HETEROCYCLES, Vol. 74, 2007, pp. 293 - 307. © The Japan Institute of Heterocydic Chemistry
Received, 31st May, 2007, Accepted, 26th July, 2007, Published online, 27th July, 2007. COM-07-S(W)6

SYNTHESIS AND TRANSFORMATION OF *N*,*N*-DIMETHYLAMINO-METHYLIDENE DERIVATIVES OF INDOLYLGLYCINES AND SOME OTHER DIPEPTIDES

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Dedicated to Prof. Dr. Ekkehard Winterfeldt, University of Hannover, on the occasion of his 75th birthday.

Abstract – Indolyl glycinates (**3**, **7**, and **11**) were transformed with *t*-butoxybis(dimethylamino)methane (Bredereck's reagent) into 3-[(dimethylamino)methylidene]-2,3-dihydropyrazino[1,2-*a*]indole-1,4-dione (**4**), 3-(dimethylamino)-2-[(1*H*-indol-3-ylcarbonyl)amino]propenoate (**8**), and 2-(1-methyl-1*H*-indol-2-yl)-1,3-oxazol-5(4*H*)-one derivative (**12**). Dipeptides (**16a-c**) were transformed with Bredereck´s reagent into the hydantoin (imidazolidine-2,4-dione) derivatives (**17a-c**).

INTRODUCTION

Recently, a series of 2-substituted alkyl 3-(dimethylamino)propenoates and related enaminones have been prepared as versatile reagents for the preparation of various didehydroalanine derivatives, and many heterocyclic systems.[1-7] Chiral cyclic enamino lactons and lactams, derived from an α-amino acid or (+)-camphor have been used in the synthesis of functionalized heterocycles, such as heteroarylalanines, heteroarylalaninols, 3-heteroaryl-substituted (+)-camphor derivatives,[8-10] and heterocyclic compounds with an α-amino acid or a dipeptide structural element incorporated into the ring system.[6] They have been used also for the preparation of natural products and their analogues such as 3-substituted indoles,[11]

aplysinopsins,[12-15] meridianines,[16] and dipodazines,[17-19] and employed in combinatorial synthesis of heterocycles.[20-23]

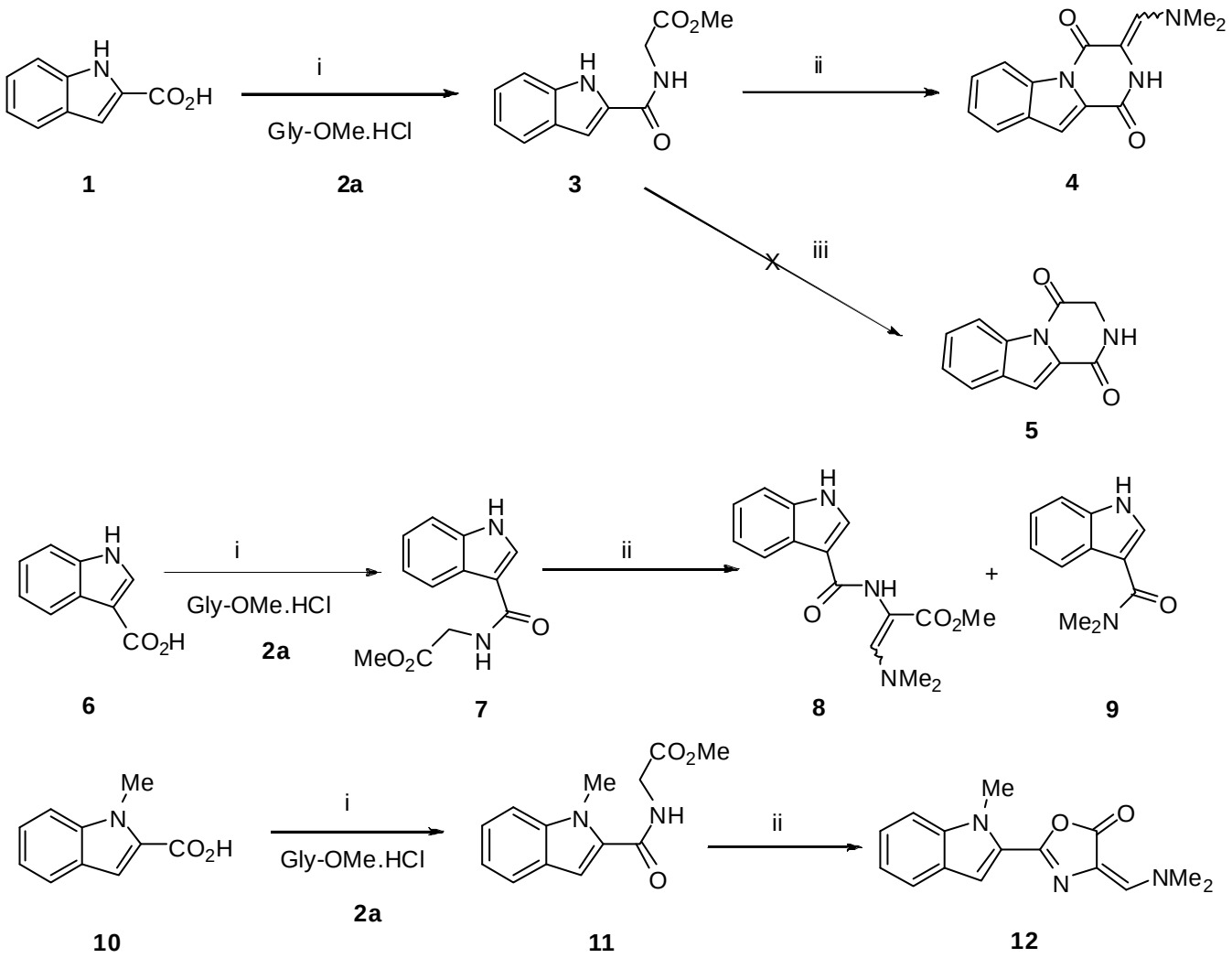
Hydantoins (= imidazolidine-2,4-diones) are a significant class of heterocycles, since many of hydantoin containing natural and synthetic products exhibit diverse biological activities, such as antitumor, antiarrytmic, anticonvulsant, herbicidal and other. Aplysinopsins, isolated from marine organisms, are examples of hydantoin containing natural products exhibiting cytotoxicity towards cancer cells and the ability to affect neurotransmitters.[24,25] In this paper we report on the preparation of dimethylaminomethylidene derivatives of some dipeptides and some further transformations into hydantoin derived (dimethylamino)propenoates, such as analogues of gliotoxin degradation products.

