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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 70th Anniversary

Ugi Reaction with Isocyanoindoles

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Abstract—Ugi reaction with 5-isocyanoindoles afforded a number of amino acids, β-lactams, and tetrazoles. The described approach can be applied to combinatorial synthesis of biologically active compounds of the indole series.

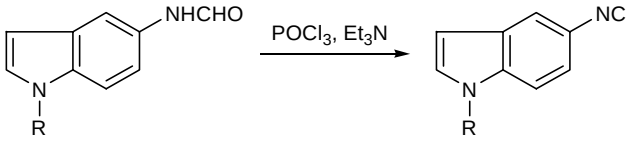
The indole fragment constitutes a part of various naturally occurring compounds, a number of which exhibit pronounced biological activity. Therefore, development of synthetic routes to indole-containing structures attracts persistent interest of researchers. Indoles having an isocyano group are produced by some bacteria of the *Pseudomonas* family [1]. Examples are antibiotic B 371 and its derivatives which possess a high antibacterial and fungicidal activity [2]. It was shown that the presence of an isocyano group is a necessary condition endowing such compounds with the above sort of biological activity [3]. In addition, the ability of isocyanides to participate in various multicomponent reactions opens wide prospects in the application of isocyanoindoles as base structures for combinatorial libraries. For example, indoles having a side-chain isocyano group were recently used to search for new antibiotics by highly efficient semiautomatic procedures [4].

Studies in the field of biological and chemical properties of isocyanoindoles are limited due to the lack of convenient methods for their preparation since classical procedures are often inapplicable to the synthesis of heterocyclic isocyanides [5]. We previously reported on the first synthesis of 5-isocyanoindoles by reaction of 1,4-diisocyanobenzene with tertiary amines [6]. The goal of the present study was to elucidate the possibility of involving 5-isocyanoindoles in the Ugi reaction with a view to obtain a wide series of their derivatives as potential biologically active compounds.

The procedure proposed by us previously makes it possible to synthesize 5-isocyanoindole derivatives having only a few definite substituents in positions *2* and *3* of the indole ring. On the other hand, the classical procedure described in [7] turned out to be unsuitable for the preparation of isocyanoindoles having no substituents in positions *2* and *3* from the corresponding formamides **I**. Therefore, we developed a novel method which allowed us to obtain 5-isocyano-1*H*-indole (**IIa**) and 1-methyl-1*H*-indole (**IIb**) with account taken of their instability (Scheme 1). To prevent polymerization of compounds **II**, the reaction time was shortened, and all operations were performed at reduced temperature with strict control of pH. Initial formamides **I** were synthesized from dihydroindole following the known procedure [8]. Isocyanides **II** are fairly unstable compounds which readily undergo polymerization in solution, while crystalline samples can be stored for several days at –18°C. Unfortunately, compounds **IIa** and **IIb** cannot be subjected to biological testing; however, they can be used as starting materials for the synthesis of various derivatives.

The structure of compounds **II** was confirmed by the IR and ^{1}H NMR spectra. Both **IIa** and **IIb** showed

Scheme 1.



Ia, **Ib** **IIa**, **IIb**

R = H (**a**), Me (**b**).

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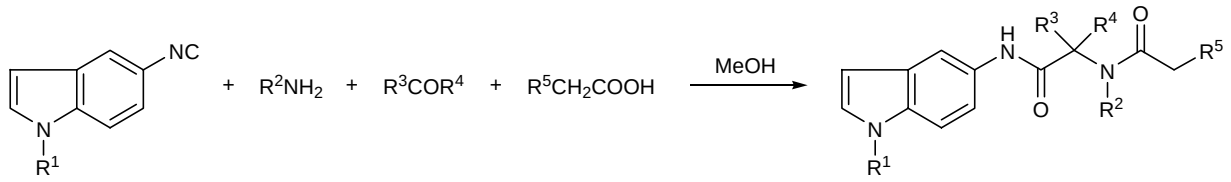
Scheme 2.



IIa, **IIb** **IIIa–IIId** **IVa**, **IVb** **Va**, **Vb** **VIa–VIf**

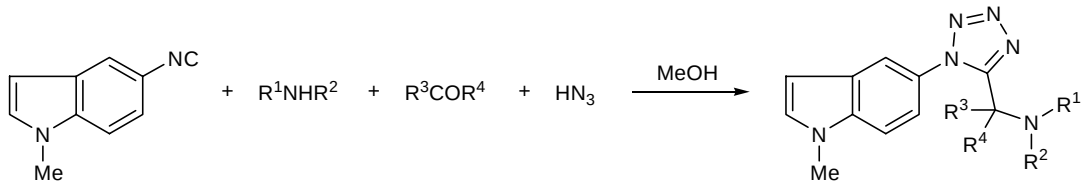
IIa, **VIa**, **VIb**, R^1 = H; **IIb**, **VIc–VIf**, R^1 = Me; **IIIa**, **VIa**, **VIb**, R^2 = 1-benzylpiperidin-4-yl; **IIIb**, **VIc**, R^2 = benzyl; **IIIc**, **VId**, R^2 = cyclopropyl; **IIId**, **VIe**, **VIf**, R^2 = 2-(1*H*-indol-3-yl)ethyl; **IVa**, **VIa**, **VIc**, **VIe**, **VIf**, R^3 = R^4 = Me; **IVb**, **VIb**, **VId**, R^3R^4 = $(CH_2)_5$; **Va**, **VIa**, **VIb**, **VIe**, **VIf**, R^5 = Ph; **Vb**, **VIc**, **VId**, R^5 = phthalimido.

