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2*H*-Pyran-2-ones as Synthons for (*E*)-α,β-Didehydroamino Acid Derivatives

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Abstract

2*H*-Pyran-2-ones with the defined (*E*)-structure of a α,β-didehydroamino acid unit were used as synthons for a series of configurationally stable (*E*)-α,β-didehydroamino acid derivatives containing a benzoyl protected amino function and a pyrazolyl residue. They were derived from 2*H*-pyran-2-ones and hydrazines under various reaction conditions. A possibility of the formation of (*Z*)-isomers from the above-mentioned precursors is also discussed.

Keywords: Amino acids and derivatives; Pyrazoles; Isomerisation; NMR

Dehydroamino acids and their derivatives play an important role as constituents of various natural products and as synthetic intermediates.[1] Amongst others, they are valuable synthons for the preparation of optically pure amino acids.[2] For this reason their isolation from natural sources[1] as well as their synthesis have attracted much attention.[3] α,β-Didehydroamino acid derivatives in the defined pure isomeric form can be prepared by various methods, though some of them result in *E*/*Z* mixtures of isomers. The synthesis of pure (*Z*)-isomers can be performed easier and with higher yields than the synthesis of their (*E*)-analogs, most probably due to higher thermodynamic stability of the former.[1,3] It is well-known that esters of (*E*)-α,β-didehydroamino acid derivatives can be transformed into the (*Z*)-esters under either acidic[3a,h,i] or basic[3g,h] conditions, by radical processes[3h] or by illumination.[3d,e,f] *E*→*Z* Isomerisation occurred even during homogenous catalytic hydrogenation of (*E*)-2-(acylamino)propenoic acid derivatives with chiral rhodium-phosphine catalysts.[2b,c] This can be avoided by the use of THF[2b] or benzene[2c] as solvents. However, (*Z*)-isomers seem to be better substrates for the synthesis of enantiomerically pure amino acids, but there are also efficient methods for their formation from (*E*)-isomers.[2a-c] For this reason, (*E*)-didehydroamino acid derivatives are highly important compounds as well. The most frequently used method for their synthesis was the cleavage of (*E*)-arylmethylene-5(4*H*)-oxazolones, but yields were higher for (*Z*)-isomers.[1a,3b] Elimination of water from appropri-

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ately substituted β-hydroxy-α-amino acid derivatives is the second general method for the synthesis of pure (*E*)-isomers.[1,3g,i] Recently, a conversion of *N*-(5-acetyl-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (**1**) with a heterocyclic hydrazine under acidic conditions into (*E*)-*N*-[5-[1-[(imidazo[1,2-*b*]pyridazin-6-yl)hydrazono]-ethyl]-6-methyl-2-oxo-2*H*-pyran-3-yl]benzamide and further into (*E*)-2-(benzoylamino)-3-[1-(imidazo[1,2-*b*]-pyridazin-6-yl)-3,5-dimethyl-1*H*-pyrazol-4-yl]propenoic acid (*E*-**4e**) under basic conditions was described.[4]

We report here a novel synthesis of isomerically pure (*E*)-α,β-didehydroamino acid derivatives **4**, accompanied in one case by isomeric product **5**, starting from 2*H*-pyran-2-one derivatives **1**–**2** and various hydrazines **3**. A brief investigation towards (*Z*)-analogs of the above-mentioned compounds is also discussed. 2*H*-Pyran-2-ones are known to react with nitrogen-containing nucleophiles either at a side chain or by opening of the pyran-2-one ring and the acyclic products may cyclize again to give the corresponding pyridin-2(1*H*)-ones, pyrazoles or other rings.[5] In our case, pyran derivatives **1**[6] and **2**,[7] containing a masked (*E*)-α,β-didehydroamino acid unit, were transformed in high yields into (*E*)-products **4** and **5** (Scheme 1, Table 1). Reactions were performed under basic conditions in a mixture of ethanol and pyridine, which gave much higher yields of the desired products than the previously used mixture of ethanol, water and triethylamine for the transformation of a hydrazone precursor into product *E*-**4e**.[4] For the synthesis of the pure product *E*-**4h** the employment of ethanol as a solvent is advantageous, since in the mixture of ethanol and pyridine we obtained products *E*-**4h** and *Z*-**4h** in the ratio 87:13. The application of a mixture of ethanol, water and triethylamine as a solvent resulted in a 1:1 mixture of both products. Similarly, in toluene and triethylamine as the solvent and under argon atmosphere (run 11) both products were obtained again. In the reaction between compound **2** and benzyl hydrazine two products were isolated, namely *E*-**4k** and *E*-**5**. Several attempts to prepare pure isomers **4k** or **5** failed (runs 15-18).

