Parallel Synthesis of 1-Substituted 5-(5-Oxopyrrolidin-3-yl)-1*H*-pyrazole-4-carboxamides

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Abstract: A parallel solution-phase synthesis of 5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxamide derivatives as conformationally constrained pyrazole analogues of histamine starting from itaconic acid was developed. The synthetic method comprises a five-step preparation of 1-substituted 5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxylic acids followed by parallel amidation with various primary and secondary amines to give a library of 24 histamine analogues in good overall yields and in very high purities. The method is general and substrate-independent. All the amidations proceed smoothly and no major difference in reactivity is observed with respect to the structures of the reactants.

Key words: pyrrolidinone, pyrazole, cyclocondensations, amidations, histamine analogues

Many heterocyclic compounds represent important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications and for utilization in materials science.[1,2] Since 2-[(hetero)aryl]ethylamines, such as dopamine, histamine, tryptamine, serotonin and melatonin are representative chemical messengers that play a crucial role in biological processes, the preparation of their novel synthetic analogues represents an important target in medicinal and synthetic organic chemistry. Within this context, the synthesis of libraries of novel 2-(heteroaryl)ethylamine derivatives and analogues is of particular interest.[1–3]

A part of our research has focused on the synthesis of functionalized heterocycles via 1,3-dipolar cycloadditions of (4*R**,5*R**)-4-benzoylamino-5-phenyl-3-pyrazolidinone derived azomethine imines to various dipolarophiles,[4] and cyclocondensations of functionalized enaminones with nucleophiles.[5] Both approaches have been applied in high-throughput[6,7] and bioorganic synthesis.[8] We have reported a 'ring-switching' synthesis of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **2**[9] as pyrazole analogues of histamine (**1**), in addition to a one-pot, parallel solution-phase synthesis of compounds **2**.[10] The syntheses of 1-substituted 5-(2-aminoethyl)-1*H*-pyrazole-4-carboxamides **3**,[11] their bicyclic analogues **4**,[12] and 5-(2-aminophenyl)pyrazole derivatives **5**[13] have also been developed. In continuation of this work, we concentrated our attention on another type of histamine analogue, **6**, where the aminoethyl functionality is replaced by a 2-pyrrolidinone moiety. The structures of histamine (**1**) and its analogues **2**–**6** are depicted in Figure 1.

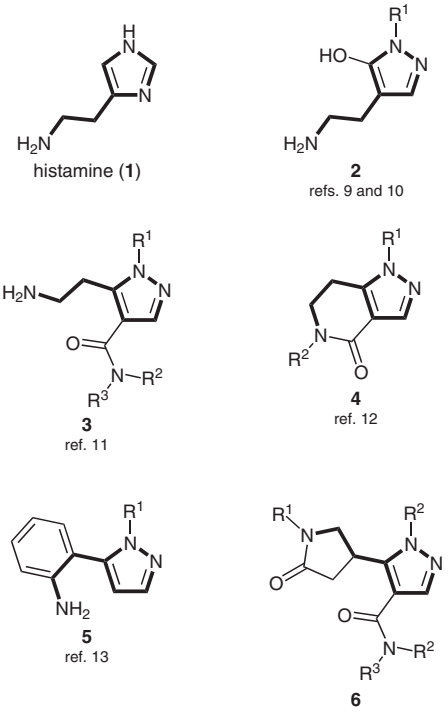

Figure 1 Histamine (**1**) and its pyrazole analogues **2**–**6**

As a result of our research efforts in this field, we now report a simple enaminone-based parallel solution-phase synthesis of 1-substituted 5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxamides **6** as novel types of conformationally constrained histamine analogues.

Initially, the starting compound **8** was prepared from commercially available itaconic acid (**7**) and aniline following the literature procedure.[14] Masamune–Claisen condensation of **8** with potassium monomethyl malonate as a C_2-synthon was carried out using 1,1′-carbonyldiimidazole (CDI) as the activating agent in anhydrous acetonitrile at room temperature to give the β-keto ester **9** in 83% yield. Treatment of **9** with *N*,*N*-dimethylformamide–dimethyl acetal (DMF–DMA) in toluene at reflux temperature gave the enamino ketone intermediate **10**, which was subse-

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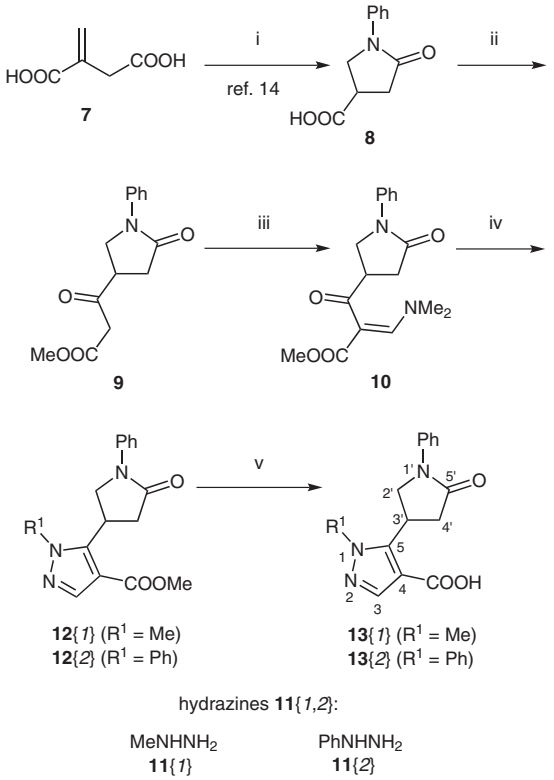
quently cyclized with methylhydrazine **11**{*1*} or phenylhydrazine **11**{*2*} to afford pyrazole-4-carboxylates **12**{*1*} and **12**{*2*} in 70% and 81% yields, respectively. Finally, hydrolysis of esters **12**{*1,2*} with sodium hydroxide in aqueous methanol at 50 °C furnished the corresponding carboxylic acids **13**{*1*} and **13**{*2*} in yields of 89% and 82% (Scheme 1).

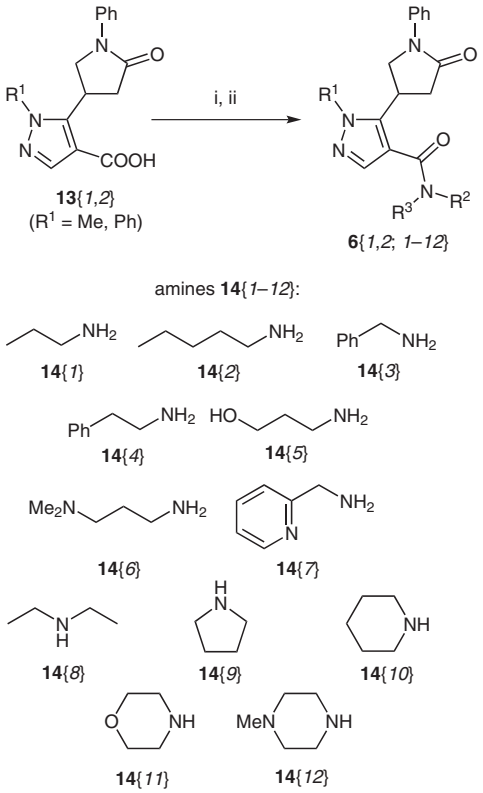


Scheme 1 *Reagents and conditions*: (i) $PhNH_2$, H_2O, reflux (reference 14); (ii) CDI, MeCN, r.t., 1 h, then potassium monomethyl malonate, $MgCl_2$, MeCN, r.t.; (iii) DMF–DMA, toluene, reflux; (iv) R^1NHNH_2 **11**{*1,2*}, MeOH, r.t.→reflux; (v) NaOH, MeOH–H_2O (2:1), 50 °C.

