A Novel Fragmentation of 7-Azabicyclo[2.2.1]hepta-2,5-dienes: Synthesis of *cis*-5-Amidino-pyrrolidine-2-acetic Acid Derivatives

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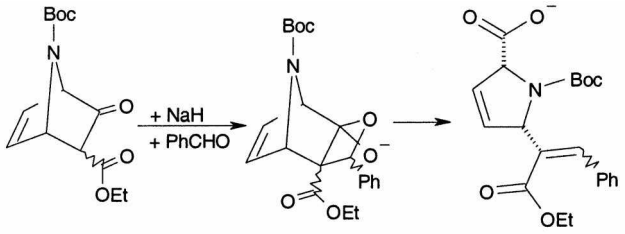
Abstract: A new fragmentation reaction of 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene carboxylic esters with 2-amino or 2-aminomethyl anilines is described. It leads to *cis*-5-(benzimidazol-2-yl)- or cis-5-(3,4-dihydroquinazolin-2-yl)-pyrroline-2-acetic acid esters. Substituents on the nitrogen atoms or in the aromatic ring are tolerated as long as they do not strongly reduce the nucleophilicity of the nitrogen atoms. The primary reaction products are not very stable but hydrogenation of the pyrroline and/or cleavage of the ester give products that are suitable for subsequent structural modifications, particularly ones that are interesting for combinatorial syntheses.

Key words: amines, ring closure, ring opening, heterocycles, nucleophilic additions

This report describes a new fragmentation reaction, which leads to the synthesis of novel pyrroline and pyrrolidine 2-acetic acid derivatives that carry a cyclic amidine function in 5-position *cis* to the acetic acid moiety.

Pyrrolidines represent a very important class of heterocycles. They are not only found in a large number of alkaloids[3] and biologically active molecules such as the neuraminidase inhibitors A-192558, A-315675, and others.[4] They have also gained attention as precursors in the synthesis of dipeptide mimics[5] or as chiral ligands[6] and chiral auxiliaries.[7]

The significance of pyrrolidines is also witnessed by the many reported stereoselective syntheses of 2,5-disubstituted pyrrolines and pyrrolidines (reviews: syntheses in general,[8] via intramolecular N-addition to a double bond,[9] via ring closing metathesis,[10] via [3+2] cycloadditions[11]). Specifically, pyrrol-2-yl-acetic acid derivatives have been synthesized in various ways, e.g., hydrogenation of pyrrol-2-acetic acid esters,[12] reduction of the C=C double bond of pyrrolidin-2-ylidene acetic and malonic esters,[13] intramolecular Michael addition,[14] iodocylization,[14d,15] intramolecular reductive amination of a (4-aminobutyryl)acetic acid ester,[16] intramolecular nucleophilic substitution,[17] from crotyl silanes, methylcarbamate and aromatic aldehyde acetals with a Lewis acid,[18] carbonylation and reductive cyclization starting from 3-(*N*-phenylselenoethylamino)acrylates,[19] ring contraction,[20] by *retro* Dieckmann reaction from a 2-oxo-7-azabicyclo[2.2.1]heptane-1-carboxylate,[21] and by *retro* Diels–Alder reaction.[22] A side-chain benzylidene derivative of ethyl (5-carboxy-2,5-dihydropyrrol-2-yl acetate was obtained by a fragmentation that resembles the one reported here (Scheme 1).[23] Many of these syntheses are aimed at 5-carboxy-pyrrolidin-2-yl acetic acids as precursors of carbapenam antibiotics.[12,13c,14a,17b,20,24]



Scheme 1

The present work originates from our interest in non-planar molecular scaffolds as a basis for combinatorial library synthesis in drug research. Such scaffolds open additional possibilities for adapting the shape of drug molecules to the requirements of binding sites on biological targets.

In this connection we became interested in 7-azabicyclo[2.2.1]hepta-2,5-dienes of type **1** (Figure 1) whose synthesis had been reported in the literature.[25] These compounds contain four functional groups that can be further modified with well established chemistry: the bromoalkene, the (protected) carboxyl and secondary amino groups, as well as the unsubstituted C=C double bond.

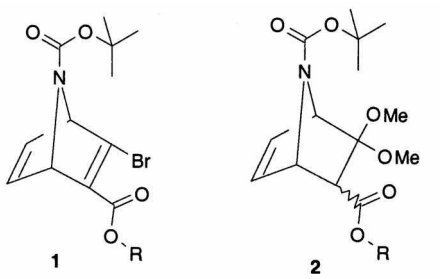


Figure 1

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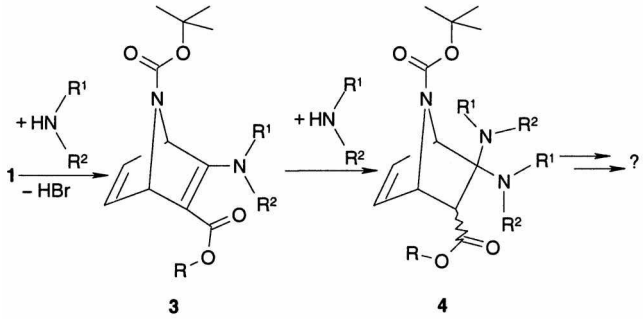
According to literature reports the bromine of **1** is readily replaced by nucleophiles such as Et_2NH[23] or MeO^-.[25c] In the former case the substitution product was not isolated but converted to the corresponding ketone whereas in the latter case the final product was the acetal **2** (Figure 1). However, our attempts to exchange this bromine for substituted amino groups gave only mixtures of products.[26] Therefore, we looked for modifications of the reaction that would make it more uniform.

The failure of the reaction between **1** and amines to give defined products may be due to a relative instability of the primarily formed enamines **3** under the reaction conditions, e.g. addition of a second molecule of the amine **4**, followed perhaps by further structural changes (Scheme 2).

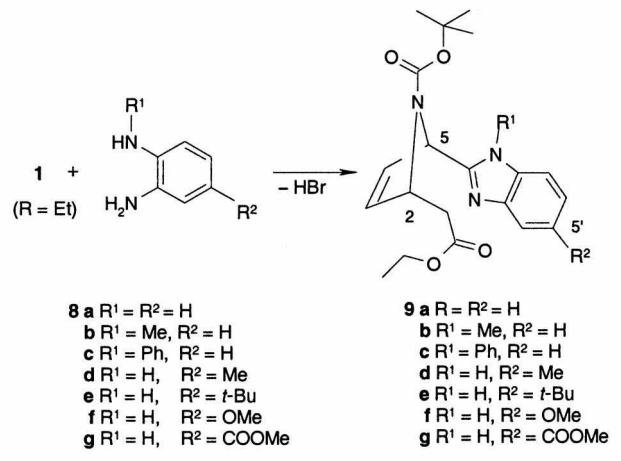


Scheme 2

Provided this assumption is correct, a greater uniformity may be achieved with diamines in which the two amino groups are positioned so that the second addition forms a five- or six-membered ring (**6**). If at least one of the two amino groups is primary, a further stabilization is conceivable, in which simultaneous ring opening to a *cis*-2,5-disubstituted pyrroline and conversion of the aminal to an amidine takes place (**7**). The driving force for this reaction would come from relief of steric strain and from the formation of a functional group that is stabilized by resonance (Scheme 3).

