Condensation Reaction Between α-Amino Acid Phenylhydrazides and Carbonyl Compounds

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The natural α-amino acid phenylhydrazides **1a**–**d** readily react with the aldehydes **2a**–**d** and ketones **2e**–**h** to produce the 3-(phenylamino)imidazolidin-4-one derivatives **4** in good yields. Their structures were confirmed by X-ray structural analysis. Polycyclic systems were obtained from the reaction of L-tryptophan phenylhydrazide (**1d**) and L-histidine phenylhydrazide (**1e**) with benzaldehyde (**2c**), which gave 1,10-diphenyl-2-(phenylamino)-2,9,10a-triazacyclopenta[*b*]fluoren-3-one (**5dc**) and 4,6-diphenyl-7-(phenylamino)-3,4,6,7,8a,9-hexahydro-8*H*-diimidazo[1,5-*a*:4′,5′-*d*]pyridin-8-one (**5ec**), respectively.

Introduction

We have recently described the products — derivatives of the six-membered heterocyclic hexahydro-1,2,4-triazin-6-one system —from the reaction of some phenylhydrazides of natural amino acids with aqueous formaldehyde.[1] In an attempt to extend this reaction scheme to more complex carbonyl compounds, we have established unambiguously, by X-ray analysis, that the structure of the condensation derivatives obtained are five-membered heterocycles, namely imidazolidin-4-ones, and not six-membered rings. This finding prompted us to study this reaction to investigate how the nature of both the carbonyl compound and the side chain of the α-amino acid phenylhydrazide employed influence the structures of these condensation products.

The imidazolidin-4-one ring has been widely studied because of its pharmacological activity, which is influenced by the type and position of the substituents present in the heterocycle. Among all the reported procedures, the most efficient are those involving the condensation reaction between carbonyl compounds and α-amino,[2] α-(alkylamino),[2a,3] α-(methylsulfonylamino),[2c,4] and α-(benzyloxycarbonylamino)[2c,4,5] acid amides. The same reaction scheme has been followed to obtain 3-hydroxy-4-imidazolidinone[6] starting from the hydroxamic derivatives of glycine and alanine. Surprisingly, the 3-(phenylamino)-substituted imidazolidin-4-ones that we have prepared in our laboratory do not appear to have precedent in the chemical literature.

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Results and Discussion

When an α-amino acid phenylhydrazide of type **1** and a carbonyl compound like **2** were mixed under appropriate experimental conditions, a ring-forming condensation took place yielding imidazolidin-4-ones (**4**, Scheme 1).

Initially, we examined the behaviour of a variety of carbonyl compounds with the phenylhydrazides of alanine (**1a**), phenylalanine (**1b**) and leucine (**1c**), amino acids whose side chains do not induce further reactions other than the cyclisation to **4**. As expected, the reactivity depended both on the electrophilicity and the bulkiness of the substituents of the carbonyl compound.

The reaction of propanal (**2a**), benzaldehyde (**2c**) and 2-nitrobenzaldehyde (**2d**) in hot EtOH (50−70 °C) occurred within 2 h using a slight excess of **2**. We did not observe any significant difference in reactivity among these aldehydes, but ring closure did not occur when the sterically hindered 2,2-dimethylpropanal (**2b**) was used in connection with **1a**, even under the forcing reaction conditions previously described. The use of an acidic catalyst (PTSA) and toluene as solvent (6 h, 60 °C) allowed us to obtain a practically quantitative yield of the cyclisation product **4ab**. In fact, under these experimental conditions, both **2b** and the imine **3ab** formed were more reactive because of partial protonation. The reaction temperature was kept at 60 °C because of the low stability of **2b**.

When we extended this process to ketones under the same experimental conditions used for the sterically unhindered

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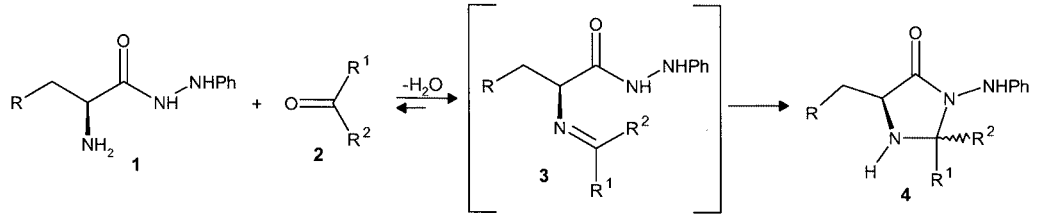


1	R	2	R^1	R^2	4	R	R^1	R^2	conditions
a	H	**a**	Et	H	**ab**	H	*tert*-Bu	H	d
b	Ph	**b**	*tert*-Bu	H	**ac**	H	Ph	H	a
c	Me_2CH	**c**	Ph	H	**ae**	H	Me	Me	e
d	indolyl	**d**	2-$NO_2C_6H_4$	H	**ag**	H	Ph	Me	f
e	imidazolyl	**e**	Me	Me	**ba**	Ph	Et	H	b
		f	Pr	Me	**bc**	Ph	Ph	H	a
		g	Ph	Me	**bd**	Ph	2-$NO_2C_6H_4$	H	a
		h	4-$NO_2C_6H_4$	Me	**be**	Ph	Me	Me	e
					bf	Ph	Pr	Me	f
					bh	Ph	4-$NO_2C_6H_4$	Me	f
					cc	Me_2CH	Ph	H	a
					cd	Me_2CH	2-$NO_2C_6H_4$	H	a
					ce	Me_2CH	Me	Me	e
					dc	indolyl	Ph	H	c
					de	indolyl	Me	Me	e
					ee	imidazolyl	Me	Me	e

Scheme 1. Reagents and conditions: a) **2** (1.10 equiv.), EtOH, 70 °C, 2 h; b) **2** (1.10 equiv.), EtOH, 50 °C, 2 h; c) **2** (1.05 equiv.), EtOH, 50 °C, 3 h; d) **2** (3.00 equiv.), PTSA (0.10 equiv.), toluene, 60 °C, 6 h; e) **2** (5.00 equiv.), EtOH, 50 °C, 5 h; f) **2** (2.00 equiv.), PTSA (0.10 equiv.), toluene, 85 °C, 24 h

aldehydes **2a** and **2c**−**d**, the rates of the reactions decreased because of the lower electrophilicity of their carbonyl groups. With acetone (**2e**), 2-pentanone (**2f**) and 4-nitroacetophenone (**2h**), an excess (fivefold) of the ketone and longer reaction times (5−16 h) were required to obtain the corresponding imidazolidin-4-ones (**4**). In contrast to the more electrophilic 4-nitroacetophenone (**2h**), acetophenone (**2g**) appeared not to react at all without the use of acid catalysis. To avoid problems in the purification of the final products, the reactions involving **2f**−**h** were carried out in the presence of PTSA, using toluene as solvent and with twice the stoichiometric amount of ketone.

From this comparison of the reactivity of these four ketones, we infer that the electrophilicity of the carbonyl car-

Table 1. Yields and some properties of compounds **4**

4	Yield (%)[a]	A/B ratio[b]	M.p. (°C)	$[\alpha]_D$ (*c*, MeOH)	Formula (mass)	C, H, N found (C, H, N calcd.)
ab	86	100:0	125	−61.7 (1.0)	$C_{14}H_{21}N_3O$ (247.34)	67.96, 8.53, 17.00 (67.98, 8.56, 16.99)
ac	70	52:48	197 (dec.)		$C_{16}H_{17}N_3O$ (267.33)	71.86, 6.39, 15.74 (71.89, 6.41, 15.72)
ae	98		106	+100.0 (1.0)	$C_{12}H_{17}N_3O$ (219.29)	65.70, 7.80, 19.18 (65.73, 7.81, 19.16)
ag	82	74:26	glass		$C_{17}H_{19}N_3O$ (281.36)	72.59, 6.80, 14.90 (72.57, 6.81, 14.93)
ba	83	55:45	108		$C_{18}H_{21}N_3O$ (295.38)	73.21, 7.15, 14.20 (73.19, 7.17, 14.23)
bc	75	57:43	62		$C_{22}H_{21}N_3O$ (343.43)	76.92, 6.18, 12.25 (76.94, 6.16, 12.24)
bd	90	50:50	80		$C_{22}H_{20}N_4O_3$ (388.43)	68.00, 5.21, 14.40 (68.03, 5.19, 14.42)
be	95		(glass)	−19.8 (0.8)	$C_{18}H_{21}N_3O$ (295.38)	73.21, 7.15, 14.22 (73.19, 7.17, 14.23)
bf	89	60:40	(glass)		$C_{20}H_{25}N_3O$ (323.44)	74.24, 7.78, 13.01 (74.27, 7.79, 12.99)
bh	80	77:33	86		$C_{23}H_{22}N_4O_3$ (402.45)	68.62, 5.54, 13.90 (68.64, 5.51, 13.92)
cc	72	60:40	45		$C_{19}H_{23}N_3O$ (309.41)	73.77, 7.51, 13.56 (73.76, 7.49, 13.58)
cd	91	50:50	135		$C_{19}H_{22}N_4O_3$ (354.41)	64.41, 6.24, 15.83 (64.39, 6.26, 15.81)
ce	98		(glass)	+57.2 (2.0)	$C_{15}H_{23}N_3O$ (261.37)	68.92, 8.86, 16.10 (68.93, 8.87, 16.08)
dc	84	50:50	144		$C_{24}H_{22}N_4O$ (382.46)	75.35, 5.81, 14.63 (75.37, 5.80, 14.65)
de	98		124	−19.6 (0.8)	$C_{20}H_{22}N_4O$ (334.42)	71.80, 6.64, 16.77 (71.83, 6.63, 16.75)
ee	95		164	+33.8 (0.7)	$C_{15}H_{19}N_5O$ (285.35)	63.11, 6.72, 24.55 (63.14, 6.71, 24.54)

[a] Isolated yields. [b] Diastereoisomer ratio (A/B) determined by ^1H NMR spectroscopy.

bon atom is the key factor in both the initial and subsequent steps of the reactions sequence.

