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Synthesis and transformations of a pyrazole containing α,β-didehydro-α-amino acid derivatives*

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Summary. 2*H*-Pyran-2-ones **1** were transformed with various hydrazines into (*E*)- or (*Z*)-α,β-didehydro-α-amino acid (DDAA) derivatives **4** (and **7**) containing a highly substituted pyrazolyl moiety attached at the β-position. With heterocyclic hydrazines, the products **4** were accompanied also by decarboxylated enamines *E*-**6**. In order to separate (*E*/*Z*)-mixtures of acids, they were transformed to the corresponding methyl esters **9** and **10** by the application of diazomethane. Catalytic hydrogenation under high pressures with Pd/C as a catalyst resulted in the formation of racemic alanine derivatives **11**.

Key words: Amino acids – Dehydroamino acid derivatives – Esterification – Hydrogenation – Pyrazoles – Alanines

Introduction

DDAA and their derivatives can be found as constituents of various natural products and as synthetic intermediates for the preparation of optically pure amino acids (Schmidt et al., 1988; Duthaler, 1994; Kreutzfeld et al., 1996; Nagel et al., 1998). Many heterocyclic amino acid derivatives have been prepared for different reasons, for example, as potential agonists or antagonists for central glutamate receptors in connection with (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA), a bioisostere of (*S*)-glutamic acid (Bowler et al., 1997; Adlington et al., 2000; Stensbøl et al., 2002; Burkhart et al., 2001), some others as potential antibacterial agents (Stanchev et al., 2000), etc. β-Hetaryl-α,β-didehydroalanines might serve as conformationally constrained AMPA analogues and from the synthetic point of view they might be useful synthons for the novel types of AMPA congeners *via* their hydrogenation. Pyrazole derivatives are also very important biologically active compounds and synthetic intermediates (Elguero, 1984, 1996; Makino et al., 1999). Recently, we have described a synthesis of β-pyrazolyl- and β-isoxazolyl-DDAA derivatives from two 2*H*-pyran-2-one derivatives (Trebše et al., 1997; Vraničar et al., 1999 and 2002; Kočevar et al., 2001). Now we would like to report further scope and limitations of this method as well as transformation of DDAA derivatives into their esters and into substituted α-amino acid derivatives by the catalytic hydrogenation.

Results and discussion

Transformation of 2*H*-pyran-2-one derivative **1a** (Vraničar et al., 1999) with various aryl- and hetarylhydrazines **2** (R = aryl, hetaryl) led to the novel types of isomerically pure DDAA derivatives **4** containing a highly substituted β-pyrazolyl moiety (Kočevar et al., 2001). With heterocyclic hydrazines a decarboxylation to the corresponding enamines **6** also occurred (Scheme 1, Table 1). Starting from **1a** and various phenylhydrazines, containing different electron donating or electron withdrawing substituents, the isomerically pure derivatives *E*-**4** were obtained in very high yields (runs 1–4), while with *p*-methoxyphenylhydrazine (run 5) a mixture of *E*-**4e** and *E*-**7a** (R^2 = *p*-MeO-C_6H_4) in the ratio 63:37 was isolated. The reactions were carried out in a mixture of

* Dedicated with deep respect to Professor Waldemar Adam on the occasion of his 65th birthday.

Table 1. Reaction conditions and yields of products **4**, **6**, and **7**

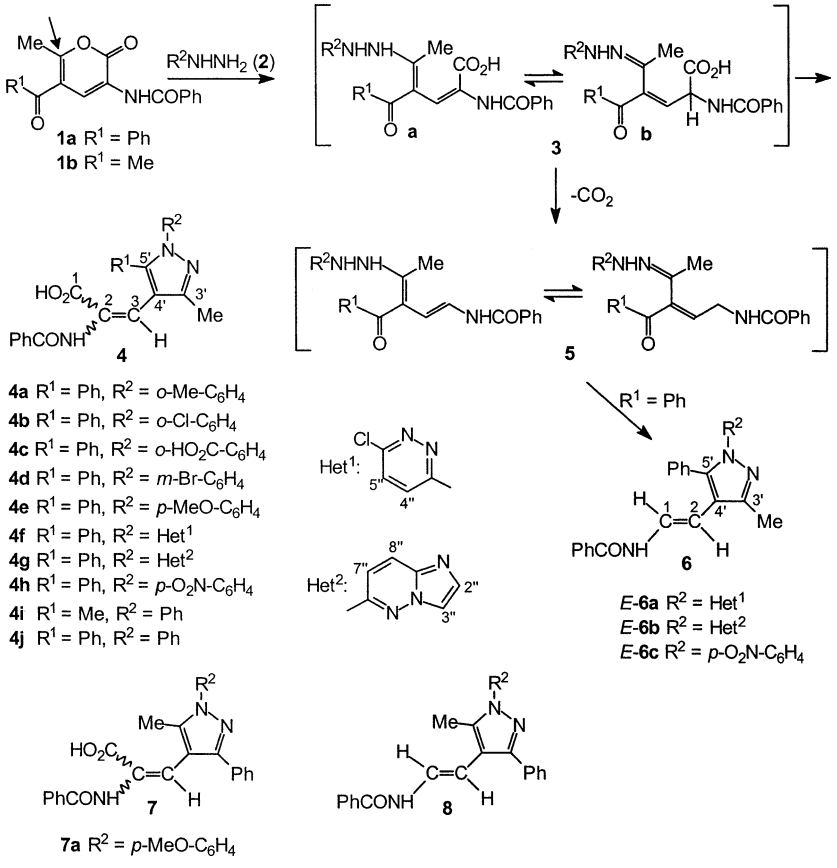
Run	SM	Reagent **2** (R^2 =)	Conditions	Products	Yield (%)[a]
1	**1a**	*o*-Me-C_6H_4[b]	EtOH/Py, 7 h, Δ (65°C)	*E*-**4a**	98
2	**1a**	*o*-Cl-C_6H_4[b]	EtOH/Py, 250 min, Δ	*E*-**4b**	98
3	**1a**	*o*-HO_2C-C_6H_4[b]	EtOH/Py, 200 min, rt	*E*-**4c**	98
4	**1a**	*m*-Br-C_6H_4[b]	EtOH/Py, 2 h, Δ	*E*-**4d**	97
5	**1a**	*p*-MeO-C_6H_4[b]	EtOH/Py, 15 min, Δ	*E*-**4e**/*E*-**7a** 63/37[c]	96
6	**1a**	Het[1]	EtOH/Py, 2 h, rt	*E*-**4f**/*Z*-**4f**/*E*-**6a** 37/37/26[c]	90
7	**1a**	Het[1]	EtOH/AcOH[d], 3 h, Δ	*E*-**4f**/*Z*-4**f**/*E*-**6a** 50/25/25[c]	97
8	**1a**	Het[2]	EtOH/Py, 25 min, Δ	*E*-**4g**/*Z*-**4g**/*E*-**6b** 78/8/14[c]	96
9	**1a**	*p*-O_2N-C_6H_4	EtOH/Py, 3 h, rt	*E*-**4h**/*Z*-**4h**/*E*-**6c** 60/13/20[c]	91[e]
10	**1b**	Ph	EtOH/Py, 2 h, Δ	*E*-**4i**	97[f]
11	**1a**	Ph	EtOH/Py, 4.5 h, rt	*E*-**4j**	96[e]