To test the principal validity of this concept, *ortho*-phenylene diamines were chosen as reaction partners because they are set up for ring formation. Moreover, in this case, an aromatic system develops during fragmentation, which should therefore be especially favored.

These experiments showed that **1** (R = Et) reacted with a variety of differently substituted *ortho*-phenylene diamines (**8**) in the expected way and afforded the corresponding ethyl *cis*-5-(benzimidazol-2-yl)pyrrolidin-2-yl acetates **9** (Scheme 4).

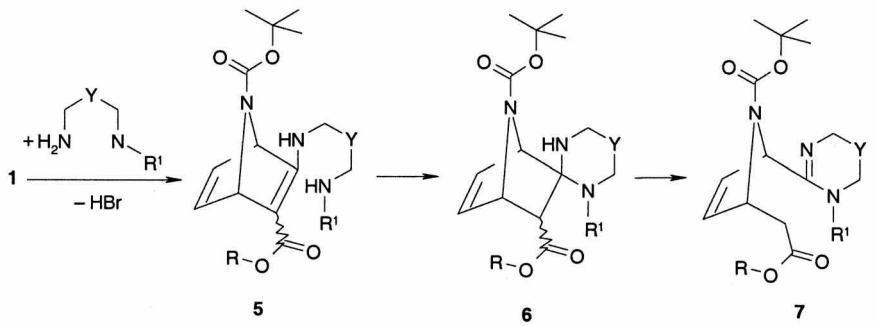


Scheme 4

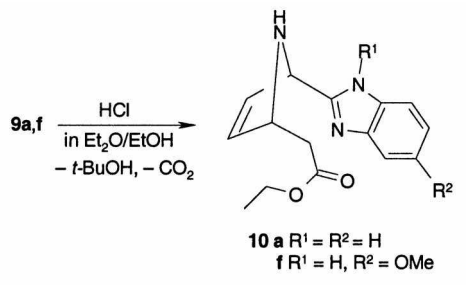
The ^1H NMR signals were in accordance with structure **9**. However, the signals were not well resolved and some of them appeared as two sets (as did some of the ^{13}C signals) probably due to *syn*,*anti* isomerism of the *tert*-butoxycarbonyl (Boc) amino moiety. This view was supported by the reduction to a single set of NMR signals on cleavage of the Boc group of **9a** and **9f** to the corresponding free pyrrolidines **10a** and **10f**, respectively (Scheme 5).

The *cis* position of the 2- and 5-substituents was confirmed by an NOE between the two H-atoms in this position. An NOE between the CH_2 group of the acetic acid side chain and the 5-H-atom was not observed.

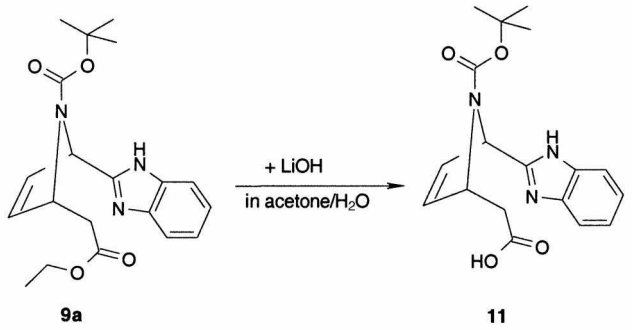
The compounds of type **9** turned out to be relatively unstable and could therefore be characterized only via NMR data. In order to obtain additional support for the structures, **9a** was converted to the free carboxylic acid **11**, which was a solid and could be more easily characterized (Scheme 6).



Scheme 3



Scheme 5

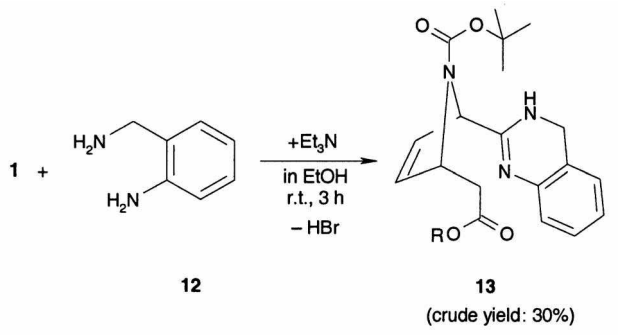


Scheme 6

Contrary to the methoxycarbonyl derivative, three other *ortho*-phenylene diamines which carried electronegative groups in the 5-position (NO_2, COPh, CF_3) gave, in addition to others, mainly products that had the mass of the expected pyrrolines but differed in the ^{1}H NMR spectra. In all three cases (some of the) aromatic H-atoms appeared between δ = 6.5 and 6.8 ppm (in $CDCl_3$) indicating the presence of an aniline-type phenyl ring. In addition, there were signals at δ = 4.8–5.3 ppm (2 H) as well as at 3.75 ppm and 3.18–3.21 ppm (together 1 H). The former signals correspond to the bridgehead H-atoms and the latter one to the H-atom next to the ester group (double set due to *syn*,*anti* isomerism of the Boc-amino moiety). Even though it was not possible to purify these products sufficiently, the NMR data suggest that the reaction has stopped at the intermediates **6** (Scheme 3). Possibly, the electron-withdrawing character of the substituents prevented the fragmentation of the bicyclic system.

Nevertheless, considering the successful examples listed in Scheme 4, this chemistry appears to have a relatively broad scope and its products would be suitable as starting materials for combinatorial syntheses. However, their use for such purposes meets with two obstacles: First, the synthesis of **1** requires a large excess of *N*-Boc-pyrrol which afterwards needs to be separated from the product by chromatography.[25c] In our hands this procedure did not work satisfactorily on a larger scale. Secondly, compounds **8** were oily and decomposed too rapidly to be stored.

The first problem may be circumvented by removing the excess *N*-Boc-pyrrol not until after the fragmentation step in which a principally basic function is created which allows separation from *N*-Boc-pyrrol by a convenient acid-base workup. However, the basicity of the new function must be high enough to allow complete protonation at pH values that leave the *N*-Boc group unaffected. Benzimidazoles do not generally meet this requirement satisfactorily. On the other hand, very basic amidines like those derived from aliphatic diamines are less favorable as they would in general be too highly soluble in water. Therefore, diamines that lead to amidines with intermediate basicity should be ideal for the procedure discussed here. In this respect, diamines containing one aromatic and one aliphatic amino group ought to be most suitable. As a model for such diamines we chose 2-amino-benzylamine (**12**), which would give dihydroquinazolines of type **13** (Scheme 7). However, these compounds turned out to share the instability of their benzimidazole analogues **9**.

