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Investigations into the mechanism of lactamization of lactones yielding in a novel route to biologically active tryptamine derivatives

Michael Decker, Thi Thanh Huyen Nguyen and Jochen Lehmann*

Lehrstuhl für Pharmazeutische/Medizinische Chemie, Institut für Pharmazie, Friedrich-Schiller-Universität Jena, Philosophenweg 14, D-07743 Jena, Germany

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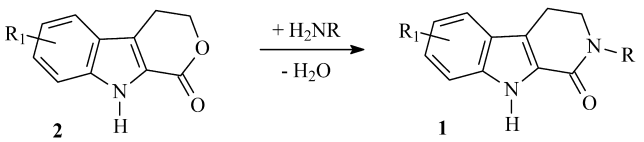
Abstract—The mechanism of lactamization of corresponding lactones was investigated by means of gas chromatography and synthesis of possible intermediates as references. Lactones react with amines via the amino acid with subsequent elimination of water to the corresponding lactams. In the first step, also hydroxyamides are in equilibrium with the lactones and amines, respectively, which are not able to form the amide though. This mechanism opens a new approach for the synthesis of N^{β}-disubstituted tryptamines.

1. Introduction

The reaction of lactones to lactams is of general importance in organic chemistry. Especially in the field of medicinal chemistry, where this reaction is relevant for the synthesis of versatile intermediates like tetrahydro-9*H*-pyrido[3,4-*b*]indolones (**1**) out of 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) (Scheme 1), for preparation of β-carbolines, serotonin derivatives, and other substances, that are lead substances for drugs for the treatment of diseases of the central nervous system, like psychosis, or are made responsible for causing Parkinson's disease, respectively.[1–3]



Scheme 1. Lactamization of 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) with primary amines yielding tetrahydro-9*H*-pyrido[3,4-*b*]indolones (**1**).

Different relevant experimental data has been found for the course of this reaction: first, Späth and Lintner found that in general lactams are formed with primary amines out of the corresponding lactones at temperatures above 250 °C.[4] Later, this could be proved by the preparation of pyrrolidin-2-ones out of γ-butyrolactones, in which case at temperatures below 180 °C mainly *N*-alkyl-4-hydroxy-butanamide is formed.[5]

The formation of either hydroxy acid amides or lactams is dependent on the applied conditions: *N*-methyl-phthalimidine can be synthesized under high pressure (**3**) out of (2-hydroxymethyl)-*N*-methylbenzamide (**4**). Under normal pressure, the lactone (**5**) and methylamine are formed (Scheme 2).[6] The more basic the amine, the higher are the temperatures to be applied for lactam formation.[4] Also the ring size of the corresponding lactone strongly influences the course of the reaction. Aniline reacts with δ-valerolactone (tetrahydro-2*H*-pyran-2-one) to the hydroxyamide, whereas γ-butyrolactone (dihydrofuran-3(2*H*)-one) gives the lactam.[7] An important hint concerning the mechanism gives the reaction of lactones with secondary amines, in which no cyclization to a lactam is possible. Depending on temperature and reaction time, apart from the hydroxy amide an amino amide is formed, the formation of which could be explained by reaction of an amino acid as intermediate with excess amine.[5,8] Also other experimental data, for example the facts that neither 4-hydroxy-*N*-phenylbutanamide nor compound **6** do form a lactam, leads to the assumption of an amino acid as an intermediate (Scheme 3).[9,10]

The following scheme (Scheme 4) gives an illustration which ways can lead from the lactone (**7**) to the lactam (**8**). For our purposes, we decided to use γ-butyrolactone (**7**) as the reacting lactone and benzylamine (**9**) as the respective amine. Path **a** would mean, that in the first step the hydroxyamide is formed, which could eliminate water to form the

Keywords: Lactamization; Lactones; Amino acids; Hydroxyamides; Tryptamines; Hallocinogens.
* Corresponding author. Tel.: +49-3641-949803; fax: +49-3641-949802; e-mail address: j.lehmann@uni-jena.de

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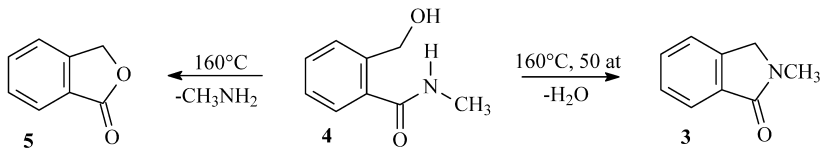
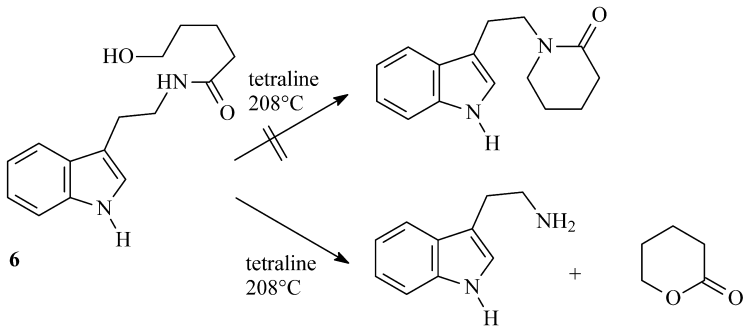
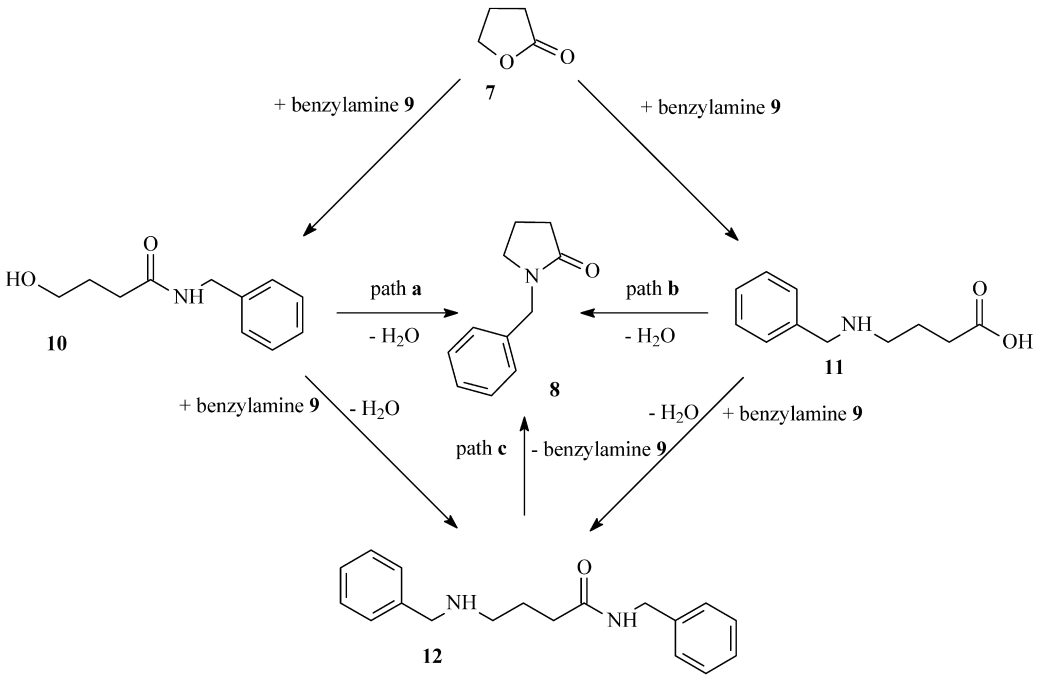


Scheme 2. Dependence of *N*-methyl-phthalimidine (**3**) formation out of (2-hydroxymethyl)-*N*-methylbenzamide (**4**) on the applied pressure.



Scheme 3. 5-Hydroxy-*N*-[2-(1*H*-indol-3-yl)ethyl]pentanamide does not cyclize to the corresponding lactam at elevated temperatures.