in the IR spectra an absorption band at 2120 cm^{-1}, which belongs to the isocyano group. The ^{1}H NMR spectra of **II** contained a set of signals typical of 5-substituted indoles. In the ^{1}H NMR spectrum of **IIb** we observed signals from the aromatic protons as two doublets at δ 7.63 ppm (^4J = 1.5 Hz) and 7.43 ppm (^3J = 8.9 Hz) and a doublet of doublets at δ 7.18 ppm (^3J = 8.9, ^4J = 1.5 Hz) (4-H, 7-H, and 6-H, respectively). Also, signals from protons in the pyrrole fragment were present as two doublets at δ 7.35 and 6.45 ppm (^3J = 3.4 Hz). Protons in the *N*-methyl group of **IIb** appeared as a singlet at δ 3.83 ppm.

It should be noted that the use of isocyanides as a base structure for combinatorial libraries implies application of the whole diversity of the Ugi reaction [9]. However, the real choice is limited by the ability of initial isocyanides to undergo polymerization: The Ugi reaction should be faster than undesirable polymerization process. Taking into account published data [10], we selected appropriate reagents, namely strongly basic primary amines, aliphatic ketones, formaldehyde, phthalylglycine, and phenylacetic acid. By reactions of amines **IIIa**–**IIId**, ketones **IVa** and **IVb**, acids **Va** and **Vb**, and isocyanides **IIa** and **IIb** in methanol we obtained amino acid derivatives **VIa**–**VIf** (Scheme 2) in good yields (70–75%). However, we failed to isolate the desired products by reaction with formaldehyde, presumably as a result of concurrent Mannich condensation at the *3*-position of the initial isocyanide. Thus the optimal set of initial reactants should include such compounds which selectively react with the isocyano group, the indole fragment remaining intact (aliphatic ketones, strongly basic amines, and carboxylic, as well as some mineral, acids). Benzylpiperidine, cyclopropylamine, benzylamine, and tryptamine (**IIId**) were used as amine component. By reactions with compound **IIId** we succeeded in introducing one more indole fragment into the products (**VIe** and **VIf**).

The structure of compounds **VI** was proved with account taken of published data [11, 12]. The ^{1}H NMR spectra of compounds **VIa**–**VIf** contained signals from the indole fragment (see above). In the aromatic region, signals from the second indole fragment, phthalimide moiety, and other aromatic groups were also present. The NH proton gave a signal at δ 8.61–8.87 ppm. Compounds **VIa**, **VIc**, **VIe**, and **VIf** showed in the ^{1}H NMR spectra a singlet from the methyl protons at δ 1.40–1.62 ppm, and in the spectra of **VIb** and **VId** we observed signals from the cyclohexane fragment as a two-proton multiplet at δ 2.30–2.65 ppm and eight-proton multiplet at δ 1.25–2.00 ppm. The spectra of **VIe** and **VIf** also contained signals from the

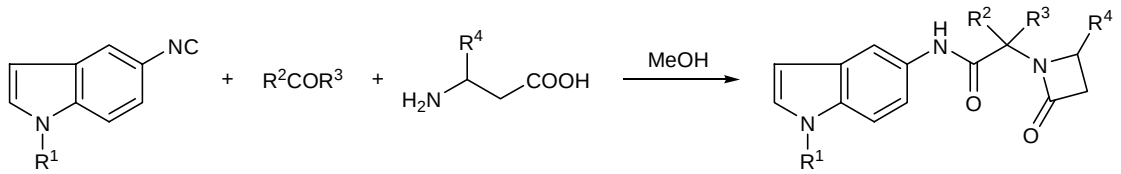
Scheme 3.



IIb **IIId**, **IIIe** **IVa**, **IVb** **VIIa–VIId**

IIIe, **VIIa**, **VIIb**, R^1R^2 = $(C_2H_4)_2O$; **IIId**, **VIIc**, **VIId**, R^1 = H, R^2 = 2-(1*H*-indol-3-yl)ethyl; **IVa**, **VIIa**, **VIIc**, R^3 = R^4 = Me; **IVb**, **VIIb**, **VIId**, R^3R^4 = $(CH_2)_5$.

Scheme 4.



