Stereoselective ring opening of dimethyl 5-aryl-2,3-dihydro-3,3-dimethyl-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates with hydrazine hydrate. Synthesis of *rel*-(4'*R*,5'*S*)-3-[5-Aryl-3,4-bis(hydrazino-carbonyl)]-4,5-dihydro-1*H*-pyrazol-1-yl)-3-methylbutano-hydrazides

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Dedicated to Prof. Emeritus Miha Tišler on the occasion of his 75th birthday
(received 08 Jan 01; accepted 28 Jan 02; published on the web 05 Feb 02)

Abstract
Reactions of dimethyl 5-aryl-2,3-dihydro-3,3-dimethyl-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates **3a–e** with excess of hydrazine hydrate gave propanohydrazides **5a–e** in 70–99% yields. The ring opening of pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates **3a–e** proceeded stereoselectively, furnishing the *rel*-(4'*R*,5'*S*)-isomers of 3-[5-aryl-3,4-bis(hydrazinocarbonyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-3-methyl-butanohydrazides **5a–e**. The X–ray structure of **5a** was determined.

Keywords: Heterocycles, pyrazoles, 1*H*,5*H*-pyrazolo[1,2–*a*]pyrazol-1-ones, hydrazides, ring opening, x–ray

Introduction

3-Pyrazolidinones and their fused analogues, 1*H*,5*H*-pyrazolo[1,2–*a*]pyrazol-1-ones, are interesting classes of heterocyclic compounds which, since the beginning of a systematic work in this area more than four decades ago, found a widespread use in various applications.[1] For example, phenidone and its derivatives and analogues are used in photographic applications[2] and as inhibitors of cyclooxygenase, lipooxygenase, and γ-aminobutyrate transferase.[3] Bicyclic pyrazolo[1,2–*a*]pyrazol-1-ones have been prepared as scaffolds for β-turn mimics.[4] Such an example is Lilly's bicyclic pyrazolidinone LY 186826 exhibiting antibiotic activity which is larger than that of several penicillins and cephalosporins (Figure 1).[5]

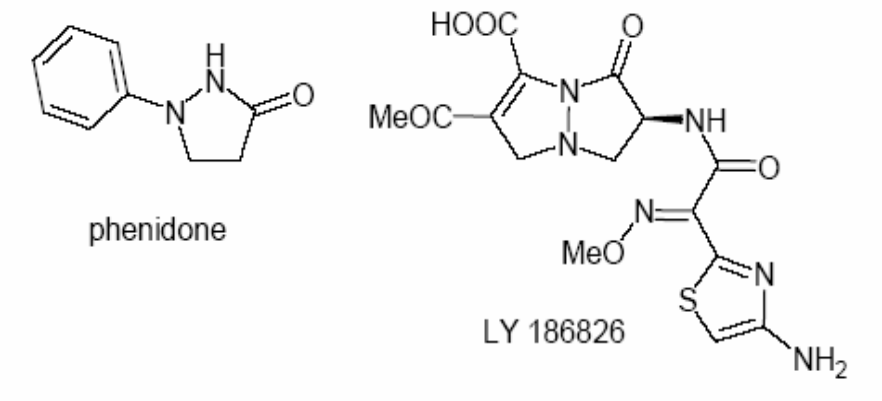
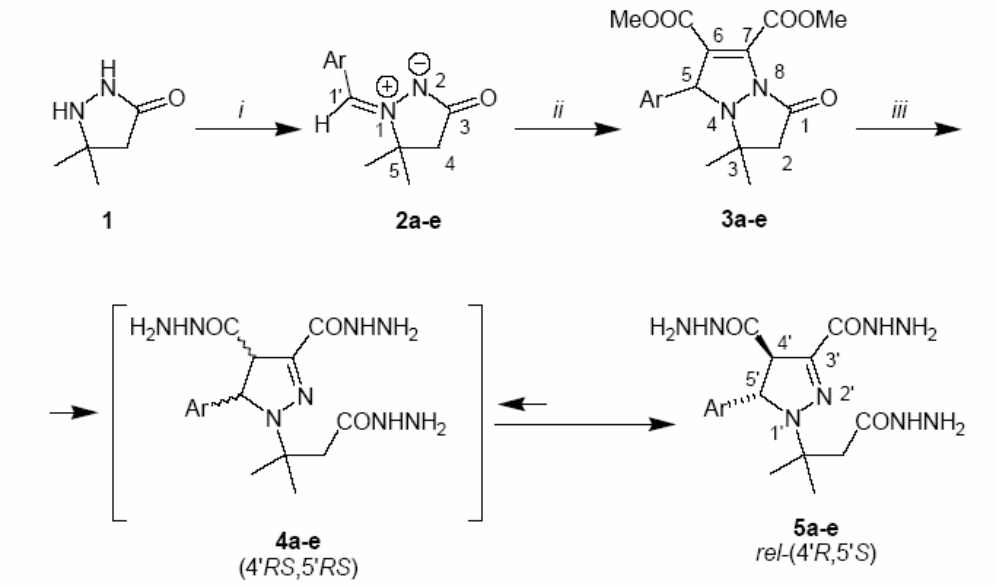


