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A Convenient Preparation of β-Acetamido Substituted Tryptamine Derivatives

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Summary. In view of finding new 5-HT_6 receptor ligands various β-acetamido substituted tryptamine and *N*,*N*-dimethyltryptamine derivatives were synthesized from a common intermediate. A trimolecular condensation between indole, *Meldrum*'s acid and *N*-phthalimidoacetaldehyde followed by careful deprotection and functional group manipulations were proposed for this purpose.

Keywords. Tryptamine derivatives; Heterocycles; Serotonine receptor ligand; Protecting groups; Chemoselectivity.

Introduction

Tryptamine still remains an useful starting material toward 1,2,3,4-tetrahydro- or 3,4-dihydro-β-carbolines of biological interest *via* the well-known *Pictet-Spengler* and *Bischler-Napieralski* condensation reactions.

Simple tryptamine derivatives such as serotonin or melatonin are endogenous neurotransmitting agents of the central nervous system, whereas some 2-substituted-*N*(b)-dimethyltryptamine derivatives have recently been found to be powerful ligands of the 5-HT_6 serotonin receptor [1].

For a biological program aimed at the preparation of new serotonin receptor inhibitors, we needed new tryptamine derivatives **1**, appended on the β-position with various acetamides as a peptide chain mimics. For this purpose, we took the opportunity of exploiting our trimolecular condensation reaction [2], using

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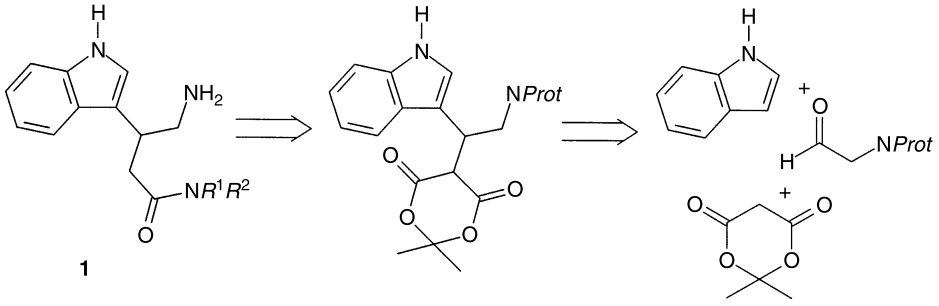


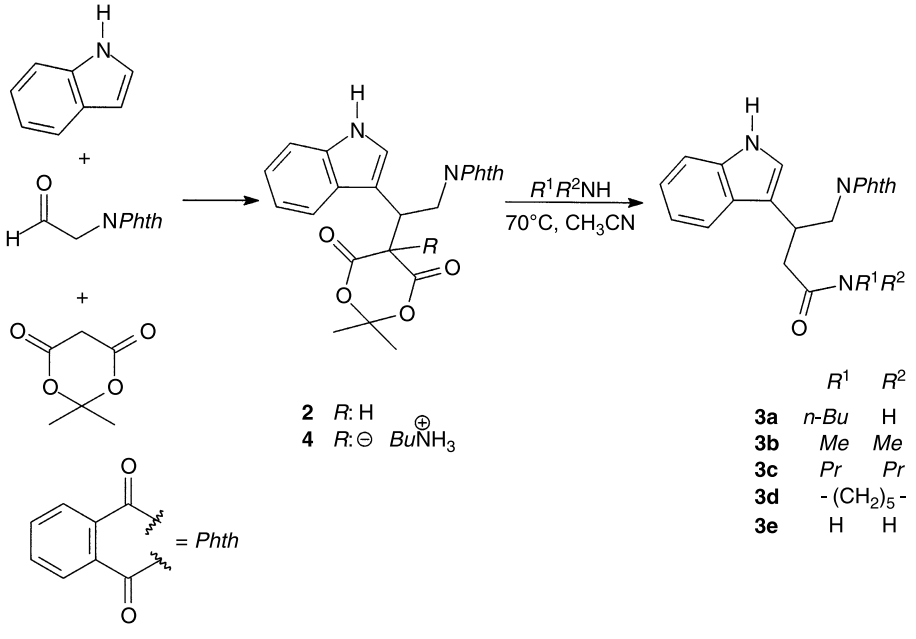
Scheme 1

N-protected aminoacetaldehyde (as tryptamine chain precursor) and *Meldrum*'s acid as acetamide source (Scheme 1).