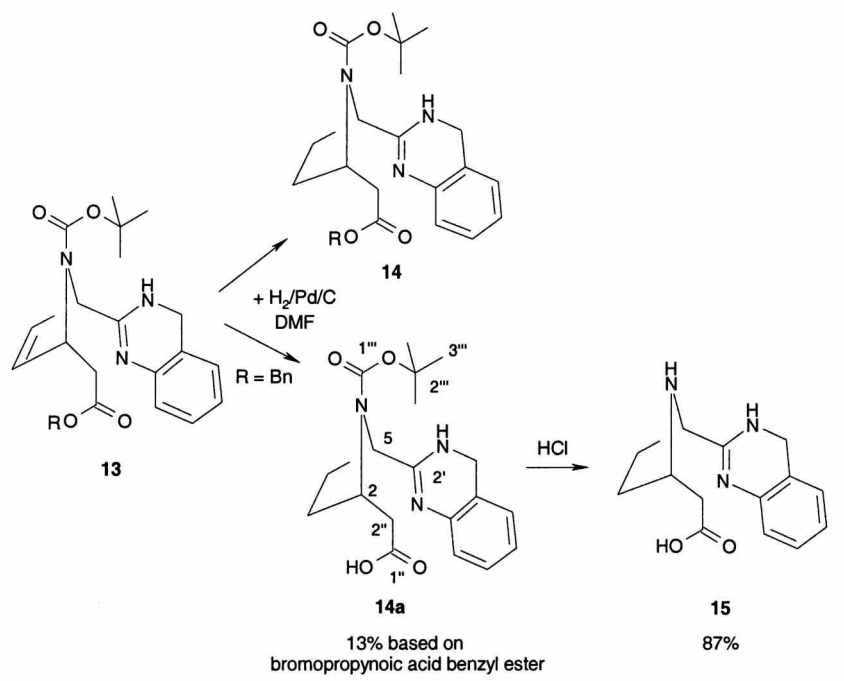


Scheme 7

The reason for this instability is not clear. Conceivably, an oxidation process takes place in which a free radical in position 5 is involved. Its formation would be facilitated by captodative effects[27] from the amidino group and the ring nitrogen in conjunction with the mesomeric effect of the double bond. Hydrogenation of the latter might therefore lead to more stable products. Consequently, compounds of type **13** were only isolated in crude form and subjected to hydrogenation prior to further purification.

The resulting pyrrolidine derivatives **14** need to be at least partially deprotected before they can serve as starting materials for combinatorial syntheses. As a means of increasing synthesis economy, deprotection of the carboxylate can be combined with the hydrogenation step by working with benzyl instead of ethyl esters (**13a**, Scheme 8).

Following the strategy outlined above, **1** (R = Bn) was prepared from bromopropynoic acid benzyl ester and a ten-fold excess of *N*-Boc-pyrrole. Treating the reaction mixture directly with 2-(aminomethyl)aniline (**12**) in ethanol afforded **13** (R = Bn), which could be separated from the excess *N*-Boc-pyrrole by extraction with 0.01 M citric acid. After hydrogenation of crude **13** (isolated from the extracts) the resulting **14a** was stable and could be purified by column chromatography in 13% yield over all three steps.



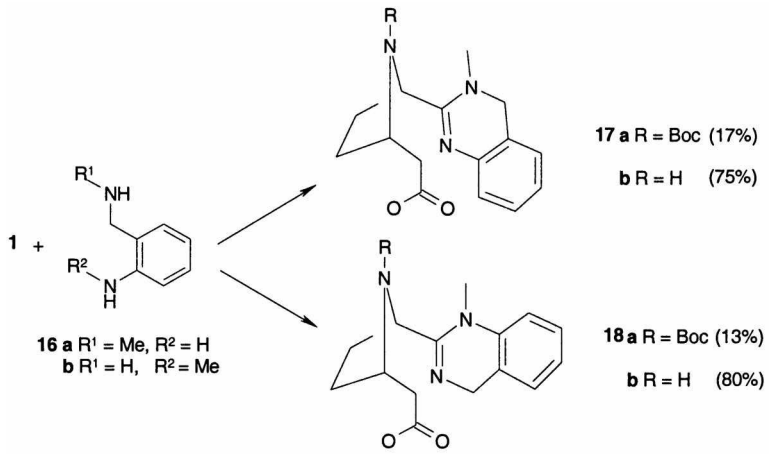
Scheme 8

Like in the case of the benzimidazoles **8** the presence of the *N*-Boc group gave rise to a number of poorly resolved NMR signals. In order to improve the quality of the spectrum the Boc group was removed with concentrated HCl (Scheme 8). The resulting dihydrochloride of **15** was well-crystallized and showed well-resolved signals in the ^{1}H NMR spectrum.

In an attempt to extend the fragmentation reaction to the synthesis of N-alkylated quinazoline derivatives, diamines **16a**,**b** were investigated. The two methyl derivatives behaved like the parent compound yielding products **17a** and **18a**, respectively (Scheme 9), which on treatment with aqueous HCl afforded the well-crystallized products **17b** and **18b**. The corresponding phenyl derivatives did not give satisfactory results probably due to the electron-withdrawing effect of the aromatic systems.

The *cis* relationships between the substituents in the 2- and 5-positions are demonstrated by ROESY experiments with **14a**, **17a**, and **18b**, which all showed an NOE between the H-atoms in the 2- and 5-positions of the pyrrolidine. Additional support came from an X-ray analysis of the dihydrochloride of **7b** (Figure 2).

A novel fragmentation reaction has been found by which *cis*-5-amidino-pyrrolidine-2-acetic acid esters can be prepared from readily accessible starting materials, i.e., *N*-Boc-pyrrol, propynoic acid esters, and N-unsubstituted or N-monosubstituted diamines. Aliphatic as well as aromatic amino groups can participate unless the latter ones are deactivated by strong electron-withdrawing substituents. The *cis*-relationship of the substituents in the 2- and 5-positions of the pyrrolin ring was proven by X-ray crystal-



Scheme 9

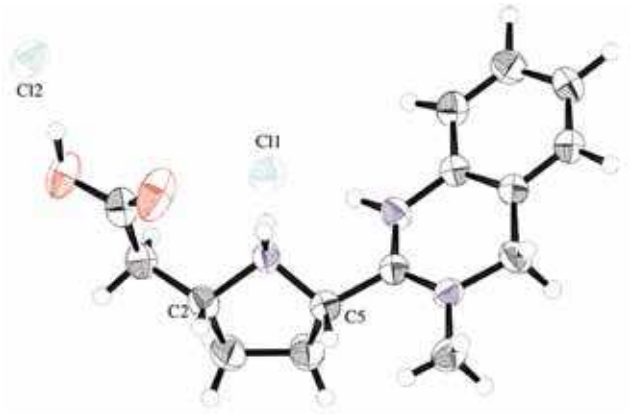


Figure 2 X-ray molecular structure of **17b**. The *cis*-relationship between the substituents in the 2- and 5-positions could be confirmed.

lography and additionally supported by NOEs between the H-atoms in these positions.

The problem inherent in purifying the intermediate Diels–Alder product **1** whose preparation requires a large excess of *N*-Boc-pyrrol can be circumvented by removing the latter after the subsequent fragmentation step if the resulting amidines exert a moderate basicity. These are separated from the *N*-Boc-pyrrol by extraction into a weakly acidic aqueous phase. The primary products of the fragmentation reaction are not stable, particularly if they do not crystallize, which makes a final purification impossible or at least impractical. However, as could be demonstrated for the dihydroquinazolines, hydrogenating the pyrroline double bond abolishes the instability. Additional conversion of the esters into the free acids gives crystalline products, which can be purified and subsequently used as starting materials in combinatorial syntheses. Starting from propynoic acid benzyl ester these starting materials may be obtained in a one-pot synthesis from the initial fragmentation products.