The configuration of the stereocentre of the amino acid was retained in the corresponding phenylhydrazide, but, with the exception of 2-*tert*-butyl-5-methyl-3-(phenylamino)-imidazolidin-4-one (**4ab**), which contains the bulky *tert*-butyl group, the ^{1}H NMR spectroscopic analysis of the reaction mixtures reveals the presence of two diastereoisomers in ca. 1:1 ratio (Table 1) in all cases where the substituents R^1 and R^2 of the carbonyl group are different. This absence of asymmetric induction by the chiral centre of **1** can be taken as an indication that the final step is very fast, i.e., the intermediate is a very reactive species.

We infer the formation of a cyclic adduct from the presence of one or, when two diastereoisomers are produced, two signals in the range $\delta = 70-80$ ppm in the ^{13}C NMR spectra (Table 2) belonging to the N−C−N moiety of the ring. ^{1}H NMR spectra of compounds **4** (Table 2), derived from the condensation reaction of **1** with benzaldehyde (**2c**), show two doublets, one for each diastereoisomer, in the range $\delta = 5.3-5.7$ ppm for the proton of the closed ring with a coupling constant of 1.0−1.5 Hz with the proton of the α-chiral centre. These signals are shifted downfield ($\delta = 6.2-6.4$ ppm; $J = 1.0-1.3$ Hz) in the 2-nitrobenzaldehyde derivatives **4bd** and **4cd**, and upfield ($\delta = 4.2-4.4$ ppm), as two multiplets, in the propanal derivative **4ba**. Further confirmation for the ring closure is the lack, in the ^{1}H NMR spectra of **4**, of one of the two proton resonances of the NHNHPh skeleton of **1** in the range $\delta = 6.0-10.0$ ppm.[1]

The presence of the imidazolidinone ring in compounds **4** was confirmed unambiguously by X-ray diffraction analysis of 5-isobutyl-2-(2-nitrophenyl)-3-(phenylamino)imidazolidin-4-one (**4cd**). The resulting structure, shown in Figure 1, has the following features (see Figure 1 for atom numbering):

− There are two diastereoisomers present, both of which retain the same configuration of the α-chiral centre at C5 of the starting phenylhydrazide **1a**.

− The two diastereoisomers have opposite configurations at the ring closure carbon atom (C6) but, apart from that, the geometrical parameters of the two molecules are similar.

− The imidazolidinone ring is almost planar — it is distorted slightly by the steric requirements of the substituents. The N2−C7−C5 bond angle has the peculiarity of being much smaller (106.3° in diastereoisomer A and 109.2° in diastereoisomer B) than that expected for an sp^2-hybridized carbon atom.

− The nitrophenyl and aminophenyl groups are oriented *anti* to one another and are almost perpendicular to the imidazolidinone ring (torsion angles N1−C6−C8−C9 and C7−N2−N4−C14 are 93.6 and 73.2°, respectively, in diastereoisomer A and −89.7 and −61.8°, respectively, in diastereoisomer B).

− The two nitrogen atoms of the phenylhydrazide moiety and the phenyl ring are approximately coplanar (the torsion angle C19−C14−N4−N2 is 12.4° in diastereoisomer A and −17.7° in diastereoisomer B).

Figure 1 shows that even if the amino nitrogen atom of the phenylhydrazide moiety of **1** is more reactive[7] than the amide one, the condensation reaction involves the latter exclusively to give a five-membered ring. The six-membered ring structure proposed for the condensation products obtained from formaldehyde[1] might be incorrect, but, unfortunately, we have not been able to obtain suitable crystals for X-ray structural analysis.

We have also investigated the reaction of phenylhydrazides of amino acids that bear reactive sites in their side chains, such as tryptophan (**1d**) and histidine (**1e**), with benzaldehyde (**2c**) and acetone (**2e**). While the reaction of both of these phenylhydrazides with **2e** gave the expected imidazolidin-4-ones **4de** and **4ee** under the experimental conditions previously described (EtOH, 50 °C), with **2c** their behaviour was different. In fact, after 3 h in EtOH at 50 °C with a slight excess of **2c**, tryptophan phenylhydrazide (**1d**) gave only a mixture of the two diastereoisomers of 5-(1*H*-indol-3-ylmethyl)-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4dc**), but, when the reaction was carried out for 40 h with 3 equiv. of **2c**, a compound formed by double ring closure was obtained, namely 1,10-diphenyl-2-(phenylamino)-1,2,3a,4,9,10a-triazacyclopenta[*b*]fluoren-3-one (**5dc**, Scheme 2). The reaction of histidine phenylhydrazide (**1e**) with **2c** was not be limited to the production of 5-(1*H*-imidazol-4-ylmethyl)-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4ec**) because a second, and at least equally fast, ring closure involving the imidazole ring gave a tricyclic compound, namely 4,6-diphenyl-7-(phenylamino)-3,4,6,7,8a,9-hexahydro-8*H*-diimidazo[1,5-*a*:4′,5′-*d*]pyridin-8-one (**5ec**, Scheme 2).

The ^{13}C NMR spectra of **5dc** and **5ec** obtained using the PENDANT method show signals of a number of tertiary and quaternary carbon atoms in the aromatic region that are consistent with a second ring closure involving the 2-position of the indole unit in **4dc** and the 5-position of the imidazole unit in **4ec**. On the basis of the experimental data, the formation of the imidazolidin-4-one ring was the first step of the reaction sequence leading to **5** in reactions of both **1d** and **1e**, with the subsequent electrophilic substitution being faster for the imidazole ring than for the indole ring. These results are in contrast with those obtained from the reaction involving tryptophan phenylhydrazide hydrochloride and formaldehyde[1] because we observed only the product of ring closure at the 2-position of the indole ring, i.e., 1,2,3,4-tetrahydro-3-(2-phenylcarbazoyl)-β-carboline.

Surprisingly, the ^{1}H and ^{13}C NMR spectra of **5dc** and **5ec** reveal a single set of peaks consistent with the presence of a single diastereoisomer. The structure of **5dc** (Figure 2) was determined tentatively by means of NMR spectroscopy.

Two-dimensional C,H correlation experiments allowed us to assign the doublet centred at $\delta = 5.00$ ppm ($J = 2.4$ Hz) in the ^{1}H NMR spectrum obtained in [D_6]acetone to the benzylidene proton (H^4) derived from the benzaldehyde unit involved in the imidazolidinone ring closure and the doublet at $\delta = 5.14$ ppm ($J = 0.5$ Hz) to that of the second ring closure (H^5) involving the 2-position of the indole system. H,H-Decoupling and H,H-COSY spectra of **5dc**