The structure of products was determined on the basis of NOESY spectra. In the case of (*E*)-products we observed NOE between PhCON*H* and 3-H, while this enhancement was not observed in the case of *Z*-**4h**. Furthermore, chemical shifts for 3-H of all (*E*)-products are in narrow δ ranges (6.53 –6.71). Chemical shift for 3-H of product *Z*-**4h** shows a downfield shift of 0.45 ppm with respect to *E*-**4h**. This data is in disagreement with many previously described data for α,β-didehydroamino acids and esters containing alkyl moieties, but is in agreement with those for derivatives containing aryl or heterocyclic moieties.[3b,d,g,4] The structure of the pyrazole moiety of products **4j**, **4k** and **5** was determined on the basis of the NOE between substituents at positions 1 and 5 in the pyrazole ring.[8]

Based on the results obtained, the following reaction pathways can be postulated. In the starting material (**1** or **2**) three nucleophilic attacks might occur, namely (a), (b) or (c) (Scheme 2). Since we did not obtain pyridinones of types **7** or **8**, the attack of the hydrazine reagent at position 2 in the pyran-2-one ring is excluded. Attack (b) would result in the formation of the intermediate **9**, which would further give exclusively *E*-**4** if pyran-2-one ring was not opened to give intermediate **11**. The latter could be transformed into *E*-**4**, but also to *Z*-**4** via **11b**. However, the formation of product **5** cannot be explained by intermediate **11**. Further-