[a] Yields of isolated products are given. [b] Reagent was used as a hydrochloride. [c] Products ratio was determined on the basis of a ^{1}H NMR spectrum of the crude mixture of products. [d] EtOH (5 ml) and AcOH (0.1 ml). [e] (Vraničar et al., 2002). [f] (Vraničar et al., 1999)

ethanol and pyridine at room temperature or on heating. On the other side, with heterocyclic hydrazines (3-chloro-6-hydrazinopyridazine and 6-hydrazinoimidazo[1,2-*b*]pyridazine) the reactions became more complex and we isolated (*E/Z*)-mixtures of DDAA derivatives **4** together with enamines *E*-**6a** or *E*-**6b**, which were the products of decarboxylation (runs 6–8). Changing the reaction conditions as shown in run 7, where acetic acid was employed instead of pyridine, slightly altered the amounts of products. For comparison, previously described transformations starting from 2*H*-pyran-2-ones **1a** and **1b** with *p*-nitrophenylhydrazine and phenylhydrazine are also included in the Table 1 (runs 9–11) (Vraničar et al., 1999 and 2002). The most likely mechanism for the formation of the products of types **4** and **6** would include the tautomeric intermediate **3** (Scheme 1) resulting from the nucleophilic attack at position 6 in the 2*H*-pyran-2-one **1**. The intermediate **3** can be transformed into products *E*-**4** *via* the tautomeric form **3a** or eventually *via* **3b** (probably in addition to *Z*-**4**), but *Z*-**4** can only be formed *via* intermediate **3b**, which possesses a single bond between C-2 and C-3 allowing rotation to occur. The formation of enamines **6** can be explained by decarboxylation of the intermediate **3** giving a new tautomeric intermediate **5**, which then cyclised into the final *E*-**6**. We have shown previously that the reaction tends toward the formation of decarboxylated products under more basic conditions, where the anionic form of the carboxylic group is formed (Vraničar et al., 2002). Here (runs 6 and 7) this is not so evident, but one can note a tendency towards the formation of total amounts of *Z*-**4f** and *E*-**6a** at the cost of a lower amount of *E*-**4f** under basic conditions. The reason for the formation of the *Z*-**4** products (and also *E*-**6**) seems to be the diminished nucleophilicity of the second nitrogen in the intermediate **3**, due to the group on it, and consequently to the longer life of the intermediate **3** which is transformed to the form **3b** and into intermediate **5**.

The proposed mechanism is supported by the structure of products as determined by various techniques. It is clearly evident that the nucleophilic attack of the nitrogen-containing nucleophile at the exocyclic benzoyl moiety (Trebše et al., 1997) of the 2*H*-pyran-2-one derivative **1a** would finally result in the formation of isomeric 5-methyl-3-phenylpyrazolyl derivatives **7** and **8**, but (with the only exception of *E*-**7a**) we have not found any firm evidence for the formation of the products of these types.

The structure determination of (*E*)- and (*Z*)-DDAA derivatives **4** was based on some our previous results (Trebše et al., 1997; Vraničar et al., 1999 and 2002) and on the X-ray diffraction study (Meden et al., unpublished), which was performed for one of our compounds, namely, (*E*)-2-benzoylamino-3-[3-methyl-1-(3-methylphenyl)-5-phenyl-1*H*-pyrazol-4-yl]propenoic acid (*E*-**4**, R^1 = Ph, R^2 = *m*-Me-C_6H_4)



Scheme 1

(Vraničar et al., 2002). One can see that the orientation around the double bond in the DDAA moiety is *E* and that methyl group is attached at the position 3′ and phenyl group at the position 5′ of the pyrazolyl moiety. The structure around the C_2,C_3 double bond in derivatives **4** was also determined on the basis of their NOESY spectra, which were taken for the compound *E*-**4d** (R^1 = Ph, R^2 = *m*-Br-C_6H_4) and for the mixture of compounds *E/Z*-**4f** (R^1 = Ph, R^2 = Het[1]). In the investigated (*E*)-products we observed NOE between PhCON*H* and 3-H, while such enhancement was not observed in the case of *Z*-**4f** product. Furthermore, chemical shifts for the 3-H of the (*E*)-didehydroamino acid derivatives are in the δ range between 6.43 and 6.53 ppm, while the same signals for (*Z*)-didehydroamino acid derivatives can be found in the range between 6.81 and 6.87 ppm. The structure around the C_1,C_2 double bond in the enamine derivatives *E*-**6** was determined on the basis of the magnitude of the ^{1}H coupling constant of vinylic enamine protons (15.1 Hz) and also on the basis of the chemical shifts of vinylic protons. The chemical shifts for 2-H of the *E*-**6** are in the δ range at 6.26–6.30 ppm as shown also in our previous results (Vraničar et al., 2002).