Table 2. Spectroscopic and mass spectrometric data for compounds **4**

	IR (KBr), $\tilde{\nu}$ (cm^{-1})	^1H NMR[a], δ (ppm), *J* (Hz)	^{13}C NMR, δ (ppm)	MS (70 eV), *m/z* (%)
4ab	3300, 3220, 3040, 3000, 2960, 2870, 1710, 1605, 1500, 1485, 1440, 1400, 1390, 1380, 1310, 1230, 1195, 1180, 1140, 870, 775, 745, 690	0.99 (s, 9 H, 3 × CH_3), 1.37 (d, J = 6.6 Hz, 3 H, *CHCH_3), 1.88 (br. s, 1 H, NH), 3.67 (q, J = 6.6 Hz, 1 H, *CH), 4.48 (s, 1 H, NCHN), 6.46 (s, 1 H, PhNH), 6.58−6.72 (m, 2 H, $H_{arom.}$), 6.80−6.92 (m, 1 H, $H_{arom.}$), 7.10−7.24 (m, 2 H, $H_{arom..}$)[b]	18.5, 25.7, 35.1, 52.9, 80.1, 114.0, 121.2, 129.6, 146.1, 176.0[b]	247 [M^+] (31), 190 (100), 134 (8), 119 (45), 112 (17), 107 (8), 98 (27), 93 (13), 92 (40), 86 (30), 77 (14), 69 (11), 65 (18), 44 (18)
4ac	3280, 1718, 1605, 1500, 1455, 1395, 1315, 1270, 1180, 1080, 1030, 850, 755, 700	1.50 (d, J = 6.86 Hz, 3 H + 3 H, *CHCH_3 A + B), 2.55 (br. s, 1 H + 1 H, NH A + B), 3.82 (dq, J_1 = 6.9, J_2 = 1.2, 1 H, *CHCH_3 A), 3.92 (dq, J_1 = 6.9, J_2 = 1.1 Hz, 1 H, *CHCH_3 B), 5.56 (d, J = 1.2 Hz, 1 H, NCHN A), 5.61 (d, J = 1.1 Hz, 1 H, NCHN B), 5.67 (s, 1 H, PhNH A), 5.74 (s, 1 H, PhNH B), 6.56−6.74 (m, 2 H + 2 H, $H_{arom.}$ A + B), 6.80−6.96 (m, 1 H + 1 H, $H_{arom.}$ A + B), 7.08−7.44 (m, 7 H + 7 H, $H_{arom.}$ A + B)[b]	18.0, 18.5, 52.5, 53.3, 74.4, 74.8, 113.6, 113.9, 121.4, 121.5, 126.7, 127.4, 128.9, 129.0, 129.1, 129.2, 129.3, 129.7, 137.6, 138.4, 145.0, 145.3, 174.5, 174.7[b]	267 [M^+] (88), 134 (15), 133 (29), 132 (100), 106 (53), 105 (28), 92 (10), 91 (9), 77 (25), 65 (13)
4ae	3300, 1685, 1595, 1490, 1390, 1370, 1310, 1260, 1235, 1210, 1175, 1155, 1100, 1000, 835, 740, 690	1.30−1.50 [m, 9 H, *CHCH_3 + C(CH_3)$_2$], 2.02 (br. s, 1 H, NH), 3.58 (q, J = 6.9 Hz, 1 H, *CH), 6.22 (s, 1 H, PhNH), 6.73−6.94 (m, 3 H, $H_{arom.}$), 7.13−7.26 (m, 2 H, $H_{arom.}$)[b]	17.8, 24.9, 27.6, 52.6, 77.3, 114.0, 121.5, 129.5, 147.5, 176.6[b]	219 [M^+] (91), 134 (19), 112 (15), 105 (13), 93 (29), 92 (27), 85 (43), 84 (100), 77 (28), 65 (17), 58 (56)
4ag	3280, 1710, 1605, 1500, 1450, 1390, 1310, 1245, 1110, 755, 700, 670, 630	1.41 (d, J = 6.8 Hz, 3 H, *CHCH_3 A), 1.46 (d, J = 6.8 Hz, 3 H, *CHCH_3 B), 1.79 (s, 3 H, CCH_3 A), 1.82 (s, 3 H, CCH_3 B), 1.95 (br. s, 1 H + 1 H, NH A + B), 3.52 (q, J = 6.8 Hz, 1 H, *CH B), 3.54 (q, J = 6.8 Hz, 1 H, *CH A), 5.94 (s, 1 H, PhNH A), 6.11 (s, 1 H, PhNH B), 6.58−7.62 (m, 10 H + 10 H, $H_{arom.}$ A + B)[b]	17.9, 18.4, 25.5, 27.6, 52.4, 52.9, 79.5, 79.6, 114.0, 114.1, 114.4, 121.5, 121.7, 126.0, 126.5, 128.6, 128.9, 129.1, 129.3, 129.5, 142.3, 142.8, 146.6, 147.2, 175.2, 176.1[b]	281 [M^+] (80), 147 (16), 146 (100), 134 (10), 121 (8), 120 (82), 119 (17), 105 (39), 104 (36), 103 (22), 93 (12), 92 (13), 78 (15), 77 (54)
4ba	3270, 1700, 1600, 1500, 1450, 1440, 1260, 1240, 1200, 1180, 1025, 920, 890, 810, 755, 700, 665	0.78 (t, J = 7.5 Hz, 3 H, CH_3 A), 0.89 (t, J = 7.5 Hz, 3 H, CH_3 B), 1.05−1.31 (m, 1 H, CH_3CHH A), 1.37−1.62 (m, 1 H, CH_3CHH B), 1.64−1.88 (m, 1 H + 1 H, CH_3CHH A + B), 2.15 (br. s, 1 H + 1 H, NH A + B), 2.98−3.28 (m, 2 H + 2 H, *CHCH_2 A + B), 3.76−3.85 (m, 1 H, *CH A), 3.85−3.94 (m, 1 H, *CH B), 4.27 (ddd, J_1 = 7.4, J_2 = 2.9, J_3 = 1.1 Hz, 1 H, NCHN B), 4.36 (ddd, J_1 = 7.9, J_2 = 3.0, J_3 = 1.0 Hz, 1 H, NCHN A), 6.18 (s, 1 H, PhNH A), 6.25 (s, 1 H, PhNH B), 6.38−6.48 (m, 2 H, $H_{arom.}$ B), 6.52−6.62 (m, 2 H, $H_{arom.}$ A), 6.80−6.92 (m, 1 H + 1 H, $H_{arom.}$ A + B), 7.04−7.20 (m, 2 H + 2 H, $H_{arom..}$ A + B), 7.22−7.42 (m, 5 H + 5 H, $H_{arom.}$ A + B)[b]	8.1, 8.2, 26.3, 26.4, 36.4, 36.7, 57.6, 58.5, 74.0, 75.1, 113.3, 113.6, 121.0, 121.1, 126.9, 127.0, 128.6, 128.7, 128.9, 129.0,129.8, 130.0, 136.1 136.2, 145.8, 146.4, 173.5,175.2[b]	295 [M^+] (100), 266 (15), 204 (29), 160 (70), 147 (15), 134 (25), 133 (5), 131 (31), 120 (13), 93 (14), 92 (20), 91 (19), 65 (11), 58 (15)
4bc	3290, 1710, 1600, 1500, 1450, 1395, 1335, 1260, 1225, 1175, 1155, 1110, 1080, 1025, 750, 700, 665, 620	2.24 (br. s, 1 H + 1 H, NH A + B), 3.08−3.25 (m, 2 H + 1 H, *CHCH_2 A + *CHCHH B), 3.34 (dd, J_1 = 14.0, J_2 = 5.6 Hz, 1 H, *CHCHH B), 4.00−4.10 (m, 1 H, *CH A), 4.14−4.24 (m, 1 H, *CH B), 5.34 (d, J = 1.5 Hz, 1 H, NCHN B), 5.43 (d, J = 1.3 Hz, 1 H, NCHN A), 5.46 (s, 1 H, PhNH A), 5.54 (s, 1 H, PhNH B), 6.30−6.38 (m, 2 H, $H_{arom..}$ A), 6.51−6.60 (m, 2 H, $H_{arom..}$ B), 6.81−6.92 (m, 2 H + 2 H, $H_{arom..}$ A + B), 7.04−7.46 (m, 11 H + 11 H, $H_{arom..}$ A + B)[b]	37.4, 38.4, 58.5, 59.0, 75.0, 75.7, 114.3, 114.7, 122.0, 122.1, 127.4, 127.7, 127.8, 128.2, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.0, 130.3, 130.7, 130.8, 137.0, 137.1, 138.0, 139.4, 145.6, 145.7, 173.3, 174.0[b]	343 [M^+] (100), 209 (12), 208 (21), 146 (11), 134 (10), 131 (16), 118 (11), 117 (18), 106 (29), 104 (19), 92 (13), 91 (22)
4bd	3280, 1710, 1600, 1530, 1500, 1390, 1350, 1305, 1260, 1180, 1110, 1080, 1030, 855, 785, 750, 700, 675, 620	2.67 (br. s, 1 H + 1 H, NH A + B), 2.98−3.32 (m, 2 H + 2 H, *CHCH_2 A + B), 3.91−4.02 (m, 1 H, *CH A), 4.06−4.17 (m, 1 H, *CH B), 5.95 (s, 1 H, PhNH A), 6.10 (s, 1 H, PhNH B), 6.17 (d, J = 1.2 Hz, 1 H, NCHN B), 6.23 (d, J = 1.3 Hz, 1 H, NCHN A), 6.35−6.45 (m, 2 H, $H_{arom..}$ B), 6.47−6.57 (m, 2 H, $H_{arom..}$ A), 6.73−6.93 (m, 1 H + 1 H, $H_{arom..}$ A + B), 7.01−7.64 (m, 10 H +10 H, $H_{arom..}$ A + B), 7.70−7.80 (m, 1 H, $H_{arom..}$ A), 7.85−7.95 (m, 1 H, $H_{arom..}$ B)[b]	37.4, 39.0, 57.6, 58.9, 70.4, 70.8, 114.1, 114.3, 122.0, 122.2, 124.8, 125.7, 127.2, 127.7, 127.8, 128.9, 129.4, 129.6, 129.9, 130.4, 130.5, 133.6, 134.0, 134.1, 134.4, 136.2, 136.3, 137.7, 145.3, 145.5, 149.8, 150.5, 172.9, 173.6[b]	388 [M^+] (100), 254 (24), 151 (42), 134 (58), 131 (28), 120 (61), 118 (19), 108 (39), 107 (19), 105 (25), 104 (18), 93 (24), 92 (47), 91 (84), 77 (28)

