPh), 2.32 (s, 3H; *Me*$_{\text{Tos}}$) ppm; ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, 25 °C): δ 167.2, 160.5, 146.5, 136.2, 134.9, 134.4, 131.1, 130.9, 130.6, 128.9, 127.9, 127.8, 127.6, 126.3, 126.0, 124.5, 134.4, 120.5, 115.1, 113.9, 103.6, 57.1, 21.9 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3196, 3066, 3035, 2922, 2849, 1674, 1636, 1604, 1446, 1373, 1170, 1122, 1099, 978, 814, 761 cm^{-1}.

B$_{12}$: R_f = 0.42 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ 11.62 (br s, 1H; NH_{indole}), 9.48 (br s, 1H; CONHC=), 8.30 (br s, 1H; CONHCH), 7.91 (d, ^3J(H,H) = 2.1 Hz, 1H; C = CHNH$_{\text{indole}}$), 7.63 (d, ^3J(H,H) = 7.0 Hz, 1H; CH_{indole}), 7.42 (d, ^3J(H,H) = 7.4 Hz, 1H; CH_{indole}), 7.22–7.04 (m, 2H; CH_{indole}), 6.98 (s, 1H; C = CH-Indole), 3.77 (t, ^3J(H,H) = 3.3 Hz, 1H; CHCH(Me)$_2$), 2.57–2.47 (m, 1H; CH(Me)$_2$), 0.95 (d, ^3J(H,H) = 7.0 Hz, 3H; *Me*), 0.88 (d, ^3J(H,H) = 7.0 Hz, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, 25 °C): δ 166.2, 161.1, 135.6, 126.9, 126.3, 122.5, 122.0, 119.8, 118.0, 111.8, 107.9, 107.3, 60.7, 33.3, 18.3, 17.1 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3415, 2965, 2932, 2851, 1742, 1676, 1657, 1463, 1434, 1387 cm^{-1}.

B$_{14}$: R_f = 0.37 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 11.64 (br s, 1H; NH_{indole}), 9.43 (br s, 1H; CONHC=), 8.25 (s, 1H; CONHCH), 7.94 (s, 1H; C = CHNH$_{\text{indole}}$), 7.63 (d, ^3J(H,H) = 7.8 Hz, 1H; CH_{indole}), 7.43 (d, ^3J(H,H) = 7.8 Hz, 1H; CH_{indole}), 7.17 (t, ^3J(H,H) = 7.3 Hz, 1H; CH_{indole}),7.10 (t, ^3J(H,H) = 7.3

Hz, 1H; CH_{indole}), 6.99 (s, 1H; C=CH-Indole), 4.16–4.10 (m, 1H; CHCH$_3$), 1.35 (d, ^3J(H,H) = 6.9 Hz, 3H; *Me*) ppm.

B$_{21}$: R_f = 0.50 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 12.62 (br s, 1H; CONHC=), 8.61 (d, ^3J(H,H) = 4.4 Hz, 1H; CH_{pyrid}), 7.71 (ddd, ^4J(H,H) = 1.9 Hz, ^3J(H,H) = 7.9, 7.9 Hz, 1H; CH_{pyrid}), 7.36–7.23 (m, 5H; Ph), 7.31 (d, ^3J(H,H) = 7.6 Hz, 1H; CH_{pyrid}), 7.19 (dd, ^3J(H,H) = 7.2, 5.2 Hz, 1H; CH_{pyrid}), 6.65 (s, 1H; C=CH-Pyridine), 6.04 (br s, 1H; CHNHCO), 4.41 (ddd, ^3J(H,H) = 2.3, 3.2, 9.2 Hz, 1H; CHCH$_2$Ph), 3.49 (dd, ^2J(H,H) = 13.9 Hz, ^3J(H,H) = 3.6 Hz, 1H; CHHPh), 3.01 (dd, ^2J(H,H) = 13.9 Hz, ^3J(H,H) = 9.5 Hz, 1H; CHHPh) ppm; ^{13}C NMR (125.7 MHz, CDCl$_3$, 25 °C): δ 164.9, 159.0, 154.7, 148.4, 137.0, 134.9, 129.5, 129.1, 128.8, 127.6, 126.0, 122.1, 109.0, 57.1, 41.2 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3437, 3205, 3087, 3061, 2961, 2926, 2852, 1735, 1693, 1645, 1593, 1463, 1435, 1388, 1345, 1292, 1100 cm^{-1}.