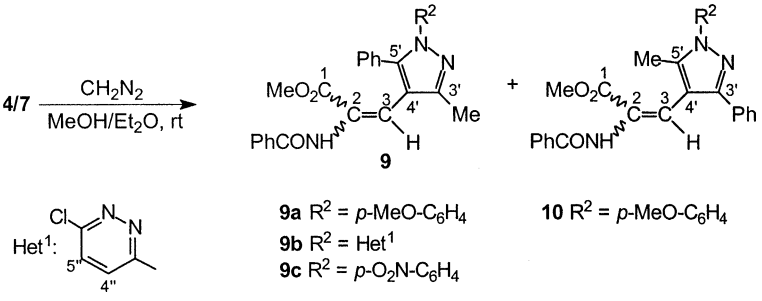
On the other hand, the pyrazole structure determination of DDAA derivatives **4** and their decarboxylated analogues **6** was not so evident. We assumed that chemical shifts for C-3′ and C-5′ in the ^{13}C spectrum (Begtrup et al., 1993) and the correlation in the two-dimensional spectrum of these carbon atoms with protons of attached methyl and phenyl groups at positions 3′ and 5′ should be relevant for the elucidation of the structure of the pyrazolyl moieties. On the basis of the previously mentioned X-ray structure determination and using the ^{1}H-^{13}C HMBC spectra, we defined the positions of signals for C-3′ and C-5′ (signal for C-3′ being shifted downfield with respect to the signal for C-5′) in all described products. Chemical shifts of C-3′ atoms in compounds **4** and **6** were found in the range at 146.8–150.3 ppm and for all C-5′ atoms at 140.2–143.1 ppm, thus supporting the same structural pattern.

In the reactions, where more than one product was obtained (runs 5–8), enamines **6** were separated from (*E/Z*)-**4** mixtures by different techniques, while

Table 2. Reaction conditions and yields of products **9** and **10**

Run	SM (R^2 =)	Conditions	Products	Yield (%)[a]
1	*E*-**4e**/*E*-**7a** (*p*-MeO-C_6H_4) 63/37	1 h, rt	*E*-**9a**/*E*-**10** 63/37[b]	69
2	*E*-**4f**/*Z*-**4f** (Het[1]) 74/26	2,5 h, rt	*E*-**9b**	22[c]
3	*E*-**4h**/*Z*-**4h** (*p*-O_2N-C_6H_4) 83/17	1 h, rt	*E*-**9c**/*Z*-**9c** 83/17[b]	71

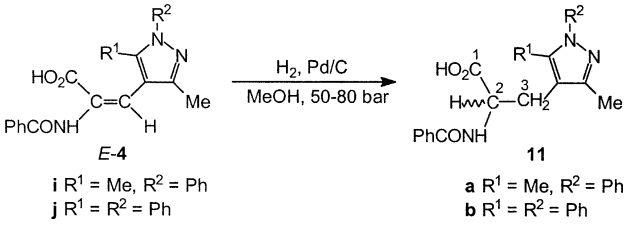
[a] Yields of isolated products are given. [b] Products ratio was determined on the basis of ^{1}H NMR spectrum of the crude mixture of products. [c] Non-optimised yield



Scheme 2

separation of *E*-**4** from *Z*-**4** with crystallisation or isolation with any kind of chromatography was, due to close R_f factors, impossible. The structures of compounds *Z*-**4f** and *Z*-**4g** were ascribed on the basis of their ^{1}H NMR, ^{13}C NMR, ^{1}H-^{13}C HMBC and ^{1}H-^{13}C HMQC spectra (recorded for all *E/Z*-mixtures), which supported the proposed structures (δ_H for 3-H within the range of 6.81–6.87 ppm and for 3′-Me within 2.15–2.17 ppm; δ_C for 3′-Me group 13.4 ppm). An analysis of ^{1}H NMR spectrum of a mixture of isomers *E*-**4e** and *E*-**7a** revealed the same chemical shifts (2.20 ppm) for 3′-Me and 5′-Me groups, but the position of 3-H proton in *E*-**7a** (6.74 ppm) was different from that in *E*-**4e** (6.43 ppm) and very close to those for *Z*-**4** isomers (6.81–6.87). ^{13}C NMR spectra of both isomers have shown larger differences. Namely, chemical shift (11.9 ppm) of the methyl carbon atom (5′-Me) of *E*-**7a** was lower from that of *E*-**4e** (3′-Me; 13.0 ppm). ^{1}H-^{13}C HMBC spectrum of *E*-**7a** revealed position of the carbon atom bearing methyl group (C-5′) at 138.3 ppm comparing to that of *E*-**4e** bearing a phenyl moiety (C-5′) at 140.6 ppm. Positions of C-3′ atoms are at 148.5 ppm (*E*-**7a**) and 146.8 ppm (*E*-**4e**). Similar data were also obtained for the corresponding esters (see below).

Since we had problems to separate *E/Z*-**4** (and *E*-**4e**/*E*-**7a**) mixtures of acids, we wanted to transform them into separable mixtures of their esters. We decided to use diazomethane (Arndt et al., 1943) for this purpose; it had been known to react with carboxylic acids to give esters, but its 1,3-dipolar cycloaddition reactions with alkenes and some other reactions had also been documented (Askai et al., 1991). Since our DDAA derivatives **4** and **7a** contained both the acid moiety and the C=C double bond which both are known to react with diazomethane, rather complex reactions might be expected (Schmidt et al., 1988; Cativiela et al., 1985; Wakamiya et al., 1986). However, by the application of excess of diazomethane and with relatively short reaction times we successfully transformed some of our (*E/Z*)-**4** and *E*-**4**/*E*-**7** acids into mixtures of their esters **9** and **10** (accompanied by traces of impurities as observed by ^{1}H NMR spectroscopy and by TLC) (Scheme 2, Table 2). The reactions were carried out with three mixtures: (*E*-**4e**/*E*-**7a** (R^1 = Ph, R^2 = *p*-MeO-C_6H_4), (*E/Z*)-**4f** (R^1 = Ph, R^2 = 6-chloropyridazin-3-yl) and with previously described (*E/Z*)-**4h** (R^1 = Ph, R^2 = *p*-O_2N-C_6H_4) (Vraničar et al., 2002). In the case of (*E/Z*)-**4f** only the main product (*E*-**9b**) was separated from the reaction mixture (run 2); in other two cases (runs 1 and 3) the corresponding esters **9** and **10** were separated on a chromatotron. The structures of esters **9** and **10** were completely analysed as previously described for the acids **4** and **7a**. NOESY, HMBC and HMQC spectra were taken for all esters and NOEs between PhCON*H*