Table 2. *(Continued)*

	IR (KBr), $\tilde{\nu}$ (cm^{-1})	^1H NMR[a], δ (ppm), *J* (Hz)	^{13}C NMR, δ (ppm)	MS (70 eV), *m/z* (%)
4be	3280, 3040, 2990, 1710, 1605, 1500, 1455, 1445, 1440, 1395, 1360, 1260, 1240, 1180, 1155, 755, 700, 610	1.17 (s, 3 H), 1.32 (s, 3 H), 1.92 (br. s, 1 H, NH), 3.05 and 3.32 (AB of ABX, 2 H, J_{AB} = 14.1, $J_{AX} = J_{BX}$ = 4.8 Hz, *CHCH_2), 3.84 (*app* t, 1 H, *CH), 5.96 (s, 1 H, PhNH), 6.45−6.58 (m, 2 H, $H_{arom..}$), 6.82−6.95 (m, 1 H, $H_{arom..}$), 7.07−7.20 (m, 2 H, $H_{arom..}$), 7.21−7.42 (m, 5 H, $H_{arom.}$)[c]	25.5, 27.2, 36.5, 57.8, 77.5, 114.4, 121.9, 127.9, 129.5, 129.6, 130.7, 136.5, 147.6, 175.4[c]	295 [M^+] (100), 160 (45), 134 (13), 131 (21), 104 (28), 98 (14), 92 (28), 91 (26), 77 (15), 65 (16), 58 (40)
4bf	3259, 3063, 3006, 2962, 2932, 2872, 1704, 1603, 1496, 1455, 1396, 1306, 1250, 1218, 1176, 1157, 1141, 1088, 749, 695, 668, 603, 505	0.74 (t, *J* = 7.0 Hz, CH_2CH_3 A), 0.92 (t, *J* = 7.1 Hz, CH_2CH_3 B), 1.07 (s, 3 H, CH_3 B), 1.30 (s, 3 H, CH_3 A), 1.06−1.65 (m, 4 H + 4 H, CH_2CH_2 A + B), 1.91 (br. s, 1 H + 1 H, NH A + B), 2.93−3.12 (m, 1 H + 1 H, *CHC*H*H A + B), 3.16−3.40 (m, 1 H + 1 H, *CHCH*H* A + B), 3.77−3.89 (m, 1 H + 1 H, *CH A + B), 5.99 (s, 1 H, PhNH A), 6.05 (s, 1 H, PhNH B), 6.40−6.50 (m, 2 H, $H_{arom..}$ B), 6.52−6.62 (m, 2 H, $H_{arom..}$ A), 6.79−6.93 (m, 1 H + 1 H, $H_{arom..}$ A + B), 7.03−7.44 (m, 7 H + 7 H, $H_{arom..}$ A + B)[b]	14.6, 14.7, 16.9, 17.7, 23.6, 25.8, 36.6, 36.7, 41.5, 41.7, 57.5, 58.2, 79.4, 79.5, 114.2, 114.4, 121.4, 121.6, 127.6, 127.7, 129.1, 129.2, 129.3, 129.4, 130.5, 130.7, 136.2, 136.6, 147.2, 147.3, 175.0, 175.2[b]	323 [M^+] (100), 232 (14), 188 (56), 134 (10), 131 (23), 126 (15), 105 (18), 104 (19), 98 (13), 93 (17), 92 (33), 91 (33), 86 (50), 77 (15), 65 (16), 42 (16)
4bh	3428, 1713, 1602, 1519, 1496, 1455, 1380, 1337, 1261, 1096, 1026, 859, 803, 756	1.49 (s, 3 H, CH_3 A), 1.79 (s, 3 H, CH_3 B), 2.29 (br. s, 1 H + 1 H, NH A + B), 3.04−3.47 (m, 2 H + 2 H CH_2 A + B), 3.69−3.87 (m, 1 H, *CH A), 4.04−4.18 (m, 1 H, *CH B), 6.12 (s, 1 H, PhNH B), 6.20 (s, 1 H, PhNH A), 6.35−6.60 (m, 2 H + 2 H, $H_{arom..}$ A + B), 6.72−7.61 (m, 8 H + 10 H, $H_{arom..}$ A + B), 7.78−7.90 (m, 2 H, $H_{arom..}$ A), 7.95−8.06 (m, 2 H, $H_{arom..}$ B), 8.13−8.23 (m, 2 H, $H_{arom..}$ A)[b]	25.1, 26.5, 35.4, 37.4, 55.8, 57.0, 77.8, 78.2, 113.5, 113.8, 121.4, 121.5, 123.1, 123.5, 126.7, 126.8, 127.4, 127.6, 128.7, 128.8, 128.9, 129.9, 130.2, 134.9, 135.1, 145.7, 146.2, 147.5, 147.7, 148.9, 149.0, 172.7, 173.7[b]	402 [M^+] (100), 267 (35), 165 (42), 164 (25), 149 (34), 134 (61), 131 (83), 119 (52), 108 (27), 103 (55), 93 (55), 92 (43), 91 (70), 77 (41), 65 (31)
4cc	3295, 2970, 1715, 1605, 1500, 1460, 1390, 1370, 1290, 1265, 1225, 1175, 1090, 1070, 755, 700, 670	0.93−1.07 [m, 6 H + 6 H, $CH(CH_3)_2$ A + B], 1.44−1.72 [m, 1 H + 1 H, CH A + B], 1.73−2.07 (m, 2 H + 2 H, CH_2 A + B), 2.25 (br. s, 1 H + 1 H, NH A + B), 3.71−3.82 (m, 1 H, *CH A), 3.82−3.92 (m, 1 H, *CH B), 5.56 (d, *J* = 1.3 Hz, 1 H, NCHN A), 5.59 (d, *J* = 1.3 Hz, 1 H, NCHN B), 5.68 (s, 1 H, PhNH A), 5.72 (s, 1 H, PhNH B), 6.55−6.73 (m, 2 H + 2 H, $H_{arom..}$ A + B), 6.80−6.94 (m, 1 H + 1 H, $H_{arom.}$ A + B), 6.10−7.43 (m, 7 H + 7 H, $H_{arom.}$ A + B)[b]	21.8, 21.9, 23.8, 23.9, 25.4, 25.5, 42.5, 55.6, 56.4, 75.1, 75.4, 114.1, 114.4, 121.8, 121.9, 127.3, 128.0, 129.4, 129.6, 129.7, 129.8, 130.1, 138.2, 139.1, 145.6, 145.8, 174.9, 175.2[b]	309 [M^+] (99), 196 (14), 175 (12), 174 (36), 134 (10), 132 (100), 108 (23), 106 (83), 105 (30), 92 (26), 91 (23), 90 (28), 76 (26), 65 (15)
4cd	3230, 2970, 1710, 1605, 1525, 1500, 1410, 1350, 1315, 1255, 1225, 1090, 860, 830, 755, 700, 670, 645, 610	0.84−1.06 [m, 6 H + 6 H, $CH(CH_3)_2$ A + B], 1.36−1.66 [m, 1 H + 1 H, CH A + B], 1.66−2.00 (m, 2 H + 2 H, CH_2 A + B), 2.73 (br. s, 1 H + 1 H, NH A + B), 3.61−3.75 (m, 1 H, *CH A), 3.84−3.98 (m, 1 H, *CH B), 6.32−6.39 (m, 1 H + 1 H + 1 H, PhNH A + B, NCHN A), 6.42 (d, *J* = 1.0 Hz, 1 H, NCHN B), 6.54−6.65 (m, 2 H, $H_{arom.}$ B), 6.65−6.76 (m, 2 H, $H_{arom.}$ A), 6.78−6.95 (m, 1 H + 1 H, $H_{arom.}$ A + B), 7.05−7.27 (m, 2 H + 2 H, $H_{arom.}$ A + B), 7.38−8.00 (m, 4 H + 4 H, $H_{arom.}$ A + B)[b]	21.8, 22.0, 23.7, 23.8, 25.1, 25.4, 42.2, 43.1, 54.8, 55.7, 70.6, 71.0, 113.9, 114.0, 121.8, 122.1, 125.1, 125.8, 127.7, 129.1, 129.6, 129.7, 129.9, 130.0, 134.0, 134.2, 134.5, 134.9, 145.5, 145.6, 149.7, 150.2, 174.6, 175.2[b]	354 [M^+] (42), 151 (100), 134 (49), 108 (51), 105 (29), 93 (43), 92 (45), 86 (53), 77 (62), 65 (36), 57 (37), 55 (34), 43 (52), 41 (45)
4ce	3260, 2960, 2930, 2870, 1700, 1600, 1495, 1390, 1370, 1255, 1235, 1155, 800, 750, 695, 665, 620	0.88−1.06 [m, 6 H, $CH(CH_3)_2$], 1.34 (s, 3 H, CCH_3), 1.44 (s, 3 H, CCH_3), 1.75−2.03 [m, 4 H, $CHCH_2$, NH], 3.53 (dd, J_1 = 10.0, J_2 = 9.6 Hz, 1 H, *CH), 6.21 (s, 1 H, PhNH), 6.72−6.82 (m, 2 H, $H_{arom.}$), 6.82−6.93 (m, 1 H, $H_{arom.}$), 7.12−7.25 (m, 2 H, $H_{arom.}$)[b]	21.9, 23.7, 24.9, 25.4, 27.6, 42.0, 55.2, 77.4, 114.1, 121.4, 129.4, 147.6, 176.7[b]	261 [M^+] (91), 126 (49), 108 (39), 98 (19), 93 (31), 92 (26), 83 (72), 76 (17), 69 (17), 64 (20), 58 (100), 43 (20), 42 (35), 41 (29)
4dc	3300, 1710, 1600, 1495, 1455, 1430, 1390, 1360, 1340, 1305, 1230, 1090, 745, 700, 665	2.92−3.34 (m, 2 H + 2 H, CH_2 A + B), 3.44 (br. s, 1 H + 1 H, NH A + B), 3.85−4.09 (m, 1 H + 1 H, *CH A + B) 5.39 (d, *J* = 0.8 Hz, 1 H, NCHN A), 5.42 (d, *J* = 0.5 Hz, 1 H, NCHN B),6.32−6.44 (m, 2 H, $H_{arom.}$ A), 6.44−6.56 (m, 2 H, $H_{arom.}$ B), 6.56−6.72 (m, 1 H + 1 H, $H_{arom.}$ A + B), 6.90−7.49 (m, 11 H + 11 H, $H_{arom.}$ A + B), 7.52−7.69 (m, 1 H + 1 H, $H_{arom.}$ A + B), 7.71 (s, 1 H, PhNH B), 7.76 (s, 1 H, PhNH A), 10.9 (br. s, 1 H + 1 H, $NH_{arom.}$ A + B)[c]	27.3, 27.5, 57.1, 57.7, 74.4, 74.9, 109.8, 109.9, 111.1, 111.9, 112.1, 118.2, 118.3, 118.5, 118.6, 120.7, 120.8, 123.9, 124.0, 127.1, 127.4, 127.5, 127.6, 127.8, 128.2, 128.4, 128.5, 136.1, 136.2, 139.2, 139.9, 146.6, 146.7, 172.8, 173.3[c]	382 [M^+] (46), 170 (44), 161 (18), 146 (18), 143 (16), 131 (17), 130 (100), 117 (18), 93 (41), 92 (18), 77 (18)

