Synthesis of 1-substituted 4-[4-(1*H*-indol-3-yl)butyl]piperazines

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Abstract

A convenient synthetic route for preparation of various 4-[4-(1*H*-indol-3-yl)butyl]piperazines bearing heterocyclic and aliphatic substituents in position 1 has been developed. During this work some synthetic possibilities of common precursor, 4-[4-(1*H*-indol-3-yl)butyl]piperazine, were studied and evaluated.

Keywords: 4-[4-(1*H*-Indol-3-yl)butyl]piperazine, 1-hetaryl-4-[4-(1*H*-indol-3-yl)butyl]-piperazines, 1-alkyl-4-[4-(1*H*-indol-3-yl)butyl]piperazines, mono-substituted piperazines

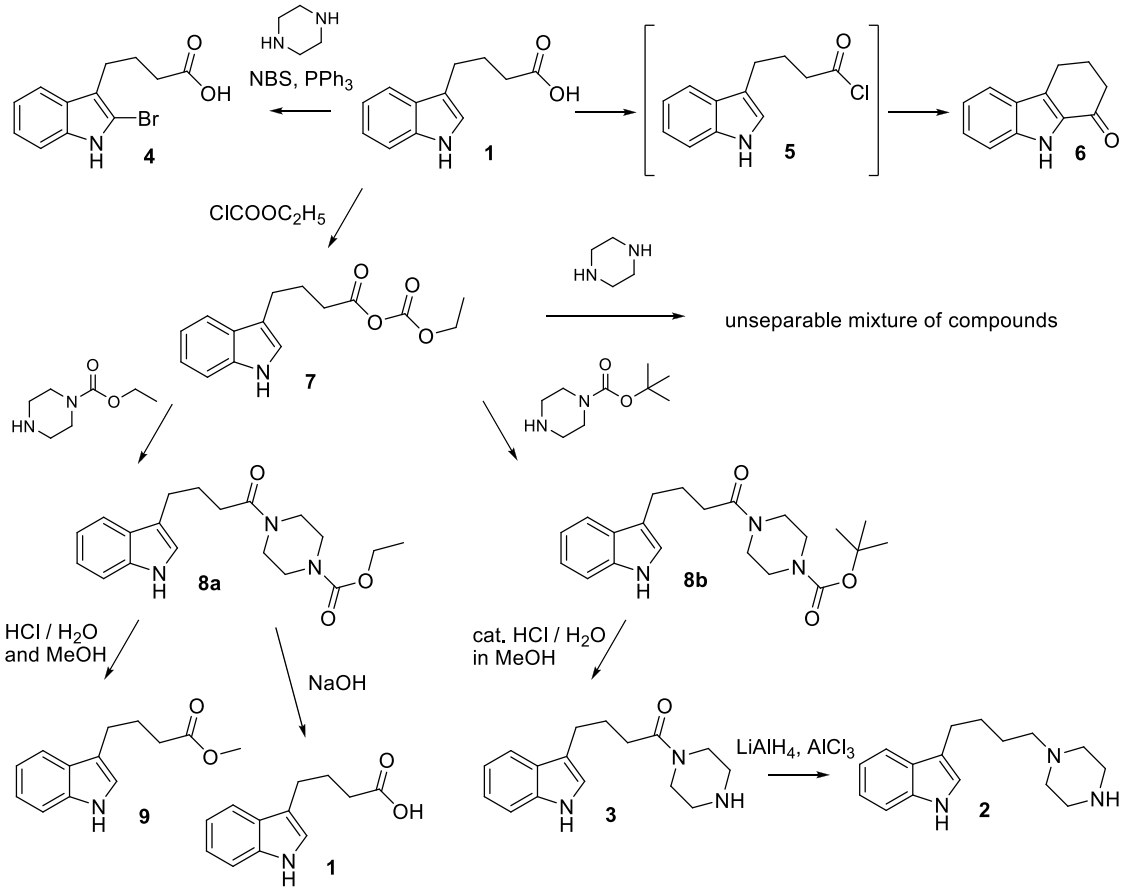
Introduction

4-[4-(1*H*-Indol-3-yl)alkyl]piperazine derivatives have substantial interest in medicinal chemistry for treatment of central nervous system disorders,[1] as dopamine D_4 receptors agonists[2] and 5-hydroxytryptamine 5-HT_{1D} agonists.[3,4] We have synthesized a series of 1-substituted 4-[4-(1*H*-indol-3-yl)butyl]piperazines and hydroxamic acid derivatives, containing 1-substituted 4-[4-(1*H*-indol-3-yl)butyl]piperazine scaffold. Known methods for the synthesis of compounds of this type are based on the reaction of (1*H*-indol-3-yl)alkyl methanesulfonate,[5,6] iodide[7]or chloride[8] with mono-substituted piperazines, or by the formation of piperazine[9] or indole[10] rings. The most attractive way for the preparation of 4-(1*H*-indol-3-yl)butyl]piperazine derivatives is the modification of commercially available 4-(1*H*-indol-3-yl)butanoic acid (**1**).[11,12]

Results and Discussion

It is well known from the literature that mono-acylpiperazines can be easily synthesized from the corresponding acids and excess of piperazine using *N*-bromosuccinimide and

triphenylphosphine. This method allows the preparation of desired compounds under mild conditions and in high (up to 95%) yields.[13] So, we expected to convert 4-(1*H*-indol-3-yl)butanoic acid (**1**) to 4-(1*H*-indol-3-yl)butyl]piperazine (**2**) in two steps. However, instead of expected 3-(4-oxo-4-piperazin-1-ylbutyl)-1*H*-indole (**3**) we isolated the product of bromination – the 4-(2-bromo-1*H*-indol-3-yl)butanoic acid (**4**, yield 92%, scheme 1). Another methodology, which involves the reaction between alkylchloroformates with an excess of piperazine, was applied.[14] The 4-(1*H*-indol-3-yl)butanoyl chloride (**5**)[15] appeared to be quite unstable under reaction conditions and immediately participated in intramolecular acylation by forming 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**6**).[16] Therefore another active compound ethyl 4-(1*H*-indol-3-yl)butanoyl carbonate (**7**) was synthesized by treating 4-(1*H*-indol-3-yl)butanoic acid (**1**) with ethyl chlorformate and triethylamine. Treatment of compound **7** with the triple excess of piperazine resulted formation of an inseparable mixture of several products. Since product mixture didn't contain even traces of target mono-acylpiperazine, protected piperazines were introduced into the reaction. Reaction of compound **7** with ethyl piperazine-1-carboxylate or *tert*-butyl piperazine-1-carboxylate led to the formation of 1-protected 4-[4-(1*H*-indol-3-yl)butyl]piperazines **8a** and **8b** in moderate yields.