Scheme 3

and 3-H were observed for all *E*-products (and for none of *Z*-products), while NOE between protons of the methyl group (3′-Me or 5′-Me) and group at the position 1 (R^2) was observed only in the case of product *E*-**10**, thus supporting structure *E*-**10** with the methyl group at position 5′ and all other structures with 3′-Me group. Finally, this analysis confirmed also structures of starting acids.

The third reaction we report here is the hydrogenation of the isomerically pure DDAA derivatives *E*-**4i** (Vraničar et al., 1999) and *E*-**4j** (Vraničar et al., 2002). We successfully hydrogenated them under heterogeneous conditions at pressures of hydrogen 80 or 50 bars, using 5% or 10% Pd/C as a catalyst in methanolic solutions, and isolated the racemic mixtures of substituted alanine derivatives **11** (Scheme 3). At lower pressures of hydrogen the reaction did not take place or it required longer reaction times.

Conclusions

We have presented an efficient method for the synthesis of novel types of (*E*)- and (*Z*)-DDAA derivatives containing the β-pyrazolyl moieties and have also shown the transformation into their esters as well as the hydrogenation of such compounds under heterogeneous catalytic conditions. Furthermore, we have described a useful method for the structure determination of our types of products. The NMR data reported here might also be a helpful tool for the structure determination of related types of compounds.

Materials and methods

General

Melting points were determined on a Kofler micro hot stage and are uncorrected. IR spectra, reported in cm^{-1}, were recorded with a Perkin Elmer 1310 spectrophotometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 spectrometer in DMSO-d_6 with TMS as an internal standard. ^{13}C spectra were referred on a chemical shift of DMSO-d_6 (39.5 ppm). Mass spectra, reported in units of *m/z*, were measured with a VG-Analytical AutospecQ instrument. Elemental analyses were performed with a Perkin Elmer 2400 CHN Analyzer. Thin-layer chromatography was carried out on FLUKA silica gel plates (F_{254}), column chromatography on Silica gel 60 (220–240 mesh). Merck silica gel 60 PF_{254} containing gypsum was used to prepare chromatotron plates.

General procedure for the transformation of 2H-pyran-2-one derivatives ***1*** *into DDAA derivatives* ***4a–g*** *(and* ***7a****) and the corresponding decarboxylated enamines* ***6a–b***

A mixture of the 2*H*-pyran-2-one derivative (**1**, 1 mmol) and a hydrazine (**2**, 1.1 mmol) in a mixture of absolute ethanol (4 ml) and pyridine (1 ml) or in a mixture of absolute ethanol (5 ml) and AcOH (0.1 ml) was stirred at room temperature or heated under reflux. The solvent was removed *in vacuo* and water (4 ml) was added to the residue. If not otherwise stated, the separation proceeded in the following way: the pH value of the resulting aqueous mixture was adjusted to 2 by 9% hydrochloric acid. Upon cooling the products were separated by filtration and washed with a small amount of water. Reaction conditions and yields are given in Table 1.

*(E)-2-(Benzoylamino)-3-[3-methyl-1-(2-methylphenyl)-5-phenyl-1H-pyrazol-4-yl)propenoic acid (****4a****)*

Mp 183–186°C (from EtOAc); IR (KBr) ν_{max}/cm^{-1} 1698, 1677, 1523, 1503. ^1H NMR δ 1.90 (s, 3H, *Me*-C_6H_4), 2.21 (s, 3H, Me), 6.53 (s, 1H, 3-H), 7.16 (m, 2H, C_6H_4), 7.27 (m, 7H, Ph and C_6H_4), 7.54 (m, 3H, PhCO), 7.92 (m, 2H, PhCO), 10.14 (s, 1H, NH), 12.66 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 17.1 (*Me*-C_6H_4), 113.6 (C-4′), 116.5 (C-3), 126.4, 127.6 (C-2 and C-6 of PhCO), 128.1, 128.2, 128.3, 128.4, 128.7, 129.1, 129.5, 130.6 (C_6H_4), 131.0 (C-2), 131.8 (C-4 of PhCO), 133.3 (C-1 of PhCO), 135.0 (C_6H_4), 138.8 (C_6H_4), 141.9 (C-5′), 146.8 (C-3′), 165.0 (*C*ONH), 165.7 (C-1); EIMS *m/z* 437 (M^+, 7%), 105 (100). Anal. Calcd. for $C_{27}H_{23}N_3O_3$: C, 74.13; H, 5.30; N, 9.60. Found C, 74.20; H, 5.25; N, 9.51.

*(E)-2-(Benzoylamino)-3-[1-(2-chlorophenyl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]propenoic acid (****4b****)*

Mp 179–182°C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1738, 1651 br, 1578, 1552, 1506; ^1H NMR δ 2.21 (s, 3H, Me), 6.52 (s, 1H, 3-H), 7.17 (m, 2H, Ph), 7.29 (m, 3H, Ph and C_6H_4), 7.51 (m, 7H, Ph, PhCO and C_6H_4), 7.91 (m, 2H, PhCO), 10.13 (s, 1H, NH), 12.67 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 114.0 (C-4′), 116.0 (C-3), 127.6 (C-2 and C-6 of PhCO), 127.9, 128.32, 128.38, 129.0, 129.2, 129.9, 130.4, 130.6, 131.04, 131.07 (C-2), 131.8 (C-4 of PhCO), 133.2, 137.2, 142.5 (C-5′), 147.5 (C-3′), 165.0 (*C*ONH), 165.6 (C-1) (one signal is hidden); EIMS *m/z* 457 (M^+, 4%), 100 (100). Anal. Calcd. for $C_{26}H_{20}ClN_3O_3$: C, 68.20; H, 4.40; N, 9.18. Found C, 67.95; H, 4.36; N, 9.02.