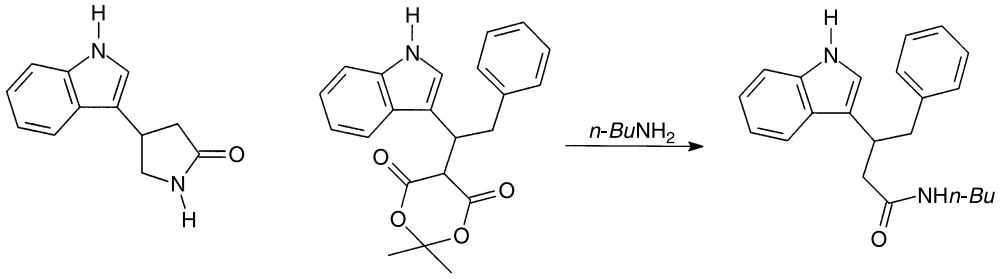
Results and Discussions

As we have already pointed out that secondary amide or carbamate *N*-protecting groups were reactive toward *Meldrum*'s acid cyclising into pyrrolidone [3], *N*-phthalimido protection was chosen for the aminoacetaldehyde. It was prepared following a slightly modified procedure of Ref. [4]. Condensation of *N*-phthalimidoacetaldehyde with indole and *Meldrum*'s acid smoothly gave the trimolecular adduct **2**, isolated in good yield (73%) (Scheme 2).

Transformation of **2** into amide **3** by nucleophilic cleavage of the *Meldrum*'s ring by amines is not trivial: to the best of our knowledge, this kind of reaction has only been performed with weakly basic amines [5] otherwise the salt **4** could be



Scheme 2



5 6 7

Scheme 3

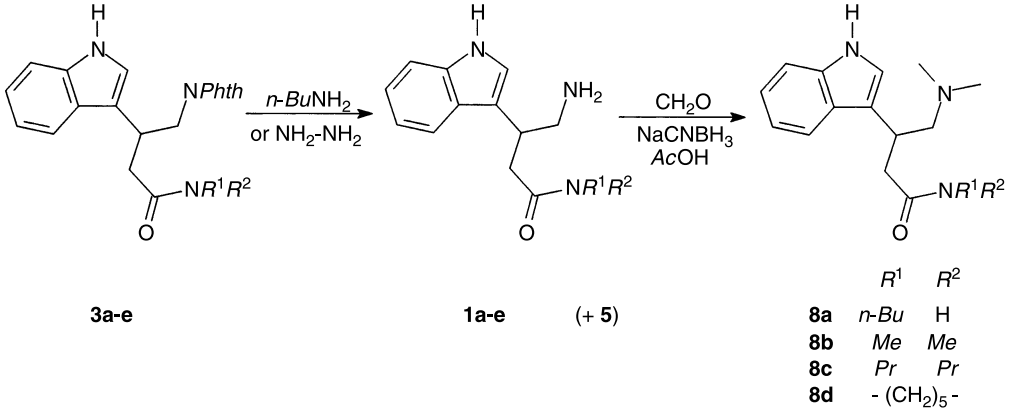
obtained. It was evident that finetuning between nucleophilicity and basicity was required for selective transformations: for example, basic amines were known to cleave the phthalimido group releasing a primary amine function which reacted [3] instantaneously with *Meldrum*'s acid to give lactam **5** (Scheme 3). Despite of double reaction sites, we found experimental conditions allowing the selective transformation $\mathbf{2} \rightarrow \mathbf{3}$.

When heated at 70°C with various amounts of *n*-butylamine in acetonitrile, the trimolecular product **2** gave a precipitate, which was characterized as the *n*-butylamine salt of **4**. The result of the reaction strongly depended on the stoichiometry. Using five (or more) fold excess of *n*-butylamine after five-day heating we obtained lactam **5** (36%) together with some starting material. Heated in the presence of one equiv. of *n*-butylamine, the salt **4** slowly disappeared, whereas after three days at 70°C acetamide **3** ($R^1 = \mathrm{H}$, $R^2 = n - Bu$) was isolated in 72% yield. The phthalimido group is not involved in this procedure as proved the aminolysis of its phenyl substituted counterpart **6** [2]. Heated with one equiv. of *n*-butylamine in acetonitrile for five days, **6** afforded amide **7** in 68% yield, however, in neat *n*-butylamine 18% yield was only observed (Scheme 3).

The reason why better yield of aminolysis was obtained with a stoichiometrical (or nearly stoichiometrical) amount of amine could be that the salt **4** is in equilibrium with **2** and the amine. In presence of an excess of amine, the balance was shifted toward the salt **4**, whose negative charge located near the carbonyl group precluded further nucleophilic attack on the carbonyl groups of the *Meldrum*'s acid. Finally, numerous protected tryptamine amides **3** were synthesized along this procedure (Scheme 2).

Cleavage of the phthalimido group of **3** to the target compounds **1** proved to be difficult when *n*-butylamine was used (Scheme 4; method A). Although easier to remove than the commonly used hydrazine, *n*-butylamine is less nucleophile and requires prolonged heating, leading to cyclisation into lactam **5** with loss of $R^1R^2\mathrm{NH}$. This reaction was observed exclusively in the case of primary amide **3e** ($R^1 = R^2 = \mathrm{H}$), but less pronounced with other substituents. In fact, using hydrazine in place of *n*-butylamine (method B) allowed the preparation of **1b** and **1d** in better yields.