RESULTS AND DISCUSSION

Indole-2-carboxylic acid (**1**) was coupled to methyl glycinate hydrochloride (**2a**) to form methyl *N*-(1*H*-indol-2-ylcarbonyl)glycinate (**3**). It was then converted with *tert*-butoxy-bis(dimethylamino)-methane (*Bredereck*'s reagent) into the corresponding 3-[(dimethylamino)methylidene]-2,3-dihydropyrazino[1,2-*a*]indole-1,4-dione (**4**). Intramolecular amide formation occured instead of the cyclisation to a β-carboline analogue. The formation of a similar system has already been reported. It has been isolated as a degradation product of the antibiotic substance gliotoxin, prepared by the reduction of gliotoxin by HI and red phosphorus.[26-29] It has been also reported that 2-indolecarboxamides spontaneously cyclise to the indole NH group only in the cases when the exocyclic nitrogen atom is protected. This coincides with our observation that no cyclization (pyperazine) product (**5**) was formed, when methyl *N*-(1*H*-indol-2-ylcarbonyl)glycinate (**3**) was heated under the same reaction conditions but without the presence of Bredereck's reagent (Scheme 1).

When methyl *N*-(1*H*-indol-3-ylcarbonyl)glycinate (**7**), was treated with Bredereck's reagent under milder reaction conditions (70 - 80 ˚C), the expected methyl 3-(dimethylamino)-2-[(1*H*-indol-3-ylcarbonyl)-amino]propenoate (**8**) was isolated in 47% yield with the parallel formation of *N*,*N*-dimethyl-1*H*-indole-3-carboxamide (**9**), which was also isolated from the reaction mixture (Scheme 1). The structure of this compound was determined by X-ray analysis (Figure 1).

Our next step was to employ *N*-methyl protected indole derivative. Methyl *N*-(1-methyl-1*H*-indol-2-ylcarbonyl)glycinate (**11**), prepared from 1-methyl-1*H*-indolecarboxylic acid and (**10**) and methyl glycinate hydrochloride (**2a**), was treated with Bredereck's reagent to give 4(*E*)-4-[(dimethylamino)-methylidene]-2-(1-methyl-1*H*-indol-2-yl)-1,3-oxazol-5(4*H*)-one (**12**) (Scheme1) The structure of compound (**12**) was determined by x-ray analysis (Figure 2).



Scheme 1. Reagents and reaction conditions: i $ClCO_2Et$, CH_2Cl_2, *N*-methylmorpholine (NMM), methyl glycinate hydrochloride, rt.; ii Bredereck's reagent, MeCN, reflux; iii AcOH, reflux.

Table 1. Transformations of indole-2-carboxylic acid (**1**), indole-3-carboxylic acid (**6**), and 1-methylindole-2-carboxylic acid (**10**).

Compound	Reaction time [h]	Yield [%]
3	24	74
4	1	75
7	24	46
8	1	47
14	3	60

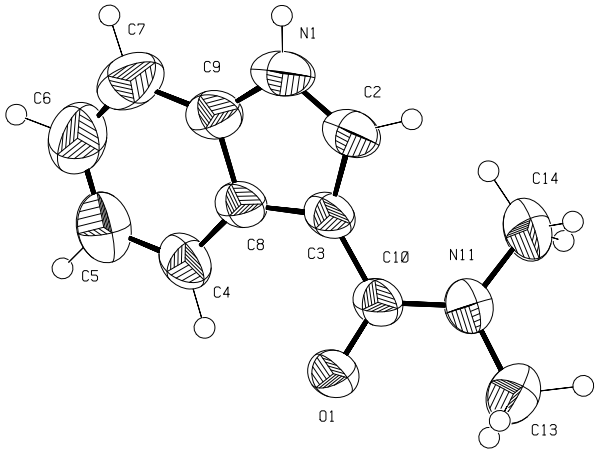


Figure 1. Ortep view of compound (**9**) at the 50% probability level. H atoms are drawn as ellipsoids of arbitrary radii.