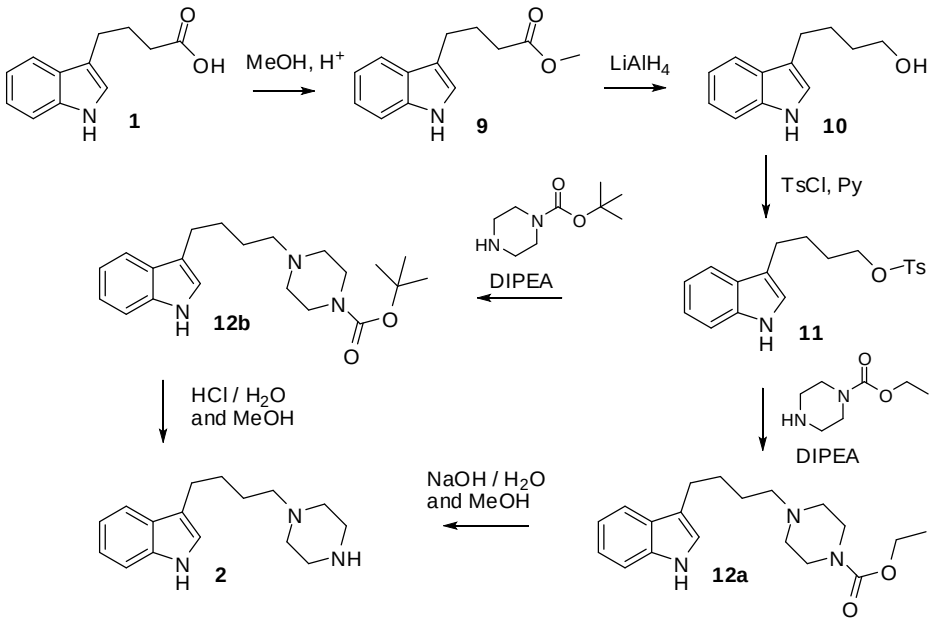
Scheme 1. Synthesis of 4-(1*H*-indol-3-yl)butyl]piperazine (**2**). The 4-(1*H*-indol-3-yl)butanoic acid (**1**) derivativization route.

Unfortunately, the hydrolysis of compound **8a** could not be accomplished selectively to compound **3**. Both basic and acidic hydrolysis led to the formation of initial acid **1** or its methyl ester **9**, and significant amount of tar-like side products. In contrast, the hydrolysis of *t*-butyl-4-[4-(1*H*-indol-3-yl)butanoyl]piperazine-1-carboxylate (**8b**) was accomplished successfully. The hydrolysis using catalytic amount of hydrochloric acid in methanol resulted quantitative yield of target 3-(4-oxo-4-piperazin-1-ylbutyl)-1*H*-indole (**3**) in milligram scale. The same reaction carried out in multi-gram scale yielded 50% of target compound **3**. Significant amount of the starting 4-(1*H*-indol-3-yl)butanoic acid (**1**) was isolated too. It seems that *t*-butyl-4-[4-(1*H*-indol-3-yl)butanoyl]piperazine-1-carboxylate, even being more reactive under examined hydrolysis conditions than ethyl-4-[4-(1*H*-indol-3-yl)butanoyl]piperazine-1-carboxylate, is not reactive enough and hydrolysis of these compounds is not very consistent.

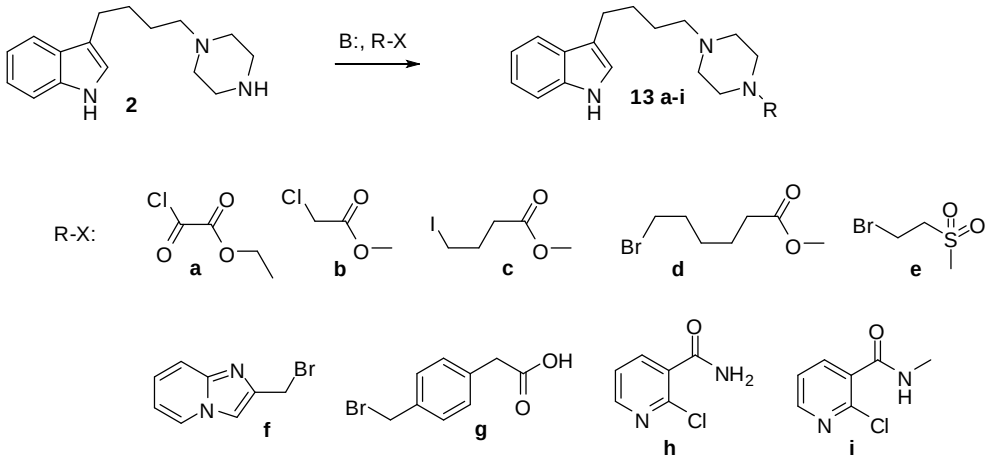
The reduction of compound **3** using lithium aluminum hydride yielded only 52% of expected 3-[4-(1-piperazinyl)butyl]-1*H*-indole **2**. An addition of equimolar amount of aluminum chloride improved the yield of compound **2** up to 67%.

Since the overall yield of product **2** starting from 4-(1*H*-indol-3-yl)butanoic acid (**1**) was unsatisfying (20%) and the hydrolysis step was inconsistent, we decided to search for more efficient method for synthesis of the compound **2**. An alternative route involving modification of 4-(1*H*-indol-3-yl)butan-1-ol[1] (**10**) was employed. The starting alcohol was synthesized by esterification of 4-(1*H*-indol-3-yl)butanoic acid (**1**) to methyl 4-(1*H*-indol-3-yl)butanoate (**9**), which was subsequently reduced with lithium aluminum hydride (Scheme 2). Alcohol **10** was tosylated in ethyl acetate using pyridine as a base and the resulting product **11** was used for alkylation of *N*-protected piperazines. Surprisingly, the yield of *tert*-butyl 4-[4-(1*H*-indol-3-yl)butyl]piperazine-1-carboxylate (**12b**) was very low (11%), while ethyl 4-[4-(1*H*-indol-3-yl)butyl]piperazine-1-carboxylate (**12a**) was isolated in good yield (69%). Both of compounds **12a** and **12b** were successfully hydrolyzed to piperazine derivative **2** in high yields. This alternative method allows to synthesize target 3-[4-(1-piperazinyl)butyl]-1*H*-indole (**2**) in overall 52% yield.

Further alkylation or arylation of 4-(1*H*-indol-3-yl)butyl]piperazine (**2**) with various alkyl halides was carried out in acetonitrile in the presence of base (DIPEA or potassium carbonate) and gave desired products **13a-i** in high yields (Scheme 3). In contrast, arylation with various pyridine or pyrimidine halides was inconsistent, target products have not formed or formed in very low yields even when copper or palladium catalysis was applied.

