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Amino Acid Derivatives, VII [1]: Synthesis and Antiviral Evaluation of α-Amino Acid Esters Bearing an Indazole Side Chain

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Summary. A series of peptide and dipeptide derivatives conjugated with an indazole residue were synthesized. The new compounds were evaluated *in vitro* for cytotoxicity against Hepatitis-A virus (HAV-27), *Herpes Simplex* virus-1 (*HSV*-1), and Hepatitis-B virus (HBV) and showed moderate to high activity.

Keywords. Indazole; Regioisomers; Amino acids; Dipeptides; Antiviral activity.

Introduction

The indazole nucleus is a pharmaceutically important structure and constitutes the key subunit in many drugs with a broad range of pharmacological activities [2] including antitumor [3], antimicrobial [4], antiplatelet [5], and anti-inflammatory activities [6]. However, there is still a lack of general and efficient methodologies for the synthesis of *N*-substituted indazoles [7]. On the other hand, a new target for the development of anti-HIV and antitumor therapies has been reported by the use, *in vivo* and *in vitro*, of amino acid derived heterocycles. Such compounds are the lysyl amide prodrug of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole [8], amino acid derivatives of paclitaxel [9], cysteine-modifying agents [10], and isoquinoline carboxylic acid derivatives as building blocks for HIV protease inhibitors [11]. In connection with our strategy in synthesis of new α-amino acid derivatives [12] and due to the pharmacological properties of indazoles and amino acid derivatives we were prompted to prepare new N^1- and N^2-indazole bearing amino acid derivatives to study, *in vitro*, their inhibitory activity for HAV-27, *HSV*-1, and HBV.

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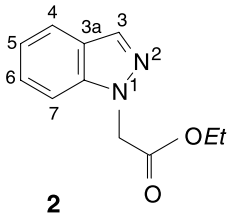
Results and Discussion

Chemistry

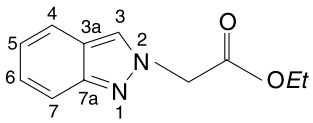
Indazole (**1**) was treated with ethyl chloroacetate in dry acetone containing anhydrous K_2CO_3 at reflux temperature to afford N^1- and N^2-regioisomers, which were separated by means of column chromatography on silica gel. For both compounds **2** and **3**, elemental analysis and mass spectral data [m/z 204 (M^+), 227 ($M + Na^+$)] established their molecular formula as $C_{11}H_{12}N_2O_2$, suggesting that they are possibly the 1-(ethoxycarbonylmethyl)-1*H*-indazole (**2**) and 2-(ethoxycarbonylmethyl)-2*H*-indazole (**3**) regioisomers. Although MS and ^{1}D NMR spectral analysis could not distinguish them, their HMBC spectra were used successfully to confirm their isomeric structures. As shown in Fig. 1, the signal of *N*–CH_2-moiety of compound **2** showed a ^3J-correlation with its 7_a-carbon. In contrast, the signal of the *N*–CH_2-moiety of compound **3** exhibited a ^3J-correlation with its 3-carbon. Based on these data, compound **2** was identified as N^1-(ethoxycarbonylmethyl)-1*H*-indazole and compound **3** was confirmed as N^2-(ethoxycarbonylmethyl)-2*H*-indazole. The ^{1}H NMR



2

^{1}H	^{13}C
H-4	C-6, C-7_a
H-5	C-3_a, C-7
H-6	C-4, C-7_a
H-7	C-3_a, C-5
N-CH_2	C-7_a

$^3J_{CH}$ Correlation



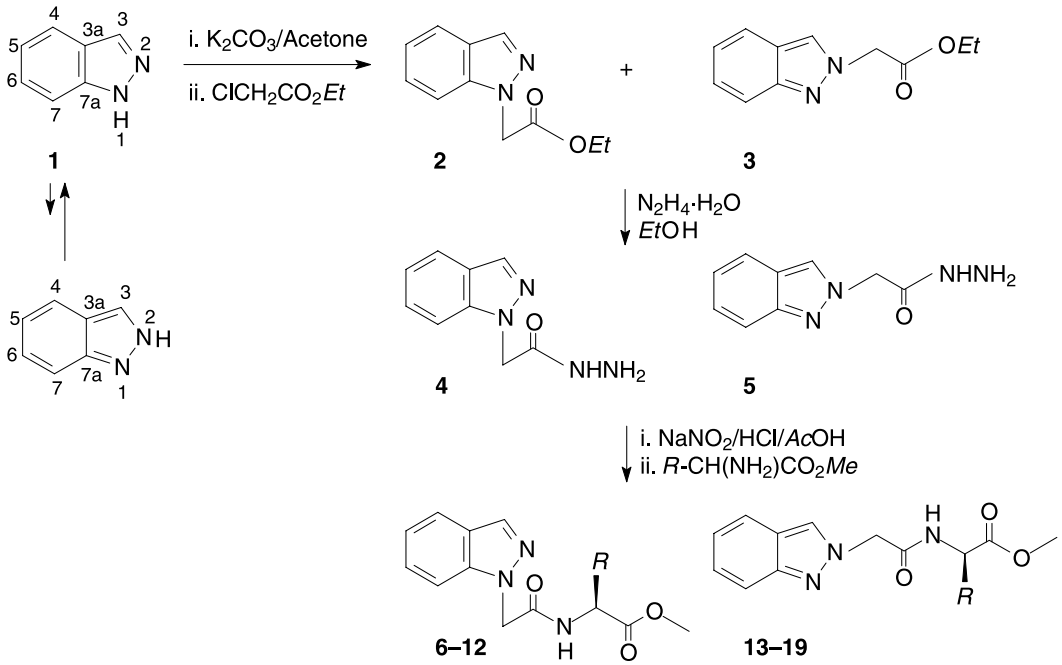
3

^{1}H	^{13}C
H-4	C-6, C-7_a
H-5	C-3_a, C-7
H-6	C-4, C-7_a
H-7	C-3_a, C-5
N-CH_2	C-3

$^3J_{CH}$ Correlation

Fig. 1. $^3J_{CH}$ Correlations in **2** and **3**

spectrum of **2** showed a triplet at $\delta = 1.23$ ppm and a quartet at $\delta = 4.20$ ppm corresponding to O*Et*. The singlet at $\delta = 5.14$ ppm corresponds to N^1-CH_2. The signals of four aromatic protons appeared as two triplets and two doublets at $\delta = 7.16$, 7.33, 7.40, and 7.74 ppm, while the singlet at $\delta = 8.05$ ppm corresponds to H-3. The ^{13}C NMR spectrum showed signals at $\delta = 13.9$ and 61.5 ppm pertaining to O*Et*. The signal at $\delta = 50.1$ ppm for N^1-CH_2, signals at $\delta = 108.6$–140.0 ppm for *Ar*-carbons, and the signal at $\delta = 167.8$ ppm to the C=O group were assigned. The ^{1}H NMR spectrum of **3** showed a triplet at $\delta = 1.25$ ppm and a quartet at $\delta = 4.24$ ppm corresponding to O*Et*. The singlet at $\delta = 5.17$ ppm corresponds to N^2-CH_2. The signals of four aromatic protons appeared as two triplets and two doublets at $\delta = 7.08$, 7.28, 7.65, and 7.69 ppm, while the singlet at $\delta = 7.98$ ppm corresponds to H-3. The ^{13}C NMR spectrum showed signals at $\delta = 13.9$ and 62.0 ppm corresponding to O*Et*. The signal at $\delta = 54.4$ ppm for N^2-CH_2, signals at $\delta = 117.4$–149.1 ppm for *Ar*-carbons, and a signal at $\delta = 167.0$ ppm to the C=O group