Figure 1

Recently, we have shown that *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone and 5,5-dimethyl-3-pyrazolidinone (**1**) can be used for various synthetic purposes, such as for the regio- and stereoselective preparation of substituted pyrazolo[1,2–*a*]pyrazol-1-one derivatives,[6,7] *rel*-(2*R*,3*R*)-3-alkylamino-3-phenylalaninamides,[8] *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-(pyrazol-1-yl)alanine esters,[9,10] and alkaloid-like tetracyclic system.[11] In continuation of our work in this field, we now report a stereoselective formation of *rel*-(4'*R*,5'*S*)-3-[5-aryl-3,4-bis(hydrazinocarbonyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-3-methylbutanohydrazides **5a–e** from easily available dimethyl 5-aryl-2,3-dihydro-3,3-dimethyl-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates **3a–e**.

Results and Discussion

Starting compounds, dimethyl 5-aryl-2,3-dihydro-3,3-dimethyl-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates **3a–e** were prepared in two steps from 5,5-dimethyl-3-pyrazolidinone (**1**)[12] *via* azomethine imines **2a–e** according to the general procedure described previously.[7] Treatment of compounds **3a–e** with excess of hydrazine hydrate in ethanol at room temperature gave *rel*-(4'*R*,5'*S*)-3-[5-aryl-3,4-bis(hydrazinocarbonyl)-4,5-dihydro-1*H*-pyrazol-1-yl)]-3-methylbutanohydrazides **5a–e** in 70–99% yields. An explanation for the high stereoselectivity of ring opening transformations of **3a–e** with excess of hydrazine hydrate could be initial formation of the (4'*RS*,5'*RS*)-3-[5-aryl-3,4-bis(hydrazinocarbonyl)-4,5-dihydro-1*H*-pyrazol-1-yl)]-3-methylbutanohydrazides **4a–e** followed by isomerization of **4a–e** into thermodynamically more stable *rel*-(4'*R*,5'*S*)-isomers **5a–e** with the *trans* relative configuration. On the other hand, the kinetic factors should not be excluded, since they might also contribute to the stereoselectivity of these transformations (Scheme 1).



Scheme 1

Reagents and conditions: (i) ArCHO, EtOH, CF_3COOH, 20°. (ii) dimethyl acetylenedicarboxylate, 110–150°. (iii) N_2H_4 x H_2O, EtOH, 20°.

Structures of novel compounds **2e**, **3e**, and **5a–e** were determined by spectroscopic methods and by analyses for C, H, and N. The *trans* relative configuration around the C(4')–C(5') single bond in the pyrazoline part of compounds **5a–e** was established on the basis of the magnitude of the $J_{H4',H5'}$ coupling contants. The coupling constants ($J_{H4',H5'}$ = 7.0–9.8 Hz) in compounds **5a–e** are in agreement with the literature values for the *trans*-4,5-dihydro-4,5-disubstituted-1*H*-pyrazoles ($J_{H4,H5}$ = 3–10 Hz for the *trans*-isomers and $J_{H4,H5}$ = 10–14 Hz for the *cis*-isomers).[1,13] Moreover, configuration of compounds **4a–e** was unambigously established upon X–ray structural determination of a 1:1 adduct of ethanol and **5a** (Figure 2).