*(E)-2-(Benzoylamino)-3-[1-(2-carboxyphenyl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]propenoic acid (****4c****)*

Mp 274–276°C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1726, 1695, 1631, 1602; ^1H NMR δ 2.17 (s, 3H, Me), 6.46 (s, 1H, 3-H), 7.06 (m, 1H), 7.19 (m, 2H), 7.30 (m, 3H), 7.52 (m, 5H) and 7.76 (m, 1H) (Ph, PhCO, C_6H_4), 7.90 (m, 2H, PhCO), 10.10 (s, 1H, NH), 12.79 (br s, 2H, two OH); ^{13}C NMR δ 13.2 (Me), 114.2 (C-4′), 116.7 (C-3), 127.6 (C-2 and C-6 of PhCO), 128.1, 128.25, 128.32, 128.38, 128.43, 129.3, 129.5, 130.0, 130.2 (C-2), 130.4, 131.6, 131.8 (C-4 of PhCO), 133.3, 138.3, 141.7 (C-5′), 147.0 (C-3′), 165.0 (*C*ONH), 165.8 (C-1), 167.0 (CO_2H); EIMS *m/z* 467 (M^+, 14%), 105 (100). Anal. Calcd. for

$C_{27}H_{21}N_3O_5 \times$ EtOH: C, 67.83; H, 5.30; N, 8.18. Found C, 67.68; H, 5.02; N, 8.17.

*(E)-2-(Benzoylamino)-3-[1-(3-bromophenyl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]propenoic acid (**4d**)*

Mp >110°C decomp. (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1703, 1671 br, 1590, 1579, 1519; ^{1}H NMR δ 2.22 (s, 3H, Me), 6.44 (s, 1H, 3-H), 7.13 (m, 1H, C_6H_4), 7.26 (m, 3H, Ph and C_6H_4), 7.39–7.61 (m, 8H, Ph, PhCO and C_6H_4), 7.91 (m, 2H, PhCO), 10.15 (s, 1H, NH), 12.75 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 115.5 (C-3), 116.0 (C-4′), 121.3, 122.9, 126.7, 127.6 (C-2 and C-6 of PhCO), 128.4, 128.7, 128.8, 129.4, 129.6, 130.7, 131.3 (C-2), 131.8 (C-4 of PhCO), 133.2, 140.5, 140.7 (C-5′), 148.0 (C-3′), 165.0 (*C*ONH), 165.6 (C-1). EIMS *m/z* 503 (M$^+$ with ^{81}Br, 23%), 501 (M$^+$ with ^{79}Br, 23%), 105 (100). Anal. Calcd. for $C_{26}H_{20}BrN_3O_3$: C, 62.16; H, 4.01; N, 8.36. Found C, 62.37; H, 4.06; N, 8.66.

Run **5:** *(E)-2-(Benzoylamino)-3-[3-methyl-1-(4-methoxyphenyl)-5-phenyl-1H-pyrazol-4-yl]propenoic acid (**4e**)*

^{1}H NMR δ 2.20 (s, 3H, Me), 3.74 (s, 3H, OMe), 6.43 (s, 1H, 3-H), 6.9–8.0 (m, 14H, Ph, PhCO and C_6H_4), 10.13 (s, 1H, NH), 12.7 (br s, 1H, OH); selected data from ^{13}C NMR δ 13.0 (Me), 55.3 (OMe), 114.9 (C-4′), 116.4 (C-3), 130.7 (C-2), 140.6 (C-5′), 146.8 (C-3′), 165.0 (*C*ONH), 165.8 (C-1).

*(E)-2-(Benzoylamino)-3-[5-methyl-1-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-4-yl]propenoic acid (**7a**)*

^{1}H NMR δ 2.20 (s, 3H, Me), 3.84 (s, 3H, OMe), 6.74 (s, 1H, 3-H), 6.88–7.98 (m, 14H, Ph, PhCO and C_6H_4), 10.24 (s, 1H, NH), 12.7 (br s, 1H, OH); selected data from ^{13}C NMR δ 11.9 (Me), 55.4 (OMe), 112.8 (C-4′), 117.1 (C-3), 131.1 (C-2), 138.3 (C-5′), 148.5 (C-3′), 165.1 (*C*ONH), 165.6 (C-1). These data were obtained from the ^{1}H and ^{13}C NMR spectra of the mixture of compounds *E*-**4e** and *E*-**7a**.

Run **6:** After the addition of water (4 ml), the pH value of the resulting mixture was adjusted to 12 by 1 M NaOH. The undissolved product *E*-**6a** was separated by filtration and washed with a small amount of water. The pH value of the filtrate was then adjusted to 2 by 9% hydrochloric acid. Upon cooling the (*E*/*Z*)-mixture of products **4f** was separated by filtration and washed with a small amount of water.

*(E/Z)-2-(Benzoylamino)-3-[1-(6-chloropyridazin-3- l)-5-methyl-3-phenyl-1H-pyrazol-4-yl]propenoic acid (**4f**)*

(E)-isomer – ^{1}H NMR δ 2.25 (s, 3H, Me), 6.45 (s, 1H, 3-H), 7.26–7.62 (m, 8H, Ph and PhCO), 7.91 (m, 2H, PhCO), 8.06 (d, 1H, *J* 9.4 Hz, 4″-H), 8.11 (d, 1H, *J* 9.4 Hz, 5″-H), 10.18 (s, 1H, NH), 12.7 (br s, 1H, OH); selected data from ^{13}C NMR δ 12.9 (Me), 114.7 (C-3), 118.0 (C-4′), 141.5 (C-5′), 150.3 (C-3′), 165.5 (C-1). *(Z)-isomer* – ^{1}H NMR: δ 2.15 (s, 3H, Me), 6.81 (s, 1H, 3-H), 7.26–7.62 (m, 8H, Ph and PhCO), 7.91 (m, 2H, PhCO), 8.05 (d, 1H, *J* 9.4 Hz, 4″-H), 8.14 (d, 1H, *J* 9.4 Hz, 5″-H), 9.85 (s, 1H, NH), 12.7 (br s, 1H, OH); selected data from ^{13}C NMR δ 13.4 (Me), 117.4 (C-4′), 122.1 (C-3), 143.0 (C-5′), 149.8 (C-3′), 165.7 (C-1). These data were obtained from the ^{1}H and ^{13}C NMR spectra of the mixture of compounds *E*-**4f** and *Z*-**4f**.