Scheme 1

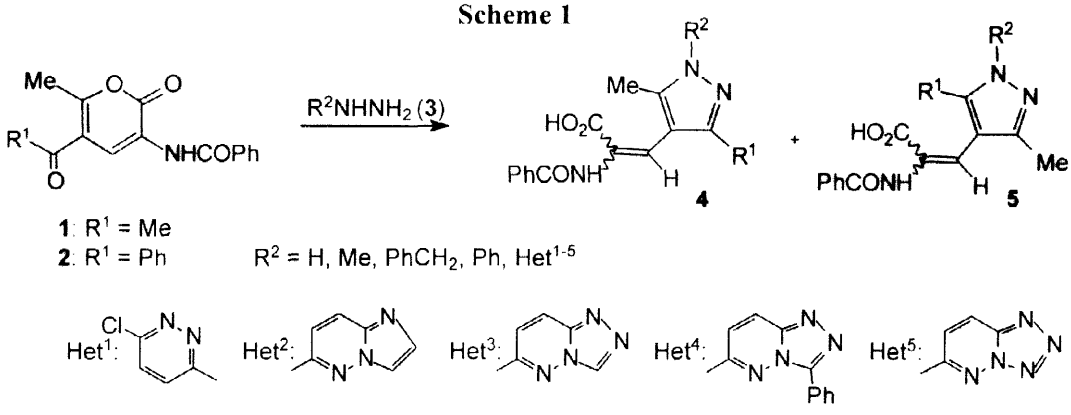


Table 1

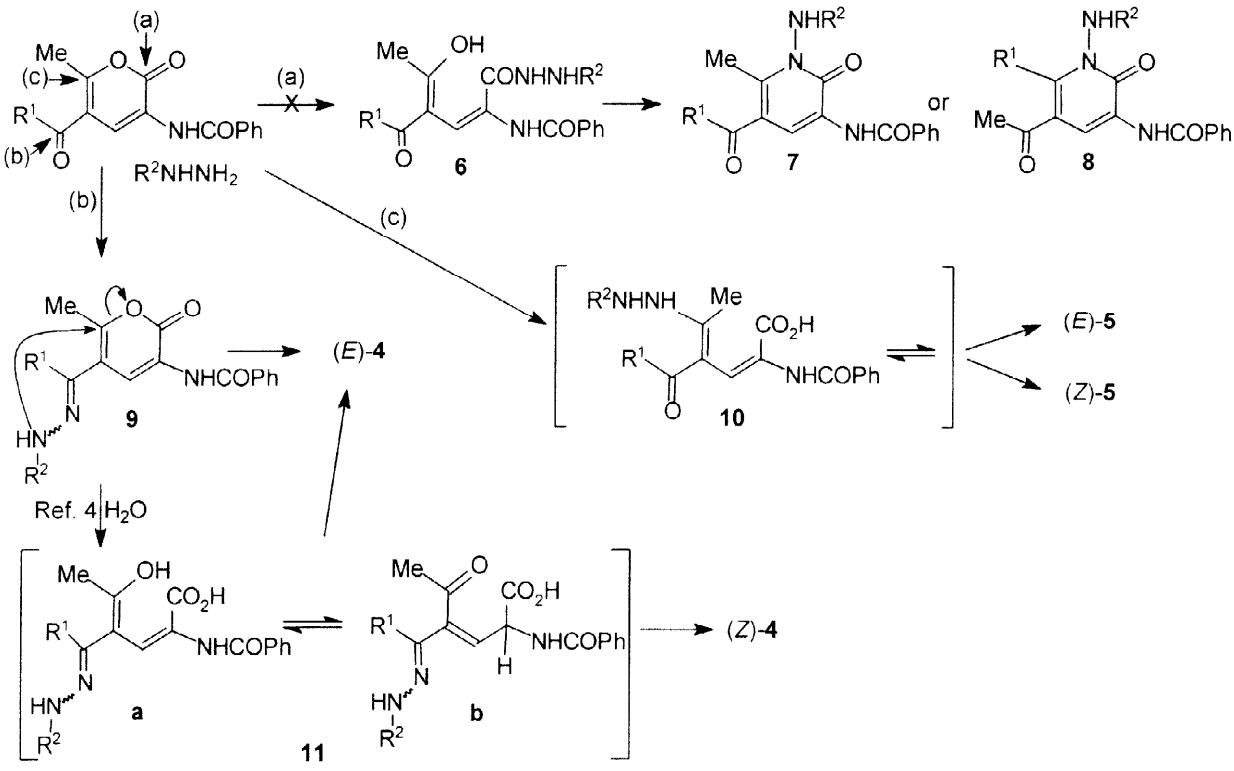
Reaction Conditions and Yields of Products **4** and **5**

Run	SM	Substrate **3** (R^2=)	Conditions	Product (yield, %)[a]
1	**1**	H	EtOH/Py, 70 min, rt	*E*-**4a** (96)
2	**1**	$PhCH_2$[b]	EtOH/Py, 7 h, Δ	*E*-**4b** (96)
3	**1**	Ph	EtOH/Py, 2 h, Δ	*E*-**4c** (97)
4	**1**	Het[1]	EtOH/Py, 1 h, rt	*E*-**4d** (99)
5	**1**	Het[2]	EtOH/Py, 1 h, Δ	*E*-**4e** (92)
6	**1**	Het[3]	EtOH/Py, 2.5 h, Δ	*E*-**4f** (93)
7	**1**	Het[4]	EtOH/Py, 0.5 h, Δ	*E*-**4g** (86)
8	**1**	Het[5]	EtOH, 6 h, Δ	*E*-**4h** (97)
9	**1**	Het[5]	EtOH/Py, 190 min, Δ	**4h** (93); *E*/*Z* 87/13[c]
10	**1**	Het[5]	$EtOH/H_2O/Et_3N$,[d] 6 h, Δ	**4h** (98); *E*/*Z* 1/1[c]
11	**1**	Het[5]	Ph-Me/Et_3N,[e] 6h, Δ	**4h** (79); *E*/*Z* 77/23[c]
12	**2**	H	EtOH/Py, 100 min, rt	*E*-**4i** (78)
13	**2**	Me	EtOH/Py, 15 min, rt	*E*-**4j** (94)
14	**2**	$PhCH_2$[b]	EtOH/Py, 7 h, Δ	*E*-**4k**/*E*-**5** 56/44 (96)[c,f]
15	**2**	$PhCH_2$[b]	EtOH/DABCO,[g] 8 h, rt	*E*-**4k**/*E*-**5** 59/41 (87)[c]
16	**2**	$PhCH_2$[b]	EtOH/1 M NaOH,[h] 5 h, rt	*E*-**4k**/*E*-**5** 63/37 (82)[c]
17	**2**	$PhCH_2$[b]	CH_2Cl_2/DABCO,[i] 5.5 h, Δ	*E*-**4k**/*E*-**5** 77/23 (96)[c]
18	**2**	$PhCH_2$[b]	CH_2Cl_2/Py,[j] 14.5 h, Δ	*E*-**4k**/*E*-**5** 66/34 (93)[c]

