Convenient synthesis of some methyl-*N*-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)-acetylamino]amino acid esters

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Abstract

An efficient *one-pot* synthesis of methyl-*N*-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)-acetylamino]amino acid esters **5a-j** and dipeptides **8a-f** were successfully synthesized starting from amino acid esters **4** and azides **3**, **7,** respectively. The hydrazide **6a** was further reacted with selected aldehydes to give the corresponding hydrazones **9a-c**.

Keywords: Amino acids, dipeptide, azide coupling, hydrazones

Introduction

Pyridazines represent an important class of biologically active compounds. Recently, a number of 6-aryl-4,5-dihydropyridazin-3(2*H*)-ones have been reported to possess antimicrobial,[1,2] potent analgesic,[3] anti-inflammatory,[3-7] antifeedant,[8] herbicidal,[9] antihypertensive,[10-12] antiplatelet activities,[13-15] anticancer effects[16] and other anticipated biological[17] and pharmacological properties.[8,19] Imazodan **I** is reported to show ionotropic properties comparable to milrinone and amrinone **II**. Emorfazone **III** is an analgesic and anti-inflammatory compound marketed as pentoil and nandron.[20-23]

Also, a series of benzyl pyridazinones **IV** were evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs).[24] Several members of this series showed good activity against the wild-type virus and NNRTI resistant viruses. Crystal structures of inhibitors bound to HIV-RT demonstrated that the pyridazinones **V** interact with the protein backbone through a pair of hydrogen bonds between the amide of the K103 amino acid and the N-NH acceptor–donor motif of the pyridazinone. Inspection of the small molecule crystal structures of the inhibitors themselves revealed that in the solid state the pyridazinones were associated through extensive aromatic stacking interactions.[25]

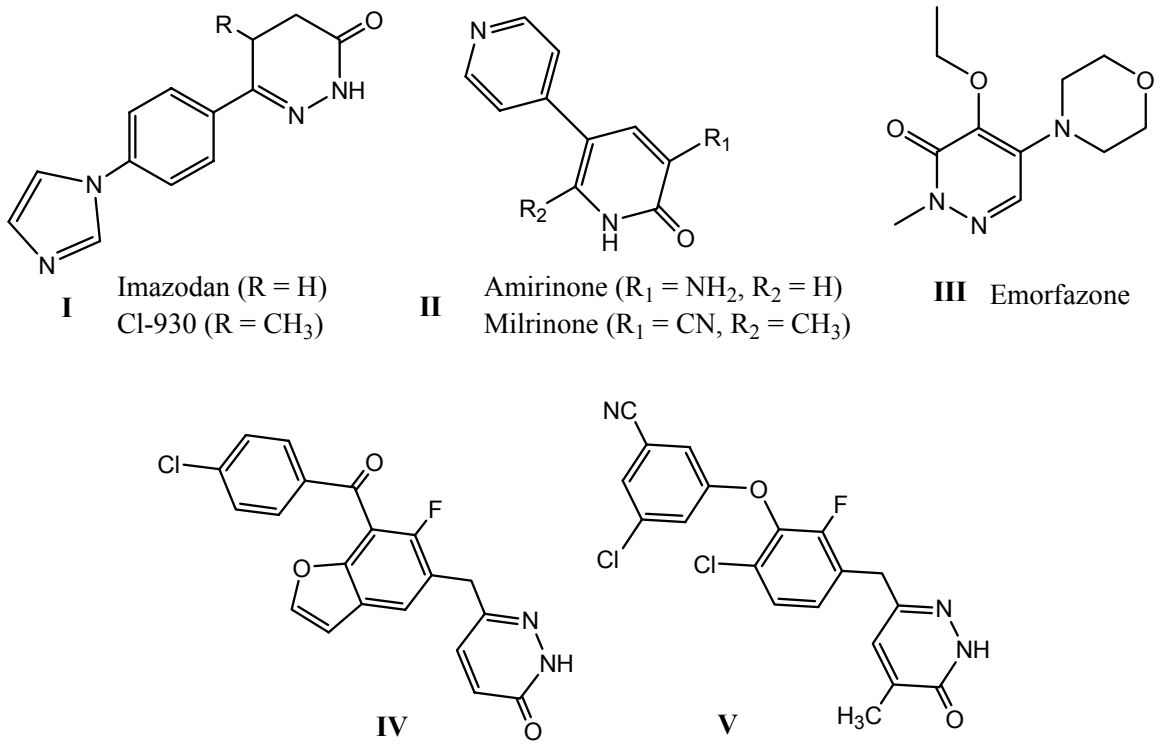
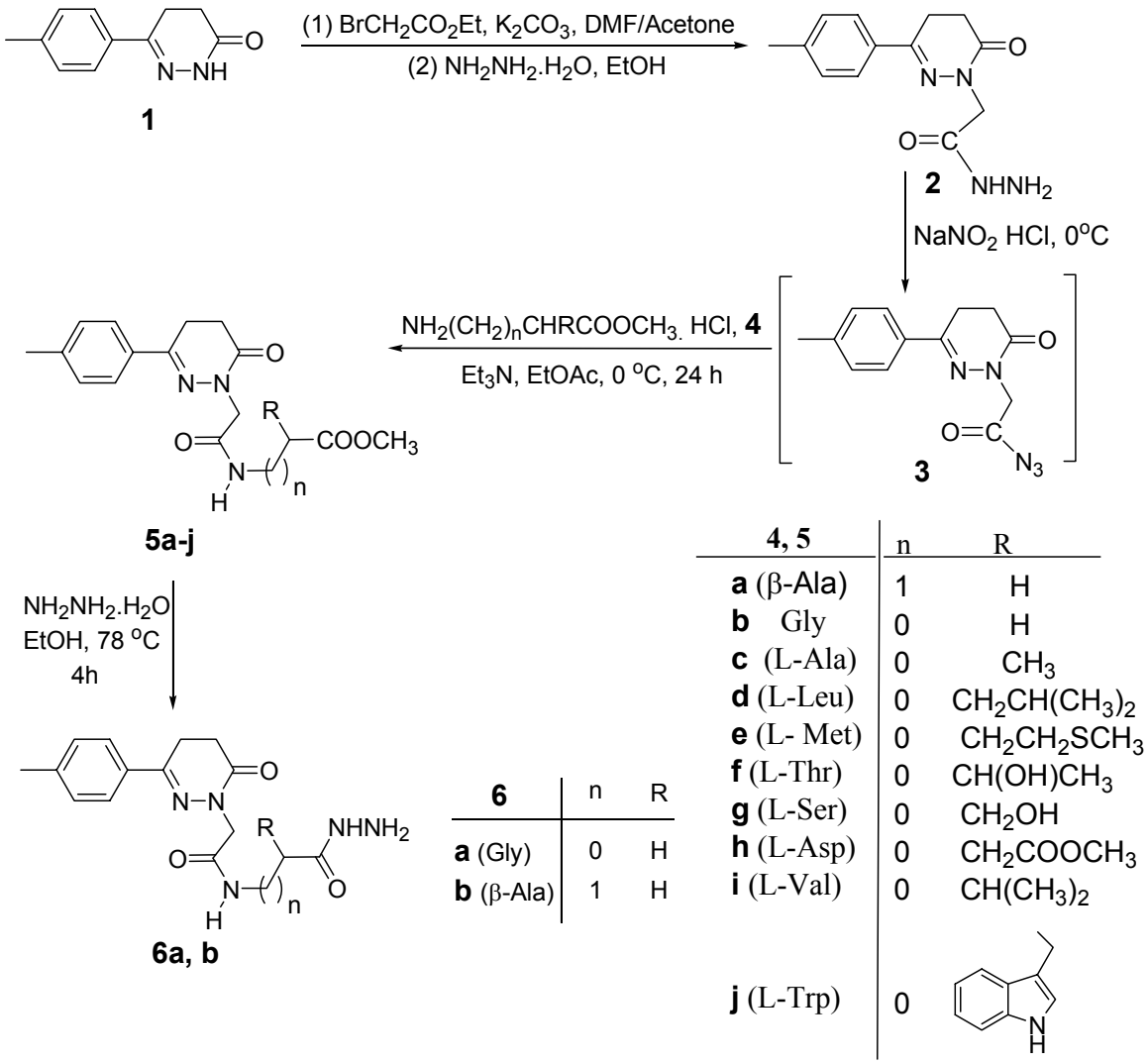