IIa, **IIb** **IVb–IVe** **VIIIa**, **VIIIb** **IXa–IXf**

IIa, **IXa–IXc**, R^1 = H; **IIb**, **IXd–IXf**, R^1 = Me; **IVb**, **IXc**, **IXd**, **IXf**, $R^2R^3 = (CH_2)_5$; **IVc**, **IXa**, $R^2R^3 = (CH_2)_4$; **IVd**, **IXe**, $R^2R^3 = (C_2H_4)_2S$; **IVe**, **IXb**, R^2 = H, R^3 = *i*-Pr; **VIIIa**, **IXa**, **IXb**, **IXd**, **IXe**, R^4 = H; **VIIIb**, **IXc**, **IXf**, R^4 = 3,4-$(OCH_2O)C_6H_3$.

tryptamine fragment. All compounds **VIa–VIf** showed in the mass spectra the molecular ion peaks whose *m*/*z* values were consistent with the calculated molecular weights. The mass spectra also contained peaks from the fragment ion $[M - 18]^+$ which is typical of decomposition of the linear Ugi reaction products under electron impact [11]. Compounds **VIe** and **VIf** containing a tryptamine moiety gave rise to the fragment ion with *m/z* 143, which corresponds to 3-vinylindole.

Some inorganic acids, e.g., thiocyanic, hydrochloric, and hydrazoic, can successfully be involved in the Ugi reaction [9]. In paticular, the reactions with hydrazoic acid afforded tetrazolyl-substituted indoles **VIIa–VIId** in high yield (Scheme 3). The mass spectra of **VIIa–VIId** contained the molecular ion peaks and fragment ion peaks from the amine–ketone moiety and indole ring (*m/z* 130). Tryptamine derivatives **VIIc** and **VIId** are characterized by the fragment ion peak with *m/z* 143, and the ion peak with *m/z* 86 in the mass spectra of **VIIa** and **VIIb** arises from the morpholine moiety. In the ^{1}H NMR spectra of **VIIa–VIId** we observed signals from protons of the indole and methyl and methylene groups. Protons of the morpholine ring in **VIIa** and **VIIb** gave rise to two triplets (^3J = 4.3 Hz) at δ 3.40–3.56 and 2.33–2.44 ppm, and the spectra of **VIIc** and **VIId** contained signals from the tryptamine fragment.

It is known that the use in the Ugi reaction of difunctional reagents, such as amino acids, opens wide synthetic prospects; specifically, nonaromatic heterocyclic structures can be obtained in this way [9]. By reaction of isocyanides **IIa** and **IIb**, ketones **IVb–IVd**, and amino acids **VIIIa** and **VIIIb** in methanol we obtained β-lactams **IXa** and **IXc–IXf** (Scheme 4). In the reaction with isobutyraldehyde (**IVe**) we isolated compound **IXb**, but the yield was lower than in the reactions with aliphatic ketones.

All compounds **IXa–IXf** showed the molecular ion peak in the mass spectra. The main fragmentation pattern includes dissociation of the C–C bond between the ketone and isocyanide moieties, so that the mass spectra contained the fragment ion corresponding to oxoazetidine + ketone. In the ^{1}H NMR spectra of lactams **IXa**, **IXb**, **IXd**, and **IXe**, signals from protons of the oxoazetidine ring appeared as two triplets in the δ region 2.86–3.27 ppm with a coupling constant of 4.0–4.3 Hz.

Thus, our results showd that 5-isocyanoindoles can be used as starting material for synthesis of a large number of derivatives, such as amino acids, β-lactams, and tetrazoles, via Ugi reaction. Possible versions of the Ugi reaction were examined, and limitations concerning the initial reactants were determined. A wide variety of structures available from isocyanoindoles by the Ugi reaction demonstrates excellent prospects for combinatorial synthesis. We plan to further extend the developed approach to search for new indole-containing biologically akcive compounds with the aid of new highly productive methods.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by thin-layer chromatography on Silufol-254 and Sorbfil-254 plates using the following solvent systems: chloroform; chloroform–ethanol, 9:1, 15:1, 20:1; chloroform–hexane, 1:1, 1:2, 2:1. The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H NMR spectra were obtained on a Bruker WM-250 instrument at 250 MHz using DMSO-d_6 or DMSO-d_6–CCl_4 as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were run on a Varian MAT 311A instrument (accelerating voltage 3 kV) with direct sample admission into the ion source. The melting points were not corrected.

5-Isocyanoindoles IIa and IIb (*general procedure***).** *N*-(1*H*-Indol-5-yl)formamide **Ia** or **Ib**, 7 mmol, was added to a mixture of 20 ml of dry methylene chloride, 3.36 ml of triethylamine, and 0.84 ml of phosphoryl chloride. The mixture was stirred for 30 min at 5°C and was washed with 15 ml of a 10% solution of KOH on cooling. The organic layer was separated, and the solvent was quickly (within 5–10 min) distilled off at a temperature not exceeding 30°C. The residue was carefully recrystallized from hexane.