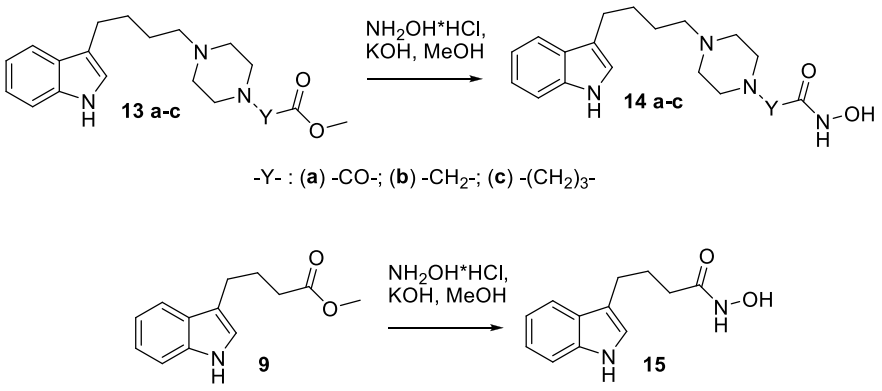


Scheme 2 Synthesis of 4-(1*H*-indol-3-yl)butyl]piperazine (**2**). The 4-(1*H*-indol-3-yl)butan-1-ol (**10**) derivativization route.



Scheme 3. Alkylation and arylation of 4-(1*H*-indol-3-yl)butyl]piperazine (**2**).

Esters **9** and **13a-c** were treated with hydroxylamine hydrochloride at room temperature and converted to corresponding hydroxamic acids **14a-c** and **15** (Scheme 4) in a moderate to good yields.



Scheme 4. Synthesis of hydroxamic acids, containing 4-(1*H*-indol-3-yl)butyl]piperazine scaffold (**14a-c**, **15**)

Due to the structural similarity of compounds **13-15** with Panobinostat (LBH-589) we expected their possible anti-cancer activity. Thus the antiproliferative activity of these compounds was tested *in vitro*.[17] All compounds were inactive against tested human solid tumor cancer cell lines (HeLa (cervix), Ishikawa (endometrial), SW1573 (non-small cell lung), T-47D (breast), and WiDr (colon).

Conclusions

We have investigated two synthetic routes for synthesis of 4-(1*H*-indol-3-yl)butyl]piperazine starting form 4-(1*H*-indol-3-yl)butanoic acid. In multi-gram scale five step synthesis through intermediate 4-(1*H*-indol-3-yl)butan-1-ol (total yield 52%) was twice as efficient as four step synthesis through intermediate 3-(4-oxo-4-piperazin-1-ylbutyl)-1*H*-indole (total yield 20%). We have synthesized several alkylated and arylated derivatives of 4-(1*H*-indol-3-yl)butyl]piperazine and tested their antiproliferative activity *in vitro*.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. NMR spectra were recorded on Varian Unity Inova (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using residual solvent peaks as internal standards. The purity of compounds was monitored by TLC using silica gel 60 F254 aluminum plates (Merck). Column chromatography was carried out using silica gel 60 (0.04 – 0.063 mm) (Roth).

General procedure for the synthesis of compounds 8a and 8b. Ethyl 4-[4-(1*H*-indol-3-yl)butanoyl]-1-piperazinecarboxylate (8a). To the stirred solution of 4-(1*H*-indol-3-yl)butanoic

acid (1 g, 4.9 mmol) and trimethylamine (0.5 g, 4.9 mmol) in 10 mL of THF, ethyl chlorocarbonate (0.54 g, 4.9 mmol) solution in 10 mL of THF was added dropwise at 0-3 ºC. After the formation of white precipitate the reaction mixture was stirred at 0-3 ºC for 1 h. Then the precipitate (triethylamine hydrochloride) was filtered off and washed with 10 mL of THF. Filtrate was used in the next step without isolation of the intermediate product. Filtrate was added dropwise to a solution of ethyl piperazine-1-carboxylate (1.2 g, 7.35 mmol) in 10 mL of THF at 0-3 ºC and the resulting mixture was stirred at room temperature overnight. The precipitate was filtered off, washed with 5 mL of THF and the mother liquid was concentrated under the reduced pressure. The solid residue was dissolved in 5 mL of dichloromethane and washed twice with 5 mL of saturated sodium carbonate aqueous solution, and with 5 mL of water. Organic phase were dried with anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. Product was purified by recrystallization from toluene/hexane mixture yielding 1.1 g (65%) of pure product **8a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 1.27 (t, 3H, *J* 7.1 Hz, CH_3); 2.07 (p, 2H, *J* 7.4 Hz, CH_2); 2.38 (t, 2H, *J* 7.5 Hz, CH_2); 2.84 (t, 2H, *J* 7.1 Hz, CH_2); 3.29-3.30 (m, 2H, CH_2); 3.37-3.45 (m, 4H, $2CH_2$); 3.58-3.61 (m, 2H, CH_2); 4.15 (q, 2H, *J* 7.1 Hz, CH_2); 6.99 (d, 1H, *J* 2.2 Hz, Ar-H); 7.10 (t, 1H, *J* 8.0 Hz, Ar-H); 7.18 (t, 1H, *J* 7.5 Hz, Ar-H), 7.35 (d, 1H, *J* 8.0 Hz, Ar-H); 7.60 (d, 1H, *J* 7.7 Hz, Ar-H); 8.18 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.9, 27.2, 29.8, 37.4, 44.6, 45.9, 46.3, 46.7, 61.5, 111.5, 116.0, 118.7, 119.1, 122.0, 122.3, 128.2, 136.6, 155.6, 171.5. Anal. Calcd for $C_{19}H_{25}N_3O_3$ (343.42): C, 66.45; H, 7.34; N, 12.24%. Found: C, 66.71; H, 7.31; N, 12.35%.