No.	*R*	amino acid
6, 13	H	L-glycine
7, 14	*Me*	L-alanine
8, 15	CH_2OH	L-serine
9, 16	$CHMe_2$	L-valine
10, 17	CH_2CHMe_2	L-leucine
11, 18	CH_2CH_2SMe	L-methionine
12, 19	*Ph*	L-phenylglycine

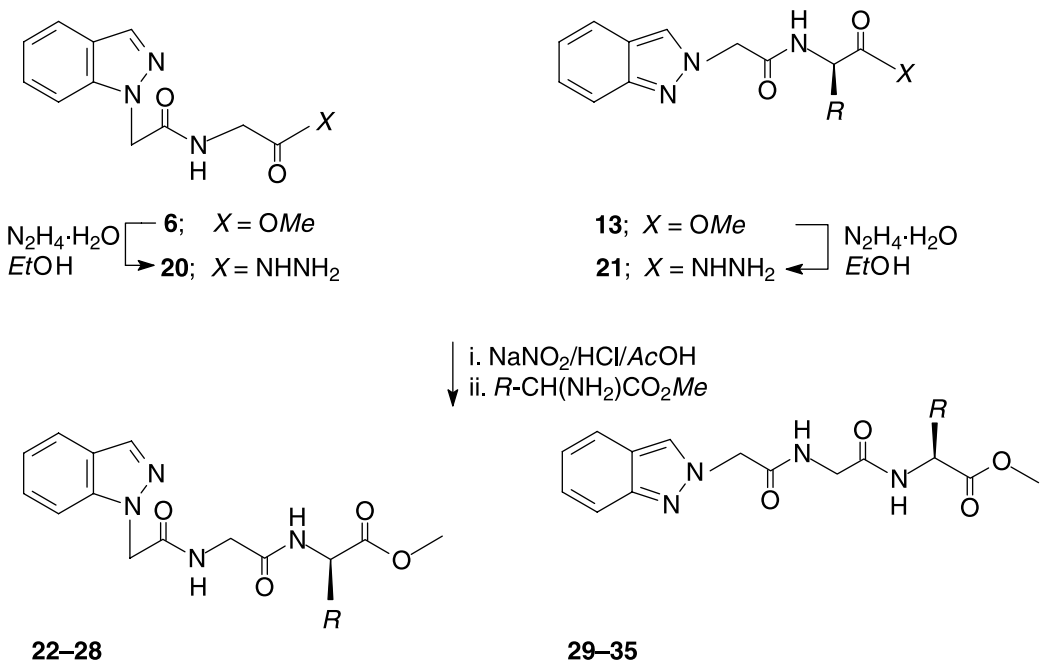
Scheme 1

were assigned. Treatment of **2** or **3** with hydrazine hydrate in ethanol gave the corresponding hydrazide derivatives **4** or **5** in 90–93% yield. These hydrazides were selected as starting materials for the coupling reaction with the appropriate acylated amino acides, *via* the azide-coupling method [13]. Thus, treatment of **4** or **5** at −5°C in *Ac*OH and 1 *N* HC1 with $NaNO_2$ afforded the inseparable azide derivative. The yellow syrupy azide compound was then treated, *in situ*, with the appropriate amino acid methyl esters in ethyl acetate containing Et_3N at 0°C to give, after neutralization, the desired peptides **6–12** in 78–84% or **13–19** in 72–77% yields. The structures of **6–19** were assigned from their ^1H, ^{13}C NMR, and mass spectra (Scheme 1).

Treating of **6** or **13** with $N_2H_4 \cdot H_2O$ in ethanol at reflux temperature afforded the corresponding hydrazides **20** or **21** in 96–98% yields. Treatment of **20** or **21** at −5°C in *Ac*OH and 1 *N* HCl with $NaNO_2$ afforded the inseparable azide derivatives. The yellow syrupy azide compounds were treated, as mentioned above, with the appropriate amino acid methyl esters in ethyl acetate containing Et_3N at 0°C to afford **22–28** in 75–80% and **29–35** in 70–73% yields. The structures of the dipeptide derivatives were confirmed by their ^1H, ^{13}C NMR, and mass spectra (Scheme 2).

Antiviral Activity

The plaque infectivity assay [14] was carried out to test the prepared compounds for antiviral activity. The test was performed to include three possibilities for antiviral activity, virucidal effect, virus adsorption, and effect on virus replication for both Hepatitis-A virus (HAV-27) and *Herpes Simplex* virus-1 (*HSV*-1).



No.	*R*	dipeptides
22,29	H	L-glycyl-L-glycine
23,30	*Me*	L-glycyl-L-alanine
24,31	CH_2OH	L-glycyl-L-serine
25,32	$CHMe_2$	L-glycyl-L-valine
26,33	CH_2CHMe_2	L-glycyl-L-leucine
27,34	CH_2CH_2SMe	L-glycyl-L-methionine
28,35	*Ph*	L-glycyl-L-phenylglycine

Scheme 2

For the antiviral activity against HAV-27 it was noted that, at both concentrations 10 and 20 $\mu g/10^5$ cells, compounds **7**, **9–12**, **18**, and **25–28** revealed the highest antiviral activity in this series of compounds and compounds **8**, **14**, **17**, **19**, **23**, and **24** revealed high activity at 10 $\mu g/10^5$ cells using amantadine (C^*) as a control. Compounds **15**, **16**, and **33–35**, showed moderate activity, while at concentrations of 20 $\mu g/10^5$ cells, compounds **6**, **13**, **22**, **29**, and **30–32** revealed little antiviral activity.

For the antiviral activity against *HSV*-1 the results revealed that compounds **7–12** and **22–25** showed the highest effect on *HSV*-1 at concentration 10 $\mu g/10^5$ cells, while compounds **6**, **13–19**, and **29–35** showed moderate activity.