Biological tests showed that tryptamine derivatives **1** bind at the 5-HT_6 receptors with modest affinity. However, among the corresponding *N*,*N*-dimethyltryptamines **8**, prepared from **1** by reductive amination (CH_2O, $NaCNBH_3$, *Ac*OH)



Scheme 4

(Scheme 4) in good yield dipropyl- (**8c**) and piperidine (**8d**) substituted derivatives were active on 5-HT_7 (27% inhibition at 10^{-6} *M*) and 5-HT_4 (24% at 10^{-8} *M*) receptors, respectively. Work is in progress in our laboratory in order to find more active and selective 5-HT antagonists.

Experimental

Melting points were determined on a *Reichert* Thermovar hot-stage apparatus and are uncorrected. IR spectra were measured with a Bomem FTIR instrument. UV spectra were obtained with a UNICAM 8700 UV/VIS spectrophotometer in MeOH. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker AC 300 spectrometer and chemical shifts were expressed in ppm (δ) using *TMS* as internal standard. Mass spectra were recorded with a VG Autospec apparatus, except for compound **1d** (ThermoFinnigan MSQ Electrospray). All solvents were purified by following standard literature methods. Chromatography was performed on silicagel 60 (Merck). Reactions were monitored on Merck TLC aluminum sheets (Kieselgel 60F_{254}). The results of elemental analyses were found to be in satisfactory agreement ($\pm$ 0.4%) with the calculated values. Abbreviations: ol.: overlapped, brs: broad singlet. Biological tests based on protein radioligand binding assays were carried out on 5-HT_4, 5-HT_6, and 5-HT_7 receptor samples, prepared according to the detailed experimental methods published in Refs. [6–8].

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-2-(1H-indol-3-yl)ethyl]isoindole-1,3-dione (**2**, $C_{24}H_{20}N_2O_6$)

Deprotection of the Acetal

To a stirred solution of 22.18 g of 2-(2,2-dimethoxyethyl)isoindole-1,3-dione (94.30 mmol) in 440 cm^3 of CH_3CN was added 400 cm^3 of 10% HCl solution. The reaction mixture was stirred at room temperature for 24 h. The organic solvent was evaporated, and the aqueous residue was extracted with 3×150 cm^3 of *Et*OA*c*. The combined extracts were washed with 2×150 cm^3 of brine, dried (Na_2SO_4), and concentrated to give white crystals.

Condensation with Indole and Meldrum's Acid

The aldehyde was dissolved in 250 cm^3 of CH_3CN and to this solution 5.52 g of indole (47.15 mmol), 6.79 g of *Meldrum*'s acid (47.15 mmol), and 272 mg of *D,L*-proline (2.36 mmol) were added under N_2.

The reaction mixture was stirred at room temperature for 48 h. The resulting suspension was filtered and the precipitate was washed with a 1:1 mixture of CH_2Cl_2 and Et_2O ($2\times50\,cm^3$) and then with $50\,cm^3$ of Et_2O to obtain a white powder. Two further crystallisations of the filtrate in CH_3CN gave in total 14.84 g (73%) of white powder. Mp 153°C (CH_3CN); UV(CH_3OH): λ (rel. int.) = 203 (66), 220 (100), 240 (23), 270 (26), 292 (9) nm; IR (KBr): $\bar{\nu} = 3412$, 3059, 3001, 2941, 1771, 1744, 1711, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.43$ (3H, s), 1.68 (3H, s), 4.01 (1H, d, $J = 2.0$ Hz), 4.48 (2H, d, $J = 8.0$ Hz), 4.70 (1H, dt, $J = 2.0$, 8.0 Hz), 7.08 (1H, t, $J = 8.0$ Hz), 7.12 (1H, t, $J = 8.0$ Hz), 7.30 (1H, d, $J = 8.0$ Hz), 7.39 (1H, d, $J = 2.0$ Hz), 7.65 (2H, m), 7.77 (3H, m), 8.47 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 27.2$, 28.0, 34.5, 40.5, 49.0, 105.0, 111.0, 112.0, 118.8, 119.8, 122.1, 123.2, 124.2, 126.8, 131.8, 135.3, 135.3, 164.5, 165.1, 168.5 ppm; MS (EI): m/z (%) = 432 ($M^{+\cdot}$, 6), 368 (11), 346 (11), 330 (5), 289 (15), 236 (10), 188 (7), 181 (11), 170 (100), 160 (11); HREIMS: calcd. 432.13161, found 432.13221.

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-2-(1H-indol-3-yl)ethyl]isoindole-1,3-dione Butylammonium Salt (**4**, $C_{28}H_{31}N_3O_6$)