Once the desired key intermediates **13**{*1,2*} had been prepared, the parallel solution-phase synthesis of 1-substituted 5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxamides **6** was studied. First, suitable reaction conditions and activating reagents for parallel amidation of the acids **13** had to be found. Based on literature data,[15] and on our previous experience with related amidations,[7i,11] 2-ethoxy-1-ethoxycarbonyldihydroquinoline (EEDQ), and bis(pentafluorophenyl) carbonate (BPC) were our primary choices as activating reagents, as amidations with these two substrates produce volatile by-products removable by evaporation. The acids **13**{*1*} and **13**{*2*} were subjected to amidation with benzylamine **14**{*3*} and pyrrolidine **14**{*9*} using the above activating reagents. However, amidation of acids **13**{*1,2*} did not take place in the presence of 2-ethoxy-1-ethoxycarbonyldihydroquinoline, while bis(pentafluorophenyl) carbonate mediated coupling proceeded smoothly with both amines, **14**{*3*} and **14**{*9*}. *N*-Benzylcarboxamides **6**{*1,2; 3*} precipitated from the reaction mixtures and were isolated by filtration. On the other hand, tertiary amides **6**{*1,2; 9*} did not precipitate and the reaction mixtures were instead evaporated in vacuo to afford the crude products **6**{*1; 9*} and **6**{*2; 9*}. Crystallization of **6**{*1; 9*} was induced by trituration with diethyl ether, whereas **6**{*2; 9*} precipitated upon similar treatment of the crude product with aqueous methanol. Once the reaction conditions and workup had been established, a parallel synthesis of a library of 24 carboxamides **6**{*1,2; 1–12*} was carried out. Thus, the acids **13**{*1,2*} were activated with triethylamine and bis(pentafluorophenyl) carbonate in acetonitrile at room temperature to give the intermediate pentafluorophenyl esters, which were subsequently treated with equimolar amounts of amines **14**{*1–12*} and triethylamine at room temperature for 12 hours to furnish carboxamides **6**{*1,2; 1–12*}. A total of 24 products were isolated by sequential filtration and evaporation in this way. Eight compounds, **6**{*1; 3,7*} and **6**{*2; 1–4,6,11*}, precipitated from the reaction mixtures and were isolated by filtration. The remaining reaction mixtures were evaporated and the residues triturated with diethyl ether. Four compounds, **6**{*1; 4–6,9*}, which precipitated from these reaction mixtures, were collected by filtration. The remaining reaction mixtures were again evaporated and the residues triturated with aqueous methanol to afford 10 compounds, **6**{*1; 1,2,11,12*} and **6**{*2; 5,7–10,12*} as precipitates, which were isolated by filtration. The last two compounds, **6**{*1; 8*} and **6**{*1; 10*}, were obtained by evaporation of the corresponding solutions. Finally, all the products were dried thoroughly in vacuo at 80 °C. In this manner, the title compounds **6**{*1,2; 1–12*} were obtained in 29–100% yields and in very high purities. Of the 24 library members, 20 were ≥95% pure, one was 92% pure, and three were 85–89% pure (Scheme 2, Table 1).

The structures and purities of novel compounds **6**{*1,2; 1–12*}, **9**, **12**{*1,2*}, and **13**{*1,2*} were determined by spectroscopic methods (IR, ^{1}H NMR and ^{13}C NMR, MS, HRMS), by LC–MS, and by elemental analyses. Characterization data for compounds **6**{*1,2; 1–12*} are given in Tables 2 and 3.

Next, we tried to find suitable conditions for separation of the enantiomers of racemic compounds **6** by HPLC using an analytical chiral stationary phase column [Chiralcel® OD-H (0.46 cm × 25 cm)] and *n*-hexane–isopropanol as the mobile phase. To our surprise, 16 of the 24 racemic compounds, **6**{*1; 1–5,9–12*} and **6**{*2; 1–4,8,10,12*}, were resolved, while five racemic compounds, **6**{*1; 6,8*} and **6**{*2; 5–7*}, were partially resolved. We were unable to find suitable conditions for the separation of only three racemic mixtures, **6**{*1; 7*} and **6**{*2; 9,11*}. Thus, the above separation conditions were suitable for resolution of the enantiomers of the majority of the racemic secondary and tertiary carboxamides **6**. We believe that the results obtained using the analytical column should be applicable for the (semi)preparative separation of enantiomers of **6**{*1; 1–6,8–12*} and **6**{*2; 1–8,10,12*}. Moreover, these separation conditions could prove valuable for the resolu-



Scheme 2 *Reagents and conditions*: (i) Et_3N, bis(pentafluorophenyl) carbonate, MeCN, r.t.; (ii) R^2R^3NH **14**{*1–12*}, Et_3N, MeCN, r.t.

tion of analogous racemic compounds (Table 4, and Supporting Information).

In conclusion, 5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxamides **6**, as novel conformationally-constrained pyrazole analogues of histamine, are available in six steps from itaconic acid (**7**). The synthetic pathway consists of a five-step preparation of pyrazole-4-carboxylic acids **13**{*1,2*} as the key intermediates followed by parallel solution-phase, bis(pentafluorophenyl) carbonate mediated amidation of **13**{*1,2*} with primary and secondary amines **14**{*1–12*} to give the title compounds **6**{*1,2; 1–12*} in good overall yields and in very high purities upon simple workup. The method is general and substrate-independent. All 24 amidations proceeded smoothly and no major difference in reactivity was observed, neither with respect to the N(1) substituent on the pyrazole-4-carboxylic acids **13**, nor regarding the structure of the amine **14**. These results also indicate that the above synthetic method could also serve as a useful tool for the preparation of novel compound libraries for pharmaceutical and other practical applications.

Melting points were determined using a Stanford Research Systems MPA100 OptiMelt automated melting point system. Compounds **6** and **13** were dried in a Büchi drying oven. IR spectra were obtained using a Perkin-Elmer Spectrum BX FTIR spectrophotometer. The NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300 MHz (^{1}H) and 75.5 MHz (^{13}C), using DMSO-d_6 or $CDCl_3$ as solvent and TMS as the internal standard. Mass spectra were recorded on a Q-Tof Premier spectrometer. Microanalyses were obtained using a Perkin-Elmer CHN Analyzer 2400 II. LC–MS/MS experiments were performed using a liquid chromatograph Perkin Elmer Series 200 (Perkin Elmer, Shelton, CT, USA) with a UV detector and a 3200 QTRAP LC/MS/MS System equipped with ESI and APCI ion sources (Applied Biosystems/MDS Sciex, Foster City, CA, USA). A Gemini HPLC column (150 mm × 4.6 mm, 3 μm particles) supplied by Phenomenex (Torrance, CA, USA) was used. The mobile phase consisted of a gradient of MeCN (A) and deionized H_2O (B): 0 min, 10% A; 25 min, 100% A; a 3 min equilibration time with initial mobile phase (10% A) was allowed for column equilibration. The mobile phase flow rate was 1 mL/min and the injection volume was 20 μL. Signals were recorded using a UV detector at 254 nm, and mass spectra were obtained using positive (ESI+) and negative (ESI–) ionization modes, simultaneously. The mass range was from 70–500 amu. The electrospray ion source (ESI) conditions were as follows: cone voltage 5500 V (ESI+) and –4500 V (ESI–), ion source temperature 4000 °C, curtain gas N_2 pressure was set to 10 psi, nebulizer gas N_2 pressure was set to 20 psi and turbo gas (air) pressure was set to 40 psi. A declustering potential of 30 V and an entrance potential of 10 V were employed. Resolution of the enantiomers of **6**{*1,2; 1–12*} was performed on a Agilent Technologies 1260 Infinity HPLC apparatus equipped with a quaternary pump and a UV detector. A Chiralcel® OD-H (0.46 cm × 25 cm, particle size 5 μm, Part No. 14325) HPLC column was used. The mobile phase consisted of an isocratic mixture of *n*-hexane and *i*-PrOH; the mobile phase flow rate was 1 mL/min and the injection volume was 5 μL.

Itaconic acid (**7**), 1,1′-carbonyldiimidazole, DMF–DMA, methylhydrazine **11**{*1*}, phenylhydrazine **11**{*2*}, bis(pentafluorophenyl) carbonate, and amines **14**{*1–12*} were commercially available (Sigma-Aldrich). 5-Oxo-1-phenylpyrrolidin-3-carboxylic acid (**8**) was prepared according to the literature procedure.[14] Parallel stirring was carried out on a Büchi Syncore® Polyvap parallel reactor (24 positions, vortex stirring, 400 rpm in all cases)**.** Parallel filtrations were carried out on a Mettler-Toledo Bohdan MiniBlock™ Compact Shaking and Washing Station and Vacuum Collection Base (12 positions). Parallel evaporations and drying were carried out on (a) a Büchi Syncore® Polyvap parallel evaporator (24 positions, vortex stirring, 400 rpm in all cases), and (b) a Hettlab IR-Dancer Infra-Red Vortex-Evaporator (42 positions, vortex stirring, 400 rpm in all cases).

Methyl 3-Oxo-3-(5-oxo-1-phenylpyrrolidin-3-yl)-propanoate (9)

This compound was prepared from pyrrolidinone **8** following a modified literature procedure.[11] CDI (8.5 g, 52 mmol) was added to a stirred suspension of **8**[14] (10.2 g, 50 mmol) in anhyd MeCN (120 mL), and the mixture stirred at r.t. for 1.5 h. Next, a well homogenized and powdered solid mixture of anhyd $MgCl_2$ (4.1 g, 43 mmol) and potassium monomethyl malonate (11.8 g, 75 mmol) was added and the mixture stirred at r.t. for 16 h. Volatile components were evaporated in vacuo, aq HCl (2 M, 150 mL) was added and the mixture stirred at r.t. for 3 h. The resulting precipitate was collected by filtration, washed with H_2O (3 × 20 mL) and dried to give β-keto ester **9**.

Yield: 10.8 g (83%); white solid; mp 86–90 °C.

IR (KBr): 3358 (NH), 2959 (NH), 1748 (C=O), 1715 (C=O), 1682 (C=O), 1601, 1498, 1396, 1300, 1097, 1007, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.75 (m, 2 H, CH_2-4′), 3.64 (m, 4 H, OMe, H-3′), 3.82 (s, 2 H, CH_2-2), 4.00 (m, 2 H, CH_2-2′), 7.14 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.38 (tt, *J* = 2.1, 8.4 Hz, 2 H, ArH), 7.60–7.65 (m, 2 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 34.0, 42.1, 47.1, 48.5, 51.9, 119.5, 124.1, 128.7, 139.1, 167.6, 171.4, 202.6.