[a]Yields of isolated products are given. [b]Benzylhydrazine dihydrochloride was used. [c]*E*/*Z* ratio was determined on the basis of ^1H NMR spectrum of the crude mixture of products. [d]EtOH (2 mL), H_2O (2 mL) and Et_3N (1 mL). [e]Ph-Me (4 mL) and Et_3N (1 mL); under argon atmosphere. [f]Products were separated by column chromatography ($CHCl_3$/MeOH 10:1 as eluent). [g]EtOH (4 mL) and 269 mg (2.4 mmol of 1,4-diazabicyclo[2.2.2]octane. [h]EtOH (4 mL) and 1 M NaOH (3 mL). [i]CH_2Cl_2 (4 mL) and 269 mg (2.4 mmol of DABCO. [j]CH_2Cl_2 (4 mL) and pyridine (1 mL).

more, for the formation of product **4h**, we performed several experiments under conditions where water was excluded from the reaction mixture and obtained again product *Z*-**4h** together with *E*-**4h**. On the other hand, starting from **1** and 6-hydrazinotetrazolo[1,5-*b*]pyridazine we prepared a product of type **9** under acidic conditions,[4] which remained unchanged under conditions used for the synthesis of **4h** from **1** and the hydrazine derivative (runs 8 and 9). An attempt to transform compound *E*-**4h** into *Z*-**4h** under the same conditions as required for their synthesis (run 10) resulted in the recovery of the starting *E*-**4h** in 84% yield. On the basis of the described experiments, pathway (c) and intermediate **10** should be postulated for the formation of product **5** and possibly also for the formation of at least some of products **4** from starting compound **1**. The fact that we did not observe the formation of (*Z*)-isomers in other cases might be explained by the assumption that intermediates **10** and **11** have not been transformed into the tautomer possessing a single bond between C-2 and C-3, where the rotation could occur (like in **11b**), as the formation of (*E*)-product seems to be faster process.

Scheme 2



In conclusion, we have developed a novel and very efficient method for the synthesis of (*E*)-α,β-didehydroamino acid derivatives and have shown its limitation for the synthesis of (*Z*)-isomers.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. Proton and carbon NMR spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 spectrometer in DMSO-d_6 with TMS as an internal standard. IR spectra, reported in cm^{-1}, were recorded with a Perkin Elmer 1310 spectrophotometer. Mass spectra, reported in units of m/z, were obtained with a VG-Analytical AutospecQ instrument. Elemental analysis (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. TLC was carried out on FLUKA silica gel plates (F_{254}). Column chromatography was performed using Silica gel 60 (220-240 mesh). Toluene and triethylamine were distilled from P_4O_{10} and stored over molecular sieves (toluene) or KOH (triethylamine). 2*H*-Pyran-2-one derivative **1**,[6] 3-chloro-6-hydrazinopyridazine,[9a] 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine,[9b] 6-hydrazinotetrazolo[1,5-*b*]pyridazine[9b] and 6-hydrazino-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine[9c] were prepared as described in the literature. 2*H*-Pyran-2-one **2** was prepared by a known method.[7] Other solvents and reagents were used as received from commercial sources.

General Procedure. A mixture of the pyran-2-one derivative (**1** or **2**, 1 mmol) and a hydrazine **3** (1.1 mmol) in a mixture of absolute ethanol (4 mL) and pyridine (1 mL) or other solvent was stirred at room temperature or heated under reflux. The solvent was removed *in vacuo* and water (4 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. Reaction conditions and yields are given in Table 1. Products **4d**, **4f** and **4g** were obtained as light yellow solids, **4c** was light pink. All other products were isolated as white solids.