***tert*-Butyl 4-[4-(1*H*-indol-3-yl)butanoyl]-1-piperazinecarboxylate (8b).** *tert*-Butyl 4-[4-(1*H*-indol-3-yl)butanoyl]-1-piperazinecarboxylate was synthesized employing the same procedure as for the ethyl 4-[4-(1*H*-indol-3-yl)butanoyl]-1-piperazinecarboxylate (**8a**), using di-tert-butyl dicarbonate instead of ethyl chlorocarbonate. Yield 60%, white crystals, mp 58-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 1.46 (s, 9H, $3CH_3$); 2.07 (p, 2H, *J* 7.4 Hz, CH_2); 2.38 (t, 2H, *J* 7.5 Hz, CH_2); 2.84 (t, 2H, *J* 7.3 Hz, CH_2); 3.32-3.40 (m, 4H, $2CH_2$); 3.58 (t, 2H, *J* 5.3 Hz, CH_2); 7.00 (d, 1H, *J* 0.9 Hz, Ar-H); 7.10 (t, 1H, *J* 8.0 Hz, Ar-H); 7.19 (t, 1H, *J* 8.1 Hz, Ar-H); 7.36 (d, 1H, *J* 8.0 Hz, Ar-H); 7.60 (d, 1H, *J* 7.3 Hz, Ar-H); 8.04 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.8, 26.6, 28.4, 36.9, 44.7, 46.3, 47.4, 47.5, 81.1, 111.6, 115.3, 118.0, 119.3, 121.8, 121.0, 127.9, 135.7, 155.6, 171.9. Anal. Calcd for $C_{21}H_{29}N_3O_3$ (371.47): C, 67.90; H, 7.87; N, 11.31%. Found: C, 67.59; H, 7.64; N, 11.42%.

3-[4-Oxo-4-(1-piperazinyl)butyl]-1*H*-indole (3). To a solution of compound **8b** (1.1 g, 3 mmol) in 15 mL of methanol, 1 mL of conc. HCl was added and the solution was stirred under reflux temperature for 1.5 h. Reaction mixture was cooled down and after the addition of 5 mL of water neutralized with saturated sodium carbonate solution. The product was extracted with DCM (2 × 5 mL). Organic phases were combined, washed with water (2 × 5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Product was purified by column chromatography eluting with methanol/ammonium hydroxide mixture. Yield 0.4 g (50%) of pure product **3**. ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 2.80-2.94 (m, 3H), 2.10 (qt, *J* 7.2 Hz, 2H, CH_2), 2.41 (t, *J* 7.2 Hz, 2H, CH_2), 2.77-2.88 (m, 6H, NCH_2), 3.32-3.38 (m, 2H, NCH_2), 3.69-3.65 (m,

2H, NCH_2), 7.00 (d, 1H, *J* 0.9 Hz, Ar-H); 7.10 (m, 1H, Ar-H); 7.07-7.12 (m, 1H, Ar-H); 7.15-7.20 (m, 1H, Ar-H); 7.60 (td, 1H, *J* 8.0 and 1.0 Hz, Ar-H); 8.25 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.1, 30.0, 36.1, 42.1, 46.1, 47.5, 109.7, 112.3, 118.3, 119.4, 121.3, 121.9, 129.5, 136.6, 171.4. Anal. Calcd for $C_{16}H_{21}N_3O$ (271.36): C, 70.82; H, 7.80; N, 15.49%. Found: C, 70.66; H, 7.68; N, 15.38%.

3-[4-(1-Piperazinyl)butyl]-1*H*-indole (2)

Method A Reduction of 3-(4-oxo-4-piperazin-1-ylbutyl)-1*H*-indole (3) without $AlCl_3$. To a stirred suspension of $LiAlH_4$ (0.1 g, 2.7 mmol) in dry THF (5 mL) the solution of compound **3** (0.4 g, 1.5 mmol) in dry THF (10 mL) was added dropwise. The resulted mixture was stirred under reflux temperature for 10 h. Reaction mixture was cooled down to room temperature, quenched with acetone (5 mL) and ice cold 10% aqueous solution of KOH (20 mL). Precipitate was filtered off, washed with THF and filtrate was concentrated under reduced pressure. Resulting solid residue was partitioned between dichloromethane and water (3 mL : 2 mL). Organic phase washed with water (2×2 mL) dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Product **2** was purified by column chromatography (eluted with ethyl acetate) yielding 0.2 g (52%) of pure product. White crystals, mp 143-144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61-1.82 (m, 5H, 2×CH_2, NH), 2.45-2.83 (m, 12H, 5×NCH_2, Ar-CH_2), 7.00-7.01 (m, 1H, Ar-H), 7.12-7.25 (m, 2H, Ar-H), 7.38-7.41 (m, 1H, Ar-H), 7.61-7.65 (m, 1H, Ar-H), 8.05 (s, NH, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.2, 30.3, 36.5, 45.6, 52.8, 54.4, 110.7, 112.5, 119.2, 119.3, 121.0, 122.9, 129.9, 136.4. Anal. Calcd for $C_{16}H_{23}N_3$ (257.37): C, 74.67; H, 9.01; N, 16.33%. Found: C, 75.01; H, 8.72; N, 16.28%.

Method B. Reduction of 3-(4-oxo-4-piperazin-1-ylbutyl)-1*H*-indole (3) with $AlCl_3$. To the ice cold suspension of $LiAlH_4$ (0.9 g, 24.3 mmol) in dry THF (50 mL) the suspension of $AlCl_3$ (1.1 g, 8.1 mmol) in dry ether (50 mL) was added keeping the reaction mixture temperature below 3°C. To the resulting solution the solution of compound **3** (2.2 g, 8.1 mmol) in dry THF (50 mL) was added dropwise keeping the reaction mixture temperature below 3 °C. Reaction mixture was stirred for 30 min, quenched with 2 mL of water and 4 mL of 25% solution of NaOH in water, and stirred for additional 2 h. Formed precipitate was filtered off, washed with THF and filtrate was concentrated under reduced pressure. Product was purified in the same way as described above. Yield 1.4 g (67%) of title compound.

Method C. Hydrolysis of *tert*-butyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate (12b). The solution of *tert*-butyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate (**12b**) (1.3 g, 3.6 mmol) and conc. HCl (1 mL) was refluxed in 5 mL of methanol for 2 h. After the addition of water (50 mL) the resulted solution was basified with sodium carbonate solution to pH 8-9 and the product extracted with DCM (3×10 mL). Organic phases were combined, washed with water (2×5 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure yielding 1 g (99%) of pure product **2**.

Method D. Hydrolysis of ethyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate (12a). To the solution of ethyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate (**12a**) (82 g, 0.25 mol)

in ethanol (850 mL) the 50% aqueous solution of NaOH (880 g, 22 mol of NaOH) was added and the resulting mixture was refluxed with stirring for 4 h. Ethanol was evaporated under reduced pressure, resulting residue was extracted with DCM (3×150 mL), organic phase washed with water (3×100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 59 g (93%) of pure product **2**.

