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Scaffold Preparation and Parallel Synthesis of Arrays of 5,6,7,8-Tetrahydropyrrolo-azepinones in the Solution Phase

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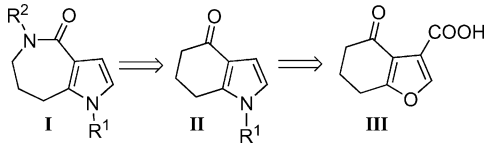
An efficient synthesis of a pyrrolo-azepine scaffold for the parallel preparation of an array of (oxo-pyrrolo-azepinyl)-acetamides is described. The Stetter cyclisation of 1,3-cyclohexanedione with ethyl bromopyruvate was the key reaction in the assembly of a tetrahydrobenzofuran substrate which was submitted to a rapid transformation into a tetrahydroindole by microwave-assisted cyclocondensation in the presence of glycine. The carbonyl group was then stereoselectively transformed into the corresponding (*Z*)-oxime which gave the pyrrolo-azepinone by Beckmann rearrangement in the presence of polyphosphoric acid. Trimethylaluminium-mediated amidation gave the corresponding amides which were finally *N*-alkylated at the 5-position to give 52 diverse (pyrrolo-azepinyl)acetamides, showing an appreciable exploration of the chemical space around the central heterocyclic core.

Introduction

Combinatorial synthesis of small molecules is a powerful tool for the identification of new lead compounds for drug discovery.[1] One possible library design is based on building a central core scaffold carrying different functional groups that can be further decorated. The choice of a rigid scaffold in which substituents point in well-defined directions is often important for biological activity and establishes the nature of the library. The possibility of accessing new scaffolds allows the preparation of original proprietary and patentable libraries that can be used in high-throughput screening.

Amongst the broad range of templates available, heterocyclic molecules represent one of the most utilised scaffolds for the discovery of biologically active compounds.[2] Pyrrolo-azepines and pyrrolo-benzoazepines have been reported to display biological activity as cytotoxic,[3] H1 antihistaminic,[4] as well as antihypertensive and antiplatelet aggregation agents.[5] They can also be considered peptidomimetic scaffolds[6] and some natural products containing this moiety have been isolated.[7] In spite of their evident biological interest, not many combinatorial approaches to this family of molecules have been described in the literature.[8] As one of the most efficient procedures for preparing benzoazepines involves the Beckman rearrangement of tetralone-derived oximes,[9] we decided to investigate the possibility of preparing the pyrrolo-azepine scaffold **I** starting from 1-substituted-6,7-dihydroindol-4(5*H*)-one (**II**).[10] This compound is reported[11] to be available from 6,7-dihydrobenzofuran-4(5*H*)-one (**III**) (Scheme 1). The main limitations preventing extensive application of this last transformation are the harsh conditions required, typically heating at 150 °C for 12–24 hours in a Carius tube. However, confident that microwave irradiation could be employed to obtain 6,7-dihydroindol-4(5*H*)-ones and all other intermediates requiring long-term heating more easily, we decided to study the general synthesis of compounds of type **II** and their transformation into the azepine scaffold **I**. The introduction of an R^1 group suitable for further functionalisation allows the solution-phase synthesis of an array of azepines based on scaffold **I** with a diverse range of substituents in the 1- and 5-positions.



Scheme 1. General scheme for the preparation of the pyrrolo-azepine scaffold.

Results and Discussion

Amongst the several possible methods for the preparation of dihydrobenzofurans of general formula **III**, we chose the Stetter cyclocondensation starting from 1,3-cyclohexanedione (**1**).[11] Reaction with ethyl bromopyruvate in MeOH/KOH afforded compound **5** probably via intermedi-

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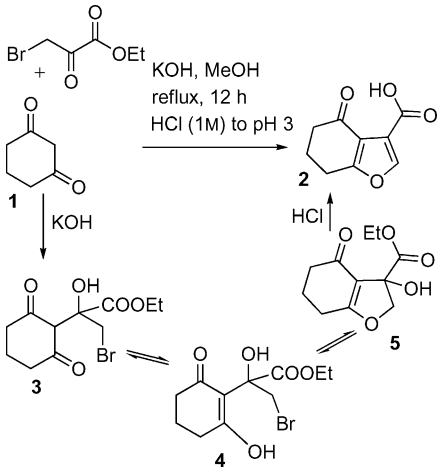
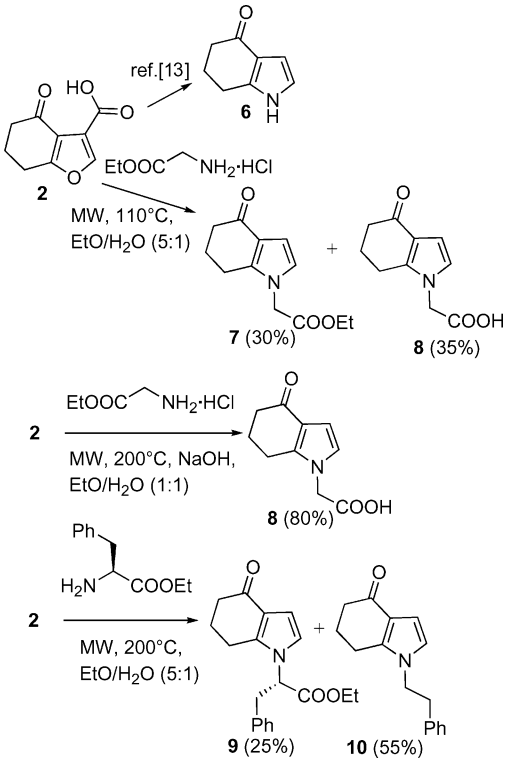
ates **3** and **4** (Scheme 2). Although isolable, compound **5** was directly transformed into **2** by acidifying the reaction mixture and heating it at reflux.[12] After this two-step/one-pot reaction, compound **2** was isolated as a white solid in 80% overall yield.



Scheme 2. Preparation of dihydrobenzofuran-3-carboxylic acid.

Transformation of **2** into pyrrole **6** is reported to take place by heating benzofuran **2** in the presence of ammonium hydroxide in a sealed tube for 12 hours (Scheme 3).[13] Analogously, the preparation of several 1-substituted tetrahydroindol-4-ones by heating furan **2** at 100 °C in the presence of different amines as solvent has been described.[14] With the goal of introducing a carboxylic group into the 1-position to allow further functionalisation, we explored the possibility of using glycine as the amine in the cyclocondensation step. Following our experience in the field,[15] we found that the expected reaction occurred rapidly by microwave irradiation of a mixture of **2** and glycine ethyl ester hydrochloride in EtOH/H_2O (5:1). However, the product obtained after heating the mixture in a sealed tube at 120 °C for 8 min was a mixture of ester **7** and acid **8**. We tried to change the reaction conditions in order to prevent decarboxylation at the 3-position and to reduce the extent of the hydrolysis, but unfortunately we were not able to stop the decarboxylation or to achieve the required cyclocondensation to furnish ester **7** in acceptable yields.

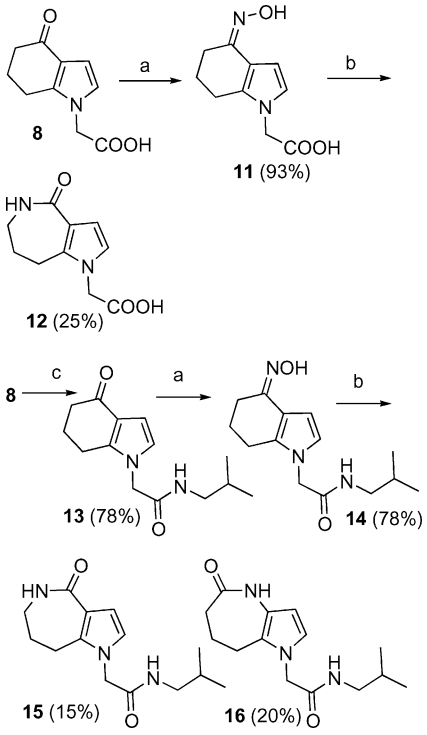
As compound **7** could not be isolated in appreciable yields, we modified the reaction conditions, focusing on the preparation of acid **8**. Thus, compound **2** was treated with glycine ethyl ester hydrochloride in the presence of 4.5 equiv. of NaOH and with a higher amount of water in the solvent system. Microwave-assisted heating for 10 minutes at 120 °C exclusively afforded compound **8** which was isolated in 80% yield after acidification of the reaction mixture and extraction with AcOEt. Unfortunately, when we tried to increase the scope of substitution at the 1-position by reacting **2** with phenylalanine ethyl ester, partial hydrolysis of the ethyl ester followed by decarboxylation was observed, giving predominantly compound **10** (Scheme 3).



Scheme 3.

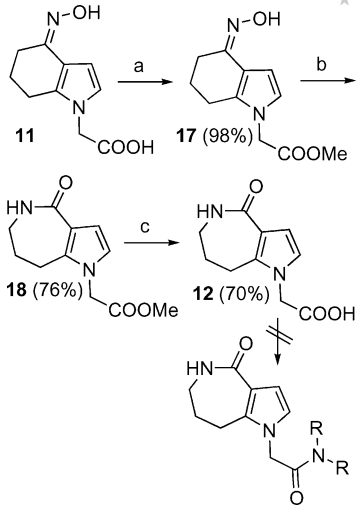
Attempts to transform acid **8** into oxime **11** proved successful using hydroxylamine hydrochloride and AcONa (Scheme 4).[16] Beckmann rearrangement of product **11** was attempted under different reaction conditions. Mildly acidic conditions did not give any results,[17] whereas the starting material (TLC analysis) totally disappeared on addition of **11** to polyphosphoric acid (PPA) at 120 °C and by stirring the mixture at this temperature for 15 min. Pyrrolo-azepine-carboxylic acid **12** was obtained in high conversion (all the starting material was consumed after 15 min), but in poor isolated yields. The highly hydrophilic character of acid **12** probably prevents its complete extraction from the PPA solution. Acid neutralisation and saturation of the aqueous phase with sodium chloride did not improve the extraction efficiency. Although the isolation of acid **12** would probably be possible by continuous liquid–liquid extraction, we tried to bypass the problem by bringing forward the amide formation step in the synthetic scheme. Thus, in an initial trial, acid **8** was coupled with isobutylamine with DMTMM[18] as the coupling agent to produce amide **13** in 78% isolated yield. From this amide, oxime **14** was obtained in good yield with hydroxylamine hydrochloride in the presence of AcONa.

Compound **14** was submitted to a Beckmann rearrangement under the same conditions as those used for **11**. Unfortunately, in this case we observed two spots by TLC that, when isolated, turned out to be the two isomeric pyrroloazepines **15** and **16** (15 and 20% isolated yields, respectively).



Scheme 4. Reagents and conditions: a) $NH_2OH{\cdot}HCl$, AcONa, $MeOH/H_2O$, room temp., 24 h; b) PPA, 120 °C, 15 min; c) $Me_2CHCH_2NH_2$, DMTMM, NMM, THF, room temp., 12 h.

Given the stereospecificity of the Beckmann rearrangement, this outcome should result from the formation of oxime **14** as a mixture of *E*/*Z* isomers.[19] With the aim of obtaining a single pyrrolo-azepine, we returned to the stereoselective synthesis of **11**, converting it into the more lipophilic oxime methyl ester **17** prior to Beckmann rearrangement.[20] Esterification of (*Z*)-oxime acid **11** with MeOH/$SOCl_2$ (1 equiv. with respect to **11**) at room temperature produced (*Z*)-oxime **17** in a very good yield. This compound was then submitted to standard PPA-mediated Beckmann rearrangement to afford pyrrolo-azepinone **18** in 70% isolated yield. The nature of the product [5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one vs. 4,6,7,8-tetrahydropyrrolo[3,2-*b*]azepin-5-one] was determined by ^1H NMR/COSY analysis. The CH_2 at the 6-position showed a resonance at δ = 3.32 ppm with a low-field shift compared with the resonance of the same CH_2 in compound **11**, consistent with the proposed isomer. Moreover, the COSY spectrum showed a cross peak between these protons and the amide NH (Scheme 5).