Analytical and Spectroscopic Data of Compounds 4 and 5:

(*E*)-2-(Benzoylamino)-3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4a): mp 132–135 °C (EtOAc/EtOH); ^{1}H NMR δ 2.08 (s, 6H, two Me), 6.53 (s, 1H, 3-H), 7.55 (m, 3H, Ph), 7.93 (m, 2H, Ph), 10.12 (s 1H, NH), 12.35 (br s, 1H, OH); ^{13}C δ 11.6, 111.2, 118.5, 127.6, 128.0, 128.5, 131.8, 133.5, 142.0, 165.2, 166.3; IR 1680 br, 1650, 1610; MS 285 (M^+, 20), 105 (100). Anal. Calcd for $C_{15}H_{15}N_3O_3 \cdot 0.5\ H_2O$: C, 61.22; H, 5.48; N, 14.28. Found: C, 61.59; H, 5.83, N, 14.52.

(*E*)-2-(Benzoylamino)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4b): mp 198–200 °C (EtOAc/petroleum ether); ^{1}H NMR δ 2.07 (s, 3H, Me), 2.10 (s, 3H, Me), 5.23 (s, 2H, CH_2), 6.56 (s, 1H, 3-H), 7.10 (m, 2H, Ph), 7.30 (m, 3H, Ph), 7.55 (m, 3H, Ph), 7.93 (m, 2H, Ph), 10.13 (s, 1H, NH), 12.52 (br s, 1H, OH); ^{13}C NMR δ 10.5, 12.7, 51.9, 112.8, 118.3, 126.9, 127.4, 127.7, 128.6, 128.7, 128.9, 131.9, 133.5, 137.58, 137.62, 145.6, 165.4, 166.2; IR 1685 br, 1660, 1640; MS 375 (M^+, 21), 105 (100). Anal. Calcd for $C_{22}H_{21}N_3O_3 \cdot 0.5\ H_2O$: C, 68.74; H, 5.77; N, 10.93. Found: C, 68.98; H, 6.05, N, 10.82.

(*E*)-2-(Benzoylamino)-3-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4c): mp 168–170 °C (EtOAc); ^{1}H NMR δ 2.15 (s, 3H, Me), 2.22 (s, 3H, Me), 6.63 (s, 1H, 3-H), 7.40 (m, 1H, Ph), 7.54

(m, 7H, Ph), 7.95 (m, 2H, Ph), 10.22 (s, 1H, NH), 12.65 (br s, 1H, OH); ^{13}C NMR δ 12.1, 12.8, 114.6, 117.3, 124.2, 127.4, 127.8, 128.6, 129.3, 129.8, 132.0, 133.5, 137.5, 139.4, 147.3, 165.5, 166.1; IR 1705, 1647; MS 361 (M^+, 13), 105 (100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.81; H, 5.51; N, 11.59.

(*E*)-2-(Benzoylamino)-3-[1-(6-chloro-3-pyridazin-6-yl)-3,5-dimethyl-1*H*-pyrazol-4-yl]propenoic acid (*E*-4d): mp 187–189 °C (EtOH/DMF); ^{1}H NMR δ 2.20 (s, 3H, Me), 2.55 (s, 3H, Me), 6.63 (s, 1H, 3-H), 7.57 (m, 3H, Ph), 7.96 (m, 2H, Ph), 8.04 (d, 1H, J = 9.4 Hz, 4'-H), 8.19 (d, 1H, J = 9.4 Hz, 5'-H), 10.28 (s 1H, NH), 12.80 (br s, 1H, OH); IR 1705, 1634; MS 397 (M^+, 2), 105 (100). Anal. Calcd for $C_{19}H_{16}ClN_5O_3$: C, 57.36; H, 4.05; N, 17.60. Found: C, 57.19; H, 4.00; N, 17.49.

(*E*)-2-(Benzoylamino)-3-[1-(imidazo[1,2-*b*]pyridazin-6-yl)-3,5-dimethyl-1*H*-pyrazol-4-yl]propenoic acid (*E*-4e): mp 242–244 °C (DMF/EtOH), mp lit.[4] 241–243 °C.