Figure 1. Biological active pyridazinones.

In this paper, we describe the development of a new series of dihydro-2*H*-pyridazin-3-one derivatives, whose chemical modifications include *N*-terminal coupled amino acid and dipeptide derivatives.

Results and Discussion

The synthesis of new amino acid derivatives coupled with biologically active heterocyclic moieties such as triazole quinazoline[26] and quinoline[27] attracted our attention. In this work we studied 6-*p*-tolyl-4,5-dihydropyridazin-3(2*H*)-one (**1**) as biologically active heterocyclic moiety. The hydrazide **2** could be prepared by regioselective *N*-alkylation from **1** with ethyl bromoactetate which was subsequently hydrazinolyzed by hydrazine hydrate (Scheme 1). The procedures of those steps were already established in the literature.[28-30]

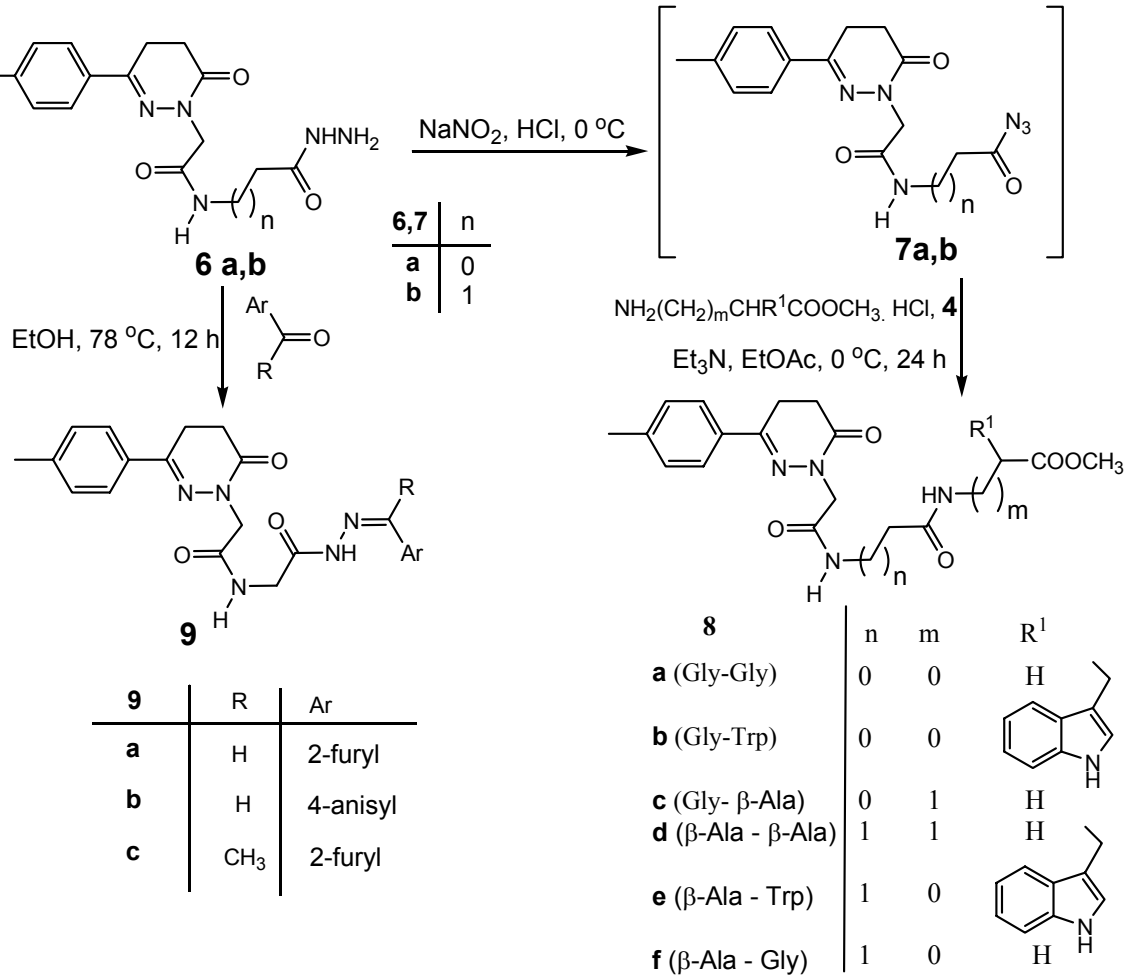


Scheme 1

The acyl azide route is one of the first routes developed for peptide coupling by Curtius.[31] The synthesis of the target amino acid derivatives **5a-j** were efficiently formed *via* the azide coupling method,[26,27,32-34] which was reported to minimize the degree of racemization in amino acid coupling. The *in situ* generated azide **3** solution in ethyl acetate reacted with an amino acid methyl ester hydrochloride **4** in the presence of triethyl amine to afford methyl-*N*-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)-acetylamino]amino acid esters **5a-j** in good yield. Further development of the azide coupling was obtained by the synthesis of *N*-substituted dipeptide derivatives **8a-f**. Thus, boiling the amino acid ester derivatives **5a,b** (β-Ala, Gly) with hydrazine hydrate gave the acyl hydrazides **6a,b** (Scheme1).