On testing preliminary a viral screening against Hepatitis-B virus (HBV) (Hep G2 2.2.15 cell method) [15] indicated that compounds **10–12**, **23** and **25–28** were active against HBV replication with IC_{50} 85–95 μM and CC_{50} 90–100 μM, while compounds **6–9**, **13–19**, **22**, **24**, and **29–35** showed moderate viral replication inhibition and moderate cytotoxicity. The drug Lamivudine, which is a potent selective inhibitor of HBV replication [16] was used as a standard for the comparative studies.

Conclusions

New α-amino acid derivatives bearing indazole side chain were synthesized in order to increase the number of tested compounds screened for antiviral activity. Some of them displayed promising activities.

Experimental

General

Melting points were determined using a *Kofler* block instrument. TLC was performed on plastic plates Silica Gel 60 F_{254} (*E. Merck*, layer thickness 0.2 mm). NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^{1}H NMR and 62.9 MHz for ^{13}C NMR with *TMS* as an internal standard. ES mass spectra were obtained from an Esquire 3000plus iontrap mass spectrometer from Bruker Daltonics. The microanalyses were performed at the microanalytical unit, Tokyo University, Japan, and were found to agree favourably with the calculated values. Viral screening against HAV and *HSV* was conducted at the Environmental Virology Lab., Department of Water Pollution Research, National Research Centre, Cairo, Egypt. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Egypt.

General Procedure for the Preparation of 1-(Ethoxycarbonylmethyl)-1H-indazole (**2**, $C_{11}H_{12}N_2O_2$) *and 2-(Ethoxycarbonylmethyl)-2H-indazole* (**3**, $C_{11}H_{12}N_2O_2$)

A mixture of 11.8 g **1** (0.1 mol), 14.7 g ethyl chloroacetate (0.12 mol), and 13.8 g anhydrous K_2CO_3 (0.1 mol) in 36 cm^3 dry acetone was refluxed for 5 h (TLC). The solvent was removed *in vacuo* and the residue was diluted with H_2O and extracted with CH_2Cl_2 (3×30 cm^3). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by silica gel column chromatography using petroleum ether:ethylacetate = 7:1 to afford 12.24 g **2** (60%) and 6.12 g **3** (30%).

Compound **2**: Colorless syrup; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.23$ (t, $J = 6.1$ Hz, CH_3CH_2O), 4.21 (q, $J = 6.1$ Hz, CH_3CH_2O), 5.14 (s, N^1-CH_2), 7.16 (t, $J = 7.5$ Hz, H-5), 7.33 (t, $J = 7.6$ Hz, H-6), 7.40 (d, $J = 8.6$ Hz, H-4), 7.74 (d, $J = 8.5$ Hz, H-7), 8.05 (s, H-3) ppm; ^{13}C NMR ($CDC1_3$, 62.5 MHz): $\delta = 13.9$ (CH_3CH_2O), 50.1 (N^1-CH_2), 61.5 (CH_3CH_2O), 108.6 (C-7), 120.8 (C-5), 121.1 (C-4), 124.1 (C-3$_a$), 126.6 (C-6), 134.1 (C-3), 140.0 (C-7$_a$), 167.8 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

Compound **3**: Colorless syrup; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.25$ (t, $J = 6.1$ Hz, CH_3CH_2O), 4.24 (q, $J = 6.1$ Hz, CH_3CH_2O), 5.17 (s, N^2-CH_2), 7.08 (t, $J = 7.5$ Hz, H-5), 7.28 (t, $J = 7.6$ Hz, H-6), 7.65 (d, $J = 8.6$ Hz, H-4), 7.70 (d, $J = 8.5$ Hz, H-7), 7.98 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 13.9$ (CH_3CH_2O), 54.4 (N^2-CH_2), 62.0 (CH_3CH_2O), 117.4 (C-7), 120.2 (C-5), 121.9 (C-4), 122.1 (C-3$_a$), 124.3 (C-6), 134.1 (C-3), 149.0 (C-7$_a$), 167.0 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

General Procedure for the Preparation of 1-Acetylhydrazine-1H-indazole (**4**, $C_9H_{10}N_4O$) *and 2-Acetylhydrazine-2H-indazole* (**5**, $C_9H_{10}N_4O$)

A mixture of **2** or **3** (10 mmol) and 1.25 g $N_2H_4 \cdot H_2O$ (25 mmol) in 30 cm^3 ethanol was heated under reflux for 2 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol, to give **4** (93%) and **5** (90%).

Compound **4**: Mp 120–122°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 4.90$ (br, s, NHNH_2), 5.16 (s, N^1-CH_2), 7.18 (t, $J = 7.5$ Hz, H-5), 7.40 (t, $J = 7.6$ Hz, H-6), 7.50 (d, $J = 8.6$ Hz, H-4), 7.78 (d, $J = 8.5$ Hz, H-7), 8.11 (s, H-3), 9.80 (br, s, N*H*NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 50.15$ (N^1-CH_2), 110.0 (C-7), 120.0 (C-5), 121.4 (C-4), 124.8 (C-3$_a$), 126.9 (C-6), 134.6 (C-3), 140.1 (C-7$_a$), 168.7 (C=O) ppm; MS (ESI): $m/z = 213$ $[M + Na]^+$.

Compound **5**: Mp 167–169°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 4.88$ (br, s, NHNH_2), 5.22 (s, N^2-CH_2), 7.19 (t, $J = 7.5$ Hz, H-5), 7.31 (t, $J = 7.6$ Hz, H-6), 7.69 (d, $J = 8.6$ Hz, H-4), 7.75 (d, $J = 8.5$ Hz, H-7), 8.00 (s, H-3), 9.77 (br, s, N*H*NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 55.04$ (N^2-CH_2), 118.1 (C-7), 120.7 (C-5), 121.1 (C-4), 122.8 (C-3$_a$), 125.5 (C-6), 134.9 (C-3), 149.6 (C-7$_a$), 168.4 (C=O) ppm; MS (ESI): $m/z = 213$ $[M + Na]^+$.