5-Isocyanoindole (IIa). Yield 0.81 g (82%), mp 92–93°C. IR spectrum, cm^{-1}: 2117 (NC). ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.81 br.s (1H, NH), 7.67 d (1H, 4-H, ^4J = 1.5 Hz), 7.27 d (1H, 7-H, J = 8.5 Hz), 7.19 t (1H, 2-H, ^3J = 2.7 Hz), 7.10 d.d (1H, 6-H, ^3J = 8.5, ^4J = 1.5 Hz), 6.33 t (1H, 3-H, ^3J = 2.7 Hz).

5-Isocyano-1-methylindole (IIb). Yield 0.85 g (78%), mp 70–71°C. IR spectrum, cm^{-1}: 2115 (NC). ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 7.63 d (1H, 4-H, ^4J = 1.5 Hz), 7.43 d (1H, 7-H, ^3J = 8.9 Hz), 7.35 d (1H, 2-H, ^3J = 3.4 Hz), 7.18 d.d (1H, 6-H, ^3J = 8.9, ^4J = 1.5 Hz), 6.45 d (1H, 3-H, ^3J = 3.4 Hz), 3.83 s (3H, NCH_3).

General procedure for the synthesis of compounds VI. Amine **IIIa**–**IIId**, 0.2 mmol, ketone **IVa** or **IVb**, 0.2 mmol, and acid **Va** or **Vb**, 0.2 mmol, were added to a solution of 0.2 mmol of 5-isocyanoindole in 0.2 ml of methanol, and the mixture was kept for 2–3 h. The precipitate was filtered off and recrystallized from ethanol.

***N*-(1*H*-Indol-5-yl)-2-[1-benzylpiperidin-4-yl-(phenylacetyl)amino]-2-methylpropionamide (VIa).** Yield 0.077 g (76%), mp 256–257°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.74 s (1H, NH), 8.20 s (1H, NH), 7.58 d (1H, 4-H, indole, ^4J = 1.6 Hz), 7.15–7.32 m (12H, 2Ph, 2-H, 7-H, indole), 7.01 d.d (1H, 6-H, ^3J = 8.5, ^4J = 1.6 Hz), 6.29 br.s (1H, 3-H, indole), 3.78 s (2H, CH_2), 3.55–3.61 m (1H, CH), 3.44 s (2H, CH_2), 2.87 br.t (2H, CH_2N), 2.25 br.t (2H, CH_2N), 1.76–1.91 m (4H, $2CH_2$), 1.54 s (6H, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 508 $[M]^+$ (5), 490 (6), 372 (31), 246 (42), 166 (32), 132 (25), 91 (100). Found, %: C 75.35; H 7.00; N 11.13. $C_{32}H_{36}N_4O_2$. Calculated, %: C 75.56; H 7.08; N 11.01.

***N*-(1*H*-Indol-5-yl)-2-[1-benzylpiperidin-4-yl-(phenylacetyl)amino]cyclohexanecarboxamide (VIb).** Yield 0.081 g (74%), mp 263–264°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.76 s (1H, NH), 8.59 s (1H, NH), 7.56 d (1H, 4-H, indole, ^4J = 1.5 Hz), 7.16–7.30 m (12H, 2Ph, 2-H, 7-H, indole), 7.00 d.d (1H, 6-H, ^3J = 8.6, ^4J = 1.5 Hz), 6.29 br.s (1H, 3-H, indole), 3.78 s (2H, CH_2), 3.45–3.56 m (1H, CH), 3.44 s (2H, CH_2), 2.88 br.t (2H, CH_2N), 2.26 br.t (2H, CH_2N), 2.25–1.30 m (14H, $7CH_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 548 $[M]^+$ (4), 530 (8), 426 (24), 346 (37), 192 (29), 145 (38), 122 (26), 91 (100). Found, %: C 76.44; H 7.26; N 10.14. $C_{35}H_{40}N_4O_2$. Calculated , %: C 76.61; H 7.29; N 10.21.

***N*-(1-Methyl-1*H*-indol-5-yl)-2-[benzyl(2-phthalimidoacetyl)amino]-2-methylpropionamide (VIc).** Yield 0.07 g (69%), mp 301–302°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 8.85 s (1H, NH), 7.79–7.88 m (4H, H_{arom}, phthalimide), 7.58 d (1H, 4-H, indole, ^4J = 1.8 Hz), 7.52 d (1H, 7-H, indole, ^3J = 8.2 Hz), 7.12–7.46 m (7H, Ph, 2-H, 6-H, indole), 6.31 d (1H, 3-H, indole, ^3J = 2.5 Hz), 4.88 s (2H, CH_2), 4.63 s (2H, CH_2), 3.78 s (3H, NCH_3), 1.40 s (6H, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel},%): 508 $[M]^+$ (2), 490 (5), 363 (31), 160 (28), 148 (33), 146 (31), 91 (100). Found, %: C 71.00; H 5.68; N 11.18. $C_{30}H_{28}N_4O_4$. Calculated, %: C 70.85; H 5.55; N 11.02.