Nitrosation of acyl hydrazides **6a,b** finally gave the acyl azides **7a,b** by treatment with $NaNO_2$ and HCl mixture. The *in situ* generated azides **7a,b** in ethyl acetate reacted with amino acid methyl esters hydrochloride **4** in the presence of triethyl amine produced dipeptide

derivatives **8a-f** in good yield. On the other hand, various *N*-acylheteroarylhydrazones (NAH) have been synthesized and were found to possess very interesting biological activities.[33,35] The Glycyl hydrazide **6a** was condensed with aldehydes and 2-acetyl furan to exhibit the hydrazone **9a-c** (Scheme 2).



6,7	n
a	0
b	1

9	R	Ar
a	H	2-furyl
b	H	4-anisyl
c	CH_3	2-furyl

8	n	m	R^1
a (Gly-Gly)	0	0	H
b (Gly-Trp)	0	0	
c (Gly- β-Ala)	0	1	H
d (β-Ala - β-Ala)	1	1	H
e (β-Ala - Trp)	1	0	
f (β-Ala - Gly)	1	0	H

Scheme 2

The structural assignment of the *N*-substituted amino acid esters **5a-j**; acyl hydrazide **6;** the *N*-substituted dipeptides **8a-f** and acyl hydrazones **9a-c** is based on ^{1}H NMR spectral and physicochemical analyses, Figure 2.

The ^{1}H NMR spectra clearly confirm the regioselective *N*-alkylation for all isolated products. Thus, the ^{1}H NMR spectrum of **5a** gave a singlet at 4.51 ppm typically associated with NCH_2. Furthermore, a multilplet, a triplet, and two singlets at 3.49-3.46, 2.51, 3.55 and 6.63 ppm associated with two CH_2, OMe and NH groups, respectively. Also, the ^{1}H NMR spectra of all compounds showed two triplets at 2.64 and 3.01 ppm associated with the two CH_2 groups of the pyridazine skeleton.

The ^{1}H NMR spectrum of the *N*-substituted dipeptide **8f** exhibits signals at δ 2.83-2.81, 3.80-3.78, 4.09, 6.83 and 8.97 ppm corresponding to functionalities found at the dipeptide chain; two CH_2 (β-alanine residue), CH_2 (glycyl residue) and two NH groups, respectively.

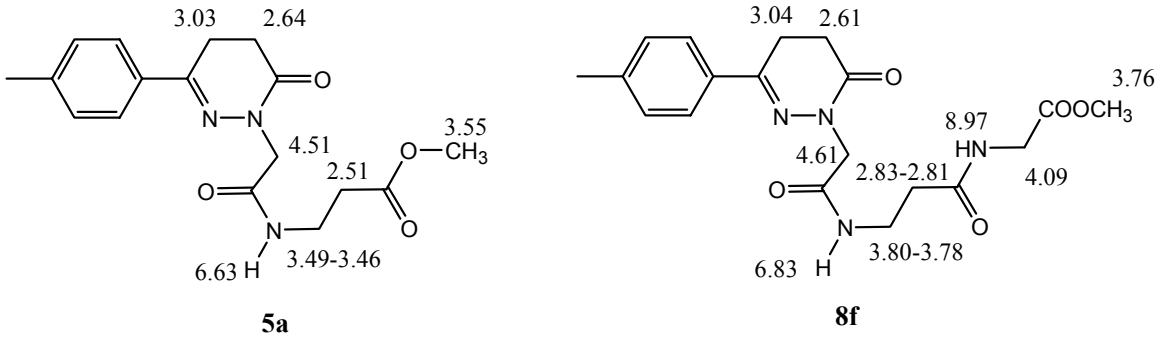
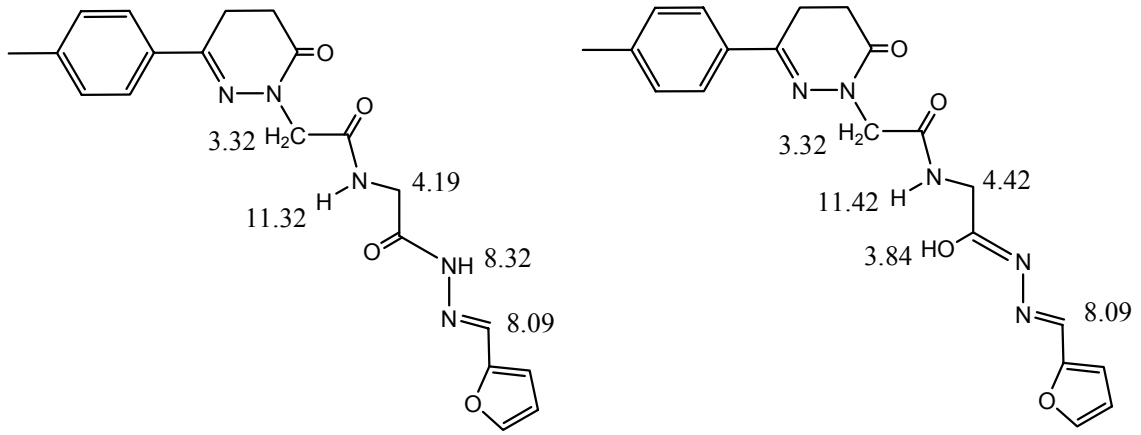