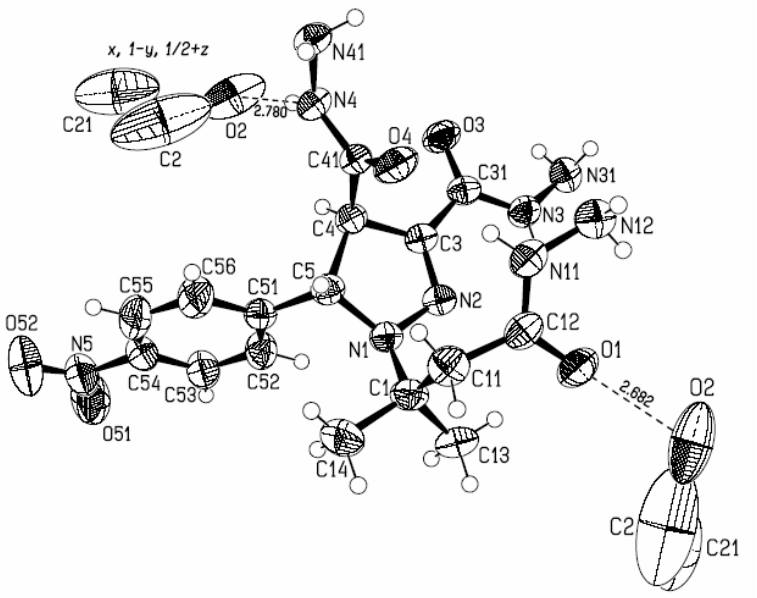


Figure 2. Ortep view of the adduct of compound **5a** and EtOH at the 50% probability level. H atoms are drawn as circles of arbitrary radii. X-Ray structure determination

Structure of adduct of compound **5a** and EtOH was solved by direct method using the SIR92 program.[14] All hydrogen atoms, except those of the disordered ethanol molecule, were located by difference Fourier synthesis and included in refinement with positional parameters and fixed individual isotropic displacement parameters of the bonded atoms. Full-matrix least-squares refinement on *F* of all non-hydrogen atoms with anisotropic displacement parameters and an empirical weighting scheme: $w = w_f * w_s$, wf (Fo<9.5) = $(Fo/9.5)^{1.5}$, w_f (Fo>14.0) = $(14.0/Fo)^{0.7}$, w_f (9.5<F_o<14.0)=1.0, $w_s(\sin\theta/\lambda<0.6) = ((\sin\theta/\lambda)/0.6)^2$, $w_s(\sin\theta/\lambda>0.64) = (0.64/(\sin\theta/\lambda))$, $w_s(0.6<\sin\theta/\lambda<0.64) = 1.0$ was applied.

Crystal data

$C_{18}H_{29}N_9O_6$	D_x = 1.319 Mg m^{-3}
M_r = 467.485	Mo *K*α radiation
Monoclinic, *C2/c*	Cell parameters from 75
a = 35.281(3) Å	reflections
b = 8.4045(6) Å	θ = 8.02 - 14.57°
c = 16.033(1) Å	μ = 0.09484 mm^{-1}
β = 97.942(7)°	*T* = 293(1) K
V = 4708.5(6) Å^3	Irregular form, colorless
Z = 8	0.42 x 0.57 x 0.76 mm

Data collection

Enraf-Nonius CAD-4 diffractometer	θ*max* = 28°

Profile data from ω scans	h = -46 → 46
Absorption correction: none	k = -11 → 11
22728 measured reflections	l = -21 → 20
5657 independent reflections	3 standard reflections
3414 reflections with $I > 2.5\sigma(I)$	frequency: 333 min
R_{int} = 0.0181	intensity decay 1.15%

Refinement

Refinement on F	w = empirical
R = 0.061	$(\Delta/\sigma)_{max}$ = 0.019
wR = 0.073	$(\Delta/\sigma)_{aver}$ = 0.0007
S = 0.979	$\Delta\rho_{max}$ = 1.0 e Å^{-3}
3414 reflections	$\Delta\rho_{min}$ = -0.6 e Å^{-3}
386 parameters	

The atoms of the solvent ethanol molecule have high displacement parameters showing a disorder of the ethyl group. The highest residual electron density in final difference map of 1.0 e Å^{-3} is close to this group too. The ethanol O atom is hydrogen bonded to O(1) of one molecule with a distance of 2.682(6) Å and to N(4) of another molecule with a distance of 2.780(7) Å.