(*E*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]-propenoic acid (*E*-4f): mp 253–255 °C (EtOH/DMF); ^{1}H NMR δ 2.21 (s, 3H, Me), 2.57 (s, 3H, CH_3), 6.63 (s, 1H, 3-H), 7.57 (m, 3H, Ph), 7.92 (d, J = 10.0 Hz, 1H, 7'-H), 7.96 (m, 2H, Ph), 8.46 (dd, 1H, J = 10.0 and 1 Hz, 8'-H), 9.62 (d, 1H, J = 1 Hz, 3'-H), 10.30 (s 1H, NH), 12.82 (br s, 1H, OH); ^{13}C NMR δ 12.7, 13.6, 114.8, 117.6, 117.8, 126.2, 127.7, 128.6, 132.0, 132.1, 133.3, 139.3, 139.5, 142.5, 150.1, 150.3, 165.4, 165.6; IR 1710 br, 1660, 1620; MS 403 (M^+, 16), 105 (100). Anal. Calcd for $C_{20}H_{17}N_7O_3$: C, 59.55; H, 4.25; N, 24.31. Found: C, 59.32; H, 4.18; N, 24.48.

(*E*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]propenoic acid (*E*-4g): mp 285–288 °C (EtOH/DMF); ^{1}H NMR δ 2.23 (s, 3H, Me), 2.60 (s, 3H, Me), 6.65 (s, 1H, 3-H), 7.60 (m, 6H, Ph), 7.96 (m, 2H, Ph), 8.00 (d, 1H, J = 10.0 Hz, 7'-H), 8.31 (m, 2H, Ph), 8.52 (d, 1H, J = 10.0 Hz, 8'-H), 10.33 (s 1H, NH), 12.85 (br s, 1H, OH); IR 1665 br, 1625; MS 479 (M^+, 7), 105 (100). Anal. Calcd for $C_{26}H_{21}N_7O_3$: C, 65.13; H, 4.41; N, 20.45. Found: C, 65.04; H, 4.50; N, 20.49.

(*E*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(tetrazolo[1,5-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]-propenoic acid (*E*-4h): mp 246–248 °C (EtOH/DMF); ^{1}H NMR δ 2.24 (s, 3H, Me), 2.63 (s, 3H, Me), 6.66 (s, 1H, 3-H), 7.58 (m, 3H, Ph), 7.96 (m, 2H, Ph), 8.36 (d, 1H, J = 9.8 Hz, 7'-H), 8.83 (d, 1H, J = 9.8 Hz, 8'-H), 10.32 (s 1H, NH), 12.89 (br s, 1H, OH); ^{13}C NMR δ 12.7, 13.8, 114.2, 118.6, 121.7, 126.5, 127.7, 128.5, 132.0, 132.5, 133.2, 139.6, 142.0, 151.3, 151.4, 165.3, 165.5; IR 1703, 1630 br; MS 404 (M^+, 4), 105 (100). Anal. Calcd for $C_{19}H_{16}N_8O_3$: C, 56.43; H, 3.99; N, 27.71. Found: C, 56.17; H, 4.10; N, 27.62.

(*Z*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(tetrazolo[1,5-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]-propenoic acid (*Z*-4h): ^{1}H NMR δ 2.21 (s, 3H, Me), 2.53 (s, 3H, Me), 7.11 (s, 1H, 3-H), 7.54 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.32 (d, 1H, J = 9.8 Hz, 7'-H), 8.82 (d, 1H, J = 9.8 Hz, 8'-H), 9.84 (s 1H, NH), 12.8 (br s, 1H, OH). These data were obtained from ^{1}H NMR spectrum of the mixture of compounds *E*-**4h** and *Z*-**4h**.

(*E*)-2-(Benzoylamino)-3-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4i): mp 219–222 °C ($CHCl_3$/MeCN); ^{1}H NMR δ 2.13 (s, 3H, Me), 6.64 (s, 1H, 3-H), 7.30 (m, 1H, Ph), 7.41 (m, 2H, Ph), 7.57 (m,

5H, Ph), 7.93 (m, 2H, Ph), 10.14 (s, 1H, NH), 12.5 (br s, 1H, OH); ^{13}C δ 11.2, 110.6, 118.1, 126.9, 127.5, 127.6, 128.4, 128.5, 129.9, 131.8, 132.8, 133.4, 141.0, 145.9, 165.1, 165.8; IR 1660 br; MS FAB 348 (MH^+). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.15; H, 4.96; N, 12.20.