Figure 2. Selected ^{1}H NMR of compounds **5a** and **8f**.

The ^{1}H NMR spectrum of **9a** in DMSO (figure 3), gave two D_2O exchangeable broad signals at δ 11.32 and 8.32 ppm with similar intensities, in addition to two D_2O exchangeable broad signals at δ 11.42 and 3.84 ppm with larger intensities. We might conclude that the hydrazone **9a** solution in DMSO is present in the form of two tautomers (structure A) and (structure B)[26] with intramolecular hydrogen bonds of the type N–H···N=C stabilizing each form in 1:2, respectively. The participation of the NH group in the N–H···N=C system is confirmed by a signal at δ 11.32 (structure A). Structure B is induced by enolization of the hydrazide carbonyl which gave a signal at δ 11.42 and 3.84 ppm corresponding to an NH group and an exocyclic OH group, respectively.



Structure A Structure B

Figure 3. Selected ^{1}H NMR of compounds **9a**.

In conclusion we have developed the synthesis of a new series of dihydro-2*H*-pyridazin-3-one derivatives coupled to *N*-terminal amino acids and dipeptide derivatives.

Experimental Section

General Procedures. Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 ^{o}C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Elemental analyses were performed on a *Flash EA-1112* instrument. at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. NMR spectra measured with Bruker (200 MHz) and TMS (0.00 ppm) was used as internal standard. The mass spectra were measured with a KRATOS Analytical Kompact spectrometer.
The starting compounds **1** - **3** were prepared according to described methods.[30]

General procedure for azide method; preparation of 5
To a cold solution (-5 ^{o}C) of hydrazide **2** (1.0 mmol, 0.26 g) in acetic acid (6 mL), 1 N HCl (3 ml), and water (25 mL), a solution of $NaNO_2$ (0.87 g, 1.0 mmol) was added in cold water (3 mL). The reaction mixture was stirred at -5 ^{o}C for 15 min. The yellow syrup formed was extracted with cold ethyl acetate (30 mL), washed with cold 3% $NaHCO_3$, H_2O and finally dried (Na_2SO_4). To this solution amino acid ester **4** (1.0 mmol) in ethyl acetate (20 mL) containing 0.2 mL of Et_3N was added. The reaction mixture was kept at -5 ^{o}C for 24 h., then at 25 ^{o}C for another 24 h. The solution was evaporated to dryness, and the residue was crystallized from petroleum ether/ethyl acetate to give the desired product.
Methyl-3-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino]-propanoate (5a). From β-AlaOCH$_3$·HCl **4a** (0.14 g). Colorless crystals (0.23 g, 69 %); mp 161 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.63 (2H, d, J = 8.4, ArH), 7.21 (2H, d, J = 8.2, ArH), 6.63 (1H, bs, D_2O exchangeable, NH), 4.51 (2H, s, NCH_2), 3.55 (3H, s, OMe), 3.49-3.46 (2H, m, NCH_2), 3.03 (2H, t, J = 8.4, CH_2 ring), 2.64 (2H, t, J = 8.4, CH_2 ring), 2.51 (2H, t, J = 6.0, CH_2); 2.38 (3H, s, Me), ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 20.7, 26.8, 32.3, 35.1, 38.2, 50.8, 52.6, 128.0, 128.4, 128.6, 139.3, 154.9, 171.4, 172.0, 179.3;
Anal. Calcd. For $C_{17}H_{21}N_3O_4$ (331.37): C, 61.62; H, 6.39; N, 12.68; Found: C, 61.47; H, 6.41; N, 12.59.
Methyl-2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino]-acetate (5b). From GlyOCH$_3$·HCl **4b** (0.13 g). Colorless crystals (0.24 g, 76%); mp 139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.68 (2H, d, J = 8.2, ArH), 7.24 (2H, d, J = 8.2, ArH), 6.63 (1H, bs, D_2O exchangeable, NH), 4.60 (2H, s, NCH_2), 4.09 (2H, d, J = 5.0, CH_2), 3.76 (3H, s, OMe), 3.03 (2H, t, J = 8.2, CH_2 ring), 2.71 (2H, t, J = 8.2, CH_2 ring), 2.41 (3H, s, Me), ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 20.8, 27.0, 32.5, 45.7, 50.3, 52.5, 128.2, 128.4, 128.5, 139.4, 155.2, 171.2,

171.8, 179.0; Anal. Calcd. For $C_{16}H_{19}N_3O_4$ (317.34): C, 60.56; H, 6.03; N, 13.24; Found: C, 60.44; H, 6.11; N, 13.01, Mass spectrum, m/z (I_r/%): 318(2), 317(11), 202 (8), 201(54), 200(22), 144(26), 130(6), 91(30), 90(36), 55(100).