General Procedure for the Preparation of N^1- and N^2-Indazole Bearing Amino Acid Esters ***6–19***

A solution of 1.90 g **4** or **5** (4 mmol) in 30 cm^3 HO*Ac*, 15 cm^3 1 *N* HCl, and 125 cm^3 H_2O was cooled in an ice-bath (−5°C). Sodium nitrite (4.35 g, 63 mmol) in 15 cm^3 cold H_2O was added with stirring. After stirring at −5°C for 15 min, the yellow syrup was formed. The azide was taken in cold 150 cm^3 ethyl acetate, washed with 150 cm^3 $NaHCO_3$ (3%), 150 cm^3 H_2O, and dried (Na_2SO_4). A solution of the appropriate amino acid methyl ester hydrochloride (4.5 mmol) in 100 cm^3 ethyl acetate containing 1.0 cm^3 Et_3N was stirred at 0°C for 20 min, filtered, and the filtrate was added to the azide solution. The mixture was kept at −5°C for 12 h, then at room temperature for another 12 h, followed by washing with 150 cm^3 0.5 *N* HC1, 150 cm^3 $NaHCO_3$ (3%), 150 cm^3 H_2O, and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether:ethylacetate = 7:1 to afford **6–12** in 78–84% and **13–19** in 72–77% yields.

1-Acetyl-1H-indazole L-glycine methyl ester (**6**, $C_{12}H_{13}N_3O_3$)
Colorless syrup (78%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.60$ (s, OCH_3), 4.18 (s, CH_2), 5.54 (s, N^1-CH_2), 7.15 (t, $J = 7.5$ Hz, H-5), 7.20 (br, s, NH) 7.35 (t, $J = 7.6$ Hz, H-6), 7.41 (d, $J = 8.6$ Hz, H-4), 7.76 (d, $J = 8.5$ Hz, H-7), 8.07 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 51.0$ (N^1-CH_2), 52.7 (CH_2), 53.8 (OCH_3), 108.6 (C-7), 120.4 (C-5), 121.4 (C-4), 124.0 (C-3_a), 126.5 (C-6), 134.6 (C-3), 140.2 (C-7_a), 167.6 (C=O), 172.7 (C=O) ppm; MS (ESI): $m/z = 270$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-alanine methyl ester (**7**, $C_{13}H_{15}N_3O_3$)
Colorless syrup (79%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.45$ (d, $J = 5.0$ Hz, CH_3), 3.58 (s, OCH_3), 4.67 (q, $J = 5.0$ Hz, CH), 5.57 (s, N^1-CH_2), 7.15 (t, $J = 7.5$ Hz, H-5), 7.25 (br, s, NH), 7.38 (t, $J = 7.6$ Hz, H-6), 7.47 (d, $J = 8.6$ Hz, H-4), 7.79 (d, $J = 8.5$ Hz, H-7), 8.08 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 17.5$ (CH_3), 47.7 (CH), 52.5 (N^1-CH_2), 54.3 (OCH_3), 108.9 (C-7), 120.4 (C-5), 121.3 (C-4), 124.8 (C-3_a), 126.9 (C-6), 134.7 (C-3), 140.5 (C-7_a), 168.0 (C=O), 173.6 (C=O) ppm; MS (ESI): $m/z = 284$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-serine methyl ester (**8**, $C_{13}H_{15}N_3O_4$)
Colorless syrup (78%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta =$ 3.30–3.40 (m, CH_2) 3.61 (s, OCH_3), 4.50–4.58 (m, CH), 5.53 (s, N^1-CH_2), 6.60 (br, s, OH), 7.10 (br, s, NH), 7.19 (t, $J = 7.5$ Hz, H-5), 7.37 (t, $J = 7.6$ Hz, H-6), 7.43 (d, $J =$ 8.6 Hz, H-4), 7.79 (d, $J = 8.5$ Hz, H-7), 8.10 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 52.3$ (N^1-CH_2), 53.9 (OCH_3), 54.9 (CH), 71.8 (OCH_2), 109.0 (C-7), 121.1 (C-5), 121.9 (C-4), 124.0 (C-3_a), 126.9 (C-6), 134.7 (C-3), 140.3 (C-7_a), 167.6 (C=O), 173.6 (C=O) ppm; MS (ESI): $m/z = 300$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-valine methyl ester (**9**, $C_{15}H_{19}N_3O_3$)
Colorless syrup (79%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.95$ (dd, $J = 1.9$, 7.2 Hz, $2CH_3$), 2.22–2.29 (m, CH), 3.62 (s, OCH_3), 4.40–4.50 (m, CH), 5.52 (s, N^1-CH_2), 7.15 (t, $J = 7.5$ Hz, H-5), 7.33 (t, $J = 7.6$ Hz, H-6), 7.40 (d, $J =$ 8.6 Hz, H-4), 7.77 (d, $J = 8.5$ Hz, H-7), 8.09 (s, H-3), 8.40 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 16.5$ (CH_3), 18.6 (CH_3), 31.6 (CH), 51.0 (CH), 52.8 (N^1-CH_2), 54.5 (OCH_3), 109.2 (C-7), 120.9 (C-5), 121.4 (C-4), 124.8 (C-3_a), 127.2 (C-6), 134.6 (C-3), 141.0 (C-7_a), 167.4 (C=O), 175.1 (C=O) ppm; MS (ESI): $m/z = 312$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-leucine methyl ester (**10**, $C_{16}H_{21}N_3O_3$)
Colorless syrup (81%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.90$ (dd, $J = 1.9$, 7.2 Hz, $2CH_3$), 1.40–1.69 (m, CH_2, CH), 3.60 (s, OCH_3), 4.22–4.31 (m, CH), 5.53 (s, N^1-CH_2), 7.15 (t, $J =$ 7.5 Hz, H-5), 7.37 (t, $J = 7.6$ Hz, H-6), 7.45 (d, $J = 8.6$ Hz, H-4), 7.81 (d, $J = 8.5$ Hz, H-7), 8.08 (s, H-3), 8.15 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 21.6$ ($2CH_3$), 25.8 (CH), 39.6 (CH_2), 51.6 (CH), 53.7 (N^1-CH_2), 54.3 (OCH_3), 108.6 (C-7), 120.5 (C-5), 121.8 (C-4), 124.3 (C-3_a), 126.9 (C-6), 134.0 (C-3), 140.5 (C-7_a), 167.5 (C=O), 172.5 (C=O) ppm; MS (ESI): $m/z = 326$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-methionine methyl ester (**11**, $C_{15}H_{19}N_3O_3S$)
Pale yellow syrup (78%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.34$–2.57 (m, $2CH_2$, SCH_3), 3.63 (s, OCH_3), 4.40–4.55 (m, CH), 5.52 (s, N^1-CH_2), 7.14 (t, $J = 7.5$ Hz, H-5), 7.36 (t, $J = 7.6$ Hz, H-6), 7.40 (d, $J = 8.6$ Hz, H-4), 7.80 (d, $J = 8.5$ Hz, H-7), 8.09 (br, s, H-3, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.5$ (SCH_3), 30.0 (CH_2), 31.5 (CH_2), 46.9 (CH), 52.5 (N^1-CH_2), 53.5 (OCH_3), 109.6 (C-7), 121.2 (C-5), 121.9 (C-4), 124.3 (C-3_a), 126.6 (C-6), 134.2 (C-3), 140.4 (C-7_a), 167.8 (C=O), 177.0 (C=O) ppm; MS (ESI): $m/z = 344$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-phenylglycine methyl ester (**12**, $C_{18}H_{17}N_3O_3$)
Colorless syrup (84%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.65$ (s, OCH_3), 4.70 (s, CH), 5.53 (s, N^1-CH_2), 7.10 (t, $J = 7.5$ Hz, H-5), 7.20–7.27 (m, *Ph*-H), 7.33–7.44 (m, *Ph*-H, H-4, H-6), 7.80 (d, $J = 8.5$ Hz, H-7), 8.08 (s, H-3), 9.08 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 52.4$ (N^1-CH_2), 53.9 (OCH_3), 56.5 (CH), 108.6 (C-7), 120.8 (C-5), 121.1 (C-4), 124.1 (C-3_a), 125.5, 126.9, 132.1, 134.6, 137.9 (*Ph*-C, C-3, C-6), 141.0 (C-7_a), 167.4 (C=O), 172.4 (C=O) ppm; MS (ESI): $m/z = 346$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycine methyl ester (**13**, $C_{12}H_{13}N_3O_3$)
Colorless syrup (73%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.60$ (s, OCH_3), 4.17 (s, CH_2), 5.17 (s, N^2-CH_2), 7.11 (t, $J = 7.5$ Hz, H-5), 7.22 (br, s, NH), 7.30 (t, $J = 7.6$ Hz, H-6), 7.63 (d, $J =$ 8.6 Hz, H-4), 7.73 (d, $J = 8.5$ Hz, H-7), 7.95 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 52.5$ (N^2-CH_2), 52.9 (CH_2), 53.2 (OCH_3), 117.0 (C-7), 120.5 (C-5), 121.9 (C-4), 122.4 (C-3_a), 124.8 (C-6), 134.5 (C-3), 149.2 (C-7_a), 167.1 (C=O), 172.6 (C=O) ppm; MS (ESI): $m/z = 270$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-alanine methyl ester (**14**, $C_{13}H_{15}N_3O_3$)
Colorless syrup (74%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.50$ (d, $J = 5.0$ Hz, CH_3), 3.67 (s, OCH_3), 4.68 (q, $J = 5.0$ Hz, CH),