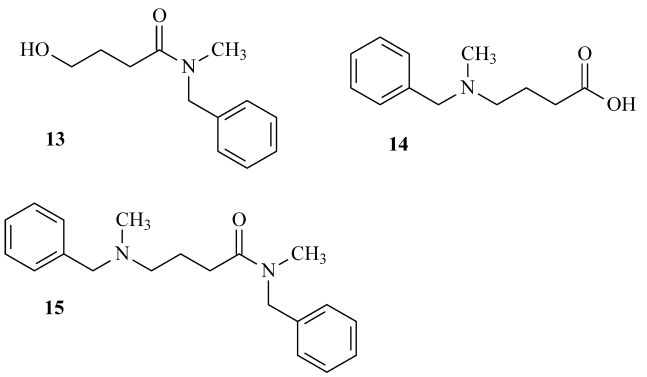


Scheme 4. Different mechanistic routes to the formation of 1-benzylpyrrolidin-2-one (**8**) out of benzylamine (**9**) and γ-butyrolactone (**7**).

lactam. In path **b** addition of the amine leads to an amino acid that cyclizes to the lactam. Both hydroxyamide and amino acid could add a second molecule amine to form the amino amide, that might in turn eliminate amine to give the lactam (path **c**). An interesting possibility to evaluate the mechanism lies in the use of secondary amines to react with the lactone, because the intermediates cannot further react to the lactam.

All possible intermediates and products, that is, hydroxyamide (**10**), amino acid (**11**), amino amide (**12**), and the lactam (**8**) were synthesized, in order to get references to investigate the reaction using gas chromatography. One major problem is of course, that amino acids have never been identified as intermediates, because at the high temperatures necessary for lactamization (and also for gas chromatography) they might directly eliminate water to form the lactam. This should be circumvented by using *N*-benzyl-*N*-methylamine as the amine component, so that no lactams can be formed. Corresponding hydroxyamide (**13**), amino acid (**14**) and amino amide (**15**) should be synthesized as references (Scheme 5).

If indeed the reaction proceeds through the amino acid, it should also be possible to make use of this fact for the synthesis of compounds which are used in medicinal chemistry concerned with drugs for the central nervous system. 4,9-Dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) could then react to an indole-2-carboxylic acid (**16**), which easily decarboxylates to an N^{β}-disubstituted

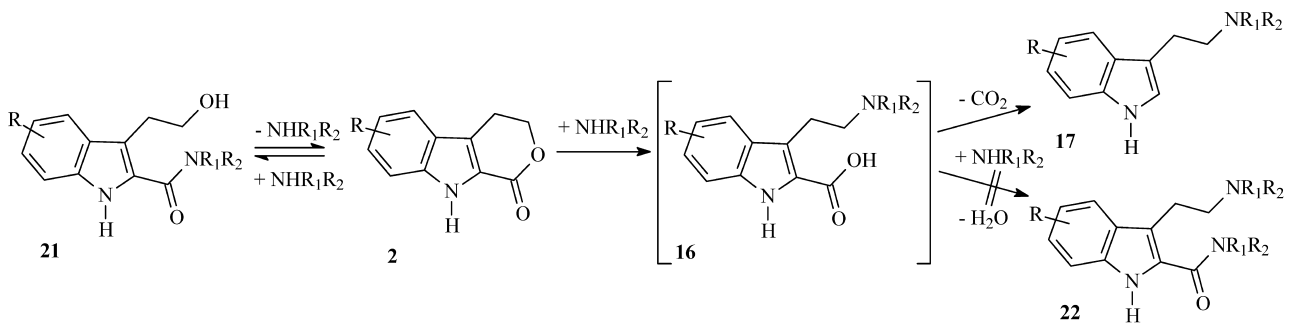


Scheme 5. Possible intermediates for the reaction of *N*-benzyl-*N*-methylamine with γ-butyrolactone (**7**).

Table 1. Gas chromatographic retention times of the compounds specified in Scheme 4 and their silylated derivatives

t_R (min) (silylated compound)	Compound
0.78	γ-Butyrolactone **7**
1.25 (2.84)	Benzylamine **9**
6.45	Lactam **8**
6.45[a] (7.54)	Amino acid **11**
8.15 (8.65)	Hydroxyamide **10**
12.5	Amino amide **12**

[a] The lactam **8**, which is formed under the applied conditions.



Scheme 6. Formation of N^{β}-disubstituted tryptamines (**17**) from 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) and secondary amines.

tryptamine (**17**) (Scheme 6). Also the toxic bufotenin (5-hydroxy-*N*,*N*-dimethyltrytamine) from *Bufo* sp. and the hallucinogenic compound psilocine (4-hydroxy-*N*,*N*-dimethyltryptamine) from *Psilocybe mexicana* (Agaricaceae) belong to this class of compounds, which are derivatives of the neurotransmitter serotonin (5-hydroxy-tryptamine).

2. Results and discussion

The hydroxyamide **10** was synthesized by reaction of γ-butyrolactone with benzylamine at room temperature, the amino acid **11** by hydrolysis of lactam **8** with barium hydroxide solution. The lactam **8** was formed by reaction of γ-butyrolactone with benzylamine at 220 °C. The amino amide **12** was prepared in a two-step synthesis out of 4-chlorobutanoyl chloride: aminolysis with benzylamine (**9**) at room temperature yielded *N*-benzyl-4-chlorobutanamide, which gave the amino amide (**12**) by refluxing with excess benzylamine.

Retention times of the above mentioned compounds were determined with a gas chromatograph (Table 1). Through derivatization with MSTFA (*N*-methyl-trimethylsilyl-trifluoroacetamide) benzylamine **9**, amino acid **11** and hydroxyamide **10** were silylated, so that their retention times changed (Table 1). Silylation was necessary to determine the amino acid, because cyclisation occurs at the temperatures necessary for gas chromatography yielding the lactam **8**. This could be easily proved by heating the amino acid, followed by silylation and gas chromatography. Heating to the melting point (142 °C) and direct cooling yielded 90% lactam, and after heating to 200 °C no amino acid was detectable any more.

For studying the reaction, two equimolar mixtures of γ-butyrolactone and benzylamine were heated for 20 h; one at 150 °C, the other one at 200 °C. After 15 min, 1, 4, 20 h, respectively, samples were taken and chromatographed. It was proved in advance, that the amino acid directly lactamizes, therefore no derivatization was necessary. The changes in the amounts of starting materials and products are given in Figure 1. For estimating the quantitative amounts, the peak area was used. For our qualitative investigation this was precise enough, using naphthalene as an internal standard for determining a correction factor did not improve accuracy, because different reference substances, that are closely related to the respective compounds would have been necessary.

As can be seen from Figure 1, in the 150 °C batch only very low amounts of lactam **8** are formed. The hydroxyamide **10** is rapidly formed. After 1 h the maximum amount is reached, after this time, its amount significantly decreases, while the lactone and the amine peaks, respectively, increase. These results indicate that there might be an equilibrium between the hydroxyamide on the one hand, and lactone and amine on the other hand. In the 200 °C batch, the lactam peak rapidly increases, while the amine and lactone peaks, respectively, decrease. In analogy to the 150 °C batch, the amount of hydroxyamide rapidly increases within the first 15 min, but decreases to almost zero shortly after. This might be either due to the fact, that the hydroxyamide is a direct intermediate, or it exists in equilibrium with the lactone, which can in turn react to