Table 1 Physical and Analytical Data on Histamine Analogues **6**{*1,2; 1–12*}

Product	R^1	R^2R^3NH **14**	Workup[a]	Yield (%)	Purity (%)[b]	Mp (°C)
6{*1; 1*}	Me	1-propylamine	C	89	100[c]	195–198
6{*2; 1*}	Ph	1-propylamine	A	29	100[c]	208–210
6{*1; 2*}	Me	1-pentylamine	C	92	99[c]	131–135
6{*2; 2*}	Ph	1-pentylamine	A	65	100[c]	177–180
6{*1; 3*}	Me	benzylamine	A	73	100[c]	206–208
6{*2; 3*}	Ph	benzylamine	A	87	100[c]	194–198
6{*1; 4*}	Me	2-phenylethylamine	B	82	100	119–122
6{*2; 4*}	Ph	2-phenylethylamine	A	66	100[c]	204–208
6{*1; 5*}	Me	3-amino-1-propanol	B	99	100[c]	130–132
6{*2; 5*}	Ph	3-amino-1-propanol	C	73	100[c]	200–204
6{*1; 6*}	Me	3-dimethylamino-1-propylamine	B	56	92[c]	169–171
6{*2; 6*}	Ph	3-dimethylamino-1-propylamine	A	42	100[c]	151–155
6{*1; 7*}	Me	2-picolylamine	A	73	100[c]	182–185
6{*2; 7*}	Ph	2-picolylamine	C	89	100[c]	149–151
6{*1; 8*}	Me	diethylamine	D	100	98[c]	resin
6{*2; 8*}	Ph	diethylamine	C	67	89[c]	150–154
6{*1; 9*}	Me	pyrrolidine	B	92	100[c]	174–176
6{*2; 9*}	Ph	pyrrolidine	C	90	89[c]	197–203
6{*1; 10*}	Me	piperidine	D	100	97	57–60
6{*2; 10*}	Ph	piperidine	C	80	100[c]	170–172
6{*1; 11*}	Me	morpholine	C	95	100[c]	161–165
6{*2; 11*}	Ph	morpholine	A	93	100[c]	241–244
6{*1; 12*}	Me	4-methylpiperazine	C	73	97[c]	146–149
6{*2; 12*}	Ph	4-methylpiperazine	C	89	85[c]	135–140

[a] Workup A: filtration of the reaction mixture. Workup B: evaporation of the reaction mixture, trituration with Et_2O, filtration. Workup C: evaporation of the reaction mixture, trituration with 50% aq MeOH, filtration. Workup D: evaporation of the reaction mixture.
[b] Determined by LC–MS and ^{1}H NMR spectroscopy.
[c] Confirmed by elemental analysis. The found values for C, H, and N were within ±0.4% with respect to the calculated values.

Table 2 Analytical Data for Compounds **6**{*1,2; 1–12*}

Product	Molecular Formula	Elem. Anal.	LC–MS Anal.[a]			ESI-MS (*m/z*)	ESI-HRMS (*m/z*)[b]
			R_t (min)	Area (%)	*m/z*[b]		
6{*1; 1*}	$C_{18}H_{22}N_4O_2$ (326.39)	Calcd: C, 66.24; H, 6.79; N, 17.17. Found: C, 66.38; H, 6.84; N, 17.45	11.69	100	327	327 $[M + H]^+$	Calcd: 327.1821; found: 327.1812
6{*2; 1*}	$C_{23}H_{24}N_4O_2$ (388.46)	Calcd: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.03; H, 6.32; N, 14.34	15.49	100	389	389 $[M + H]^+$	Calcd: 389.1978; found: 389.1985
6{*1; 2*}	$C_{20}H_{26}N_4O_2$ (354.45)	Calcd: C, 67.77; H, 7.39; N, 15.83. Found: C, 67.58; H, 7.48; N, 15.83	14.63	99	355	355 $[M + H]^+$	Calcd: 355.2134; found: 355.2122
6{*2; 2*}	$C_{25}H_{28}N_4O_2$ (416.52)	Calcd: C, 72.09; H, 6.78; N, 13.45. Found: C, 72.26; H, 6.88; N, 13.46	18.43	100	417	417 $[M + H]^+$	Calcd: 417.2291; found: 417.2292

Table 2 Analytical Data for Compounds **6**{*1,2; 1–12*} (continued)

Product	Molecular Formula	Elem. Anal.	LC–MS Anal.[a]			ESI-MS (*m*/*z*)	ESI-HRMS (*m*/*z*)[b]
			R_t (min)	Area (%)	*m*/*z*[b]		
6{*1; 3*}	$C_{22}H_{22}N_4O_2$ (374.44)	Calcd: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.30; H, 5.99; N, 14.92	13.68	100	375	375 $[M + H]^+$	Calcd: 375.1821; found: 375.1823
6{*2; 3*}	$C_{27}H_{24}N_4O_2$ (436.51)	Calcd: C, 74.29; H, 5.54; N, 12.84. Found: C, 74.10; H, 5.66; N, 12.83	17.49	100	437	437 $[M + H]^+$	Calcd: 437.1978; found: 437.1976
6{*1; 4*}	$C_{23}H_{24}N_4O_2 \cdot H_2O$ (406.48)	Calcd: C, 67.96; H, 6.45; N, 13.78. Found: C, 67.65; H, 6.48; N, 13.71	14.38	100	389	389 $[M + H]^+$	Calcd: 389.1978; found: 389.1969
6{*2; 4*}	$C_{28}H_{26}N_4O_2$ (450.53)	Calcd: C, 74.65; H, 5.82; N, 12.44. Found: C, 74.81; H, 5.88; N, 12.46	18.06	100	451	451 $[M + H]^+$	Calcd: 451.2134; found: 451.2138
6{*1; 5*}	$C_{18}H_{22}N_4O_3 \cdot {}^1/_8H_2O$ (344.64)	Calcd: C, 62.73; H, 6.51; N, 16.26. Found: C, 62.99; H, 6.55; N, 16.29	8.87	100	343	343 $[M + H]^+$	Calcd: 343.1770; found: 343.1768
6{*2; 5*}	$C_{23}H_{23}N_4O_3 \cdot H_2O$ (408.06)	Calcd: C, 67.55; H, 6.04; N, 13.70. Found: C, 67.47; H, 5.97; N, 13.40.	12.06	100	405	403 $[M - H]^+$	Calcd: 403.1770; found: 403.1772.
6{*1; 6*}	$C_{20}H_{27}N_5O_2 \cdot C_6F_5OH$ (553.52)	Calcd: C, 56.42; H, 5.10; N, 12.65. Found: C, 56.25; H, 5.01; N, 12.44	1.54, 16.18[c]	92	370	370 $[M + H]^+$	Calcd: 370.2243; found: 370.2246
6{*2; 6*}	$C_{25}H_{29}N_5O_2 \cdot {}^1/_2C_6F_5OH \cdot 1{}^1/_2H_2O$ (550.58)	Calcd: C, 60.08; H, 5.95; N, 12.72. Found: C, 60.82; H, 5.72; N, 12.87	1.99, 5.78[c]	100	432	432 $[M + H]^+$	Calcd: 432.2400; found: 432.2405
6{*1; 7*}	$C_{21}H_{21}N_5O_2 \cdot {}^1/_3H_2O$ (381.43)	Calcd: C, 66.13; H, 5.73; N, 18.36. Found: C, 66.14; H, 5.45; N, 18.36	10.31	100	376	376 $[M + H]^+$	Calcd: 376.1774; found: 376.1780
6{*2; 7*}	$C_{26}H_{23}N_5O_2 \cdot {}^4/_7C_6F_5OH$ (542.67)	Calcd: C, 65.13; H, 4.38; N, 12.91. Found: C, 65.21; H, 4.41; N, 12.94	13.40	100	438	438 $[M + H]^+$	Calcd: 438.1930; found: 438.1916
6{*1; 8*}	$C_{19}H_{24}N_4O_2 \cdot {}^1/_5C_6F_5OH$ (377.23)	Calcd: C, 64.31; H, 6.47; N, 14.85. Found: C, 64.18; H, 6.85; N, 15.19	11.31	98	341	341 $[M + H]^+$	Calcd: 341.1972; found: 341.1976
6{*2; 8*}	$C_{24}H_{26}N_4O_2 \cdot {}^1/_6C_6F_5OH$ (433.17)	Calcd: C, 69.32; H, 6.09; N, 12.93. Found: C, 69.44; H, 5.96; N, 12.82	14.93	89	403	403 $[M + H]^+$	Calcd: 403.2134; found: 403.2140
6{*1; 9*}	$C_{19}H_{22}N_4O_2$ (338.40)	Calcd: C, 67.44; H, 6.55; N, 16.56. Found: C, 67.50; H, 6.66; N, 16.93	10.53	100	339	339 $[M + H]^+$	Calcd: 339.1821; found: 339.1833
6{*2; 9*}	$C_{24}H_{24}N_4O_2 \cdot H_2O$ (409.48)	Calcd: C, 70.40; H, 6.15; N, 13.68. Found: C, 70.65; H, 5.84; N, 13.36	13.93	89	401	401 $[M + H]^+$	Calcd: 401.1978; found: 401.1989
6{*1; 10*}	$C_{20}H_{24}N_4O_2 \cdot {}^2/_3C_6F_5OH$ (475.14)	Calcd: C, 60.67; H, 5.23; N, 11.79. Found: C, 60.82; H, 5.92; N, 11.94[d]	11.67	97	353	353 $[M + H]^+$	Calcd: 353.1972; found: 353.1977
6{*2; 10*}	$C_{25}H_{26}N_4O_2$ (414.50)	Calcd: C, 72.44; H, 6.32; N, 13.52. Found: C, 72.31; H, 6.41; N, 13.42	15.44	100	415	415 $[M + H]^+$	Calcd: 415.2134; found: 415.2119
6{*1; 11*}	$C_{19}H_{22}N_4O_3 \cdot {}^1/_5H_2O$ (358.01)	Calcd: C, 63.74; H, 6.31; N, 15.63. Found: C, 63.76; H, 6.30; N, 15.56	9.18	100	355	355 $[M + H]^+$	Calcd: 355.1770; found: 355.1772
6{*2; 11*}	$C_{24}H_{24}N_4O_3$ (416.47)	Calcd: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.24; H, 6.02; N, 13.56	12.55	100	417	417 $[M + H]^+$	Calcd: 417.1927; found: 417.1926
6{*1; 12*}	$C_{20}H_{25}N_5O_2 \cdot {}^1/_3H_2O$ (373.45)	Calcd: C, 64.32; H, 6.93; N, 18.75. Found: C, 64.59; H, 6.76; N, 18.35	1.70	97	368	368 $[M + H]^+$	Calcd: 368.2087; found: 368.2078
6{*2; 12*}	$C_{25}H_{27}N_5O_2 \cdot C_6F_5OH$ (613.58)	Calcd: C, 60.68; H, 4.60; N, 11.41. Found: C, 60.29; H, 4.76; N, 11.36	1.99, 6.43[c]	5	430	430 $[M + H]^+$	Calcd: 430.2243; found: 430.2245