To a suspension of 300 mg of **2** (0.69 mmol) in $10\,cm^3$ of CH_3CN was added $69\,mm^3$ of *n*-butylamine (0.69 mmol) under N_2. The resulting suspension was stirred at room temperature for 12 h, then filtered and washed with $3\times3\,cm^3$ Et_2O to give 345 mg (98%) of **4**. Yellow powder; mp 152°C (Et_2O); UV (CH_3OH): λ (rel. int.) = 203 (71), 220 (100), 269 (41) nm; IR (KBr): $\bar{\nu} = 3381$, 2934, 1769, 1707, 1551, 1391 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 0.91$ (3H, t, $J = 7.2$ Hz), 1.35 (8H, m), 1.52 (2H, m), 2.79 (2H, t, $J = 7.5$ Hz), 3.42 (3H, brs), 4.18 (1H, m), 4.35 (1H, m), 4.70 (1H, t, $J = 7.5$ Hz), 6.85 (1H, t, $J = 8.0$ Hz), 6.96 (1H, t, $J = 8.0$ Hz), 7.20 (2H, m), 7.72 (1H, d, $J = 8.0$ Hz), 7.80 (4H, m), 10.51 (1H, brs) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 13.6$, 19.3, 26.0, 29.2, 30.7, 38.8, 41.0, 74.0, 99.1, 110.8, 117.5, 117.8, 119.4, 120.1, 122.7, 122.8, 128.0, 131.9, 134.2, 135.7, 165.2, 168.2 ppm; MS (EI): m/z (%) = 403 (2), 288 (4), 256 (15), 170 (15), 160 (50), 144 (100).

General Procedure for the Syntheses of 4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(1H-indol-3-yl)butyramides ***3a–3e***

To a stirred suspension of 200 mg of **2** (0.46 mmol) in $10\,cm^3$ of CH_3CN an equimolar amount of the corresponding amine (0.27 *M* NH_3 solution in *THF* for **3e** and a 40% (*w*/*v*) aqueous dimethylamine solution for **3b**) was added. The reaction mixture was stirred under N_2 at 70°C for 48 h. The solvent was evaporated and the residue was dissolved in $30\,cm^3$ of *Et*O*Ac*. The organic phase was washed with $3\times30\,cm^3$ of 5% $NaHCO_3$ solution, $3\times30\,cm^3$ of 5% citric acid solution, $2\times30\,cm^3$ of brine, and then dried (Na_2SO_4), and concentrated. In the case of **3a**, **3b**, and **3d** the residue was purified by column chromatography on silica gel (eluent: *Et*O*Ac*:*n*-hexane, 5:5, 7:3, 6:4, respectively) to give a white powder or colourless oil (**3d**). In the case of **3e** and **3c** the residue was cristallised in a 1:1 mixture of CH_2Cl_2:Et_2O and *Et*O*Ac*:Et_2O.

N-Butyl-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(1H-indol-3-yl)butyramide (**3a**, $C_{24}H_{25}N_3O_3$)

Yield: 84%; white powder; mp 179°C (Et_2O); UV (CH_3OH): λ (rel. int.) = 227 (100), 275 (25), 283 (26), 290 (24) nm; IR (KBr): $\bar{\nu} = 3393$, 3326, 1769, 1707, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.72$ (3H, t, $J = 7.2$ Hz), 1.02 (2H, m), 1.13 (2H, m), 2.71 (2H, d, $J = 6.3$ Hz), 2.95 (2H, m), 4.03 (1H, m), 4.05 (1H, m), 5.81 (1H, m), 6.68 (2H, m), 7.10 (2H, m), 7.15 (1H, t, $J = 8.0$ Hz), 7.35 (1H, d, $J = 8.0$ Hz), 7.78 (1H, m), 8.74 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.5$, 19.7, 31.1, 33.2, 39.2, 40.4, 42.8, 111.4, 114.9, 118.9, 119.4, 121.9, 122.0, 123.1, 126.4, 131.8, 133.9, 136.4, 168.5, 171.5 ppm; MS (EI): m/z (%) = 403 ($M^{+\cdot}$, 38), 288 (15), 256 (68), 243 (30), 157 (37), 144 (100); HREIMS: calcd. 403.1896, found 403.1885.

4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(1H-indol-3-yl)-N,N-dimethylbutyramide (**3b**, $C_{22}H_{21}N_3O_3$)

Yield: 76%; white-grey powder; mp 146°C (*Et*$_2$O); UV (CH_3OH): λ (rel. int.) = 222 (100), 240 (23), 283 (15), 291 (14) nm; IR (KBr): $\bar{\nu} = 3337$, 1775, 1713, 1622 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.64$ (3H, s), 2.80 (2H, m), 2.85 (3H, s), 4.06 (2H, d, $J = 7.5$ Hz), 4.21 (1H, m), 5.81 (1H, m), 7.10 (2H, m), 7.15 (1H, t, $J = 8.1$ Hz), 7.31 (1H, d, $J = 8.1$ Hz), 7.65 (2H, m), 7.78 (3H, m), 8.34 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 32.4$, 35.3, 37.2, 37.3, 42.8, 111.3, 116.3, 119.3, 119.4, 121.6, 122.0, 123.0, 126.6, 132.1, 133.7, 136.3, 168.5, 171.1 ppm; MS (EI): m/z (%) = 375 ($M^{+\cdot}$, 38), 228 (100), 215 (73), 157 (67), 143 (65); HREIMS: calcd. 375.15831, found 375.16172.