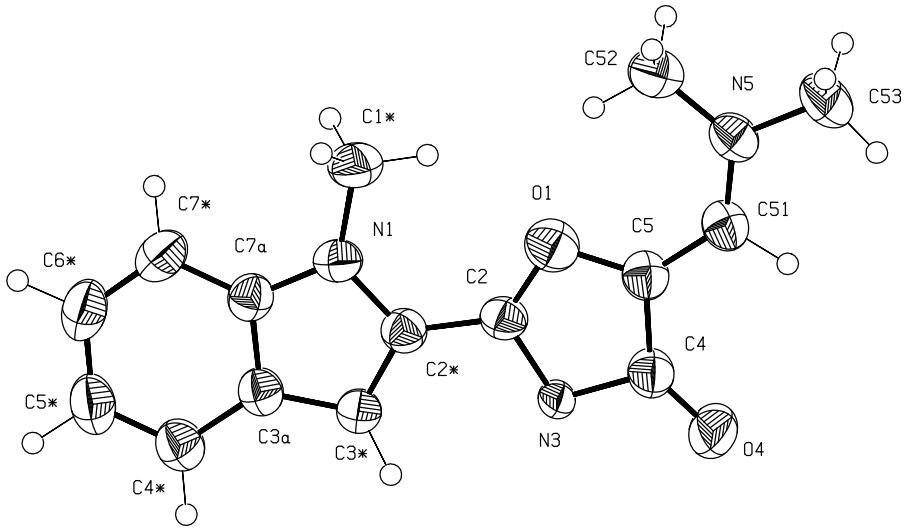
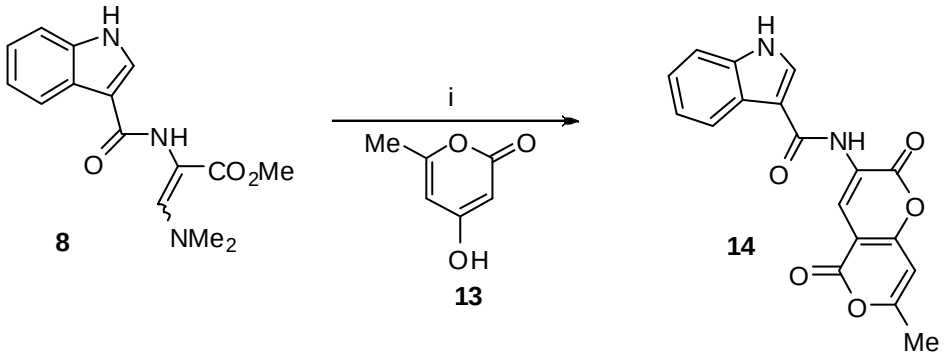


Figure 2. Ortep view of compound (**12**) at the 50% probability level. H atoms are drawn as ellipsoids of arbitrary radii.

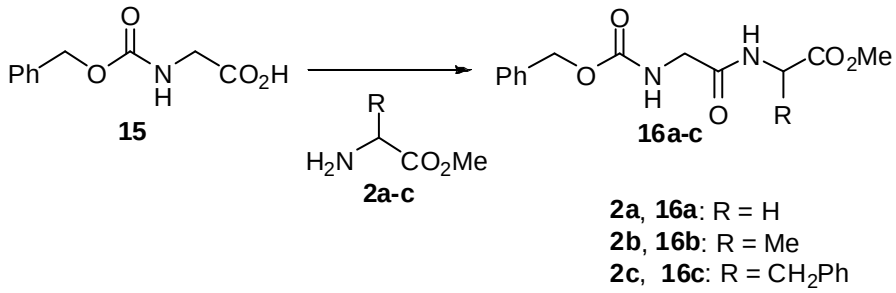
Compound (**8**) and the equivalent of 4-hydroxy-6-methyl-2-pyranone (**13**) were dissolved in acetic acid and the mixture was heated under reflux for 3 to 4 h. The product *N*-(7-methyl-2,5-dioxo-2*H*,5*H*-pyirano[4,3-*b*]pyran-3-yl)-1*H*-indole-3-carboxamide (**14**) was isolated with 60% yield.

Dipeptides (**16a-c**) derived from benzyloxycarbonylglycine afforded by treatment with *Bredereck*'s reagent the corresponding hydantoin dimethylaminomethylidene derivative (**17a-c**). Thus, benzyl-oxycarbonylglycine (Z-Gly; **15**) was coupled to a methyl amino acid esters (**2a-c**) (GlyOMe, AlaOMe,



Scheme 2. Reagents and reaction conditions: i AcOH, reflux.