Chemicals were purchased from VWR International (Darmstadt, Germany), Sigma–Aldrich (Taufkirchen, Germany), or ABCR (Karlsruhe, Germany). Diels–Alder reactions were carried out in 7 mL clear vials (screw cap, solid cap with PTFE liner) from Supelco (Bellefonte, PA, USA) or in 50 mL sealed glass tubes (Schütt Labortechnik, Germany). For chromatography, silica gel 60 (230–400 mesh) from Merck (Darmstadt, Germany) was used. Melting points were determined on a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra of compounds **9**–**11** were recorded in $CDCl_3$ (internal reference: TMS δ = 0.00 ppm for ^{1}H; $^{13}CDCl_3$ δ = 77.16 ppm for ^{13}C) on a Bruker AC 200 or AMX500 spectrometer unless otherwise stated. ^{1}H, ^{13}C, and 2D NMR spectra of compounds **9a**, **14a**–**18** were recorded at T = 303 K on a Bruker DPX 400 spectrometer at 303 K using DMSO-d_6 and one drop of trifluoroacetic acid as solvent (internal reference: TMS δ = 0.00 ppm for ^{1}H and ^{13}C-DMSO δ = 39.50 ppm for ^{13}C). Peak assignment of compounds **14a**–**18** are based on 2D COSY, HSQC, and HMBC experiments. IR spectra were recorded on a Perkin-Elmer Spectrum 2000 instrument. CI mass spectra were obtained on a Finnigan SSQ7000 mass spectrometer and ESI mass spectra on a Micromass ZMD mass spectrometer. High-resolution mass spectra were recorded for: **9a** on a Varian MAT 711, **9e** and **10a** on a Varian MAT 8200, **14a**–**18** on a Micromass QTOF-2 instrument.

Single-Crystal Structure Determination

A suitable crystal of **7b** was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled N_2 gas stream at 100 K on a Rigaku AFC7R graphite monochromated Cu K_α (1.5418 Å) diffractometer. The data were collected using the ω-2θ scan technique to a maximum 2θ value of 119.8°. Data collection, indexing, and initial cell refinements were all carried out using WinAFC software. Frame integration and final cell refinements were done using WinAFC software. The TEXSAN program was used to carry out absorption corrections. The structure was solved using direct methods and difference Fourier techniques.[28] Hydrogen atoms were placed at their expected chemical positions and were included in the final cycles of least squares with isotropic Uij's related to the atoms ridden upon. All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from the International Tables for X-ray Crystallography.[29] Structure solution, refinement, graphics, and generation of publication materials were performed by using TEXSAN software. CCDC 257637 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Additional details of data collection and structure refinement are given in Table 1.

Table 1 Data Collection and Structure Refinement Details of Crystal Structure of Compound **7b**

Empirical formula	$C_{15}H_{21}N_3O_2Cl_2$
Formula mass	346.26
Crystal color, habit	colorless, prismatic
Crystal dimensions	0.20 × 0.20 × 0.05 mm
Crystal system	Monoclinic
Lattice type	Primitive
No. of reflections used for unit cell determination (2θ range)	25 (51.2 – 66.6°)
Omega scan peak width at half-height	0.26
Lattice parameters	a = 18.207(1) Å
	b = 6.3905(5) Å
	c = 14.3122(9) Å
	β = 102.153(6) °
	V = 1627.9(2) Å^3
Space group	$P2_1/n$ (#14)
Z value	4
D_{calc}	1.413 g/cm^3
F_{000}	728.00
μ(CuKα)	36.79 cm^{-1}
Diffractometer	Rigaku AFC7R

Table 1 Data Collection and Structure Refinement Details of Crystal Structure of Compound **7b** (continued)

Radiation	CuKα (λ = 1.54178 Å)
	Graphite monochromated
Attenuator	Ni foil (factor = 9.77)
Take-off angle	6.0°
Detector aperture	3.0 mm horizontal
	3.0 mm vertical
Crystal to detector distance	235 mm
Voltage, current	50 kV, 100 mA
Temperature	100 K
Scan type	ω – 2θ
Scan rate	16.0–32.0°/min (in ω) (up to 4 scans)
Scan width	(0.68 + 0.30 tanθ)°
$2\theta_{max}$	119.8°
No. of reflections measured	Total: 4036
	Unique: 2555 (R_{int} = 0.031)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.8216–0.9953)
	Decay (3.27% decline)
Structure solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares on F^2
Function minimized	Σ w (|Fo| – |Fc|)^2
Anomalous dispersion	All non-hydrogen atoms
No. observations (I > 3.00 σ(I))	1792
No. variables	199
Reflection/parameter ratio	9.01
Residuals: *R*1 (I > 3.00 σ(I))	0.032
Residuals: *wR*2 (I > 3.00 σ(I))	0.033
Goodness-of-fit indicator	1.108
Max shift/error in final cycle	0.022
Maximum peak in final diff. map	0.18 $e^-/Å^3$
Minimum peak in final diff. map	–0.21 $e^-/Å^3$

Benzimidazole Derivatives

***cis*-5-(1*H*-Benzimidazol-2-yl)-2-(ethoxycarbonylmethyl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9a)**

Compound **1** (R = Et) (0.69 g, 2.0 mmol), **8a** (0.24 g, 2.2 mmol), and Et_3N (0.6 mL, 4.0 mmol) were dissolved in EtOH (80 mL) and stirred at r.t. for 24 h. The solvent was removed in vacuo and the residue was passed through basic Al_2O_3 (EtOAc). After removal of the solvent the product was purified by column chromatography (neutral Al_2O_3; petroleum ether–EtOAc, 1:1) to give **9a** (0.69 g, 93%) as a yellowish oil.

^{1}H NMR: δ = 11.1, 10.7 (br, 1 H, NH), 7.58 (br, 2 H, H4′, H7′), 7.22 (m, 2 H, H5′, H6′), 6.28, 5.85 (br, 1 H, H4), 6.14, 5.85 (br, 1 H, H3), 5.85 (q, *J* = 2.4 Hz. 1 H, H5), 4.94 (br, 1 H, H2), 4.10 (br, 2 H, OCH_2), 3.26, 2.82 (br, 1 H, CH_2), 2.73, 2.52 (br, 1 H, CH_2), 1.52, 1.27 (s, 9 H, *t*-Bu), 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR: δ = 170.9 (COOEt), 153.4 (COO*t*-Bu), 130.8, 129.0 (C3), 128.5, 126.2 (C4), 122.2 (C5′, C6′), 119.0, 110.9 (C4′, C7′), 81.3 (C*t*-Bu), 64.3 (C5), 61.8 (C2), 60.9, 60.4 (OCH_2), 39.8, 38.0 (CCH_2), 28.2 (*t*-BuCH_3), 13.9 ($EtCH_3$); assignments were made via cross peaks in a 500 MHz/125 MHz HMQC spectrum.