B$_{22}$: R_f = 0.37 (CH$_2$Cl$_2$/MeOH 95:5); ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 12.59 (br s, 1H; CONHC=), 8.61 (d, ^3J(H,H) = 4.1 Hz, 1H; CH_{pyrid}), 7.71 (ddd, ^4J(H,H) = 1.7 Hz, ^3J(H,H) = 7.7, 7.7 Hz, 1H; CH_{pyrid}), 7.33 (d, ^3J(H,H) = 7.9 Hz, 1H; CH_{pyrid}), 7.19 (ddd, ^4J(H,H) = 0.8 Hz, ^3J(H,H) = 4.9, 7.5 Hz, 1H; CH_{pyrid}), 6.75 (br s, 1H; CHNHCO), 6.72 (s, 1H; C=CH-Pyridine), 4.11 (t, ^3J(H,H) = 2.7 Hz, 1H; CHCH(CH$_3$)$_2$), 2.52–2.44 (m, 1H; CH(Me)$_2$), 1.09 (d, ^3J(H,H) = 7.1 Hz, 3H; *Me*), 0.97 (d, ^3J(H,H) = 6.8 Hz, 3H; *Me*) ppm; ^{13}C NMR (125.8 MHz, CDCl$_3$, 25 °C): δ 165.5, 160.0, 154.9, 148.4, 137.0, 130.1, 125.9, 122.0, 108.7, 61.2, 33.3, 18.6, 15.9 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3442, 3231, 3085, 3053, 2964, 2931, 2875, 2861, 1693, 1643, 1592, 1461, 1435, 1379, 1349, 1285, 1233, 918, 789, 742 cm^{-1}.

B$_{23}$: R_f = 0.50 (CHCl$_3$/MeOH 9:1); m.p. 190–193 °C; ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 12.54 (br s, 1H; CONHC=), 8.61 (br d, ^3J(H,H) = 3.8 Hz, 1H; CH_{pyrid}), 7.73–6.68 (m, 1H; CH_{pyrid}), 7.33 (d, ^3J(H,H) = 7.9 Hz, 1H; CH_{pyrid}), 7.18 (ddd, ^4J(H,H) = 0.9 Hz, ^3J(H,H) = 4.8, 7.4 Hz, 1H; CH_{pyrid}), 6.73 (s, 1H; C=CH-Pyridine), 4.31–4.16 (m, 1H; CHCH$_2$), 3.91–3.83 (m, 1H; NCHHCH$_2$), 3.67–3.59 (m, 1H; NCHHCH$_2$), 2.55–2.49 (m, 1H; CHCHHCH$_2$), 2.14–2.07 (m, 1H; CHCHHCH$_2$), 2.05–1.92 (m, 2H; CH$_2$CH_2CH$_2$) ppm; ^{13}C NMR (125.8 MHz, CDCl$_3$, 25 °C): δ 148.4, 136.9, 130.8, 125.9, 121.9, 108.6, 59.4, 45.7, 29.7, 21.6 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3056, 2957, 2921, 2849, 1733, 1682, 1625, 1591, 1456, 1409, 1382, 1353, 1278, 1263, 1244, 1120, 1075 cm^{-1}.

B$_{24}$: R_f = 0.20 (CH$_2$Cl$_2$/MeOH 95:5); m.p. 230–232 °C; ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 12.57 (br s, 1H; CONHC=), 8.62 (br d, ^3J(H,H) = 3.4 Hz, 1H; CH_{pyridin}), 7.72 (ddd, ^4J(H,H) = 1.7 Hz, ^3J(H,H) = 7.7, 7.7 Hz, 1H; CH_{pyridin}), 7.33 (d, ^3J(H,H) = 7.7 Hz, 1H; CH_{pyridin}), 7.19 (ddd, ^4J(H,H) = 0.9 Hz, ^3J(H,H) = 4.7, 7.3 Hz, 1H; CH_{pyridin}), 6.95 (br s, 1H; CHNHCO), 6.72 (s, 1H; C=CH-Pyridine), 4.36–4.30 (m, 1H; CHCH$_3$), 1.62 (d, ^3J(H,H) = 7.3 Hz, 3H; *Me*) ppm; ^{13}C NMR (125.8 MHz, CDCl$_3$, 25 °C): δ 166.3, 159.4, 154.8, 148.4, 137.3, 130.4, 125.9, 122.1, 108.9, 51.7, 21.2 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3426, 3059, 2919, 2850, 1693, 1646, 1593, 1442, 1386, 1337, 1306, 1237, 824 cm^{-1}.