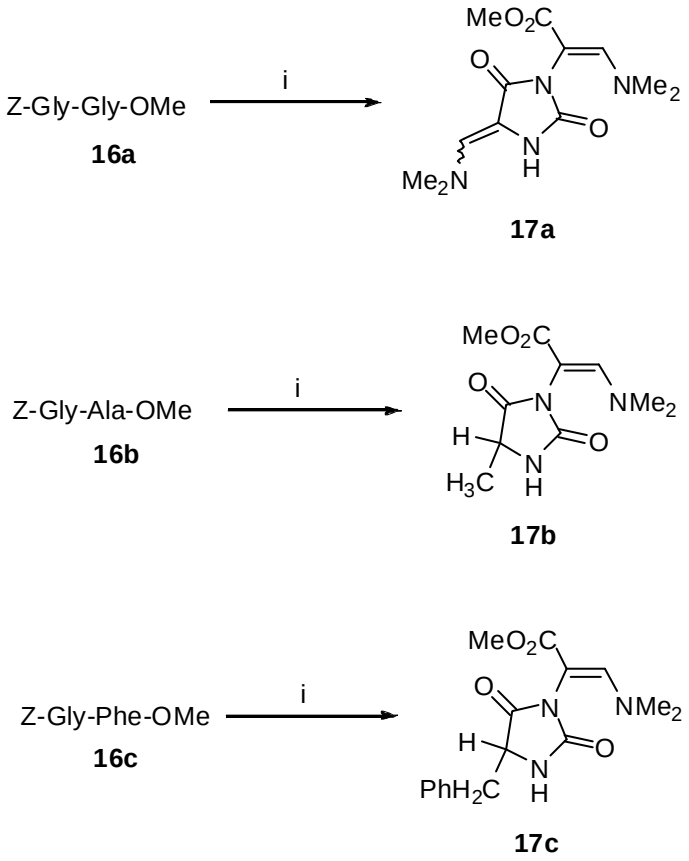
PheOMe) and the corresponding dipeptides (**16a-c**) were obtained (Scheme 3).[30-32] They were converted with *tert*-butoxy-bis(dimethylamino)methane (*Bredereck*'s reagent) into the corresponding methyl 3-(dimethylamino)-2-{4-[(dimethylamino)methylidene]-2,5-dioxoimidazolidin-1-yl}propenoate (**17a**), methyl 3-(dimethylamino)-2-(4-methyl-2,5-dioxoimidazolidin-1-yl)propenoate (**17b**), and methyl 2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)-3-(dimethylamino)propenoate (**17c**) (Scheme 4). The orientation around the double bond that was analogous in all three compounds was proven to be *cis*, as the longe range coupling constant was shown to be, $^{3}J_{H,CO}$ = 4.0 Hz. Both dimethylamino groups in compoud (**17a**) were substituted with 3-methyl-1-phenyl-2-pyrazolin-5-one (**18**) and methyl 3-(5-hydroxy-1-phenyl-3-methyl-1*H*-pyrazol-4-yl)-2-{4-[(5-hydroxy-1-phenyl-3-methyl-1*H*-pyrazol-4-yl)methilidene]-2,5-dioxoimidazolidin-1-yl}propenoate (**19**) was isolated (Scheme 5).



Scheme 3. Reagents and reaction conditions: i CH_2Cl_2, *N*-methylmorpholine (NMM), dicyclohexyl-carbodiimide, 0 °C, 2 h.

The structures of new compounds were determined on the basis of their MS spectra, elemental analyses for *C*, *H*, and *N*, ^{13}C NMR and ^{1}H NMR spectra. The (*E*)-configuration around the exocyclic double bond in compounds (**17**) was determined by NMR (HMBC technique) on the basis of the magnitude of

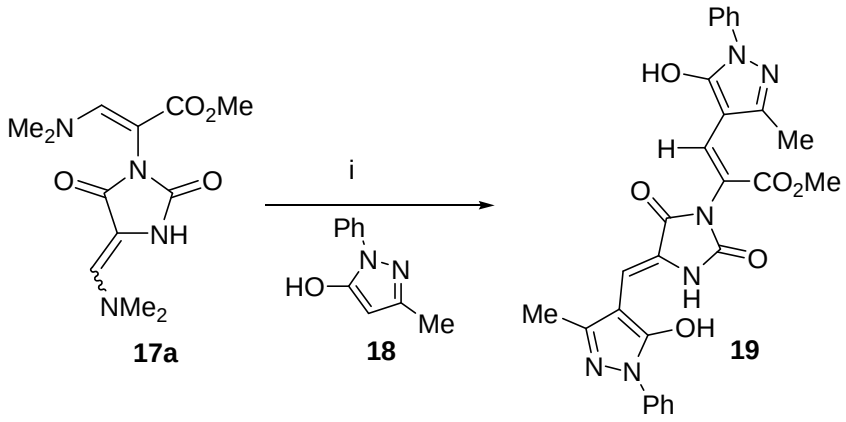
longe-range heteronuclear coupling constant, $^{3}J_{C\text{-}H}$ = 4.0 Hz , indicates the *cis*-relationship between the methine proton at the 3-position and the carbonyl carbon atom. This is also in agreement with the literature data.[33-38] Furtheron, X-ray analysis proved the orientation around the double bond to be *E* in product (**12**).



Scheme 4. Reagent and reaction conditions: i DMF, *t*-BuO$(Me_2N)_2$CH (Bredereck's reagent), reflux.

Table 2. Transformation of dipeptides **16a-c** into hydantoin derivatives **17a-c**.

Compound	Time (h)	m.p. [°C]	Yield [%]
17a	3	260-263	79
17b	3	198-200	25
17c	2.5	184-185	18



Scheme 5. Substitution of dimethylamino groups in compound **17a**
Reagents and reaction conditions: i AcOH, reflux.

X-Ray structure analysis

Single crystal X-ray diffraction data of compounds (**9**) and (**12**) were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[39] DENZO and SCALEPACK[40] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[41] Refinement was done using Xtal3.4[42] program package. Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in both cases, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined for compound (**9**), while hydrogen atoms were refined isotropically for compund (**12**). Absorption correction was not necessary. Regina[43] weighting scheme was used in all cases. Difference fuorier maps for compounds (**9**) and (**12**) do not show any significant features, respectively. The resulting crystal data and details concerning data collection and refinement for the two compounds are quoted in Table 3. Final atomic coordinates and equivalent isotropic displacement parameters with their e.s.d.'s are reported in Tables 2 and 3. Bond distances and bond angles for nonhydrogen atoms for compounds (**9**) and (**12**) are listed in Tables 4 and 5, respectively. ORTEP III [44] drawing of the content of asymmetric units of the two compounds showing the atom-labeling scheme are presented in Figures 1 and 2. The crystallographic data for compounds (**9**) and (**12**) have been deposited with the *Cambridge Crystallographic Data Centre* as deposition number CCDC 646899 (for **9**) and CCDC 646900 (for **12**). The data can be obtained, free of charge, at http://www.ccdc.cam.ac.uk/data_reques/cif.