[a] Conditions: Gemini column, dimensions: 150 mm × 4.6 mm, 3 μm particles. Flow rate = 1 mL/min. Mobile phase = MeCN–H_2O. Gradient profile: MeCN–H_2O = 10:90 (0→3 min), MeCN–H_2O = 100:0 (3→25 min); a 3 min column equilibration time with the initial mobile phase (MeCN–H_2O = 10:90) was permitted.

[b] $[M + H]^+$ values.

[c] The compound elutes in the protonated and non-protonated forms as two peaks of identical mass.

[d] The found value for %H was outside the ±0.4% range with respect to the calculated value.

Table 3 Spectral Data for Compounds **6**{*1,2; 1–12*}

Product	IR (cm^{-1})	^1H NMR (300 MHz) (δ ppm)
6{*1; 1*}	3384, 2970, 2944, 1738, 1673, 1633, 1560, 1496, 1397, 1232, 983, 768, 694.	^1H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.60 (sext, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.85 (dd, *J* = 9.6, 16.8 Hz, 1 H, H-4′a), 3.30 (dd, *J* = 9.9, 16.8 Hz, 1 H, H-4′b), 3.29–3.37 (m, 2 H, CH_2NH), 3.93 (s, 3 H, CH_3-1), 4.02 and 4.39 [2 × t (1:1), *J* = 8.7 Hz, 2 H, CH_2-2′], 4.24 (quin, *J* = 9.0 Hz, 1 H, H-3′), 5.84 (br s, 1 H, NHCO), 7.16 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.33–7.40 (m, 2 H, ArH), 7.62 (s, 1 H, H-3), 7.59–7.64 (m, 2 H, ArH). ^{13}C NMR ($CDCl_3$): δ = 11.6, 23.2, 28.2, 37.6, 37.8, 41.4, 52.7, 115.8, 120.5, 125.0, 129.0, 137.4, 139.2, 143.9, 163.3, 172.6.
6{*2; 1*}	3303, 2954, 1739, 1685, 1642, 1561, 1498, 1398, 1282, 1237, 769, 754, 691.	^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.63 (sext, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.63–2.74 (m, 1 H, H-4′a), 3.33–3.48 (m, 3 H, H-4′b, CH_2NH), 3.81–3.93 (m, 2 H, H-2′a, H-3′), 4.51–4.61 (m, 1 H, H-2′b), 5.90 (br s, 1 H, NHCO), 7.12 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.30–7.39 (m, 4 H, ArH), 7.50–7.60 (m, 5 H, ArH), 7.83 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 11.6, 23.2, 29.5, 38.3, 41.5, 53.1, 116.3, 120.5, 124.8, 126.4, 128.9, 129.76, 129.79, 138.8, 139.0, 139.3, 144.6, 163.1, 172.5.
6{*1; 2*}	3364, 2951, 1737, 1670, 1636, 1557, 1499, 1417, 1306, 1266, 854, 755, 688, 657.	^1H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 6.9 Hz, 3 H, CH_3 of pentyl), 1.29–1.38 (m, 4 H, 2 × CH_2 of pentyl), 1.57 (quin, *J* = 7.2 Hz, 2 H, CH_2 of pentyl), 2.84 and 3.30 [2 × dd (1:1), *J* = 9.6, 16.8 Hz, 2 H, CH_2-4′], 3.35 (dd, *J* = 5.6, 7.0 Hz, 2 H, CH_2NH), 3.92 (s, 3 H, CH_3-1), 4.01 and 4.38 [2 × t (1:1), *J* = 8.7 Hz, 2 H, CH_2-2′], 4.24 (quin, *J* = 9.0 Hz, 1 H, H-3′), 5.88 (br t, *J* = 4.8 Hz, 1 H, NH), 7.15 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.33–7.40 (m, 2 H, ArH), 7.60–7.65 (m, 2 H, ArH), 7.62 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.5, 28.2, 29.2, 29.6, 37.6, 37.8, 39.7, 52.7, 115.8, 120.5, 124.9, 128.9, 137.5, 139.1, 143.8, 163.2, 172.6.
6{*2; 2*}	3381, 2930, 1751, 1686, 1651, 1593, 1556, 1495, 1401, 1297, 959, 766, 755.	^1H NMR ($CDCl_3$): δ = 0.92 (br t, *J* = 6.9 Hz, 3 H, CH_3 of pentyl), 1.32–1.41 (m, 4 H, 2 × CH_2 of pentyl), 1.60 (br quin, *J* = 7.0 Hz, 2 H, CH_2 of pentyl), 2.64–2.74 (m, 1 H, H-4′a), 3.36–3.49 (m, 3 H, H-4′b, CH_2NH), 3.81–3.93 (m, 2 H, H-2′a, H-3′), 4.50–4.60 (m, 1 H, H-2′b), 5.87 (br t, *J* = 5.4 Hz, 1 H, NHCO), 7.12 (tt, *J* = 1.2, 7.2 Hz, 1 H, ArH), 7.30–7.39 (m, 4 H, ArH), 7.50–7.60 (m, 5 H, ArH), 7.82 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 14.2, 22.5, 29.3, 29.5, 29.6, 38.3, 39.8, 53.1, 116.3, 120.5, 124.7, 126.4, 128.8, 129.7, 129.8, 138.8, 139.1, 139.2, 144.5, 163.0, 172.5.
6{*1; 3*}	3327, 3038, 2955, 1668, 1643, 1558, 1410, 1304, 1288, 1269, 1241, 1226, 954, 855, 753, 685, 663.	^1H NMR ($CDCl_3$): δ 2.86 and 3.31 [2 × dd (1:1), *J* = 9.6, 16.8 Hz, 2 H, CH_2-4′], 3.92 (s, 3 H, CH_3-1), 4.03 and 4.38 [2 × t (1:1), *J* = 8.8 Hz, 2 H, CH_2-2′), 4.26 (quin, *J* = 8.7 Hz, 1 H, H-3′), 4.55 (d, *J* = 6.0 Hz, 2 H, CH_2NH), 6.11 (t, *J* = 5.1 Hz, 1 H, NH), 7.17 (tt, *J* = 1.2, 7.2 Hz, 1 H, ArH), 7.28–7.41 (m, 7 H, ArH), 7.60–7.65 (m, 2 H, ArH), 7.62 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 28.2, 37.7, 37.9, 43.7, 52.8, 115.5, 120.7, 125.1, 127.8, 128.1, 129.0, 129.1, 137.5, 138.4, 139.2, 144.3, 163.1, 172.5.
6{*2; 3*}	3318, 1738, 1647, 1561, 1498, 1284, 951, 765, 759, 692.	^1H NMR (DMSO-d_6): δ = 2.74 and 3.20 [2 × dd (1:1), *J* = 9.9, 16.4 Hz, 2 H, CH_2-4′], 3.82 (quin, *J* = 9.3 Hz, 1 H, H-3′), 4.02 and 4.23 [2 × t (1:1), *J* = 9.0 Hz, 2 H, CH_2-2′], 4.45 (d, *J* = 6.0 Hz, 2 H, CH_2NH), 7.11 (tt, *J* = 1.0, 7.4 Hz, 1 H, ArH), 7.20–7.38 and 7.40–7.63 [2 × m (1:1), 14 H, ArH], 8.28 (s, 1 H, H-3), 8.88 (t, *J* = 6.9 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 29.3, 38.3, 43.7, 53.2, 115.9, 120.6, 124.8, 126.4, 127.7, 128.0, 128.89, 128.91, 129.80, 129.81, 138.5, 138.7, 139.1, 139.2, 145.0, 163.0, 172.5.
6{*1; 4*}	3477, 3284, 2970, 1738, 1668, 1563, 1497, 1401, 1293, 1232, 742, 697, 683.	^1H NMR ($CDCl_3$): δ = 2.84 and 3.27 [2 × dd (1:1), *J* = 9.9, 16.8 Hz, 2 H, CH_2-4′], 2.85 (t, *J* = 6.9 Hz, 2 H, CH_2Ph), 3.63 (ddd, *J* = 1.0, 5.8, 6.9 Hz, 2 H, CH_2NH), 3.91 (s, 3 H, CH_3-1), 4.01 and 4.36 [2 × t (1:1), *J* = 8.7 Hz, 2 H, CH_2-2′], 4.22 (quin, *J* = 9.0 Hz, 1 H, H-3′), 5.81 (t, *J* = 5.3 Hz, 1 H, NH), 7.13–7.25 (m, 4 H, ArH), 7.28–7.42 (m, 4 H, ArH), 7.47 (s, 1 H, H-3), 7.59–7.65 (m, 2 H, ArH). ^{13}C NMR ($CDCl_3$): δ = 27.9, 35.8, 37.5, 37.6, 40.6, 52.7, 115.5, 120.5, 124.9, 126.5, 128.6, 128.8, 128.9, 137.5, 139.00, 139.01, 143.8, 163.2, 172.6.
6{*2; 4*}	3334, 1666, 1641, 1561, 1500, 1432, 1288, 1135, 959, 767, 695.	^1H NMR ($CDCl_3$): δ = 2.63–2.74 and 3.35–3.46 [2 × m (1:1), 2 H, CH_2-4′], 2.91 (t, *J* = 6.9 Hz, 2 H, CH_2Ph), 3.68 (dq, *J* = 1.8, 6.8 Hz, 2 H, CH_2NH), 3.81–3.91 (m, 2 H, H-2′a, H-3′), 4.48–4.58 (m, 1 H, H-2′b), 5.87 (br t, *J* = 5.4 Hz, 1 H, NH), 7.13 (tt, *J* = 1.1, 7.4 Hz, 1 H, ArH), 7.21–7.29 (m, 3 H, ArH), 7.30–7.38 (m, 6 H, ArH), 7.49–7.61 (m, 5 H, ArH), 7.68 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 29.4, 35.9, 38.2, 40.7, 53.1, 116.1, 120.6, 124.8, 126.3, 126.7, 128.8, 128.9, 129.0, 129.7, 129.8, 138.7, 139.0, 139.1, 139.2, 144.7, 163.0, 172.5.
6{*1; 5*}	3371, 3329, 2944, 1763, 1670, 1558, 1496, 1460, 1294, 1160, 985.	^1H NMR ($CDCl_3$): δ = 1.76 (br tt, *J* = 5.5, 6.7 Hz, 2 H, $CH_2CH_2CH_2$), 2.86 and 3.26 [2 × dd (1:1), *J* = 9.6, 16.8 Hz, 2 H, CH_2-4′], 3.54 (dq, *J* = 1.2, 6.3 Hz, 2 H, CH_2NH), 3.71 (t, *J* = 5.4 Hz, 2 H, CH_2OH), 3.93 (s, 3 H, CH_3-1), 4.03 and 4.36 [2 × t (1:1), *J* = 8.7 Hz, 2 H, CH_2-2′], 4.24 (quin, *J* = 8.7 Hz, 1 H, H-3′), 6.34 (t, *J* = 6.0 Hz, 1 H, NH), 7.17 (tt, *J* = 1.1, 7.4 Hz, 1 H, ArH), 7.34–7.41 (m, 2 H, ArH), 7.59–7.64 (m, 2 H, ArH), 7.63 (s, 1 H, H-3), OH not observed. ^{13}C NMR ($CDCl_3$): δ = 28.0, 32.1, 36.8, 37.70, 37.73, 53.0, 59.9, 115.3, 120.9, 125.2, 129.0, 138.0, 139.0, 144.1, 164.1, 172.8.