Methyl 4-(1*H*-indol-3-yl)butanoate (9). The solution of 4-(1*H*-indol-3-yl)butanoic acid (**1**) (90 g, 0.443 mol) and 10 mL of conc. HCl in 1L of methanol was refluxed for 3 h. Methanol was evaporated under reduced pressure and the resulting solid was purified by recrystallization from 2-propanol, yielding 86 g (89%) of pure product **7**. mp 58-60 ºC. (mp 59-60 ºC).[1] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.79-1.93 (m, 2H, CH_2), 2.41 (t, *J* 6.5 Hz 2H, CH_2), 2.73 (t, *J* 6.5 Hz 2H, CH_2), 3.67 (s, 3H, CH_3), 6.98 (t, *J* 8.5 Hz 1H, Ar-H), 7.07 (t, *J* 8.5 Hz 1H, Ar-H), 7.13 (s, 1H, Ar-H), 7.35 (d, *J* 8.5 Hz 1H, Ar-H), 7.52 (d, *J* 8.5 Hz 1H, Ar-H), 10.81 (s, NH, 1H) ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.6, 30.2, 36.1, 51.4, 110.1, 112.3, 119.2, 119.2, 120.7, 122.5, 129.4, 135.8, 174.1. Anal. Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45%. Found: C, 72.03; H, 7.12; N, 6.68%.

4-(1*H*-Indol-3-yl)butan-1-ol (10). $LiAlH_4$ (18 g, 0.473 mol) was added in small portions to 750 mL of dry THF, then the solution of methyl 4-(1*H*-indol-3-yl)butanoate (**9**) (86 g, 0.394 mol) in 750 mL of THF was added to the reaction mixture dropwise (reaction is exotermic) and the resulting mixture was stirred at reflux temperature for 10 min. After cooling the reaction mixture to 15 ºC, an excess of lithium aluminum hydride was carefully quenched with acetone (approximately 300 mL, until gel is destroyed and small grey particles are formed) and 10% KOH ice cold solution in water (approximately 250 mL, until precipitate becomes white). The precipitated white solid was filtered off, washed with THF, the mother liquid was concentrated under reduced pressure. The resulted residue was dried by coevaporation twice with DCM and twice with toluene yielding 74 g (99%) of compound **10**. Product was used in the next step without additional purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54-1.65 (m, 2H, CH_2), 1.75-1.84 (m, 2H, CH_2), 2.58 (s, 1H, OH), 2.65-2.73 (m, 2H, CH_2), 3.61-3.75 (m, 2H, CH_2O), 7.01-7.02 (m, 1H, Ar-H), 7.12-7.24 (m, 2H, 2×Ar-H), 7.37-7.40 (m, 1H, Ar-H), 7.59-7.62 (m, 1H, Ar-H), 8.04 (s, NH, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.1, 30.3, 36.1, 35.4, 62.9, 112.0, 112.9, 120.0, 119.7, 121.1, 123.0, 131.0, 138.1. Anal. Calcd for $C_{11}H_{15}NO$ (189.25): C, 76.16; H, 7.99; N, 7.40%. Found: C, 76.32; H, 7.81; N, 7.33%.

4-(1*H*-Indol-3-yl)butyl 4-methylbenzenesulfonate (11). To a stirred solution of compound **10** (74 g, 0.391 mol) and pyridine (60 mL, 0.78 mol) in 1000 mL of ethyl acetate, toluenesulfonyl chloride (112 g, 0.587 mol) was added and the resulting mixture was stirred at room temperature for 4 days. Then the solution was subsequently washed with 2 x 300 mL of water, 2 x 200 mL of 20% H_2SO_4 aq. and with 2 x 200 mL of saturated $NaHCO_3$ solution. Organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. White crystals were washed twice with 200 mL of hot hexane yielding 125 g (91%) of pure compound **11**. mp 64-66 ºC (mp 65-66 ºC).[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.69-1.78 (m, 4H, 2×CH_2), 2.46 (s, 3H, CH_3), 2.70-2.81 (m, 2H, CH_2), 2.65-2.73 (m, 2H, CH_2), 4.01-4.08 (m, 2H, CH_2O), 6.94-6.97 (m, 1H, Ar-H),

7.11-7.16 (m, 1H, Ar-H), 7.18-7.41 (m, 1H, Ar-H), 7.33-7.42 (m, 3H, 3×Ar-H), 7.52-7.57 (m, 1H, Ar-H), 7.82 (d, *J* 9 Hz, 2H, 2×Ar-H), 8.00 (s, NH, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.0, 27.1, 30.0, 33.2, 70.0, 111.6, 112.6, 119.9, 120.6, 121.3, 122.2, 123.4, 128.2, 130.6, 132.7, 137.5, 147.5. Anal. Calcd for $C_{19}H_{21}NO_3S$ (343.44): C, 66.45; H, 6.16; N, 4.08%. Found: C, 66.57; H, 5.98; N, 3.87%.

General procedure for the synthesis of compounds 12a and 12b. *tert*-Butyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate (12b). A mixture of compound **11** (7.5 g, 21.9 mmol), *tert*-butyl piperazine-1-carboxylate (6.1 g, 32.8 mmol) and *N*,*N*-diisopropylethylamine (4.3 g, 32.8 mmol) in 2-propanol (50 mL) was refluxed for 10 h. After the cooling to room temperature, the solvent was evaporated under reduced pressure. Then residue was partitioned between DCM and water (30 mL : 50 mL), organic phase was dried over Na_2SO_4 and evaporated in vacuum. Resulting residue was purified by silica gel chromatography, eluting with 50% EtOAc/hexane to give 1.3 g (11%) of the title compound **12b**. mp. 123-125 ºC
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.46 (s, 9H, $3CH_3$), 1.56-1.66 (m, 2H, CH_2), 1.71-1.81 (m, 2H, CH_2), 2.42-2.52 (m, 6H, $3\times CH_2$), 2.78-2.86 (m, 2H, CH_2), 3.44-3.48 (m, 2H, CH_2), 3.66-3.69 (m, 2H, CH_2), 6.99-7.01 (m, 1H, Ar-H), 7.11-7.16 (m, 1H, Ar-H), 7.19-7.24 (m, 1H, Ar-H), 7.37-7.40 (m, 1H, Ar-H), 7.61-7.64 (m, 1H, Ar-H), 8.05 (s, NH, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.2, 28.4, 29.8, 34.9, 41.5, 44.3, 45.9, 47.0, 80.5, 111.3, 115.8, 119.0, 118.8, 121.9, 122.5, 127.9, 136.6, 154.5. Anal. Calcd for $C_{21}H_{31}N_3O_2$ (357.49): C, 70.55; H, 8.74; N, 11.75%. Found: C, 70.69; H, 8.58; N, 11.62%.
Ethyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate (12a). Ethyl 4-[4-(1*H*-indol-3-yl)butyl]-1-piperazinecarboxylate was synthesized using the same procedures as in the compound **12b** synthesis, only ethyl piperazine-1-carboxylate was used instead of *tert*-butyl piperazine-1-carboxylate.Yield: 69%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, *J* 6 Hz, 3H, CH_3), 1.52-1.62 (m, 2H, CH_2), 1.68-1.75 (m, 2H, CH_2), 2.41-2.51 (m, 6H, $3\times CH_2$), 2.77-2.85 (m, 2H, CH_2), 3.44-3.48 (m, 2H, CH_2), 3.66-3.69 (m, 2H, CH_2), 4.12 (q, *J* 6 Hz, 2H, CH_2), 6.99-7.01 (m, 1H, Ar-H), 7.10-7.15 (m, 1H, Ar-H), 7.18-7.23 (m, 1H, Ar-H), 7.38-7.41 (m, 1H, Ar-H), 7.62-7.63 (m, 1H, Ar-H), 8.03 (s, NH, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.7, 27.2, 29.8, 35.1, 41.8, 44.6, 45.9, 46.7, 61.2, 111.5, 116.0, 118.7, 119.1, 122.0, 122.3, 128.2, 136.6, 155.6. Anal. Calcd for $C_{19}H_{27}N_3O_2$ (329.44): C, 69.27; H, 8.26; N, 12.76%. Found: C, 68.98; H, 8.07; N, 12.54%.