^{1}H NMR (400 MHz, DMSO): δ = 12.2 (v br, 1 H, NH), 7.52 (m, 2 H, H4′, H7′), 7.15 (m, 2 H, H5′, H6′), 6.05 (d, *J* = 5.8 Hz, 1 H, H3), 5.97 (br, 1 H, H4), 5.68 (br, 1 H, H5), 4.82 (m, 1 H, H2), 4.12 (q, *J* = 7.0 Hz, 2 H, OCH_2), 3.29, 3.08 (br d, *J* = 12.5 Hz, 1 H, CH_2), 2.73 (m, 1 H, CH_2), 1.41, 1.19 (s, 9 H, *t*-Bu), 1.20 (m, 3 H, Me).

^{13}C NMR (100 MHz, DMSO): δ = 170.6 (COOEt), 153.7, 153.0 (COO*t*-Bu), 130.0 (C3), 127.9 (C4), 121.5 (C5′, C6′), 115.9 (C4′, C7′), 79.7, 79.3 (C*t*-Bu), 62.9, 62.4 (C5), 61.1 (C2), 60.0 (OCH_2), 40.1, 38.9 (CCH_2), 27.8 (*t*-BuCH_3), 14.0 ($EtCH_3$); strong NOEs (ROESY spectrum) between H4 and H5, and between H2 and H3 respectively, NOEs between H2 and H5; assignments were made via cross peaks in a 400 MHz HC–HSQC–TOCSY spectrum.

MS (CI): *m*/*z* = 372 [M + H^+].

HRMS: *m*/*z* calcd for $C_{20}H_{25}N_3O_4$: 371.1845; found: 371.1843.

***cis*-2-(Ethoxycarbonylmethyl)-5-(1-methyl-1*H*-benzimidazol-2-yl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9b)**

Prepared analogously to **9a**. Reaction time: 1.5 d; yield: 67%; yellowish oil.

IR (film): 1733, 1700 cm^{-1}.

^{1}H NMR: δ = 7.74 (m, 1 H, H7′), 7.33 (m, 1 H, H4′), 7.25 (m, 2 H, H5′, H6′), 6.30, 6.27 (br, 1 H, H3), 5.86 (br, 1 H, H5), 5.70–5.90 (1 H, H4), 4.94 (br, 1 H, H2), 4.18 (q, *J* = 7.4, 2 H, OCH_2), 4.02, 3.82 (s, 3 H, NMe), 3.55, 3.10 (br, 1 H, CH_2), 2.93 (dd, A of AB, J_1 = 16.7 Hz, J_2 = 10.3 Hz, 1 H, CH_2), 1.43, 1.24 (br, 9 H, *t*-Bu), 1.27 (t, *J* = 7.4 Hz, 3 H, CCH_3).

^{13}C NMR: δ = 171.5, 153.0, 142.6, 135.7, 131.7, 126.8, 122.4, 121,9, 119.9, 109.6, 80.4, 61.6, 60.3, 59.2, 40.1, 30.2, 28.4, 14.2.

***cis*-2-(Ethoxycarbonylmethyl)-5-(1-phenyl-1*H*-benzimidazol-2-yl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9c)**

Prepared analogously to **9a.** Reaction time: 1.5 d; yield: 78%; yellowish oil.

IR (film): 1733, 1700 cm^{-1}.

^{1}H NMR: δ = 7.77 (d, *J* = 6.9, 1 H, H7′), 7.55 (m, 4 H, H2″, H3″, H5″, H6″), 7.38 (m, 1 H, H4″), 7.22 (m, 2 H, H5′, H6′), 7.06 (m, 1 H, H4′), 6.08 (d, *J* = 5.4 Hz, 1 H, H3), 5.71 (br, 1 H, H5), 5.70 (d, *J* = 5.4 Hz, 1 H, H4), 4.87 (br, 1 H, H2), 4.16 (m, 2 H, OCH_2), 3.46, 3.23 (br d, B of AB, *J* = 15.5 Hz, 1 H, CH_2), 2.87, 2.54 (dd, A of AB, J_1 = 15.5 Hz, J_2 = 10.0 Hz, 1 H, CH_2), 1.44, 1.24 (s, 9 H, *t*-Bu), 1.25 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR: δ = 171.7, 153.2, 136.9, 135.7, 131.2, 129.8, 129.0, 127.5, 126.6, 122.7, 122.3, 119.8, 110.0, 80.2, 62.0, 61.4, 61.2, 60.8, 60.1, 39.7, 38.4, 28.3, 28.0, 14.1.

MS (CI): *m*/*z* = 448 [M + H$^+$].

***cis*-2-(Ethoxycarbonylmethyl)-5-(5-methyl-1*H*-benzimidazol-2-yl)- 2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9d)**

Prepared analogously to **9a**. Reaction time: 24 h. Yield: 75%; Yellowish oil.

IR (film): 1733, 1705 cm^{-1}.

^{1}H NMR: δ = 10.93, 10.57 (br, 1 H, NH), 7.48 (br, 1 H, H4′), 7.36 (br, 1 H, H7′), 7.03 (dd, J_1 = 8.4 Hz, J_2 = 1.3 Hz, 1 H, H6′), 6.28, 5.93 (br, 1 H, H4), 6.14, 5.88 (br, 1 H, H3), 5.82 (q, *J* = 2.2 Hz. 1 H, H5), 4.93 (br, 1 H, H2), 4.10 (br, 2 H, OCH_2), 3.26, 2.80 (br d, *J* = 13.2 Hz, 1 H, CH_2), 2.69, 2.49 (br, 1 H, CH_2), 2.45 (s, 3 H, arom. CH_3), 1.51, 1.26 (s, 9 H, *t*-Bu), 1.24 (m, 3 H, aliph. CH_3).

^{13}C NMR: δ = 170.9, 155.1, 153.2, 130.8, 128.6, 128.5, 126.3, 123.6, 118.6, 110.9, 81.3, 64.3, 61.8, 61.8, 60.9, 60.5, 39.9, 38.1, 28.3, 21.5, 14.0.

***cis*-5-(5-*tert*-Butyl-1*H*-benzimidazol-2-yl)-2-(ethoxycarbonylmethyl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9e)**

Prepared analogously to **9a**. Reaction time: 1.5 d; yield: 77%; yellowish oil.

IR (film): 1733, 1705 cm^{-1}.

^{1}H NMR: δ = 11.10, 10.75 (br, 1 H, NH), 7.59 (br s, 1 H, H4′), 7.53 (d, *J* = 8.4 Hz, 1 H, H7′), 7.30 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H, H6′), 6.25, 5.93 (br, 1 H, H4), 6.14, 5.85 (br, 1 H, H3), 5.84 (s, 1 H, H5), 4.93 (br, 1 H, H2), 4.10 (br, 2 H, OCH_2), 3.19, 2.82 (br d, *J* = 15 Hz, 1 H, CH_2), 2.70, 2.49 (br dd, J_1 = 15 Hz, J_2 = 9 Hz, 1 H, CH_2), 1.50, 1.37 (s, 9 H, O*t*-Bu), 1.37, 1.28 (s, 9 H, C*t*-Bu), 1.28 (m, 3 H, CH_3).

^{13}C NMR: δ = 170.8, 155.0, 153.2, 145.5, 130.6, 129.0, 128.3, 126.3, 120.2, 115.0, 81.1, 64.1, 61.6, 61.6, 60.8, 60.3, 39.8, 38.3, 34.6, 28.1, 13.9.

MS (CI): *m*/*z* = 428 [M + H$^+$].

