Synthesis of 1,5,6,7-Tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones as Conformationally Constrained Pyrazole Analogues of Histamine

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Received 21 April 2010; revised 9 June 2010

Abstract: Three synthetic methods for the preparation of 1,5-disubstituted 1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones as heterocyclic histamine analogues were developed. The first method starts from easily available methyl 5-(2-aminoethyl)-1*H*-pyrazole-4-carboxylates, which were N-alkylated and the resulting secondary amines were cyclised in the presence of a base to give the title compounds in 17–92% yields (method A). Alternatively, the amines were first cyclised to the 5-unsubstituted pyrazolo[4,3-*c*]pyridin-4-ones. Subsequent N-benzylation afforded three of the title compounds in 36–49% yields (method B). The third method comprises a six-step transformation of methyl acrylate into 1-benzylpiperidine-2,4-dione. Treatment of the latter with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) followed by acid-catalysed cyclisation of the formed enaminone with methyl-, phenyl- and *tert*-butylhydrazine afforded the same three title compounds in 79–87% yields (method C).

Key words: enaminones, cyclisation, alkylation, pyrazolo[4,3-*c*]pyridine, histamine

Functionalised heterocycles represent important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications, due to their ability to mimic structures of peptides and to reversibly bind to proteins.[1,2] Because of the crucial role of histamine, tyramine, dopamine, tryptamine, serotonin and melatonin (Figure 1) as chemical messengers in biological processes, the preparation of novel synthetic analogues based on the 2-(heteroaryl)ethylamine scaffold represents an important target in medicinal and synthetic organic chemistry.[3,4]

Despite their rare occurrence in nature, pyrazole and its derivatives are certainly an important class of heterocyclic compounds. Numerous pyrazole derivatives have found use in various applications, and a general interest in the chemistry of pyrazoles is still continuing. Among the various synthetic options available for the construction of the pyrazole ring, two classical approaches are most frequently employed. The first is based on a cyclocondensation reaction between a 1,3-dicarbonyl compound (or its analogue) and a hydrazine derivative, whilst the second is based on the cycloaddition of a C–N–N type 1,3-dipole (diazoalkane, nitrile imine or azomethine imine) to a C=C multiple bond.[5]

SYNTHESIS 2010, No. 19, pp 3363–3373
Advanced online publication: 22.07.2010
DOI: 10.1055/s-0030-1257864; Art ID: T09210SS

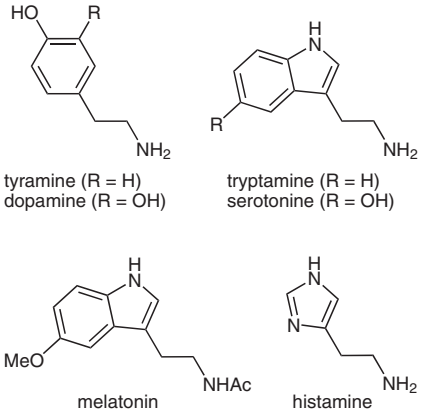
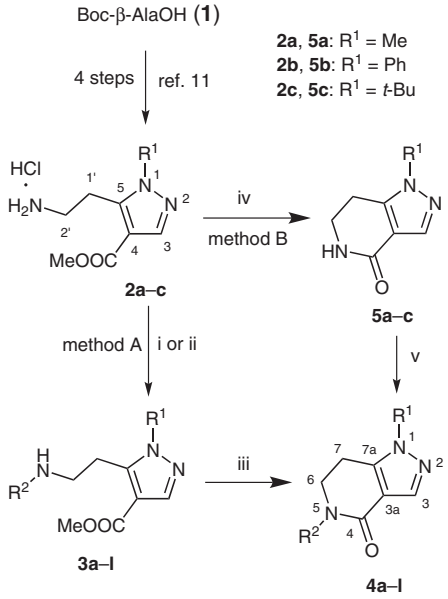


Figure 1

In the last decade, a substantial part of our research has been focused on the synthesis of functionalised pyrazoles through (a) 1,3-dipolar cycloaddition of (4*R**,5*R**)-4-benzoylamino-5-phenyl-3-pyrazolidinone-derived azomethine imines to various dipolarophiles,[6] and (b) cyclocondensation of functionalised enaminones with monosubstituted hydrazines.[7] In particular, β-(dimethylamino)-enones, which are stable β-keto aldehyde analogues, have found use as versatile reagents in heterocyclic synthesis including combinatorial applications.[8] Within this context, we recently reported a simple four-step synthesis of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols as pyrazole analogues of histamine.[9] Soon after, a one-pot, parallel, solution-phase synthesis of these compounds was also developed.[10] In a continuation, we reported the synthesis of 5-(2-aminoethyl)-1*H*-pyrazol-4-carboxamides as related pyrazole analogues of histamine analogues.[11] In an extension of this study, we found some intriguing further transformations of the above histamine analogues. Namely, N-alkylation of the 5-aminoethyl group followed by cyclisation to the 4-carboxyl group should provide access to 4*H*-pyrazolo[4,3-*c*]pyridin-4-ones as bicyclic analogues of histamine. Herein, we report the results of our study on the synthesis of 1,5-disubstituted 1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones **4**, as novel and conformationally constrained histamine analogues.

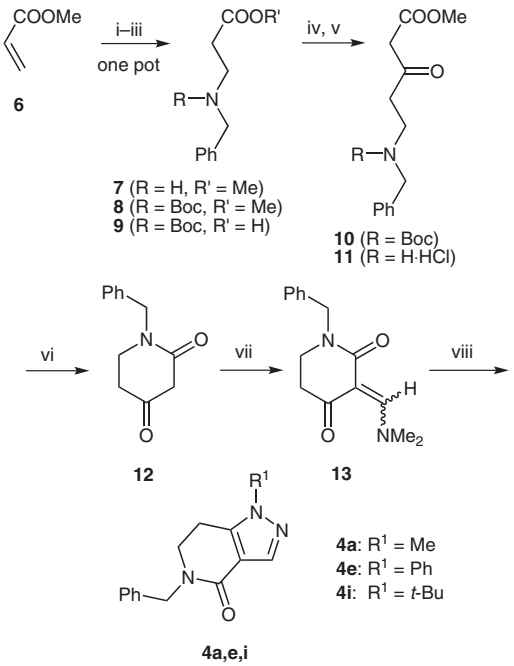
First, we undertook the synthesis of the title compounds **4** via δ-amino esters **2** as the key intermediates. Compounds **2a** and **2b** were prepared in four steps from commercially available Boc-β-alanine (**1**) following a literature proce-

dure.[11] In the same manner, the novel compound **2c** was also obtained in 86% yield by acidolytic deprotection of its known Boc-derivative.[11] Two methods were studied for the preparation of title compounds: alkylation of the primary amino group followed by base-catalysed lactamisation (method A), and base-catalysed lactamisation followed by alkylation of the amido group (method B). Alkylations of amines **2a–c** were carried out in two ways: (a) with either benzaldehyde or pyridine-2-carbaldehyde in the presence of sodium borohydride and acetic acid (procedure A),[12] or (b) by catalytic hydrogenation in the presence of 10% Pd/C and tetrahydrofuran-3-carbaldehyde or acetone (procedure B). In this manner, the monoalkylated amines **3a–i**, **3k** and **3l** were obtained in 22–80% yield. Reductive alkylation of **2c** with pyridine-2-carbaldehyde was exceptional, since it directly afforded the cyclisation product **4j** in 22% yield. Somewhat surprisingly, compounds **3a–i**,**k**,**l** were more reluctant to cyclise, and required harsher reaction conditions. Treatment of these compounds with excess potassium *tert*-butoxide in 1-propanol heated at reflux for 15 hours furnished the title compounds **4a–i**,**k**,**l** in 11–92% yield (Scheme 1, method A, Table 1).



Scheme 1 Synthesis of **4** by methods A and B. *Reagents and conditions*: (i) benzaldehyde or pyridine-2-carbaldehyde, $NaBH_4$, MeOH, AcOH, 0 °C→r.t. (procedure A[12]); (ii) tetrahydrofuran-3-carbaldehyde or acetone, H_2 (3 bar), 10% Pd–C, r.t. (procedure B); (iii) *t*-BuOK, 1-propanol, reflux; (iv) Et_3N, DMF, reflux; (v) *t*-BuOK, DMF, r.t., then BnBr, r.t.