*N-{(E)-2-[1-(6-Chloro-3-pyridazin-6-yl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]ethenyl}benzamide (**6a**)*

Mp 164–166°C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1642, 1600, 1562, 1545; ^{1}H NMR δ 2.49 (s, 3H, Me), 6.26 (d, 1H, *J* 15.1 Hz, 2-H), 7.29–7.60 (m, 9H, 1-H, Ph and PhCO), 7.92 (m, 2H, PhCO), 8.02 (d, 1H, *J* 9.4 Hz, 4″-H), 8.10 (d, 1H, *J* 9.4 Hz, 5″-H), 10.50 (d, 1H, *J* 10 Hz, NH); ^{13}C NMR δ 14.5 (Me), 103.1 (C-2), 118.6 (C-4′), 124.8 (C-1), 125.4 (C-5″), 127.6 (C-2 and C-6 of PhCO), 128.54, 128.55, 129.9, 130.3 (C-4″), 131.1, 132.0, 133.3, 140.3 (C-5′), 148.9 (C-3′), 154.0 (C-3″), 154.9 (C-6″), 163.8 (*C*ONH) (one signal is hidden); EIMS *m/z* 415 (M$^+$, 24%), 105 (100). HRMS Calcd. for $C_{23}H_{18}ClN_5O$: 415.1199. Found: 415.1209. Anal. Calcd. for $C_{23}H_{18}ClN_5O \times 0.5\ H_2O$: C, 65.02; H, 4.51; N, 16.48. Found C, 65.33; H, 4.42; N, 16.34.

Run **8:** The mixture of compounds (*E*/*Z*)-**4g** and *E*-**6b** was separated by column chromatography (chloroform/methanol 25:1) to give pure *E*-**6b** and a mixture (*E*/*Z*)-**4g**. (*E*)-isomer was obtained after crystallization of the mixture of compounds (*E*/*Z*)-**4g** from EtOAc/EtOH.

*(E/Z)-2-(Benzoylamino)-3-[1-(imidazo[1,2-b]pyridazin-6-yl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]propenoic acid (**4g**)*

(E)-isomer; mp 138–140°C; IR (KBr) ν_{max}/cm^{-1} 1717, 1650 br, 1542, 1522; ^{1}H NMR δ 2.26 (s, 3H, Me), 6.49 (s, 1H, 3-H), 7.30 (m, 2H, Ph), 7.38 (m, 3H, Ph), 7.51 (m, 3H, 7″-H and PhCO), 7.59 (m, 1H, PhCO), 7.75 (d, *J* 1 Hz, 1H, 2″-H), 7.91 (m, 3H, 3″-H and PhCO), 8.24 (dd, 1H, J_1 9.6 Hz, J_2 0.7 Hz, 8″-H), 10.19 (s, 1H, NH), 12.84 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 114.88 and 114.94 (C-3 and C-7″), 117.1 and 117.3 (C-4′ and C-3″), 127.2 (C-8″), 127.6 (C-2 and C-6 of PhCO), 128.38, 128.43, 128.6, 129.38, 129.45, 131.9 (C-4 of PhCO), 132.2 (C-2), 133.1, 134.5 (C-2″), 137.3 (C-8a″), 141.5 (C-5′), 147.8 (C-6″), 149.5 (C-3′), 165.0 (*C*ONH), 165.5 (C-1); EIMS *m/z* 464 (M$^+$, 10%), 105 (100). Anal. Calcd. for $C_{26}H_{20}N_6O_3$: C, 67.23; H, 4.34; N, 18.09. Found C, 67.15; H, 4.27; N, 17.95. ^{1}H NMR data of *(Z)-isomer* were obtained from spectrum of the crude (*E*/*Z*)-mixture: δ 2.17 (s, 3H, Me), 6.87 (s, 1H, 3-H), 7.23–8.30 (m, 14H, Ph, PhCO, 2″-H, 3″-H, 7″-H, 8″-H), 9.81 (s, 1H, NH), 12.8 (br s, 1H, OH); selected data from ^{13}C NMR δ 13.4 (Me), 116.7 (C-4′), 124.7 (C-3), 143.1 (C-5′), 149.3 (C-3′).

*N-{(E)-2-[1-(imidazo[1,2-b]pyridazin-6-yl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]ethenyl}benzamide (**6b**)*

Mp 188–190°C; IR (KBr) ν_{max}/cm^{-1} 1672, 1646, 1558, 1541; ^{1}H NMR δ 2.49 (s, 3H, Me), 6.30 (d, 1H, *J* 15.1 Hz, 2-H), 7.32–7.60 (m, 10H, 7″-H, 1-H, Ph and PhCO), 7.73 (d, 1H, *J* 1.1 Hz, 2″-H), 7.81 (deg dd, 1H, 3″-H), 7.93 (m, 2H, PhCO), 8.20 (dd, 1H, J_1 9.6 Hz, J_2 0.7 Hz, 8″-H), 10.50 (d, 1H, *J* 9.4 Hz, NH); ^{13}C NMR δ 14.3 (Me), 103.0 (C-2), 114.7, 117.1, 117.7 (C-4′), 124.6 (C-1), 127.0, 127.5, 128.36, 128.45, 128.5, 129.84, 129.87, 131.7, 133.2, 134.3, 137.2 (C-8a″), 140.2 (C-5′), 147.7 (C-3′), 147.9 (C-6″), 163.5 (*C*ONH); EIMS *m/z* 420 (M$^+$, 70%), 105 (100). HRMS Calcd. for $C_{25}H_{20}N_6O$: 420.1698. Found: 420.1702.