Table 3 Spectral Data for Compounds **6**{*1,2; 1–12*} (continued)

Product	IR (cm^{-1})	^1H NMR (300 MHz) (δ ppm)
6{*2; 5*}	3442, 3343, 1737, 1646, 1497, 1297, 980, 971, 763, 696.	^1H NMR ($CDCl_3$): δ = 1.77 (br quin, *J* = 5.7 Hz, 2 H, $CH_2CH_2CH_2$), 2.67–2.77 and 3.33–3.45 [2 × m (1:1), 2 H, CH_2-4′], 3.55 (q, *J* = 6.0 Hz, 2 H, CH_2NH), 3.72 (t, *J* = 5.4 Hz, 2 H, CH_2OH), 3.80–3.95 (m, 2 H, H-2′a, H-3′), 4.50–4.57 (m, 1 H, H-2′b), 6.74 (t, *J* = 5.7 Hz, 1 H, NH), 7.13 (tt, *J* = 1.1, 7.4 Hz, 1 H, ArH), 7.29–7.38 (m, 4 H, ArH), 7.50–7.56 (m, 5 H, ArH), 7.89 (s, 1 H, H-3), OH not observed. ^{13}C NMR ($CDCl_3$): δ = 29.2, 32.1, 37.2, 38.3, 53.4, 60.3, 115.7, 121.0, 125.2, 126.4, 129.0, 129.88, 129.92, 138.6, 139.0, 139.3, 145.1, 164.0, 172.8.
6{*1; 6*}	3304, 2963, 2341, 1686, 1638, 1495, 1392, 1234, 1161, 1009, 976, 760.	^1H NMR ($CDCl_3$): δ = 1.87–1.98 (m, 2 H, $CH_2CH_2CH_2$), 2.55 (s, 6 H, NMe_2), 2.79 (br dt, *J* = 2.6, 6.5 Hz, 2 H, CH_2NMe_2), 2.84 and 3.31 [2 × dd (1:1), *J* = 9.8, 16.8 Hz, 2 H, CH_2-4′], 3.38–3.58 (m, 2 H, CH_2NH), 3.92 (s, 3 H, CH_3-1), 4.01 and 4.39 [2 × t (1:1), *J* = 8.9 Hz, 2 H, CH_2-2′], 4.21 (quin, *J* = 9.3 Hz, 1 H, H-3′), 7.15 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.37 (tt, *J* = 1.9, 8.0 Hz, 2 H, ArH), 7.60–7.65 (m, 2 H, ArH), 7.78 (s, 1 H, H-3), 7.82 (br s, 1 H, NH), 8.10 (br s, 1 H, Me_2NH^+). ^{13}C NMR ($CDCl_3$): δ = 25.2, 28.2, 37.3, 37.78, 37.79, 44.0, 52.9, 56.6, 115.5, 120.6, 125.0, 129.1, 138.2, 139.2, 144.1, 163.7, 172.8.
6{*2; 6*}	3277, 2970, 2466, 1737, 1691, 1637, 1494, 1387, 1291, 1005, 981, 758.	^1H NMR ($CDCl_3$): δ = 1.84–1.97 (m, 2 H, $CH_2CH_2CH_2$), 2.53 (s, 6 H, NMe_2), 2.69 (dd, *J* = 9.2, 16.3 Hz, 1 H, H-4′a), 2.73–2.84 (m, 2 H, CH_2NMe_2), 3.37–3.54 (m, 3 H, H-4′b, CH_2NH), 3.81–3.89 (m, 2 H, H-2′a, H-3′), 4.50–4.57 (m, 1 H, H-2′b), 7.12 (br t, *J* = 7.4 Hz, 1 H, ArH), 7.30–7.38 (m, 4 H, ArH), 7.48–7.58 (m, 5 H, ArH), 8.01 (s, 1 H, H-3), 8.24 (br s, 1 H, NH), 11.45 (br s, 1 H, Me_2NH^+). ^{13}C NMR ($CDCl_3$): δ = 25.1, 29.2, 37.7, 38.3, 44.0, 53.2, 56.8, 116.0, 120.5, 124.8, 126.4, 128.9, 129.7, 129.8, 138.8, 139.3, 139.7, 144.7, 163.4, 172.8.
6{*1; 7*}	3339, 3042, 3010, 1737, 1670, 1642, 1558, 1496, 1410, 1272, 959, 948, 744, 686.	^1H NMR (DMSO-d_6): δ = 2.75 and 3.15 [2 × dd (1:1), *J* = 9.5, 16.5 Hz, 2 H, CH_2-4′], 3.90 (s, 3 H, CH_3-1), 4.00–4.23 (m, 3 H, CH_2-2′, H-3′), 4.66 and 4.72 [2 × dd (1:1), *J* = 4.9, 17.1 Hz, 2 H, CH_2NH], 7.12 (tt, *J* = 1.0, 7.5 Hz, 1 H, ArH), 7.24 (br dd, *J* = 4.8, 7.7 Hz, 1 H, H-5″), 7.27 (br d, *J* = 7.7 Hz, 1 H, H-3″), 7.32–7.40 (m, 2 H, ArH), 7.60–7.66 (m, 2 H, ArH), 7.73 (dt, *J* = 1.8, 7.7 Hz, 1 H, H-4″), 8.03 (s, 1 H, H-3), 8.48 (d, *J* = 4.8 Hz, 1 H, H-6″), 8.76 (t, *J* = 6.0 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 28.2, 37.7, 37.8, 44.4, 52.8, 115.5, 120.6, 122.3, 122.6, 124.9, 129.0, 137.0, 137.9, 139.2, 144.1, 149.2, 156.3, 163.3, 172.6.