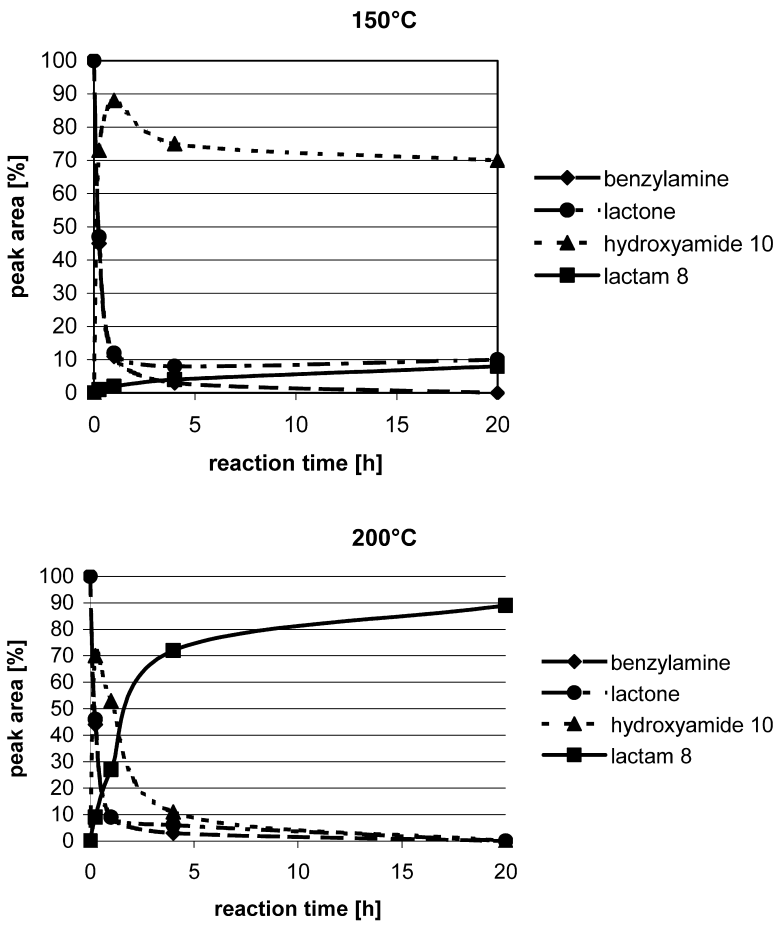


Figure 1. Product formation during the course of reaction of γ-butyrolactone (**7**) and benzylamine (**9**) at different reaction temperatures (150 and 200 °C, respectively) measured by gas chromatography.

another intermediate (the amino acid). It could be easily proved, that hydroxyamide **10** is not a direct intermediate, by heating the hydroxyamide at 200 °C and determine the accruing products. As can be seen from Table 2, small amounts of lactone and amine, respectively, are formed, but even after 20 h only negligible amounts of lactam **8**. Heating the amino amide **12** at 200 °C for 1 h gave the lactam, but large amounts of starting material could be isolated (data not shown). Taking into account this thermal stability of **12**, and the fact, that it could not be determined during the lactamization process, makes it an improbable intermediate.

Table 2. Amounts of products/starting material during the course of pyrolysis of hydroxyamide **10**

t_R (min)	Compound	Area at 200 °C after (%)		
		15 min	1 h	20 h
0.79	γ-Butyrolactone **7**	2.2	3.82	3.16
1.25	Benzylamine **9**	0	0	4.19
6.46	Lactam **8**	0	0	1.83
8.15	Hydroxyamide **10**	83.17	88.27	71.33

We also investigated the reaction of γ-butyrolactone with *N*-benzyl-*N*-methylamine. The reference substances (Scheme 5) were synthesized as follows. Heating γ-butyrolactone with *N*-benzyl-*N*-methylamine for 18 h at 100 °C yielded the hydroxyamide **13**. The amino acid **14** was obtained in two steps out of ethyl 4-bromobutanoate. In the first step the bromine atom was replaced by the *N*-benzyl-*N*-methylamine group, in the second step the ester was hydrolyzed with hydrochloric acid. The corresponding amino amide **15** was also prepared in two steps with *N*-benzyl-*N*-methylamine out of 4-chlorobutanoyl chloride (**16**) via *N*-benzyl-4-bromo-*N*-methylbutanamide (**17**).

Retention times of the respective compounds and their silylated derivatives are given in Table 3. An equimolar mixture of *N*-benzyl-*N*-methylamine and γ-butyrolactone was heated at 200 °C for 7h. Samples were taken after 15 min, 30 min, 2 h, 4 h and 7 h. As can be seen from Figure 2, the starting materials are consumed quite fast; the hydroxyamide **18** is readily formed (it is the kinetically formed product), but disappears rapidly, while the amino

Table 3. Gas chromatographic retention times of the compounds specified in Scheme 5 (reaction of γ-butyrolactone **7** with *N*-benzyl-methylamine) and their silylated derivatives

t_R (min) (silylated compound)	Compound
0.79	γ-Butyrolactone **7**
1.47 (3.13)	*N*-Benzyl-*N*-methylamine
5.85 (7.31)	Amino acid **14**
6.86 (8.75)	Hydroxyamide **13**
10.0	Amino amide **15**

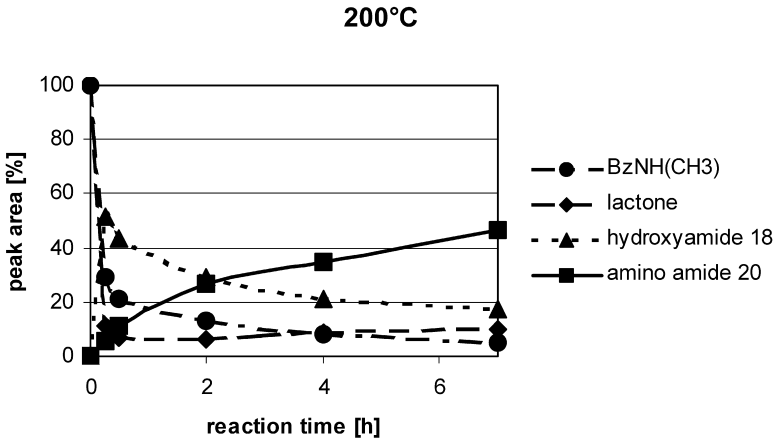


Figure 2. Product formation during the course of reaction of γ-butyrolactone (**7**) and *N*-benzyl-*N*-methylamine at 200 °C measured by gas chromatography.

amide **20** is formed. The formation of an amino amide out of the hydroxyamide does not take place, because heating the hydroxyamide **18** with *N*-benzyl-*N*-methylamine for 3 h at 200 °C gave only low amounts of amino amide, probably via γ-butyrolactone formation, which in turn reacted with *N*-benzyl-*N*-methylamine to the amino amide. Therefore, the amino amide **20** has to be formed via the amino acid **19**, which accrues out of lactone and amine and subsequent reaction with a second amine molecule. The hydroxyamide exists in equilibrium with the starting materials, which are consumed to form the amino amide. In order to prove this assumption, the amino acid **19** was heated with *N*-benzyl-*N*-methylamine at 200 °C. After 30 min, no starting material was found anymore because of complete amino amide formation.

We also examined the reaction of 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) with secondary amines. In this case, hydroxyamide **21**, amino acid **16**, amino amide **22** and trytamines **17** are possible products (Scheme 6). Taking into account the results we obtained with γ-butyrolactone, suppression of formation of the kinetic product **21** is possible by using long reaction times and high temperatures. Decarboxylation occurs faster than reaction with excess amine to the amino amide **22**, therefore reaction of lactones with secondary amines opens a new way for the preparation of the pharmacologically relevant N^{β}-disubstituted tryptamines (**17**), for example, reaction of lactone **2** with *N*-methylaniline leads to *N*-[2-(1*H*-indol-2-yl)ethyl]-*N*-methyl-*N*-phenylamine in 44% yield (Table 4). The formation of tryptamines is of course a further prove for the reaction mechanism previously described. Other different N^{β}-disubstituted tryptamines (**17a**–**p**) were prepared using this reaction, which are listed in Table 4. Compounds **17i** and **17k**, respectively, incorporate a 2-piperidin-4-yl-1*H*-isoindole-1,3(2*H*)-dione moiety, which is a structural feature of the dopaminergic antipsychotic pimocid. They were screened for their affinity to different receptors (Table 5), including the dopamine receptor. Some of these compounds showed high, nanomolar affinities to D_2, α_1 and various serotonin (5-HT) receptors (Table 6).

In summary, the formation of lactams out of lactones goes via the amino acid, but not via the hydroxyamide, which is the kinetic product, that exists in an equilibrium with the starting materials. This information could be used for the preparation of tryptamines, which can be regarded as the amino acid intermediate after decarboxylation.