The *Xtal3.4* system of crystallographic programs was used for the reduction of data, structure refinement and interpretation.[15] *ORTEPII* was used to produce molecular graphics.[16]

Supplementary data for this structure have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number **CCDC 155999**.

Fractional coordinates and equivalent displacement parameters (Å^2) for adduct of compound **5a** and EtOH. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U
O(1)	0.33594(7)	0.8203(3)	0.8941(1)	0.0618(7)
O(3)	0.27187(6)	0.4162(2)	0.5809(1)	0.0579(6)
O(4)	0.31768(7)	0.2641(2)	0.7929(1)	0.0614(7)
O(51)	0.5199(1)	0.2618(5)	0.4994(3)	0.100(1)
O(52)	0.5273(1)	0.0548(5)	0.5804(3)	0.105(1)
O(2)	0.3337(1)	1.0030(4)	1.0304(2)	0.111(2)
N(1)	0.38447(6)	0.5608(2)	0.7328(1)	0.0421(6)
N(11)	0.31206(7)	0.5735(3)	0.8795(2)	0.0521(7)
N(12)	0.27364(8)	0.6248(4)	0.8763(2)	0.0583(8)
N(2)	0.34821(6)	0.6148(3)	0.7026(1)	0.0411(6)
N(3)	0.27362(7)	0.6701(3)	0.6282(1)	0.0470(7)
N(31)	0.23744(7)	0.7132(3)	0.5853(2)	0.0501(7)
N(4)	0.31661(6)	0.0857(2)	0.6881(1)	0.0428(6)
N(41)	0.29546(8)	-0.0309(3)	0.7252(2)	0.0477(7)
N(5)	0.51121(8)	0.1794(4)	0.5571(2)	0.072(1)

C(1)	0.40203(7)	0.6409(3)	0.8112(2)	0.0482(8)
C(11)	0.38012(9)	0.6041(4)	0.8863(2)	0.0538(9)
C(12)	0.34077(8)	0.6751(3)	0.8857(1)	0.0473(8)
C(13)	0.4034(1)	0.8191(4)	0.7931(2)	0.059(1)
C(14)	0.44293(9)	0.5785(5)	0.8331(2)	0.065(1)
C(3)	0.32789(7)	0.5018(3)	0.6663(1)	0.0387(6)
C(31)	0.28836(7)	0.5262(3)	0.6216(1)	0.0401(6)
C(4)	0.34698(7)	0.3405(3)	0.6734(2)	0.0400(7)
C(41)	0.32510(7)	0.2260(3)	0.7230(1)	0.0390(6)
C(5)	0.38639(7)	0.3847(3)	0.7251(2)	0.0422(7)
C(51)	0.41975(7)	0.3331(3)	0.6813(2)	0.0432(7)
C(52)	0.43364(8)	0.4293(4)	0.6222(2)	0.0522(8)
C(53)	0.46354(9)	0.3795(4)	0.5810(2)	0.0566(9)
C(54)	0.47906(8)	0.2313(4)	0.6001(2)	0.0548(9)
C(55)	0.4660(1)	0.1330(4)	0.6582(3)	0.071(1)
C(56)	0.4363(1)	0.1850(4)	0.6993(3)	0.066(1)
C(2)	0.3724(5)	1.089(1)	1.0365(5)	0.216(7)
C(21)	0.3743(4)	1.200(1)	0.9844(6)	0.179(5)

Bond Distances（Å^2）and Bond Angles (°) for adduct of compound **5a** and EtOH with e.s.d.'s in parentheses