Table 2. *(Continued)*

	IR (KBr), ν̃ (cm^{-1})	^1H NMR[a], δ (ppm), *J* (Hz)	^{13}C NMR, δ (ppm)	MS (70 eV), *m/z* (%)
4de	3310, 1705, 1605, 1500, 1460, 1395, 1375, 1345, 1260, 1180, 1160, 750, 700, 670, 640, 630	1.13 (s, 3H CH_3), 1.23 (s, 3H CH_3), 3.01 and 3.18 (AB of ABX, J_{AB} = 14.9, J_{AX} = 7.3, J_{BX} = 4.1 Hz, 2 H, CH_2), 3.30 (br. s, 1 H, NH), 3.76 (dd, J_1 = 7.3, J_2 = 4.1 Hz, 1 H, *CH), 6.47−6.62 (m, 2 H, $H_{arom.}$), 6.62−6.75 (m, 1 H, $H_{arom.}$), 6.90−7.15 (m, 5 H, $H_{arom.}$), 7.18−7.24 (m, 1 H, $H_{arom.}$), 7.34−7.44 (m, 1 H, $H_{arom.}$), 7.52−7.64 (m, 1 H, $H_{arom.}$), 7.91 (s, 1 H, PhNH), 10.9 (s, 1 H, $NH_{arom.}$)[c]	25.2, 26.6, 26.7, 56.6, 75.8, 109.8, 111.2, 112.1, 118.3, 118.5, 120.8, 124.0, 127.4, 128.4, 136.1, 148.0, 173.3[c]	334 [M^+] (68), 205 (13), 170 (73), 143 (29), 131 (19), 130 (100), 117 (17), 98 (46), 93 (44), 92 (27), 77 (17), 58 (14), 42 (16)
4ee	3400−2300, 1700, 1630, 1600, 1500, 1430, 1395, 1370, 1330, 1310, 1260, 1235, 1980, 1110, 1080, 940, 900, 820, 750, 700, 630	1.20 (s, 1 H, CH_3), 1.23 (s, 1 H, CH_3), 2.88 (*app* d, *J* = 5.1 Hz, 2 H, CH_2), 3.68 (*app* t, *J* = 5.1 Hz, 1 H, *CH), 6.35−6.53 (m, 2 H, $H_{arom.}$), 6.61−6.74 (m, 1 H, $H_{arom.}$), 6.83 (d, *J* = 1.2 Hz, 1 H, $H_{imidazole}$), 7.00−7.15 (m, 2 H, $H_{arom.}$), 7.28 (br. s, 1 H, NH), 7.65 (d, *J* = 1.2 Hz, 1 H, $H_{imidazole}$), 7.89 (s, 1 H, PhNH), 8.21 (s, 1 H, $NH_{imidazole}$)[c]	25.3, 25.9, 27.9, 56.0, 75.9, 112.1, 116.6, 118.4, 128.4, 133.8, 134.6, 148.1, 172.9[c]	285 [M^+] (100), 178 (21), 150 (65), 123 (25), 121 (46), 108 (24), 98 (38), 93 (39), 92 (46), 82 (80), 81 (44), 65 (23), 58 (42)

[a] A: Diastereoisomer A; B: diastereoisomer B. [b] Solvent: $CDCl_3$. [c] Solvent: [D_6]DMSO.

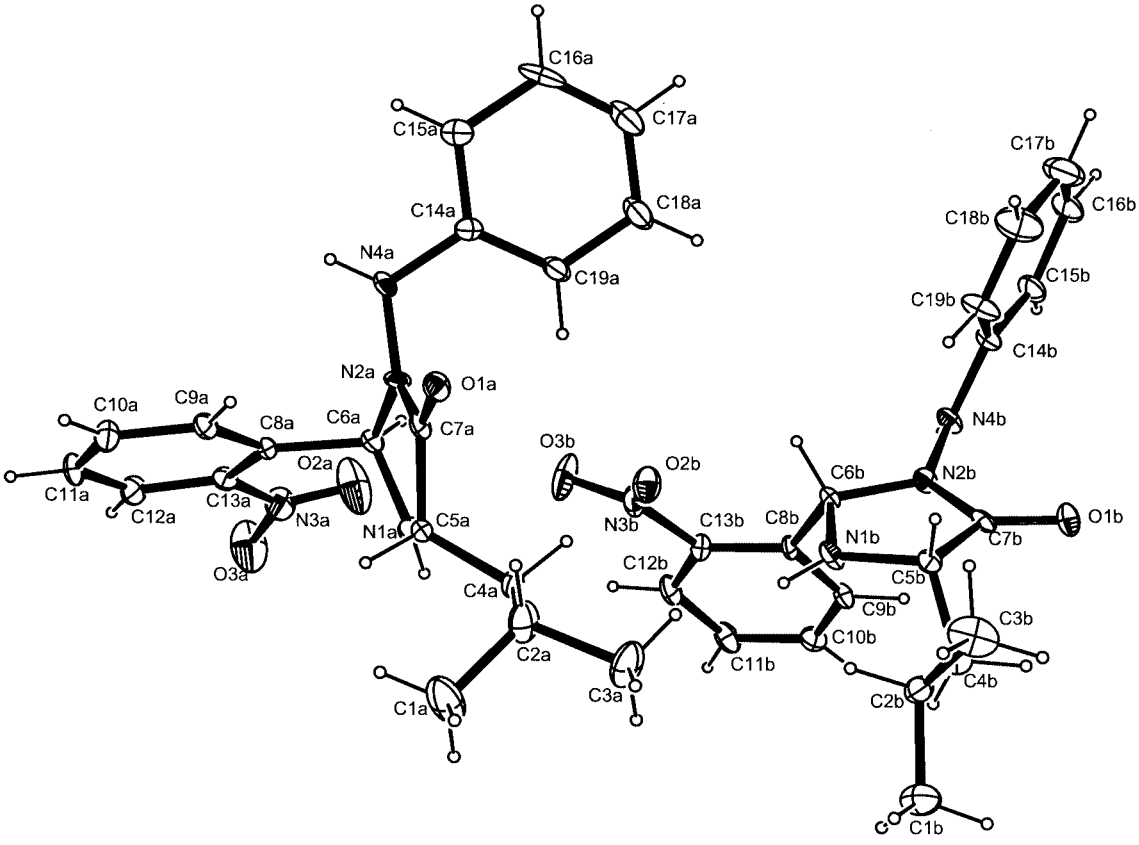
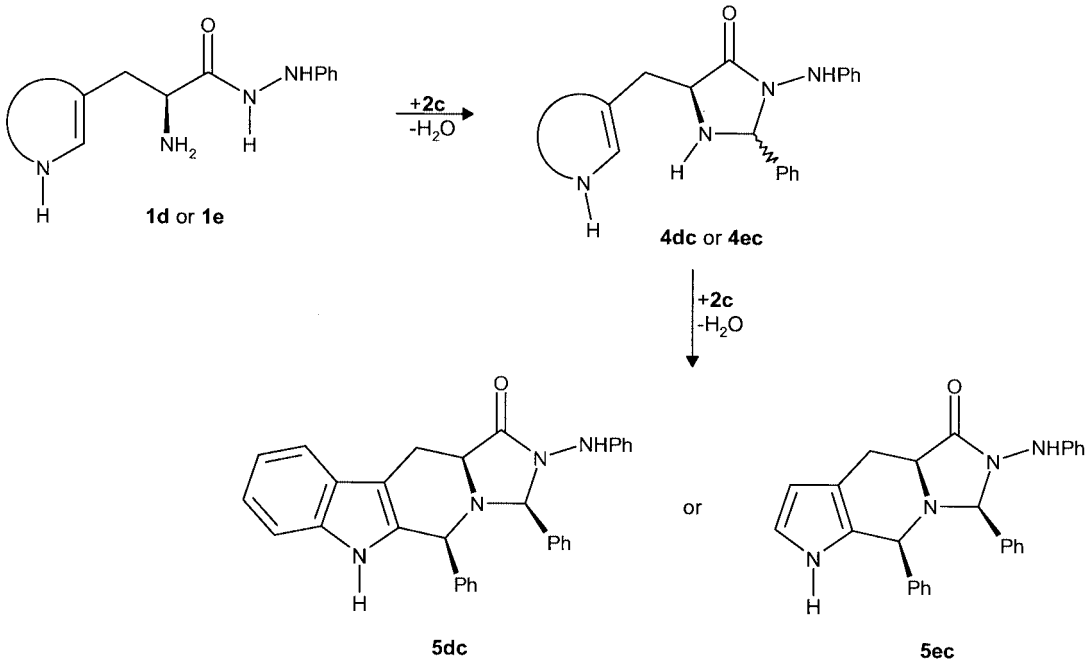