HRMS: *m*/*z* calcd for $C_{24}H_{33}N_3O_4$: 427.24714; found: 427.24711.

***cis*-2-(Ethoxycarbonylmethyl)-5-(5-methoxy-1*H*-benzimidazol-2-yl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9f)**

Prepared analogously to **9a**. Reaction time: 2 d; yield: 75%; yellowish oil.

IR (film): 1733, 1708 cm^{-1}.

^{1}H NMR: δ = 8.6–9.7 (1 H, NH), 7.46 (d, *J* = 8.9 Hz, 1 H, H7′), 7.03 (d, *J* = 2.4 Hz, 1 H, H4′), 6.84 (dd, J_1 = 8.9 Hz, J_2 = 2.4 Hz, 1 H, H6′), 6.26, 5.91 (br, 1 H, H4), 6.10, 5.87 (br, 1 H, H3), 5.79 (q, *J* = 1.9 Hz. 1 H, H5), 4.90 (br, 1 H, H2), 4.08 (m, 2 H, OCH_2), 3.81 (s, 3 H, OCH_3), 3.25, 2.78 (br d, *J* = 14.7 Hz, 1 H, CH_2), 2.70, 2.44 (br dd, J_1 = 14.7 Hz, J_2 = 9.3 Hz, 1 H, CH_2), 1.49, 1.23 (s, 9 H, *t*-Bu), 1.23 (m, 3 H, CH_3).

^{13}C NMR: δ = 170.9, 156.3, 155.3, 153.1, 130.8, 129.0, 128.5, 126.3, 116.5, 111.7, 97.4, 81.4, 64.1, 61.9, 61.9, 61.1, 60.5, 55.2, 40.0, 38.0, 28.3, 27.9, 14.0.

MS (CI): *m*/*z* = 402 [M + H$^+$].

***cis*-2-(Ethoxycarbonylmethyl)-5-(5-methoxycarbonyl-1*H*-benzimidazol-2-yl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (9g)**

Prepared analogously to **9a**. Reaction time: 7 d; yield: 56%; yellowish oil.

IR (film): 1713 (br) cm^{-1}.

^{1}H NMR: δ = 11.52, 11.00 (br, 1 H, NH), 8.44, 8.25 (br, 1 H, H4′), 7.96 (dd, J_1 = 8.4 Hz, J_2 = 0.9 Hz, 1 H, H6′), 7.71, 755 (br, 1 H, H7′), 6.24, 5.92 (br, 1 H, H4), 6.14, 5.86 (br, 1 H, H3), 5.86 (q, *J* = 2.2 Hz, 1 H, H5), 4.96 (m, 1 H, H2), 4.12 (m, 2 H, OCH_2), 3.94 (s, 3 H, CH_3), 3.36, 2.81 (br d, *J* = 12.6 Hz, 1 H, CH_2), 2.50–2.80 (m, 1 H, CH_2), 1.52, 1.25 (s, 9 H, O*t*-Bu), 1.25 (m, 3 H, CH_3).

^{13}C NMR: δ = 170.9, 167.5, 155.1, 130.8, 129.3, 129.3, 128.2, 124.1,123.4, 113.4,110.7, 81.6, 64.4, 62.2, 61.8, 61.2, 60.5, 60.2, 51.9, 39.6, 37.6, 14.0.

***cis*-5-(1*H*-Benzimidazol-2-yl)-2-ethoxycarbonylmethyl-2,5-dihydropyrrole dihydrochloride (10a)**

Compound **9a** (0.90 g, 2.4 mmol) was dissolved in anhyd Et_2O (100 mL). EtOH–HCl (2 M, 10 mL) solution was added and the mixture was left for 12 h at r.t. On cooling to 4 °C a solid material precipitated which was crystallized from Et_2O–EtOH. Yield: 0.58 g (70%) of crude beige-colored **10a**, which decomposed at 180 °C.

IR (KBr): 1718 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 7.95 (m, 2 H, H4′, 7′), 7.73 (m, 2 H, H5′, 6′), 6.57 (m, 1 H, H3), 6.32 (dt, J_1 = 5.9 Hz, J_2 = 2.0 Hz, 1 H, H4), 6.29 (m, 1 H, H5), 5.15 (m, 1 H, H2), 4.22 (q, *J* = 7.1 Hz, 2 H, OCH_2), 3.26 (B of ABM, J_1 = 18.2 Hz, J_2 = 3.9 Hz, 1 H, CH_2), 3.05 (A of ABM, J_1 = 18.2 Hz, J_2 = 9.3 Hz, 1 H, CH_2), 1.30 (t, *J* = 7.1 Hz, 3 H, Me).

^{13}C NMR: δ = 171.5, 147.0, 136.3, 133.2, 128.9, 124.2, 115.9, 65.9, 62.9, 61.1, 37.8, 14.7.

MS (CI): *m*/*z* = 272 [M + H$^+$].

HRMS: *m*/*z* calcd for $C_{15}H_{17}N_3O_2$: 271.13072; found: 271.13208.

***cis*-2-(Ethoxycarbonylmethyl)-5-(5-methoxy-1*H*-benzimidazol-2-yl)-2,5-dihydropyrrole dihydrochloride (10f)**

Prepared analogously to **10a** from **9f** (0.12 g, 0.3 mmol), Et_2O (20 mL), EtOH–HCl (2 mL), 3 h, r.t. The precipitate was a glassy material that did not crystallize. Yield: 70 mg (54%).

IR (KBr): 1718 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 7.80 (d, *J* = 8.9 Hz, 1 H, H7′), 7.37 (d, *J* = 2.4 Hz, 1 H, H4′), 7.31 (dd, J_1 = 8.9 Hz, J_2 = 2.4 Hz, 1 H, H6′), 6.56 (m, 1 H, H3), 6.32 (m, 1 H, H4), 6.30 (m, 1 H, H5), 5.13 (br, 1 H, H2), 4.22 (q, *J* = 7.0 Hz, 2 H, OCH_2), 3.96 (s, 3 H, OCH_3), 3.25 (B of ABM, J_1 = 18.2 Hz, J_2 = 4.4 Hz, 1 H, CH_2), 3.06 (A of ABM, J_1 = 18.2 Hz, J_2 = 9.4 Hz, 1 H, CH_2), 1.29 (t, *J* = 6.9 Hz, 3 H, Me).

^{13}C NMR: δ = 171.5, 161.5, 145.5, 136.2, 134.3, 127.4, 124.2, 119.7, 116.7, 97.3, 65.8, 62.8, 61.1, 57.0, 37.9, 14.7.

***cis*-5-(1*H*-Benzimidazol-2-yl)-2-(carboxymethyl)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (11)**

Compound **9a** (0.44 g, 1.2 mmol) was dissolved in a mixture of acetone (20 mL) and water (10 mL) and treated with 1 M LiOH (6 mL) at r.t. for 1 h. The solvents were removed in vacuo. To the remainder were added a 20% NaH_2PO_4–H_3PO_4 aq buffer (30 mL) to adjust pH to 5.5 and sat. aq NaCl (30 mL). The mixture was extracted CH_2Cl_2 (3 × 50 mL). The organic phase was evaporated to dryness and the residue crystallized from MeCN–cyclohexane; yield: 0.29 g (70%); colorless crystals; mp 216–218 °C (decomp.).