In another synthetic approach to the title compounds **4**, the δ-amino esters **2** were first cyclised to the 5-unsubstituted pyrazolo[4,3-*c*]pyridin-4-ones **5**, followed by N-alkylation. The δ-amino esters **2a–c** were cyclised thermally in a mixture of *N*,*N*-dimethylformamide and triethylamine, to afford pyrazolo[4,3-*c*]pyridin-4-ones **5a–c** in 45–66% yield. Subsequent N-benzylation of **5a–c** with benzyl bromide and potassium *tert*-butoxide in *N*,*N*-dimethylformamide then furnished compounds **4a**, **4e** and **4i** in moderate yields (Scheme 1, Method B, Table 1).



Scheme 2 Synthesis of **4** by method C. *Reagents and conditions*: (i) benzylamine, DBU (0.05 equiv), r.t.; (ii) Boc_2O, MeCN, r.t.; (iii) aq 2 M NaOH, MeOH, r.t., then acidification with aq 6 M HCl (0.9 equiv) and aq 1 M $NaHSO_4$ (0.2 equiv) r.t.; (iv) CDI, THF, r.t., then $MeO_2CCH_2CO_2K$, $MgCl_2$, THF, r.t.; (v) 2 M HCl–EtOAc, 0–20 °C; (vi) aq 1 M NaOH, r.t., then aq 1 M HCl, r.t.; (vii) DMFDMA, toluene, r.t.; (viii) R^3NHNH_2·HCl, 2-methoxyethanol, r.t.→reflux.

In the third synthetic approach, 1-benzylpiperidine-2,4-dione (**12**)[13] was used as the key intermediate, which was transformed into the title compounds **4** (method C). Solvent-free 1,8-diazabicyclo[5.4.0]undec-7-ene-catalysed Michael addition of benzylamine to methyl acrylate (**6**) gave the *N*-benzyl-β-alanine ester (**7**),[14] which was treated with Boc_2O. The so-formed methyl *N*-benzyl-β-alaninate (**8**)[15] was hydrolysed with aqueous sodium hydroxide to give **9**[16] in 79% yield over three steps. Thus, our synthetic procedure for the preparation of **9** was simpler and more efficient than previously described methods,[16a,c] which gave **9** in significantly lower overall yields. Subsequent Masamune–Claisen condensation[17] of the crude product **9** with magnesium monomethyl malonate was performed according to the procedure described previously for homologation of closely related Boc-β-alanine[11] and gave β-keto ester **10** in 92% yield. Acidolytic removal of the Boc group afforded methyl 5-(benzylamino)-3-oxopentanoate hydrochloride (**11**), which was then cyclised under basic conditions to give 1-benzylpiperidine-2,4-dione (**12**) in 66% yield over three steps (from **9**). From this point on, formation of the condensed pyrazole ring was achieved by using the standard enaminone protocol, i.e., by reaction of the active methylene compound **12** with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) followed by cyclocondensation of the so-formed enamino ketone **13** with hydrazines. Thus, treatment of **12** with DMFDMA in an-

hydrous toluene at room temperature gave the enaminoderivative **13** in 88% yield. Subsequent cyclisation of **13** with methylhydrazine, phenylhydrazine or *tert*-butylhydrazine was carried out in 2-methoxyethanol at reflux to furnish the desired pyrazolo[4,3-*c*]pyridin-4-ones **4a**,**e**,**i** in 79–87% yield (Scheme 2, Table 1).

The structures of novel compounds **2c**, **3a**–**i**,**k**,**l**, **4a**–**l**, **10**, **11** and **13** were determined by spectroscopic (IR, NMR and MS) methods and by CHN elemental analyses. Compounds **4c**,**d**,**k**, **10** and **13** were not obtained in analytically pure form; their identities were confirmed by ^{13}C NMR and HRMS analyses. Physical and spectral data for known compounds **2a**,**b**,[11] **7**,[14] **8**,[15] **9**[16] and **12**[13] were in agreement with data reported in the literature. Intermediates **7**[14] and **8**[15] were not isolated in pure form and were characterised only by ^1H NMR analysis. Additional characterisation data for known compound **9**[16] are also given in Table 1 and Table 2. The structures of compounds **4a** and **4i** were also determined by X-ray diffraction analyses.

In conclusion, twelve 1,5-disubstituted 1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones **4** as novel, conformationally constrained pyrazole analogues of histamine were synthesised. Three complementary synthetic methods were developed. Methods A and B are six-step syntheses starting from Boc-β-alanine (**1**), which is transformed in four steps into the key intermediates **2** according to the procedure reported previously.[11] From this point on, two complementary synthetic pathways are feasible: (a) reductive N-alkylation of the amine **2** followed by cyclisation to **4** (method A), and (b) cyclisation of **2** into the 4*H*-pyrazolo[4,3-*c*]pyridin-4-one **5** followed by N-alkylation with alkyl halide (method B). Method C comprises a seven-step transformation of methyl acrylate (**6**) into 1-benzyl-3-[(dimethylamino)methylidene]piperidine-2,4-dione (**13**) and subsequent cyclisation with monosubstituted hydrazines. At first glance, all three methods seem somewhat lengthy, however, steps **1**→**2** (methods A and B) and **6**→**9** (method C) can be carried out as one-pot transformations. In summary, methods A–C represent efficient synthetic approaches to bicyclic histamine analogues **4** with variable substituents at N(1) and N(5). Each of the N-substituents can be introduced at different stages of the synthesis, while three different types of common reagents (aldehydes and ketones, alkyl halides, and primary amines) can be employed for the introduction of the N(5)-substituent.

Table 1 Experimental Data for Compounds **2**–**5**, **9**–**11** and **13**

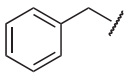
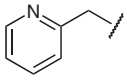
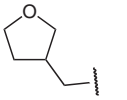
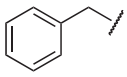
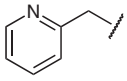
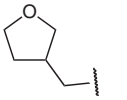
Compd	R^1	R^2	Proc.	Yield (%)	Mp (°C)	Molecular formula, analysis data	ESI-MS (*m*/*z*), HRMS
2c	*t*-Bu	–	–	86	173–179	$C_{11}H_{19}N_3O_2 \cdot HCl$ Calcd.: C, 50.40; H, 7.70; N, 16.05 Found: C, 50.04; H, 7.89; N; 16.18	226 $[M + H]^+$ Calcd.: 226.1556 Found: 226.1547
3a	Me		A	22	183–188	$C_{15}H_{19}N_3O_2 \cdot 1HCl$ Calcd.: C, 57.31; H, 6.45; N, 13.37 Found: C, 57.37; H, 6.60; N, 13.41	274 $[M + H]^+$ Calcd.: 274.1556 Found: 274.1552
3b	Me		A	47	123–127	$C_{14}H_{18}N_4O_2 \cdot 2HCl$ Calcd.: C, 47.80; H, 5.77; N, 15.93 Found: C, 47.97; H, 6.56; N, 15.87	275 $[M + H]^+$ Calcd.: 275.1508 Found: 275.1509
3c	Me		B	73	141–144	$C_{13}H_{21}N_3O_3 \cdot 1HCl$ Calcd.: C, 50.64; H, 7.23; N, 13.63 Found: C, 50.69; H, 7.45; N, 13.47	268 $[M + H]^+$ Calcd.: 268.1661 Found:268.1660
3d	Me		B	33	220–225	$C_{11}H_{19}N_3O_2 \cdot HCl$ Calcd.: C, 50.48; H, 7.70; N, 16.05 Found: C, 50.10; H, 7.79; N, 15.84	226 $[M + H]^+$
3e	Ph		A	52	176–180	$C_{20}H_{21}N_3O_2 \cdot HCl$ Calcd.: C, 64.60; H, 5.96; N, 11.30 Found: C, 64.65; H, 6.08; N, 11.38	336 $[M + H]^+$
3f	Ph		A	47	166–174	$C_{19}H_{20}N_4O_2 \cdot 2HCl$ Calcd.: C, 55.75; H, 5.42; N, 13.69 Found: C, 55.71; H, 5.69; N, 13.51	337 $[M + H]^+$
3g	Ph		B	63	148–155	$C_{18}H_{23}N_3O_3 \cdot 1HCl$ Calcd.: C, 58.37; H, 6.56; N, 11.34 Found: C, 58.28; H, 6.84; N, 11.30	330 $[M + H]^+$ Calcd.: 330.1818 Found: 330.1810