Figure 1. ORTEP view of the two diastereoisomers (A and B) of 5-isobutyl-2-(2-nitrophenyl)-3-(phenylamino)imidazolidin-4-one (**4cd**)

(Table 3) show that H^4 and H^5 exhibit a long-range ^4J correlation to H^3, and H^5 exhibits a long-range ^5J correlation to H^1. These results are consistent with the structure proposed in Figure 2 where H^3, H^4 and H^5 are all in a *syn* relationship.

To explain the stereochemical course of the reaction, we suggest the following mechanism, using **5dc** as the example (Scheme 3). Compound **1d** reacts with **2c** to form the imine **3dc**, which promptly cyclizes to give a mixture of the two diastereoisomers **4dc(A)** and **4dc(B)**. At this point, only **4dc(A)** has the correct geometry to react with a second molecule of **2c**, leading to **5dc**, while **4dc(B)**, with its disfavoured structure, isomerises to **4dc(A)** via the imine **3dc**.

We suggested a similar mechanism for the formation of **5ec**. Cyclisation reactions like this one involving the imidazole ring have been reported for histamine and histidine un-



Scheme 2

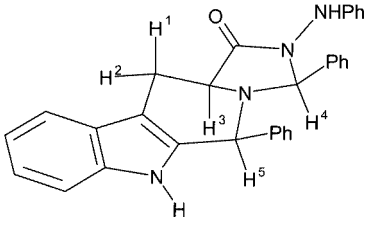


Figure 2. Structure of 1,10-diphenyl-2-(phenylamino)-2,9,10a-triazacyclopenta[*b*]fluoren-3-one (**5dc**)

Table 3. ^{1}H NMR spectroscopic data of **5dc** and corresponding H,H-COSY correlations in the aliphatic region (Figure 2)

	δ (ppm), [*J* (Hz)]	H,H-COSY
H^1	3.00 (ddd) [14.8; 11.0; 1.6 Hz]	H^2, H^3, H^5
H^2	3.35 (dd) [14.8; 4.2 Hz]	H^1, H^3
H^3	4.06 (dddd) [11.0; 4.2; 2.4; 0.5 Hz]	H^1, H^2, H^4, H^5
H^4	5.00 (d) [2.4 Hz]	H^3
H^5	5.14 (d) [0.5 Hz]	H^1

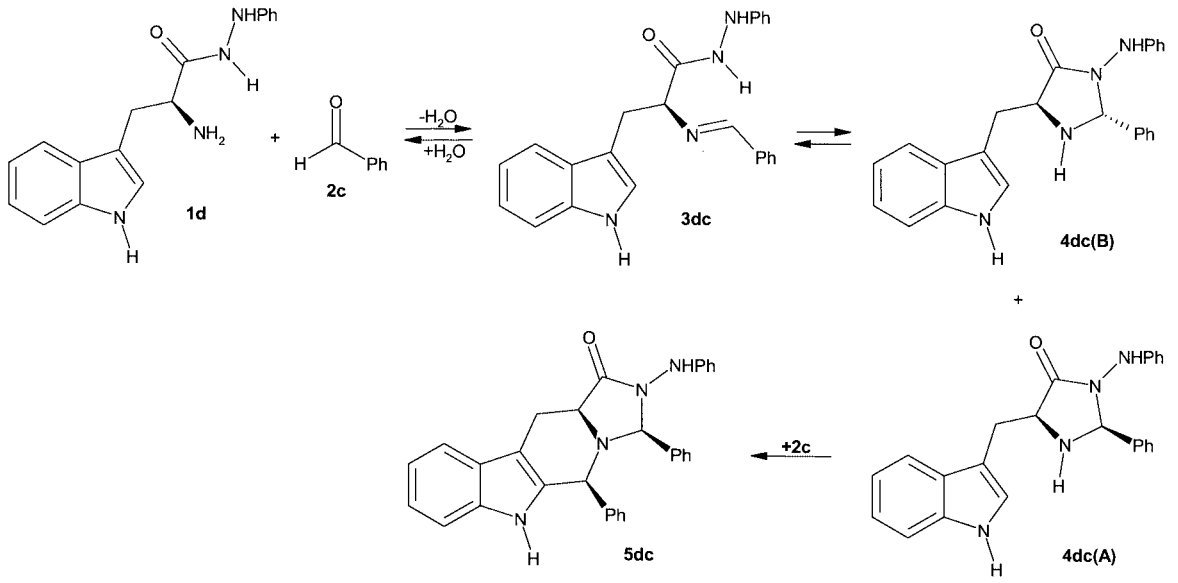
der acidic conditions.[8] Additionally, many derivatives containing the β-carboline moiety present in **5dc** have been described extensively in the literature. This subunit, found in many naturally occurring compounds, is the subject of extensive chemical and biochemical research[9] because of its pharmacological importance. Furthermore, the β-carboline system containing a reduced form of its pyridine ring has received special attention because this framework is present in several alkaloids.[10]

Conclusions

The results described herein widen the synthetic availability of a variety of heterocyclic compounds with rigid frameworks containing natural amino acid moieties. Furthermore, the presence of two amino nitrogen atoms of different reactivity could be attractive for the design of new peptidomimetic structures having biological activity.

Experimental Section

General: All reagents were commercial quality (Aldrich, Fluka) and were used without further purification. The α-amino acid phenylhydrazides **1a**−**c** were prepared as described previously.[1] The reactions were monitored by TLC performed on silica gel plates (Kieselgel 60 F_{254}, Merck). Preparative thick-layer chromatography was performed on silica gel (Kieselgel 60 F_{254}, 2 mm thickness, Merck). The imidazolidin-4-one derivatives **4** obtained could not be purified by absorption chromatography since they decompose extensively upon prolonged contact on silica gel or alumina. Direct-inlet mass spectra (DI-MS) were obtained with a Fisons TRIO 2000 gas chromatograph/mass spectrometer, working in the positive-ion, 70-eV, electron-impact mode. Spectra were recorded in the range 35−450 u. Temperatures between 150 and 250 °C were suitable for volatilising all the compounds into the ion source. IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using the KBr technique for solids and recorded in the range 4000−400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ at room temperature or [D_6]DMSO at 40 °C as solvents. The positions of the peaks are reported as δ values relative to TMS. Some ^{1}H multiplets are characterised by the term *app* (apparent): this refers only to their appearance and may be an oversimplification. Optical rotations were determined at 20 °C (concentration in g/



Scheme 3

100 mL of solvent) using a POLAX-D polarimeter purchased from ATAGO (Japan). Elemental analyses were performed with a Carlo Erba Mod. 1106 elemental analyser. Melting points were determined with an automatic Mettler (Mod. FP61) melting point apparatus and are not corrected.