3. Experimental

3.1. General

Melting points were measured on 'Melting Point Apparatus' by Gallenkamp and are uncorrected. IR spectra were recorded on a Perkin–Elmer '1420'. Elemental analyses were determined with 'CHNO-Analyser Rapid' by Heraeus. ^{1}H NMR spectra were recorded with 'WH-90' (90 MHz, Bruker) and 'AC-200' (200 MHz, Bruker). Chemical shifts (δ) are given in parts per million relative to tetramethylsilane (δ=0.00) as internal standard. Coupling constants (J) are given in Hz. EI mass spectra were measured with MS-30 and MS-50, respectively, A.E.I., Manchester, UK. Analytical thin-layer chromatography (tlc) was conducted on precoated aluminium plates: silica gel 60 F_{254} (Merck Darmstadt, Germany), layer thickness 0.2 mm. For detection iodine vapour or UV light (254 nm), respectively, was used. Silica gel column chromatography utilized silica gel 60 63–200 μm (Baker).

Gas chromatography was performed with Hewlett–Packard model 5890 series II in connection with HP 3396 series II integrator. A capillary column DB-5 (fused silica, 30 m×0.32 mm, film thickness 0.25 μm) by J & W Scientific Inc., California, was applied. Gas supply was adjusted in the following manner: carrier gas hydrogen (15 mL/min); make-up-gas nitrogen (15 mL/min); FID detector: hydrogen (30 mL/min), air (400 mL/min); prepressure: 23 psi; split ratio: 1/20. Injection volume was 1 μL of a 0.1% sample solution. Temperature programme: injector: 200 °C; FID detector: 270 °C; initial temperature: 80 °C (1 min); rate: 15 °C/min; final temperature: 270 °C (2 min). For the reaction of γ-butyrolactone with *N*-benzylmethylamine, conditions were the same, apart from the final temperature [300 °C (2 min)] and the rate (20 °C/min). Silylation was conducted by adding 100 μL MSTFA (*N*-methyl-trimethylsilyl-trifluoroacetamide) and afterwards 200 μL acetonitrile to 1 mg of the respective sample.

Table 4. N^{β}-Disubstituted tryptamines (**17a**–**p**) formed by reaction of 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) with secondary amines

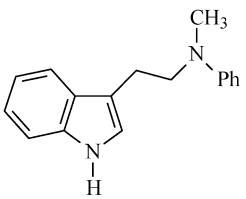
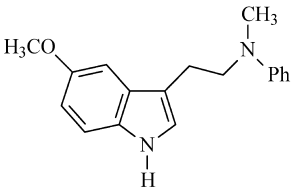
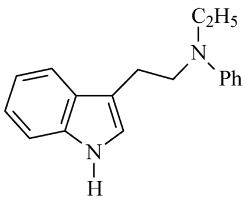
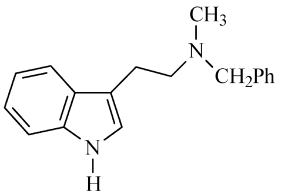
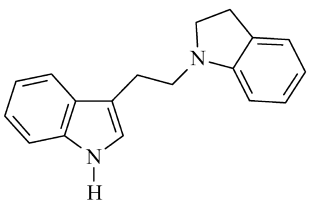
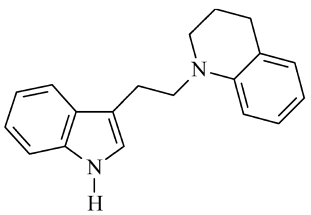
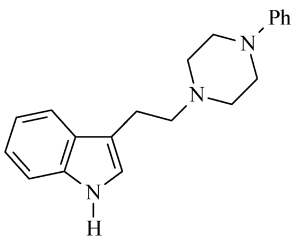
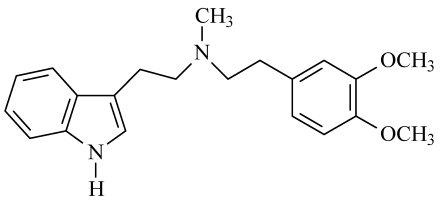
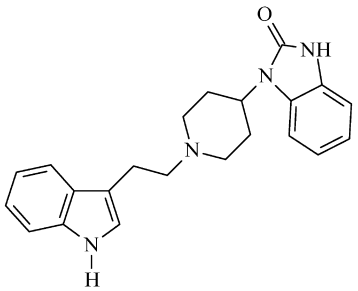
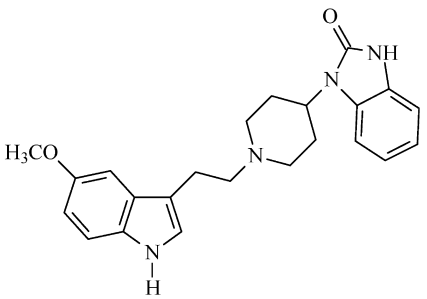
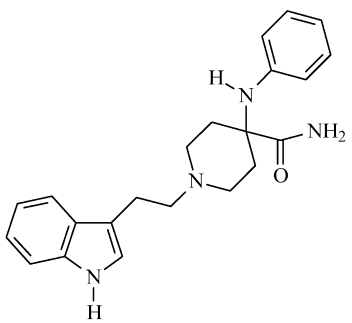
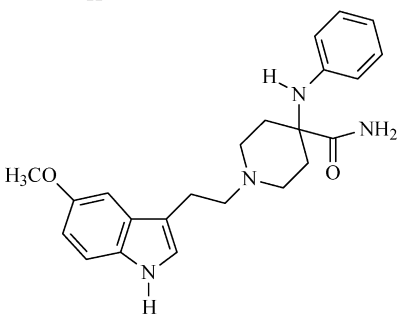
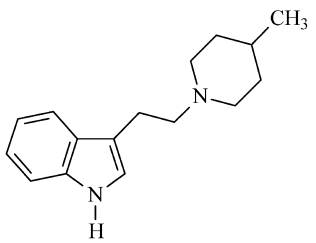
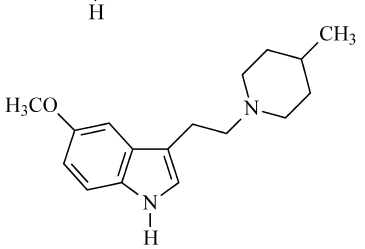
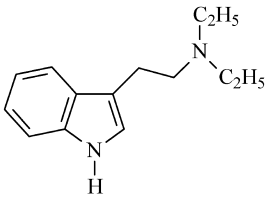
Compound	Compound number	Reaction temperature (°C)	Reaction time (h)	Yield (%)
	**17a**	200	12	44
	**17b**[a]	200	12	38
	**17c**	200	12	41
	**17d**[a]	200	12	18
	**17e**	150	12	16
	**17f**[a]	200	12	33
	**17g**[a]	200	12	47
	**17h**[a]	200	12	37

Table 4 (*continued*)

Compound	Compound number	Reaction temperature (°C)	Reaction time (h)	Yield (%)
	**17i**	200	2	46
	**17k**	200	2	49
	**17l**	200	2	20
	**17m**	200	2	21
	**17n**	180	12	33
	**17o**[a]	180	12	39

(*continued on next page*)

Table 4 (*continued*)

Compound	Compound number	Reaction temperature (°C)	Reaction time (h)	Yield (%)
	**17p**[a]	180	9	39

[a] As the hydrochloride.

This mixture was heated for 15 min at 70 °C. The solution obtained was injected.

3.1.1. *N*-Benzyl-4-hydroxybutanamide (10). To 3.1 mL (40 mmol) of γ-butyrolactone were added 4.4 mL (40 mmol) of benzylamine. The mixture was allowed to stand for 24 h at room temperature. The white precipitate was filtered off and recrystallized from ethanol/diethylether (1/1).