Table 1 Experimental Data for Compounds **2–5**, **9–11** and **13** (continued)

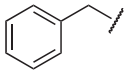
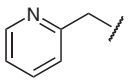
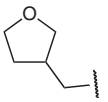
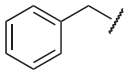
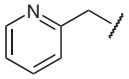
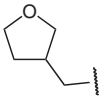
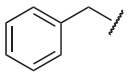
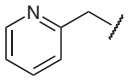
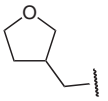
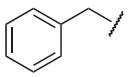
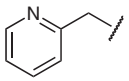
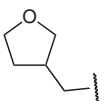
Compd	R^1	R^2	Proc.	Yield (%)	Mp (°C)	Molecular formula, analysis data	ESI-MS (*m*/*z*), HRMS
3h	Ph		B	80	209–213	$C_{16}H_{21}N_3O_2 \cdot 1$ HCl Calcd.: C, 58.52; H, 6.79; N, 12.80 Found: C, 58.52; H, 7.01; N, 12.74	288 $[M + H]^+$ Calcd.: 288.1712 Found: 288.1713
3i	*t*-Bu		A	44	176–180	$C_{18}H_{25}N_3O_2 \cdot HCl$ Calcd.: C, 61.44; H, 7.45; N, 11.94 Found: C, 61.71; H, 7.49; N, 12.17	316 $[M + H]^+$
3j[a]	*t*-Bu		A	–	–	–	–
3k	*t*-Bu		B	54	172–177	$C_{16}H_{27}N_3O_3 \cdot HCl$ Calcd.: C, 55.56; H, 8.16; N, 12.15 Found: C, 55.57; H, 8.28; N, 12.10	310 $[M + H]^+$
3l	*t*-Bu		B	43	188–194	$C_{14}H_{25}N_3O_2 \cdot 1$ HCl Calcd.: C, 54.53; H, 8.54; N, 13.63 Found: C, 54.71; H, 8.75; N, 13.74	268 $[M + H]^+$ Calcd.: 268.2025 Found: 268.2023
4a	Me		–	72[b] 36[c] 79[d]	97–100	$C_{14}H_{15}N_3O$ Calcd.: C, 69.69; H, 6.27; N, 17.41 Found: C, 69.96; H, 6.20; N, 17.33	242 $[M + H]^+$ Calcd.: 242.1293 Found: 242.1291
4b	Me		–	45	111–114	$C_{13}H_{14}N_4O \cdot H_2O$ Calcd.: C, 62.89; H, 5.95; N, 22.57 Found: C, 62.93; H, 5.42; N, 22.40	243 $[M + H]^+$ Calcd.: 243.1246 Found: 243.1250
4c	Me		–	54	oil	$C_{12}H_{17}N_3O_2$	236 $[M + H]^+$ Calcd.: 236.1399 Found: 236.1400
4d	Me		–	52	72–75	$C_{10}H_{15}N_3O$	194 $[M + H]^+$ Calcd.: 194.1293 Found: 194.1285
4e	Ph		–	89[b] 49[c] 86[d]	136–138	$C_{19}H_{17}N_3O$ Calcd.: C, 75.23; H, 5.65; N, 13.85 Found: C, 75.06; H, 5.76; N, 13.80	304 $[M + H]^+$
4f	Ph		–	66	95–99	$C_{18}H_{16}N_4O$ Calcd.: C, 71.04; H, 5.30; N, 18.41 Found: C, 70.62; H, 5.23; N, 18.32	305 $[M + H]^+$
4g	Ph		–	77	79–83	$C_{17}H_{19}N_3O_2$ Calcd.: C, 68.67; H, 6.44; N, 14.13 Found: C, 68.76; H, 6.46; N, 14.02	298 $[M + H]^+$
4h	Ph		–	17	212–217	$C_{15}H_{17}N_3O$ Calcd.: C, 70.56; H, 6.71; N, 16.46 Found: C, 70.50; H, 6.81; N, 16.55	256 $[M + H]^+$
4i	*t*-Bu		–	92[b] 38[c] 87[d]	77–79	$C_{17}H_{21}N_3O$ Calcd.: C, 72.06; H, 7.47; N, 14.83 Found: C, 71.85; H, 7.37; N, 14.85	284 $[M + H]^+$
4j	*t*-Bu		–	22	136–143	$C_{16}H_{20}N_4O \cdot 2HCl$ Calcd.: C, 51.18; H, 6.04; N, 14.92 Found: C, 51.24; H, 6.49; N, 14.68	285 $[M + H]^+$ Calcd.: 285.1715 Found: 285.1704
4k	*t*-Bu		–	81	oil	$C_{15}H_{23}N_3O_2$	278 $[M + H]^+$ Calcd.: 278.1869 Found: 278.1870

Table 1 Experimental Data for Compounds **2–5**, **9–11** and **13** (continued)

Compd	R^1	R^2	Proc.	Yield (%)	Mp (°C)	Molecular formula, analysis data	ESI-MS (*m*/*z*), HRMS
4l	*t*-Bu		–	70	135–138	$C_{13}H_{21}N_3O$ Calcd.: C, 66.35; H, 8.99; N, 17.86 Found: C, 66.75; H, 9.21; N, 17.85	236 $[M + H]^+$
5a	Me	–	–	45	197–200	$C_7H_9N_3O$ Calcd.: C, 55.62; H, 6.00; N, 27.80 Found: C, 55.49; H, 6.27; N, 27.63	152 $[M + H]^+$ Calcd.: 152.0824 Found: 152.0821
5b	Ph	–	–	66	202–205	$C_{12}H_{11}N_3O$ Calcd.: C, 67.59; H, 5.20; N, 19.71 Found: C, 67.65; H, 5.15; N, 19.69	214 $[M + H]^+$ Calcd.: 214.0980 Found: 214.0990
5c	*t*-Bu	–	–	51	164–166	$C_{10}H_{15}N_3O$ Calcd.: C, 62.15; H, 7.82; N, 21.74 Found: C, 62.06; H, 8.11; N, 21.66	194 $[M + H]^+$ Calcd.: 194.1293 Found: 194.1291
9	–	–	–	79	oil	$C_{15}H_{21}NO_4$	278 $[M - H]^+$ Calcd.: 278.1392 Found: 278.1396
10	–	–	–	70	oil	$C_{18}H_{25}NO_5$	358 $[M + Na]^+$ Calcd.: 358.1644 Found: 358. 1630
11	–	–	–	93	141–148	$C_{18}H_{18}NO_3 \cdot HCl$ Calcd.: C, 57.46; H, 6.68; N, 5.15 Found: C, 57.45; H, 6.77; N, 5.44	236 $[M + H]^+$ Calcd.: 236.1287 Found: 236.1290
13	–	–	–	83	oil	$C_{15}H_{18}N_2O_2$	259 $[M + H]^+$ Calcd.: 259.1447 Found: 259.1443

[a] Not isolated.
[b] Method A (Scheme 1).
[c] Method B (Scheme 1).
[d] Method C (Scheme 2).