Tryptophan Phenylhydrazide (1d): L-Tryptophan methyl ester hydrochloride (3.00 g, 11.80 mmol) and freshly distilled phenylhydrazine (6.00 mL, 61.03 mmol) were mixed and stirred under Ar at 60 °C for 16 h. The resulting solid reaction mixture was cooled to room temperature, triturated in Et_2O (70 mL) and then stirred vigorously for 1 h. The solid was filtered off, vigorously stirred with $Na_2CO_3 \cdot 10H_2O$ (6.70 g) and H_2O (25 mL) for 2 h and then filtered and washed with H_2O (10 mL). Spectroscopically pure product **1d** was obtained (3.13 g, 90%). M.p. 182 °C. $[\alpha]_D = +53.0$ ($c = 1.0$, MeOH). IR (KBr): $\tilde{\nu}$ = 3328, 3286, 1667, 1603, 1543, 1499, 1476, 1430, 1231, 1099, 934, 862, 770, 743, 695, 490 cm^{-1}. MS (70 eV): *m/z* (%) = 294 [M^+] (13), 277 (3), 170 (10), 164 (12), 163 (6), 159 (11), 143 (5), 130 (100), 117 (7), 115 (5), 108 (7), 93 (37), 92 (15), 77 (12). ^1H NMR ([D$_6$]DMSO): δ = 2.84 and 3.12 (AB of ABX, 2 H, J_{AB} = 14.0, J_{AX} = 7.4, J_{BX} = 6.7 Hz, *CHCH_2), 3.17 (br. s, 2 H, NH_2), 3.63 (*app* t, 1 H, J = 6.3 Hz, *CH), 6.50−7.45 (m, 12 H, $H_{arom.}$ + 2 NH), 10.92 (s, 1 H, NH_{indole}) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 31.5, 54.5, 110.6, 111.3, 112.2, 118.2, 118.3, 118.6, 120.9, 123.8, 127.4, 128.5, 136.3, 149.2, 174.5 ppm. $C_{17}H_{18}N_4O$ (294.36): calcd. C 69.37, H 6.16, N 19.03; found C 69.33, H 6.18, N 19.00.

Histidine Phenylhydrazide (1e): L-Histidine methyl ester dihydrochloride (3.00 g, 12.40 mmol) and freshly distilled phenylhydrazine (6.10 mL, 61.90 mmol) were mixed and stirred under Ar at 60 °C for 16 h. The resulting solid reaction mixture was cooled to room temperature, triturated in Et_2O (70 mL) and then stirred vigorously for 1 h. The solid was filtered off, added to a mixture of $Na_2CO_3 \cdot 10H_2O$ (7.00 g), H_2O (2.00 mL) and CH_2Cl_2 (70 mL) and then stirred vigorously for 1 h. The solid was filtered off, washed with CH_2Cl_2 (2 × 20 mL) and dissolved in boiling *i*PrOH. The insoluble material was filtered off and, after partial evaporation of the solvent under reduced pressure, the remaining solution was added dropwise to Et_2O (50 mL) whilst stirring to form a solid white precipitate, which was filtered under Ar, dried and then stored in a dessicator because of its hygroscopicity. Spectroscopically pure product **1e** was obtained (2.49 g, 82%). M.p. (dec.) 122 °C. $[\alpha]_D = +19.1$ ($c = 1.0$, MeOH). IR (KBr): $\tilde{\nu}$ = 3654−2549 broad, 1674, 1605, 1494, 1247, 756, 696, 625 cm^{-1}. MS (70 eV): *m/z* (%) = 245 [M^+] (21), 164 (5), 138 (6), 123 (5), 121 (7), 110 (100), 108 (20), 93 (36), 92 (21), 83 (25), 82 (74), 81 (26), 77 (13). ^1H NMR ([D$_6$]DMSO): δ = 2.67 and 2.90 (AB of ABX, 2 H, J_{AB} = 14.4, J_{AX} = 7.8, J_{BX} = 5.8 Hz, *CHCH_2), 3.58 (dd, J_1 = 7.6, J_2 = 5.9 Hz, 1 H, *CH), 3.71 (br. s, 2 H, NH_2), 6.58−6.77 (m, 4 H, $H_{arom.}$ + NH), 6.81 (d, J = 1.0 Hz, 1 H, $H_{imidazole}$), 7.02−7.17 (m, 2 H, $H_{arom.}$), 7.54 (d, J = 1.0 Hz, 1 H, $H_{imidazole}$), 7.56 (s, 1 H, NH), 8.21 (s, 1 H, $NH_{imidazole}$) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 32.8, 54.0, 112.2, 116.2, 118.3, 128.4, 133.0, 134.5, 149.2, 174.2 ppm. $C_{12}H_{15}N_5O$ (245.28): calcd. C 58.76, H 6.16, N 28.55; found C 58.78, H 6.15, N 28.52.

Reactions of the Phenylhydrazides of Alanine (1a), Phenylalanine (1b) and Leucine (1c) with Propanal (2a), Benzaldehyde (2c) and 2-Nitrobenzaldehyde (2d): A solution of the appropriate L-amino acid phenylhydrazide (**1a**−**c**, 2.80 mmol) and aldehyde (**2a**,**c**,**d**, 3.08 mmol) in absolute EtOH (30 mL) was stirred under Ar at 70 °C (50 °C when **2a** was used) for 2 h (monitored by TLC: silica; EtOAc). The EtOH was distilled off under reduced pressure and excess aldehyde was removed by dissolving the residue in CH_2Cl_2 (10 mL) and stirring with saturated aqueous $Na_2S_2O_5$ (0.5 mL) for 1 h. The organic phase was separated and dried with anhydrous Na_2SO_4 and then the solvent was evaporated to afford a residue consisting of the two diastereoisomers of either 5-methyl-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4ac**), 5-benzyl-2-ethyl-3-(phenylamino)imidazolidin-4-one (**4ba**), 5-benzyl-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4bc**), 5-benzyl-2-(2-nitrophenyl)-3-(phenylamino)imidazolidin-4-one (**4bd**), 5-isobutyl-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4cc**) or 5-isobutyl-2-(2-nitrophenyl)-3-(phenylamino)imidazolidin-4-one (**4cd**).

Reaction of Tryptophan Phenylhydrazide (1d) and Benzaldehyde (2c): A solution of **1d** (0.44 g, 1.50 mmol) and **2c** (0.16 mL, 1.58 mmol) in EtOH (15 mL) was stirred under Ar at 50 °C for 3 h (monitored by TLC: silica; EtOAc/TEA, 99:1). The EtOH was distilled off under reduced pressure and excess **2c** was removed by dissolving the residue in CH_2Cl_2 (10 mL) and stirring with satu-

rated aqueous $Na_2S_2O_5$ (0.3 mL) for 1 h. The organic phase was separated and dried with anhydrous Na_2SO_4 and then the solvent was evaporated to afford a residue consisting of the two diastereoisomers of 5-(1*H*-indol-3-ylmethyl)-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4dc**).

Reaction of Alanine Phenylhydrazide (1a) with 2,2-Dimethylpropanal (2b): A solution of **1a** (0.50 g, 2.80 mmol), **2b** (0.91 mL, 8.40 mmol) and PTSA (0.05 g, 0.28 mmol) in toluene (30 mL) was stirred under Ar at 60 °C for 6 h (monitored by TLC: silica; EtOAc). After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (10 mL) and stirred vigorously with $Na_2CO_3{\cdot}10H_2O$ (0.48 g) and H_2O (0.13 mL) for 30 min. The mixture was dried with anhydrous Na_2SO_4 and filtered and then the CH_2Cl_2 was evaporated. Removal of excess **2b** under vacuum (45 °C, 50 Pa) and trituration of the residue in pentane yielded one of the two diastereoisomers of 2-*tert*-butyl-5-methyl-3-(phenylamino)-imidazolidin-4-one (**4ab**).

Reactions of the Phenylhydrazides of Alanine (1a), Phenylalanine (1b), Leucine (1c), Tryptophan (1d) and Histidine (1e) with Acetone (2e): A solution of the appropriate L-amino acid phenylhydrazide (**1a**−**e**, 2.80 mmol) and **2e** (1.03 mL, 14.00 mmol) in EtOH (30 mL) was stirred under Ar at 50 °C for 5 h (monitored by TLC: silica; EtOAc). Evaporation of EtOH and excess **2e** under reduced pressure afforded a residue consisting of either 2,2,5-trimethyl-3-(phenylamino)imidazolidin-4-one (**4ae**), 5-benzyl-2,2-dimethyl-3-(phenylamino)imidazolidin-4-one (**4bc**), 5-isobutyl-2,2-dimethyl-3-(phenylamino)imidazolidin-4-one (**4ce**), 5-(1*H*-indol-3-ylmethyl)-2,2-dimethyl-3-(phenylamino)imidazolidin-4-one (**4dc**) or 5-(1*H*-imidazol-4-ylmethyl)-2,2-dimethyl-3-(phenylamino)imidazolidin-4-one (**4ee**) in a spectroscopically pure form.