***N*-(1-Methyl-1*H*-indol-5-yl)-1-[cyclopropyl-(2-phthalimidoacetyl)amino]cyclohexanecarboxamide (VId).** Yield 0.074 g (74%), mp 174–175°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 8.85 s (1H, NH), 7.81–7.90 m (4H, H_{arom}, phthalimide), 7.56 d (1H, 4-H, indole, ^4J = 1.8 Hz), 7.22 d (1H, 7-H, indole, ^3J = 8.6 Hz), 7.13 d (1H, 2-H, indole, ^3J = 2.4 Hz), 7.04 d.d (1H, 6-H, indole, ^3J = 8.6, ^4J = 1.8 Hz), 6.29 d (1H, 3-H, indole, ^3J = 2.4 Hz), 4.74 s (2H, CH_2), 3.77 s (3H, NCH_3), 2.85–3.00 m [1H, C**H**$(CH_2)_2$], 2.30–2.47 m [2H, $C(CH_2)_5$], 1.90–2.10 m [2H, $C(CH_2)_5$], 1.30–1.80 m [6H, $C(CH_2)_5$], 0.95–1.18 m [4H, $CH(CH_2)_2$]. Mass spectrum, *m*/*z* (I_{rel}, %): 499 $[M + 1]^+$ (2), 498 $[M]^+$ (8), 480 (2), 353 (72), 325 (49), 255 (12), 173 (4), 160 (86), 146 (70), 138 (100). Found, %: N 11.23. $C_{29}H_{30}N_4O_4$. Calculated, %: N 11.24.

***N*-(1-Methyl-1*H*-indol-5-yl)-2-methyl-2-{(2-phthalimidoacetyl)[2-(1*H*-indol-3-yl)ethyl]-amino}propionamide (VIe).** Yield 0.084 g (75%), mp 253–254°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.85 s (1H, NH, indole), 8.82 s (1H, NH), 7.81–7.90 m (4H, H_{arom}, phthalimide), 7.59 s (1H, 4-H, indole), 7.56 d (1H, 4-H, tryptamine, ^3J = 8.9 Hz), 7.36 d (1H, 7-H, tryptamine, ^3J = 7.9 Hz), 7.25 s (1H, 2-H, tryptamine), 7.22 d (1H, 7-H, indole, ^3J = 8.9 Hz),

7.13 d (1H, 2-H, indole, ^3J = 2.8 Hz), 6.99–7.09 m (3H, 6-H, indole, 5-H, 6-H, tryptamine), 6.30 d (1H, 3-H, indole, ^3J = 2.8 Hz), 4.60 s (2H, CH_2), 3.60–3.95 m (2H, CH_2), 3.77 s (3H, NCH_3), 3.10–3.30 m (2H, CH_2), 1.60 s (6H, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 562 $[M + 1]^+$ (6), 561 $[M]^+$ (14), 542 (52), 401 (100), 212 (24), 160 (27), 143 (79), 130 (15). Found, %: C 70.51; H 5.53; N 12.34. $C_{33}H_{31}N_5O_4$. Calculated, %: C 70.57; H 5.56; N 12.47.

***N*-(1-Methyl-1*H*-indol-5-yl)-2-methyl-2-{[2-(1*H*-indol-3-yl)ethyl]phenylacetylamino}propionamide (VIf).** Yield 0.075 g (76%), mp 217–218°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.79 s (1H, NH, indole), 8.61 s (1H, NH), 7.63 d (1H, 4-H, indole, ^4J = 1.8 Hz), 7.51 d (1H, 4-H, tryptamine, ^3J = 7.6 Hz), 7.34 d (1H, 7-H, tryptamine, ^3J = 8.2 Hz), 6.98–7.25 m (11H, 3-H, 6-H, 7-H, indole, 2-H, 5-H, 6-H, tryptamine, Ph), 6.30 d (1H, 3-H, indole, ^3J = 2.8 Hz), 3.78 s (3H, NCH_3), 3.70–3.95 m (2H, CH_2), 3.64 s (2H, CH_2), 2.90–3.10 m (2H, CH_2), 1.62 s (6H, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 493 $[M + 1]^+$ (1), 492 $[M]^+$ (2), 474 (3), 332 (100), 143 (79), 130 (11), 91 (16). Found, %: N 11.58. $C_{31}H_{32}N_4O_2$. Calculated, %: N 11.37.

General procedure for the synthesis of tetrazolyl-substituted indoles VII. Amine **IIId** or **IIIe**, 0.2 mmol, ketone **IVa** or **IVb**, 0.2 mmol, and a 1 mM solution of hydrazoic acid in 0.2 ml of benzene, were added to a solution of 0.2 mmol of 5-isocyanoindole **IIb** in 0.2 ml of methanol, and the mixture was kept for 2–3 h. The precipitate was filtered off and recrystallized from ethanol.