O(1)-C(12)	1.242(3)	C(1)-C(11)	1.549(4)
O(3)-C(31)	1.230(3)	C(1)-C(13)	1.528(4)
O(4)-C(41)	1.228(3)	C(1)-C(14)	1.530(4)
O(51)-N(5)	1.229(6)	C(11)-C(12)	1.510(4)
O(52)-N(5)	1.224(5)	C(3)-C(31)	1.492(3)
O(2)-C(2)	1.53(2)	C(3)-C(4)	1.511(3)
N(1)-N(2)	1.381(3)	C(4)-C(41)	1.524(4)
N(1)-C(1)	1.484(3)	C(4)-C(5)	1.563(3)
N(1)-C(5)	1.487(3)	C(5)-C(51)	1.516(4)
N(11)-N(12)	1.416(4)	C(51)-C(52)	1.386(4)
N(11)-C(12)	1.318(4)	C(51)-C(56)	1.388(4)
N(2)-C(3)	1.280(3)	C(52)-C(53)	1.384(5)
N(3)-N(31)	1.411(3)	C(53)-C(54)	1.378(4)
N(3)-C(31)	1.327(3)	C(54)-C(55)	1.372(5)
N(4)-N(41)	1.412(3)	C(55)-C(56)	1.382(6)
N(4)-C(41)	1.321(3)	C(2)-C(21)	1.26(2)
N(5)-C(54)	1.472(5)		
N(2)-N(1)-C(1)	114.0(2)	O(3)-C(31)-N(3)	124.5(2)

N(2)-N(1)-C(5)	110.4(2)	O(3)-C(31)-C(3)	119.6(2)
C(1)-N(1)-C(5)	120.2(2)	N(3)-C(31)-C(3)	115.9(2)
N(12)-N(11)-C(12)	121.8(3)	C(3)-C(4)-C(41)	110.7(2)
N(1)-N(2)-C(3)	110.4(2)	C(3)-C(4)-C(5)	100.4(2)
N(31)-N(3)-C(31)	122.2(2)	C(41)-C(4)-C(5)	110.5(2)
N(41)-N(4)-C(41)	122.9(2)	O(4)-C(41)-N(4)	123.7(2)
O(51)-N(5)-O(52)	124.0(4)	O(4)-C(41)-C(4)	119.9(2)
O(51)-N(5)-C(54)	118.3(3)	N(4)-C(41)-C(4)	116.3(2)
O(52)-N(5)-C(54)	117.7(4)	N(1)-C(5)-C(4)	103.5(2)
N(1)-C(1)-C(11)	111.9(2)	N(1)-C(5)-C(51)	111.8(2)
N(1)-C(1)-C(13)	107.7(2)	C(4)-C(5)-C(51)	112.1(2)
N(1)-C(1)-C(14)	108.0(2)	C(5)-C(51)-C(52)	121.4(2)
C(11)-C(1)-C(13)	112.1(3)	C(5)-C(51)-C(56)	119.5(3)
C(11)-C(1)-C(14)	108.1(2)	C(52)-C(51)-C(56)	119.1(3)
C(13)-C(1)-C(14)	109.0(3)	C(51)-C(52)-C(53)	121.0(3)
C(1)-C(11)-C(12)	118.3(2)	C(52)-C(53)-C(54)	118.3(3)
O(1)-C(12)-N(11)	121.9(3)	N(5)-C(54)-C(53)	118.2(3)
O(1)-C(12)-C(11)	121.8(3)	N(5)-C(54)-C(55)	119.5(3)
N(11)-C(12)-C(11)	116.2(3)	C(53)-C(54)-C(55)	122.3(3)
N(2)-C(3)-C(31)	123.0(2)	C(54)-C(55)-C(56)	118.8(3)
N(2)-C(3)-C(4)	114.6(2)	C(51)-C(56)-C(55)	120.6(3)
C(31)-C(3)-C(4)	122.5(2)	O(2)-C(2)-C(21)	116(1)

Experimental Section

General Procedures. Melting points were taken with a Kofler micro hot stage. The ^{1}H–NMR and ^{13}C–NMR spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with [D_6]DMSO as solvent and Me_4Si as internal standard. The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400. The mass spectra were recorded with an Autospeck Q (VG-Analytical) spectrometer in Laboratory for Mass Spectroscopy (Jožef Stefan Institute, Ljubljana). All starting materials were commercially available (in most cases from Fluka) and purified following the standard techniques. 5,5-Dimethyl-3-pyrazolidinone (**1**)[12] and dimethyl 5-aryl-2,3-dihydro-3,3-dimethyl-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates **3a–d** were prepared according to the procedures described previously.[7]

