Synthesis of substituted tryptamines and their homologs: a new aspect in the Fischer reaction

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A number of cyclic imines and amino ketones were studied as the starting material for indole synthesis. Amino ketone arylhydrazones are key intermediates undergoing the Fischer rearrangement; the possibility of the reaction is determined by the structure of an amino carbonyl compound. A convenient one-step method for the synthesis of indolylalkylamines allowed tryptamines and their homologs to be obtained in high yields.

Key words: amino ketones, cyclic imines, Fischer reaction, indoles, tryptamines.

Indolylalkylamines form the basis for many indole alkaloids, which are biologically active substances and drugs.[1] 2-Substituted 3-aminoalkylindoles attract much attention because they are highly selective with respect to serotonin[2] and melatonin[3] receptors and receptors controlling the secretion of gonadotropin.[4]

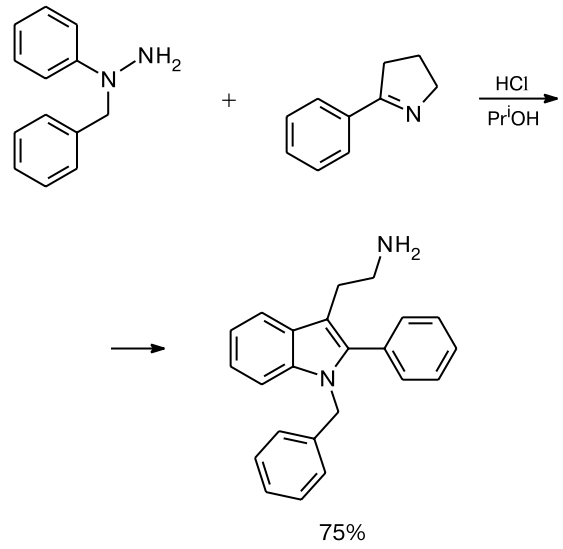
There are three general approaches to the synthesis of 2-substituted 3-aminoalkylindoles. The first approach is that an aminoalkyl fragment is introduced into the indole ring.[5] According to the second approach, substituents in the indole system are modified into the aminoalkyl fragment[6] or a desired group in position 2.[7] The third approach involves simultaneous creation of an aminoalkyl fragment and the indole ring and thus is preferred.

This approach can be effected by the Fischer,[8—12] Grandberg,[13,14] and Japp—Klingemann reactions.[15] The latter is restricted to the synthesis of 3-aminoalkylindole-2-carboxylic acids. It was found[13,16] that 3-aminoalkyl-2-arylindoles cannot be obtained by the Grandberg reaction. The Fischer reaction is usually used in the synthesis of 2-unsubstituted 3-aminoalkylindoles from amino aldehydes,[17] which are unstable and should be protected before use.

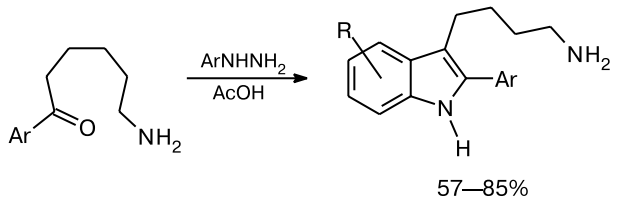
An analysis of the literature data showed that the synthetic potential of substituted cyclic imines and especially amino ketones in the Fischer reaction had not been studied systematically. 2-Phenylpyrroline is known[18] to react with 1-benzyl-1-phenylhydrazine to give the corresponding indole (Scheme 1). We found that phenylhydrazine $PhNHNH_2$ does not enter into the Fischer reaction under these conditions.

Recently, we developed a new approach to the synthesis of 2-substituted 3-aminoalkylindoles that involves reactions of arylhydrazines with amino ketones (Scheme 2).