Methyl-2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino]- propanoate (5c). From L AlaOCH$_3$·HCl **4c** (0.14 g). Colorless crystals (0.21 g, 63%); mp 116 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.67 (2H, d, *J* = 8.0, ArH), 7.24 (2H, d, *J* = 8.2, ArH), 6.75 (1H, bs, D_2O exchangeable, NH), 4.66-4.64 (1H, m, CH), 4.58 (2H, s, NCH_2), 3.75 (3H, s, OMe), 3.05 (2H, t, *J* = 8.2, CH_2 ring), 2.67 (2H, t, *J* = 8.2, CH_2 ring), 2.41 (3H, s, Me), 1.44 (3H, d, *J* = 7.2, Me). Anal. Calcd. For $C_{17}H_{21}N_3O_4$ (331.37): C, 61.62; H, 6.39; N, 12.68; Found: C, 61.53; H, 6.37; N, 12.64.

Methyl-4-methyl-2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetylamino]-pentanoate (5d). From LeuOCH$_3$·HCl **4d** (0.18 g). Colorless crystals (0.27 g, 72%); mp 88 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.67 (2H, d, *J* = 8.4 Hz, ArH), 7.24 (2H, d, *J* = 8.4 Hz, ArH), 6.63 (1H, bs, D_2O exchangeable, NH), 4.72-4.70 (1H, m, CH), 4.59 (2H, s, NCH_2), 3.73 (3H, s, OMe), 3.04 (2H, t, *J* = 7.2 Hz, CH_2 ring), 2.70 (2H, t, *J* = 7.2 Hz, CH_2 ring), 2.41 (3H, s, Me), 1.66-1.64 (3H, m, CH_2CH), 0.94-0.92 (6H, m, 2 CH_3). Anal. Calcd. For $C_{20}H_{27}N_3O_4$ (373.20): C, 64.32; H, 7.29; N, 11.25; Found: C, 64.21; H, 7.37; N, 11.13.

Methyl-4-methylsulfanyl-2[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetylamino]-butanoate (5e). From MetOCH$_3$·HCl **4e** (0.20 g). Colorless crystals (0.25 g, 64%); mp 82 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.67 (2H, d, *J* = 8.2 Hz, ArH), 7.24 (2H, d, *J* = 8.2 Hz, ArH), 6.63 (1H, d, D_2O exchangeable, *J* = 7.2 Hz, NH), 4.76 (1H, m, CH), 4.59 (2H, s, NCH_2), 3.75 (3H, s, OMe), 3.05 (2H, t, *J* = 7.0 Hz, CH_2 ring), 2.67 (2H, t, *J* = 7.0 Hz, CH_2 ring), 2.51 (2H, t, *J* = 7.4 Hz, CH_2), 2.41 (3H, s, Me), 2.19 (2H, m, CH_2), 2.05 (3H, s, SMe). Anal. Calcd. For $C_{19}H_{25}N_3O_4S$ (391.48): C, 58.29; H, 6.44; N, 10.73; Found: C, 58.08; H, 6.23; N, 10.55.

Methyl-3-hydroxy-2[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetylamino]-butanoate (5f). From ThrOCH$_3$·HCl **4f** (0.12 g). Colorless crystals (0.22 g, 61%); mp 166 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 8.05 (1H, bs, D_2O exchangeable, NH), 7.65 (2H, d, *J* = 8.0 Hz, ArH), 7.24 (2H, d, *J* = 8.0 Hz, ArH), 5.00-4.98 (1H, m, CH), 4.59 (2H, d, *J* = 4.0 Hz, NCH_2), 4.13 - 4.34 (1H, m, CH), 3.64 (3H, s, OMe), 3.29 (H, bs, D_2O exchangeable, OH), 2.99 (2H, t, *J* = 8.2 Hz, CH_2 ring), 2.54 (2H, t, *J* = 8.2 Hz, CH_2 ring), 2.34 (3H, s, Me), 1.06 (3H, d, *J* = 6.4 Hz, CH_3), ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 19.8, 20.7, 27.3, 32.6, 50.5, 51.0, 52.7, 63.2, 128.1, 128.3, 128.7, 140.0, 155.1, 170.8, 174.1, 178.8; Anal. Calcd. For $C_{18}H_{23}N_3O_5$ (361.39): C, 59.82; H, 6.41; N, 11.63; Found: C, 59.54; H, 6.44; N, 11.51.

Methyl-3-hydroxy-2[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetylamino]-propanoate (5g). From SerOCH$_3$·HCl **4g** (0.11 g). Colorless crystals (0.24 g, 69%); mp 153 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 8.22 (1H, bs, D_2O exchangeable, NH), 7.67 (2H, d, *J* = 8.2 Hz, ArH), 7.28 (2H, d, *J* = 8.2 Hz, ArH), 5.06-5.04 (1H, m, CH), 4.62 (2H, d, *J* = 3.8 Hz, NCH_2), 4.24-4.22 (2H, m, CH_2), 3.71 (3H, s, OMe), 3.34 (1H, bs, D_2O exchangeable, OH), 3.05 (2H, t,

J = 8.0 Hz, CH_2 ring), 2.66 (2H, t, *J* = 8.2 Hz, CH_2 ring), 2.42 (3H, s, Me). Anal. Calcd. For $C_{17}H_{21}N_3O_5$ (374.37): C, 58.78; H, 6.09; N, 12.10; Found: C, 58.71; H, 5.99; N, 12.18.