1-(1-Methyl-1*H*-indol-5-yl)-5-(1-methyl-1-morpholinoethyl)tetrazole (VIIa). Yield 0.047 g (72%), mp 196–197°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 7.73 d (1H, 4-H, indole, ^4J = 1.8 Hz), 7.54 d (1H, 7-H, indole, ^3J = 8.6 Hz), 7.41 d (1H, 2-H, indole, ^3J = 3.1 Hz), 7.27 d.d (1H, 6-H, indole, ^3J = 8.6, ^4J = 1.8 Hz), 6.52 d (1H, 3-H, indole, ^3J = 3.1 Hz), 3.91 s (3H, NCH_3), 3.40 t [4H, $O(CH_2)_2$, ^3J = 4.3 Hz], 2.33 t [4H, $N(CH_2)_2$, ^3J = 4.3 Hz], 1.36 s (6H, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 327 $[M + 1]^+$ (4), 326 $[M]^+$ (21), 241 (100), 198 (9), 156 (46), 128 (86), 86 (11). Found, %: C 62.63; H 6.81; N 25.80. $C_{17}H_{22}N_6O$. Calculated, %: C 62.56; H 6.79; N 25.75.

1-(1-Methyl-1*H*-indol-5-yl)-5-(1-methyl-1-morpholinocyclohexyl)tetrazole (VIIb). Yield 0.058 g (80%), mp 242–243°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 7.77 d (1H, 4-H, indole, ^4J = 1.8 Hz), 7.55 d (1H, 7-H, indole, ^3J = 8.6 Hz), 7.42 d (1H, 2-H, indole, ^3J = 3.1 Hz), 7.31 d.d (1H, 6-H, indole, ^3J = 8.6, ^4J = 1.8 Hz), 6.53 d (1H, 3-H, indole, ^3J = 3.1 Hz), 3.91 s (3H, NCH_3), 3.56 t [4H, $O(CH_2)_2$, ^3J = 4.3 Hz], 2.44 t [4H, $N(CH_2)_2$, ^3J = 4.3 Hz], 1.90–2.00 m [2H, $C(CH_2)_5$], 1.15–1.78 m [8H, $C(CH_2)_5$]. Mass spectrum, *m*/*z* (I_{rel}, %): 367 $[M + 1]^+$ (4), 366 $[M]^+$ (16), 281 (100), 168 (70), 156 (43), 86 (8). Found, %: N 23.10. $C_{20}H_{26}N_6O$. Calculated, %: N 22.93.

5-{1-[2-(1*H*-Indol-3-yl)ethylamino]-1-methylethyl}-1-(1-methyl-1*H*-indol-5-yl)tetrazole (VIIc). Yield 0.069 g (87%), mp 207–208°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.71 s (1H, NH, indole), 7.32–7.41 m (4H, 4-H, indole, 2-H, 4-H, 7-H, tryptamine), 7.24 d (1H, 7-H, indole, ^3J = 8.6 Hz), 7.04 d.d (1H, 5-H, tryptamine, ^3J = 8.6, ^3J = 7.9 Hz), 6.99 d (1H, 2-H, indole, ^3J = 2.8 Hz), 6.92 d.d (1H, 6-H, tryptamine, ^3J = 7.9, ^3J = 7.9 Hz), 6.78 d.d (1H, 6-H, indole, ^3J = 8.6, ^4J = 1.8 Hz), 6.43 d (1H, 3-H, indole, ^3J = 2.8 Hz), 3.13 s (3H, NCH_3), 2.64–2.68 m [4H, $(C\mathbf{H}_2)_2NH$], 1.25–1.53 m [1H, $(CH_2)_2N\mathbf{H}$], 1.36 s (6H, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 399 $[M]^+$ (2), 269 (10), 200 (20), 184 (24), 171 (31), 143 (40), 130 (90), 70 (100). Found, %: C 69.23; H 6.39; N 24.64. $C_{23}H_{25}N_7$. Calculated, %: C 69.15; H 6.31; N 24.54.