5,5-Dimethyl-1-[(*Z*)-(2-hydroxyphenyl)methylidene]-3-pyrazolidinone-1-azomethine imine (2e). This compound was prepared according to general procedure described previously.[7] Trifluoroacetic acid (1 mL) was added to a stirred mixture of 5,5-dimethyl-3-pyrazolidinone **1** (1.14 g, 10 mmol), 2-hydroxybenzaldehyde (1.22 g, 10 mmol), and anhydrous ethanol (40 mL).

The mixture was stirred at 20° for 24 h. Volatile compounds were evaporated *in vacuo*, the residue was triturated with diethyl ether (30 mL), and the precipitate was collected by filtration to give azomethine imine **2e**. Yield: 1.99 g (91%), white crystals, m.p. 164–167°C (from toluene). ^{1}H–NMR ($CDCl_3$): δ 1.75 (6H, s, 2Me); 2.80 (2H, s, CH_2); 6.86 (1H, s, 1H–Ar); 6.97 (1H, m, 1H–Ar); 7.28 (1H, s, 1'–H); 7.37–7.44 (2H, m, 2H–Ar); 11.26 (1H, br s, OH). Anal. calcd. for $C_{12}H_{13}N_3O_3$ (218.26): C 66.04, H 6.47, N 12.83; found: C 65.77, H 6.79, N 12.84.

Dimethyl 2,3-Dihydro-3,3-dimethyl-5-(2'-hydroxyphenyl)-1-oxo-1*H*,5*H*-pyrazolo-[1,2–*a*]pyrazole (3e). This compound was prepared according to general procedure described previously.[7] A mixture of 5,5-dimethyl-1-[(Z)-(2-hydroxyphenyl)methylidene]-3-pyrazolidinone-1-azomethine imine **2e** (2.18 g, 10 mmol), dimethyl acetylenedicarboxylate (1.2 mL, 10 mmol), and xylene (40 mL) was heated under reflux for 30 min. Volatile components were evaporated *in vacuo*, the residue was triturated with diethyl ether (20 mL), and the precipitate was collected by filtration to give **3e**. Yield: 2.32g (64%), pale yellow crystals, m.p. 185–186°C (from toluene/ethanol, 3:1). ^{1}H–NMR (DMSO-d_6): δ 1.17 and 1.20 (2x3H, 2s, 5–Me_2); 2.41 (1H, d, *J* = 15.7 Hz, 2–Ha); 2.84 (1H, d, *J* = 15.7 Hz, 2–Hb); 3.50 and 3.87 (2x3H, 2s, 2OMe); 5.89 (1H, s, 5–H); 6.79 (2H, m, 2H–Ar); 7.08 (2H, m, 2H-Ph); 9.65 (1H, s, OH); ^{13}C–NMR (DMSO-d_6): 19.9, 25.2, 49.4, 52.6, 54.0, 62.5, 65.0, 114.5, 118.3, 121.0, 125.2, 130.0, 130.1, 134.7, 155.4, 159.8, 164.0, 166.4; Anal. calcd. for $C_{18}H_{20}N_2O_6$ (360.37): C, 59.99; H, 5.59; N, 7.77. Found: C, 60.05; H, 5.75; N, 7.94.