Compound **10**. White, glittering flat crystals (4.35 g, 56% yield). Mp 74–75 °C (lit.[4] mp 74–75 °C). ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.62 (2H, qi, J=8 Hz, C(O)CH_2), 2.16 (2H, t, J=8 Hz, HOCH_2), 3.36 (2H, tt, J=5, 8 Hz, $CH_2CH_2CH_2$), 4.2–4.3 (2H, d, J=6 Hz, benzyl), 4.46 (1H, t, J=5 Hz, OH), 7.22 (5H, m, arom.) ppm. IR (KBr): 1649 cm^{-1} (C=O-valence).

3.1.2. *N*-Benzyl-pyrrolidin-2-one (8). A mixture of 6.2 mL

Table 5. Pharmacological screening results of compounds **17g**, **17i**, **17k**, **17n**, **17o** (N^{β}-disubstituted tryptamines) at different receptors

Receptor/ligand	Decrease in receptor-bound radioactivity (%)					Concentration of test solution (M)
	17g	**17i**	**17k**	**17n**	**17o**	
Adenosine receptors						
^{3}H-CPDPX (A_1)	19	21	14	22	26	10^{-6}
^{3}H-NBTI	9	−62	−50	10	10	10^{-5}
Adrenoceptors						
^{3}H-Prazosin (α_1)	**−98**	**−100**	**−96**	**−92**	−44	10^{-6}
Peptide receptors						
^{3}H-Angiotensin-II	3	3	1	−1	9	10^{-5}
^{3}H-Bradykinin	0	−7	−9	5	2	10^{-5}
^{3}H-Sarafot (ET)	2	−3	3	−1	0	10^{-5}
Dopamine receptors						
^{3}H-Spiperone	**−91**	**−76**	**−72**	−38	−29	10^{-5}
GABA receptor						
^{3}H-Muscimol (GABA-A)	−5	−14	−11	−17	−19	10^{-5}
Glutamate receptors						
^{3}H-MK801	−20	−22	−16	−30	−26	10^{-5}
^{3}H-AMPA	3	−9	10	−9	−14	10^{-5}
ACh receptors						
^{3}H-Cytisin (Nic)	7	−9	−11	−4	−1	10^{-5}
^{3}H-Pirenzipin (M_1)	−5	−29	−29	−9	−11	10^{-6}
Serotonin receptors						
^{3}H-8OH-DPAT (5-HT_{1A})	**−92**	**−71**	**−94**	−32	**−87**	10^{-6}
^{3}H-Ketanserin (5-HT_2)	**−92**	**−100**	**−100**	−48	−49	10^{-6}
^{3}H-Paroxetin (5-HT_{car})	**−95**	**−93**	**−71**	−33	−33	10^{-6}
^{3}H-PDBU (Phorbol)	−3	−13	−4	−11	−4	10^{-5}
^{3}H-Glibenclamide (K^+)	7	−2	−4	0	0	10^{-5}

Bold numbers mark high affinities (i.e. more than −75% decrease).

Table 6. Inhibition constants of compounds **17g**, **17i**, **17k**, **17n**, **17o** (N^{β}-disubstituted tryptamines) at α_1, 5-HT_{1A}, 5-HT_2, and 5-HT_{car} receptors, respectively

Compound	^{3}H-Prazosin (α_1)	^{3}H-8OH-DPAT (5-HT_{1A})	^{3}H-Ketanserin (5-HT_2)	^{3}H-Paroxetin (5-HT_{car})	^{3}H-Spiperone (D_2)
17g	K_I=11 nM	K_I=79.1 nM	K_I=17.2 nM	K_I=146 nM	K_I=101 nM
17i	K_I=3.3 nM	K_I=504 nM	K_I=17.9 nM	K_I=362 nM	Not determined
17k	K_I=6.7 nM	K_I=40.6 nM	K_I=19.1 nM	K_I=101 nM	Not determined
17n	K_I=28 nM	Low affinity	Moderate affinity	Low affinity	Not determined
17o	Moderate affinity	K_I=12.5 nM	Moderate affinity	Low affinity	Not determined

(80 mmol) of γ-butyrolactone and 8.8 mL (80 mmol) of benzylamine was heated for 24 h in a metal bath (bath temperature 220 °C) under reflux and afterwards distilled to yield 11 g of colourless oil (79% yield).

Compound **8**. Bp 124–125 °C/0.8 mm (lit.[4] bp 130–140 °C/1 mm). n_D^{20}=1.5527 (lit.[4] n_D^{20}=1.5520) ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.89 (2H, qui, J=8 Hz, $CH_2CH_2CH_2$), 2.29 (2H, t, J=8 Hz, $C(O)CH_2$), 3.20 (2H, tt, J=8 Hz, CH_2N), 4.37 (2H, s, benzyl), 7.29 (5H, m, arom.) ppm. IR (KBr): 1680 cm^{-1} (C═O-valence).

3.1.3. 4-(Benzylamino)butanoic acid (11). To a solution of 200 mL of 10% aqueous barium hydroxide were added 17.5 g (100 mmol) of *N*-benzyl-pyrrolidin-2-one (**8**). The mixture was heated for 24 h under reflux. After cooling dry ice was added in small pieces until pH=7 was reached. Barium carbonate was filtered off, and the solvent was evaporated to give a solid, which was recrystallized from ethanol/diethylether (1/1) to yield 12 g (62% yield) of white crystals.

Compound **11**. Mp 142 °C (decomp., lit.[11] mp 139 °C). n_D^{20}=1.5527 (lit.[4] n_D^{20}=1.5520) ^{1}H NMR (90 MHz, methanol-d_4) δ 1.87 (2H, qui, J=6 Hz, $CH_2CH_2CH_2$), 2.38 (2H, t, J=6 Hz, CH_2COOH), 3.05 (2H, t, J=6 Hz, CH_2N), 4.13 (2H, s, benzyl), 7.44 (5H, m, arom.) ppm. IR (KBr): 1640 cm^{-1} (C═O-valence).

3.1.4. *N*-Benzyl-4-(benzylamino)butanamide (12). To a solution of 20 mL (183 mmol) of benzylamine in 250 mL of diethylether were added under stirring and ice cooling 10 mL (89 mmol) of 4-chlorobutanoyl chloride. Stirring was continued for 1 h at room temperature. The precipitated amine hydrochloride was filtered off, and the filtrate concentrated under reduced pressure. A white solid (*N*-benzyl-4-chlorobutanamide) was formed (14.8 g, 79% yield), that was recrystallized from acetone/petrolether (40/60) (1/1). Mp 66 °C (lit.[12] mp 68 °C), no further spectroscopic characterization.

A solution of *N*-benzyl-4-chlorobutanamide (11 g, 50 mmol), 11 mL (100 mmol) of benzylamine, and 0.1 g of sodium iodide in 100 mL of ethanol was heated under reflux for 12 h. After cooling, 200 mL of diethylether were added, the precipitated hydrochloride filtered and dried. The hydrochloride was dissolved in 100 mL of water, alkalized with saturated $NaHCO_3$-solution and extracted three times with dichloromethane. Dichloromethane is removed under reduced pressure, and the white solid is recrystallized from diethylether to give 7.2 g (63% yield) of **12** as a white solid.

Compound **12**. Mp 62–63 °C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.67 (2H, qui, J=7.5 Hz, $CH_2CH_2CH_2$), 2.18 (2H, t, J=7.5 Hz, CH_2CO), 2.47 (2H, t, J=7.5 Hz, CH_2N), 3.1–3.4 (1H, brd amine-N*H*), 3.64 (2H, s, amine-benzyl), 4.24 (2H, d, J=6 Hz, amide-benzyl), 7.2–7.3 (10H, m, arom.), 8.1–8.4 (1H, brd t, J=6 Hz, amide-N*H*) ppm. IR (KBr): 1640 cm^{-1} (C═O-valence).

3.1.5. *N*-Benzyl-4-hydroxy-*N*-methylbutanamide (13). A mixture of 3.8 mL (50 mmol) of γ-butyrolactone and 6.5 mL (50 mmol) of *N*-benzyl-methylamine were heated at 100 °C (inner temperature) for 18 h. After cooling, the product was purified by column chromatography with dichloromethane as eluent to give 4.5 g (43.5% yield) of a viscous, colourless oil consisting of two conformers.