5.18 (s, N^2-CH_2), 7.13 (t, $J = 7.5$ Hz, H-5), 7.26 (br, s, NH), 7.34 (t, $J = 7.6$ Hz, H-6), 7.69 (d, $J = 8.6$ Hz, H-4), 7.79 (d, $J = 8.5$ Hz, H-7), 7.99 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 17.8$ (CH_3), 47.9 (CH), 52.6 (N^2-CH_2), 54.6 (OCH_3), 117.2 (C-7), 120.5 (C-5), 121.9 (C-4), 122.7 (C-3_a), 124.0 (C-6), 134.0 (C-3), 149.0 (C-7_a), 167.0 (C=O), 173.5 (C=O) ppm; MS (ESI): $m/z = 284$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-serine methyl ester (**15**, $C_{13}H_{15}N_3O_4$) Colorless syrup (72%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.30$–3.40 (m, CH_2) 3.61 (s, OCH_3), 4.48–4.59 (m, CH), 5.17 (s, N^2-CH_2), 6.67 (br, s, OH), 7.06 (t, $J = 7.5$ Hz, H-5), 7.15 (br, s, NH), 7.29 (t, $J = 7.6$ Hz, H-6), 7.62 (d, $J = 8.6$ Hz, H-4), 7.77 (d, $J = 8.5$ Hz, H-7), 7.96 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 52.5$ (N^2-CH_2), 53.5 (OCH_3), 54.5 (CH), 72.1 (OCH_2), 117.4 (C-7), 120.6 (C-5), 122.0 (C-4), 122.7 (C-3_a), 124.8 (C-6), 134.3 (C-3), 149.2 (C-7_a), 167.0 (C=O), 173.3 (C=O) ppm; MS (ESI): $m/z = 300$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-valine methyl ester (**16**, $C_{15}H_{19}N_3O_3$) Colorless syrup (76%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.93$ (dd, $J = 1.9$, 7.2 Hz, $2CH_3$), 2.22–2.33 (m, CH), 3.63 (s, OCH_3), 4.44–4.54 (m, CH), 5.12 (s, N^2-CH_2), 7.09 (t, $J = 7.5$ Hz, H-5), 7.26 (t, $J = 7.6$ Hz, H-6), 7.60 (d, $J = 8.6$ Hz, H-4), 7.74 (d, $J = 8.5$ Hz, H-7), 7.95 (s, H-3), 8.00 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 16.5$ (CH_3), 18.5 (CH_3), 31.6 (CH), 51.9 (CH), 52.8 (N^2-CH_2), 57.7 (OCH_3), 117.4 (C-7), 120.5 (C-5), 121.6 (C-4), 122.5 (C-3_a), 124.9 (C-6), 134.3 (C-3), 149.1 (C-7_a), 167.0 (C=O), 175.7 (C=O) ppm; MS (ESI): $m/z = 312$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-leucine methyl ester (**17**, $C_{16}H_{21}N_3O_3$) Colorless syrup (76%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.91$ (dd, $J = 1.9$, 7.2 Hz, $2CH_3$), 1.52–1.68 (m, CH_2, CH), 3.66 (s, OCH_3), 4.26–4.36 (m, CH), 5.17 (s, N^2-CH_2), 7.07 (t, $J = 7.5$ Hz, H-5), 7.25 (t, $J = 7.6$ Hz, H-6), 7.62 (d, $J = 8.6$ Hz, H-4), 7.70 (d, $J = 8.5$ Hz, H-7), 7.98 (s, H-3), 8.15 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 21.9$ ($2CH_3$), 24.9 (CH), 40.2 (CH_2), 51.2 (CH), 53.5 (N^2-CH_2), 53.9 (OCH_3), 117.7 (C-7), 121.2 (C-5), 121.9 (C-4), 122.5 (C-3_a), 124.0 (C-6), 134.0 (C-3), 149.4 (C-7_a), 167.1 (C=O), 172.1 (C=O) ppm; MS (ESI): $m/z = 326$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-methionine methyl ester (**18**, $C_{15}H_{19}N_3O_3S$) Pale yellow syrup (73%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.20$–2.55 (m, $2CH_2$, SCH_3), 3.62 (s, OCH_3), 4.45–4.59 (m, CH), 5.13 (s, N^2-CH_2), 7.12 (t, $J = 7.5$ Hz, H-5), 7.25 (t, $J = 7.6$ Hz, H-6), 7.68 (d, $J = 8.6$ Hz, H-4), 7.72 (d, $J = 8.5$ Hz, H-7), 7.91 (s, H-3), 8.01 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.5$ (SCH_3), 29.5 (CH_2), 30.9 (CH_2), 46.7 (CH), 52.5 (N^2-CH_2), 53.3 (OCH_3), 117.5 (C-7), 120.7 (C-5), 121.9 (C-4), 122.6 (C-3_a), 124.0 (C-6), 134.0 (C-3), 149.1 (C-7_a), 167.2 (C=O), 177.0 (C=O) ppm; MS (ESI): $m/z = 344$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-phenylglycine methyl ester (**19**, $C_{18}H_{17}N_3O_3$) Colorless syrup (77%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.65$ (s, OCH_3), 5.17 (s, N^2-CH_2), 4.73 (s, CH), 7.03 (t, $J = 7.5$ Hz, H-5), 7.20–7.44 (m, *Ph*-H, H-6), 7.68 (d, $J = 8.6$ Hz, H-4), 7.79 (d, $J = 8.5$ Hz, H-7), 7.97 (s, H-3), 8.16 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 52.6$ (N^2-CH_2), 53.5 (OCH_3), 56.5 (CH), 117.4 (C-7), 120.2 (C-5), 121.8 (C-4), 122.2 (C-3_a), 124.4 (C-6), 125.5, 129.9, 131.1, 134.5, 137.7 (*Ph*-C, C-3), 149.5 (C-7_a), 167.6 (C=O), 173.3 (C=O) ppm; MS (ESI): $m/z = 346$ $[M + Na]^+$.