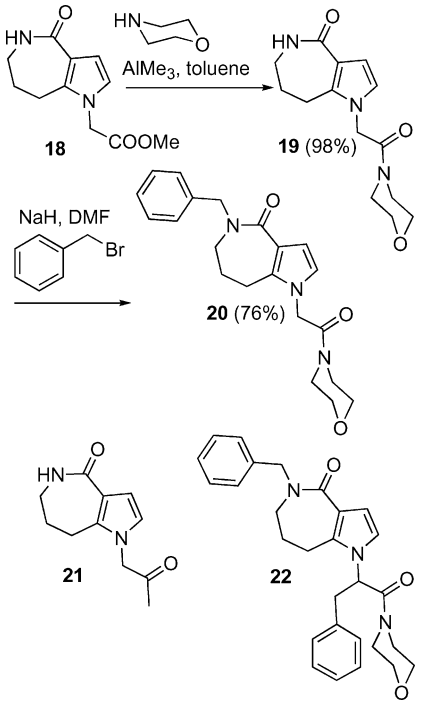
Scheme 5. Reagents and conditions: a) $SOCl_2$, MeOH, reflux, 2 h; b) PPA, 120 °C, 15 min; c) NaOH, $MeOH/H_2O$.

Ester **18** was then hydrolysed to form **12** in a very good yield [45% overall yield from (*Z*)-**9**]. Unfortunately, this acid proved very unreactive towards coupling with secondary amines. The use of a variety of coupling agents (DMTT, DCC, EDC or PyBOP) in the reaction of **12** with *N*-methylpiperazine led to the recovery of the starting material.[21]

Direct aminolysis of ester **18** mediated by Me_3Al was then attempted with the aim of preparing the corresponding amides. Morpholine was used to optimise the reaction conditions (in terms of both yield and purity). By using a ratio of **18**/morpholine/Me_3Al of 1:2:3 in refluxing toluene, amide **19** was obtained in acceptable yields (65%) together with unreacted starting material. Surprisingly, attempts to force the reaction to completion by using microwave dielectric heating did not improve the results (conversion of less that 25% after 1 hour of MW irradiation). To improve the conversion, the amount of Me_3Al was increased up to 6 equiv. with respect to the starting material **18**. Under these conditions the starting material disappeared after heating at reflux for 12 hours, but the formation of approximately 35% of ketone **21** was revealed by chromatographic separation. We attributed the formation of this product to competitive methyl transfer from Me_3Al due to the large excess of reagent used. Finally, we found that the best conditions were a 1:3:3 ratio of **18**/amine/Me_3Al, which gave amide **19** in 98% isolated yield (Table 1, Scheme 6).

Table 1. Optimised reaction conditions for trimethylaluminium-mediated amidation.

Ratio **18**/morpholine/$MeAl_3$	Conditions	Products (% yield)
1:2:3	toluene, reflux, 12 h	**19** (65%)
1:2:3	toluene, reflux, MW, 1 h	**19** (<25%)
1:2:6	CH_2Cl_2, reflux, 12 h	**19** (50%), **21** (35%)
1:3:3	CH_2Cl_2, reflux, 12 h	**19** (98%)



Scheme 6.

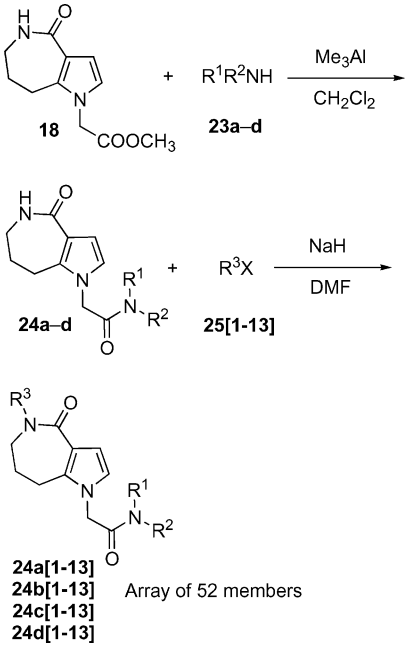
The last step, to functionalise our pyrrolo-azepine scaffold at the 5-position (the amidic NH), was first attempted by reacting substrate **19** with NaH in DMF at room temperature followed by alkylation with benzyl bromide. The use of stoichiometric amounts of NaH and benzyl bromide gave a relatively low conversion to **20** with some starting material recovered at the end of the reaction. Use of an excess of the alkylating mixture gave complete conversion of the starting material, but the reaction was accompanied by the formation of different amounts of dialkylated product **22**.

In order to prevent α alkylation of the terminal carboxamide, different bases were tried for selective deprotonation at the 5-position. Unfortunately, the use of KO*t*Bu in DMF at room temperature, or Cs_2CO_3/DMF, K_2CO_3/KOH/Bu_4NI or phosphazene base in CH_2Cl_2, either at room temperature or under MW dielectric heating, returned exclusively the starting material (Table 2). Finally, the best reaction conditions were found to be the use of 2.5 equiv. of NaH and 1.1 equiv. of benzyl bromide in DMF at room temperature for 15 minutes (Scheme 6). Compound **20** was thus obtained with a purity higher than 95% after a short passage through a silica gel cartridge.

Table 2. Other reaction conditions tested for the *N*-alkylation of compound **19**.

Bases	Conditions
KO*t*Bu	DMF, room temp., 12 h
Cs_2CO_3	DMF, 120 °C, 5 min, MW
K_2CO_3, KOH, Bu_4NI	DMF, 2 min, MW
Phosphazene base	CH_2Cl_2, reflux, 12 h

An array of molecules related to compound **20** was then prepared starting from ester **18** (Scheme 7) in a parallel fashion using the above described conditions. Four different amines (**23a**–**d** in Figure 1) were employed to give amides **24a**–**d** (Table 3), which were treated (on a 200 mg scale) with 12 different benzyl halides (**25[1–12]**) plus MeI (**25[13]**) (Figure 2) to give 52 new products (**24a[1–13]**, **24b[1–13]**, **24c[1–13]** and **24d[1–13]**), which were all isolated by short silica gel cartridge purification in amounts varying from 11 to 237 mg, with purities higher than 91% (except in a few cases, see Table 4) and variable overall yields. The structures, yields and purities of the components of the array are reported in Table 4.



Scheme 7.

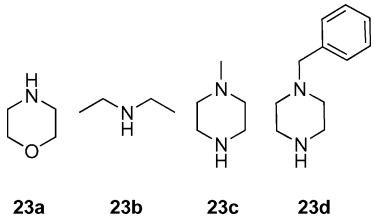
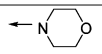
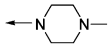
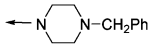


Figure 1. Structures of amines **23a**–**d**.

All the members of the final array are in good agreement with the Lipinski "Rule of Five" (see Figures 3 and 4 for selected calculated properties which show a good distribution across the range of product molecular weights; the rotatable bonds as well as hydrogen-bond donor and acceptor counts are well within the rules).[22]

Table 3. Structures, purities and yields of amides **24a**–**d**.

	–NR^{1}R^2	% Yield	^{1}H NMR purity	LC-MS purity
24a		95	>95 %	>95 %
24b		75	>95 %	>95 %
24c		93	>95 %	[a]
24d		73	>95 %	>95 %

[a] Not determined as compound **24c** runs very close to the solvent front.

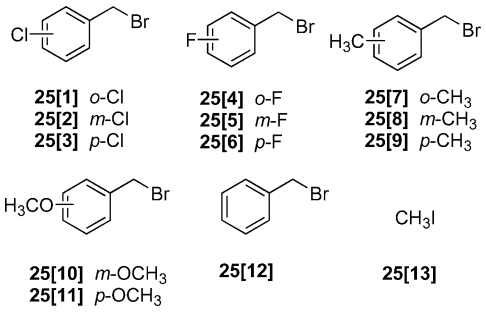


Figure 2. Structures of alkylating agents **25[1–13]**.

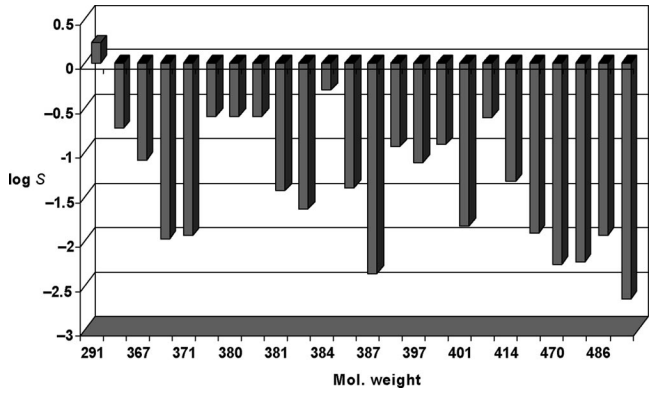


Figure 3. Distribution of molecular weight and log *S* in the array.

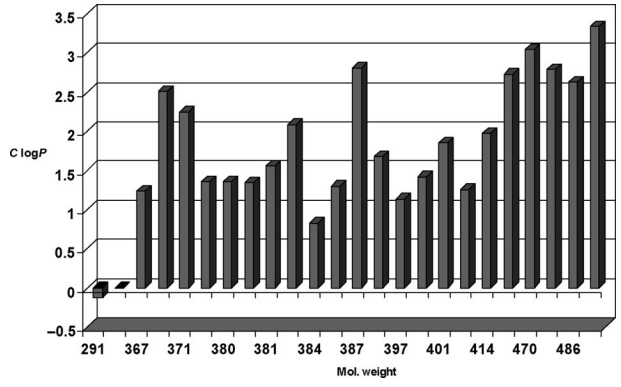


Figure 4. Distribution of molecular weight and log *P* in the array.

Table 4. Structures, purities and yields of final azepines.