6{*2; 7*}	3469, 1755, 1687, 1615, 1499, 1460, 1398, 1308, 1288, 1132, 974, 760, 694.	^1H NMR ($CDCl_3$): δ = 2.71 and 3.44 [2 × dd (1:1), *J* = 9.9, 16.4 Hz, 2 H, CH_2-4′], 3.81–3.95 (m, 2 H, H-2′a, H-3′), 4.47–4.57 (m, 1 H, H-2′b), 4.78 and 4.75 [2 × dd (1:1), *J* = 4.9, 15.9 Hz, 2 H, CH_2NH], 7.13 (tt, *J* = 0.9, 7.2 Hz, 1 H, ArH), 7.24–7.40 (m, 7 H, ArH, H-5″, H-3″), 7.50–7.58 (m, 5 H, NH, ArH), 7.72 (td, *J* = 1.8, 7.8 Hz, 1 H, H-4″), 8.00 (s, 1 H, H-3), (d, *J* = 5.1 Hz, 1 H, H-6″). ^{13}C NMR ($CDCl_3$): δ = 29.3, 38.3, 44.2, 53.3, 115.7, 120.7, 123.0, 123.1, 124.9, 126.4, 128.9, 129.84, 129.87, 137.8, 138.6, 139.1, 139.4, 145.0, 148.7, 156.4, 163.1, 172.8.
6{*1; 8*}	2972, 2941, 1698, 1614, 1554, 1500, 1394, 1282, 1269, 1222, 761.	^1H NMR (DMSO-d_6): δ = 1.18 (t, *J* = 7.1 Hz, 6 H, 2 × CH_2CH_3), 2.90 (dd, *J* = 9.3, 16.7 Hz, 1 H, H-4′a), 3.04 (dd, *J* = 9.8, 16.7 Hz, 1 H, H-4′b), 3.44 (t, *J* = 6.8 Hz, 4 H, 2 × CH_2CH_3), 3.91 (s, 3 H, CH_3-1), 3.97 (quin, *J* = 8.2 Hz, 1 H, H-3′), 4.05 (t, *J* = 9.0 Hz, 1 H, H-2′a), 4.32 (t, *J* = 8.8 Hz, 1 H, H-2′b), 7.16 (t, *J* = 7.4 Hz, 1 H, ArH), 7.37 (t, *J* = 8.0 Hz, 2 H, ArH), 7.46 (s, 1 H, H-3), 7.59 (d, *J* = 7.7 Hz, 2 H, ArH). ^{13}C NMR ($CDCl_3$): δ = 12.8, 14.7, 28.9, 37.4, 37.7, 39.8, 43.6, 52.6, 115.8, 120.3, 125.0, 129.0, 136.6, 138.9, 141.4, 165.1, 172.0.
6{*2; 8*}	2963, 1753, 1686, 1619, 1498, 1395, 1305, 1277, 767, 755.	^1H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 6 H, 2 × CH_2CH_3), 2.74 (dd, *J* = 9.1, 16.6 Hz, 1 H, H-4′a), 3.06 (dd, *J* = 10.1, 16.6 Hz, 1 H, H-4′b), 3.51 (q, *J* = 7.2 Hz, 4 H, 2 × CH_2CH_3), 3.80 (quin, *J* = 9.0 Hz, 1 H, H-3′), 3.89 and 4.42 [2 × t (1:1), *J* = 8.7 Hz, 2 H, CH_2-2′], 7.31 (tt, *J* = 1.0, 7.5 Hz, 1 H, ArH), 7.30–7.43 (m, 4 H, ArH), 7.48–7.61 (m, 5 H, ArH), 7.68 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 12.9, 14.9, 29.6, 38.5, 39.8, 43.6, 53.3, 116.4, 120.3, 124.9, 126.4, 128.9, 129.6, 129.8, 138.3, 138.93, 138.99, 142.4, 164.9, 171.8.
6{*1; 9*}	2981, 2871, 1737, 1681, 1594, 1432, 1385, 1352, 1226, 893, 760.	^1H NMR ($CDCl_3$): δ = 1.94 (br quin, *J* = 3.4 Hz, 4 H, CH_2-3″, 4″), 2.91 and 3.14 [2 × dd (1:1), *J* = 9.2, 16.8 Hz, 2 H, CH_2-4′], 3.46–3.63 (br m, 4 H, CH_2-2″, 5″), 3.93 (s, 3 H, CH_3-1), 4.08 (t, *J* = 8.7 Hz, 1 H, H-2′a), 4.18 (m, 1 H, H-3′), 4.39 (dd, *J* = 7.5, 8.7 Hz, 1 H, H-2′b), 7.18 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.39 (tt, *J* = 2.0, 8.0 Hz, 2 H, ArH), 7.61 (s, 1 H, H-3), 7.60–7.67 (m, 2 H, ArH). ^{13}C NMR ($CDCl_3$): δ = 24.4, 26.5, 28.4, 37.6, 37.7, 46.3, 49.2, 52.6, 116.3, 120.2, 124.8, 128.9, 137.8, 139.0, 142.7, 163.5, 172.3.
6{*2; 9*}	2956, 2876, 1754, 1611, 1514, 1500, 1354, 1298, 993, 978, 766, 697.	^1H NMR ($CDCl_3$): δ = 1.96 (br s, 4 H, CH_2-3″, 4″), 2.73 (dd, *J* = 9.2, 16.5 Hz, 1 H, H-4′a), 3.18 (dd, *J* = 9.8, 16.5 Hz, 1 H, H-4′b), 3.59 and 3.66 [2 × br s (1:1), 4 H, CH_2-2″, 5″], 3.80–3.89 (m, 2 H, H-3′, H-2′a), 4.46–4.68 (m, 1 H, H-2′b), 7.12 (t, *J* = 7.5 Hz, 1 H, ArH), 7.29–7.43 (m, 4 H, ArH), 7.48–7.59 (m, 5 H, ArH), 7.82 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 24.4, 26.6, 29.5, 38.4, 46.4, 49.3, 53.2, 116.7, 120.3, 124.7, 126.4, 128.8, 129.6, 129.7, 138.9, 139.1, 139.4, 143.5, 163.4, 172.1.

Table 3 Spectral Data for Compounds **6**{*1,2; 1–12*} (continued)