4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(1H-indol-3-yl)-N,N-dipropylbutyramide (**3c**, $C_{26}H_{29}N_3O_3$)

Yield: 76%; white-grey powder; mp 150°C (*Et*$_2$O + *Et*OAc); UV (CH_3OH): λ (rel. int.) = 220 (100), 240 (17), 282 (11), 291 (10) nm; IR (KBr): $\bar{\nu} = 3297$, 1767, 1711, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.68$ (3H, t, $J = 7.4$ Hz), 0.80 (3H, t, $J = 7.4$ Hz), 1.27 (2H, m), 1.44 (2H, m), 2.86 (2H, m), 3.05 (4H, m), 4.09 (2H, d, $J = 7.5$ Hz), 4.21 (1H, m), 7.10 (3H, m), 7.32 (1H, d, $J = 8.1$ Hz), 7.65 (2H, m), 7.80 (3H, m), 8.51 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 11.1$, 11.2, 20.7, 22.0, 32.6, 37.3, 42.9, 47.8, 49.7, 111.3, 116.1, 119.2, 119.3, 121.6, 121.9, 123.0, 126.5, 132.1, 133.6, 136.4, 168.5, 170.7 ppm; MS (EI): m/z (%) = 431 ($M^{+\cdot}$, 100), 284 (80), 271 (29), 160 (45), 156 (36), 143 (28); HREIMS: calcd. 431.22091, found 431.22492.

2-[2-(1H-Indol-3-yl)-4-oxo-4-(piperidin-1-yl)butyl]isoindole-1,3-dione (**3d**, $C_{25}H_{25}N_3O_3$)

Yield: 89%; colourless oil; UV (CH_3OH): λ (rel. int.) = 220 (100), 241 (34), 273 (21), 283 (23), 290 (22) nm; IR (KBr): $\bar{\nu} = 3287$, 2937, 1771, 1713, 1614, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.21$ (3H, m), 1.41 (3H, m), 2.76 (2H, d, $J = 6.5$ Hz), 3.18 (3H, s), 3.28 (3H, m), 4.06 (2H, d, $J = 7.2$ Hz), 4.12 (1H, m), 7.00 (3H, m), 7.21 (1H, d, $J = 7.9$ Hz), 7.57 (2H, m), 7.68 (3H, m), 8.44 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.4$, 25.3, 26.0, 32.5, 37.3, 42.5, 42.9, 46.7, 111.3, 116.0, 119.2, 119.3, 121.5, 121.9, 123.0, 126.6, 132.0, 133.7, 136.3, 169.4 ppm; MS (EI): m/z (%) = 415 ($M^{+\cdot}$, 10), 288 (15), 268 (35), 164 (20), 157 (40), 142 (100); HREIMS: calcd. 415.18961, found 415.18262.

4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(1H-indol-3-yl)butyramide (**3e**, $C_{20}H_{17}N_3O_3$)

Yield: 69%; white-grey powder; mp 240°C (*Et*$_2$O + CH_2Cl_2); UV (CH_3OH): λ (rel. int.) = 220 (100), 240 (17), 280 (10), 290 (9) nm; IR (KBr): $\bar{\nu} = 3462$, 3351, 1763, 1711, 1661 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 2.55$ (2H, m), 3.75 (1H, m), 3.88 (2H, m), 6.68 (2H, brs), 6.98 (1H, t, $J = 8.1$ Hz), 7.04 (1H, t, $J = 8.1$ Hz), 7.22 (1H, d, $J = 1.8$ Hz), 7.30 (1H, m), 7.68 (1H, d, $J = 8.1$ Hz), 7.81 (4H, m), 10.85 (1H, brs) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 32.2$, 38.9, 43.4, 111.6, 114.9, 118.5, 118.6, 121.2, 122.1, 123.1, 126.8, 131.8, 134.5, 136.4, 168.2, 173.0 ppm; MS (EI): m/z (%) = 347 ($M^{+\cdot}$, 30), 200 (60), 187 (74), 144 (100); HREIMS: calcd. 347.12701, found 347.12572.

4-(1H-Indol-3-yl)pyrrolidin-2-one (**5**, $C_{12}H_{12}N_2O$)

Yellowish powder; mp 170°C (*Et*$_2$O); UV (CH_3OH): λ (rel. int.) = 204 (65), 221 (100), 274 (21), 282 (22), 290 (20) nm; IR (KBr): $\bar{\nu} = 3352$, 3318, 1680, 1645 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 2.38$ (1H, dd, $J = 8.6$, 16.2 Hz), 2.60 (1H, dd, $J = 8.6$, 16.2 Hz), 3.30 (1H, t, $J = 8.2$ Hz), 3.72 (1H, t, $J = 8.2$ Hz), 3.85 (1H, m), 7.00 (1H, t, $J = 8.0$ Hz), 7.10 (1H, t, $J = 8.0$ Hz), 7.25 (1H, d, $J = 2.4$ Hz),

7.38 (1H, d, $J = 8.0$ Hz), 7.55 (1H, d, $J = 8.0$ Hz), 7.70 (1H, s), 10.88 (1H, brs) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 31.9, 37.5, 48.2, 111.8, 116.1, 118.6, 118.8, 121.4, 121.7, 126.4, 136.8, 176.6$ ppm; MS (EI): m/z (%) = 200 ($M^{+\cdot}$, 93), 170 (7), 143 (100); HREIMS: calcd. 200.09501, found 200.09512.