Table 2 Spectral Data for Compounds **2–5**, **9–11** and **13**

Compd	IR (cm^{-1})	NMR (δ, ppm)[a]
2c	3449, 2965, 2913, 2828, 2752, 2654, 2616, 2552, 2512, 2454, 2047, 1709, 1605, 1551, 1508, 1465, 1438, 1402, 1368, 1291, 1244, 1213, 1154, 1099, 1004, 942, 872, 809, 783, 753, 614, 555, 497	^{1}H NMR: 1.64 (s, 9 H, *t*-Bu), 2.93–3.05 (m, 2 H, 1′-CH_2), 3.44–3.52 (m, 2 H, 2′-CH_2), 3.77 (s, 3 H, OCH_3), 7.79 (s, 1 H, 3-H), 8.38 (br s, 3 H, NH_3^+) ^{13}C NMR: 24.1, 30.1, 37.7, 51.1, 61.3, 112.9, 138.3, 141.8, 163.1
3a	3518, 3428, 3057, 2938, 2759, 2616, 2415, 1819, 1717, 1553, 1495, 1441, 1358, 1293, 1237, 1177, 1147, 1097, 1027, 980, 931, 894, 806, 780, 746, 700, 625, 594, 536, 501, 424	^{1}H NMR: 3.03–3.15 (m, 2 H, 1′-CH_2), 3.44 (dd, *J* = 7.2, 9.0 Hz, 2 H, 2′-CH_2), 3.74 (s, 3 H, 1-CH_3), 3.89 (s, 3 H, OCH_3), 4.17 (t, *J* = 5.8 Hz, 2 H, CH_2Ph), 7.40–7.49 (m, 3 H, *o*,*p*-PhH), 7.57–7.64 (m, 2 H, *m*-PhH), 7.80 (s, 1 H, 3-H), 9.85 (br s, 2 H, NH_2^+) ^{13}C NMR: 21.2, 36.8, 44.4, 49.8, 51.0, 111.2, 128.5, 128.8, 130.0, 132.0, 139.9, 142.0, 163.0
3b	3460, 3243, 2917, 2697, 2557, 2412, 1711, 1667, 1618, 1561, 1472, 1445, 1406, 1372, 1299, 1275, 1242, 1194, 1156, 1110, 1087, 1021, 997, 959, 925, 883, 808, 779, 753, 652, 623, 596, 510	^{1}H NMR: 3.14–3.24 (m, 2 H, 1′-CH_2), 3.40–3.47 (m, 2 H, 2′-CH_2), 3.75 (s, 3 H, 1-CH_3), 3.88 (s, 3 H, OCH_3), 4.36 (br s, 2 H, CH_2Py), 7.49 (ddd, *J* = 1.0, 4.9, 7.6 Hz, 1 H, 5″-H), 7.62 (d, *J* = 7.8 Hz, 1 H, 3″-H), 7.81 (s, 1 H, 3-H), 7.95 (dt, *J* = 1.8, 7.7 Hz, 1 H, 4″-H), 8.67 (ddd, *J* = 0.8, 1.6, 4.9 Hz, 1 H, 6″-H), 9.77 (br s, 2 H, NH_2^+) ^{13}C NMR: 21.3, 36.9, 44.8, 48.7, 51.2, 111.4, 125.0, 125.3, 140.0, 140.6, 141.9, 146.5, 150.0, 163.0

Table 2 Spectral Data for Compounds **2–5**, **9**–**11** and **13** (continued)

Compd	IR (cm^{-1})	NMR (δ, ppm)[a]
3c	3450, 3424, 2950, 2870, 2791, 2616, 2478, 2438, 1717, 1555, 1493, 1458, 1408, 1371, 1301, 1279, 1232, 1190, 1157, 1130, 1109, 1080, 1029, 992, 941, 902, 865, 807, 787, 751, 710, 652, 609, 542, 459, 414	^{1}H NMR: 1.66 (tdd, *J* = 6.9, 7.4, 12.8 Hz, 1 H, 4″-Ha), 2.03 (dtd, *J* = 5.5, 7.8, 12.8 Hz, 1 H, 4″-Hb), 2.58 (br sept., *J* = 7.0 Hz, 1 H, 3″-H), 2.96 (br s, 2 H, CHCH_2N), 3.07 (br s, 2 H, 1′-CH_2), 3.35–3.43 (m, 2 H, 2′-CH_2), 3.50 (dd, *J* = 5.8, 8.8 Hz, 1 H, 2″-Ha), 3.64 (q, *J* = 7.6 Hz, 1 H, 5″-Ha), 3.72 (dd, *J* = 6.3, 7.4 Hz, 1 H, 5″-Hb), 3.74 (s, 3 H, 1-CH_3), 3.77 (t, *J* = 8.7 Hz, 1 H, 2″-Hb), 3.89 (s, 3 H, OCH_3), 7.81 (s, 1 H, 3-H), 9.21 (br s, 2 H, NH_2^+) ^{13}C NMR: 21.0, 29.9, 35.9, 36.8, 45.0, 49.2, 51.0, 66.7, 70.4, 111.2, 139.9, 142.0, 163.0
3d	3437, 3172, 2828, 2797, 2739, 2701, 2597, 2506, 2459, 2334, 2055, 1704, 1598, 1564, 1500, 1460, 1435, 1395, 1374, 1339, 1299, 1282, 1249, 1186, 1166, 1130, 1110, 1079, 1059, 1023, 981, 949, 924, 890, 810, 795, 777, 745, 705, 655, 543, 511, 467	^{1}H NMR: 1.26 [d, *J* = 6.5 Hz, 6 H, $(CH_3)_2$CH], 3.00–3.10 (m, 2 H, 1′-CH_2), 3.30–3.40 [m, 3 H, C*H*$(CH_3)_2$ and 2′-CH_2], 3.77 (s, 3 H, 1-CH_3), 3.89 (s, 3 H, OCH_3), 7.81 (s, 1 H, 3-H), 9.21 (br s, 2 H, NH_2^+)
3e	3470, 2992, 2951, 2927, 2845, 2807, 2751, 2663, 2615, 2477, 2360, 1964, 1905, 1824, 1713, 1634, 1595, 1557, 1502, 1454, 1440, 1413, 1379, 1306, 1258, 1230, 1196, 1096, 1029, 972, 918, 877, 808, 783, 757, 744, 698, 653, 593, 492, 441	^{1}H NMR: 3.05–3.13 (m, 2 H, 1′-CH_2), 3.28–3.36 (m, 2 H, 2′-CH_2), 3.80 (s, 3 H, OCH_3), 4.09 (br s, 2 H, CH_2Ph), 7.39–7.44 (m, 3 H, 3H of Ph), 7.44–7.54 (m, 4 H, 4H of Ph), 7.56–7.61 (m, 3 H, 3H of Ph), 8.08 (s, 1 H, 3-H), 9.33 (br s, 2 H, NH_2^+)