Product	IR (cm^{-1})	^1H NMR (300 MHz) (δ ppm)
6{*1; 10*}	2942, 1699, 1617, 1515, 1500, 1444, 1397, 1282, 1254, 983, 761	^1H NMR (DMSO-d_6): δ = 1.56 (br s, 4 H, CH_2-3″, 5″), 1.67 (m, 2 H, CH_2-4″), 2.93 (dd, *J* = 9.3, 16.8 Hz, 1 H, H-4a), 3.02 (dd, *J* = 9.5, 16.9 Hz, 1 H, H-4b), 3.53 (br s, 4 H, CH_2-2″, 6″), 3.91 (s, 3 H, CH_3-1), 3.97 (quin, *J* = 9.1 Hz, 1 H, H-3′), 4.07 (t, *J* = 9.0 Hz, 1 H, H-2′a), 4.36 (dd, *J* = 8.1, 9.0 Hz, 1 H, H-2′b), 7.17 (tt, *J* = 1.1, 7.4 Hz, 1 H, ArH), 7.38 (t, *J* = 8.0 Hz, 2 H, ArH), 7.43 (s, 1 H, H-3), 7.60 (dd, *J* = 0.9, 8.6 Hz, 2 H, ArH). ^{13}C NMR ($CDCl_3$): 24.2, 25.4, 26.5, 28.2, 36.8, 37.5, 42.8, 48.6, 52.4, 114.6, 119.9, 124.6, 128.5, 136.8, 138.6, 141.7, 164.0, 172.0.
6{*2; 10*}	2945, 1738, 1691, 1612, 1500, 1408, 1307, 1231, 756, 693.	^1H NMR ($CDCl_3$): δ = 1.56–1.65 (m, 4 H, CH_2-3″, -5″), 1.65–1.75 (m, 2 H, CH_2-4″), 2.76 (dd, *J* = 9.3, 16.7 Hz, 1 H, H-4′a), 3.06 (dd, *J* = 9.9, 16.7 Hz, 1 H, H-4′b), 3.61 (t, *J* = 4.5 Hz, 4 H, CH_2-2″, 5″), 3.80 (quin, *J* = 9.0 Hz, 1 H, H-3′), 3.91 and 4.45 [2 × t (1:1), *J* = 8.7 Hz, 2 H, CH_2-2′], 7.14 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.31–7.42 (m, 4 H, ArH), 7.49–7.57 (m, 5 H, ArH), 7.63 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 24.7, 25.9, 27.0, 29.6, 31.1, 38.7, 43.3, 48.9, 53.4, 115.9, 120.4, 124.9, 126.4, 129.0, 129.6, 129.8, 138.97, 139.02, 142.7, 164.0, 171.9.
6{*1; 11*}	2893, 1738, 1684, 1618, 1593, 1497, 1411, 1243, 1112, 987, 766, 695.	^1H NMR ($CDCl_3$): δ = 2.95 and 3.04 [2 × dd (1:1), *J* = 9.2, 16.8 Hz, 2 H, CH_2-4′], 3.60–3.71 (m, 8 H, 4 × CH_2 of morpholine), 3.94 (s, 3 H, CH_3-1), 4.02 (br dd, *J* = 7.6, 8.7 Hz, 1 H, H-2′a), 4.10 (quin, *J* = 8.9 Hz, 1 H, H-3′), 4.37 (dd, *J* = 7.4, 9.1 Hz, 1 H, H-2′b), 7.20 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.40 (tt, *J* = 2.0, 8.0 Hz, 2 H, ArH), 7.44 (s, 1 H, H-3), 7.61–7.66 (m, 2 H, ArH). ^{13}C NMR ($CDCl_3$): δ = 28.6, 37.5, 37.9, 42.6, 48.1, 52.6, 66.9, 114.3, 120.2, 125.0, 129.0, 137.4, 138.9, 142.5, 164.3, 171.9.
6{*2; 11*}	2969, 1691, 1624, 1596, 1561, 1499, 1408, 1309, 1236, 1118, 974, 762, 756, 692.	^1H NMR ($CDCl_3$): δ = 2.79 and 3.06 [2 × dd (1:1), *J* = 9.3, 16.8 Hz, 2 H, CH_2-4′], 3.64–3.76 (m, 8 H, 4 × CH_2 of morpholine), 3.81 (quin, *J* = 8.7 Hz, 1 H, H-3′), 3.93 (t, 1 H, *J* = 9.0 Hz, H-2′a), 4.44 (dd, *J* = 8.1, 8.7 Hz, 1 H, H-2′b), 7.15 (tt, *J* = 0.9, 7.4 Hz, 1 H, ArH), 7.32–7.42 (m, 4 H, ArH), 7.50–7.59 (m, 5 H, ArH), 7.64 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 29.3, 38.7, 42.9, 48.1, 53.4, 67.1, 114.8, 120.3, 125.0, 126.3, 129.0, 129.7, 129.8, 138.7, 138.9, 139.0, 143.7, 164.1, 171.8.
6{*1; 12*}	2834, 1748, 1687, 1615, 1516, 1497, 1390, 1353, 1293, 1225, 1015, 982, 758, 692.	^1H NMR ($CDCl_3$): δ = 2.36 (s, 3 H, CH_3-4″), 2.48 (br t, *J* = 4.5 Hz, 4 H, CH_2-3″, 5″), 2.89–3.05 (m, 2 H, CH_2-4′), 3.61–3.81 (m, 4 H, CH_2-2″, 6″), 3.92 (s, 3 H, CH_3-1), 3.94–4.04 (m, 1 H, H-3′), 4.08 (t, *J* = 9.0 Hz, 1 H, H-2′a), 4.36 (dd, *J* = 7.5, 9.3 Hz, 1 H, H-2′b), 7.17 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.38 (tt, *J* = 2.0, 8.0 Hz, 2 H, ArH), 7.43 (s, 1 H, H-3), 7.59–7.65 (m, 2 H, ArH). ^{13}C NMR ($CDCl_3$): δ = 28.5, 37.4, 37.9, 41.3, 45.4, 46.8, 52.7, 54.7, 114.3, 120.3, 125.1, 129.0, 137.5, 138.8, 142.7, 164.2, 172.0.
6{*2; 12*}	3466, 1755, 1687, 1615, 1501, 1410, 1309, 1288, 982, 761, 694.	^1H NMR ($CDCl_3$): δ = 2.37 (s, 3 H, CH_3-4″), 2.51 (t, *J* = 4.8 Hz, 4 H, CH_2-3″, 5″), 2.79 and 3.04 [2 × dd (1:1), *J* = 9.3, 16.7 Hz, 2 H, CH_2-4′], 3.67–3.88 (m, 5 H, H-3′, CH_2-2″, 6″), 3.93 (t, *J* = 8.7 Hz, 1 H, H-2′a), 4.44 (dd, *J* = 0.6, 8.1 Hz, 1 H, H-2′b), 7.14 (tt, *J* = 1.2, 7.5 Hz, 1 H, ArH), 7.31–7.41 (m, 4 H, ArH), 7.49–7.58 (m, 5 H, ArH), 7.65 (s, 1 H, H-3). ^{13}C NMR ($CDCl_3$): δ = 29.3, 38.7, 41.6, 45.8, 47.2, 53.5, 55.0, 114.9, 120.4, 125.0, 126.4, 129.0, 129.78, 129.82, 138.7, 138.9, 139.1, 143.7, 164.1, 171.9.

Table 4 Separation of the Enantiomers of **6**{*1,2; 1–12*} by HPLC[a]

Product	*n*-hexane–*i*-PrOH	R_t (min)	
		Enantiomer A	Enantiomer B
6{*1; 1*}	80:20	20.045	23.670
6{*2; 1*}	80:20	15.936	21.047
6{*1; 2*}	80:20	20.016	23.618
6{*2; 2*}	80:20	14.541	19.793
6{*1; 3*}	50:50	14.716	25.280
6{*2; 3*}	50:50	9.785	12.180
6{*1; 4*}	50:50	10.715	13.779
6{*2; 4*}	80:20	31.121	36.948
6{*1; 5*}	50:50	6.484	7.885

Table 4 Separation of the Enantiomers of **6**{*1,2; 1–12*} by HPLC[a] (continued)

Product	*n*-hexane–*i*-PrOH	R_t (min)	
		Enantiomer A	Enantiomer B
6{*2; 5*}	80:20	25.719	27.962
6{*1; 6*}	70:30	13.634	16.526
6{*2; 6*}	80:20	19.088	24.227
6{*1; 7*}	70:30	29.247[b]	29.247[b]
6{*2; 7*}	80:20	39.932	44.427
6{*1; 8*}	50:50	9.452	14.751
6{*2; 8*}	50:50	8.059	11.756
6{*1; 9*}	50:50	13.939	23.783
6{*2; 9*}	70:30	32.845[b]	32.845[b]

Table 4 Separation of the Enantiomers of **6**{*1,2; 1–12*} by HPLC[a] (continued)

Product	*n*-hexane–*i*-PrOH	R_t (min)	
		Enantiomer A	Enantiomer B
6{*1; 10*}	50:50	9.630	15.916
6{*2; 10*}	50:50	10.370	13.213
6{*1; 11*}	50:50	17.374	28.327
6{*2; 11*}	50:50	36.187[b]	36.187[b]
6{*1; 12*}	50:50	11.266	17.321
6{*2; 12*}	80:20	17.367	28.620

[a] Separation conditions: Chiralcel OD-H column, dimensions 0.46 cm × 25 cm, 5 μm particles. Flow rate = 1 mL/min. Mobile phase = *n*-hexane–*i*-PrOH.
[b] Enantiomers were not resolved.

MS (ESI): *m*/*z* = 262 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}NO_4$: 262.1079; found: 262.1077.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.77; N, 5.35.

LC–MS: R_t = 11.317 min, *m*/*z* = 262 $[M + H]^+$, area = 94%.

Methyl 5-(5-Oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxylates 12; General Procedure

A mixture of β-keto ester **9** (10.4 g, 40 mmol), anhyd toluene (40 mL), and DMF–DMA (6 mL, 40 mmol) was heated at reflux temperature for 2 h. Volatile components were evaporated in vacuo to give crude amine **10** as a yellow-brown oil. Crude **10** was dissolved in MeOH (80 mL) and the appropriate hydrazine derivative **11** (40 mmol) added. The mixture was stirred at r.t. for 2 and then at reflux temperature for another 2 h. The mixture was cooled to r.t. and the resulting precipitate collected by filtration, and washed with MeOH (2 × 20 mL) to give pyrazole-4-carboxylate **12**.

Methyl 1-Methyl-5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxylate Hemihydrate (12{*1*})

Prepared from **9** and methylhydrazine **11**{*1*} (1.84 g, 2.13 mL, 40 mmol).

Yield: 8.38 g (70%); white solid; mp 199–204 °C.