N-Butyl-3-(1H-indol-3-yl)-4-phenylbutyramide (**7**, $C_{22}H_{26}N_2O$)

To a stirred solution of 300 mg of **6** (0.83 mmol) in 10 cm^3 of CH_3CN 82 mm^3 (if 1.0 equiv), 139 mm^3 (if 1.7 equiv), or 408 mm^3 (if 5.0 equiv were used) of *n*-butylamine were added. In another experiment **6** was directly dissolved in *n*-butylamine. In all cases the reaction mixture gave a clear solution and was stirred under N_2 at 70°C for 5 days. The solvent was removed in vacuo and the residue was dissolved in 30 cm^3 of *Et*OA*c*. The organic phase was washed with 3×30 cm^3 of 5% $NaHCO_3$ solution, then with 3×30 cm^3 of 5% citric acid solution and with 2×30 cm^3 of brine, then dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (eluent: *Et*OA*c*:hexane, 3:7) to give **7** as a colourless oil. Yields: 186 mg (67% with 1.0 equiv of *n*-butylamine); 190 mg (69% with 1.7 equiv of *n*-butylamine); 163 mg (59% with 5.0 equiv of *n*-butylamine); 50 mg (18% with *n*-butylamine used as solvent); UV (CH_3OH): λ (rel. int.) = 208 (85), 222 (100), 275 (20), 282 (21), 292 (18) nm; IR (film): $\bar{\nu} = 3416, 3308, 2957, 2930, 1653, 1541$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.72$ (3H, t, $J = 7.2$ Hz), 0.95 (2H, m), 1.09 (2H, m), 2.60 (2H, d, $J = 7.3$ Hz), 2.95 (2H, m), 3.03 (1H, dd, $J = 7.3$, 13.4 Hz), 3.12 (1H, dd, $J = 7.3$, 13.4 Hz), 3.69 (1H, m), 5.25 (1H, m), 6.76 (1H, d, $J = 2.0$ Hz), 6.95–7.20 (7H, m), 7.32 (1H, d, $J = 8.0$ Hz), 7.66 (1H, d, $J = 8.0$ Hz), 8.42 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 13.5, 19.6, 31.2, 36.4, 38.9, 41.7, 42.1, 111.5, 117.3, 119.0, 119.1, 121.7, 121.9, 125.9, 126.1, 128.0, 129.2, 140.1, 172.1$ ppm; MS (EI): m/z (%): 334 ($M^{+\cdot}$, 12), 243 (35), 219 (15), 144 (100); HREIMS: calcd. 334.20452, found 334.20741.

General Procedure for the Syntheses of 4-Amino-3-(1H-indol-3-yl)-N,N-dialkylbutyramides ***1a–d***

Deprotection of the Phthalimido Group

Method A: A solution of compounds **3a**–**3e** (0.27–0.99 mmol) was stirred at 50°C in 10 cm^3 of *n*-butylamine under N_2 for 24 (**1b**, **1d**, **1e**) or 48 h (**1a**, **1c**). The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: *Me*OH:CH_2Cl_2, 1:9, to which were added a few drops of NH_4OH) to give **1a**–**1d** and white crystals of **5**.

Method B: Compound **3b** or **3d** (0.30 mmol) was dissolved in 11 cm^3 of dry *Et*OH, then 0.11 cm^3 of hydrazine hydrate were added. The reaction mixture was stirred for 3 h at room temperature. The solvent was evaporated and the residue was dissolved in a mixture of 5 cm^3 of 10% aqueous K_2CO_3 solution and 8 cm^3 of CH_2Cl_2. The two layers were separated and the aqueous phase was extracted with 2×5 cm^3 of CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated to afford **1b** or **1d**.

4-Amino-N-butyl-3-(1H-indol-3-yl)butyramide (**1a**, $C_{16}H_{23}N_3O$)

Yield: 80% (Method A); pale yellowish oil; UV (CH_3OH): λ (rel. int.) = 226 (100), 274 (57), 281 (61), 290 (52) nm; IR (KBr): $\bar{\nu} = 3279, 2957, 2930, 1640, 1562, 1458$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.89$ (3H, t, $J = 7.2$ Hz), 1.08 (2H, m), 1.12 (2H, m), 2.55 (4H, ol.m), 3.05 (2H, m), 2.95 (2H, d, $J = 6.3$ Hz), 3.44 (1H, m), 6.05 (1H, t, $J = 5.3$ Hz), 6.95 (1H, s), 7.04 (1H, t, $J = 8.1$ Hz), 7.12 (1H, t, $J = 8.1$ Hz), 7.32 (1H, d, $J = 8.1$ Hz), 7.54 (1H, d, $J = 8.1$ Hz), 9.20 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.6, 19.8, 31.3, 36.9, 39.1, 40.4, 45.6, 111.6, 115.3, 118.8, 119.2, 122.0, 122.4, 126.2, 136.7, 172.0$ ppm; MS (EI): m/z (%) = 274 (18), 273 ($M^{+\cdot}$, 2), 256 (25), 244 (97), 200 (39), 143 (100); HREIMS: calcd. 273.18412, found 273.18403.