3f	3418, 2984, 2945, 2831, 2604, 2570, 2466, 2407, 2013, 1958, 1702, 1634, 1560, 1495, 1454, 1414, 1375, 1311, 1269, 1105, 1070, 1005, 975, 933, 874, 810, 777, 700, 623, 598, 486, 444	^{1}H NMR: 3.17–3.25 (m, 2 H, 1′-CH_2), 3.33–3.41 (m, 2 H, 2′-CH_2), 3.81 (s, 3 H, OCH_3), 4.29 (br s, 2 H, CH_2Py), 7.47 (ddd, *J* = 1.0, 5.0, 7.5 Hz, 1 H, 5″-H), 7.51 (dd, *J* = 2.0, 7.4 Hz, 1 H, 3″-H), 7.51–7.54 (m, 1 H, *p*-PhH), 7.55–7.61 (m, 4 H, *o*,*m*-PhH), 7.92 (dt, *J* = 1.8, 7.7 Hz, 1 H, 4″-H), 8.08 (s, 1 H, 3-H), 8.62 (ddd, *J* = 0.9, 1.6, 4.9 Hz, 1 H, 6″-H), 9.64 (br s, 2 H, NH_2^+)
3g	3455, 3088, 2947, 2852, 2767, 2704, 2607, 2434, 1715, 1595, 1548, 1499, 1458, 1434, 1404, 1242, 1092, 1043, 972, 910, 772, 693	^{1}H NMR: 1.59 (tdd, *J* = 6.9, 7.6, 12.6 Hz, 1 H, 4″-Ha), 1.98 (dtd, *J* = 5.4, 7.9, 12.8 Hz, 1 H, 4″-Hb), 2.49 (br sept., *J* = 7.0 Hz, 1 H, 3″-H), 2.87 (br s, 2 H, CHCH_2N), 3.10 (br s, 2 H, 1′-CH_2), 3.26–3.35 (m, 2 H, 2′-CH_2), 3.42 (dd, *J* = 5.9, 8.8 Hz, 1 H, 2″-Ha), 3.61 (q, *J* = 7.7 Hz, 1 H, 5″-Ha), 3.71 (t, *J* = 8.5 Hz, 1 H, 2″-Hb), 3.73 (dd, *J* = 7.0, 8.1 Hz, 1 H, 5″-Hb), 3.83 (s, 3 H, OCH_3), 7.52–7.65 (m, 5 H, PhH), 8.09 (s, 1 H, 3-H), 9.10 (br s, 2 H, NH_2^+) ^{13}C NMR: 21.6, 29.8, 35.7, 44.8, 48.9, 51.4, 66.7, 70.3, 112.5, 126.0, 129.3, 129.6, 138.0, 141.4, 142.6, 163.0
3h	3418, 2963, 2833, 2711, 2601, 2457, 2052, 1711, 1595, 1556, 1497, 1462, 1438, 1404, 1300, 1256, 1213, 1188, 1134, 1087, 1065, 1001, 966, 809, 772, 694, 656, 616, 503, 463	^{1}H NMR: 1.18 [d, *J* = 6.5 Hz, 6 H, $(CH_3)_2$CH], 3.02–3.11 (m, 2 H, 1′-CH_2), 3.15–3.33 [m, 3 H, 2′-CH_2 and C*H*$(CH_3)_2$], 3.83 (s, 3 H, OCH_3), 7.52–7.64 (m, 5 H, PhH), 8.09 (s, 1 H, 3-H), 8.98 (br s, 2 H, NH_2^+) ^{13}C NMR: 18.3, 22.0, 41.3, 48.8, 51.4, 112.5, 126.0, 129.2, 129.6, 138.0, 141.5, 142.6, 163.0
3i	3422, 3129, 2955, 2772, 2701, 2363, 1868, 1724, 1645, 1582, 1549, 1499, 1472, 1436, 1391, 1298, 1237, 1192, 1151, 1098, 1032, 878, 802, 781, 737, 702, 608, 490, 458	^{1}H NMR: 1.62 (s, 9 H, *t*-Bu), 3.05–3.18 (m, 2 H, 1′-CH_2), 3.56–3.64 (m, 2 H, 2′-CH_2), 3.73 (s, 3 H, OCH_3), 4.22 (br t, *J* = 5.9 Hz, 2 H, CH_2Ph), 7.40–7.49 (m, 3 H, *o*,*p*-PhH), 7.58–7.63 (m, 2 H, *p*-PhH), 7.79 (s, 1 H, 3-H), 9.77 (br s, 2 H, NH_2^+)
3j	3453, 2948, 2776, 2479, 1707, 1549, 1464, 1437, 1400, 1374, 1277, 1238, 1215, 1150, 1098, 1046, 984, 933, 868, 810, 781, 615, 470	^{1}H NMR: 1.65 (s, 9 H, *t*-Bu), 1.69 (tdd, *J* = 6.9, 7.6, 12.4 Hz, 1 H, 4″-Ha), 2.06 (dtd, *J* = 5.4, 7.9, 12.4 Hz, 1 H, 4″-Hb), 2.61 (br sept., *J* = 7.1 Hz, 1 H, 3″-H), 3.01 (br s, 2 H, CHCH_2N), 3.10 (br s, 2 H, 1′-CH_2), 3.51 (dd, *J* = 5.9, 8.8 Hz, 1 H, 2″-Ha), 3.55–3.63 (m, 2 H, 2′-CH_2), 3.65 (q, *J* = 7.7 Hz, 1 H, 5″-Ha), 3.71–3.81 (m, 2 H, 2″-Hb and 5″-Hb), 3.77 (s, 3 H, OCH_3), 7.80 (s, 1 H, 3-H), 9.40 (br s, 2 H, NH_2^+)
3k	3439, 2972, 2949, 2833, 2801, 2740, 2698, 2648, 2597, 2569, 2507, 2458, 2327, 2052, 1710, 1587, 1553, 1467, 1442, 1400, 1373, 1298, 1275, 1238, 1211, 1152, 1099, 1052, 1028, 1009, 981, 945, 925, 866, 828, 810, 781, 769, 740, 613, 555, 529, 467	^{1}H NMR: 1.28 [d, *J* = 6.5 Hz, 6 H, $(CH_3)_2$CH], 1.65 (s, 9 H, *t*-Bu), 3.09 (m, 2 H, 1′-CH_2), 3.29–3.41 [m, 1 H, C*H*$(CH_3)_2$], 3.50–3.59 (m, 2 H, 2′-CH_2), 3.77 (s, 3 H, OCH_3), 7.80 (s, 1 H, 3-H), 9.19 (br s, 2 H, NH_2^+) ^{13}C NMR: 18.4, 22.9, 30.1, 42.2, 49.0, 51.1, 61.3, 112.9, 138.4, 141.5, 163.1
4a	3445, 3426, 3102, 3026, 2949, 2921, 2434, 1915, 1792, 1653, 1552, 1526, 1479, 1453, 1422, 1361, 1336, 1288, 1231, 1159, 1067, 1045, 1028, 1002, 980, 936, 903, 862, 800, 772, 748, 702, 671, 645, 614, 554, 489, 469, 453	^{1}H NMR: 2.94 (t, *J* = 6.9 Hz, 2 H, 7-CH_2), 3.50 (t, *J* = 6.9 Hz, 2 H, 6-CH_2), 3.74 (s, 3 H, 1-CH_3), 4.61 (s, 2 H, CH_2Ph), 7.22–7.36 (m, 5 H, PhH), 7.69 (s, 1 H, 3-H) ^{13}C NMR: 21.0, 36.1, 45.8, 49.0, 113.9, 127.5, 128.1, 128.7, 137.8, 138.0, 142.8, 162.9