***rel*-(4'*S*,5'*R*)-3-[3,4-Bis(hydrazinocarbonyl)-4,5-dihydro-5-(4-nitrophenyl)-1*H*-pyrazol-1-yl]-3-methylbutanohydrazide (5a).** Hydrazine hydrate (98%, 2 mL, 40 mmol) was added to a stirred suspension of **3a** (1.560 g, 4 mmol) in anhydrous ethanol (15 mL) and the resulting solution was stirred at 20° until the precipitation of the product (0.5–1 h). The precipitate was collected by filtration and washed with ethanol to give **5a**. Yield: 1.670 g (99%), white ctrystals, m. p. 204–210°C (from ethanol). MS (FAB): m/z = 422 (MH^+). ^{1}H–NMR (DMSO-d_6): δ 1.05 (3H, s, Me); 1.09 (3H, s, Me); 2.28 (1H, d, *J* = 12.9 Hz, 2–Ha); 2.57 (1H, d, *J* = 12.9 Hz, 2–Hb); 3.64 (1H, d, *J* = 9.3 Hz, 4'–H); 4.27 (6H, br s, $3NH_2$); 5.07 (1H, d, *J* = 9.3 Hz, 5'–H); 7.47 (2H, d, *J* = 8.7 Hz, o–C_6H_4); 8.21 (2H, d, *J* = 8.7 Hz, m–C_6H_4); 8.88, 9.23, and 9.35 (3x1H, 3br s, 3NHCO). Anal. calcd. for $C_{16}H_{23}N_9O_5$ (421.42): C, 45.60; H, 5.50; N, 29.91. Found: C, 45.60; H, 5.64; N, 29.92.

***rel*-(4'*S*,5'*R*)-3-[3,4-Bis(hydrazinocarbonyl)-4,5-dihydro-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]-3-methylbutanohydrazide (5b).** Hydrazine hydrate (98%, 0.5 mL, 10 mmol) was added to a stirred suspension of **3b** (0.434 g, 1 mmol) in anhydrous ethanol (5 mL) and the resulting solution was stirred at 20° for 30 min. Volatile components were evaporated *in vacuo*, and the residue was triturated with with a mixture of diethyl ether (~ 5 mL) and ethanol (a few drops). The precipitate was collected by filtration and washed with diethyl ether to give **5b**. Yield: 0.448 g (96%), white crystals, m. p. 212–214°C (from ethanol). MS (EI): m/z = 466 (M^+). ^{1}H–NMR (DMSO-d_6) δ-ppm: 1.06 (3H, s, Me); 1.13 (3H, s, Me); 2.26 (1H, d, *J* = 13.2 Hz, 2–Ha); 2.62 (1H, d, *J* = 13.2 Hz, 2–Hb); 3.57 (1H, d, *J* = 9.6 Hz, 4'–H); 3.63 and 3.76 (3H and 6H, 2s, 3OMe); 4.20 (6H, br s, $3NH_2$); 4.83 (1H, d, *J* = 9.6 Hz, 5'–H); 6.48 (2H, s, *o*–C_6H_2); 8.92 and

9.20 (1H and 2H, 2br s, 3NHCO). HRMS calcd. for $C_{19}H_{30}N_8O_6$: 466.228831. Found: 466.229930. Anal. calcd. for $C_{19}H_{30}N_8O_6$ (466.49): C, 48.92; H, 6.48; N, 24.02. Found: C, 48.91; H, 6.79; N, 24.20.

***rel*-(4'*S*,5'*R*)-3-[3,4-Bis(hydrazinocarbonyl)-4,5-dihydro-5-(2,4,6-trimethoxyphenyl)-1*H*-pyrazol-1-yl]-3-methylbutanohydrazide (5c).** Hydrazine hydrate (98%, 1 mL, 20 mmol) was added to a stirred suspension of **3c** (0.868 g, 2 mmol) in anhydrous ethanol (10 mL) and the resulting solution was stirred at 20° for 30 min. Volatile components were evaporated in vacuo, and the residue was triturated with anhydrous ethanol (5 mL). The precipitate was collected by filtration and washed with ethanol to give **5c**. Yield: 0.730 g (78%), white crystals, m. p. 131–133°C (from ethanol). MS (EI): m/z = 466 (M^+). ^{1}H–NMR (DMSO-d_6) δ-ppm: 1.01 (3H, s, Me); 1.06 (3H, s, Me); 2.16 (1H, d, *J* = 13.6 Hz, 2–Ha); 2.69 (1H, d, *J* = 13.6 Hz, 2–Hb); 3.66, 3.74, and 3.76 (3x3H, 3s, 3OMe); 3.79 (1H, d, *J* = 8.7 Hz, 4'–H); 4.03, 4.15, and 4.27 (3x2H, 3br s, $3NH_2$); 5.28 (1H, d, *J* = 8.7 Hz, 5'–H); 6.18 and 6.23 (2x1H, 2s, m–C6H2); 8.59 and 9.06 (1H and 2H, 2br s, 3NHCO). HRMS calcd. for $C_{19}H_{30}N_8O_6$: 466.228831. Found: 466.229930. Anal. calcd. for $C_{19}H_{30}N_8O_6$ (466.49): C, 48.92; H, 6.48; N, 24.02. Found: C, 48.82; H, 6.55; N, 23.62.