Scheme 1



Scheme 2



R = H, Hal, Alk, OAlk

Application of this approach (earlier, no aliphatic amino ketones were employed in the Fischer reaction) allowed substituted dihomotryptamines to be obtained in

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one step from accessible 6-aminohexanones in high yields.[19]

To determine the area of application of this method for the synthesis of substituted tryptamines, we studied in the present work the effect of the nature of the amino carbonyl compound (the character of the substituent and the length of the aminoalkyl fragment) on the pathway of the Fischer reaction. For this purpose, we prepared a number of cyclic imines and amino ketones. The syntheses of the starting reagents, namely, 6-aminohexanones,[19] five-membered cyclic imines,[20] and 3-acyllactams,[21] were described by us earlier; six- and seven-membered imines were prepared according to the published procedure.[22]

The Fischer indole synthesis involves the formation of arylhydrazones of carbonyl compounds followed by their rearrangements.[11,12] All the amino ketones and cyclic imines obtained smoothly react with salts of various arylhydrazines to give amino ketone hydrazones in virtually quantitative yields, regardless of the substituents in the starting reagents. The reaction was found to occur in water, alcohols, and weakly acidic solutions of mineral and organic acids (Scheme 3). Hydrazones **1** and **2** were isolated and characterized.

The purity and yields of the products did not depend on whether the Fischer reaction is carried out with prepared hydrazones (Scheme 4) or as part of a "*one-pot*" process. Using model systems (R = Ph and 3-Py; n = 1, 2, and 3), we varied temperatures and catalysts used for rearrangement of arylhydrazones. It turned out that the reaction pathway is only slightly affected by variations of catalysts, solvents, and temperatures; the use of 5 *M* HCl, solutions of HCl in AcOH, and AcOH alone was found to be optimal, depending on the nature of the cyclic imine or amino ketone (Table 1). However, under these conditions, aminoalkylindoles **3** and **8** could not be obtained.

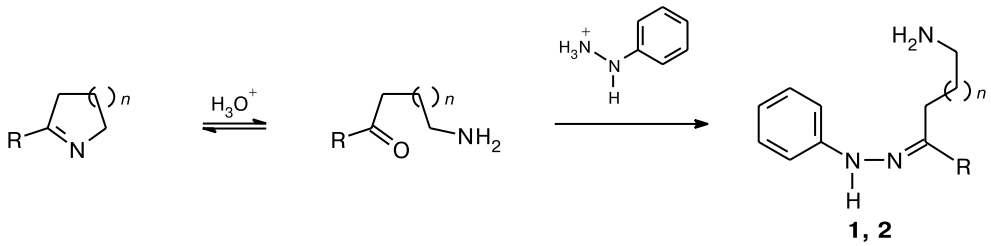
Table 1. Synthesis of 2-substituted 3-aminoalkylindoles

Product	n	R	Yield (%)
3	1	Ph	0[a–c]
4	1	2-Py	94[a]
5	1	3-Py	79[a]
6	1	4-Py	97[a]
7	1	3-Quinolinyl	73[a]
8	2	Ph	0[a–c]
9	2	3-Py	80[a]
10	3	Ph	85[c]
11	3	3-MeC_6H_4	65[b]
12	3	3,4-$Cl_2C_6H_3$	77[b]
13	3	3-$MeOC_6H_4$	57[b]
14	3	4-ClC_6H_4	72[b]
15	3	4-BrC_6H_4	62[b]
16	3	2-Py	87[c]
17	3	3-Py	88[c]
18	3	4-Py	82[c]
19	3	2-Thienyl	82[b]

[a] 5 *M* HCl, refluxing, removal of H_2O/HCl.
[b] AcOH, HCl, refluxing.
[c] AcOH, refluxing.