*General procedure for the synthesis of DDAA methyl esters **9a–c** and **10***

Diazomethane (~7 mmol) in 14 ml of diethyl ether was added dropwise into the stirred suspension of the (*E*/*Z*) mixture of DDAA derivatives (0.5 mmol of mixtures **4e/7a**, **4f** or **4h**) in 6 ml of MeOH. After stirring at room temperature the reaction mixture was evaporated under reduced pressure. The reaction conditions and yields are given in Table 2.

Run **1:** The mixture of *E*-**9a**/*E*-**10** was separated on a chromatotron (petroleum ether/EtOAc 3:1) to give isomerically pure esters.

*Methyl (E)-2-(benzoylamino)-3-[3-methyl-1-(4-methoxyphenyl)-5-phenyl-1H-pyrazol-4-yl]propenoate (**9a**)*

Mp 88–90°C (from MeOH); IR (KBr) ν_{max}/cm^{-1} 1728, 1672, 1561; ^{1}H NMR δ 2.15 (s, 3H, Me), 3.50 (s, 3H, CO_2Me), 3.74 (s, 3H, MeO), 6.43 (s, 1H, 3-H), 6.89 (m, 2H, C_6H_4), 7.13 (m, 4H) and 7.36 (m, 3H) (Ph, C_6H_4), 7.50 (m, 2H, PhCO), 7.59 (m, 1H, PhCO), 7.90 (m, 2H, PhCO), 10.34 (s, 1H, NH); ^{13}C NMR δ 12.5 (Me), 51.7 (CO_2Me), 55.3 (MeO), 113.9 and 114.0 (C-4′ and Ph), 116.3 (C-3), 126.2, 127.6 (C-2 and C-6 of PhCO), 128.4, 128.5, 129.5, 129.6, 132.0, 132.5, 132.8, 140.8 (C-5′), 146.6 (C-3′), 158.1 (C_6H_4), 164.6 (C-1), 165.0 (*C*ONH) (two signals are hidden); EIMS *m/z* 467 (M$^+$, 36%), 105 (100). HRMS Calcd. for $C_{28}H_{25}N_3O_4$: 467.1845. Found: 467.1859.

*Methyl (E)-2-(benzoylamino)-3-[5-methyl-1-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-4-yl]propenoate (**10**)*

Mp 188–189°C (from EtOAc/petroleum ether); IR (KBr) ν_{max}/cm^{-1} 1731, 1710, 1666; ^{1}H NMR δ 2.19 (s, 3H, Me), 3.49 (s, 3H, CO_2Me), 3.84 (s, 3H, MeO), 6.72 (s, 1H, 3-H), 7.11 (m, 2H, C_6H_4), 7.31–7.65 (m, 8H) and 7.72 (m, 2H) (Ph, PhCO and C_6H_4), 7.97 (m, 2H, PhCO), 10.45 (s, 1H, NH); ^{13}C NMR δ 11.5 (Me), 51.7 (CO_2Me), 55.4 (MeO), 112.2 (C-4′), 114.3, 117.2 (C-3), 126.1, 127.1, 127.66, 127.68, 128.43, 128.44, 129.9, 132.0, 132.2, 132.9, 133.3, 138.3 (C-5′), 148.6 (C-3′), 158.6, 164.6 (C-1), 165.2 (*C*ONH); EIMS *m/z* 467 (M$^+$, 41%), 105 (100). Anal. Calcd. for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found C, 71.96; H, 5.42; N, 8.63.

Run **2:** MeOH (4 ml) was added to the solid material after evaporation followed by cooling and filtering off the precipitated product *E*-**9b**.

*Methyl (E)-2-(benzoylamino)-3-[1-(6-chloropyridazin-3-yl)-3-methyl-5-phenyl-1H-pyrazol-4-yl]propenoate (**9b**)*

Mp 216–219°C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1730, 1637, 1543, 1526; ^{1}H NMR δ 2.22 (s, 3H, Me), 3.52 (s, 3H, OMe), 6.43 (s, 1H, 3-H), 7.25 (m, 2H, Ph), 7.38 (m, 3H, Ph), 7.51 (m, 2H, PhCO), 7.60 (m, 1H, PhCO), 7.91 (m, 2H, PhCO), 8.06 (d, 1H, *J* 9.4 Hz, 4″-H), 8.14 (d, 1H, *J* 9.4 Hz, 5″-H), 10.42 (s, 1H, NH); ^{13}C NMR δ 12.5 (Me), 51.8 (OMe), 114.8 (C-3), 117.1 (C-4′), 125.7 (C-5″), 127.7 (C-2 and C-6 of PhCO), 128.3, 128.4, 129.3, 129.7, 131.16, 131.24, 132.1 (C-4 of PhCO), 132.7, 141.7 (C-5′), 150.0 (C-3′), 154.2 (C-6″), 154.9 (C-3″), 164.4 (C-1), 165.1 (*C*ONH) (one signal is hidden); EIMS *m/z* 473 (M$^+$, 3%), 105 (100). Anal. Calcd. for $C_{25}H_{20}ClN_5O_3$: C, 63.36; H, 4.25; N, 14.78. Found C, 63.28; H, 4.15; N, 14.84.

Run **3:** The mixture of esters (*E/Z*)-**9c** was separated on a chromatotron (petroleum ether/EtOAc 3:1) to give isomerically pure esters.