	R^3	% Purity ^{1}H NMR	% Purity LC–MS	% Yield
24a[1]	*o*-Cl-$C_6H_4CH_2$	>95	97.70	43
24a[2]	*m*-Cl-$C_6H_4CH_2$	>95	100	41
24a[3]	*p*-Cl-$C_6H_4CH_2$	>95	100	34
24a[4]	*o*-F-$C_6H_4CH_2$	>95	100	39
24a[5]	*m*-F-$C_6H_4CH_2$	>95	100	47
24a[6]	*p*-F-$C_6H_4CH_2$	>95	100	32
24a[7]	*o*-H_3C-$C_6H_4CH_2$	>95	100	45
24a[8]	*m*-H_3C-$C_6H_4CH_2$	>95	100	42
24a[9]	*p*-H_3C-$C_6H_4CH_2$	>95	100	43
24a[10]	*m*-H_3CO-$C_6H_4CH_2$	>95	100	30
24a[11]	*p*-H_3CO-$C_6H_4CH_2$	>95	100	33
24a[12]	$PhCH_2$	>95	100	47
24a[13]	CH_3	>95	100	64
24b[1]	*o*-Cl-$C_6H_4CH_2$	>95	100	51
24b[2]	*m*-Cl-$C_6H_4CH_2$	>95	100	59
24b[3]	*p*-Cl-$C_6H_4CH_2$	>95	97.87	57
24b[4]	*o*-F-$C_6H_4CH_2$	>95	100	68
24b[5]	*m*-F-$C_6H_4CH_2$	>95	98.43	60
24b[6]	*p*-F-$C_6H_4CH_2$	>95	96.07	70
24b[7]	*o*-H_3C-$C_6H_4CH_2$	>95	96.96	36
24b[8]	*m*-H_3C-$C_6H_4CH_2$	>95	96.85	20
24b[9]	*p*-H_3C-$C_6H_4CH_2$	85	76.91	16
24b[10]	*m*-H_3CO-$C_6H_4CH_2$	93	87.94	46
24b[11]	*p*-H_3CO-$C_6H_4CH_2$	94	91.49	47
24b[12]	$PhCH_2$	95	93.68	71
24b[13]	CH_3	>95	100	95
24c[1]	*o*-Cl-$C_6H_4CH_2$	25	100	–
24c[2]	*m*-Cl-$C_6H_4CH_2$	20	100	–
24c[3]	*p*-Cl-$C_6H_4CH_2$	>95	100	8
24c[4]	*o*-F-$C_6H_4CH_2$	>95	100	30
24c[5]	*m*-F-$C_6H_4CH_2$	>95	100	26
24c[6]	*p*-F-$C_6H_4CH_2$	>95	100	16
24c[7]	*o*-H_3C-$C_6H_4CH_2$	>95	100	22
24c[8]	*m*-H_3C-$C_6H_4CH_2$	>95	100	18
24c[9]	*p*-H_3C-$C_6H_4CH_2$	>95	100	17
24c[10]	*m*-H_3CO-$C_6H_4CH_2$	>95	100	11
24c[11]	*p*-H_3CO-$C_6H_4CH_2$	>95	100	4
24c[12]	$PhCH_2$	>95	100	19
24c[13]	CH_3	98	–	10
24d[1]	*o*-Cl-$C_6H_4CH_2$	>95	100	17
24d[2]	*m*-Cl-$C_6H_4CH_2$	>95	100	19
24d[3]	*p*-Cl-$C_6H_4CH_2$	>95	100	26
24d[4]	*o*-F-$C_6H_4CH_2$	>95	100	23
24d[5]	*m*-F-$C_6H_4CH_2$	>95	100	29
24d[6]	*p*-F-$C_6H_4CH_2$	>95	100	24
24d[7]	*o*-H_3C-$C_6H_4CH_2$	>95	100	31
24d[8]	*m*-H_3C-$C_6H_4CH_2$	>95	100	14
24d[9]	*p*-H_3C-$C_6H_4CH_2$	>95	100	16
24d[10]	*m*-H_3CO-$C_6H_4CH_2$	>95	100	10
24d[11]	*p*-H_3CO-$C_6H_4CH_2$	>95	100	17
24d[12]	$PhCH_2$	>95	100	20
24d[13]	CH_3	>95	100	40

Conclusion

We have developed an optimised procedure for the preparation of novel scaffold **18** in multigram scale and a simple procedure for the parallel decoration of the 1- and 5-positions of the ring. An efficient route was then developed for the rapid solution-phase combinatorial synthesis of an array of disubstituted pyrrolo-azepinyl)acetamides by using this scaffold.

Experimental Section

General Information: All commercially available reagents and solvents were used without further purification unless mentioned otherwise. Solution-phase reactions were monitored by analytical thin-layer chromatography (TLC; silica gel 60 F254 plates 0.25 mm) and purified by column chromatography on silica gel 60. LC–MS data were recorded with a Waters Alliance HT 2792 electrospray mass spectrometer equipped with a detector Photodiode Array 2996 and micromass ZQ using a Phenomenex C18 column. HPLC–MS method: mixture A (99.9% water, 0.1% HCOOH) and mixture B (99.9% acetonitrile, 0.1% HCOOH) were used as the eluents as follows: 0–6.85 min, 95% mixture A; 6.85–9.10 min 95–0% mixture A; 9.10–9.15 min 0–95% mixture A, 9.15–10 min 95% mixture A; flow 1.0 mL/min, T = 40 °C. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 200 MHz and 400 MHz instruments; chemical shifts were quoted in parts per million and referenced to the solvent used. The cyclisations were performed in a CEM Discover microwave reactor. The alkylation step to deliver the final library was performed in a Büchi-Syncore parallel synthesiser. Compound **2** was obtained as described in ref.[13]

Synthesis of 2-(4,5,6,7-Tetrahydro-4-oxoindol-1-yl)acetic Acid (8): NaOH (1 g, 25 mmol) was dissolved in a H_2O/EtOH (1:1, 12 mL) solution. Acid **2** (1 g, 5.55 mmol) and glycine ethyl ester hydrochloride (2.32 g, 16.83 mmol) were added to the stirred solution and the reaction mixture was heated under microwave irradiation (250 W) at 120 °C for 10 min. The ethanol was evaporated under reduced pressure and the aqueous solution was acidified with 4 N HCl and extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give **8** (0.85 g, yield 80%) as a yellow crystalline solid; m.p. 202 °C. ^{1}H NMR (200 MHz, [D]methanol): δ = 6.53 (d, J = 2.8 Hz, 1 H, CHN), 6.47 (d, J = 2.8 Hz, 1 H, CH), 4.45 (s, 2 H, CH_2N), 2.61 (m, 2 H, CH_2CO), 2.38 (m, 2 H,CH_2C), 2.08 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]methanol): δ = 197.6, 171.4, 150.2, 147.6, 125.2, 121.5, 106.1, 38.3, 24.7, 22.3 ppm. MS (EI, 70 eV): m/z = 192 $[M - H]^+$. $C_{10}H_{11}NO_3$ (193.07): calcd. C 62.17, H 5.74, N 7.25; found C 62.15, H 5.76, N 7.27.

Synthesis of Ethyl 2-(4,5,6,7-Tetrahydro-4-oxoindol-1-yl)-3-phenylpropanoate (9) and 6,7-Dihydro-1-phenethyl-1*H*-indol-4(5*H*)-one (10): Phenylalanine ethyl ester (716 mg, 3.33 mmol) and triethylamine (0.7 mL, 4.99 mmol) were added to a solution of **2** (200 mg, 1.11 mmol) in a mixture of H_2O/EtOH (5:1, 2 mL). The reaction mixture was heated under microwave irradiation (250 W) at 120 °C for 10 min. The ethanol was evaporated under reduced pressure and the aqueous solution was acidified with 1 N HCl and extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the crude obtained was purified by flash chromatography (SiO_2 chloroform/ethyl acetate, 3:1) to give 83 mg of **9** (yield 25%) and 146 mg of **10** (yield 55%). **9**: ^{1}H NMR (200 MHz, [D]chloroform): δ = 6.70–6.60 (m, 5 H, CH arom.), 6.63 (d, J = 2.8 Hz, 1 H, CHN), 6.51 (d, J = 2.8 Hz, 1 H, CH), 5.23 (t, J = 7.3 Hz, CHN), 4.25 (q, J = 7.0 Hz, 2 H, CH_2O), 3.41 (d, J = 7.3 Hz, 2 H, CH_2Ph), 2.35 (m, 2 H, CH_2CO), 1.87 (m, 2 H, CH_2C), 1.78 (m, 2 H, $CH_2CH_2CH_2$), 1.3 (t, J = 7.0 Hz, 3 H, 3 H, OCH_2CH_3) ppm. MS (EI, 70 eV): m/z = 312 $[M + H]^+$. **10**: ^{1}H NMR (200 MHz, [D]-chloroform): δ = 7.35–6.65 (m, 5 H, CH arom.), 6.63 (d, J = 3.2 Hz, 1 H, CHN), 6.52 (d, J = 3.2 Hz, 1 H, CH), 4.03 (t, J = 6.4 Hz, 2 H, CH_2N), 3.01 (t, J = 6.4 Hz, 2 H, CH_2Ph), 2.4 (m, 2 H, CH_2CO), 2.27 (m, 2 H, CH_2C), 1.87 (m, 2 H, $CH_2CH_2CH_2$) ppm. MS (EI, 70 eV): m/z = 240 $[M + H]^+$.

Synthesis of 2-[4,5,6,7-Tetrahydro-4-(hydroxyimino)indol-1-yl]acetic Acid [(*Z*)-11]: A mixture of acid **8** (1.5 g, 7.77 mmol), hydroxylamine hydrochloride (1.62 g, 23.31 mmol), sodium acetate (1.9 g, 23.31 mmol), methanol (105 mL) and H_2O (42 mL) was stirred at room temperature for 24 h. The reaction mixture was evaporated under reduced pressure to about half its initial volume and diluted with water (50 mL). The resulting crystals were collected, washed with water and dried. Recrystallisation from chloroform/hexane gave **11** (1.5 g, yield 93%); m.p. 208 °C. ^{1}H NMR (200 MHz, [D]-methanol): δ = 6.76 (d, J = 3.2 Hz, 1 H, CHN), 6.48 (d, J = 3.2 Hz, 1 H, CH), 4.45 (s, 2 H, CH_2N), 2.49 (m, 2 H, CH_2C), 2.32 (m, 2 H, 2 H, CH_2CO), 2.25 (m, 2 H, 2H $CH_2CH_2CH_2$) ppm. MS (EI, 70 eV): m/z = 209 $[M + H]^+$.

Synthesis of *N*-Isobutyl-2-(4,5,6,7-tetrahydro-4-oxoindol-1-yl)acetamide (13): Isobutylamine (0.103 mL, 1.04 mmol), DMTMM (316 mg, 1.14 mmol) and *N*-methylmorpholine (0.228 mL, 2.08 mmol) were added to a stirred suspension of **8** (200 mg, 1.04 mmol) in THF (8 mL),. The mixture was stirred at room temperature for 12 h, then THF was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 1 N HCl (twice), Na_2CO_3 (twice), dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give **13** (201 mg, yield 78%). ^{1}H NMR (200 MHz, [D]-chloroform): δ = 6.63 (d, J = 3.0 Hz, 1 H, CHN), 6.57 (d, J = 3.0 Hz, 1 H, CH), 5.27 (br., 1 H, NH), 4.52 (s, 2 H, CH_2N), 3.04 (m, 2 H, CH_2NH), 2.69 (m, 2 H, CH_2CO), 2.56 (m, 2 H, CH_2C), 2.22 (m, 2 H, $CH_2CH_2CH_2$), 1.68 (q, J = 6.60 Hz, 1 H, $CHCH_3$), 0.92 (d, J = 6.58 Hz, 6 H, CH_3) ppm. MS (EI, 70 eV): m/z = 249 $[M + H]^+$.

Synthesis of *N*-Isobutyl-2-[4,5,6,7-tetrahydro-4-(hydroxyimino)indol-1-yl]acetamide [(*E*,*Z*)-14]: A mixture of **13** (160 mg, 0.63 mmol), hydroxylamine hydrochloride (134 mg, 1.94 mmol), sodium acetate (159 mg, 1.94 mmol), methanol (8.6 mL) and H_2O (3.45 mL) was heated at reflux until disappearance of the starting amide by TLC analysis (4 h). The reaction mixture was evaporated under reduced pressure to about half its initial volume, diluted with water (10 mL) and then extracted with ethyl acetate; the organic phase was dried with anhydrous Na_2SO_4 and crystallised from chloroform/hexane to give **14** [*E*:*Z* = 1:1] as a white solid (130 mg, yield 78%); m.p. 171–174 °C. ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.90 (d, J = 2.8 Hz, 1 H, CHN, isomer *E* or *Z*), 6.67 (d, J = 3.2 Hz, 1 H, CHN, isomer *E* or *Z*), 6.58 (d, J = 2.8 Hz, 1 H, CH, isomer *E* or *Z*), 6.35 (d, J = 3.2 Hz, 1 H, CH, isomer *E* or *Z*), 4.51 (s, 2 H, CH_2N, isomer *E* or *Z*), 4.49 (s, 2 H, CH_2N, isomer *E* or *Z*), 3.02 (d, J = 5.6 Hz, 2 H, CH_2NH), 2.60 (m, 2 H, CH_2CO), 2.37 (m, 2 H, CH_2C), 1.95 (m, 2 H, $CH_2CH_2CH_2$), 1.75 (q, J = 6.61 Hz, 1 H, $CHCH_3$), 0.87 (d, J = 6.60 Hz, 6 H, CH_3) ppm. MS (EI, 70 eV): m/z = 264 $[M + H]^+$.