IR (KBr): 1698 (vs, br) cm^{-1}.

^{1}H NMR (DMF-d_7): δ = 12.39 (v br, 1 H, OH), 7.62 (m, 2 H, H4′, H7′), 7.22 (m, 2 H, H5′, H6′), 6.20 (m, 1 H, H4), 6.10 (br, 1 H, H3), 5.89 (br, 1 H, H5), 4.97 (m, 1 H, H2), 3.43, 3.18 (br d, *J* = 13.8 Hz, 1 H, CH_2), 2.83 (br, 1 H, CH_2), 1.51, 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR: δ = 172.6, 154.3, 139.1, 130.6, 127.8, 121.6, 114.9, 79.6, 63.6, 61.7, 40.7, 27.5.

MS (CI): *m*/*z* = 344 [M + H$^+$].

Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.79; H, 6.25; N, 12.07.

Dihydroquinazoline Derivatives

Propynoic Acid Benzyl Ester

The compound has been prepared previously from propynoic acid and benzyl alcohol[30,31] but the present method gives higher yields. Propynoic acid (7.98 g, 113.9 mmol) was added to a solution of KOH (6.39 g, 113.9 mmol) in MeOH (70 mL). After 15 min at r.t. the solution was evaporated to dryness. The residue was twice suspended in toluene, which was subsequently removed in vacuo. The remaining solid was dissolved in DMSO (70 mL), (bromomethyl)benzene (15.12 g, 88.7 mmol) was added and the mixture kept at 40 °C for 2 h. EtOAc (150 mL) and water (100 mL) were added. The organic layer was separated, washed with aq $NaHCO_3$ and water, and the solvent removed under vacuum. Yield: 12.4 g [87% based on (bromomethyl)benzene].

Bromopropynoic Acid Benzyl Ester[25a,32]

Prepared according to a literature method.[33]

***cis*-2-(Carboxymethyl)-5-(3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (14a)**

A mixture of bromopropynoic acid benzyl ester (16.0 g, 66.9 mmol) and *N*-Boc pyrrole (111.8 g, 669 mmol) was shaken at 80 °C for 48 h in a sealed vial under argon. After cooling to r.t., EtOH (300 mL), **12** (9.0 g, 73.6 mmol), and Et_3N (13.5 g, 133.6 mmol) were added. After stirring at r.t. for 3 h the mixture was concentrated in vacuo, EtOAc (300 mL) and EtOH (75 mL) were added and the solution was extracted with 0.01 M aq citric acid (6 × 250 mL). The combined aqueous layers were brought to pH = 8 with $NaHCO_3$ and extracted with EtOAc (2 × 400 mL). The organic phase was concentrated to 300 mL in vacuo and extracted with 0.01 M aq citric acid (4 × 400 mL) and then 0.1 M aq citric acid (250 mL). The combined aqueous layers were saturated with NaCl and the product was extracted (as a hydrochloride) twice with a mixture of EtOAc (250 mL) and EtOH (150 mL). The organic layers were concentrated in vacuo, the residue dissolved in EtOAc (300 mL) and treated with aq citric acid/NaCl as before. The combined final organic phases were washed with sat. aq $NaHCO_3$ (2 × 500 mL) and evaporated in vacuo leaving a brown foam (6.73 g). It was dissolved in DMF (130 mL) and hydrogenated (10% Pd/C, 14 h, atmospheric pressure). After filtration the solvent was removed in vacuo and the residue purified by column chromatography [SiO_2; aq NH_3 (25%)–MeOH–CH_2Cl_2, 1:10:100, then aq NH_3 (25%)–MeOH–CH_2Cl_2, 1:10:50], which gave **14a** (3.22 g, 13% overall) as an amorphous material.

^{1}H NMR (400 MHz, DMSO-d_6, TFA): δ = 11.74 (br, 1 H, NH^+), 10.08 (br, 1 H, NH), 7.35 (dt, J_1 = 7.4 Hz, J_2 = 2.0 Hz, 1 H, H7′), 7.26 (dt, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1 H, H6′), 7.23 (d, J = 6 Hz, 1 H, H5′), 7.14 (d, J = 7.7 Hz, 1 H, H8′), 4.82 (AB, J_{AB} = 17.5 Hz, 2 H, H4′), 4.57 (t, J = 7.7 Hz, 1 H, H5), 4.14–4.23 (m, 1 H, H2), 2.61–2.93 (m, 2 H, H2″), 2.32–2.45 (m, 1 H, H4), 2.10–2.25 (m, 2 H, 3-H3, H4), 1.77-1.85 (m, 1 H, H3), 1.23–1.54 (br, 9 H, H3‴).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 174.2 (br, C1″), 163.7 (br, C2′), 153.0–154.5 (br, C1‴), 131.3 (C9′), 129.1 (C7′), 127.1 (C5′, C6′), 117.7 (C10′), 116.8 (C8′), 80.5–81.3 (br, C2‴), 59.0 (C5), 55.7 (C2), 42.0 (C4′), 38.4 (C2″), 29.5 (C3, C4), 27.9 (C3‴); peak assignments are based on 2D COSY, HSQC and HMBC experiments.

MS (ESI): m/z = 360.4 [M + H^+].

HRMS: m/z [M + H^+] calcd for $C_{19}H_{26}N_3O_4$: 360.1923; found: 360.1930.

***cis*-2-(Carboxymethyl)-5-(3-methyl-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (17a)**

Prepared analogously to **14a** from **16a**[34] (10.0 g, 73.6 mmol); hydrogenation for 10 h. Purification by column chromatography [SiO_2; aq NH_3 (25%)–MeOH–CH_2Cl_2, 1:10:140 then aq NH_3 (25%)–MeOH–CH_2Cl_2, 1:10:120) yielded **17a** (4.34 g, 17%) as a beige amorphous material.

^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ = 11.25 (s, 1 H, NH^+), 7.38 (t, J = 7.0 Hz, 1 H, H7′), 7.28 (dt, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1 H, H6′), 7.24 (d, J = 7.2 Hz, 1 H, H5′), 7.21 (m, 1 H, H8′), 5.09 (t, J = 7.7 Hz, 1 H, H5), 4.93 (AB, J_{AB} = 15.7 Hz, 2 H, H4′), 4.18–4.35 (m, 1 H, H2), 3.33 (s, 3 H, CH_3), 2.73 (m, 1 H, H2″), 2.56 (m, 1 H, H2″), 2.50 (m, 1 H, H4), 2.08–2.24 (m, 2 H, H3, H4), 1.75–1.88 (m, 1 H, H3), 1.20–1.49 (br, 9 H, H3‴).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 175.5 (C1″), 161.9–162.7 (br, C2′), 152.9–154.0 (br, C1‴), 130.4 (C9′), 129.1 (C7′), 127.0 (C6′), 126.3 (C5′), 117.6 (C10′), 116.2 (C8′), 80.6–81.6 (br, C2‴), 57.6 (C5), 55.3 (C2), 51.4 (C4′), 38.5 (CH_3), 37.8 (C2″), 29.2–30.6 (br, C3), 27.6 (C3‴), 26.9 (C4).

MS (ESI): m/z = 374 [M + H^+].