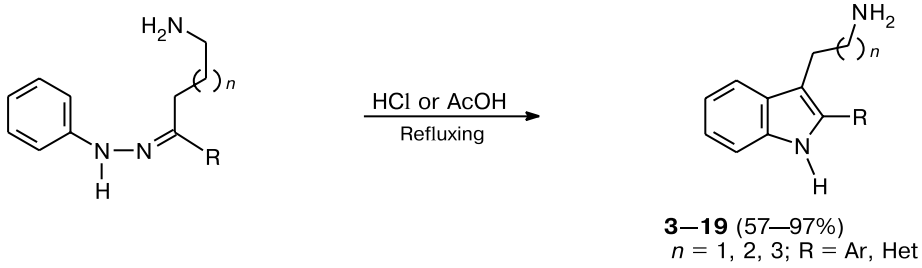
These experiments revealed that the possibility of the Fischer rearrangement is dictated by the length of the

Scheme 3



1: R = Ph, n = 1, 95%; **2:** R = 3-Py, n = 1, 97%

Scheme 4



aminoalkyl fragment and the nature of the substituent in amino ketone arylhydrazones. In the case of arylhydrazones prepared from seven-membered cyclic imines or aminohexanones, the Fischer rearrangement is independent of the nature of the substituent in the carbonyl compound; however, arylhydrazones prepared from five- and six-membered cyclic imines containing no pyridine ring did not enter into the Fischer reaction under these conditions.

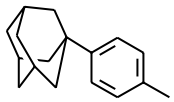
To compare the effects of the phenyl and 3-pyridyl substituents in aminohexanones and the substituents in arylhydrazines on the yields of indoles, various arylhydrazines were synthesized[23] and used in the Fischer reaction (Scheme 5, Table 2).

It was found that the nature of the substituent in aminohexanones does not affect the possibility of the Fischer reaction; the reaction is high-yielding in nearly all the cases. Even from arylhydrazines with strong electron-withdrawing substituents (2,4-difluoro- and 2,4-dichlorophenylhydrazines), the yields exceeded 50 and 60%, respectively. The reactions with these hydrazines should be carried out in AcOH—HCl (9 : 1, v/v); otherwise, the yields of the products are very low. 4-Nitro-2-trifluoromethyl- and 2-methyl-5-nitrophenylhydrazines and 5-trifluoromethyl-2-pyridylhydrazine were not converted into the corresponding indoles. It should be noted that we obtained the first representative of indolylalkylamines with the adamantyl substituent (compound **25**) in 86% yield.

High yields were also attained in the reactions with 1,1-disubstituted arylhydrazines (Scheme 6).

We assumed that the dependence of the Fischer reaction on the length of the aminoalkyl fragment and the nature of the substituents in amino ketone arylhydrazones is associated with differences in their behavior: in an acidic medium under the conditions of the Fischer reaction, arylhydrazones can either undergo the rearrangement into indoles or be hydrolyzed into the starting arylhydrazines and amino ketones (or cyclic imines).

Table 2. Synthesis of 2-substituted dihomotryptamines

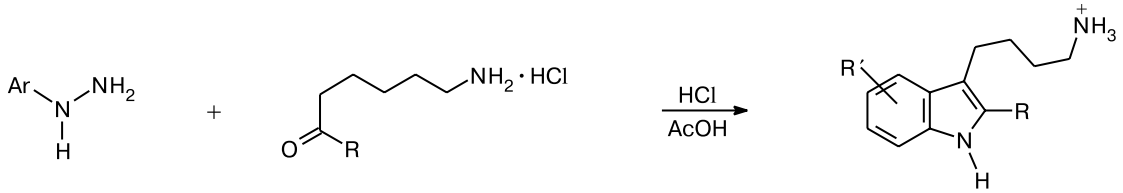
Product	Ar	R	R´	Yield (%)
20	4-BrC_6H_4	Ph	5-Br	78
21	4-$MeOC_6H_4$	Ph	5-MeO	80
22	3,5-$Me_2C_6H_3$	Ph	4,6-Me_2	84
23	2,4-$F_2C_6H_3$	Ph	5,7-F_2	57*
24	4-BuC_6H_3	Ph	5-Bu	85
25		3-Py	5-(1-Ad)	86
26	4-$BnOC_6H_4$	3-Py	5-BnO	75
27	2,4-$Cl_2C_6H_3$	3-Py	5,7-Cl_2	66*

* The mixture AcOH—HCl (9 : 1, v/v) should be used.