B$_{25}$: R_f = 0.25 (CH$_2$Cl$_2$/MeOH 95:5); ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 12.71 (br s, 1H; CONHC=), 8.62 (d, ^3J(H,H) = 4.4 Hz, 1H; CH_{pyrid}), 7.72 (ddd, ^4J(H,H) = 1.5 Hz, ^3J(H,H) = 7.8, 7.8 Hz, 1H; CH_{pyrid}), 7.34 (d, ^3J(H,H) = 7.8 Hz, 1H; CH_{pyrid}), 7.21 (dd, ^3J(H,H) = 5.2, 6.9 Hz, 1H; CH_{pyrid}), 6.56 (s, 1H; C=CH-Pyridine), 6.03 (br s, 1H; CHNHCO), 4.27 (br d, ^3J(H,H) = 1.5 Hz, 2H; CH_2) ppm; ^{13}C NMR (125.8 MHz, CDCl$_3$, 25 °C): δ 148.4, 137.1, 130.9, 126.1, 122.2, 109.4, 45.6 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3190, 3156, 3050, 2958, 2925, 2851, 1733, 1704, 1646, 1467, 1450, 1435, 1387, 1288, 1079, 807, 741 cm^{-1}.

B$_{31}$: R_f = 0.31 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 10.06 (br s, 1H; CONHC=), 8.60 (br s, 1H; CHNHCO), 8.47 (d, ^3J(H,H) = 4.6 Hz, 2H; CH_{pyrid}), 7.25–7.08 (m, 7H; CH_{ar}), 6.21 (s, 1H; C=CH-Pyridine), 4.58 (t, ^3J(H,H) = 4.6 Hz, 1H; CHCH$_2$Ph), 3.16 (dd, ^2J(H,H) = 13.4 Hz, ^3J(H,H) = 3.1 Hz, 1H; CHHPh), 2.96 (dd, ^2J(H,H) = 12.8 Hz, ^3J(H,H) = 4.3 Hz, 1H; CHHPh) ppm; ^{13}C NMR (125.8 MHz, [D$_6$]DMSO, 25 °C): δ 167.1, 160.1, 150.4, 141.6, 135.9, 132.4, 131.0, 129.0, 127.7, 124.2, 111.0, 57.1, 46.4 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3196, 3147, 3062, 3029, 2964, 2936, 2879, 2854, 1735, 1686, 1633, 1442, 1357, 1291, 1124, 1030, 998, 822, 773 cm^{-1}.

B$_{32}$: R_f = 0.45 (CHCl$_3$/MeOH 9:1); m.p. 240–241 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 10.32 (br s, 1H; CONHC=), 8.66 (br s, 1H; CHNHCO), 8.56 (d, ^3J(H,H) = 5.0 Hz, 2H; CH_{pyrid}), 7.41 (d, ^3J(H,H) = 4.6 Hz, 2H; CH_{pyrid}), 6.62 (s, 1H; C=CH-Pyrid), 3.85 (br t, ^3J(H,H) = 3.2 Hz, 1H; CHCH(CH$_3$)$_2$), 2.18–2.08 (m, 1H; CH(CH$_3$)$_2$), 0.97 (d, ^3J(H,H) = 6.9 Hz, 3H; *Me*), 0.90 (d, ^3J(H,H) = 6.9 Hz, 3H; *Me*) ppm; ^{13}C NMR (125.8 MHz, CDCl$_3$, 25 °C): δ 166.5, 159.7, 149.8, 140.9, 129.9, 123.4, 110.6, 60.5, 33.5, 18.2, 16.9 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3205, 3068, 3040, 2967, 2850, 1687, 1630, 1602, 1441, 1397, 1361, 1183, 885 cm^{-1}.

B$_{33}$: Mixture of Z/E isomers (1:1); R_f = 0.43 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ 10.05 (br s, 1H; CONHC=), 8.40 (d, ^3J(H,H) = 5.6 Hz, 2H; CH_{pyrid}), 8.37 (d, ^3J(H,H) = 5.6 Hz, 2H; CH_{pyrid}), 7.47 (d, ^3J(H,H) = 5.5 Hz, 2H; CH_{pyrid}), 7.45 (d, ^3J(H,H) = 5.0 Hz, 2H; CH_{pyrid}), 6.14 (s, 1H; C=CH-Pyridine), 6.11 (s, 1H; C=CH-Pyridine), 4.43 (dd, ^3J(H,H) = 6.1, 9.2 Hz, 1H; CHCH$_2$), 4.13 (t, ^3J(H,H) = 5.5 Hz, 1H; CHCH$_2$), 3.77–3.65 (m, 2H; NCHHCH$_2$), 3.51–3.39 (m, 2H; NCHHCH$_2$), 2.45–2.20 (m, 4H; CHCH_2CH$_2$), 2.02–1.80 (m, 4H; CH$_2$CH_2CH$_2$N) ppm.

B$_{34}$: R_f = 0.25 (CHCl$_3$/MeOH 9:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ 10.19 (br s, 1H; CONHC=), 8.58 (s, 1H; CHNHCO), 8.54 (d, ^3J(H,H) = 5.2 Hz, 2H; CH_{pyrid}), 7.43 (d, ^3J(H,H) = 5.7 Hz, 2H; CH_{pyrid}), 6.59 (s, 1H;

C = C*H*-Pyrid), 4.18 (q, ^3J(H,H) = 6.5 Hz, 1H; C*H*CH$_3$), 1.35 (d, ^3J(H,H) = 6.9 Hz, 3H; *Me*) ppm.