Table 2 Spectral Data for Compounds **2–5**, **9**–**11** and **13** (continued)

Compd	IR (cm^{-1})	NMR (δ, ppm)[a]
4b	3414, 3105, 2951, 2911, 1642, 1591, 1530, 1480, 1423, 1346, 1326, 1294, 1234, 1167, 1045, 1003, 932, 885, 822, 762, 670, 637, 610, 567, 492, 467	^{1}H NMR: 2.99 (t, J = 6.9 Hz, 2 H, 7-CH_2), 3.64 (t, J = 6.9 Hz, 2 H, 6-CH_2), 3.76 (s, 3 H, 1-CH_3), 4.70 (s, 2 H, CH_2Py), 7.23–7.29 (m, 2 H, 3′-H and 5′-H), 7.68 (s, 1 H, 3-H), 7.75 (dt, J = 1.8, 7.7 Hz, 1 H, 4′-H), 8.50 (dd, J = 1.7, 5.3 Hz, 1 H, 6′-H) ^{13}C NMR: 21.1, 36.1, 46.9, 51.4, 113.9, 122.4, 122.5, 136.9, 138.1, 143.0, 149.3, 157.9, 162.9
4c	3458, 3437, 2934, 2868, 2417, 1714, 1637, 1531, 1485, 1452, 1325, 1292, 1232, 1069, 984, 907, 708, 671	^{1}H NMR: 1.55 (br sext., J = 6.6 Hz, 1 H, 4′-Ha), 1.90 (br sext., J = 6.6 Hz, 1 H, 4′-Hb), 2.53 (br sept., J = 6.7 Hz, 1 H, 3″-H), 2.95 (t, J = 6.9 Hz, 2 H, 7-CH_2), 3.33–3.47 (m, 3 H, CHCH_2N and 2″-Ha), 3.59 (t, J = 6.8 Hz, 2 H, 6-CH_2), 3.61 (q, J = 7.6 Hz, 1 H, 5″-Ha), 3.68 (br t, J = 7.9 Hz, 1 H, 5″-Hb), 3.72–3.81 (m, 1 H, 2″-Hb), 3.75 (s, 3 H, 1-CH_3), 7.63 (s, 1 H, 3-H) ^{13}C NMR: 20.3, 29.5, 35.8, 37.9, 46.3, 47.2, 66.8, 70.5, 113.2, 136.5, 143.6, 162.0
4d	3442, 2965, 1634, 1531, 1464, 1427, 1363, 1305, 1241, 1216, 1175, 1126, 1069, 1040, 985, 876, 800, 770, 681, 634, 502, 476, 438	^{1}H NMR: 1.09 [d, J = 6.8 Hz, 6 H, (CH_3)$_2$CH], 2.90 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.44 (t, J = 6.8 Hz, 2 H, 6-CH_2), 3.75 (s, 3 H, 1-CH_3), 4.75 [sept., J = 6.8 Hz, 1 H, CH(CH_3)$_2$], 7.61 (s, 1 H, 3-H) ^{13}C NMR: 21.6, 29.9, 36.2, 42.7, 52.8, 114.9, 139.8, 142.7, 162.5
4e	3469, 3087, 2947, 2916, 1834, 1655, 1597, 1558, 1506, 1450, 1421, 1354, 1329, 1298, 1261, 1236, 1156, 1115, 1076, 999, 969, 923, 770, 732, 696, 616, 573, 528, 502, 473, 415	^{1}H NMR: 3.14 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.52 (t, J = 6.8 Hz, 2 H, 6-CH_2), 4.66 (s, 2 H, CH_2Ph), 7.23–7.38 (m, 5 H, PhH), 7.40–7.48 (m, 1 H, p-PhH), 7.51–7.64 (m, 4 H, o,m-PhH), 8.01 (s, 1 H, 3-H)
4f	3416, 3063, 2932, 1656, 1590, 1560, 1508, 1425, 1300, 1238, 1151, 1115, 1057, 989, 964, 920, 766, 692, 540, 500, 477	^{1}H NMR: 3.19 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.67 (t, J = 6.8 Hz, 2 H, 6-CH_2), 4.75 (s, 2 H, CH_2Py), 7.28 (ddd, J = 1.0, 4.9, 7.4 Hz, 1 H, 5″-H), 7.33 (br d, J = 7.8 Hz, 1 H, 3″-H), 7.42–7.48 (tt, J = 1.4, 7.1 Hz, 1 H, p-PhH), 7.53–7.65 (m, 4 H, o,m-PhH), 7.77 (dt, J = 1.8, 7.7 Hz, 1 H, 4′-H), 8.00 (s, 1 H, 3-H), 8.52 (ddd, J = 0.9, 1.7, 4.8 Hz, 1 H, 6′-H)
4g	3441, 3063, 2967, 2926, 2870, 1965, 1735, 1645, 1598, 1562, 1509, 1473, 1456, 1415, 1366, 1317, 1298, 1256, 1241, 1211, 1184, 1163, 1109, 1082, 1065, 1001, 968, 899, 868, 766, 739, 694, 651, 633, 602, 544, 501, 475, 413	^{1}H NMR: 1.58 (tdd, J = 6.7, 7.6, 12.3 Hz, 1 H, 4″-Ha), 1.93 (dtd, J = 5.5, 7.5, 12.3 Hz, 1 H, 4″-Hb), 2.55 (br sept., J = 7.0 Hz, 1 H, 3″-H), 3.15 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.36–3.52 (m, 3 H, CHCH_2N and 2″-Ha), 3.62 (t, J = 6.8 Hz, 2 H, 6-CH_2), 3.63 (br q, J = 7.5 Hz, 1 H, 5″-Ha), 3.71 (dd, J = 6.9, 8.3 Hz, 1 H, 5″-Hb), 3.77 (dt, J = 5.1, 8.1 Hz, 1 H, 2″-Hb), 7.41–7.49 (m, 1 H, p-PhH), 7.53–7.65 (m, 4 H, o,m-PhH), 7.95 (s, 1 H, 3-H)
4h	3488, 2970, 2928, 2361, 1643, 1598, 1555, 1506, 1458, 1415, 1366, 1304, 1266, 1221, 1184, 1105, 1060, 978, 800, 766, 692, 644	^{1}H NMR: 1.12 [d, J = 6.8 Hz, 6 H, (CH_3)$_2$CH], 3.11 (t, J = 6.7 Hz, 2 H, 7-CH_2), 3.47 (t, J = 6.7 Hz, 2 H, 6-CH_2), 4.79 [sept., J = 6.8 Hz, 1 H, CH(CH_3)$_2$], 7.41–7.48 (m, 1 H, p-PhH), 7.52–7.63 (m, 4 H, o,m-PhH), 7.94 (s, 1 H, 3-H)
4i	3487, 2978, 2930, 1649, 1543, 1501, 1449, 1398, 1368, 1329, 1230, 1157, 1078, 1030, 989, 934, 864, 818, 768, 730, 702	^{1}H NMR: 1.55 (s, 9 H, t-Bu), 3.17 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.46 (t, J = 6.8 Hz, 2 H, 6-CH_2), 4.61 (s, 2 H, CH_2Ph), 7.22–7.36 (m, 5 H, PhH), 7.69 (s, 1 H, 3-H)
4j	3465, 3083, 2982, 2585, 2060, 1974, 1674, 1616, 1570, 1514, 1462, 1401, 1358, 1296, 1238, 1201, 1180, 1041, 1002, 876, 814, 767, 463	^{1}H NMR: 1.58 (s, 9 H, t-Bu), 3.32 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.73 (t, J = 6.5 Hz, 2 H, 6-CH_2), 4.95 (s, 2 H, CH_2Py), 7.25–7.31 (m, 2 H, 3″-H and 5″-H), 7.70 (s, 1 H, 3-H), 8.42 (dt, J = 1.5, 7.9 Hz, 1 H, 4″-H), 8.80 (dd, J = 0.7, 5.6 Hz, 1 H, 6″-H) ^{13}C NMR: 23.8, 29.5, 30.2, 46.8, 47.5, 60.4, 113.9, 125.6, 135.7, 141.2, 142.9, 146.3, 153.5, 163.0
4k	3493, 2974, 2931, 2865, 2361, 1645, 1542, 1503, 1397, 1369, 1328, 1287, 1228, 1158, 1068, 1040, 993, 907, 863, 770, 673	^{1}H NMR: 1.55 (tdd, J = 6.8, 7.6, 12.3 Hz, 1 H, 4″-Ha), 1.56 (s, 9 H, t-Bu), 1.91 (dtd, J = 5.5, 7.8, 12.2 Hz, 1 H, 4″-Hb), 2.52 (br sept., J = 7.0 Hz, 1 H, 3″-H), 3.18 (t, J = 6.8 Hz, 2 H, 7-CH_2), 3.33–3.46 (m, 3 H, CHCH_2N and 2″-Ha), 3.55 (t, J = 6.6 Hz, 2 H, 6-CH_2), 3.61 (br q, J = 7.5 Hz, 1 H, 5″-Ha), 3.69 (dd, J = 7.0, 8.3 Hz, 1 H, 5″-Hb), 3.75 (dt, J = 5.6, 8.3 Hz, 1 H, 2″-Hb), 7.63 (s, 1 H, 3-H) ^{13}C NMR: 23.8, 29.4, 29.5, 37.8, 46.4, 47.1, 60.1, 66.8, 70.5, 114.7, 135.5, 141.9, 162.2
4l	3472, 3417, 2975, 2934, 1639, 1545, 1500, 1442, 1396, 1366, 1301, 1220, 1185, 1156, 1070, 1031, 995, 866, 826, 800, 770, 731, 624, 482	^{1}H NMR: 1.09 [d, J = 6.8 Hz, 6 H, (CH_3)$_2$CH], 1.56 (s, 9 H, t-Bu), 3.14 (t, J = 6.7 Hz, 2 H, 7-CH_2), 3.41 (t, J = 6.7 Hz, 2 H, 6-CH_2), 4.73 [sept., J = 6.8 Hz, 1 H, CH(CH_3)$_2$], 7.62 (s, 1 H, 3-H)

Table 2 Spectral Data for Compounds **2–5**, **9**–**11** and **13** (continued)