Table 3. Crystal data, data collection and structure refinement for compounds (**9**) and (**12**).

	Compound (**9**)	Compound (**12**)
Formula	$C_{11}H_{12}N_2O$	$C_{15}H_{15}N_3O_2$
Rel. formula weight	188.23	269.303
Crystal System	orthorhombic	triclinic
Space group	P 2_1 2_1 2_1	P -1
a (Å)	8.2782(2)	7.4402(2)
b (Å)	9.3433(3)	7.9568(2)
c (Å)	12.9371(4)	12.0055(4)
α (˚)	90.0000	96.668(1)
β (˚)	90.0000	108.200(1)
γ (˚)	90.0000	92.489(1)
V (Å^3)	1000.63(5)	668.21(3)
Z	4	2
ρ (Mg m^{-3})	1.249	1.338
μ (mm^{-1})	0.082	0.0915
Color of crystal	dirty white	Yellow
Shape of crystal	plate	Prism
Dimensions (mm)	0.40×0.20×0.10	0.30×0.30×0.13
Temperature (K)	293(1)	293(1)
Wavelength (Å)	0.71073	0.71073
θ_{max} (°)	27.48	27.44
No. of integr. refl.	14430	11945
No. of indep. refl.	1348	3041
R_{int}	0.044	0.043
No. of observed refl.	1007	2150
Threshold criterion	I > 2.0σ(I)	I > 3.0σ(I)
No. of refl. param.	127	226
Final R and R_w	0.053, 0.063	0.08, 0.07
$(\Delta/\sigma)_{max}$	0.00021	0.032
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.17, 0.18	-0.52, 0.55
Diffractometer type: Nonius Kappa CCD		

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in such solvent as DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, MS spectra on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer 1310 infrared spectrophotometer and elemental analyses for *C*, *H* and *N* on a Perkin-Elmer CHN Analyser 2400.

General Procedure for the Preparation of compounds (3, 7 and 11).

Indolecarboxylic acids (**1, 6** and **10**) (0.001 mol) were dissolved in 30 mL of freshly distilled CH_2Cl_2 and

N-methylmorpholine (1.1 mL) was added and the mixture was stirred at 0 °C. Methyl chloroformate (1.2 mL, 0.011 mol) was added. The reaction mixture was left to stirr at 0 °C for 4h, after which another equivalent of *N*-methylmorpholine (1.1 mL) was added. Afetr 5 additional minutes methyl glycine hydrochloride (1.25 g, 0.010 mol) was added and the reaction was stirred overnight at r.t. The reaction was followed by TLC in $CHCl_3$/MeOH (25:1). When the reaction was finnished, CH_2Cl_2 (100 mL) was added and the solution was washed with 1% hydrochloric acid (50 mL), with a saturated aqueous $NaHCO_3$ (50mL) and finally with brine (50 mL). The organic fraction was separated and the volatile components were evaporated *in vacuo.* The products were isolated with 46-74% yield.

Methyl *N*-(1*H*-indol-2-ylcarbonyl)glycinate (3). This compound was prepared from indole-2-carboxylic acid (**1**; 1.61 g, 0.001 mol) and methyl glycinate hydrochloride (**2a**; 1.25 g, 0.010 mol), 24 h, 74% yield (1.72 g), mp 210-213 °C (from EtOH), MS 232 (M^+), HRMS: Calcd: 232.0848, Found: 232.0855, IR 3372, 3276, 1739, 1698, 1646, 1578, 1553 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 3.67 (3H, s, CH_3), 4.05 (2H, d, J = 6.0 Hz, CH_2), 7.04 (1H, dt, J = 1.1, 7.9 Hz, *H*–C(5')), 7.14 (1H, d, J = 6.8 Hz, *H*–C(3')), 7.19 (1H, ddt, J = 1.1, 6.8, 7.9 Hz, *H*–C(6')), 7.43 (1H, dd, J = 1.1, 7.9 Hz, *H*–C(7')), 7.63 (1H, dd, J = 1.1, 7.9 Hz, *H*–C(4')), 8.92 (1H, t, J = 6.0 Hz, NH), 11.59 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ: 52.6, 103.9, 113.1, 120.7, 122.5, 124.4, 127.8, 127.9, 131.7, 137.2, 162.4, 171.3. *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.42; H, 5.12; N, 11.83.

Methyl *N*-(1*H*-indol-3-ylcarbonyl)glycinate (7). This compound was prepared from indole-3-carboxylic acid (**6**; 1.61 g, 0.001 mol) and methyl glycinate hydrochloride (**2a**, 1.25 g, 0.010 mol), 24 h, 46% yield (1.07 g), mp 176-178 °C (from EtOH), MS 232 (M^+), HRMS: Calcd: 232.0848, Found: 232.0856, IR 3394, 3160, 2961, 1782, 1745, 1725, 1651 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 3.67 (3H, s, CH_3), 4.02 (2H, d, J = 6.0 Hz, CH_2), 7.33 (1H, dt, J = 1.1, 7.2 Hz, *H*–C(5')), 7.40 (1H, ddd, J = 1.1, 7.2, 8.3 Hz, *H*–C(6')), 8.13 (1H, dd, J = 1.1, 8.3 Hz, *H*–C(7')), 8.21 (1H, dd, J = 1.1, 7.2 Hz, *H*–C(4')), 8.21 (1H, s, *H*–C(2')), 8.89 (1H, t, J = 6.0 Hz, NH), 11.60 (1H, s, NH). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.13; H, 5.06; N, 11.75.