5-{1-[2-(1*H*-Indol-3-yl)ethylamino]-1-methylcyclohexyl}-1-(1-methyl-1*H*-indol-5-yl)tetrazole (VIId). Yield 0.06 g (69%), mp 195–196°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.75 s (1H, NH, indole), 7.34–7.39 m (3H, 4-H, indole, 4-H, 7-H, tryptamine), 7.25 d (1H, 2-H, tryptamine, ^3J = 1.8 Hz), 7.18 d (1H, 7-H, indole, ^3J = 8.6 Hz), 7.04 d.d (1H, 5-H, tryptamine, ^3J = 8.6, ^3J = 7.9 Hz), 6.98 d (1H, 2-H, indole, ^3J = 3.1 Hz), 6.93 d.d (1H, 6-H, tryptamine, ^3J = 7.9, ^3J = 7.9 Hz), 6.62 d.d (1H, 6-H, indole, ^3J = 8.6, ^4J = 1.8 Hz), 6.39 d (1H, 3-H, indole, ^3J = 3.1 Hz), 3.86 s (3H, NCH_3), 2.75 t [2H, $(C\mathbf{H}_2)_2NH$, ^3J = 6.1], 2.59 t [2H, $(C\mathbf{H}_2)_2NH$, ^3J = 6.1 Hz], 1.85–1.94 m [2H, $C(CH_2)_5$], 1.26–1.60 m [9H, $C(CH_2)_5$, $(CH_2)_2N\mathbf{H}$]. Mass spectrum, *m*/*z* (I_{rel}, %): 439 $[M]^+$ (1), 240 (12), 184 (12), 171 (26), 143 (25), 130 (34), 110 (100). Found, %: N 22.23. $C_{26}H_{29}N_7$. Calculated, %: N 22.31.

General procedure for the synthesis of β-lactams (IX). Ketone or aldehyde **IVb**–**IVe**, 0.2 mmol, and β-amino acid **VIIIa** or **VIIIb**, 0.2 mmol, were added to a solution of 0.2 mmol of 5-isocyanoindole **IIa** or **IIb** in 0.2 ml of methanol, and the mixture was kept for

2–3 h. The precipitate was filtered off and recrystallized from ethanol.

***N*-(1*H*-Indol-5-yl)-1-(2-oxoazetidin-1-yl)cyclopentanecarboxamide (IXa).** Yield 0.038 g (64%), mp 223–224°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.80 br.s (1H, NH), 9.21 s (1H, NH), 7.70 d (1H, 4-H, ^4J = 1.5 Hz), 7.25 d (1H, 7-H, ^3J = 8.5 Hz), 7.18 t (1H, 2-H, ^3J = 2.4 Hz), 7.14 d.d (1H, 6-H, ^3J = 8.5, ^4J = 1.5 Hz), 6.32 t (1H, 3-H, ^3J = 2.4 Hz), 3.27 t [2H, $CO(CH_2)_2N$, ^3J = 4.2 Hz], 2.83 t [2H, $CO(CH_2)_2N$, ^3J = 4.2 Hz], 2.12–2.38 m (4H, $2CH_2$), 1.85–2.00 m (4H, $2CH_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 297 $[M]^+$ (36), 186 (12), 138 (100), 110 (43). Found, %: C 68.75; H 6.32; N 14.09. $C_{17}H_{19}N_3O_2$. Calculated, %: C 68.68; H 6.39; N 14.13.

***N*-(1*H*-Indol-5-yl)-3-methyl-2-(2-oxoazetidin-1-yl)butyramide (IXb).** Yield 0.023 g (41%), mp 154–155°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.78 br.s (1H, NH), 9.84 s (1H, NH), 7.84 d (1H, 4-H, ^4J = 1.6 Hz), 7.27 d (1H, 7-H, ^3J = 8.6 Hz), 7.18 t (1H, 2-H, ^3J = 2.5 Hz), 7.13 d.d (1H, 6-H, ^3J = 8.6, ^4J = 1.6 Hz), 6.31 t (1H, 3-H, ^3J = 2.5 Hz), 4.06 d (1H, ^3J = 9.8 Hz, CH), 3.42 t [2H, ^3J = 4.2 Hz, $CO(CH_2)_2N$], 2.86 t [2H, ^3J = 4.2 Hz, $CO(CH_2)_2N$], 2.10–2.17 m (1H, CH), 0.95 d (6H, ^3J = 3.9 Hz, $2CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 285 $[M]^+$ (36), 158 (17), 126 (100), 97 (38). Found, %: C 67.18; H 6.60; N 14.65. $C_{16}H_{19}N_3O_2$. Calculated, %: C 67.28; H 6.66; N 14.73.

***N*-(1*H*-Indol-5-yl)-1-[4-(3,4-methylenedioxyphenyl)-2-oxoazetidin-1-yl]cyclohexanecarboxamide (IXc).** Yield 0.062 g (72%), mp 167–168°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 10.81 br.s (1H, NH), 9.04 s (1H, NH), 7.64 d (1H, 4-H, ^4J = 1.3 Hz), 7.27 d (1H, 7-H, ^3J = 8.5 Hz), 7.19 t (1H, 2-H, ^3J = 2.4 Hz), 7.08 d.d (1H, 6-H, ^3J = 8.5, ^4J = 1.3 Hz), 6.96 d (1H, 2-H, C_6H_3, ^4J = 1.2 Hz), 6.82 d.d (1H, 6-H, C_6H_3, ^3J = 7.9, ^4J = 1.2 Hz), 6.71 d (1H, 5-H, C_6H_3, ^3J = 7.9 Hz), 6.32 t (1H, 3-H, ^3J = 2.4 Hz), 5.91 br.s (2H, CH_2O_2), 4.69–4.71 m (1H, CH), 3.31 d.d (1H, CH_2CO, *J* = 5.4 Hz), 2.68 d.d (1H, CH_2CO, *J* = 2.2 Hz), 1.80–2.10 m [2H, $C(CH_2)_5$], 1.20–1.75 m [8H, $C(CH_2)_5$]. Mass spectrum, *m*/*z* (I_{rel}, %): 431 $[M]^+$ (22), 272 (63), 172 (7), 150 (13), 124 (100), 81 (38). Found, %: C 69.68; H 5.72; N 9.69. $C_{25}H_{25}N_3O_4$. Calculated, %: C 69.64; H 5.80; N 9.74.