Dimethyl-2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino]-succinate (5h). From AspOCH_3·HCl **4h** (0.14 g). Colorless crystals (0. 23 g, 59%); mp 123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.68 (2H, d, *J* = 7.8 Hz, ArH), 7.24 (2H, d, *J* = 7.8 Hz, ArH), 7.16 (1H, d, *J* = 8.8 Hz, D_2O exchangeable, NH), 4.92-4.89 (1H, m, CH), 4.61 (2H, s, NCH_2), 3.74 (3H, s, OMe), 3.61 (3H, s, OMe), 3.06 (2H, t, *J* = 7.8 Hz, CH_2 ring), 2.89-2.87 (2H, m, CH_2), 2.68 (2H, t, *J* = 7.8 Hz, CH_2 ring), 2.41 (3H, s, Me). Anal. Calcd. For $C_{19}H_{23}N_3O_6$ (389.40): C, 58.60; H, 5.95; N, 10.79; Found: C, 58.42; H, 5.79; N, 10.60.

Methyl-3-methyl-2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetylamino]-butanoate (5i). From ValOCH_3·HCl **4i** (0.12 g). Colorless crystals (0.21 g, 58%); mp 85°C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.68 (2H, d, *J* = 8.4 Hz, ArH), 7.24 (2H, d, *J* = 7.8 Hz, ArH), 6.78 (1H, d, *J* = 8.8 Hz, D_2O exchangeable, NH), 4.64-4.58 (1H, m, CH), 4.61 (2H, s, NCH_2), 3.74 (3H, s, OMe), 3.04 (2H, t, *J* = 7.8 Hz, CH_2 ring), 2.69 (2H, t, *J* = 8.0 Hz, CH_2 ring), 2.41 (3H, s, Me), 2.17-2.15 (1H, m, CH), 0.96 (3H, d, *J* = 7.0 Hz, Me), 0.90 (3H, d, 7 Hz, Me). Anal. Calcd. For $C_{19}H_{25}N_3O_4$ (359.42): C, 63.49; H, 7.01; N, 11.69; Found: C, 63.28; H, 6.96; N, 11.55.

Methyl-3-(1H-indol-3-yl)-2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetylamino]-propanoate (5j) From L TrpOCH_3·HCl **4j** (0.255 g). Colorless crystals (0.32 g, 74%); mp 199 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.93 (1H, bs, D_2O exchangeable, NH L Trp), 7.58 (2H, d, *J* = 8.4, ArH), 7.47 (2H, d, *J* = 8.4, ArH), 7.24-7.21 (2H, m, *J* = 7.8, ArH), 7.09-7.07 (2H, m, ArH), 6.92 (1H, s, CH), 6.54 (1H, d, D_2O exchangeable, *J* = 7.8, NH), 4.95 (1H, m, CH) 4.54 (2H, s, NCH_2), 3.64 (3H, s, OMe), 3.33-3.31 (2H, m, CH_2 ring), 2.73-2.70 (2H, m, CH_2 ring), 2.45 (2H, d, *J* = 8.8, CH_2), 2.40 (3H, s, Me). Anal. Calcd. For $C_{25}H_{26}N_4O_4$ (446.50): C, 67.25; H, 5.87; N, 12.55; Found: C, 67.13; H, 5.66; N, 12.51.

General procedure for preparation of hydrazides 6a,b

To a solution of **5a,b (**1.0 mmol**)** in ethanol (30 mL), hydrazine hydrate (0.24 mL, 5.0 mmol) was added. The reaction mixture was refluxed for 4h, afterwards it was stirred overnight at room temperature; The formed precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazide **6a,b**.

***N*-Hydrazinocarbonylmethyl-2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamine (6a).** Colorless crystals (0.29 g, 91%); mp 202-204 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 8.96 (1H, bs, D_2O exchangeable, NH), 7.66 (2H, d, *J* = 8.2, ArH), 7.28 (2H, d, *J* = 8.2, ArH), 6.67 (1H, bs, D_2O exchangeable, NH), 4.60 (2H, s, NCH_2), 4.30 (2H, bs, D_2O exchangeable, NH_2), 4.02 (2H, d, *J* = 5.4, CH_2), 3.00 (2H, t, *J* = 8.2, CH_2 ring), 2.69 (2H, t, *J* = 8.2, CH_2 ring), 2.41 (3H, s, Me). Anal. Calcd. For $C_{15}H_{19}N_5O_3$ (317.34): C, 56.77; H, 6.03; N, 22.07; Found: C, 56.55; H, 5.98; N, 21.95.

***N*-(2-Hydrazinocarbonyl-ethyl)-2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl) acetyl-amine (6b).** Colorless crystals (0.3 g, 91 %); mp 214°C. ^{1}H NMR (200 MHz, $CDCl_3$): 8.89 (1H, bs, D_2O exchangeable, NH), 7.62 (2H, d, *J* = 8.2, ArH), 7.25 (2H, d, *J* = 8.2, ArH), 6.63 (1H, bs,

D_2O exchangeable, NH), 4.51 (2H, s, NCH_2), 4.34 (2H, bs, D_2O exchangeable, NH_2), 3.44-3.42 (2H, m, CH_2), 3.05 (2H, t, J = 8.0, CH_2 ring), 2.61 (2H, t, J = 8.0, CH_2 ring), 2.49 (2H, t, J = 6.0, CH_2); 2.38 (3H, s, Me). Anal. Calcd. For $C_{16}H_{21}N_5O_3$ (331.37): C, 57.99; H, 6.39; N, 12.13; Found: C, 57.87; H, 6.24; N, 12.21.

General procedure for preparation of 8a-f

Dipeptides **8a-f** were prepared according to the previously described azide procedure.

Methyl-2-{2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino] acetylamino} acetate (8a). From hydrazide **6a** (0.32 g) and $GlyOCH_3$·HCl **4b** (0.13 g). Colorless crystals (0.20 g, 53 %); mp 110 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.3 (1H, bs, D_2O exchangeable, NH), 7.68 (2H, d, J = 8.2, ArH), 7.27 (2H, d, J = 8.2 Hz, ArH), 6.66 (1H, bs, D_2O exchangeable, NH), 4.53 (2H, s, NCH_2), 3.98 (2H, d, J = 6.0, CH_2), 3.86 (2H, d, J = 4.0, CH_2), 3.71 (3H, s, OMe), 3.05 (2H, t, J = 8.2, CH_2 ring), 2.61 (2H, t, J = 8.2, CH_2 ring), 2.41 (3H, s, Me); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 20.9, 27.7, 32.6, 46.4, 45.8, 50.0, 52.5, 128.1, 128.6, 128.8, 140.0, 155.4, 170.2, 171.5, 173.1, 179.2; Anal. Calcd. For $C_{18}H_{22}N_4O_5$ (374.39): C, 57.75; H, 5.92; N, 14.96; Found C, 57.66; H, 5.81; N, 14.84.