(*E*)-2-(Benzoylamino)-3-(1,5-dimethyl-3-phenyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4j): mp 238–240 °C (EtOH); ^{1}H NMR δ 2.17 (s, 3H, Me), 3.79 (s, 3H, Me), 6.66 (s, 1H, 3-H), 7.29 (m, 1H, Ph), 7.40 (m, 2H, Ph), 7.59 (m, 5H, Ph), 7.95 (m, 2H, Ph), 10.17 (s 1H, NH), 12.56 (br s, 1H, OH); ^{13}C δ 10.5, 36.4, 111.3, 118.1, 126.9, 127.2, 127,6, 128.4, 128.5, 130.1, 131.9, 133.4, 133.8, 138.2, 146.9, 165.1, 165.7; IR 1685 br, 1658; MS 361 (M^+, 10), 105 (100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.68; H, 5.33; N, 11.79.

(*E*)-2-(Benzoylamino)-3-(1-benzyl-5-methyl-3-phenyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4k): mp 197–200 °C (CH_3CN); ^{1}H NMR δ 2.15 (s, 3H, Me), 5.39 (s, 2H, CH_2), 6.71 (s, 1H, 3-H), 7.16 (m, 2H, Ph), 7.35 (m, 6H, Ph), 7.56 (m, 3H, Ph), 7.71 (m, 2H, Ph), 7.95 (m, 2H, Ph), 10.17 (s, 1H, NH), 12.62 (br s, 1H, OH); ^{13}C δ 10.5, 52.4, 111.8, 117.9, 126.7, 126.9, 127.3 (two signals), 127.6, 128.41, 128.44, 128.6, 130.6, 131.8, 133.4, 133.7, 137.3, 138.4, 147.4, 165.2, 165.7; IR 1688, 1640; MS 437 (M^+, 21), 105 (100). Anal. Calcd for $C_{27}H_{23}N_3O_3$: C, 74.13; H; 5.30; N, 9.60. Found: C, 74.28; H, 5.20; N, 9.71.

(*E*)-2-(Benzoylamino)-3-(1-benzyl-3-methyl-5-phenyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-5): mp 101–104 °C; ^{1}H NMR δ 2.13 (s, 3H, Me), 5.19 (s, 2H, CH_2), 6.63 (s, 1H, 3-H), 6.99 (m, 2H, Ph), 7.40 (m, 11H, Ph), 7.86 (m, 2H, Ph), 10.05 (s, 1H, NH), 12.5 (br s, 1H, OH); ^{13}C δ 13.0, 52.1, 114.2, 115.1, 126.6, 127.2, 127.4, 128.4, 128.5, 128.6, 128.7, 129.4, 129.8, 131.1, 131.7, 133.7, 137.9, 141.5, 146.1, 164.7, 166.0; IR 1660 br; MS 437 (M^+, 45), 105 (100). HRMS Calcd. for $C_{27}H_{23}N_3O_3$: 437.1739. Found: 437.1743.

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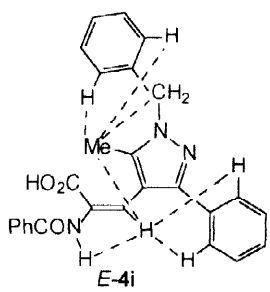
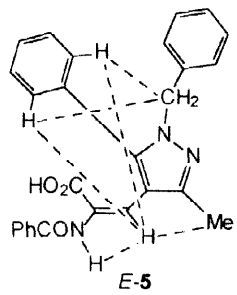
7. Compound **2** was prepared from benzoylacetone (16.5 g, 0.1 mol) and 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (21.8 g, 0.1 mol) in methylene chloride (50 mL) in 2 days at room temperature (Method: Behringer, H.; Falkenberg, K. *Chem. Ber.* **1963**, *96*, 1428–1435). After evaporation, to the remaining crude product ethanol (200 mL) was added and, upon cooling and filtering off, the resulting product was crystallized from a large amount of ethanol to give pure product **2**; mp 154–156 °C, mp lit. 158–160 °C (Svete, J.; Čadež, Z.; Stanovnik, B.; Tišler, M. *Synthesis* **1990**, 70–72).
8. The following cross-peaks observed in the NOESY spectrum of compound **4k** and of the mixture of compounds **4k** and **5** (in DMSO-d_6 solution at 29 °C, mixing time 300 or 400 ms) were determining parameters for the elucidation of the structure of both products.



E-**4i**



E-**5**

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