Compound **13**. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.7 (2H, qui, J=7 Hz, $CH_2CH_2CH_2$), 2.38 (2H, t, J=7 Hz, CH_2CO) and 2.41 (t, J=7 Hz, CH_2CO, second conformer), 2.8 (3H, s, CH_3) and 2.85 (s, CH_3, second conformer), 4.4–4.5 (1H, brd s, O*H*), 4.5 (2H, s, benzyl) and 4.58 (s, benzyl, second conformer), 3.3–3.5 (2H, m, CH_2OH), 7.12–7.42 (5H, m, arom.) ppm. IR (KBr): 1630 cm^{-1} (C═O-valence).

3.1.6. 4-[Benzyl(methyl)amino]butanoic acid (14) and 14×HCl, respectively. A solution of 11.75 g (50 mmol) of ethyl 4-[benzyl(methyl)amino]butanoate in 50 mL of 2 M hydrochloric acid was heated for 12 h under reflux. The water was removed under reduced pressure and the residue was recrystallized from acetone to give 11.2 g (92% yield) of the hydrochloride of **14**.

Compound **14**×HCl. Mp 173 °C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.8–2.0 (2H, m, $CH_2CH_2CH_2$), 2.24 (2H, t, J=8 Hz, CH_2N), 2.55 (3H, s, NCH_3), 2.98 (2H, t, J=8 Hz, CH_2COOH), 4.22 (2H, s, benzyl),7.2–7.4 (5H, m, arom.) ppm. IR (KBr): 1720 cm^{-1} (C═O-valence). Anal. calcd for $C_{12}H_{17}NO_2$: C, 59.14; H, 7.44; N, 5.75. Found: C, 58.65; H, 7.33; N, 5.80.

The hydrochloride **14**×HCl (10 g, 41 mmol) was dissolved in 10 mL of water, alkalized with saturated $NaHCO_3$-solution to pH=7–8, and the water removed under reduced pressure. The residue is suspended three times with 50 mL of acetone and filtered off. Removal of the solvent yielded 8.1 g (i.e., 95% yield related to the hydrochloride) of a colourless, viscous oil, which did not crystallize.

Compound **14**. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.4–1.9 (2H, m, $CH_2CH_2CH_2$), 2.09 (2H, s, NCH_3), 2.1–2.4 (4H, m, 2×CH_2), 3.47 (2H, s, benzyl),7.31 (5H, m, arom.) ppm. IR (KBr): 1550 cm^{-1} (C═O-valence).

3.1.7. *N*-Benzyl-4-[benzyl(methyl)amino]-*N*-methylbutanamide (15). To a solution of 23.2 mL (180 mmol) of *N*-benzyl-methylamine in 250 mL of diethylether were added under stirring and ice cooling 10 mL (89 mmol) of 4-chlorobutanoyl chloride. Stirring was continued for 1 h at room temperature. The precipitated amine hydrochloride was filtered off, and the filtrate concentrated under reduced pressure. A white solid (*N*-benzyl-4-chloro-*N*-methylbutanamide) was formed (16 g, 80% yield), that was recrystallized from acetone/petrolether (40/60) (1/1) without any further characterization.

A solution of *N*-benzyl-4-chloro-*N*-methylbutanamide (11.3 g, 50 mmol), 13 mL (100 mmol) of *N*-benzyl-methylamine, and 0.1 g of sodium iodide in 100 mL of ethanol was heated under reflux for 12 h. After cooling, the solvent was removed under reduced pressure, the solid dissolved in 100 mL of water. The hydrochloride was dissolved in 100 mL of water, alkalized with saturated $NaHCO_3$-solution and extracted three times with dichloromethane. Dichloromethane is removed under reduced pressure, and the residue

was purified by column chromatography with MeOH/CH_2Cl_2 (1/20) to give a colourless oil (11.6 g, 74% yield related to *N*-benzyl-4-chloro-*N*-methylbutanamide), consisting of two conformation isomers.

Compound **15**. Mp 62–63 °C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.5–2.0 (2H, m, $CH_2CH_2CH_2$), 2.07 (3H, s, amine-CH_3) and 2.13 (s, amine-CH_3, second conformer), 2.2–2.6 (4H, m, $CH_2CH_2CH_2$), 2.82 (3H, s, amide-CH_3) and 2.91 (s, amide-CH_3, second conformer), 3.44 (2H, s, amine-benzyl) and 3.49 (s, amine-benzyl, second conformer), 4.5 (2H, s, amide-benzyl) and 4.58 (s, amide-benzyl, second conformer),7.0–7.4 (10H, m, arom.) ppm. IR (KBr): 1640 cm^{-1} (C═O-valence).

The 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (**2**) necessary for the following reactions can be either obtained out of δ-valerolactone by reaction with oxalyl ester, followed by reaction with diazotized aniline (Japp–Klingemann-reaction),[13] or out of γ-butyrolactone and oxalyl esters, respectively, following hydrolysis and reaction with phenylhydrazones, as described previously.[14]

3.1.8. General procedure for the preparation of N^{β}-disubstituted tryptamines (17a–p) out of 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones (2). A mixture of 10 mmol pyrano-indolone (**2**) and 10–40 mmol of the secondary amine were either heated in an autoclave at 200 °C (as indicated in Table 4, in some cases lower temperatures should be applied to avoid by-product formation). After the respective reaction time (see Table 4), the mixture was allowed to cool to room temperature and the excess amine was removed by distillation under reduced pressure. The resulting brown, viscous residue was dissolved in 250 mL of methanol under warming. The insoluble solids were filtered off, the filtrate was concentrated under reduced pressure, and the residue heated for 10 min with refluxing diethylether. Again, the solids were filtered off. Depending on the water solubility of the remaining amine, the filtrate was either treated according to method a) (hardly and non-water-soluble amines) or method b) (water-soluble amines).

(a) The filtrate was extracted two times with 2 N hydrochloric acid, once with water, and dried over Na_2SO_4. The organic phase was treated with 2% hydrochloric acid in ether until the hydrochloride completely precipitated. The suspension was allowed to stand for 30 min, the ether decanted and the residue dried under reduced pressure at 40 °C. To isolate the free base, the hygroscopic hydrochloride was dissolved in 500 mL of boiling water and the hot solution was filtrated. The filtrate is alkalized with 2 N NaOH aqueous solution and extracted three times with diethylether. The organic phase was washed with water, dried over Na_2SO_4, and the ether evaporated. The solid residue was purified by recrystallization from petrolether (40/60)/diethylether (1/1).

(b) The filtrate was extracted three times with water, and dried over Na_2SO_4. The ether was removed under reduced pressure. The product was purified by recrystallization from petrolether/diethylether (1/1). The respective hydrochloride was obtained by adding 2% HCl solution in diethylether to the above filtrate, and filtering the resulting hydrochloride off. The resulting product was purified by recrystallization from methanol/diethylether (1/1).

3.1.9. *N*-[2-(1*H*-Indol-3-yl)ethyl]-*N*-methyl-*N*-phenylamine (17a). *N*-Methylaniline and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. Beige powder. Mp 140 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.0 (3H, s, NCH_3), 3.08 (2H, t, *J*=7.7 Hz, CH_2CH_2N), 3.72 (2H, t, *J*=7.7 Hz, CH_2CH_2N), 6.7–6.9 (3H, m, $2H_o$, H_p), 7.0 (1H, s, H-2), 7.2–7.5 (5H, m, H-5, H-6, H-7, $2H_m$) ppm. IR (KBr): 3400, 1600, 1500, 1450, 805, 740, 690 cm^{-1}. EI-MS *m*/*z* 250 (M^+). Anal. calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.20; H, 7.12; N, 11.01.