Synthesis of *N*-Isobutyl-2-[5,6,7,8-tetrahydro-4-oxopyrrolo[3,2-*c*]-azepin-1(4*H*)-yl]acetamide (15) and *N*-Isobutyl-2-[5,6,7,8-tetrahydro-5-oxopyrrolo[3,2-*b*]azepin-1(4*H*)-yl]acetamide (16): Acetamide **14** (200 mg, 0.76 mmol) was added to stirred PPA (2.3 g) preheated at 120 °C. After 15 min, the solution was poured into ice and water and the aqueous solution was extracted with chloroform. The organic layer was dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give the crude product that was purified by flash chromatography (SiO_2, chloroform/methanol, 98:2); 30 mg of **15** (yield 15%) and 40 mg of **16** (yield 20%) were obtained. **15**: ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.82 (d, J = 2.8 Hz, 1 H, CHN), 6.64 (d, J = 2.8 Hz, 1 H, CH), 5.45 (br., 1 H, NH), 4.50 (s, 2 H, CH_2N), 3.78 (m, 2 H, CH_2NH), 3.02 (m, 2 H, CH_2CO), 2.78 (m, 2 H, CH_2C), 2.06 (m, 2 H,

$CH_2CH_2CH_2$), 1.68 (q, J = 6.60 Hz, 1 H, $CHCH_3$), 0.87 (d, J = 6.58 Hz, 6 H, CH_3) ppm. MS (EI, 70 eV): m/z = 264 $[M + H]^+$. **16**: ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.57 (d, J = 2.4 Hz, 1 H, CHN), 6.55 (d, J = 2.4 Hz, 1 H, CH), 5.25 (br., 1 H, NH), 4.52 (s, 2 H, CH_2N), 3.03 (m, 2 H, CH_2NH), 2.76 (m, 2 H, CH_2CO), 2.57 (m, 2 H, CH_2C), 2.10 (m, 2 H, $CH_2CH_2CH_2$), 1.63 (q, J = 6.60 Hz, 1 H, $CHCH_3$), 0.88 (d, J = 6.58 Hz, 6 H, CH_3) ppm. MS (EI, 70 eV): m/z = 264 $[M + H]^+$.

Synthesis of Methyl 2-[4,5,6,7-Tetrahydro-4-(hydroxyimino)indol-1-yl]acetate (17): Thionyl chloride (525 mL, 7.2 mmol) was added to a stirred solution of **11** (1.5 g, 7.2 mmol) in methanol (83 mL) at 0 °C and the reaction was stirred at reflux for 2 h. The reaction mixture was evaporated under reduced pressure to give **17** (1.57 g, 98%) as a brown solid; m.p. 168 °C. ^{1}H NMR (400 MHz, [D]methanol): δ = 6.78 (d, J = 2.8 Hz, 1 H, CHN), 6.65 (d, J = 2.8 Hz, 1 H, CH), 4.48 (s, 2 H, CH_2N), 3.75 (s, 3 H, CH_3O), 2.73 (m, 2 H, CH_2CO), 2.52 (m, 2 H, CH_2C), 2.31 (m, 2 H, $CH_2CH_2CH_2$) ppm. MS (EI, 70 eV): m/z = 223 $[M + H]^+$, 245 $[M + Na]^+$.

Synthesis of Methyl 2-[5,6,7,8-Tetrahydro-4-oxopyrrolo[3,2-*c*]-azepin-1(4*H*)-yl]acetate (18): Ester **17** (2 g, 9 mmol) was added portionwise to stirred PPA (27 g) preheated at 120 °C. After 15 min, the solution was poured into ice/water and the aqueous solution was extracted with chloroform. The organic layer was dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give the crude product that was purified by flash chromatography (SiO_2, chloroform/methanol, 98:2); 1.32 g of the pure title compound **18** was isolated as a white solid (yield 70%); m.p. 170 °C. ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.72 (d, J = 2.8 Hz, 1 H, CHN), 6.56 (d, J = 2.8 Hz, 1 H, CH), 6.04 (br., 1 H, NH), 4.54 (s, 2 H, CH_2N), 3.75 (s, 3 H, CH_3O), 3.32 (m, 2 H, CH_2NH), 2.76 (m, 2 H, CH_2C), 2.09 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 168.5, 168.0, 133.9, 121.9, 116.9, 111.5, 52.8, 48.5, 41.8, 26.9, 26.3 ppm. MS (EI, 70 eV): m/z = 223 $[M + H]^+$, 245 $[M + Na]^+$. $C_{11}H_{14}N_2O_3$ (222): C 59.45, H 6.35, N 12.60; found 59.43, H 6.38, N 12.62.

Synthesis 2-[5,6,7,8-Tetrahydro-4-oxopyrrolo[3,2-*c*]azepin-1(4*H*)-yl]-acetic Acid (12): NaOH (120 mg dissolved in 1 mL of H_2O, 2.55 mmol) was added to a suspension of **18** (335 mg, 1.27 mmol) in MeOH (5 mL) cooled to 0 °C with an ice bath. The mixture was removed from the ice bath and the reaction was monitored by TLC (chloroform/methanol, 95:5) until disappearance of the starting material. Then HCl (0.212 mL of 37% HCl, 2.55 mmol) was added and the methanol was evaporated under reduced pressure to afford product **12** as a white crystalline residue that was filtered and dried (212 mg, yield 85%); m.p. 128 °C. ^{1}H NMR (400 MHz, [D]methanol): δ = 6.67 (d, J = 2.8 Hz, 1 H, CHN), 6.51 (d, J = 2.8 Hz, 1 H, CH), 5.66 (s, 2 H, CH_2N), 3.29 (m, 2 H, CH_2NH), 2.82 (m, 2 H, CH_2C), 2.09 (m, 2 H, $CH_2CH_2CH_2$) ppm. MS (EI, 70 eV): m/z = 207 $[M - H]^+$.

General Procedure for the Weinreb Reaction. Preparation of 5,6,7,8-Tetrahydro-1-(2-morpholino-2-oxoethyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a): A 2 M solution of $AlMe_3$ in toluene (6.7 mL, 13.51 mL) was added to a stirred solution of freshly distilled morpholine (13.51 mmol, 1.3 mL) in dry dichloromethane (20 mL) at 0 °C under an inert atmosphere and the reaction mixture was stirred at room temperature for 15 min. Acetate **18** (1 g, 4.5 mmol) was added portionwise and the mixture was heated at reflux overnight and then cooled to room temperature. The mixture was cooled to 0 °C, distilled water was added dropwise until the excess of $AlMe_3$ had been quenched and then anhydrous Na_2SO_4 was added. The suspension was stirred for 30 min then filtered through Celite® and washed with chloroform. The solvent was evaporated under reduced pressure to give the crude product that was purified by flash chromatography (SiO_2, chloroform/methanol, 98:2). The product **24a** was obtained as a white solid (1.2 g, yield 95%); m.p. 216 °C. ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.61 (d, J = 3.2 Hz, 1 H, CHN), 6.48 (d, J = 3.2 Hz, 1 H, CH), 4.56 (s, 2 H, CH_2N), 3.65–3.63 (m, 4 H, CH_2O), 3.553 (m, 2 H, CH_2NCH_2), 3.41 (m, 2 H, CH_2NCH_2), 3.25 (m, CH_2NH), 2.68 (m, 2 H, CH_2C), 2.01 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 167.3, 166.5, 134.8, 122.7, 116.8, 110.1, 66.7, 66.6, 48.6, 45.4, 42.5, 41.6, 40.8, 27.1, 26.8 ppm. LC–MS: m/z = 278 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

The products **24b**, **24c** and **24d** were obtained by the same procedure and purified by flash chromatography using chloroform/MeOH or dichloromethane/MeOH mixtures as eluents.

***N*,*N*-Diethyl-2-[5,6,7,8-tetrahydro-4-oxopyrrolo[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b):** M.p. 245 °C. ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.71 (d, J = 2.6 Hz, 1 H, CHN), 6.53 (d, J = 2.6 Hz, 1 H, CH), 5.94 (br., 1 H, NH), 4.57 (s, 2 H, CH_2N), 3.35–3.23 (m, 6 H, CH_2CH_3, CH_2NH), 2.748 (m, 2 H, CH_2C), 2.07 (m, 2 H, $CH_2CH_2CH_2$), 1.21 (t, J = 7.2 Hz, 3 H, CH_3), 1.12 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR ([D]chloroform): δ = 167.3, 166.6, 134.7, 122.9, 116.8, 109.9, 48.7, 41.6, 41.3, 40.6, 27.0, 14.7, 13.7 ppm. LC–MS: m/z = 264 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo-[3,2-*c*]azepin-4(1*H*)-one (24c): M.p. 244 °C. ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.22 (d, J = 3.2 Hz, 1 H, CHN), 6.52 (d, J = 3.2 Hz, 1 H, CH), 5.92 (br., 1 H, NH), 4.58 (s, 2 H, CH_2N), 3.63 (m, 2 H, CH_2NCH_2), 3.45 (m, 2 H, CH_2NCH_2), 3.31 (m, 2 H, CH_2NH), 2.74 (m, 2 H, CH_2C), 2.39 (m, 4 H, CH_2NCH_3), 2.29 (s, 3 H, CH_3N), 2.07 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]-chloroform): δ = 167.3, 166.2, 134.8, 122.8, 116.8, 110.1, 55.2, 54.9, 48.7, 46.3, 44.7, 42.1, 41.6, 27.1, 26.9 ppm.

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydropyrrolo-[3,2-*c*]azepin-4(1*H*)-one (24d): M.p. 261 °C. NMR (400 MHz, [D]-chloroform): δ = 7.30–7.22 (m, 5 H, CH arom.), 6.62 (d, J = 3.2 Hz, 1 H, CHN), 6.48 (d, J = 3.2 Hz, 1 H, CH), 4.56 (s, 2 H, CH_2N), 3.57 (m, 2 H, CH_2NCH_2), 3.48 (s, 2 H, NCH_2Ph), 3.41 (m, 2 H, CH_2NCH_2), 3.25 (m, 2 H, CH_2NH), 2.67 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 2.01 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 168.6, 165.1, 137.1, 134.7, 129.2, 128.4, 127.4, 122.0, 116.1, 111.1, 62.8, 52.8, 52.5, 48.6, 44.9, 42.3, 41.7, 27.0, 26.1 ppm. LC–MS: m/z = 367 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

Synthesis 5,6,7,8-Tetrahydro-1-(2-oxopropyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (21): This product was obtained by the general procedure for the Weinreb reaction using a ratio **18**/morpholine/$AlMe_3$ of 1:2:6 after purification of the crude by flash chromatography (SiO_2, chloroform/methanol, 98:2) as a white solid (yield 35%); m.p. 180 °C. NMR (400 MHz, [D]chloroform): δ = 6.74 (d, J = 2.8 Hz, 1 H, CHN), 6.52 (d, J = 2.8 Hz, 1 H, CH), 4.81 (s, 2 H, CH_2N), 3.31 (m, 2 H, CH_2NH), 2.66 (m, 2 H, CH_2C), 2.14–1.98 (m, 5 H, CH_3, $CH_2CH_2CH_2$) ppm. MS (EI, 70 eV): m/z (%) = 208 $[M + H]^+$.