B$_{41}$: R_f = 0.46 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.71 (br s, 1H; CON*H*C=), 7.92 (d, ^3J(H,H) = 3.2 Hz, 1H; C$H_{thiazol}$), 7.36 (d, ^3J(H,H) = 3.2 Hz, 1H; C$H_{thiazol}$), 7.35–7.23 (m, 5H; *Ph*), 6.78 (s, 1H; C = C*H*-Thiazol), 6.34 (br s, 1H; CHN*H*CO), 4.46–4.44 (m, 1H; C*H*CH$_2$Ph), 3.45 (dd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 3.6 Hz, 1H; C*H*HPh), 3.05 (dd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 9.1 Hz, 1H; CH*H*Ph) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 165.2, 163.1, 158.6, 143.7, 134.7, 129.6, 129.1, 127.7, 119.5, 102.5, 57.2, 41.1 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3431, 3185, 3082, 3059, 2938,. 2852, 1697, 1636, 1486, 1458, 1440, 1381, 1346, 735 cm^{-1}.

B$_{42}$: R_f = 0.40 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.74 (br s, 1H; CON*H*C=), 7.92 (d, ^3J(H,H) = 3.7 Hz, 1H; C$H_{thiazol}$), 7.36 (d, ^3J(H,H) = 3.2 Hz, 1H; C$H_{thiazol}$), 6.90 (br s, 1H; CHN*H*CO), 6.88 (s, 1H; C = C*H*-Thiazole), 4.13 (br t, ^3J(H,H) = 2.75 Hz, 1H; C*H*CH(CH$_3$)$_2$), 2.53–2.45 (m, 1H; C*H*(CH$_3$)$_2$), 1.10 (d, ^3J(H,H) = 7.3 Hz, 3H; *Me*), 0.97 (d, ^3J(H,H) = 6.9 Hz, 3H; *Me*) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 165.6, 163.3, 159.5, 144.2, 129.1, 119.4, 102.3, 61.4, 33.4, 18.5, 15.9 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3208, 3068, 3091, 2964, 2933, 2874, 1696, 1634, 1457, 1374, 1219, 1094, 920, 868 cm^{-1}.

B$_{43}$: Mixture of Z/E isomers (6:4); R_f = 0.27 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.68 (br s, 2H; CON*H*C=), 7.94 (d, ^3J(H,H) = 2.7 Hz, 1H; C$H_{thiazol}$), 7.92 (d, ^3J(H,H) = 2.7 Hz, 1H; C$H_{thiazol}$), 7.39 (d, ^3J(H,H) = 3.2 Hz, 1H; C$H_{thiazol}$), 7.37 (d, ^3J(H,H) = 3.2 Hz, 1H; C$H_{thiazol}$), 6.95 (s, 1H; C = C*H*-Thiazole), 6.91 (s, 1H; C = C*H*-Thiazole), 4.31 (dd, ^3J(H,H) = 6.4 Hz, 10.5 Hz 2H; C*H*CH$_2$), 3.96–3.79 (m, 2H; CH$_2$C*H*HN), 3.70–3.61 (m, 2H; CH$_2$CH*H*N), 2.58–2.22 (m, 4H; CHCH_2CH$_2$), 2.30–1.94 (m, 4H; CH$_2$CH_2CH$_2$N) ppm.

B$_{44}$: R_f = 0.35 (CH_2Cl_2/MeOH 95:5); m.p. 210–214 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.70 (br s, 1H; CON*H*C=), 7.93 (d, ^3J(H,H) = 3.7 Hz, 1H; C$H_{thiazol}$), 7.38 (d, ^3J(H,H) = 3.2 Hz, 1H; C$H_{thiazol}$), 6.89 (s, 1H; C = C*H*-Thiazole), 6.39 (br s, 1H; CHN*H*CO), 4.34 (dq, ^3J(H,H) = 1.3, 6.8 Hz, 1H; C*H*CH$_3$), 1.62 (d, ^3J(H,H) = 6.9 Hz, 3H; *Me*) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 166.3, 163.2, 158.6, 143.8, 129.3, 119.5, 102.5, 51.9, 21.2 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3426, 3081, 2986, 2927, 2849, 1705, 1672, 1641, 1459, 1432, 1386, 1223, 914 cm^{-1}.

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Notes

1. 1,4 Butanediol was used as a spacer of Merrified resin in order to achieve better loading yields.
2. Presumably there is an influence of the fused proline ring on the stereochemical outcome of the Wittig-type coupling. Further experimentation is needed to clarify this exception.

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