Methyl-3-(1*H*-indol-3-yl)-2-{2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetyl-amino]acetylamino}propanoate (8b). From hydrazide **6a** (0.32 g) and $TrpOCH_3$·HCl **4d** (0.255 g). Colorless crystals (0.31 g, 62 %); mp 123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.8 (1H, bs, D_2O exchangeable, NH), 7.52-6.94 (8H, m, ArH), 6.28 (1H, s, ArH), 6.24-6.02 (2H, 2bs, D_2O exchangeable, 2NH), 4.92 (3H, m, NCH_2, CH), 3.63- 3.67 (5H, m, CH_2, OMe), 3.31-3.29 (2H, m, CH_2 ring), 2.38-2.35 (2H, m, CH_2 ring), 2.04 (3H, s, Me), 1.90-1.88 (2H, m, CH_2), ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 20.9, 27.6, 30.5, 32.8, 46.7, 50.3, 52.3, 57.8, 111.3, 112.4, 119.2, 120.5, 121.2, 122.9, 131.0, 136.3, 128.3, 128.7, 128.9, 140.1, 155.3, 171.0, 171.3, 174.0, 179.4; Anal. Calcd. For $C_{27}H_{29}N_5O_5$ (503.55): C, 64.40; H, 5.80; N, 13.91; Found C, 64.22; H, 5.69; N, 13.82.

Methyl-3-{2-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino] acetylamino} propanoate (8c). From hydrazide **6a** (0.32 g) and $\beta AlaOCH_3$·HCl **4a** (0.14 g). Colorless crystals (0.23 g, 59 %); mp 92 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.0 (1H, bs, D_2O exchangeable, NH), 7.64 (2H, d, J = 8.2, ArH), 7.24 (2H, d, J = 8.2 Hz, ArH), 6.73 (1H, bs, D_2O exchangeable, NH), 4.54 (2H, s, NCH_2), 3.75 (2H, d, J = 4, CH_2), 3.60 (3H, s, OMe), 3.59-3.57 (2H, m, CH_2), 3.02 (2H, t, J = 7.2, CH_2 ring), 2.66-2.62-2.60 (4H, m, CH_2 , CH_2 ring), 2.41 (3H, s, Me). Anal. Calcd. For $C_{19}H_{24}N_4O_5$ (388.42): C, 58.75; H, 6.23; N, 14.42; Found C, 58.63; H, 6.08; N, 14.31. Mass spectrum, m/z (I_r/%): 389(17), 388(64), 329(41), 239(64), 237(29), 229(59), 228(64), 159(91(30), 115(100), 77(70).

Methyl-3-{3-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino]-propionyl-amino}propanoate (8d). From hydrazide **6b** (0.33 g) and $\beta AlaOCH_3$·HCl **4a** (0.14 g). Colorless crystals (0.22 g, 54 %); mp 90 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.99 (1H, bs, D_2O exchangeable, NH), 7.66 (2H, d, J = 7.4, ArH), 7.24 (2H, d, J = 7.4 Hz, ArH), 6.78 (1H, bs, D_2O exchangeable, NH), 4.55 (2H, s, NCH_2), 3.60 (3H, s, OMe), 3.59-3.57 (2H, m, CH_2), 3.04-3.0

(4H, m, CH_2 , CH_2 ring), 2.78-2.57 (6H, m, 2 (CH_2) , CH_2 ring), 2.41 (3H, s, Me). Anal. Calcd. For $C_{20}H_{26}N_4O_5$ (402.44): C, 59.69; H, 6.51; N, 13.92; Found C, 59.74; H, 6.36; N, 13.78.

Methyl-3-(1*H*-indol-3-yl)-2-{3-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetyl-amino]propionylamino}propanoate (8e). From hydrazide **6b** (0.33 g) and $TrpOCH_3$·HCl **4d** (0.255 g). Colorless crystals (0.29 g, 56 %); mp 112 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.89 (1H, bs, D_2O exchangeable, NH), 7.57 (2H, d, *J* = 7.4 Hz, ArH), 7.37-7.0 (7H, m, ArH), 6.42 (1H, d, *J* = 7.4 Hz, D_2O exchangeable, NH), 5.29 (1H, bs, D_2O exchangeable, NH), 4.99 (3H, m, NCH_2, CH), 3.72 (3H, s, OMe), 3.69-3.67 (2H, m, CH_2), 3.36-3.34 (4H, m, CH_2 , CH_2 ring), 2.45-2.43 (2H, m, CH_2 ring), 2.13-2.10 (2H, m, CH_2), 1.98 (3H, s, Me). Anal. Calcd. For $C_{28}H_{31}N_5O_5$ (517.58): C, 64.98; H, 6.04; N, 13.53; Found C, 64.87; H, 6.14; N, 13.41.