General Procedure for the Synthesis of the Final Products 24a[1–13], 24b[1–13], 24c[1–13] and 24d[1–13]

Preparation of 5-(3-Chlorobenzyl)-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[2]): Sodium hydride (60% oil dispersion, 43 mg, 1.81 mmol) was added to a flask equipped with a magnetic stirring bar and N_2 inlet. The sodium hydride was washed with hexane (3×) and the waste hexane was

removed each time with a glass pipette. Anhydrous DMF (1.25 mL) was added to the washed sodium hydride and the resulting suspension was cooled in an ice/water bath. 5,6,7,8-Tetrahydro-1-(2-morpholino-2-oxoethyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (200 mg, 0.72 mmol) was added to the cooled mixture and then the reaction mixture was allowed to stir for 20 min; 3-chlorobenzyl bromide (163 mg, 0.79 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 30 min. The excess sodium hydride was quenched with H_2O (1 mL). The solvent was removed under reduced pressure to give a residue that was purified on a silica gel cartridge (chloroform/methanol, 99:1) to give 99 mg of **24a[2]** (yield 41%). ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.22–7.12 (m, 5 H, CH arom.), 7.74 (d, J = 2.8 Hz, 1 H, CHN), 6.49 (d, J = 2.8 Hz, 1 H, CH), 4.66 (s, 2 H, CH_2Ph), 4.45 (s, 2 H, CH_2N), 3.64–3.62 (m, 4 H, CH_2O), 3.56 (m, 2 H, CH_2NCH_2), 3.39 (m, 2 H, CH_2NCH_2), 3.32 (m, 2 H, CH_2NH), 2.62 (m, 2 H, CH_2C), 1.94–1.88 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 166.0, 142.3, 134.8, 133.7, 131.0, 128.0, 127.5, 127.0, 122.8, 116.7, 110.7, 66.7, 66.6, 51.4, 48.6, 48.4, 45.4, 42.5, 26.3, 26.2 ppm. LC–MS: m/z = 402 [M + H]$^+$ (Phenomenex® column, 100, 254 nm).

All the compounds of the library were obtained by the same procedure and purified on a silica gel cartridge (chloroform/methanol or dichloromethane/methanol).

5-(2-Chlorobenzyl)-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[1]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.29–7.26 (m, 2 H, CH arom.), 7.15–7.08 (m, 2 H, CH arom.), 6.72 (d, J = 3.2 Hz, 1 H, CHN), 6.48 (d, J = 3.2 Hz, 1 H, CH), 4.81 (s, 2 H, CH_2Ph), 4.53 (s, 2 H, CH_2N), 3.63–3.62 (m, 4 H, CH_2O), 3.56 (m, 2 H, CH_2NCH_2), 3.39–3.35 (m, 4 H, CH_2NCH_2, CH_2NCO), 2.63 (m, 2 H, CH_2C), 1.98–1.92 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 402 [M + H]$^+$ (Phenomenex® column, 97.7%, 254 nm).

5-(4-Chlorobenzyl)-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[3]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.21–7.16 (m, 4 H, CH arom.), 6.73 (d, J = 3.2 Hz, 1 H, CHN), 6.48 (d, J = 3.2 Hz, 1 H, CH), 4.64 (s, 2 H, CH_2Ph), 4.53 (s, 2 H, CH_2N), 3.64–3.61 (m, 4 H, CH_2O), 3.55 (m, 2 H, CH_2NCH_2), 3.39 (m, 2 H, CH_2NCH_2), 3.30 (m, 2 H, CH_2NCO), 2.60 (m, 2 H, CH_2C), 1.91–1.86 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 402 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5-(2-Fluorobenzyl)-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[4]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.34 (m, 1 H, CH arom.), 7.12 (m, 1 H, CH arom.), 7.02–6.93 (m, 2 H, CH arom.), 6.71 (d, J = 2.4 Hz, 1 H, CHN), 6.47 (d, J = 2.4 Hz, 1 H, CH), 4.74 (s, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2N), 3.62 (m, 4 H, CH_2O), 3.55 (m, 2 H, CH_2NCH_2), 3.39–3.37 (m, 4 H, CH_2NCH_2, CH_2NCO), 2.60 (m, 2 H, CH_2C), 1.95–1.89 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 386 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5-(3-Fluorobenzyl)-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[5]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.20–7.15 (m, 1 H, CH arom.), 6.99 (d, J = 7.6 Hz, 1 H, CH arom.), 6.93 (d, J = 9.6 Hz, 1 H, CH arom.), 6.84 (m, 1 H, CH arom.), 6.69 (d, J = 2.8 Hz, 1 H, CHN), 6.46 (d, J = 2.8 Hz, 1 H, CH), 4.65 (s, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2N), 3.62–3.60 (m, 4 H, CH_2O), 3.53 (m, 2 H, CH_2NCH_2), 3.38 (m, 2 H, CH_2NCH_2), 3.30 (m, 2 H, CH_2NCO), 2.59 (m, 2 H, CH_2C), 1.92–1.86 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 166.0, 164.1, 161.7, 142.7, 142.6, 134.7, 131.1, 131.0, 124.29, 124.27, 122.8, 116.7, 110.7, 66.7, 66.6, 51.5, 48.6, 48.4, 45.3, 42.5, 26.3, 26.2 ppm. LC–MS: m/z = 386 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5-(4-Fluorobenzyl)-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[6]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.25 (d, J = 8 Hz, 2 H, CH arom.), 6.96 (m, 2 H, CH arom.), 6.78 (s, 1 H, CHN), 6.53 (s, 1 H, CH), 4.69 (s, 2 H, CH_2Ph), 4.58 (s, 2 H, CH_2N), 3.67 (m, 4 H, CH_2O), 3.60 (m, 2 H, CH_2NCH_2), 3.44 (m, 2 H, CH_2NCH_2), 3.36 (m, 2 H, CH_2NCO), 2.65 (m, 2 H, CH_2C), 1.93 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 386 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(2-methylbenzyl)-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[7]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.16–7.14 (m, 4 H, CH arom.), 6.79 (s, 2 H, CH arom.), 6.54 (s, 2 H, CHN), 4.76 (s, 2 H, CH_2Ph), 4.58 (s, 2 H, CH_2N), 3.68 (m, 4H. CH_2O), 3.61 (m, 2 H, CH_2NCH_2), 3.45 (m, 2 H, CH_2NCH_2), 3.34 (m, 2H CH_2NCO), 2.66 (m, 2 H, CH_2C), 2.30 (s, 3 H, CH_3), 1.91 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 382 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(3-methylbenzyl)-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[8]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.14 (m, 1 H, CH arom.), 7.09–7.02 (m, 3 H, CH arom.), 7.77 (d, J = 2.8 Hz, 1 H, CHN), 6.51 (d, J = 2.8 Hz, 1 H, CH), 4.69 (s, 2 H, CH_2Ph), 4.57 (s, 2 H, CH_2N), 3.68–3.66 (m, 4 H, CH_2O), 3.59 (m, 2 H, CH_2NCH_2), 3.44 (m, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.64 (m, 2 H, CH_2C), 2.29 (s, 3 H, CH_3), 1.95–1.89 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 165.9, 139.5, 138.1, 134.5, 129.0, 128.8, 128.2, 125.4, 122.7, 116.9, 110.7, 66.7, 66.6, 51.7, 48.6, 48.1, 45.3, 42.5, 26.3, 26.2, 21.7 ppm. LC–MS: m/z = 382 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(4-methylbenzyl)-1-(2-morpholino-2-oxoethyl)-pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[9]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.13 (d, J = 7.6 Hz, 2 H, CH arom.), 7.03 (d, J = 7.6 Hz, 2 H, CH arom.), 6.74 (d, J = 2.4 Hz, 1 H, CHN), 6.48 (d, J = 2.4 Hz, 1 H, CH), 4.65 (s, 2 H, CH_2Ph), 4.52 (s, 2 H, CH_2N), 3.62 (m, 4 H, CH_2O), 3.55 (m, 2 H, CH_2NCH_2), 3.38 (m, 2 H, CH_2NCH_2), 3.30 (m, 2 H, CH_2NCO), 2.59 (m, 2 H, CH_2C), 2.25 (m, 3 H, CH_3), 1.89–1.84 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 382 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(3-methoxybenzyl)-1-(2-morpholino-2-oxoethyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[10]): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.14 (m, 1 H, CH arom.), 6.82 (d, J = 7.6 Hz, 1 H, CH arom.), 6.78 (s, 1 H, CH arom.), 6.73 (d, J = 2.8 Hz, 1 H, CHN), 6.71 (d, J = 7.6 Hz, 1 H, CH arom.), 6.47 (d, J = 2.8 Hz, 1 H, CH), 4.61 (s, 2 H, CH_2Ph), 4.54 (s, 2 H, CH_2N), 3.71 (s, 3 H, CH_3O), 3.63–3.61 (m, 4 H, CH_2O), 3.55 (m, 2 H, CH_2NCH_2), 3.340 (m, 2 H, CH_2NCH_2), 3.31 (m, 2 H, CH_2NCO), 2.60 (m, 2 H, CH_2C), 1.88 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]-chloroform): δ = 166.5, 165.9, 160.0, 141.2, 134.6, 130.1, 122.7, 120.4, 116.9, 114.0, 112.8, 110.7, 66.7, 66.6, 55.6, 51.7, 48.6, 48.2, 45.3, 42.5, 26.3, 26.2 ppm. LC–MS: m/z = 398 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(4-methoxybenzyl)-1-(2-morpholino-2-oxoethyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24a[11]): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.16 (d, J = 8.2 Hz, 2 H, CH arom.), 6.75 (d, J = 8.1 Hz, 2 H, CH arom.), 6.71 (d, J = 2.8 Hz, 1 H, CHN), 6.45 (d, J = 2.8 Hz, 1 H, CH), 4.60 (s, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2N), 3.71 (s, 3 H, OCH_3), 3.61 (m, 4 H, CH_2O), 3.53 (m, 2 H, CH_2NCH_2), 3.38 (m, 2 H, CH_2NCH_2), 3.28 (m, 2 H, CH_2NCO), 2.57 (m, 2 H, CH_2C), 1.87–1.81 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 398 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5-Benzyl-5,6,7,8-tetrahydro-1-(2-morpholino-2-oxoethyl)pyrrolo-[3,2-*c*]azepin-4(1*H*)-one (24a[12]): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.23–7.17 (m, 5 H, CH arom.), 6.75 (d, J = 2.8 Hz, 1 H, CHN), 6.48 (d, J = 2.8 Hz, 1 H, CH), 4.70 (s, 2H. CH_2Ph), 4.54 (s, 2 H, CH_2N), 3.62 (m, 4 H, CH_2O), 3.55 (m, 2 H, CH_2NCH_2), 3.39 (m, 2 H, CH_2NCH_2), 3.32 (m, 2 H, CH_2NCO), 2.60 (m, 2 H, CH_2C), 1.88 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 368 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-methyl-1-(2-morpholino-2-oxoethyl)pyrrolo-[3,2-*c*]azepin-4(1*H*)-one (24a[13]): ^{1}H NMR (400 MHz, [D]chloroform): δ = 6.60 (d, J = 2.4 Hz, 1 H, CHN), 6.41 (d, J = 2.4 Hz, 1 H, CH), 4.50 (s, 2 H, CH_2N), 3.60 (m, 4 H, CH_2O), 3.53 (m, 2 H, CH_2NCH_2), 3.37 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 3.02 (s, 3 H, CH_3), 2.60 (m, 2 H, CH_2C), 1.98 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 165.9, 134.2, 122.5, 117.1, 110.4, 66.7, 66.6, 50.0, 48.6, 45.4, 42.5, 36.8, 26.1, 26.0 ppm. LC–MS: m/z = 292 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