Methyl *N*-(1-methyl-1*H*-indol-2-ylcarbonyl)glycinate (11). This compound was prepared from *N*-methylindole-2-carboxylic acid (**10**; 1.75 g, 0.001 mol) and methyl glycinate hydrochloride (**2a**;1.25 g, 0.010 mol), 24 h, 69% yield (1.07 g), mp 98-100 °C (from EtOH), MS 246 (M^+), 247 (MH^+), HRMS: Calcd: 247.1004, Found: 247.1010, IR 1753, 1630, 1542 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 3.68 (3H, s, CH_3), 3.98 (3H, s, NCH_3), 4.02 (2H, d, J = 6.0 Hz, CH_2), 7.11 (1H, ddd, J = 0.8, 6.8, 7.9 Hz, *H*–C(5')), 7.15 (1H, d, J = 0.8 Hz, *H*–C(3')), 7.29 (1H, ddd, J = 1.1, 6.8, 8.3 Hz, *H*–C(6')), 7.53 (1H, dd, J = 0.8, 8.3 Hz, *H*–C(7')), 7.66 (1H, ddd, J = 0.8, 1.1, 7.9 Hz, *H*–C(4')), 8.92 (1H, t, J = 6.0 Hz, NH). ^{13}C NMR

(DMSO-d_6): δ: 32.2, 41¸.7, 52.6, 105.7, 111.4, 121.1, 122.5, 124.6, 126.4, 132.2, 139.4, 163.1, 171.2. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.60; H, 5.88; N, 11.21.

General Procedure for the Preparation of Dipeptides (16a-c).

Z-Gly (**15;** 0.050 mol) and the appropriate methyl amino acid ester **2a-c** were dissolved in 200 mL of freshly distilled CH_2Cl_2 and *N*-methylmorpholine (5.5 mL) was added and the mixture was stirred at 0 °C. Dicyclohexylcarbodiimide (10.32 g, 0.050 mol) was added. The reaction mixture was left to stirr at 0 °C for 2h. The precipitated dicyclohexyl urea was collected by filtration and washed with CH_2Cl_2. The filtrate was washed with a saturated aqueous of $NaHSO_4$ (200 mL), a saturated aqueous $NaHCO_3$ (200 mL) and brine (100 mL). The organic fraction was separated and the volatile components were evaporated *in vacuo*. Compounds Z-Gly-GlyOMe, Z-Gly-AlaOMe, Z-Gly-PheOMe, were prepared in this manner in yields 77-84%.

Methyl [({[(benzyloxy)carbonyl]amino}acetyl)amino]acetate (Z-Gly-Gly-OMe) (16a). This compound was prepared from Z-Gly (**15**; 10.45 g, 0.050 mol) and methyl glycinate hydrochloride (**2a;** 6.28 g, 0.050 mol), 2 h, 77% yield (10.8 g), mp 75-77 °C (from EtOH), MS 280 (M^+), IR 3359, 3327, 3253, 2928, 2851, 1736, 1663, 1627, 1562 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 3.63 (3H, s, CH_3), 3.66 (2H, d, J = 6.0 Hz, CH_2), 3.85 (2H, d, J = 6.0 Hz, CH_2), 5.04 (2H, s, CH_2), 7.35 (5H, m, Ph), 7.48 (1H, t, J = 6. 0 Hz, NH), 8.27 (1H, t, J = 6.0 Hz, NH).

Methyl 2-[({[(benzyloxy)carbonyl]amino}acetyl)amino]propanoate (Z-Gly-Ala-OMe) (16b). This compound was prepared from Z-glycine (**15**; 10.45 g, 0.050 mol) and methyl alaninate hydrochloride (**2b**; 6.98 g, 0.050 mol), 2 h, 71% yield (10.4 g), mp 62-64 °C (from EtOH), MS 294 (M^+), IR 3410, 3295, 2958, 1740, 1655, 1540 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 1.27 (3H, d, J = 7.5 Hz, CH_3), 3.62 (3H, s, CH_3), 3.66 (2H, d, J = 7.2 Hz, CH_2), 4.29 (1H, dq, J = 7.2, 7.5 Hz, CH), 5.03 (2H, s, CH_2), 7.35 (5H, m, Ph), 7.32 (1H, t, J = 7.2 Hz, NH), 8.27 (1H, t, J = 7.2 Hz, NH).

Methyl 2-[({[(benzyloxy)carbonyl]amino}acetyl)amino]-3-phenylpropanoate (Z-Gly-Phe-OMe) (16c). This compound was prepared from Z-glycine (**15**; 10.45 g, 0.050 mol) and methyl phenylalaninate hydrochloride (**2c**; 10.85 g, 0.050 mol), 2 h, 84% yield (15.5 g), mp 125-126 °C (from EtOH), MS 370 (M^+), ^1H NMR (DMSO-d_6): δ: 2.97 (2H, m, CH_2)**,** 3.59 (3H, s, CH_3), 3.65 (2H, d, J = 5.6 Hz, CH_2), 4.48 (1H, dt, J = 5.6, 7.9 Hz, CH), 5.02 (2H, s, CH_2), 7.29 (11H, m, 2Ph in NH), 8.28 (1H, t, J = 7.9 Hz, NH).