*General Procedure for the Preparation of the Hydrazides **20** and **21***

A mixture of 1.23 g **6** or **13** (5 mmol) and 0.63 g $N_2H_4 \cdot H_2O$ (12.5 mmol) in 15 cm^3 *Et*OH was heated under reflux for 4 h. The excess of *Et*OH was removed under reduced pressure and the resulting precipitate was filtered off and recrystallized from *Et*OH to give **20** and **21** in 96–98% yields.

1-Acetyl-1H-indazole L-glycine hydrazide (**20**, $C_{11}H_{13}N_5O_2$) White powder (98%), mp 177–179°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.55$ (s, CH_2), 4.98 (br, s, NHNH_2), 5.14 (s, N^1-CH_2), 7.18 (t, $J = 7.5$ Hz, H-5), 7.38 (t, $J = 7.6$ Hz, H-6), 7.43 (d, $J = 8.6$ Hz, H-4), 7.52 (br, s, NH), 7.81 (d, $J = 8.5$ Hz, H-7), 8.07 (s, H-3), 9.45 (br, s, N*H*NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 40.4$ (CH_2), 51.3 (N^1-CH_2), 112.4 (C-7a), 151.7 (C-5), 153.2 (C-3_a), 154.7 (C-7), 164.1 (C=O), 169.6 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycine hydrazide (**21**, $C_{11}H_{13}N_5O_2$) White powder (96%), mp 190–192°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.53$ (s, CH_2), 4.82 (br, s, NHNH_2), 5.14 (s, N^2-CH_2), 7.08 (t, $J = 7.5$ Hz, H-5), 7.25 (t, $J = 7.6$ Hz, H-6), 7.51 (br, s, NH), 7.62 (d, $J = 8.6$ Hz, H-4), 7.70 (d, $J = 8.5$ Hz, H-7), 7.96 (s, H-3), 9.45 (br, s, N*H*NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 40.5$ (CH_2), 51.8 (N^2-CH_2), 112.6 (C-7_a), 151.6 (C-5), 153.1 (C-3_a), 154.9 (C-7), 164.1 (C=O), 169.3 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

*General Procedure for the Preparation of Dipeptides **22–35***

A solution of 0.19 g **20** or **21** (0.80 mmol) in 6 cm^3 HO*Ac*, 3 cm^3 1 *N* HCl, and 25 cm^3 H_2O was cooled in an ice-bath (−5°C). Sodium nitrite (0.87 g, 12.60 mmol) in 3 cm^3 cold H_2O was added with stirring. After stirring at −5°C for 15 min, the yellow syrup was formed. The azide was taken in 30 cm^3 cold ethyl acetate, washed with 30 cm^3 $NaHCO_3$ (3%), 30 cm^3 H_2O, and dried (Na_2SO_4). A solution of the appropriate amino acid methyl ester hydrochloride (0.90 mmol) in 20 cm^3 ethyl acetate containing 0.2 cm^3 Et_3N was stirred at 0°C for 20 min, filtered, and the filtrate was added to the azide solution. The mixture was kept at −5°C for 12 h, then at room temperature for another 12 h, followed by washing with 30 cm^3 0.5 *N* HCl, 30 cm^3 $NaHCO_3$ (3%), 30 cm^3 H_2O, and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether:ethylacetate = 5:1 to afford **22–28** in 75–80% and **29–35** in 70–73% yields.

1-Acetyl-1H-indazole L-glycyl-L-glycine methyl ester
(**22**, $C_{14}H_{16}N_4O_4$)
White foam (75%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.53$ (s, OCH_3), 3.69 (s, CH_2), 3.89 (s, CH_2), 5.19 (s, N^1-CH_2), 7.14 (t, $J = 7.5$ Hz, H-5), 7.38 (t, $J = 7.6$ Hz, H-6), 7.47 (d, $J = 8.6$ Hz, H-4), 7.76 (d, $J = 8.5$ Hz, H-7), 8.06 (s, H-3), 8.52 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 41.5$ (CH_2), 42.6 (CH_2), 51.6 (N^1-CH_2), 53.6 (OCH_3), 108.9 (C-7), 120.8 (C-5), 121.2 (C-4), 124.7 (C-3_a), 127.0 (C-6), 134.6 (C-3), 140.4 (C-7_a), 167.5 (C=O), 171.0 (C=O), 171.9 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-glycyl-L-alanine methyl ester
(**23**, $C_{15}H_{18}N_4O_4$)
White foam (76%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.33$ (d, $J = 5.0$ Hz, CH_3), 3.61 (s, CH_2), 3.70 (s, OCH_3), 4.52 (q, $J = 5.0$ Hz, CH), 5.18 (s, N^1-CH_2), 7.16 (t, $J = 7.5$ Hz, H-5), 7.38 (t, $J = 7.6$ Hz, H-6), 7.44 (d, $J = 8.6$ Hz, H-4), 7.75 (d, $J = 8.5$ Hz, H-7), 8.04 (s, H-3), 9.00 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 18.2$ (CH_3), 45.8 (CH_2), 48.3 (CH), 51.5 (N^1-CH_2), 52.8 (OCH_3), 108.6 (C-7), 120.8 (C-5), 121.5 (C-4), 124.5 (C-3a), 126.9 (C-6), 134.1 (C-3), 140.1 (C-7_a), 167.8 (C=O), 168.9 (C=O), 172.2 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