***N*-(1-Methyl-1*H*-indol-5-yl)-1-(2-oxoazetidin-1-yl)cyclohexanecarboxamide (IXd).** Yield 0.038 g (58%), mp 254–255°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 9.13 s (1H, NH), 7.73 s (1H, 4-H, indole), 7.17–7.29 m (2H, 6-H, 7-H, indole), 7.15 d (1H, 2-H, indole, ^3J = 2.8 Hz), 6.31 d (1H, 3-H, indole, ^3J = 2.8 Hz), 3.79 s (3H, NCH_3), 3.26 t [2H, $CO(CH_2)_2N$, ^3J = 4.3 Hz], 2.86 t [2H, $CO(CH_2)_2N$, ^3J = 4.3 Hz], 2.11–2.23 m [2H, $C(CH_2)_5$], 1.91–2.00 m [2H, $C(CH_2)_5$], 1.15–1.78 m [6H, $C(CH_2)_5$]. Mass spectrum, *m*/*z* (I_{rel}, %): 326 $[M + 1]^+$ (6), 325 $[M]^+$ (28), 172 (3), 152 (100), 110 (51). Found, %: C 70.15; H 7.13; N 12.97. $C_{19}H_{23}N_3O_2$. Calculated, %: C 70.13; H 7.12; N 12.91.

***N*-(1-Methyl-1*H*-indol-5-yl)-4-(2-oxoazetidin-1-yl)tetrahydrothiopyran-4-carboxamide (IXe).** Yield 0.053 g (78%), mp 193–194°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 9.34 s (1H, NH), 7.75 s (1H, 4-H, indole), 7.26 s (2H, 6-H, 7-H, indole), 7.18 d (1H, 2-H, indole, ^3J = 2.8 Hz), 6.31 d (1H, 3-H, indole, ^3J = 2.8 Hz), 3.79 s (3H, NCH_3), 3.27 t [2H, $CO(CH_2)_2N$, ^3J = 4.0 Hz], 2.89 t [2H, $CO(CH_2)_2N$, ^3J = 4.0 Hz], 2.68–2.83 m (2H, $S(CH_2)_4$), 2.10–2.65 m [6H, $S(CH_2)_4$]. Mass spectrum, *m*/*z* (I_{rel}, %): 344 $[M + 1]^+$ (11), 343 $[M]^+$ (51), 170 (100), 146 (33), 128 (45). Found, %: N 12.18. $C_{18}H_{21}N_3O_2S$. Calculated, %: N 12.23.

***N*-(1-Methyl-1*H*-indol-5-yl)-1-[4-(3,4-methylenedioxyphenyl)-2-oxoazetidin-1-yl]cyclohexanecarboxamide (IXf).** Yield 0.052 g (59%), mp 176–177°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 9.14 s (1H, NH), 7.66 d (1H, 4-H, indole, ^4J = 1.8 Hz), 7.27 d (2H, 7-H, indole, ^3J = 8.6 Hz), 7.18 d (1H, 2-H, indole, ^3J = 2.8 Hz), 7.15 d.d (1H, 6-H, indole, ^3J = 8.6, ^4J = 1.8 Hz), 6.98 d (1H, 2-H, C_6H_3, ^4J = 1.7 Hz), 6.87 d.d (1H, 6-H, C_6H_3, ^3J = 7.9, ^4J = 1.7 Hz), 6.72 d (1H, 5-H, ^3J = 7.9 Hz), 6.32 d (1H, 3-H, indole, ^3J = 2.8 Hz), 5.94 br.s (2H, CH_2O_2), 4.69–4.71 m (1H, CH), 3.80 s (3H, NCH_3), 3.27–3.35 m (1H, CH_2CO), 2.66–2.73 m (1H, CH_2CO), 1.80–2.10 m [2H, $C(CH_2)_5$], 1.20–1.75 m [8H, $C(CH_2)_5$]. Mass spectrum, *m*/*z* (I_{rel}, %): 446 $[M + 1]^+$ (5), 445 $[M]^+$ (17), 272 (10), 172 (7), 150 (13), 124 (100), 81 (38). Found, %: N 9.38. $C_{26}H_{27}N_3O_4$. Calculated, %: N 9.43.

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