General Procedure for Preparation of Compounds (4, 8, and 12):

A mixture of compound (**3**, **7**, and **12**) or of a dipeptide (**16a-c**) (0.001 mol), DMF (10 mL), and Bredereck's reagent (261 mg, 0.0015 mol), was heated under reflux for 1–3 h. Volatile components were

evaporated *in vacuo*, and the residue was triturated with an appropriate solvent (10 mL). The precipitate was collected by filtration and washed with the same solvent. The following compounds were prepared in this manner.

3-[(Dimethylamino)methylidene]-2,3-dihydropyrazino[1,2-*a*]indole-1,4-dione (4). This compound was prepared from compound **3** (0.23 g, 0.001 mol) and Bredereck's reagent (261 mg, 0.0015 mol), 1 h, 75% yield (0.69 g), mp 254-257 °C, MS 255 (M^+), 256 (MH^+), HRMS: Calcd: 255.1008, Found: 255.1011, IR 3216, 1694, 1647, 1598 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 3.22 (6H, s, $N(CH_3)_2$), 7.40 (1H, ddd, J = 0.8, 7.5, 8.3 Hz, *H*–C(5')), 7.42 (1H, d, J = 0.8, *H*–C(3')), 7.50(1H, s, *H*–C(5'')), 7.51 (1H, ddd, J = 0.8, 7.2, 7.5 Hz, *H*–C(6')), 7.82 (1H, dt, J = 0.8, 7.5 Hz, *H*–C(7')), 8.49 (1H, dd, J = 0.8, 8.3 Hz, *H*–C(4')), 9.98 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ: 43.9, 101.5, 109.4, 117.3, 123.0, 124.7, 126.6, 129.1, 130.0, 135.6, 139.8, 154.2, 158.4. *Anal.* Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.11; H, 5.15; N, 16.13.

Methyl 3-(dimethylamino)-2-[(1*H*-indol-3-ylcarbonyl)amino]propenoate (8). This compound was prepared from compound (**7**) (0.23 g, 0.001 mol) and Bredereck's reagent (261 mg, 0.0015 mol), 1 h, 47% yield (0.13 g), mp 272-274 °C, MS 287 (M^+), 288 (MH^+), HRMS: Calcd: 287.1270, Found: 287.1278, IR 3120, 3034, 2971, 2913, 2858, 1589, 1565, 1537, 1495 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 2.97 (6H, s, $N(CH_3)_2$), 3.53 (3H, s, Me), 7.09 (1H, dt, J = 1.1, 6.8 Hz, *H*–C(5')), 7.14 (1H, ddd, J = 1.1, 6.8, 7.1 Hz, *H*–C(6')), 7.36 (1H, s, *H*–C(3'')), 7.42 (1H, dd, J = 1.1, 7.1 Hz, *H*–C(7')), 8.10 (1H, s, *H*–C(2')), 8.14 (1H, dd, J = 1.1, 6.8 Hz, *H*–C(4')), 8.40 (1H, s, NH), 11.54 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.89; H, 5.84; N, 14.36.

4(*E*)-4-[(Dimethylamino)methiliden]-2-(1-methyl-1*H*-indol-2-yl)-1,3-oxazol-5(4*H*)-one (12). This compound was prepared from compound (**11**) (0.25 g, 0.001 mol) and Bredereck's reagent (261 mg, 0.0015 mol), 2.5 h, 89% yield (0.24 g), mp 238-239 °C, MS 269 (M^+), 270 (MH^+), HRMS: Calcd: 269.1164, Found: 269.1170, IR 1737, 1644, 1600 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 3.31 (6H, s, $N(CH_3)_2$), 3.57 (3H, s, Me), 4.11 (3H, s, NCH_3), 7.01(1H, s, *H*–C(4'')), 7.11 (1H, ddd, J = 0.8, 6.8, 7.9 Hz, *H*–C(5')), 7.28 (1H, ddd, J = 1.1, 6.8, 8.3 Hz, *H*–C(6')), 7.39 (1H, s, *H*–C(3')), 7.54 (1H, dd, J = 0.8, 8.3 Hz, *H*–C(7')), 7.63 (1H, dd, J = 1.1, 7.9 Hz, *H*–C(4')). ^{13}C NMR (DMSO-d_6): δ: 32.6, 47.1, 105.9, 106.3, 111.1, 121.1, 122.1, 124.5, 126.7, 127.2, 140.1, 144.8, 168.5, 172.1. *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.70; H, 5.81; N, 15.68.

Methyl 3-(dimethylamino)-2-{4-[(dimethylamino)methylidene]-2,5-dioxoimidazolidin-1-yl}propenoate (17a). This compound was prepared from Z-Gly-GlyOMe (**16a**; 0.28 g, 0.001 mol) and Bredereck's reagent (696 mg, 0.004 mol), 3 h, 79% yield (0.22 g), mp 260-263 °C, MS 282 (M^+), IR

3266, 1748, 1687, 1638 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 2.86 (6H, s, $N(CH_3)_2$), 2.99 (6H, s, $N(CH_3)_2$), 3.50 (3H, s, CH_3), 6.55 (1H, s, *H*–C(3)), 7.53 (1H, s, *H*–C(4)), 9.52 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ: 32.6, 47.1, 105.9, 106.3, 111.1, 121.1, 122.1, 124.5, 126.7, 127.2, 140.1, 144.8, 168.5, 172.1. *Anal.* Calcd for $C_{12}H_{18}N_4O_4$: C, 51.06; H, 6.43; N, 19.85. Found: C, 51.22; H, 6.46; N, 20.08.