General procedure for synthesis of compounds 13a-i. To a solution of compound **2** (0.1 g, 0.388 mmol) in 2 mL of acetonitrile 1.55 mmol of the corresponding base (DIPEA or K_2CO_3) and 0.388 mmol of the corresponding halide were added. The resulting reaction mixture was stirred at reflux temperature for the indicated period of time. After the completion of the reaction, the mixture was cooled to the room temperature, and concentrated under reduced pressure. The resulting residue was dissolved in 2 mL of DCM and 3 mL of water mixture,

organic layer was separated, washed with water (2 × 3 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuum. Product was purified using column chromatography.

Ethyl [4-(1*H*-indol-3-ylbutyl)piperazin-1-yl](oxo)acetate (13a). Base: DIPEA, halide R-X: ethyl 2-chloro-oxoacetate (a), reaction duration: 3h. Title compound eluted with MeOH, R_f. 0.8. Yellow oil. Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, *J* 7.2 Hz, 3H, CH_3), 1.57-1.67 (m, 2H, CH_2), 1.72-1.82 (m, 2H, CH_2), 2.43-2.52 (m, 6H, 3× CH_2), 2.79-2.84 (m, 2H, CH_2), 3.45-3.49 (m, 2H, CH_2), 3.66-3.69 (m, 2H, CH_2), 4.36 (q, *J* 7.2 Hz, 2H, CH_2), 6.99-7.01 (m, 1H, Ar-H), 7.11-7.16 (m, 1H, Ar-H), 7.19-7.24 (m, 1H, Ar-H), 7.37-7.40 (m, 1H, Ar-H), 7.61-7.64 (m, 1H, Ar-H), 8.09 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 14.3, 25.3, 26.6, 28.1, 41.4, 46.2, 52.4, 53.2, 58.4, 62.4, 111.4, 116.7, 119.1, 119.3, 121.4, 122.1, 127.7, 136.6, 160.3, 163.0. Anal. Calcd for $C_{20}H_{27}N_3O_3$ (357.45): C, 67.20; H, 7.61; N, 11.76%. Found: C, 67.51; H, 7.47; N, 11.63%.

Methyl [4-(1*H*-indol-3-ylbutyl)piperazin-1-yl]acetate (13b). Base: DIPEA, halide R-X: methyl 2-chloroactate (b), reaction duration: 3 h. Title compound eluted with MeOH, R_f 0.6. Yellow crystals, mp 160-162 ºC. Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61-1.82 (m, 4H, 2×CH_2), 2.45-2.83 (m, 12H, 6×CH_2), 3.26 (s, 2H, CH_2), 3.76 (s, 3H, CH_3), 7.00-7.01 (m, 1H, Ar-H), 7.11-7.24 (m, 2H, 2×Ar-H), 7.37-7.40 (m, 1H, Ar-H), 7.61-7.64 (m, 1H, Ar-H), 8.08 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.3, 26.7, 28.2, 41.0, 52.0, 53.1, 58.6, 59.6, 111.3, 116.7, 119.2, 119.3, 121.4, 122.1, 127.8, 136.6, 171.0. Anal. Calcd for $C_{19}H_{27}N_3O_2$ (329.44): C, 69.27; H, 8.26; N, 12.76%. Found: C, 68.96; H, 7.97; N, 13.02%.

Methyl 4-[4-(1*H*-indol-3-ylbutyl)piperazin-1-yl]butanoate (13c). Base: K_2CO_3, halide R-X: methyl 4-iodobutanoate (c), reaction duration: 4 h. Title compound eluted with ethyl acetate: MeOH (1:1), R_f. 0.4. White crystals, mp 55-57 ºC. Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57-1.89 (m, 7H), 2.35-2.55 (m, 13H), 2.81 (t, *J* 7.4 Hz, 2H, CH_2), 3.70 (s, 3H, CH_3), 6.99 (d, *J* 2.3 Hz, 1H, Ar-H), 7.11-7.15 (m, 1H, Ar-H), 7.18-7.23 (m, 1H, Ar-H), 7.38 (d, *J* 8.0 Hz, 1H, Ar-H), 7.63 (d, *J* 8.2 Hz, 1H, Ar-H), 8.08 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.4, 25.3, 27.0, 28.4, 32.3, 51.8, 53.3, 53.5, 57.9, 58.9, 111.3, 116.9, 119.2, 119.3, 121.4, 122.1, 127.5, 136.4, 174.3. Anal. Calcd for $C_{21}H_{31}N_3O_2$ (357.49): C, 70.55; H, 8.74; N, 11.75%. Found: C, 70.67; H, 8.52; N, 11.63%.

Methyl 4-[4-(1*H*-indol-3-ylbutyl)piperazin-1-yl]hexanoate (13d). Base: K_2CO_3, halide R-X: methyl 6-bromohexanoate (d), reaction duration 6 h. Title compound eluted with ethyl acetate : MeOH (1:1), R_f 0.5. White crystals, mp 109-111 ºC. Yield 96%. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 1.27-1.78 (m, 12H, 6×CH_2), 2.32-2.37 (m, 2H, CH_2), 2.44-2.83 (m, 12H, 6×CH_2), 3.69 (s, 3H, CH_3), 7.01 (d, *J* 2.3 Hz, 1H, Ar-H), 7.07-7.33 (m, 2H, 2×Ar-H), 7.34-7.44 (m, 1H, Ar-H), 7.66-7.56 (m, 1H, Ar-H), 8.19 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 25.0, 25.2, 26.1, 26.2, 27.2, 28.0, 34.2, 51.8, 52.3, 52.5, 58.2, 58.3, 111.4, 116.4, 119.1, 119.3, 121.3, 122.1, 127.7, 136.6, 174.3. Anal. Calcd for $C_{23}H_{35}N_3O_2$ (385.54): C, 71.65; H, 9.15; N, 10.90%. Found: C, 71.76; H, 8.93; N, 11.12%.