4-Amino-3-(1H-indol-3-yl)-N,N-dimethylbutyramide (**1b**, $C_{14}H_{19}N_3O$)

Yield: 81% (Method B); pale yellowish oil; UV (CH_3OH): λ (rel. int.) = 223 (100), 274 (21), 281 (29), 290 (24) nm; IR (KBr): $\bar{\nu} = 3244$, 2930, 1622, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.61$ (2H, d, $J = 6.3$ Hz), 2.70 (6H, s), 3.05 (2H, m), 3.26 (1H, m), 4.20 (2H, brs), 6.98 (1H, t, $J = 8.0$ Hz), 7.04 (2H, m), 7.32 (1H, d, $J = 8.0$ Hz), 7.50 (1H, d, $J = 8.0$ Hz), 9.60 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 35.0$, 35.4, 37.0, 37.3, 44.9, 111.8, 114.7, 118.7, 119.0, 121.7, 122.9, 126.2, 136.6, 171.9 ppm; MS (EI): m/z (%) = 245 ($M^{+\cdot}$, 1), 244 (5), 228 (16), 216 (52), 200 (25), 143 (100); HREIMS: calcd. 245.15282, found 245.15341.

4-Amino-3-(1H-indol-3-yl)-N,N-dipropylbutyramide (**1c**, $C_{18}H_{27}N_3O$)

Yield: 71% (Method A); pale yellowish oil; UV (CH_3OH): λ (rel. int.) = 221 (100), 274 (20), 282 (24), 290 (21) nm; IR (KBr): $\bar{\nu} = 3279$, 2963, 2932, 1618, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.80$ (6H, m), 1.46 (4H, m), 1.78 (2H, brs), 2.74 (2H, d, $J = 6.3$ Hz), 3.06 (4H, m), 3.21 (2H, m), 3.58 (1H, m), 7.00 (1H, s), 7.07 (1H, t, $J = 7.8$ Hz), 7.14 (1H, t, $J = 7.8$ Hz), 7.32 (1H, d, $J = 7.8$ Hz), 7.52 (1H, d, $J = 7.8$ Hz), 8.94 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 11.1$, 11.3, 20.8, 22.2, 36.9, 37.6, 46.1, 47.7, 49.6, 111.5, 116.3, 119.0, 119.1, 121.8, 122.2, 126.5, 136.7, 171.6 ppm; MS (EI): m/z (%) = 302 (30), 301 ($M^{+\cdot}$, 1), 284 (37), 272 (100), 157 (29), 143 (90); HREIMS: calcd. 301.21541, found 301.21753.

4-Amino-3-(1H-indol-3-yl)-1-(piperidin-1-yl)butan-1-one (**1d**, $C_{17}H_{23}N_3O$)

Yield: 70% (Method B); pale yellowish oil; UV (CH_3OH): λ (rel. int.) = 219 (100), 273 (21), 282 (21), 290 (18) nm; IR (KBr): $\bar{\nu} = 3242$, 2928, 2861, 1622, 1456, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.21$–1.58 (6H, m), 2.18 (2H, brs), 2.74 (2H, m), 3.05 (2H, m), 3.24 (2H, m) 3.43 (1H, m, 1H), 3.53 (1H, m), 3.55 (1H, m), 6.95 (1H, s), 7.05 (1H, t, $J = 7.8$ Hz), 7.13 (1H, t, $J = 7.8$ Hz), 7.34 (1H, d, $J = 7.8$ Hz), 7.60 (1H, d, $J = 7.8$ Hz), 9.65 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.2$, 25.3, 26.0, 36.9, 37.2, 42.6, 45.9, 46.7, 111.5, 115.6, 118.7, 118.8, 118.9, 121.5, 122.2, 126.3, 136.6, 170.2 ppm; MS (EI): m/z (%) = 286 (M + 1, 15), 285 ($M^{+\cdot}$, 1), 270 (19), 269 (100), 184 (10), 156 (14); HREIMS: calcd. 285.18413, found 285.19051.

General Procedure for the Syntheses of 4-Dimethylamino-3-(1H-indol-3-yl)-N,N-dipropylbutyramide (**8c**, $C_{20}H_{31}N_3O$)