2-[5-(2-Chlorobenzyl)-*N*,*N*-diethyl-5,6,7,8-tetrahydro-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[1]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.31 (m, 2 H, CH arom.), 7.15 (m, 2 H, CH arom.), 6.75 (s, 1 H, CHN), 6.53 (s, 1 H, CH), 4.85 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.41–3.28 (m, 6 H, CH_2CH_3, CH_2NCO), 2.67 (m, 2 H, CH_2C), 1.98 (m, 2 H, $CH_2CH_2CH_2$), 1.19 (t, J = 6.8 Hz, 3 H, CH_3), 1.10 (t, J = 6.8 Hz, 3 H, CH_3) ppm. LC–MS: m/z = 388 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

2-[5-(3-Chlorobenzyl)-*N*,*N*-diethyl-5,6,7,8-tetrahydro-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[2]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.26 (s, 1 H, CH arom.), 7.18 (m, 3 H, CH arom.), 6.77 (d, J = 2 Hz, 1 H, CHN), 6.54 (d, J = 2 Hz, 1 H, CH), 4.70 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.39–3.28 (m, 6 H, CH_2CH_3, CH_2NCO), 2.66 (m, 2 H, CH_2C), 1.94 (m, 2 H, $CH_2CH_2CH_2$), 1.19 (t, J = 7.2 Hz, 3 H, CH_3), 1.11 (t, J = 7.2 Hz, 3 H, CH_3) ppm. LC–MS: m/z = 388 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

2-[5-(4-Chlorobenzyl)-*N*,*N*-diethyl-5,6,7,8-tetrahydro-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[3]): ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.23 (m, 4 H, CH arom.), 6.75 (d, J = 2 Hz, 1 H, CH), 6.53 (d, J = 2 Hz, 1 H, CHN), 4.68 (s, 2 H, CH_2Ph), 4.54 (s, 2 H, CH_2N), 3.39–3.27 (m, 6 H, CH_2CH_3, CH_2NCO), 2.64 (s, 2 H, CH_2C), 1.92 (m, 2 H, $CH_2CH_2CH_2$), 1.19 (t, J = 7.2 Hz, 3 H, CH_3), 1.10 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 166.0, 138.7, 134.6, 132.1, 130.2, 129.0, 122.9, 116.7, 110.5, 51.2, 48.7, 48.3, 41.3, 40.8, 26.4, 62.1, 14.7, 13.7 ppm. LC–MS: m/z = 388 [M + H]$^+$ (Phenomenex® column, 97.87%, 254 nm).

***N*,*N*-Diethyl-2-[5-(2-fluorobenzyl)-5,6,7,8-tetrahydro-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[4]):** ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.36 (m, 1 H, CH arom.), 7.16 (m, 1 H, CH arom.), 7.04–6.95 (m, 2 H, CH arom.), 6.71 (s, 2 H, CHN), 6.50 (s, 2 H, CH), 4.71 (s, 2 H, CH_2Ph), 4.52 (s, 2 H, CH_2N), 3.41–3.26 (m, 6 H, CH_2CH_3, CH_2NCO), 2.62 (m, 2 H, CH_2C), 1.94 (m, 2 H, $CH_2CH_2CH_2$), 1.17 (t, J = 7.2 Hz, 3 H, CH_3), 1.08 (t, J = 7.2 Hz, 3 H, CH_3) ppm. LC–MS: m/z = 372 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

***N*,*N*-Diethyl-2-[5-(3-fluorobenzyl)-5,6,7,8-tetrahydro-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[5]):** ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.21 (m, 1 H, CH arom.), 7.05 (d, J = 7.6 Hz, 1 H, CH arom.), 6.99 (d, J = 9.6 Hz, 1 H, CH arom.), 6.76 (d, J = 2.8 Hz, 1 H, CHN), 6.53 (d, J = 2.8 Hz, 1 H, CH), 4.71 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.40–3.27 (m, 6 H, CH_2CH_3, CH_2NCO), 2.66 (m, 2 H, CH_2C), 1.95 (m, 2 H, $CH_2CH_2CH_2$), 1.19 (t, J = 6.8 Hz, 3 H, CH_3), 1.10 (t, J = 6.8 Hz, 3 H, CH_3) ppm. LC–MS: m/z = 372 [M + H]$^+$ (Phenomenex® column, 98.43%, 254 nm).

***N*,*N*-Diethyl-2-[5-(4-fluorobenzyl)-5,6,7,8-tetrahydro-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[6]):** ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.26 (m, 2 H, CH arom.), 6.95 (m, 2 H, CH arom.), 6.76 (d, J = 2.8 Hz, 1 H, CHN), 6.54 (d, J = 2.8 Hz, 1 H, CH), 4.69 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.40–3.28 (m, 6 H, CH_2CH_3, CH_2NCO), 2.65 (m, 2 H, CH_2C), 1.92 (m, 2 H, $CH_2CH_2CH_2$), 1.19 (t, J = 7.2 Hz, 3 H, CH_3), 1.11 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 165.9, 163.1, 160.7, 135.79, 135.76, 134.5, 130.4, 130.33, 130.25, 122.9, 116.8, 115.9, 115.7, 110.5, 51.0, 48.7, 48.1, 26.3, 26.1, 14.73, 13.65 ppm. LC–MS: m/z = 372 [M + H]$^+$ (Phenomenex® column, 96.07%, 254 nm).

***N*,*N*-Diethyl-5,6,7,8-tetrahydro-2-[5-(2-methylbenzyl)-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[7]):** ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.15–7.13 (m, 5 H, CH arom.), 6.77 (d, J = 2 Hz, 1 H, CHN), 6.54 (d, J = 2 Hz, 1 H, CH), 4.75 (s, 2 H, CH_2Ph), 4.55 (m, 2 H, CH_2N), 3.38–3.29 (m, 6 H, CH_2CH_3, CH_2NCO), 2.65 (m, 2 H, CH_2C), 2.29 (s, 3 H, CH_3), 1.89 (m, 2 H, $CH_2CH_2CH_2$), 1.18 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.11 (t, J = 6.8 Hz, 3 H, CH_2CH_3) ppm. LC–MS: m/z = 368 [M + H]$^+$ (Phenomenex® column, 96.96%, 254 nm).

***N*,*N*-Diethyl-5,6,7,8-tetrahydro-2-[5-(3-methylbenzyl)-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[8]):** ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.14 (m, 1 H, CH arom.), 7.08–7.01 (m, 3 H, CH arom.), 6.78 (d, J = 2.8 Hz, 1 H, CHN), 6.54 (d, J = 2.8 Hz, 1 H, CH), 4.71 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.40–3.28 (m, 6 H, CH_2CH_3, CH_2NCO), 2.25 (m, 2 H, CH_2C), 2.29 (s, 3 H, CH_3), 1.92 (m, 2 H, $CH_2CH_2CH_2$), 1.19 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.11 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 165.9, 139.5, 138.1, 134.5, 128.9, 128.8, 128.2, 125.4, 122.9, 116.9, 110.6, 51.7, 48.7, 48.1, 41.3, 26.3, 26.1, 21.7, 14.74, 14.68, 13.6 ppm. LC–MS: m/z = 368 [M + H]$^+$ (Phenomenex® column, 96.85%, 254 nm).

***N*,*N*-Diethyl-5,6,7,8-tetrahydro-2-[5-(4-methylbenzyl)-4-oxopyrrolo-[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[9]):** ^{1}H NMR (400 MHz, [D]-chloroform): δ = 7.17 (d, J = 7.6 Hz, 2 H, CH arom.), 7.07 (d, J = 7.6 Hz, 2 H, CH arom.), 6.77 (d, J = 2.8 Hz, 1 H, CHN), 6.53 (d, J = 2.8 Hz, 1 H, CH), 4.69 (s, 2 H, CH_2Ph), 4.54 (s, 2 H, CH_2N), 3.39–3.27 (s, 6 H, CH_2CH_3, CH_2NCO), 2.64 (m, 2 H, CH_2C), 1.91 (m, 2 H, $CH_2CH_2CH_2$), 1.18 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.11 (t, J = 6.8 Hz, 3 H, CH_2CH_3) ppm. LC–MS: m/z = 368 [M + H]$^+$ (Phenomenex® column, 76.91%, 254 nm).

***N*,*N*-Diethyl-5,6,7,8-tetrahydro-2-[5-(3-methoxybenzyl)-4-oxopyrrolo[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[10]):** ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.16 (m, 1 H, CH arom.), 6.83 (m, 3 H, CH arom.), 6.67 (d, J = 3.2 Hz, 1 H, CHN), 6.50 (d, J = 3.2 Hz, 1 H, CH), 4.68 (s, 2 H, CH_2Ph), 4.521 (s, 2 H, CH_2N), 3.73 (s, 3 H, CH_3), 3.36–3.21 (m, 6 H, CH_2CH_3, CH_2NCO), 2.61 (m, 2 H, CH_2C), 1.90 (m, 2 H, $CH_2CH_2CH_2$), 1.16 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.08 (t, J = 6.8 Hz, 3 H, CH_2CH_3) ppm. LC–MS: m/z = 384 [M + H]$^+$ (Phenomenex® column, 87.94%, 254 nm).

***N*,*N*-Diethyl-5,6,7,8-tetrahydro-2-[5-(4-methoxybenzyl)-4-oxopyrrolo[3,2-*c*]azepin-1(4*H*)-yl]acetamide (24b[11]):** ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.18 (d, J = 8 Hz, 2 H, CH arom.), 6.78 (d, J = 8.2 Hz, 2 H, CH arom.), 6.72 (d, J = 2.8 Hz, 1 H, CHN), 6.49 (d, J = 2.8 Hz, 1 H, CH), 4.63 (s, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2N), 3.73 (s, 3 H, CH_3O), 3.36–3.24 (m, 6 H, CH_2CH_3,

CH_2NCO), 2.56 (m, 2 H, CH_2C), 1.86 (m, 2 H, $CH_2CH_2CH_2$), 1.15 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.07 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 165.8, 158.9, 134.4, 131.4, 129.7, 122.8, 117.0, 114.4, 110.5, 55.7, 51.0, 48.7, 47.9, 41.3, 26.4, 26.1, 14.7, 13.7 ppm. LC–MS: m/z = 384 $[M + H]^+$ (Phenomenex® column, 91.49%, 254 nm).

2-[5-Benzyl-5,6,7,8-tetrahydro-4-oxopyrrolo[3,2-*c*]azepin-1(4*H*)-yl]-*N*,*N*-diethylacetamide (24b[12]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.26–7.23 (m, 5 H, CH arom.), 6.75 (d, J = 3.2 Hz, 1 H, CHN), 6.51 (d, J = 3.2 Hz, 1 H, CH), 4.71 (s, 2 H, CH_2Ph), 4.52 (s, 2 H, CH_2N), 3.37–3.25 (m, 6 H, CH_2CH_3, CH_2NCO), 2.62 (m, 2 H, CH_2C), 1.89 (m, 2 H, $CH_2CH_2CH_2$), 1.16 (t, J = 7.2 Hz, 3 H, CH_3), 1.09 (t, J = 7.2 Hz, 3 H, CH_3) ppm. LC–MS: m/z = 354 $[M + H]^+$ (Phenomenex® column, 93.68%, 254 nm).