Reactions of the Phenylhydrazides of Alanine (1a) and Phenylalanine (1b) with 2-Pentanone (2f), Acetophenone (2g) and 4-Nitroacetophenone (2h): A solution of the appropriate L-amino acid phenylhydrazide (**1a**−**b**, 2.80 mmol), ketone (**2f**−**h**, 5.60 mmol) and PTSA (0.05 g, 0.28 mmol) in toluene (30 mL) was stirred under Ar at 85 °C for 24 h (monitored by TLC: silica; EtOAc). After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (10 mL) and then stirred vigorously with $Na_2CO_3{\cdot}10H_2O$ (0.48 g) and H_2O (0.13 mL) for 30 min. The mixture was dried with anhydrous Na_2SO_4 and filtered and then the CH_2Cl_2 was evaporated. The excess ketone was removed by preparative TLC on silica gel (eluent: EtOAc) to give a mixture of the two distereoisomers of either 2,5-dimethyl-2-phenyl-3-(phenylamino)imidazolidin-4-one (**4ag**), 5-benzyl-2-methyl-3-(phenylamino)-2-propylimidazolidin-4-one (**4bf**) or 5-benzyl-2-methyl-2-(4-nitrophenyl)-3-(phenylamino)-imidazolidin-4-one (**4bh**).

1,10-Diphenyl-2-(phenylamino)-1,2,3a,4,9,10a-triazacyclopenta[*b*]-fluoren-3-one (5dc): A solution of tryptophan phenylhydrazide (**1d**, 0.44 g, 1.50 mmol) and benzaldehyde (**2c**, 0.76 mL, 4.50 mmol) in EtOH (15 mL) was stirred under Ar at 50 °C for 40 h (monitored by TLC: silica; MTBE/EtOH, 70:30). The EtOH was distilled off under reduced pressure and excess **2c** was removed by dissolving the residue in CH_2Cl_2 (10 mL) and then stirring with saturated aqueous $Na_2S_2O_5$ (2.5 mL) for 1 h. The organic phase was separated and dried with anhydrous Na_2SO_4 and then the solvent was evaporated. Spectroscopically pure product **5dc** was obtained (0.68 g, 96%). M.p. 194 °C. $[\alpha]_D = -76.0$ ($c = 0.6$, MeOH). IR (KBr): $\tilde{\nu}$ = 3340, 1635, 1605, 1500, 1460, 1410, 1330, 1310, 1270, 1230, 1060, 1050, 840, 750, 705, 650, 630 cm^{-1}. MS (70 eV): *m*/*z* (%) = 470 [M^+] (28), 335 (20), 245 (6), 244 (17), 243 (14), 232 (39), 220 (21), 219 (59), 218 (100), 217 (33), 146 (33), 93 (31), 77 (15). ^1H NMR ([D$_6$]acetone): δ = 3.00 (ddd, J_1 = 14.8, J_2 = 11.0, J_3 = 1.6 Hz, 1 H, *CHCH*H*), 3.35 (dd, J_1 = 14.8, J_2 = 4.2 Hz, 1 H, *CHC*H*H), 4.06 (dddd, J_1 = 11.0, J_2 = 4.2, J_3 = 2.4, J_4 = 0.5 Hz, 1 H, *CH), 5.00 (d, J = 2.4 Hz, 1 H, NCHNCO), 5.14 (d, J = 0.5 Hz, 1 H, $NCHC_{indole}$), 6.45−6.55 (m, 2 H, $H_{arom.}$), 6.61−6.68 (m, 1 H, $H_{arom.}$), 6.74 (s, 1 H, PhNH), 6.93−7.15 (m, 6 H, $H_{arom.}$), 7.30−7.46 (m, 7 H, $H_{arom.}$), 7.53−7.68 (m, 3 H, $H_{arom.}$), 9.72 (s, 1 H, NH_{indole}) ppm. ^1H NMR ([D$_6$]DMSO): δ = 2.94 (br. dd, J_1 = 14.4, J_2 = 11.0 Hz, 1 H, *CHCH*H*), 3.32 (dd, J_1 = 14.8, J_2 = 4.3 Hz, 1 H, *CHC*H*H), 4.01 (*app* dq, J_1 = 10.9, J_2 = 3.9, J_3 = 2.4 Hz, 1 H, *CH), 4.90 (d, J = 2.4 Hz, 1 H, NCHNCO), 5.00 (s, 1 H, $NCHC_{indole}$), 6.34−6.46 (m, 2 H, $H_{arom.}$), 6.53−6.66 (m, 1 H, $H_{arom.}$), 6.88−7.13 (m, 6 H, $H_{arom.}$), 7.19−7.30 (m, 1 H, $H_{arom.}$), 7.32−7.63 (m, 10 H, $H_{arom.}$), 7.67 (s, 1 H, PhNH), 10.62 (s, 1 H, NH_{indole}) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 23.7, 52.6, 55.8, 76.0, 107.3, 111.1, 111.8, 117.9, 118.5, 118.7, 121.1, 126.2, 128.1, 128.4, 129.2, 129.3, 129.5, 133.3, 135.3, 136.1, 136.3, 146.8, 170.2 ppm. $C_{31}H_{26}N_4O$ (470.57): calcd. C 79.12, H 5.57, N 11.91; found C 79.10, H 5.55, N 11.92.

4,5-Diphenyl-6-(phenylamino)-3,4,5,6,7a,8-hexahydro-1,3,4a,6-tetraaza-*s*-indacen-7-one (5ec): A solution of histidine phenylhydrazide (**1e**, 0.34 g, 1.40 mmol) and benzaldehyde (**2c**, 0.57 mL, 5.60 mmol) in EtOH (15 mL) was stirred at 50 °C under Ar for 15 h (monitored by TLC: silica; MTBE/EtOH, 70:30). After evaporation of the solvent under reduced pressure, the residue was triturated in hexane and filtered. Spectroscopically pure product **5ec** was obtained (0.47 g, 79%). M.p. 142 °C. $[\alpha]_D = +16.5$ ($c = 1.5$, MeOH). IR (KBr): $\tilde{\nu}$ = 3500−2760 broad, 1730, 1610, 1500, 1455, 1320, 1290, 1225, 1100, 940, 755, 705, 665 cm^{-1}. MS (70 eV): *m*/*z* (%) = 421 [M^+] (24), 196 (40), 165 (23), 194 (26), 170 (19), 169 (24), 105 (36), 104 (30), 103 (24), 93 (100), 92 (33), 91 (26), 77 (42). ^1H NMR ([D$_6$]DMSO): δ = 2.42 (dd, J_1 = 16.0, J_2 = 9.1 Hz, 1 H, *CHCH*H*), 3.18 (dd, J_1 = 15.9, J_2 = 1.1 Hz, 1 H, *CHC*H*H), 4.34 (*app* dt, J_1 = 9.1, J_2 = 1.6 Hz, 1 H, *CH), 5.07 (d, J = 2.2 Hz, 1 H, NCHNCO), 6.02−6.20 (m, 2 H, $H_{arom.}$ + $NCHC_{imidazole}$), 6.49 (s, 1 H, PhNH), 6.60−7.70 (m, 14 H, $H_{arom.}$), 7.90 (s, 1 H, $H_{imidazole}$), 8.13 (s, 1 H, $NH_{imidazole}$) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 21.9, 53.9, 70.9, 78.1, 111.8, 119.1, 122.8, 125.0, 125.9, 128.1, 128.2, 128.4, 128.6, 128.7, 129.2, 137.7, 138.3, 145.8, 146.6, 170.0 ppm. $C_{26}H_{23}N_5O$ (421.50): calcd. C 74.09, H 5.50, N 16.62; found C 74.10, H 5.53, N 16.65.

X-ray Crystallography: X-ray diffraction analysis of the sample was carried out using a Bruker-Axs three-circle diffractometer with a Smart-Apex CCD detector using graphite-monochromated Mo-K_α radiation (λ = 0.7107 Å) at 298 K. 10601 reflections were obtained up to 2θ = 59.4° from a monoclinic crystal [molecular formula $C_{38}H_{44}N_8O_6$, space group $P2_1$, a = 9.769(5), b = 22.121(9), c = 9.798(5) Å, β = 115.49(3), V = 1911.14, Z = 2, D = 1.23 g·cm^{-3}, linear absorption coefficient 0.085 mm^{-1}] of dimension 0.48 × 0.25 × 0.07 mm. Unit-cell dimensions were calculated from least-squares refinement of the d values obtained from 3136 reflections in the θ range 2−12°. Because of the low quality of the crystal from the diffraction viewpoint, the reflections with θ > 21° were considered unobserved, thus the number of unique reflections [> 2σ(I)] used to solve and refine the crystal structure was limited to 4043 (R on the equivalent reflections 0.0288). The structure was solved using the programme SHELXS-86[11] and refined with SHELXL-97[12] using the full-matrix least-squares method. The non-hydrogen atoms were refined anisotropically; the H atoms were placed in calculated positions. The final value of R on the observed reflections was 0.0648 and the value of R on all the data set was 0.0844 (R_w = 0.1539, goodness of fit = 1.071, parameters/F_o ra-

tio = 8.63). The absolute structure was fixed by comparison with a known structure. CCDC-208797 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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