A mixture of 135 mg of a 37% w/w solution of formaldehyde (1.67 mmol) and 5 cm^3 of *Me*OH was added dropwise to a stirred solution of 150 mg of **1c** (0.50 mmol), 79 mg of glacial acetic acid (1.32 mmol), and 56 mg of $NaBH_3CN$ (0.89 mmol) in 5 cm^3 of *Me*OH at 0°C. The solution was warmed to 25°C and stirred for 2.5 h before adding 4 cm^3 of a 10% aqueous K_2CO_3 solution. The *Me*OH was removed under vacuum, 20 cm^3 of H_2O were added to the residue, and it was extracted with 3×10 cm^3 of *Et*OA*c*. The crude product was purified by chromatography on silica gel, eluted with CH_2Cl_2:*Et*OH (10:1, to which were added a few drops of NH_4OH) to give **8c**. Yield: 81%; viscous oil; UV (CH_3OH): λ (rel. int.) = 227 (100), 275 (45), 282 (14), 291 (12) nm; IR (KBr): $\bar{\nu} = 3262$, 2965, 2934, 1624, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.79$ (6H, m), 1.41 (4H, m), 2.30 (6H, s), 2.75 (4H, m), 3.18 (2H, t, $J = 7.5$ Hz), 3.61 (2H, t, $J = 7.5$ Hz), 3.80 (1H, m), 6.88 (1H, s), 7.05 (2H, m), 7.22 (1H, d, $J = 7.4$ Hz), 7.64 (1H, d, $J = 7.4$ Hz), 8.80 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 11.1$, 11.2, 20.8, 22.1, 32.3, 37.3, 45.5, 47.7, 49.6, 64.3, 111.4, 117.0, 118.8, 118.9, 121.8, 122.0, 126.3, 136.7, 171.9 ppm; MS (EI): m/z (%) = 329 ($M^{+\cdot}$, 21), 327 (24), 284 (100), 186 (43), 143 (54), 128 (30), 115 (21); HREIMS: calcd. 329.24678, found 329.24624.

N-Butyl-4-dimethylamino-3-(1H-indol-3-yl)butyramide (**8a**, $C_{18}H_{27}N_3O$)

Yield: 67%; viscous oil; UV (CH_3OH): λ (rel. int.) = 228 (100), 275 (59), 282 (63), 290 (54) nm; IR (KBr): $\bar{\nu}$ = 3410, 3298, 2957, 2932, 1641, 1551, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.82 (3H, t, J = 7.7 Hz), 1.12 (2H, m), 1.23 (2H, m), 2.30 (6H, s), 2.68–2.75 (4H, m), 3.07 (2H, dt, J = 4.2, 7.5 Hz), 3.57 (1H, m), 6.59 (1H, t, J = 4.2 Hz), 6.90 (1H, s), 7.08 (2H, m), 7.26 (1H, d, J = 7.5 Hz), 7.58 (1H, d, J = 7.5 Hz), 8.91 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.7, 19.9, 31.4, 32.2, 39.1, 41.6, 45.4, 64.8, 111.6, 116.7, 118.6, 119.0, 121.7, 121.9, 126.1, 136.6, 172.4 ppm; MS (EI): m/z (%) = 301 ($M^{+\cdot}$, 22), 186 (17), 170 (18), 156 (17), 143 (100), 130 (42), 115 (54); HREIMS: calcd. 301.21542, found 301.21534.

4-Dimethylamino-3-(1H-indol-3-yl)-N,N-dimethylbutyramide (**8b**, $C_{16}H_{23}N_3O$)

Yield: 63%; viscous oil; UV (CH_3OH): λ (rel. int.) = 204 (100), 218 (42), 282 (14), 290 (13) nm; IR (KBr): $\bar{\nu}$ = 3268, 2938, 1624, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.30 (6H, s), 2.68–2.90 (5H, m), 3.78 (1H, m), 6.92 (1H, s), 7.05 (2H, m), 7.25 (1H, d, J = 7.4 Hz), 7.58 (1H, d, J = 7.4 Hz), 8.82 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.6, 35.3, 37.1, 37.2, 45.1, 64.0, 111.3, 116.7, 118.8, 119.4, 121.4, 121.8, 126.1, 136.4, 172.2 ppm; MS (EI): m/z (%) = 273 ($M^{+\cdot}$, 26), 228 (45), 186 (51), 143 (100), 130 (46), 115 (76); HREIMS: calcd. 273.18414, found 273.18272.

4-Dimethylamino-3-(1H-indol-3-yl)-1-(piperidin-1-yl)butan-1-one (**8d**, $C_{19}H_{31}N_3O$)

Yield: 81%; viscous oil; UV (CH_3OH): λ (rel. int.) = 221 (100), 274 (28), 283 (31), 290 (26) nm; IR (KBr): $\bar{\nu}$ = 3275, 2938, 1614, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.02–1.60 (6H, m), 2.25 (6H, m), 2.75 (4H, m), 3.18–3.58 (4H, m), 3.71 (1H, m), 6.82 (1H, s), 7.04 (2H, m), 7.20 (1H, d, J = 7.1 Hz), 7.58 (1H, d, J = 7.1 Hz), 9.20 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3, 25.4, 26.0, 32.2, 37.3, 42.6, 45.4, 45.5, 46.7, 64.5, 111.5, 116.7, 118.8, 119.0, 121.3, 122.0, 126.4, 136.6, 170.7 ppm; MS (EI): m/z (%) = 314 (M + 1, 14), 313 ($M^{+\cdot}$, 2), 268 (73), 186 (91), 143 (100), 115 (49); HREIMS: calcd. 313.21541, found 313.21482.

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