HRMS: m/z [M + H^+] calcd for $C_{20}H_{28}N_3O_4$: 374.2080; found: 374.2094.

***cis*-2-(Carboxymethyl)-5-(1-methyl-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (18a)**

Prepared analogously to **14a** from **16b**[34] (10.0 g, 73.6 mmol); hydrogenation for 11 h. Purification by column chromatography [SiO_2; aq NH_3 (25%)–MeOH–CH_2Cl_2, 1:10:120] yielded **18a** [3.28 g, 13%] as a beige amorphous material.

^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ = 9.84 (br, 1 H, NH^+), 7.46 (dt, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, H7′), 7.44 (m, 1 H, H8′), 7.37 (dt, J_1 = 7.4 Hz, J_2 = 1.8 Hz, 1 H, H6′), 7.33 (d, J = 7.4 Hz, 1 H, H5′), 5.06 (t, J = 7.6 Hz, 1 H, H5), 4.73 (AB, J_{AB} = 20.2 Hz, 2 H, H4′), 4.15–4.24 (m, 1 H, H2), 3.58 (s, 3 H, CH_3), 2.80–2.97 (m, 1 H, H2″), 2.61 (dd, J_1 = 15.3 Hz, J_2 = 8.2 Hz, 1 H, H2″), 2.45–2.55 (m, 1 H, H4), 2.06–2.23 (m, 2 H, H3, H4), 1.73–1.81 (m, 1 H, H3), 1.18–1.52 (br, 9 H, H3‴).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 173.8 (br, C1″), 164.8 (br, C2′), 153.7 (br, C1‴), 134.8 (C9′), 129.1 (C7′), 127.4 (C6′), 126.8 (C5′), 119.7 (C10′), 115.7 (C8′), 80.9 (br, C2‴), 58.8 (C5), 55.8 (C2), 41.6 (C4′), 38.4 (C2″), 33.9 (CH_3), 29.8 (C3), 28.1 (C4), 27.7 (C3‴).

MS (ESI): m/z = 374.5 [M + H^+].

HRMS: m/z [M + H^+] calcd for $C_{20}H_{28}N_3O_4$: 374.2080; found: 374.2075.

[*cis*-5-(3,4-Dihydroquinazolin-2-yl)pyrrolidin-2-yl]acetic Acid Dihydrochloride (15)

Ester **14a** (50 mg, 0.139 mmol) was stirred with concd aq HCl (10 mL) at r.t. for 2 h. Evaporation of the solvent in a N_2 stream yielded **15** (40 mg, 87%) as colorless crystals; mp 238 °C.

^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ = 7.36 (dt, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1 H, H7′), 7.28 (dt, J_1 = 7.4 Hz, J_2 = 1.4 Hz, 1 H, H6′), 7.21–7.25 (m, 2 H, H5′, H8′), 4.82 (AB, J_{AB} = 16.7 Hz, 2 H, H4′), 4.63 (t, J = 8.7 Hz, 1 H, H5), 3.92–4.01 (m, 1 H, H2), 3.01 (dd, J_1 = 17.8 Hz, J_2 = 8.4 Hz, 1 H, H2″), 2.88 (dd, J_1 = 17.4 Hz, J_2 = 5.4 Hz, 1 H, H2″), 2.39–2.48 (m, 1 H, H4), 2.22–2.39 (m, 2 H, H3, H4), 1.82–1.95 (m, 1 H, H3).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 171.8 (C1″), 131.0 (C9′), 129.0 (C7′), 127.5 (C6′), 126.9 (C5′), 117.5 (C10′), 116.9 (C8′), 57.6 (C5), 56.9 (C2), 42.0 (C4′), 36.2 (C2″), 28.4 (C3), 26.9 (C4).

MS (ESI): m/z = 260 [M + H^+].

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{14}H_{18}N_3O_2$: 260.1399; found: 260.1400.

[*cis*-5-(3-Methyl-3,4-dihydroquinazolin-2-yl)pyrrolidin-2-yl]acetic Acid Dihydrochloride (17b)

Prepared analogously to **15** from **17a** (100 mg, 0.268 mmol); yield: 70 mg (75%); colorless crystals; mp 222 °C.

^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ = 7.41 (dd, J_1 = 7.9 Hz, J_2 = 1.6 Hz, 1 H, H8′), 7.37 (dt, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1 H, H7′), 7.29 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1 H, H6′), 7.21 (dd, J_1 = 7.0 Hz, J_2 = 0.8 Hz, 1 H, H5′), 5.04 (t, *J* = 9.4 Hz, 1 H, H5), 4.92 (s, 2 H, H4′), 3.91–4.00 (m, 1 H, H2), 3.35 (s, 3 H, CH_3), 3.07 (dd, J_1 = 17.2 Hz, J_2 = 8.7 Hz, 1 H, H2″), 2.91 (dd, J_1 = 17.2 Hz, J_2 = 5.4 Hz, 1 H, H2″), 2.45–2.55 (m, 1 H, H4), 2.24–2.41 (m, 2 H, H3, H4), 1.86–1.97 (m, 1 H, H3).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 172.2 (C1″), 130.6 (C9′), 129.1 (C7′), 127.5 (C6′), 126.2 (C5′), 117.8 (C10′), 116.9 (C8′), 56.9 (C2), 56.0 (C5), 51.9 (C4′), 39.8 (CH_3), 36.3 (C2″), 28.6 (C3), 27.0 (C4).

MS (ESI): *m*/*z* = 274 [M + H$^+$].

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{15}H_{20}N_3O_2$: 274.1556; found: 274.1559.

[*cis*-5-(1-Methyl-3,4-dihydroquinazolin-2-yl)pyrrolidin-2-yl]acetic Acid Dihydrochloride (18b)

Prepared analogously to **15** from **18a** (50 mg, 0.134 mmol); yield: 37 mg (80%), colorless crystals; mp 215 °C.

^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ = 7.45 (dt, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1 H, H7′), 7.41 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1 H, H8′), 7.36 (dt, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1 H, H6′), 7.32 (dd, J_1 = 7.4 Hz, J_2 = 1.4 Hz, 1 H, H5′), 4.87 (t, *J* = 7.64 Hz, 1 H, H5), 4.73 (AB, J_{AB} = 16.5 Hz, 2 H, H4′), 3.76–3.85 (m, 1 H, H2), 3.57 (s, 3 H, CH_3), 2.83 (dd, J_1 = 17.0 Hz, J_2 = 8.0 Hz, 1 H, H2″), 2.73 (dd, J_1 = 16.8 Hz, J_2 = 6.0 Hz, 1 H, H2″), 2.07–2.24 (m, 2 H, H3, H4), 2.37–2.49 (m, 1 H, H4), 1.60–1.73 (m, 1 H, H3).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 172.6 (C1″), 162.5 (br, C2′), 135.2 (C9′), 129.0 (C7′), 127.4 (C6′), 126.7 (C5′), 119.8 (C10′), 115.9 (C8′), 56.3 (C2), 56.1 (C5), 41.8 (C4′), 37.8 (C2″), 34.4 (CH_3), 29.3 (C3), 28.0 (C4).

MS (ESI): *m*/*z* = 274.5 [M + H$^+$].

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{15}H_{20}N_3O_2$: 274.1556; found: 274.1564.

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