1-Acetyl-lH-indazole L-glycyl-L-serine methyl ester
(**24**, $C_{15}H_{18}N_4O_5$)
White foam (77%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.40$–3.52 (m, OCH_2), 3.63 (s, OCH_3), 3.70 (s, CH_2), 4.45–4.56 (m, CH), 5.12 (s, N^1-CH_2), 6.66 (br, s, OH), 7.16 (t, $J = 7.5$ Hz, H-5), 7.30 (t, $J = 7.6$ Hz, H-6), 7.40 (d, $J = 8.6$ Hz, H-4), 7.70 (d, $J = 8.5$ Hz, H-7), 7.91 (br, s, NH), 8.07 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 41.5$ (CH_2), 43.6 (CH_2), 51.3 (N^1-CH_2), 53.5 (OCH_3), 54.5 (CH), 71.6 (OCH_2), 108.9 (C-7), 120.8 (C-5), 121.2 (C-4), 124.1 (C-3_a), 126.6 (C-6), 134.4 (C-3), 140.2 (C-7_a), 167.5 (C=O), 167.7 (C=O), 172.0 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-glycyl-L-valine methyl ester
(**25**, $C_{17}H_{22}N_4O_4$)
White foam (79%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.94$ (dd, $J = 1.9$, 7.3 Hz, $2CH_3$), 2.25–2.32 (m, CH), 3.53 (s, OCH_3), 3.70 (s, CH_2), 3.79 (s, CH_2), 4.36–4.48 (m, CH), 5.17 (s, N^1-CH_2), 7.18 (t, $J = 7.5$ Hz, H-5), 7.33 (t, $J = 7.6$ Hz, H-6), 7.45 (d, $J = 8.6$ Hz, H-4), 7.75 (d, $J = 8.5$ Hz, H-7), 8.05 (s, H-3), 8.88 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 17.1$, 19.1 ($2CH_3$), 32.5 (CH), 43.6 (CH_2), 51.5 (N^1-CH_2), 51.9 (CH), 55.5 (OCH_3), 108.8 (C-7), 120.8 (C-5), 121.4 (C-4), 124.0 (C-3_a), 126.7 (C-6), 134.0 (C-3), 140.0 (C-7_a), 167.5 (C=O), 168.5 (C=O), 175.1 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-glycyl-L-leucine methyl ester
(**26**, $C_{18}H_{24}N_4O_4$)
White foam (76%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.91$ (dd, $J = 1.8$, 7.3 Hz, $2CH_3$), 1.45–1.60 (m, CH_2, CH), 3.61 (s, OCH_3), 3.70 (s, CH_2), 3.72 (s, CH_2), 4.16–4.26 (m, CH), 5.19 (s, N^1-CH_2), 7.17 (t, $J = 7.5$ Hz, H-5), 7.33 (t, $J = 7.6$ Hz, H-6), 7.40 (d, $J = 8.6$ Hz, H-4), 7.76 (d, $J = 8.5$ Hz, H-7), 8.03 (s, H-3), 9.02 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 21.7$ ($2CH_3$), 24.2 (CH), 39.5 (CH_2), 49.5 (CH_2), 51.0 (CH), 51.8 (N^1-CH_2), 52.3 (OCH_3), 108.9 (C-7), 120.8 (C-5), 121.1 (C-4), 124.1 (C-3_a), 126.6 (C-6), 134.1 (C-3), 140.0 (C-7_a), 167.8 (C=O), 169.1 (C=O), 172.5 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-glycyl-L-methionine methyl ester
(**27**, $C_{17}H_{22}N_4O_4S$)
Yellow foam (76%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.22$–2.52 (m, SCH_3, $2CH_2$), 3.52 (s, OCH_3), 3.70 (s, CH_2), 4.40–4.51 (m, CH), 5.16 (s, N^1-CH_2), 7.18 (t, $J = 7.5$ Hz, H-5), 7.38 (t, $J = 7.6$ Hz, H-6), 7.42 (d, $J = 8.6$ Hz, H-4), 7.74 (d, $J = 8.5$ Hz, H-7), 8.05 (s, H-3), 8.79 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.5$ (SCH_3), 29.2 (CH_2), 30.6 (CH_2), 43.4 (CH_2), 46.5 (CH), 51.7 (N^1-CH_2), 53.5 (OCH_3), 108.5 (C-7), 120.5 (C-5), 121.5 (C-4), 124.4 (C-3_a), 126.5 (C-6), 134.3 (C-3), 140.1 (C-7_a), 167.5 (C=O), 171.5 (C=O), 175.1 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

1-Acetyl-1H-indazole L-glycyl-L-phenylglycine methyl ester
(**28**, $C_{20}H_{20}N_4O_4$)
White foam (80%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.41$ (d, $J = 5.0$ Hz, CH_3), 3.62 (s, OCH_3), 3.90 (s, CH_2), 4.60 (q, $J = 5.1$ Hz, CH), 5.13 (s, N^1-CH_2), 7.15 (t, $J = 7.5$ Hz, H-5), 7.29–7.45 (m, *Ph*-H, H-4, H-6), 7.74 (d, $J = 8.5$ Hz, H-7), 8.03 (s, H-3), 8.66 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 17.5$ (CH_3), 41.6 (CH_2), 44.6 (CH), 51.5 (N^1-CH_2), 53.5 (OCH_3), 108.6 (C-7), 120.9 (C-5), 121.5 (C-4), 124.9, 126.5, 129.9, 131.1, 137.7 (*Ph*-C, C-3, C-3_a, C-6), 140.0 (C-7_a), 167.5 (C=O), 172.6 (C=O), 173.2 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-glycine methyl ester
(**29**, $C_{14}H_{16}N_4O_4$)
White foam (70%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.50$ (s, OCH_3), 3.70 (s, CH_2), 3.97 (s, CH_2), 5.14 (s, N^2-CH_2), 7.02 (t, $J = 7.5$ Hz, H-5), 7.28 (t, $J = 7.6$ Hz, H-6), 7.66 (d, $J = 8.6$ Hz, H-4), 7.70 (d, $J = 8.5$ Hz, H-7), 7.94 (s, H-3), 8.55 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 41.5$ (CH_2), 42.9 (CH_2), 51.5 (N^2-CH_2), 53.5 (OCH_3), 117.5 (C-7), 120.5 (C-5), 121.9 (C-4), 122.5 (C-3_a), 124.5 (C-6), 134.5 (C-3), 149.0 (C-7_a), 167.0 (C=O), 170.1 (C=O), 171.3 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-alanine methyl ester
(**30**, $C_{15}H_{18}N_4O_4$)
White foam (72%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.33$ (d, $J = 5.0$ Hz, CH_3), 3.61 (s, CH_2), 3.65 (s, OCH_3), 4.51 (q, $J = 5.0$ Hz, CH), 5.18 (s, N^2-CH_2), 7.06 (t, $J = 7.5$ Hz, H-5), 7.28 (t, $J = 7.6$ Hz, H-6), 7.66 (d, $J = 8.6$ Hz, H-4), 7.73 (d, $J = 8.5$ Hz, H-7), 7.96 (s, H-3), 9.00 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 18.2$ (CH_3), 45.2 (CH_2), 48.1 (CH), 51.7 (N^2-CH_2), 52.6 (OCH_3), 117.4 (C-7), 120.4 (C-5), 121.9 (C-4), 122.7 (C-3a), 124.9 (C-6), 134.1 (C-3),