3.1.10. *N*-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]-*N*-methyl-*N*-phenylamine (17b). *N*-Methylaniline and 4,9-dihydro-6-methoxy-pyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. Brown hygroscopic crystals. Mp 88–92 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.8 (2H, m, CH_2CH_2N), 3.1 (3H, s, NCH_3), 3.5–3.8 (5H, m, CH_2CH_2N, OCH_3), 6.7 (1H, dd, *J*=10.7, 1.8 Hz, H-6), 7.0 (1H, d, *J*=1.8 Hz, H-4), 7.1 (1H, d, *J*=1.8 Hz, H-2), 7.24 (1H, d, *J*=10.7 Hz, H-7), 7.3–7.6 (5H, m, arom.), 7.6–7.8 (1H, brd, N^+H), 10.77 (1H, brd, indole-N*H*) ppm. IR (KBr): 3420, 3250, 2500, 1600, 1480, 1215, 690 cm^{-1}. Anal. calcd for $C_{18}H_{21}N_2OCl{\times}1.1H_2O$: C, 64.22; H, 6.95; N, 8.32. Found: C, 64.02; H, 6.94; N, 8.46.

3.1.11. *N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-phenylamine (17c). *N*-Ethylaniline and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. Beige powder. Mp 99–100 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.07 (3H, t, *J*=7.0 Hz, NCH_2CH_3), 2.94 (2H, t, *J*=7.8 Hz, CH_2CH_2N), 3.34 (2H, q, *J*=7.0 Hz, NCH_2CH_3), 3.52 (2H, t, *J*=7.8 Hz, CH_2CH_2N), 6.57 (1H, t, *J*=7.2 Hz, H_p), 6.7 (2H, d, *J*=8.0 Hz, $2H_o$), 6.95–7.28 (5H, m, H-5, H-6, H-2, $2H_m$), 7.39 (1H, d, *J*=7.5 Hz, H-7), 7.57 (1H, d, *J*=7.5 Hz, H-4), 10.9 (1H, brd, indole-N*H*) ppm. ^{13}C NMR (200 MHz, DMSO-d_6) δ 12.25, 22.9, 44.3, 50.83, 111.48, 111.87, 115.01, 118.22, 118.39, 120.99, 122.81, 127.33, 129.26, 136.36, 147.46 ppm. IR (KBr): 3380, 1580, 1500, 1450, 1350, 740, 690 cm^{-1}. Anal. calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.59; H, 7.56; N, 10.33.

3.1.12. *N*-Benzyl-*N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylamine (17d). *N*-Benzyl-methylamine and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method b*. The free base was purified by column chromatography with diethylether as eluent, and the product was treated with 2% hydrochloric acid in ether until the hydrochloride completely precipitated. The suspension was allowed to stand for 30 min, the ether decanted and the residue dried under reduced pressure at 40 °C. Brown crystals. Mp 92–95 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.7 (3H, d, *J*=5.0 Hz, NCH_3), 3.1–3.3 (4H, m, CH_2CH_2), 4.2–4.5 (2H, m, benzyl), 6.9–7.1 (2H, m, H-5, H-6), 7.2 (1H, d, *J*=2.5 Hz, H-2), 7.3–7.7 (7H, m, H-7, H-4, arom.), 10.98 (1H, brd, indole-N*H*), 11.17 (1H, brd, N^+H) ppm. IR (KBr): 3200, 2550, 1620, 1450, 740, 700 cm^{-1}. Anal. calcd for $C_{18}H_{21}N_2Cl{\times}0.5H_2O$: C, 69.78; H, 7.10; N, 9.04. Found: C, 69.89; H, 7.36; N, 8.92.

3.1.13. 3-[2-(2,3-Dihydro-1*H*-indol-1-yl)ethyl]-1*H*-indole (17e). Indoline and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one

as starting materials. *Method a*. Brown powder. Mp 126–128 °C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 2.7–3.1 (4H, m, $CH_2CH_2NCH_2CH_2$), 3.2–3.6 (4H, m, CH_2NCH_2), 6.4–6.7 (2H, t, J=7 Hz, H-5′, H-6′), 6.9–7.3 (5H, m, H-5, H-6, H-2, H-4′, H-7′), 7.38 (1H, dd, J=5.6, 2.6 Hz, H-7), 7.53 (1H, dd, J=5.6, 2.6 Hz, H-4), 10.85 (1H, brd, indole-N*H*) ppm. IR (KBr): 3400, 1605, 1485, 1450, 740 cm^{-1}. Anal. calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.25; H, 6.95; N, 10.62.

3.1.14. 1-[2-(1*H*-Indol-3-yl)ethyl]-1,2,3,4-tetrahydroquinoline (17f). 1,2,3,4-Tetrahydroquinoline and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. Peachy powder. Mp 148–149 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.81 (2H, qui, J=6 Hz, CH_2CH_2-CH_2N), 2.65 (2H, t, J=6 Hz, $CH_2CH_2CH_2$), 2.9 (2H, dd, J=10, 5.5 Hz, CH_2CH_2N), 3.25 (2H, t, J=6 Hz, CH_2CH_2-CH_2N), 3.49 (2H, dd, J=10, 5.5 Hz, CH_2CH_2N), 6.45 (1H, t, J=7.5 Hz, H-6′), 6.65 (1H, d, J=8 Hz, H-8′), 6.85 (1H, d, J=7.5 Hz, H-5′), 6.9–7.13 (3H, m, H-5, H-6, H-7′), 7.2 (1H, d, J=2.4 Hz, H-2), 7.34 (1H, d, J=7.5 Hz, H-7), (1H, d, J=7.5 Hz, H-4), 10.85 (1H, brd, indole-N*H*) ppm. IR (KBr): 3400, 1600, 1490, 1450, 740 cm^{-1}. Anal. calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.83; H, 7.30; N, 10.01.

3.1.15. 3-[2-(4-Methylpiperazin-1-yl)ethyl]-1*H*-indole (17g). 1-Phenylpiperazine and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. White-beige powder. Mp 130–132 °C (lit.[15] mp 132–134 °C). ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.0–3.5 [8H, m, $N(CH_2CH_2)_2N$], 3.6–3.7 (2H, m, NCH_2CH_2), 3.7–3.9 (2H, m, CH_2N), 6.85 (1H, t, J=6.5 Hz, H-5), 6.95–7.05 (3H, m, 2H$_o$, H$_p$), 7.1 (1H, t, J=6.5 Hz, H-6), 7.2–7.3 (3H, m, H-2, 2H$_m$), 7.35 (1H, t, J=6.5 Hz, H-7), 7.55 (1H, t, J=6.5 Hz, H-4), 11 (1H, brd, indole-N*H*), 11.4 (1H, brd, N^+H) ppm. IR (KBr): 3400, 1600, 1490, 1450, 740 cm^{-1}.

3.1.16. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylamine (17h). *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methylamine and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. Brown, hygroscopic crystals. Mp 88–90 °C. ^{1}H NMR (200 MHz, DMSO-d_6/D_2O) δ 2.7–2.96 (2H, m, dimethoxyphenyl-CH_2CH_2N), 2.88 (3H, s, NCH_3), 3.05 (2H, m, indole-CH_2CH_2N), 3.15–3.45 (4H, m, $CH_2N(CH_3)CH_2$), 3.6–3.8 (9H, s, s, s, 3×CH_3), 6.55–6.9 (4H, m, H-6, 3H$_{arom.}$), 7.04 (1H, d, J=2 Hz, H-4), 7.16 (1H, s H-2), 7.26 (1H, d, J=9 Hz, H-7), 10.65 (1H, brd, indole-N*H*) ppm. IR (KBr): 1620, 1580, 1510, 1480, 1210, 1020, 800 cm^{-1}. Anal. calcd for $C_{22}H_{29}N_2O_3Cl$×0.5H_2O: C, 63.83; H, 7.31; N, 6.77. Found: C, 63.53; H, 7.46; N, 7.05.