***N*,*N*-Diethyl-2-[5,6,7,8-tetrahydro-5-methyl-4-oxopyrrolo[3,2-*c*]-azepin-1(4*H*)-yl]acetamide (24b[13]):** ^1H NMR (400 MHz, [D]chloroform): δ = 6.66 (d, J = 2.8 Hz, 1 H, CHN), 6.47 (d, J = 2.8 Hz, 1 H, CH), 4.52 (s, 2 H, CH_2N), 3.38–3.25 (m, 6 H, CH_2CH_3, CH_2NCO), 3.07 (s, 3 H, CH_3), 2.65 (m, 2 H, CH_2C), 2.02 (m, 2 H, $CH_2CH_2CH_2$), 1.16 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.09 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. LC–MS: m/z = 278 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5-(4-Chlorobenzyl)-5,6,7,8-tetrahydro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[3]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.25 (m, 4 H, CH arom.), 6.76 (d, J = 2.4 Hz, 1 H, CHN), 6.52 (d, J = 2.4 Hz, 1 H, CH), 4.68 (s, 2 H, CH_2Ph), 4.56 (s, 2 H, CH_2N), 3.61 (m, 2 H, CH_2NCH_2), 3.44 (m, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.64 (m, 2 H, CH_2C), 2.38 (m, 4 H, CH_2NCH_3), 2.28 (s, 3 H, CH_3N), 1.92 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.4, 165.0, 137.0, 133.0, 129.5, 128.6, 121.6, 117.5, 111.80, 54.9, 54.5, 51.4, 48.7, 47.6, 46.0, 44.8, 42.2, 26.1 ppm. LC–MS: m/z = 415 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5-(2-Fluorobenzyl)-5,6,7,8-tetrahydro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[4]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.35 (m, 1 H, CH arom.), 7.16 (m, 1 H, CH arom.), 7.04–6.94 (m, 2 H, CH arom.), 6.71 (d, J = 2.8 Hz, 1 H, CHN), 4.75 (s, 2 H, CH_2Ph), 4.53 (s, 2 H, CH_2N), 3.57 (m, 2 H, CH_2NCH_2), 3.40 (m, 4 H, CH_2NCH_2, CH_2NCO), 2.61 (m, 2 H, CH_2C), 2.35 (m, 4 H, CH_2NCH_3), 2.26 (s, 3 H, CH_3N), 1.92 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 399 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5-(3-Fluorobenzyl)-5,6,7,8-tetrahydro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[5]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.21 (m, 1 H, CH arom.), 7.02 (d, J = 7.6 Hz, 1 H, CH arom.), 6.96 (d, J = 9.2 Hz, 1 H, CH arom.), 6.88 (m, 1 H, CH arom.), 6.73 (d, J = 2.4 Hz, 1 H, CHN), 6.49 (d, J = 2.4 Hz, 1 H, CH), 4.68 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.58 (m, 2 H, CH_2NCH_2), 3.43 (m, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.62 (m, 2 H, CH_2C), 2.36 (m, 4 H, CH_2NCH_3), 2.26 (s, 3 H, CH_3N), 1.92 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.2, 165.9, 137.0, 136.4, 134.6, 130.7, 127.9, 127.4, 126.4, 122.8, 116.9, 110.7, 55.2, 54.9, 49.8, 48.7, 48.0, 46.3, 44.7, 42.1, 26.2, 26.1, 19.4 ppm. LC–MS: m/z = 399 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5-(4-Fluorobenzyl)-5,6,7,8-tetrahydro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[6]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.22 (d, J = 7.6 Hz, 2 H, CH arom.), 6.93 (m, 2 H, CH arom.), 6.73 (d, J = 2.8 Hz, 1 H, CHN), 6.49 (d, J = 2.8 Hz, 1 H, CH), 4.66 (s, 2 H, CH_2Ph), 4.54 (s, 2 H, CH_2N), 3.58 (m, 2 H, CH_2NCH_2), 3.43 (m, 2 H, CH_2NCH_2), 3.32 (m, CH_2NCO), 2.61 (m, 2 H, CH_2C), 2.36 (m, 4 H, CH_2NCH_3), 2.26 (s, 3 H, CH_3N), 1.94 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 399 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(2-methylbenzyl)-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[7]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.12 (m, 4 H, CH arom.), 6.74 (d, J = 2.8 Hz, 1 H, CHN), 6.50 (d, J = 2.8 Hz, 1 H, CH), 4.73 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.59 (m, 2 H, CH_2NCH_2), 3.43 (m, 2 H, CH_2NCH_2), 2.63 (m, 2 H, CH_2NCO), 2.36 (m, 4 H, CH_2NCH_3), 2.27 (m, 6 H, CH_3N, CH_3Ph), 1.88 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.2, 165.9, 139.5, 134.6, 129.0, 128.3, 127.5, 122.8, 116.9, 110.6, 55.2, 54.9, 51.8, 48.7, 48.2, 46.3, 44.7, 42.1, 26.3, 26.2 ppm. LC–MS: m/z = 395 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(3-methylbenzyl)-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[8]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.14 (m, 1 H, CH arom.), 7.08–6.99 (m, 3 H, CH arom.), 6.79 (d, J = 3.2 Hz, 1 H, CHN), 6.50 (d, J = 3.2 Hz, 1 H, CH), 4.68 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.59 (m, 2 H, CH_2NCH_2), 3.43 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.62 (m, 2 H, CH_2C), 2.32 (m, 4 H, CH_2NCH_3), 2.27 (m, 6 H, CH_3N, CH_3Ph), 1.912 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 395 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(4-methylbenzyl)-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[9]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.165 (d, J = 8 Hz, 2 H, CH arom.), 7.07 (d, J = 8 Hz, 2 H, CH arom.), 6.77 (d, J = 2.8 Hz, 1 H, CHN), 6.51 (d, J = 8 Hz, 1 H, CH), 4.68 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.43 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.63 (m, 2 H, CH_2C), 2.37 (m, 4 H, CH_2NCH_3), 2.28 (m, 6 H, CH_3Ph, CH_3N), 1.90 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 395 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(3-methoxybenzyl)-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[10]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.18 (m, 1 H, CH arom.), 6.85 (d, J = 7.6 Hz, 1 H, CH arom.), 6.82 (s, 1 H, CH, arom.), 6.77 (d, J = 2.8 Hz, 1 H, CH arom.), 6.74 (d, J = 2 Hz, 1 H, CH arom.), 6.51 (d, J = 2.8 Hz, 1 H, CH), 4.70 (s, 2 H, CH_2Ph), 4.56 (s, 2 H, CH_2N), 3.75 (s, 3 H, CH_3O), 3.60 (m, 2 H, CH_2NCH_2), 3.44 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.63 (m, 2 H, CH_2C), 2.37 (4 H, CH_2NCH_3), 2.28 (s, 3 H, CH_3N), 1.92 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 411 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-(4-methoxybenzyl)-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[11]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.21 (d, J = 8.00 Hz, 2 H, CH arom.), 6.80 (d, J = 8.00 Hz, 2 H, CH arom.), 6.77 (d, J = 2.8 Hz, 1 H, CHN), 6.52 (d, J = 2.8 Hz, 1 H, CH), 4.66 (s, 2 H, CH_2Ph), 4.56 (s, 2 H, CH_2N), 3.76 (s, 3 H, CH_3O), 3.61 (m, 2 H, CH_2NCH_2), 3.44 (m, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.62 (m, 2 H, CH_2CO), 2.38 (m, 4 H, CH_2NCH_3), 2.29 (s, 3 H, CH_3N), 1.89 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 411 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5-Benzyl-5,6,7,8-tetrahydro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[12]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.24–7.18 (m, 5 H, CH arom.), 6.75 (d, J = 2.8 Hz, 1 H, CHN), 6.49 (d, J = 2.8 Hz, 1 H, CH), 4.71 (s, 2 H, CH_2Ph), 4.54 (s, 2 H, CH_2N), 3.58 (m, 2 H, CH_2NCH_2), 3.42 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.61 (m, 2 H, CH_2C),

2.35 (m, 4 H, CH_2NCH_3), 2.35 (s, 3 H, CH_3N), 1.89 (m, 2 H, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.2, 165.9, 139.5, 134.5, 129.0, 128.3, 127.5, 122.8, 116.9, 110.6, 55.2, 54.9, 51.7, 48.7, 46.3, 44.7, 42.1, 26.3, 26.2 ppm. LC–MS: *m*/*z* = 381 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

5,6,7,8-Tetrahydro-5-methyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24c[13]): ^1H NMR (400 MHz, [D]chloroform): δ = 6.59 (d, *J* = 2.8 Hz, 1 H, CHN), 6.42 (d, *J* = 2.8 Hz, 1 H, CH), 4.53 (s, 2 H, CH_2N), 3.54 (m, 2 H, CH_2NCH_2), 3.39 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, 2 H, CH_2NCO), 3.01 (s, 3 H, CH_3NCO), 2.60 (m, 2 H, CH_2C), 2.31 (m, 4 H, CH_2NCH_3), 2.22 (s, 3 H, CH_3N), 1.98 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 305 [M + H]$^+$.