Methyl-2-{3-[2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydropyridazin-2-yl)acetylamino]-propionylamino}acetate (8f). From hydrazide **6b** (0.33 g) and $GlyOCH_3$·HCl **4b** (0.13 g). Colorless crystals (0. 23 g, 59 %); mp 96 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.97 (1H, bs, D_2O exchangeable, NH), 7.67 (2H, d, *J* = 8.2, ArH), 7.24 (2H, d, *J* = 8.2 Hz, ArH), 6.83 (1H, bs, D_2O exchangeable, NH), 4.61 (2H, s, NCH_2), 4.09 (2H, d, *J* = 4.0, CH_2), 3.80-3.78 (2H, m, CH_2), 3.76 (3H, s, OMe), 3.05-3.03 (2H, m, CH_2 ring), 2.83-2.81 (2H, m, CH_2), 2.62-2.60 (2H, m, CH_2 ring), 2.41 (3H, s, Me); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ in ppm) 20.8, 27.5, 32.6, 35.1, 38.2, 45.9, 50.3, 52.4, 128.3, 128.5, 128.9, 139.9, 155.6, 170.6, 171.8, 175.1, 178.9; Anal. Calcd. For $C_{19}H_{24}N_4O_5$ (388.42): C, 58.75; H, 6.23; N, 14.42; Found C, 58.53; H, 6.11; N, 14.31.

Condensation with aldehydes. General method

To a solution of hydrazide **6a** (1.0 mmol, 0.32 g) in absolute EtOH (30 mL), aldehyde (1.0 mmol) was added. The reaction mixture was refluxed for 12 hours, cooled and the formed precipitate was filtered off and crystallized from ethanol to yield the hydrazone **9a-c**.

***N*-(Furan-2-ylmethylene-hydrazinocarbonylmethyl)-2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydro-pyridazin-2-yl)acetylamine (9a).** From furan-2-carbaldehyde (0.1 mL, 1.0 mmol). Colorless crystals (0.35 g, 88%); mp 225 °C. ^{1}H NMR (200 MHz, DMSO): δ 11.42 (1H, bs, NH, D_2O exchangeable, structure B), 11.32 (1H, bs, NH, D_2O exchangeable, structure A), 8.32 (1H, d, *J* = 7.2 Hz, NH, D_2O exchangeable, structure A), 8.09 (1H, s, CH=N), 7.84-7.82 (1H, m, CH furan-2-yl), 7.67 (2H, d, *J* = 8.0, ArH), 7.23 (2H, d, *J* = 8.0, ArH), 6.89-6.87 (1H, m, CH furan-2-yl), 6.63-6.60 (1H, m, CH furan-2-yl), 4.42 (2H, bs, CH_2, structure B), 4.19 (2H, d, *J* = 5.2 Hz, CH_2, structure A), 3.84 (1H, bs, OH, D_2O exchangeable, structure B), 3.32 (2H, s, CH_2), 3.01 (2H, t, *J* = 8.4 Hz, CH_2 ring), 2.50 (2H, t, *J* = 8.4, CH_2 ring), 2.33 (3H, s, Me). Anal. Calcd. For $C_{20}H_{21}N_5O_4$ (395.41): C, 60.75; H, 5.35; N, 17.71; Found: C, 60.69; H, 5.22; N, 17.54.

***N*-(4-Methoxy-benzylidene-hydrazinocarbonylmethyl)-2-(3-oxo-6-*p*-tolyl-2,3,4,5-tetrahydro-pyridazin-2-yl)acetylamine (9b).** From 4-methoxy-benzaldehyde (0.14 mL, 1.0 mmol). Colorless crystals (0.39 g, 89%); mp 220 °C. ^{1}H NMR (200 MHz, DMSO): δ 11.32 (1H, bs, NH, D_2O exchangeable, structure B), 11.25 (1H, bs, NH, D_2O exchangeable, structure A), 8.14 (1H, d, *J* = 7.2 Hz, NH, D_2O exchangeable, structure A), 7.92 (1H, s, CH=N), 7.66-7.64 (4H, m, ArH), 7.24 (2H, d, *J* = 7.6, ArH), 7.01-6.99 (2H, m, ArH), 4.43 (2H, bs, CH_2, structure

B), 4.27 (2H, d, *J* = 5.2 Hz, CH_2, structure A), 3.80 (1H, bs, OH, D_2O exchangeable, structure B), 3.79 (3H, s, OMe), 3.32 (2H, s, CH_2), 3.01 (2H, t, *J* = 8.0 Hz, CH_2 ring), 2.56 (2H, t, *J* = 8.0, CH_2 ring), 2.33 (3H, s, Me). Anal. Calcd. For $C_{23}H_{25}N_5O_4$ (435.48): C, 63.44; H, 5.79; N, 16.08; Found: C, 63.32; H, 5.59; N, 15.88.

***N*-(1-Furan-2-yl-ethylidene-hydrazinocarbonylmethyl)-2(3-oxo-6-*p*-tolyl-2,3,4,5-tetra-hydropyridazin-2-yl)acetylamine (9c).** From 2-acetyl-furan (0.11 mL, 1.0 mmol). Colorless crystals (0.34 g, 83%); mp 215 °C. ^{1}H NMR (200 MHz, DMSO): δ 10.74 (1H, s, NH, D_2O exchangeable, structure B), 10.38 (1H, s, NH, D_2O exchangeable, structure A), 8.17 (1H, d, *J* = 7.2 Hz, NH, D_2O exchangeable, structure A), 7.80-7.78 (1H, m, CH furan-2-yl), 7.71 (2H, d, *J* = 8.0, ArH), 7.30 (2H, d, *J* = 8.0, ArH), 6.97-6.95 (1H, m, CH furan-2-yl), 6.65-6.63 (1H, m, CH furan-2-yl), 4.50 (2H, bs, CH_2, structure B), 4.32 (2H, d, *J* = 5.6 Hz, CH_2, structure A), 4.01 (1H, bs, OH, D_2O exchangeable, structure B), 3.40 (2H, s, CH_2), 3.10 (2H, t, *J* = 8.4 Hz, CH_2 ring), 2.50 (2H, t, *J* = 8.4, CH_2 ring), 2.40 (3H, s, Me), 2.33 (3H, s, Me). Anal. Calcd. For $C_{21}H_{23}N_5O_4$ (409.44): C, 61.60; H, 5.66; N, 17.10; Found: C, 61.43; H, 5.56; N, 17.18.

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