3.1.17. 1-({1-[2-(1*H*-Indol-3-yl)ethyl]piperidin-4-yl}methyl)-1,3-dihydro-2*H*-benzimidazol-2-one (17i). 1-Piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. White powder. Mp 249–250 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.65 (2H, d, J=12 Hz, piperidine-CH_2CH_2N), 2.13 (2H, t, J=12 Hz, piperidine-CH_2CH_2N), 2.35 (2H, t, J=12 Hz, piperidine-CH_2CH_2N), 2.64 (2H, t, J=8 Hz, NCH_2CH_2), 2.88 (2H, t, J=8 Hz, NCH_2CH_2), 3.12 (2H, d, J=12 Hz, piperidine-CH_2CH_2N), 4.16 (1H, m, piperidine-C*H*), 6.9–7.1 (5H, m, H-5, 4H$_{arom.}$), 7.1–7.26 (2H, m, H-6, H-2), 7.34 (1H, d, J=7 Hz, H-7), 7.52 (1H, d, J=8.5 Hz, H-4), 10.78 (1H, brd, indole-N*H*), 10.86 (1H, brd, amide-N*H*) ppm. IR (KBr): 1690, 1470, 1370, 1100, 730, 690 cm^{-1}. Anal. calcd for $C_{22}H_{24}N_4O$×0.5H_2O: C, 71.52; H, 6.82; N, 15.17. Found: C, 71.73; H, 6.88; N, 14.88.

3.1.18. 1-({1-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]piperidin-4-yl}methyl)-1,3-dihydro-2*H*-benzimidazol-2-one (17k). 1-Piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one and 4,9-dihydro-6-methoxy-pyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. White powder. Mp 249–220 °C. ^{1}H NMR (200 MHz, CD_2Cl_2) δ 1.85 (2H, d, J=12 Hz, piperidine-CH_2CH_2N), 2.25 (2H, t, J=12 Hz, piperidine-CH_2CH_2N), 2.50 (2H, q, J=12 Hz, piperidine-CH_2CH_2N), 2.72 (2H, m, NCH_2CH_2), 2.93 (2H, m, NCH_2CH_2), 3.20 (2H, d, J=12 Hz, piperidine-CH_2CH_2N), 3.86 (3H, s, OCH_3), 4.30 (1H, m, piperidine-C*H*), 6.8 (1H, dd, J=9, 3 Hz, H-6), 7.0–7.18 (5H, m, H-4, 4H$_{arom.}$), 7.2–7.3 (2H, s, d, J=9 Hz, H-2, H-7), 8.08 (1H, brd, indole-N*H*), 9.02 (1H, brd, amide-N*H*) ppm. IR (KBr): 1690, 1480, 1370, 1210, 690 cm^{-1}. Anal. calcd for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.26; H, 6.97; N, 14.10.

3.1.19. 4-Anilino-1-[2-(1*H*-indol-3-yl)ethyl]piperidine-4-carboxamide (17l). 4-Anilinopiperidine-4-carboxamide and 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method a*. Yellow powder. Mp 127 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 (2H, d, J=13 Hz, 2×1H-piperidine-CH_2CH_2N), 2.1–2.5 (4H, m, 2H-piperidine-CH_2CH_2N, 2×1H-piperidine-CH_2CH_2N), 2.65 (2H, t, J=8.5 Hz, CH_2CH_2N), 2.8–3.0 (4H, m, CH_2N, 2×1H-piperidine-NCH_2CH_2), 4.05 (1H, brd, N*H*), 5.42 (2H, brd, CO–NH_2), 6.64 (2H, d, J=7.8 Hz, 2H$_o$), 6.75–6.95 (2H, m, H-5, H$_p$), 7.0–7.25 (4H, m, H-6, H-2, 2H$_m$), 7.35 (1H, d, J=8.3 Hz, H-7), 7.58 (1H, d, J=8.3 Hz, H-4), 8.02 (1H, brd, indole-N*H*) ppm. IR (KBr): 1670, 1600, 1500, 740, 690 cm^{-1}.

3.1.20. 4-Anilino-1-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-piperidine-4-carboxamide (17m). 4-Anilinopiperidine-4-carboxamide and 9-dihydro-6-methoxy-pyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method b*. White powder. Mp 159 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 (2H, d, J=13 Hz, 2×1H-piperidine-CH_2CH_2N), 2.1–2.5 (4H, m, 2H-piperidine-CH_2CH_2N, 2×1H-piperidine-CH_2CH_2N), 2.65 (2H, t, J=8.5 Hz, CH_2CH_2N), 2.8–3.0 (4H, m, CH_2N, 2×1H-piperidine-NCH_2CH_2), 3.84 (3H, s, OCH_3), 4.05 (1H, brd, N*H*), 5.42 (2H, brd, CO–NH_2), 6.64 (2H, d, J=7.8 Hz, 2H$_o$), 6.75–6.95 (2H, m, H-6, H$_p$), 7.0–7.05 (2H, s, s, H-2, H-4), 7.1–7.25 (3H, m, H-7, 2H$_m$), 8.02 (1H, brd, indole-N*H*) ppm. IR (KBr): 3400, 1670, 1600, 800, 690 cm^{-1}. EI-MS *m*/*z* 392 (M^+).

3.1.21. 3-[2-(4-Methylpiperidin-1-yl)ethyl]-1*H*-indole (17n). 4-Methylpiperidine and 9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method b*. White powder. Mp 108 °C (lit.[16] Mp 110 °C). ^{1}H NMR (90 MHz, DMSO-d_6) δ 0.9 (3H, s, CH_3), 1.0–2.7 (9H, m, piperidine-H), 2.8–3.0 (4H, m, CH_2CH_2N), 6.9–7.1 (2H, m, H-5, H-6), 7.2 (1H, d, J=1.8 Hz, H-2), 7.35 (1H, dd, J=7.2, 2 Hz, H-7), 7.62 (1H, dd, J=7.2, 2 Hz, H-4), 11.0 (1H, brd,

indole-N*H*) ppm. IR (KBr): 3400, 3120, 2920, 1625, 1450, 740 cm^{-1}. All the other spectroscopic data were identical with reported data in Ref. 16.

3.1.22. 5-Methoxy-3-[2-(4-methylpiperidin-1-yl)ethyl]-1*H*-indole (17o). 4-Methylpiperidine and 9-dihydro-6-methoxy-pyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method b*. Yellow, hygroscopic crystals. Mp 207–209 °C. ^{1}H NMR (200 MHz, D_2O) δ0.96 (3H, d, J=7 Hz, CH_3), 1.39 (2H, t, J=12 Hz, CHCH_2), 1.62 (1H, m, C*H*), 1.9 (2H, d, J=14 Hz, CHCH_2), 2.86 (2H, t, J=14 Hz, piperidine-N–CH_2), 3.1 (2H, m, CH_2CH_2N), 3.25 (2H, m, CH_2CH_2N), 3.52 (2H, d, J=12 Hz, piperidine-N–CH_2), 3.86 (3H, s, OCH_3), 6.9 (1H, dd, J=9.5, 2.4 Hz, H-6), 7.12 (1H, d, J=2.4 Hz, H-4), 7.22 (1H, s, H-2), 7.43 (1H, d, J=9.5 Hz, H-7) ppm. IR (KBr): 3250, 2930, 2650, 1485, 1450, 1220, 800, 640 cm^{-1}. Anal. calcd for $C_{17}H_{25}N_2OCl\times0.3H_2O$: C, 64.97; H, 8.21; N, 8.92. Found: C, 64.84; H, 8.39; N, 8.79.

3.1.23. *N*,*N*-Diethyl-*N*-[2-(1*H*-indol-3-yl)ethyl]amine (17p). Diethylamine and 9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one as starting materials. *Method b*. White powder. Mp 171 °C (lit.[17] mp 168–169 °C). ^{1}H NMR (90 MHz, D_2O) δ 1.28 (6H, t, J=7.3 Hz, 2×CH_3), 3.0–3.5 (8H, m, CH_2CH_2, 2×NCH_2), 7.1–7.4 (3H, m, H-5, H-6, H-2), 7.5–7.8 (2H, m, H-7, H-4) ppm. IR (KBr): 3200, 2640, 1450, 1430, 745, 700 cm^{-1}. All the other spectroscopic data were identical with reported data in Ref. 17.

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