Compd	IR (cm^{-1})	NMR (δ, ppm)[a]
5a	3209, 3078, 2945, 2876, 1660, 1629, 1530, 1487, 1451, 1421, 1354, 1292, 1244, 1196, 1030, 987, 932, 897, 785, 688	^{1}H NMR ($CDCl_3$): 2.90 (t, *J* = 6.8 Hz, 2 H, 7-CH_2), 3.62 (dt, *J* = 2.6, 6.8 Hz, 2 H, 6-CH_2), 3.83 (s, 3 H, CH_3), 6.08 (br s, 1 H, NH), 7.87 (s, 1 H, 3-H)
5b	3235, 3067, 1667, 1633, 1549, 1513, 1457, 1427, 1265, 979, 783, 765	^{1}H NMR: 3.06 (t, *J* = 6.8 Hz, 2 H, 7-CH_2), 3.42 (dt, *J* = 2.5, 6.8 Hz, 2 H, 6-CH_2), 7.38 (br s, 1 H, NH), 7.46 (t, *J* = 7.3 Hz, 1 H, *p*-PhH), 7.52–7.64 (m, 4 H, *o*,*m*-PhH), 7.95 (s, 1 H, 3-H)
5c	3307, 3221, 3104, 3067, 2980, 1662, 1545, 1503, 1426, 1397, 1367, 1298, 1238, 1161, 1117, 995, 794, 683	^{1}H NMR ($CDCl_3$): 1.65 (s, 9 H, *t*-Bu), 3.13 (t, *J* = 6.8 Hz, 2 H, 7-CH_2), 3.59 (dt, *J* = 2.6, 6.8 Hz, 2 H, 6-CH_2), 6.19 (br s, 1 H, NH), 7.87 (s, 1 H, 3-H)
9	2977, 2933, 1748, 1713, 1692, 1454, 1414, 1366, 1246, 1167, 876, 701	^{1}H NMR ($CDCl_3$): 1.47 (br s, 9 H, *t*-Bu), 2.56 (br s, 2 H, 2-CH_2), 3.46 (br s, 2 H, 3-CH_2), 4.46 (s, 2 H, CH_2Ph), 7.18–7.36 (m, 5 H, Ph) ^{13}C NMR: 28.6, 33.5, 42.8, 50.8, 80.5, 127.5, 127.7, 128.7, 138.3, 155.9, 177.4
10	2978, 2932, 1735, 1696, 1476, 1455, 1416, 1367, 1248, 1163, 1121, 1028, 872, 735, 700	^{1}H NMR ($CDCl_3$): 1.46 (br s, 9 H, *t*-Bu), 2.78 (br s, 2 H, 4-CH_2), 3.41 (br s, 4 H, 2-CH_2, 5-CH_2), 3.71 (s, 3 H, OCH_3), 4.44 (s, 2 H, CH_2Ph), 7.18–7.36 (m, 5 H, PhH) ^{13}C NMR ($CDCl_3$): 28.4, 41.9, 49.1, 50.6, 51.5, 52.3, 80.0, 127.3, 127.8, 128.6, 138.4, 155.6, 167.4, 201.4
11	3415, 2940, 2784, 2733, 2409, 1748, 1712, 1600, 1438, 1402, 1364, 1330, 1256, 1188, 1102, 1028, 986, 861, 750, 695	^{1}H NMR: 3.07 (br s, 4 H, 2-CH_2, 4-CH_2), 3.64 (s, 3 H, OCH_3), 3.68 (br s, 2 H, 5-CH_2), 4.12 (br s, 2 H, CH_2Ph), 7.39–7.47 (m, 3 H, *o*,*p*-PhH), 7.52–7.59 (m, 2 H, *m*-PhH), 9.39 (br s, 2 H, NH_2^+)
13	3466, 3061, 3028, 2963, 2927, 2866, 2812, 1658, 1599, 1479, 1437, 1420, 1372, 1286, 1232, 1202, 1137, 1095, 1039, 1005, 987, 866, 764, 745, 701	^{1}H NMR ($CDCl_3$): 2.46 (t, *J* = 6.4 Hz, 2 H, 5-CH_2), 3.19 and 3.30 [2 × s, 1:1, 6 H, N$(CH_3)_2$], 3.33 (t, *J* = 6.3 Hz, 2 H, 6-CH_2), 4.68 (s, 2 H, CH_2Ph), 7.20–7.37 (m, 5 H, PhH), 8.03 (s, 1 H, 3′-H) ^{13}C NMR: 37.3, 42.1, 43.3, 47.5, 49.3, 100.1, 126.6, 127.1, 127.9, 137.6, 158.4, 166.2, 190.6

[a] Recorded in DMSO-d_6 unless noted.

Melting points were determined with a Kofler micro hot stage apparatus. The NMR spectra were obtained with a Bruker Avance DPX 300 spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nuclei, using DMSO-d_6 or $CDCl_3$ as solvent with TMS as internal standard. Mass spectra were recorded with a Q-TOF Premier spectrometer, IR spectra with a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II. Column chromatography was performed on silica gel (Fluka, Silica gel 60, particle size 0.035–0.070 mm).

Pyridine-2-carbaldehyde, tetrahydrofuran-2-carbaldehyde (50% aqueous solution), methylhydrazine, phenylhydrazine, and *tert*-butylhydrazine are commercially available (Sigma–Aldrich). Methyl 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxylate, methyl 5-(2-aminoethyl)-1-methyl-1*H*-pyrazole-4-carboxylate dihydrochloride (**2a**), and methyl 5-(2-aminoethyl)-1-phenyl-1*H*-pyrazole-4-carboxylate dihydrochloride (**2b**) were prepared according to literature procedures.[11]

Methyl 5-(2-Aminoethyl)-1-*tert*-butyl-1*H*-pyrazole-4-carboxylate Hydrochloride (2c)

HCl in EtOAc (2 M, 30 mL, 60 mmol) was added to a stirred mixture of methyl 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1-*tert*-butyl-1*H*-pyrazole-4-carboxylate[11] (3.25 g, 10 mmol), anhydrous EtOH (5 mL) and EtOAc (10 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min then at r.t. for 2 h. The precipitate was collected by filtration, washed with EtOAc (2 × 20 mL), and dried in vacuo at r.t. over NaOH pellets for 12 h to give **2c**. Experimental, physical, and analytical data for compound **2c** are given in Table 1; spectral data are given in Table 2.

Reductive Alkylation of Primary Amines 2; General Procedures

1-Substituted Methyl 5-[2-(Alkylamino)ethyl]-1*H*-pyrazole-4-carboxylate Hydrochlorides 3a–i, 3k, and 3l, and 1-*tert*-Butyl-5-[(pyridin-2-yl)methyl]-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one Hydrochloride (4j)

General Procedure A

A mixture of amine dihydrochloride **2** (5 mmol), anhydrous MeOH (40 mL), and anhydrous NaOAc (820 mg, 10 mmol) was stirred at r.t. for 5 min. AcOH (605 mg, 578 μL, 10 mmol) and benzaldehyde (800 mg, 765 μL, 7.5 mmol) or pyridine-2-carbaldehyde (811 mg, 721 μL, 7.5 mmol) were added and the mixture was cooled to 0 °C (ice-bath). Then, $NaBH_4$ (191 mg, 5 mmol) was added portion-wise and the stirring at 0 °C was continued for 4 h. The reaction mixture was evaporated in vacuo and the semi-solid residue was purified by column chromatography (EtOH–EtOAc, 20%). Fractions containing the product were combined and evaporated in vacuo and the residue was dissolved in Et_2O (50 mL). HCl in Et_2O (3 M, 5 mL, 15 mmol) was added and the mixture was stirred for 5 min. The precipitate was collected by filtration to give **3**. Compounds **3a**, **3b**, **3e**, **3f**, **3i** and **4j** were prepared in this manner. Experimental, physical and analytical data for these compounds are given in Table 1; spectral data are given in Table 2.

General Procedure B

A mixture of amine dihydrochloride **2** (5 mmol), MeOH (40 mL), 4-methylmorpholine (200 μL, 184 mg, 1.8 mmol), tetrahydrofuran-3-carboxaldehyde (50% in H_2O; 1.33 g, 1.20 mL, 6.5 mmol) or acetone (10 mL, excess), and 10% Pd–C (150 mg) was hydrogenated (3 bar of H_2) at r.t. for 8 h. The catalyst was removed by filtration

through a fritted funnel and washed with MeOH (2 × 5 mL). The combined filtrate was evaporated in vacuo and the residue was triturated with EtOAc (20 mL). The precipitate was collected by filtration and washed with EtOAc (10 mL) to give **3**. Compounds **3c**, **3d**, **3g**, **3h**, **3k** and **3l** were prepared in this manner. Experimental, physical, and analytical data for these compounds are given in Table 1; spectral data are given in Table 2.