149.2 (C-7_a), 167.0 (C=O), 168.3 (C=O), 173.0 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-serine methyl ester (**31**, $C_{15}H_{18}N_4O_5$)
White foam (71%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.45$–3.53 (m, OCH_2), 3.64 (s, OCH_3), 3.70 (s, CH_2), 4.45–4.57 (m, CH), 5.12 (s, N^2-CH_2), 6.52 (br, s, OH), 7.08 (t, $J = 7.5$ Hz, H-5), 7.29 (t, $J = 7.6$ Hz, H-6), 7.66 (d, $J = 8.6$ Hz, H-4), 7.70 (d, $J = 8.5$ Hz, H-7), 7.86 (br, s, NH), 7.99 (s, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 41.6$ (CH_2), 43.5 (CH_2), 51.8 (N^2-CH_2), 53.5 (OCH_3), 54.5 (CH), 72.1 (OCH_2), 117.2 (C-7), 120.2 (C-5), 121.9 (C-4), 122.3 (C-3_a), 124.9 (C-6), 134.1 (C-3), 149.0 (C-7_a), 167.1 (C=O), 167.3 (C=O), 173.5 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-valine methyl ester (**32**, $C_{17}H_{22}N_4O_4$)
White foam (72%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.95$ (dd, $J = 1.9$, 7.3 Hz, $2CH_3$), 2.22–2.33 (m, CH), 3.54 (s, OCH_3), 3.69 (s, CH_2), 3.79 (s, CH_2), 4.34–4.47 (m, CH), 5.17 (s, N^2-CH_2), 7.07 (t, $J = 7.5$ Hz, H-5), 7.28 (t, $J = 7.6$ Hz, H-6), 7.67 (d, $J = 8.6$ Hz, H-4), 7.76 (d, $J = 8.5$ Hz, H-7), 7.91 (s, H-3), 8.88 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 17.0$, 19.0 ($2CH_3$), 33.1 (CH), 44.2 (CH_2), 51.8 (N^2-CH_2), 52.3 (CH), 54.2 (OCH_3), 117.5 (C-7), 120.5 (C-5), 122.5 (C-4), 123.2 (C-3_a), 124.3 (C-6), 134.4 (C-3), 149.0 (C-7_a), 167.0 (C=O), 168.5 (C=O), 175.1 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-leucine methyl ester (**33**, $C_{18}H_{24}N_4O_4$)
White foam (70%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.85$ (dd, $J = 1.8$, 7.3 Hz, $2CH_3$), 1.49–1.68 (m, CH_2, CH), 3.62 (s, OCH_3), 3.77 (s, CH_2), 3.81 (s, CH_2), 4.11–4.25 (m, CH), 5.19 (s, N^2-CH_2), 7.04 (t, $J = 7.5$ Hz, H-5), 7.32 (t, $J = 7.6$ Hz, H-6), 7.66 (d, $J = 8.6$ Hz, H-4), 7.72 (d, $J = 8.5$ Hz, H-7), 7.94 (s, H-3), 9.12 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 21.7$ ($2CH_3$), 24.5 (CH), 39.3 (CH_2), 49.2 (CH_2), 51.1 (CH), 51.9 (N^2-CH_2), 52.7 (OCH_3), 117.4 (C-7), 120.0 (C-5), 121.7 (C-4), 122.0 (C-3_a), 124.9 (C-6), 134.0 (C-3), 149.0 (C-7_a), 167.1 (C=O), 169.2 (C=O), 172.7 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-methionine methyl ester (**34**, $C_{17}H_{22}N_4O_4S$)
Yellow foam (71%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.24$–2.55 (m, SCH_3, $2CH_2$), 3.57 (s, OCH_3), 3.77 (s, CH_2), 4.40–4.45 (m, CH), 5.11 (s, N^2-CH_2), 7.11 (t, $J = 7.5$ Hz, H-5), 7.32 (t, $J = 7.6$ Hz, H-6), 7.65 (d, $J = 8.6$ Hz, H-4), 7.73 (d, $J = 8.5$ Hz, H-7), 7.93 (s, H-3), 8.60 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.4$ (SCH_3), 29.0 (CH_2), 30.8 (CH_2), 43.7 (CH_2), 46.5 (CH), 51.9 (N^2-CH_2), 53.7 (OCH_3), 117.4 (C-7), 120.2 (C-5), 121.9 (C-4), 122.1 (C-3_a), 124.3 (C-6), 134.1 (C-3), 149.0 (C-7_a), 167.0 (C=O), 171.0 (C=O), 172.0 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

2-Acetyl-2H-indazole L-glycyl-L-phenylglycine methyl ester (**35**, $C_{20}H_{20}N_4O_4$)
White foam (73%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.34$ (d, $J = 5.0$ Hz, CH_3), 3.62 (s, OCH_3), 3.90 (s, CH_2), 4.60 (q, $J = 5.1$ Hz, CH), 5.13 (s, N^2-CH_2), 7.12 (t, $J = 7.5$ Hz, H-5), 7.25–7.48 (m, *Ph*-H, H-6), 7.68 (d, $J = 8.6$ Hz, H-4), 7.83 (d, $J = 8.5$ Hz, H-7), 7.97 (s, H-3), 8.66 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 17.5$ (CH_3), 41.5 (CH_2), 44.6 (CH), 51.9 (N^2-CH_2), 53.5 (OCH_3), 117.0 (C-7), 120.5 (C-5), 121.9 (C-4), 122.5 (C-3a), 124.7 (C-6), 125.7, 129.9, 131.5, 134.5, 137.9 (*Ph*-C, C-3), 149.2 (C-7a), 167.1 (C=O), 172.1 (C=O), 173.0 (C=O) ppm; MS (ESI): $m/z = 227$ $[M + Na]^+$.

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