***rel*-(4'*S*,5'*R*)-3-[3,4-Bis(hydrazinocarbonyl)-4,5-dihydro-5-(2,6-dichlorophenyl)-1*H*-pyrazol-1-yl]-3-methylbutanohydrazide (5d).** Hydrazine hydrate (98%, 0.5 mL, 10 mmol) was added to a stirred suspension of **3d** (0.434 g, 1 mmol) in anhydrous ethanol (5 mL) and the resulting solution was stirred at 20° until the precipitation of the product (0.5–1 h). The precipitate was collected by filtration and washed with ethanol to give **5d**. Yield: 0.334 g (75%), white crystals, m. p. 149–152°C (from ethanol). MS (EI): m/z = 444 (M^+). ^{1}H–NMR (DMSO-d_6) δ-ppm: 1.03 (3H, s, Me); 1.08 (3H, s, Me); 2.27 (1H, d, *J* = 12.8 Hz, 2–Ha); 2.54 (1H, d, *J* = 12.8 Hz, 2–Hb); 3.97 (1H, d, *J* = 9.8 Hz, 4'–H); 4.25 (6H, br s, $3NH_2$); 5.55 (1H, d, *J* = 9.8 Hz, 5'–H); 7.32 (1H, m, *p*–C_6H_3); 7.45 (2H, m, *m*–C_6H_3); 8.77, 9.20, and 9.25 (3x1H, 3br s, 3NHCO). HRMS calcd. for $C_{16}H_{22}Cl_2N_8O_3$: 444.119192. Found: 444.118211. Anal. calcd. for $C_{16}H_{24}N_8O_4$ (392.42): C, 43.16; H, 4.98; N, 25.16. Found: C, 42.31; H, 5.24; N, 24.71.

***rel*-(4'*S*,5'*R*)-3-[3,4-Bis(hydrazinocarbonyl)-4,5-dihydro-5-(2-hydroxyphenyl)-1*H*-pyrazol-1-yl]-3-methylbutanohydrazide (5e).** Hydrazine hydrate (98%, 1 mL, 20 mmol) was added to a stirred suspension of **3e** (0.721 g, 2 mmol) in anhydrous ethanol (10 mL) and the resulting solution was stirred at 20° for 2 h. Volatile components were evaporated *in vacuo*, and the residue was triturated with anhydrous ethanol (5 mL). The precipitate was collected by filtration and washed with ethanol to give **5e**. Yield: 0.550 g (70%), white crystals, m. p. 184–186°C (from ethanol). MS (EI): m/z = 392 (M^+). ^{1}H–NMR (DMSO-d_6) δ-ppm: 1.07 (3H, s, Me); 1.09 (3H, s, Me); 2.30 (1H, d, *J* = 12.8 Hz, 2–Ha); 2.55 (1H, d, *J* = 12.8 Hz, 2–Hb); 3.59 (1H, br d, *J* = 7 Hz, 4'–H); 4.16 and 4.27 (4H and 2H, 2br s, $3NH_2$); 5.18 (1H, br d, *J* = 7 Hz, 5'–H); 6.73–6.78 (2H, m, 2H–Ar); 7.01–7.06 (2H, m, 2H–Ar); 8.86, 9.12, and 9.15 (3x1H, 3br s, 3NHCO); 9.44 (1H, br s, OH). HRMS calcd. for $C_{16}H_{24}N_8O_4$: 392.192052. Found: 392.193050. Anal. calcd. for $C_{16}H_{24}N_8O_4$ (392.42): C, 48.97; H, 6.16; N, 28.55. Found: C, 48.47; H, 6.34; N, 28.58.

Acknowledgements

The financial support from the Ministry of Science and Technology, Slovenia, is gratefully acknowledged.

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