Cyclisation of Methyl 5-(2-Aminoethyl)-1*H*-pyrazole-4-carboxylates 2 and Their *N*-Alkyl Analogues 3; General Procedures Synthesis of 1,5,6,7-Tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones 4 and 5

Preparation of Compounds 4; General Procedure

A mixture of **3** (1 mmol), 1-propanol (15 mL), and *t*-BuOK (560 mg, 5 mmol) was stirred under reflux for 15 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (EtOH–EtOAc, 20%). Fractions containing the product were combined and evaporated in vacuo to give **4**. Compounds **4a–i**, **4k** and **4l** were prepared in this manner. Experimental, physical, and analytical data for these compounds are given in Table 1; spectral data are given in Table 2.

Preparation of Compounds 5; General Procedure

A mixture of **2** (1 mmol), DMF (5 mL) and Et_3N (3.5 mL) was stirred at reflux for 5 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (EtOH–EtOAc, 20%). Fractions containing the product were combined and evaporated in vacuo. The residue was triturated with Et_2O (4 mL) and the precipitate was collected by filtration to give **5**. Experimental, physical, and analytical data for compounds **5a–c** are given in Table 1; spectral data are given in Table 2.

Synthesis of Compounds 4a, 4e and 4i by Benzylation of 4*H*-pyrazolo[4,3-*c*]pyridin-4-ones 5a–c; General Procedure

t-BuOK (112 mg, 1 mmol) was added to a solution of **5** (0.5 mmol) in DMF (2 mL) and the mixture was stirred at r.t. for 15 min. BnBr (100 μL, 144 mg, 0.83 mmol) was added and stirring at r.t. was continued for 12 h. The reaction mixture was poured into 10% aq. AcOH (10 mL) and the product was extracted with EtOAc (30 mL). The organic phase was washed with H_2O (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (EtOAc–hexanes, 67% then EtOH–EtOAc, 20%). Fractions containing the product were combined and volatile components were evaporated in vacuo to give **4**. Experimental, physical, and analytical data for compounds **4a**, **4e** and **4i** are given in Table 1; spectral data are given in Table 2.

N-Benzyl-*N*-*tert*-butoxycarbonyl-β-alanine (9)

DBU (150 mg, 150 μL, ~1 mmol) was added to a mixture of benzylamine (2.14 g, 2.18 mL, 20 mmol) and methyl acrylate (**6**; 1.74 g, 1.82 mL, 20 mmol), and the resulting mixture was stirred at r.t. for 12 h to give **7**. MeCN (40 mL) and Boc_2O (4.40 g, 20 mmol) were added, the reaction mixture was stirred at r.t. for 24 h, and volatile components were evaporated in vacuo to give **8**. The crude compound **8** was dissolved in MeOH (40 mL), aq NaOH (2 M, 30 mL, 60 mmol) was added, and the mixture was stirred at r.t. for 3 h. The reaction mixture was carefully acidified while stirring: first with aq HCl (6 M, 10 mL, 60 mmol) and then with aq $NaHSO_4$ (1 M, 30 mL, 30 mmol). The product was extracted with EtOAc (2 × 100 mL), the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give **9**, which was used for further transformations without purification. Experimental, physical, and analytical data for compound **9** are given in Table 1; spectral data are given in Table 2.

Methyl 5-[Benzyl(*tert*-butoxycarbonyl)amino]-3-oxopentanoate (10)

Under Ar, 1,1′-carbonyldiimidazole (CDI; 3.06 g, 18.9 mmol) was added to a solution of **9** (4.33 g, 15.5 mmol) in anhydrous THF (60 mL) and the mixture was stirred at r.t. for 2 h. A solid mixture of anhydrous $MgCl_2$ (1.43 g, 15 mmol) and potassium monomethyl malonate (3.63 g, 23.2 mmol) was added under Ar in one portion via a powder funnel, which was rinsed with anhydrous THF (20 mL), and the mixture was stirred under Ar at r.t. for 20 h. Volatile components were evaporated in vacuo, EtOAc (200 mL) was added to the residue and the resulting suspension was washed with aq $NaHSO_4$ (1 M, 2 × 70 mL) and brine (70 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (silica gel; EtOAc–hexanes, 50%). Fractions containing the product were combined and volatile components were evaporated in vacuo to give **10**, which was used for further transformations without purification. Experimental, physical, and analytical data for compound **10** are given in Table 1; spectral data are given in Table 2.

N-Benzyl-5-methoxy-3,5-dioxopentan-1-aminium Chloride (11)

The crude compound **10** (5.03 g, 15 mmol) was dissolved in ethereal HCl (3.6 M; 50 mL) and the mixture was stirred at r.t. for 12 h. The precipitate was collected by filtration and washed with anhydrous Et_2O (3 × 20 mL) to give **11**. Experimental, physical, and analytical data for compound **11** are given in Table 1; spectral data are given in Table 2.

1-Benzylpiperidine-2,4-dione (12)

Aq NaOH (2 M; 2.5 mL, 25 mmol) was added to a solution of **11** (3.26 g, 12 mmol) in H_2O (60 mL), the mixture was stirred at r.t. for 1 h, and acidified with aq HCl (1 M) to pH ~4. The product was extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give **12**. Physical and spectral data for compound **12** were consistent with the literature data.[13]

1-Benzyl-3-[(dimethylamino)methylidene]piperidine-2,4-dione (13)

DMFDMA (2.24 g, 2.50 mL, 18.8 mmol) was added to a solution of **12** (2.03 g, 10 mmol) in anhydrous toluene (20 mL) and the resulting reaction mixture was stirred at r.t. for 12 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (EtOH–EtOAc, 10%). Fractions containing the product were combined and volatile components were evaporated in vacuo to give **13**, which was used for further transformations without purification. Experimental, physical, and analytical data for compound **13** are given in Table 1; spectral data are given in Table 2.

Synthesis of 1-Substituted 5-Benzyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones 4a, 4e and 4i from Enaminone 13; General Procedure

A mixture of **13** (129 mg, 0.5 mmol), monosubstituted hydrazine hydrochloride (0.5 mmol), and 2-methoxyethanol (5 mL) was stirred at r.t. for 0.5 h and then at reflux for 2 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (EtOAc). Fractions containing the product were combined and volatile components were evaporated in vacuo. The residue was triturated with either Et_2O (3 mL, for **4a** and **4e**) or a mixture of Et_2O and *n*-hexane (1:1; 3 mL, for **4i**), and the precipitate was collected by filtration to give **4**. Experimental, physical, and analytical data for compounds **4a**, **4e** and **4i** are given in Table 1; spectral data are given in Table 2.

X-ray Structure Analysis

Single crystal X-ray diffraction data of compounds **4a** and **4i** (Table 3) were collected at r.t. on a Nonius Kappa CCD diffractometer (Mo-K_α radiation) using the Nonius Collect Software.[18] DENZO and SCALEPACK[19] were used for indexing and scaling of the data. The structures were solved by means of SIR97.[20] Refinement was performed using the Xtal3.4[21] program package and the crystallographic plots were prepared with ORTEP III.[22] Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in both cases, while the positions of hydrogen atoms were geometrically calculated; their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[23] weighting scheme was used in both cases.

Table 3 X-ray Crystal Data for Compounds **4a** and **4i**[24]

Compound	**4a**	**4i**
Formula	$C_{14}H_{15}N_3O$	$C_{17}H_{21}N_3O$
M_r	241.29	283.38
Crystal system	monoclinic	monoclinic
Space group	$P2_1/a$	$P2_1/a$
a (Å)	12.6263(2)	11.0738(2)
b (Å)	7.47630(10)	10.1626(2)
c (Å)	13.7210(3)	14.3918(2)
β (°)	108.8110(11)	102.1287(10)
V (Å^3)	1226.05(4)	1583.48(5)
Z[a]	4	4
ρ (Mg m^{-3})	1.307	1.189
μ (mm^{-1})	0.085	0.076
Crystal shape	white plate	white plate
Dimensions (mm)	0.27 × 0.22 × 0.07	0.25 × 0.20 × 0.10
Threshold criterion	$I > 2.0\sigma(I)$	$I > 2.0\sigma(I)$
Final *R* and R_w	0.051, 0.044	0.052, 0.034

[a] *Z*: Multiplicity of the space group.

Acknowledgment

We acknowledge with thanks the financial support from Boehringer-Ingelheim Pharma GmbH & Co. KG (Biberach, Germany). The financial support from the Slovenian Research Agency through grant P1–0179 is gratefully acknowledged.

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(24) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 770933 (**4a**) and CCDC 770934 (**4i**). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.