Methyl 3-(dimethylamino)-2-(4-methyl-2,5-dioxoimidazolidin-1-yl)propenoate (17b). This compound was prepared from Z-Gly-AlaOMe (**16b**; 0.29 g, 0.001 mol) and Bredereck's reagent (696 mg, 0.004 mol), 3 h, 25% yield (0.06 g), mp 198-200 °C, MS 241 (M^+), HRMS: Calcd: 241.1062, Found: 241.1068, IR 3266, 1748, 1687, 1638 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 1.42 (3H, d, J = 7.1 Hz, CH_3), 3.00 (6H, s, $N(CH_3)_2$**),** 3.61 (3H, s, CH_3), 4.72 (1H, q, J = 7.1 Hz, *H*–C(4)), 6.57 (1H, s, *H*–C(3)), 9.59 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ: 15.7, 42.7, 47.2, 53.1, 101.3, 130.6, 153.7, 163.9, 171.3. *Anal.* Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 50.02; H, 6.50; N, 17.54.

Methyl 3-(dimethylamino)-2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)propenoate (17c). This compound was prepared from Z-Gly-PheOMe (**16c**; 0.37 g, 0.001 mol) and Bredereck's reagent (696 mg, 0.004 mol), 2.5 h, 18% yield (0.06 g), mp 184-185 °C, MS 317 (M^+), HRMS: Calcd: 317.1376, Found: 317.1382, IR 1740, 1686, 1655 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 2.95 (6H, s, $N(CH_3)_2$), 3.66 (3H, s, CH_3), 3.96 (2H, dd, J = 6.8, 9.0 Hz, CH_2), 4.94 (1H, dd, J = 6.8, 9.0 Hz, *H*–C(4)), 6.47 (1H, s, *H*–C(3)), 7.26 – 7.12 (5H, m, Ph), 9.45 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.27; H, 6.25; N, 13.43.

General Procedure for the Substitution Products (14 and **19)**

Compounds (**8** and **17a**) (0.5 mmol) and one equivalent of the nucleophile were dissolved in AcOH (10 mL) and the mixture was heated under reflux for 3 to 4 h. The volatile components were evaporated *in vacuo* and the precipitate from ethanol was collected by filtration and washed with Et_2O.

***N*-(7-Methyl-2,5-dioxo-2*H*,5*H*-pyirano[4,3-*b*]pyran-3-yl)-1*H*-indole-3-carboxamide (14).** This compound was prepared from compound (**8**) (0.29 g, 0.001 mol) and 4-hydroxy-6-methyl-2-pyrone (**13**; 0.12g, 0.001 mol), 3 h, 60% yield (0.20 g), mp 340 °C (EtOH, decomp.), MS 336 (M^+), 337 (MH^+), HRMS: Calcd: 336.0746, Found: 336.0760, IR 3404, 1702, 1662, 1610, 1523, 1507 cm^{-1}, ^1H NMR (DMSO-d_6): δ: 2.34 (3H, s, Me), 6.68 (1H, s, *H*–C(8'')), 7.21 (2H, m, *H*–C(5') in *H*–C(6')), 7.48 (1H, m, *H*–C(7')), 8.12 (1H, m, *H*–C(4')), 8.40 (1H, s, *H*–C(2')), 8.51 (1H, s, *H*–C(4'')), 9.15 (1H, s, NH), 11.91 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ: 102.5, 110.2, 113.1, 120.7, 121.2, 122.1, 124.7, 126.5, 131.0, 137.0, 157.7, 160.6, 161.2, 164.1, 164.3. *Anal.* Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 63.99; H, 3.62; N, 8.47.

Methyl 3-(5-hydroxy-1-phenyl-3-methyl-1*H*-pyrazol-4-yl)-2-{4-[(5-hydroxy-1-phenyl-3-methyl-1*H*-pyrazol-4-yl)methylidene]-2,5-dioxoimidazolidin-1-yl}propenoate (19). This compound was prepared from compound (**17a)** (0.36 g, 0.001 mol) and 1-phenyl-3-methyl-2-pyrazolin-5-one (**18**; 0.12g, 0.001 mol), 4 h, 87% yield (0.46 g), mp 287 °C (EtOH, decomp.), MS 540 (M^+), IR 1749, 1698, 1658, 1609, 1537, 1499 cm^{-1}, ^{1}H NMR (DMSO-d_6): δ: .27 (3H, s, CH_3), 2.32 (3H, s, CH_3), 3.70 (3H, s, CH_3), 6.10 (1H, s, *H*–C(2')), 7.22 – 7.71 (11H, m, 2 Ph and *H*–C(4')), 11.36 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ: 11.4, 12.6, 21.9, 53.1, 100.2, 101.3, 101.5, 113.5, 121.5, 121.7, 125.3, 126.7, 127.2, 129.9, 130.0, 133.1, 136.2, 137.1, 148.7, 152.0, 161.4, 162.9, 165.5, 172.8. *Anal.* Calcd for $C_{28}H_{24}N_6O6_5$: C, 62.22; H, 4.48; N, 15.55. Found: C, 61.91; H, 4.70; N, 15.47.

ACKNOWLEDGEMENTS

The financial support from the *Slovenian Research Agency*, Slovenia through grants P0-0502-0103, P1-0179, and J1-6689-0103-04 is gratefully acknowledged. Financial support by the pharmaceutical companies *LEK-SANDOZ*, Ljubljana, and *KRKA*, Novo Mesto, is fully appreciated. We kindly acknowlwdgw financial contributions of the *Slovenian Research Agency*, Slovenia, which enabled the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, to purchase the *Nonius* X-ray diffractometer (grants X-2000 and PS-511-103.

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