IR (KBr): 3363 (NH), 2955 (NH), 1735 (C=O), 1697 (C=O), 1684 (C=O), 1599, 1550, 1498, 1468, 1391, 1248, 1144, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.89 (dd, *J* = 9.6, 17.1 Hz, 1 H, H-4′a), 3.20 (dd, *J* = 9.3, 17.1 Hz, 1 H, H-4′b), 3.79 (s, 3 H, NMe), 3.94 (s, 3 H, OMe), 4.04 (t, *J* = 8.1 Hz, 1 H, H-2′a), 4.15 (quin, *J* = 8.1 Hz, 1 H, H-3′), 4.27 (t, *J* = 8.1 Hz, 1 H, H-2′b), 7.18 (t, *J* = 7.4 Hz, 1 H, ArH), 7.39 (t, *J* = 8.0 Hz, 2 H, ArH), 7.62 (d, *J* = 7.7 Hz, 2 H, ArH), 7.91 (s, 1 H, 3-H).

^{13}C NMR (DMSO-d_6): δ = 26.5, 37.2, 37.4, 51.2, 51.9, 110.3, 119.5, 124.1, 128.7, 139.2, 140.8, 146.6, 163.2, 172.2.

MS (ESI): *m*/*z* = 300 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}N_3O_3$: 300.1348; found: 300.1352.

Anal. Calcd for $C_{16}H_{17}N_3O_3 \cdot H_2O$: C, 62.33; H, 5.88; N, 13.63. Found: C, 62.30; H, 5.48; N, 13.70.

LC–MS: R_t = 12.033 min, *m*/*z* = 300 $[M + H]^+$, area = 100%.

Methyl 5-(5-Oxo-1-phenylpyrrolidin-3-yl)-1-phenyl-1*H*-pyrazole-4-carboxylate (12{*2*})

Prepared from **9** and phenylhydrazine **11**{*2*} (4.33 g, 4.01 mL, 40 mmol).

Yield: 11.73 g (81%); white solid; mp 151–154 °C.

IR (KBr): 2955 (NH), 1706 (C=O), 1682 (C=O), 1596, 1551, 1497, 1403, 1267, 1106, 973, 762, 693 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.85 (dd, *J* = 10.5, 16.8 Hz, 1 H, H-4′a), 3.00 (dd, *J* = 9.3, 17.1 Hz, 1 H, H-4′b), 3.74 (s, 3 H, OMe), 3.92 (quin, *J* = 9.3 Hz, 1 H, H-3′), 4.12 (d, *J* = 9.0 Hz, 2 H, CH_2-2′), 7.14 (t, *J* = 7.4 Hz, 1 H, ArH), 7.37 (t, *J* = 8.0 Hz, 2 H, ArH), 7.49–7.55 (m, 2 H, ArH), 7.55–7.61 (m, 3 H, ArH), 7.62–7.68 (m, 2 H, ArH), 8.14 (s, 1 H, H-3).

^{13}C NMR (DMSO-d_6): δ = 27.0, 37.7, 51.5, 52.3, 111.3, 119.6, 124.1, 126.3, 128.7, 129.4, 129.6, 138.1, 139.2, 142.4, 147.5, 163.1, 171.9.

MS (ESI): *m*/*z* = 362 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3O_3$: 362.1505; found: 362.1499.

Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.63; H, 5.35; N, 11.71.

LC–MS: R_t = 16.258 min, *m*/*z* = 362 $[M + H]^+$, area = 100%.

1-Substituted 5-(5-Oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxylic Acids 13; General Procedure

Ester **12** (25 mmol) was dissolved in MeOH (100 mL), aq NaOH (2 M, 50 ml) was added and the mixture was stirred at 50 °C for 16 h. The solvent was removed by evaporation in vacuo (40 °C/100 mbar) and the aq residue acidified with aq HCl (1 M) until pH ~1. The resulting precipitate was collected by filtration and dried at 100 °C/2 mbar over P_4O_{10}–paraffin for 3 h to give carboxylic acid **13**.

1-Methyl-5-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-pyrazole-4-carboxylic Acid (13{*1*})

Prepared from ester **12**{*1*} (7.71 g, 25 mmol).

Yield: 6.35 g (89%); white solid; mp 185–187 °C.

IR (KBr): 2942 (NH), 2521, 1693 (C=O), 1635 (C=O), 1497, 1481, 1417, 1303, 1207, 1143, 756, 738, 689 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.83 (dd, *J* = 9.9, 16.6 Hz, 1 H, H-4′a), 3.03 (dd, *J* = 9.9, 16.6 Hz, 1 H, H-4′b), 3.91 (s, 3 H, NMe), 4.05–4.12 (m, 2 H, CH_2-2′), 4.20 (quin, *J* = 9.4 Hz, 1 H, H-3′), 7.15 (t, *J* = 7.4 Hz, 1 H, ArH), 7.38 (br t, *J* = 8.0 Hz, 2 H, ArH), 7.66 (br d, *J* = 8.7 Hz, 2 H, ArH), 7.81 (s, 1 H, H-3), 12.43 (s, 1 H, COOH).

^{13}C NMR (DMSO-d_6): δ = 26.7, 37.28, 37.31, 52.0, 111.5, 119.6, 124.1, 128.7, 139.3, 141.2, 146.2, 164.4, 172.3.

MS (ESI): *m*/*z* = 284 $[M - H]^+$.

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{15}H_{14}N_3O_3$: 284.1035; found: 284.1041.

Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.01; H, 5.25; N, 14.71.

LC–MS: R_t = 13.642 min, *m*/*z* = 286 $[M + H]^+$, area = 100%.

5-(5-Oxo-1-phenylpyrrolidin-3-yl)-1-phenyl-1*H*-pyrazole-4-carboxylic Acid (13{*2*})

Prepared from ester **12**{*2*} (9.03 g, 25 mmol).

Yield: 7.12 g (82%); white solid; mp 237–239 °C.

IR (KBr): 2954 (NH), 1693 (C=O), 1666 (C=O), 1549, 1499, 1401, 1283, 760, 691 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.81 (dd, *J* = 10.2, 16.8 Hz, 1 H, H-4′a), 3.07 (dd, *J* = 9.3, 16.8 Hz, 1 H, H-4′b), 3.88 (quin, *J* = 9.3 Hz, 1 H,

H-3′), 4.12 (dt, *J* = 9.3, 20.1 Hz, 2 H, CH_2-2′), 7.13 (tt, *J* = 1.0, 7.4 Hz, 1 H, ArH), 7.37 (tt, *J* = 1.9, 8.0 Hz, 2 H, ArH), 7.49–7.65 (m, 7 H, ArH), 8.08 (s, 1 H, H-3), 12.68 (br s, 1 H, COOH).

^{13}C NMR (DMSO-d_6): δ = 27.3, 37.8, 52.5, 112.6, 119.7, 124.1, 126.3, 128.6, 129.2, 129.5, 138.3, 139.2, 142.8, 147.0, 164.3, 172.0.

MS (ESI): *m*/*z* = 348 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_3$: 348.1348; found: 348.1352.

Anal. Calcd for $C_{20}H_{17}N_3O_3 \cdot {}^1/_5H_2O$: C, 68.44; H, 5.00; N, 11.97. Found: C, 68.44; H, 4.76; N, 12.03.

LC–MS: R_t = 17.375 min, *m*/*z* = 348 $[M + H]^+$, area = 100%.

Parallel Synthesis; General Procedure

A Syncore® Polyvap, equipped with 24 reaction tubes, was charged with equimolar amounts of acids **13**{*1,2*} and Et_3N in anhyd MeCN [0.125 M, 12 × 4 mL of acids **13**{*1,2*} (24 × 0.5 mmol)]. A soln of bis(pentafluorophenyl) carbonate in anhyd MeCN (0.504 M, 24 × 1 mL, 24 × 0.504 mmol) was added and the mixtures stirred at r.t. for 45 min. Next, amines **14**{*1–12*} (24 × 0.5 mmol) and Et_3N (24 × 70 μL, 24 × 0.5 mmol) were added, and stirring was continued at r.t. for 16 h. Eight reactions gave precipitates which were collected by filtration on a MiniBlock™ to give compounds, **6**{*1; 3,7*} and **6**{*2; 1–4,6,11*} (workup A).[16] The remaining reaction mixtures were evaporated in vacuo (40 °C/2 mbar→80 °C/2 mbar), then Et_2O (16 × 5 mL) was added to the residues, and the mixtures stirred at r.t. for 3 h. Four precipitates formed which were collected by filtration to give compounds **6**{*1; 4–6,9*} (workup B). The remaining mixtures were evaporated in vacuo (30 °C/2 mbar→80 °C/2 mbar), and 50% aq MeOH (12 × 5 mL) was added to the residues, and the mixtures stirred at r.t. for 12 h. The resulting precipitates were collected by filtration to afford compounds **6**{*1; 1,2,11,12*} and **6**{*2; 5,7–10,12*} (workup C). The final two reaction mixtures were evaporated in vacuo (40 °C/2 mbar→80 °C/2 mbar) to give compounds, **6**{*1; 8*} and **6**{*1; 10*} (workup D). All the products were dried at 80 °C/0.01 mbar over P_4O_{10}–paraffin for 3 h to give carboxylates **6**. The experimental, physical, analytical and spectral data, and details on the resolution of the enantiomers of compounds **6**{*1,2; 1–12*} are provided in Tables 1– 4.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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