3-({4-[2-(Methylsulfonyl)ethyl]piperazin-1-yl}buthyl)-1*H*-indole (13e). Base: K_2CO_3, halide R-X: 1-bromo-2-(methylsulfonyl)ethane (e), reaction duration: 4 h. Title compound eluted with

MeOH, R_f. 0.65. White crystals, mp 104-105 ºC. Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59-1.82 (m, 4H, 2×CH_2), 2.40-2.58 (m, 10H, 5×CH_2), 2.79-2.84 (m, 2H, CH_2), 2.88-2.92 (m, 2H, CH_2), 3.07 (s, 3H, CH_3), 3.14-3.18 (m, 2H, CH_2), 7.00-7.01 (m, 1H, Ar-H), 7.11-7.25 (m, 2H, 2×Ar-H), 7.38-7.40 (m, 1H, Ar-H), 7.62-7.65 (m, 1H, Ar-H), 8.00 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.3, 27.0, 28.3, 42.7, 52.0, 52.5, 53.2, 53.4, 58.7, 111.3, 116.9, 119.2, 119.3, 121.4, 122.1, 127.8, 136.6. Anal. Calcd for $C_{19}H_{29}N_3O_2S$ (363.52): C, 62.78; H, 8.04; N, 11.56%. Found: C, 62.53; H, 7.85; N, 11.69%.

2-{[4-(1*H*-Indol-3-ylbutyl)piperazin-1-yl]methyl}imidazo[1,2-*a*]pyridine (13f). Base: DIPEA, halide R-X: 2-(bromomethyl)imidazo[1,2-a]pyridine (f), reaction duration 4 h. Title compound eluted with MeOH:NH_4OH (10:1) R_f 0.8. Yellow oil. Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57-1.80 (m, 4H, 2×CH_2), 2.39-2.82 (m, 12H 6×CH_2), 3.76 (s, 2H, CH_2), 6.78 (td, *J* 6.8 Hz, *J* 1.2 Hz, 1H, Ar-H), 6.99 (d, *J* 2.2 Hz, 1H, Ar-H), 7.10-7.23 (m, 3H, 3×Ar-H), 7.35-7.38 (m, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.57-7.64 (m, 2H, 2×Ar-H), 8.08 (dt, *J* 6.8 Hz, *J* 1.2 Hz, 1H, Ar-H), 8.19 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 25.3, 27.1, 28.4, 53.4, 53.5, 56.8, 58.9, 111.2, 111.3, 112.4, 116.9, 117.7, 119.2, 119.2, 121.4, 122.0, 124.4, 125.7, 127.8, 136.6, 144.6, 145.3. Anal. Calcd for $C_{24}H_{29}N_5$ (387.52): C, 74.38; H, 7.54; N, 18.07%. Found: C, 74,22; H, 7.73; N, 18.31%.

4-{[4-(1*H*-Indol-3-ylbutyl)piperazin-1-yl]methyl}phenyl acetic acid (13g). Base: K_2CO_3, halide R-X: 2-(4-(bromomethyl)phenyl)acetic acid (g), reaction duration 10 h. Title compound eluted with MeOH, R_f. 0.3. White crystals, mp 146-148 ºC. Yield 80%. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.42-1.70 (m, 4H, 2×CH_2), 2.27-2.35 (m, 10H, 5×CH_2), 2.66-2.71 (m, 2H, CH_2), 3.41 (s, 2H, CH_2), 3.52 (s, 2H, CH_2), 6.94-7.10 (m, 3H, 3×Ar-H), 7.18-7.23 (m, 4H, 4×Ar-H), 7.32 (m, 1H, Ar-H), 7.50-7.52 (m, 1H, Ar-H), 10.76 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.3, 26.9, 28.5, 41.6, 53.4, 53.5, 58.4, 62.6, 112.0, 115.3, 118.7, 119.0, 121.4, 122.8, 127.9, 129.4, 129.8, 134.7, 137.0, 137.1, 173.6. Anal. Calcd for $C_{25}H_{31}N_3O_2$ (405.53): C, 74.04; H, 7.70; N, 10.36%. Found: C, 74,37; H, 7.54; N, 10.53%.

2-[4-(1*H*-Indol-3-ylbutyl)piperazin-1-yl]pyridine-3-carboxamide (13h). Base: DIPEA, halide R-X: 2-Chloronicotinamide (h), reaction duration 30 h. Title compound eluted with ethyl acetate - methanol mixture (92:8). Resulting oil recrystallized from toluene. White crystals, mp 152-153 ºC. Yield 31 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61-1.85 (m, 4H, CH_2), 2.46-2.51 (m, 2H, CH_2), 2.62-2.65 (m, 4H, 2×CH_2), 2.81-2.86 (m, 2H, CH_2), 3.28-3.31 (m, 4H, 2×CH_2), 6.04 (s, 1H, NH), 7.01-7.02 (m, 1H, Ar-H), 7.09-7.25 (m, 3H, 3×Ar-H), 7.37-7.40 (m, 1H, Ar-H), 7.64 (d, *J* 7.8 Hz, 1H, Ar-H), 8,11 (s, 1H, NH), 8.33 (dd, *J* 7.6 Hz, *J* 2.0 Hz, 1H, Ar-H), 8.43 (dd, *J* 4.8 Hz, *J* 2.0 Hz, 1H, Ar-H), 8.48 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.3, 27.0, 28.2, 51.7, 53.7, 58.8, 111.3, 116.8, 119.1, 119.2, 119.3, 121.1, 121.4, 122.1, 127.8, 136.6, 140.5, 150.5, 161.1, 168.2. Anal. Calcd for $C_{22}H_{27}N_5O$ (377.48): C, 70.00; H, 7.21; N, 18.55%. Found: C, 70.21; H, 7.41; N, 18.62%.