*Methyl (E/Z)-2-(benzoylamino)-3-[3-methyl-1-(4-nitrophenyl)-5-phenyl-1H-pyrazol-4-yl]propenoate (**9c**)*

(E)-isomer – Mp 203–205°C (from MeOH); IR (KBr) ν_{max}/cm^{-1} 1735, 1656, 1641, 1596, 1521; ^{1}H NMR δ 2.21 (s, 3H, Me), 3.51 (s, 3H, OMe), 6.44 (s, 1H, 3-H), 7.25 (m, 2H, Ph), 7.47 (m, 7H, Ph, PhCO and C_6H_4), 7.59 (m, 1H, PhCO), 7.91 (m, 2H, PhCO), 8.20 (m, 2H, C_6H_4), 10.40 (s, 1H, NH); ^{13}C NMR δ 12.5 (Me), 51.8 (OMe), 114.9 (C-3), 116.4 (C-4′), 124.2 (C_6H_4), 124.5 (C_6H_4), 127.7 (C-2 and C-6 of PhCO), 128.4 (C-3 and C-5 of PhCO), 128.96, 129.04, 129.1, 129.6, 130.8 (C-2), 132.0 (C-4 of PhCO), 132.7 (C-1 of PhCO), 141.1 (C-5′), 144.1 (C_6H_4), 145.2 (C_6H_4), 149.0 (C-3′), 164.4 (C-1), 165.1 (*C*ONH); EIMS *m/z* 482 (M$^+$, 9%), 105 (100); Anal. Calcd. for $C_{27}H_{22}N_4O_5$: C, 67.21; H, 4.60; N, 11.61. Found C, 66.93; H, 4.45; N, 11.63. *(Z)-isomer* – Mp 202–203°C (from EtOAc/petroleum ether); IR (KBr) ν_{max}/cm^{-1} 1724, 1638, 1596, 1519; ^{1}H NMR δ 2.16 (s, 3H, Me), 3.67 (s, 3H, OMe), 6.82 (s, 1H, 3-H), 7.27 (m, 2H, Ph), 7.37–7.61 (m, 8H, Ph, PhCO and C_6H_4), 7.89 (m, 2H, PhCO), 8.19 (m, 2H, C_6H_4), 9.90 (s, 1H, NH); ^{13}C NMR δ 13.3 (Me), 52.1 (OMe), 116.3 (C-4′), 122.1 (C-3), 124.3, 124.5, 127.7, 128.2, 128.3, 128.8, 129.0, 129.4, 129.5, 131.9, 133.0, 142.6 (C-5′), 143.8, 145.3, 149.0 (C-3′), 164.9 (C-1), 165.6 (*C*ONH); EIMS *m/z* 482 (M$^+$, 17%), 105 (100); Anal. Calcd. for $C_{27}H_{22}N_4O_5$: C, 67.21; H, 4.60; N, 11.61. Found C, 67.04; H, 4.72; N, 11.34.

*General procedure for the hydrogenation of DDAA derivatives E-**4i** and E-**4j***

The catalyst (60 mg 5% Pd/C for *E*-**4i**, 40 mg 10% Pd/C for *E*-**4j**) was added under an argon atmosphere to a suspension of a DDAA derivative *E*-**4** (1 mmol) in MeOH (30 ml); the reaction vessel was evacuated and filled with hydrogen gas. The reaction mixture was vigorously stirred at room temperature, and then (after 6 days with *E*-**4i** or after 7 days with *E*-**4j**) it was filtered through a column of Florisil and Celite. The solvent was evaporated *in vacuo* and water (5 ml) was added to the residue. The pH value of the resulting mixture was adjusted to 2 by 9% hydrochloric acid. Upon cooling the products were separated by filtration and washed with a small amount of water. Yields: **11a** (81%), **11b** (95%).

*2-(Benzoylamino)-3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)propanoic acid (**11a**)*

Mp 118–121°C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1733, 1643, 1539; ^{1}H NMR δ 2.18 (s, 3H, Me), 2.23 (s, 3H, Me), 2.91 (dd, 1H, $J_{3A,3B}$ 14 Hz, $J_{3A,2}$ 9 Hz, CH_2), 3.01 (dd, 1H, $J_{3A,3B}$ 14 Hz, $J_{3B,2}$ 6 Hz, CH_2), 4.52 (m, 1H, C*H*), 7.43 (m, 8H, Ph and PhCO), 7.85 (m, 2H, PhCO), 8.69 (d, 1H, *J* 7.9 Hz, NH), 12.71 (br s, 1H, OH); ^{13}C NMR δ 10.9, 11.8, 25.3, 53.3, 114.1, 124.0, 126.7, 127.3, 128.3, 129.0, 131.3, 133.9, 136.9, 139.7, 147.4, 166.3, 173.1; EIMS *m/z* 363 (M$^+$, 0.5%), 185 (100). Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found C, 69.28; H, 5.79; N, 11.48.

*2-(Benzoylamino)-3-(3-methyl-1,5-diphenyl-1H-pyrazol-4-yl)propanoic acid (**11b**)*

Mp 93–95°C (from EtOH/H_2O); IR (KBr) ν_{max}/cm^{-1} 1722, 1700, 1676 br, 1599; ^{1}H NMR δ 2.28 (s, 3H, Me), 2.88 (dd, 1H, $J_{3A,3B}$ 14 Hz, $J_{3A,2}$ 9 Hz, CH_2), 3.02 (dd, 1H, $J_{3A,3B}$ 14 Hz, $J_{3B,2}$ 6 Hz, CH_2), 4.43 (m, 1H, C*H*), 7.09 (m, 2H, Ph), 7.25 (m, 8H, Ph), 7.48 (m, 3H, PhCO), 7.79 (m, 2H, PhCO), 8.52 (d, 1H, *J* 7.8 Hz, NH), 12.62 (br s, 1H, OH); ^{13}C NMR δ 12.1, 25.3, 53.4, 115.6, 123.9, 126.4, 127.3, 128.2, 128.3, 128.5, 128.6, 129.8, 130.4, 131.3, 133.8, 139.7, 141.0, 148.1, 165.9, 173.0; FABMS *m/z* 426 (M$^+$ +1). HRMS Calcd. for $C_{26}H_{23}N_3O_3$: 425.1739. Found: 425.1755. Anal. Calcd. for $C_{26}H_{23}N_3O_3$ × 0.5 EtOH: C, 72.30; H, 5.84; N 9.37. Found C, 72.55; H, 5.57; N 9.00.

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