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5-(2-chlorobenzyl)-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[1]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.27–7.24 (m, 7 H, CH arom.), 7.16 (m, 2 H, CH arom.), 6.76 (d, *J* = 3.2 Hz, 1 H, CHN), 6.51 (d, *J* = 3.2 Hz, 1 H, CH), 4.85 (s, 2 H, $CONCH_2Ph$), 4.56 (s, 2 H, CH_2N), 3.61 (m, 2 H, CH_2NCH_2), 3.51 (s, 2 H, NCH_2Ph), 3.41 (m, 4 H, CH_2NCH_2, CH_2NCO), 2.66 (m, 2 H, CH_2C), 2.43 (m, 4 H, CH_2NCH_2Ph), 1.98 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]-chloroform): δ = 166.6, 165.1, 137.4, 135.7, 133.7, 133.3, 129.5, 129.4, 129.1, 128.4, 128.3, 127.4, 127.0, 121.6, 117.4, 111.7, 62.8, 52.9, 52.6, 49.5, 48.7, 48.1, 45.0, 42.4, 26.1 ppm. LC–MS: *m*/*z* = 491 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5-(3-chlorobenzyl)-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[2]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.32–7.24 (m, 6 H, CH arom.), 7.20–7.14 (m, 3 H, CH arom.), 6.75 (d, *J* = 2.8 Hz, 1 H, CHN), 6.50 (d, *J* = 2.8 Hz, 1 H, CH), 4.69 (s, 2 H, $CONCH_2Ph$), 4.55 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.63 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.93 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 491 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5-(4-chlorobenzyl)-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[3]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.32–7.20 (m, 9 H, CH arom.), 6.75 (d, *J* = 3.2 Hz, 1 H, CHN), 6.51 (d, *J* = 3.2 Hz, 1 H, CH), 4.67 (s, 2 H, $CONCH_2Ph$), 4.55 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.63 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.91 (s, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 491 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5-(2-fluorobenzyl)-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[4]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.40 (m, 1 H, CH arom.), 7.32–7.16 (m, 6 H, CH arom.), 7.06–6.97 (m, 2 H, CH arom.), 6.74 (d, *J* = 3.2 Hz, 1 H, CHN), 6.50 (d, *J* = 3.2 Hz, 1 H, CH), 4.77 (s, 2 H, $CONCH_2Ph$), 4.54 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.44–3.40 (m, 4 H, CH_2NCH_2, CH_2NCO), 2.62 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.95 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 475 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5-(3-fluorobenzyl)-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[5]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.34–7.20 (m, 6 H, CH arom.), 7.04 (d, *J* = 7.6 Hz, 1 H, CH arom.), 6.98 (d, *J* = 9.6 Hz, 1 H, CH arom.), 6.89 (m, 1 H, CH arom.), 6.75 (d, *J* = 2.8 Hz, 1 H, CHN), 6.50 (d, *J* = 2.8 Hz, 1 H, CH), 4.71 (s, 2 H, $CONCH_2Ph$), 4.55 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.64 (m, 2 H, CH_2C), 2.42 (m, CH_2NCH_2Ph), 1.93 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 475 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5-(4-fluorobenzyl)-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[6]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.34–7.23 (m, 7 H, CH arom.), 6.95 (t, *J* = 8.80Hz, 2 H, CH arom.), 6.75 (d, *J* = 2.8 Hz, 1 H, CHN), 6.50 (d, *J* = 2.8 Hz, 1 H, CH), 4.67 (s, 2 H, $CONCH_2Ph$), 4.54 (s, 2 H, CH_2N), 3.59 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.62 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.90 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 475 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydro-5-(2-methylbenzyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[7]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.34–7.24 (m, 5 H, CH arom.), 7.16 (m, 4 H, CH arom.), 6.76 (d, *J* = 3.2 Hz, 1 H, CHN), 6.51 (d, *J* = 3.2 Hz, 1 H, CH), 4.74 (s, 2 H,$CONCH_2Ph$), 4.54 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.32 (m, 2 H, CH_2NCO), 2.63 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 2.29 (s, 3 H, CH_3), 1.88 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 137.4, 136.6, 135.9, 133.6, 130.4, 129.1, 128.4, 127.4, 127.1, 126.0, 121.5, 117.6, 111.7, 62.8, 52.9, 52.6, 49.5, 48.7, 47.1, 45.0, 42.4, 26.0, 19.3 ppm. LC–MS: *m*/*z* = 471 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydro-5-(3-methylbenzyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[8]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.35–7.24 (m, 5 H, CH arom.), 7.16 (m, 1 H, CH arom.), 7.10–7.01 (m, 3 H, CH arom.), 6.78 (d, *J* = 2.8 Hz, 1 H, CHN), 6.51 (d, *J* = 2.8 Hz, 1 H, CH), 4.70 (s, 2 H, $CONCH_2Ph$), 4.55 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (s, 2 H, CH_2NCH_2), 3.34 (m, 2 H, CH_2NCO), 2.63 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 2.30 (s, 3 H, CH_3), 1.91 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 471 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydro-5-(3-methylbenzyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[9]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.35–7.24 (m, 5 H, CH arom.), 7.17 (d, *J* = 8 Hz, 2 H, CH arom.), 7.07 (d, *J* = 8.00 Hz, 2 H, CH arom.), 6.76 (d, *J* = 3.2 Hz, 1 H, CHN), 6.50 (d, *J* = 3.2 Hz, 1 H, CH), 4.68 (s, 2 H, $CONCH_2Ph$), 4.54 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.62 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 2.29 (s, 3 H, CH_3), 1.89 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 471 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydro-5-(3-methoxybenzyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[10]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.35–7.24 (m, 5 H, CH arom.), 7.19 (t, *J* = 8 Hz, 1 H, CH arom.), 6.69 (m, 3 H, CH arom.), 6.78 (d, *J* = 2.8 Hz, 1 H, CHN), 6.52 (d, *J* = 2.8 Hz, 1 H, CH), 4.71 (s, 2 H, $CONCH_2Ph$), 4.55 (s, 2 H, CH_2N), 3.76 (s, 3 H, CH_3O), 3.61 (m, 2 H, CH_2NCH_2), 3.51 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.35 (m, 2 H, CH_2NCO), 2.64 (m, 2 H, CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.93 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: *m*/*z* = 487 [M + H]$^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydro-5-(4-methoxybenzyl)pyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[11]): ^1H NMR (400 MHz, [D]chloroform): δ = 7.35–7.20 (m, 7 H, CH arom.), 6.81

(d, J = 8.4 Hz, 2 H, CH arom.), 6.77 (d, J = 3.2 Hz, 1 H, CHN), 6.51 (d, J = 3.2 Hz, 1 H, CH), 4.66 (s, 2 H, CONCH_2Ph), 4.54 (s, 2 H, CH_2N), 3.76 (s, 3 H, CH_3O), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (m, 2 H, CH_2NCH_2), 3.33 (m, 2 H, CH_2NCO), 2.62 (m, 2H CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.89 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 137.4, 133.5, 130.5, 129.4, 129.1, 128.4, 127.4, 121.5, 117.7, 113.9, 111.7, 62.8, 55.3, 52.9, 52.6, 51.1, 48.6, 47.2, 45.0, 42.3, 26.7, 26.1 ppm. LC–MS: m/z = 487 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

5-Benzyl-1-[2-(4-benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[12]): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.35–7.21 (m, 10 H, CH arom.), 6.78 (d, J = 2.8 Hz, 1 H, CHN), 6.51 (d, J = 2.8 Hz, 1 H, CH), 4.73 (s, 2 H, CONCH_2Ph), 4.54 (s, 2 H, CH_2N), 3.60 (m, 2 H, CH_2NCH_2), 3.50 (s, 2 H, NCH_2Ph), 3.42 (s, 2 H, CH_2NCH_2), 3.35 (m, 2 H, CH_2NCO), 2.63 (m, 2H CH_2C), 2.42 (m, 4 H, CH_2NCH_2Ph), 1.91 (m, 2 H, $CH_2CH_2CH_2$) ppm. LC–MS: m/z = 457 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

1-[2-(4-Benzylpiperazin-1-yl)-2-oxoethyl]-5,6,7,8-tetrahydro-5-methylpyrrolo[3,2-*c*]azepin-4(1*H*)-one (24d[13]): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.34–7.24 (m, 5 H, CH arom.), 6.65 (d, J = 2.8 Hz, 1 H, CHN), 6.45 (d, J = 2.8 Hz, 1 H, CH), 4.52 (s, 2 H, CH_2N), 3.58 (m, 2 H, CH_2NCH_2), 3.49 (s, 2 H, NCH_2Ph), 3.41 (m, 2 H, CH_2NCH_2), 3.36 (m, 2 H, CH_2NCO), 3.06 (s, 3 H, CH_3), 2.62 (m, 2 H, CH_2C), 2.40 (m, 4 H, CH_2NCH_2Ph), 2.01 (m, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR ([D]chloroform): δ = 166.5, 165.2, 137.4, 133.4, 129.1, 128.4, 127.4, 121.5, 117.6, 111.2, 62.8, 52.9, 52.6, 49.8, 48.6, 44.9, 42.3, 36.6, 25.8 ppm. LC–MS: m/z = 381 $[M + H]^+$ (Phenomenex® column, 100%, 254 nm).

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[1] D. S. Tan, *Nature Chem. Biol.* **2005**, *1*, 74; M. Cano, S. Balasubramanian, *Drugs Fut.* **2003**, *28*, 659.
[2] S. Shang, D. S. Tan, *Curr. Opin. Chem. Biol.* **2005**, *9*, 248; B. Kundu, *Curr. Opin. Drug Disc. Devel.* **2003**, *6*, 815.
[3] R. Martinez, J. G. Avila, M. T. Ramirez, A. Perez, A. Martinez, *Bioorg. Med. Chem.* **2006**, *14*, 4007.
[4] F. Janssens, J. Leenaerts, G. Diels, B. De Boeck, A. Megens, X. Lanlois, K. Van Rossem, J. Beetens, M. Borgers, *J. Med. Chem.* **2005**, *48*, 2154.
[5] H. Cho, K. Murakami, H. Nakanishi, A. Fujisawa, H. Isoshima, M. Niwa, K. Hayakawa, Y. Hase, I. Uchida, H. Watanabe, K. Wakitani, K. Aisaka, *J. Med. Chem.* **2004**, *47*, 101; A. Mizuno, N. Inomata, M. Miya, M. Shibata, T. Tatsuoka, M. Yoshida, C. Takiguchi, T. Miyazaki, *Chem. Pharm. Bull.* **1999**, *47*, 246.
[6] F. Gosselin, W. D. Lubell, *J. Org. Chem.* **2000**, *65*, 2163.
[7] H. Greger, *Planta Med.* **2006**, *72*, 99; J. Schinnerl, E. Kaltenegger, T. Pacher, S. Vajrodaya, O. Hofer, H. Greger, *Monatsh. Chem.* **2005**, *136*, 1671; A. C. Barrios Sosa, K. Yakushijin, D. A. Horne, *J. Org. Chem.* **2002**, *67*, 4498.
[8] To the best of our knowledge the only syntheses applicable to the preparation of pyrrolo-azepine arrays are reported in: M. Nath, R. Mukhopadhyay, A. Bhattacharjya, *Org. Lett.* **2006**, *8*, 317; F. Gosselin, W. D. Lubell, *J. Org. Chem.* **2000**, *65*, 2163.
[9] K. Hino, Y. Nagai, H. Uno, Y. Matsuda, M. Oka, T. Karasawa, *J. Med. Chem.* **1988**, *31*, 107.
[10] C. Daqher, R. Hanna, P. B. Terentiev, Y. G. Boundel, B. I. Marksimof, N. S. Kulikov, *J. Heterocycl. Chem.* **1983**, *20*, 989.
[11] H. Stetter, *Chem. Ber.* **1955**, *88*, 271.
[12] When acidification was carried out without previous removal of MeOH, a mixture of the acid and the corresponding methyl ester was obtained.
[13] H. Stetter, R. Lauterbach, *Liebigs Ann. Chem.* **1962**, *655*, 20; see also: E. Bellur, P. Langer, *Tetrahedron Lett.* **2006**, *13*, 2151; S. Wu, A. Fluxe, J. M. Janusz, J. B. Sheffer, G. Browning, B. Blass, K. Cobum, R. Hedges, M. Murawsky, B. Fang, G. M. Fadayel, M. Hare, L. Djandjighian, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5859.
[14] M. Matsumoto, N. Watanabe, *Heterocycles* **1984**, *22*, 2313.
[15] As glycine could not be used as the solvent in this reaction, we used a mixture of ethanol and water as the solvent. For our recent application of MW to the synthesis of heterocycles, see: S. Ferrini, F. Ponticelli, M. Taddei, *Org. Lett.* **2007**, *9*, 69.
[16] Oxime **11** was obtained as a single isomer after crystallisation. *Z* configuration was assigned to **11** on the basis of the structure of product **12**, obtained by Beckmann rearrangement.
[17] Y. Furuya, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 11240, and references cited therein.
[18] DMTMM: 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride. See: A. Falchi, G. Giacomelli, A. Porcheddu, M. Taddei, *Synlett* **2000**, 277.
[19] The ^{1}H and ^{13}C NMR spectra of **14** showed twin signals for most of the resonances, suggesting the presence of a mixture of *E*/*Z* diastereoisomers.
[20] Attempts to prepare the oxime starting from ethyl ester **7**, previously isolated from the microwave-assisted reaction of **2** (Scheme 2), gave a mixture of the *E* and *Z* isomers, which produced, as expected, a mixture of pyrrolo-azepinones.
[21] This low reactivity may be attributed to the poor solubility of **15** in many solvents, including DMF.
[22] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* **1997**, *23*, 3. Calculations of the parameters in Figure 3 and Figure 4 were carried out with the software ilib diverse 1.02, Inte:Ligand, Maria Enzersdorf, Austria.

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