2-[4-(1*H*-Indol-3-ylbutyl)piperazin-1-yl]-*N*-methylpyridine-3-carboxamide (13i). Base: DIPEA, halide R-X: 2-Chloro-N-methylnicotinamide (i), reaction duration 30 h. Title compound with ethyl acetate - methanol mixture (92:8). Resulting oil recrystallized from toluene. White

crystals, mp 115-117 ºC, Yield 22%. ^{1}H NMR (300 MHz, $CDCl_3$,) δ: 1.62-1.86 (m, 4H, 2×CH_2), 2.47-2.52 (m, 2H, CH_2), 2.61-2.63 (m, 4H, 2×CH_2), 2.81-2.86 (m, 2H, CH_2), 3.04 (d, *J* 4.9 Hz, 3H, CH_3), 3.25-3.28 (m, 4H, 2×CH_2), 7.02-7.03 (m, 1H, Ar-H), 7.08-7.25 (m, 3H, 3×Ar-H), 7.38-7.41 (m, 1H, Ar-H), 7.65 (d, *J* 7.9 Hz, 1H, Ar-H), 8.03 (s, 1H, NH), 8.31 (dd, *J* 7.6 Hz, *J* 2.0 Hz, 1H, Ar-H), 8.34 (dd, *J* 4.8, *J* 2.0 Hz, 1H, Ar-H), 8.56 (s, 1H, NH). ^{13}C NMR (75MHz, $CDCl_3$) δ: 25.3, 26.4, 27.0, 28.2, 51.4, 53.8, 58.8, 111.3, 116.9, 119.1, 119.2, 119.3, 121.4, 121.7, 122.1, 127.8, 136.6, 140.2, 149.9, 160.5, 166.8. Anal. Calcd for $C_{23}H_{29}N_5O$ (391.51): C, 70.56; H, 7.47; N, 17.89%. Found: C, 70.72; H, 7.61; N, 18.11%.

General procedure for synthesis of hydroxamic acids 14a-c and 15. To a solution of 0.2 g of the corresponding ester (**13a-c** or **9**) in 4 mL of methanol, 10 equiv. of hydroxylamine hydrochloride was added. The addition of 10 equiv of potassium hydroxide followed next (exothermic reaction). The resulted mixture was stirred at the room temperature for indicated period of time. The precipitate was filtered off and washed with 4 mL of methanol. The mother liquid was evaporated under reduced pressure and product was purified by silica gel chromatography.

***N*-Hydroxy-2-{4-[4-(1*H*-indol-3-yl)butyl]piperazin-1-yl}-2-oxoacetamide (14a).** Reaction duration 48 h. Title compound eluted with MeOH, R_f 0.6. Slightly yellow crystals, mp 180-182 ºC. Yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58-1.83 (m, 4H, 2×CH_2), 2.41-2.47 (m, 6H, 3×CH_2), 2.79-2.84 (m, 2H, CH_2), 3.42-3.45 (m, 4H, 2×CH_2), 4,47 (s, NHOH, 2H), 7.01-7.02 (m, 1H, Ar-H), 7.11-7.16 (m, 1H, Ar-H), 7.19-7.24 (m, 1H, Ar-H), 7.37-7.41 (m, 1H, Ar-H), 7.62-7.65 (m, 1H, Ar-H), 8.00 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.3, 26.9, 28.2, 44.3, 53.0, 58.7, 111.3, 116.8, 119.2, 119.3, 121.4, 122.1, 127.8, 136.6, 158.2, 169.8. Anal. Calcd for $C_{18}H_{24}N_4O_3$ (344.41): C, 62.77; H, 7.02; N, 16.27%. Found: C, 63.02; H, 7.15; N, 16.52%.

***N*-Hydroxy-2-{4-[4-(1*H*-indol-3-yl)butyl]piperazin-1-yl}acetamide (14b).** Reaction duration 24 h. Title compound eluted with MeOH, R_f 0.3-0.5. Slightly yellow crystals, mp 192-194 ºC. Yield 50%. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 1.64-1.80 (m, 4H, 2×CH_2), 2.59-3.07 (m, 12H, 6×CH_2), 3.38 (s, 2H, CH_2), 6.98 (td, *J* 7.4 Hz, *J* 1.0 Hz, 1H, Ar-H), 7.05-7.10 (m, 1H, Ar-H), 7.16 (d, *J* 2.1 Hz, 1H), Ar-H, 7.34-7.37 (m, 1H, Ar-H), 7.53 (d, *J* 7.7 Hz, 1H, Ar-H), 8.89 (s, 1H, NH), 10.63 (s, 1H, CONH or OH), 10.88 (s, 1H, CONH or OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 24.6, 27.7, 30.9, 49.9, 51.5, 56.1, 58.4, 112.1, 114.5, 118.8, 119.0, 121.5, 123.1, 127.8, 137.0, 165.9. Anal. Calcd for $C_{18}H_{24}N_4O_2$ (330.43): C, 65.43; H, 7.93; N, 18.96%. Found: C, 65.73; H, 7.85; N, 19.13%.

***N*-Hydroxy-4-[4-(1*H*-indol-3-ylbutyll)piperazin-1-yl]butanamide (14c).** Reaction duration 15 h. Title compound eluted with MeOH, R_f 0.4-0.5. Yellow crystals, mp 160-162 ºC. Yield 95%. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 1.54-1.73 (m, 6H, 3×CH_2), 1.91-2.01 (m, 2H, CH_2), 2.34-2.39 (m, 2H, CH_2), 2.56-2.72 (m, 12H, 6×CH_2), 6.97 (t, *J* 7.4 Hz, 1H, Ar-H), 7.06 (t, *J* 7.5 Hz, 1H, Ar-H), 7.12 (d, *J* 2.1 Hz, 1H, Ar-H), 7.34 (d, *J* 8.0 Hz, 1H, Ar-H), 7.51 (d, *J* 7.8 Hz, 1H, Ar-H), 10.44 (s, 2H, NHOH), 10.84 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 22.6, 25.1, 25.8, 28.2, 30.8, 52.0, 52.3, 57.3, 57.4, 112.0, 115.0, 118.7, 119.0, 121.5, 122.9, 127.8, 137.0, 169.6.

Anal. Calcd for $C_{22}H_{34}N_4O_2$ (386.53): C, 68.66; H, 8.87; N, 14.49%. Found: C, 68.81; H, 9.02; N, 14.31%.

***N*-Hydroxy-4-(1*H*-indol-3-yl)butanamide (15).** Reaction duration 15 h. Title compound eluted with ethyl acetate, R_f. 0.4. White crystals, mp 123-125 ºC (mp 123-124 °C).[19] Yield 80%.
^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.84-1.94 (m, 2H, CH_2), 2.05 (t, *J* 7.2 Hz, 2H, CH_2), 2.69 (t, *J* 7.2 Hz, 2H, CH_2), 6.69-7.13 (m, 3H, 3×Ar-H), 7.36 (d, *J* 8.1 Hz, 1H, Ar-H), 7.52 (d, *J* 7.8 Hz, 1H, Ar-H), 8.7 (s, 1H, NH), 10.40 (s, 1H, CONH or OH), 10.80 (s, 1H, CONH or OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.0, 26.8, 32.9, 112.1, 114.7, 118.8, 119.0, 121.5, 123.0, 127.9, 137.0, 169.9. Anal. Calcd for $C_{12}H_{12}N_2O_2$ (218.25): C, 66.04; H, 6.47; N, 12.84%. Found: C, 65.95; H, 6.73; N, 13.07%.

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