An analysis of the literature data showed that the five-membered pyridyl-containing cyclic imine exists in acidic solutions mainly as an amino ketone:[24] at pH <3, the content of the cyclic imine is vanishingly low because of its hydrolysis to a stable (under these conditions) amino ketone; for the phenyl analog, the cyclic form is dominant even at low pH values.

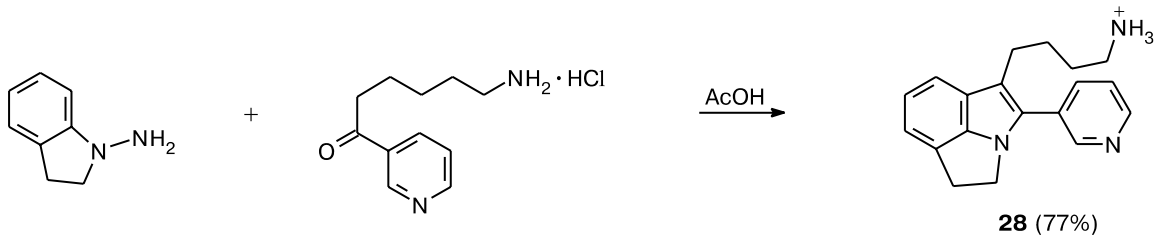
Apparently, under the conditions of the Fischer reaction, arylhydrazones containing the pyridine ring are

Scheme 5



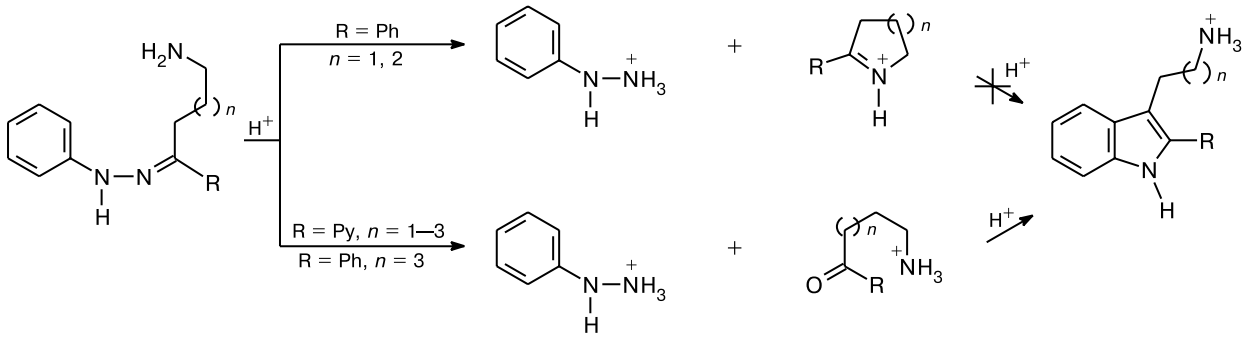
20—27

Scheme 6

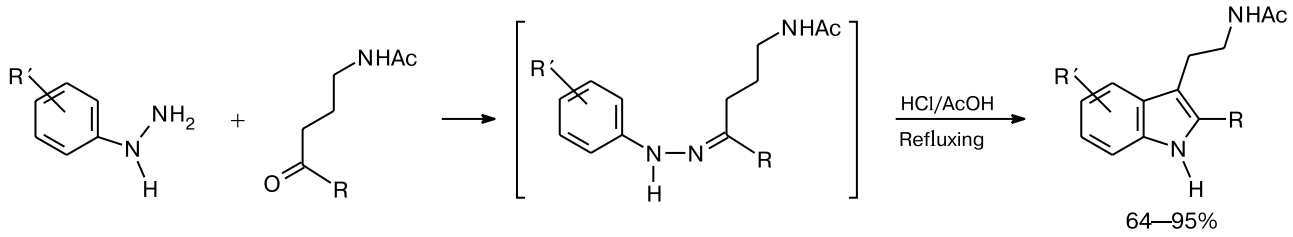


28 (77%)

Scheme 7



Scheme 8



R = Ar, Het

hydrolyzed to arylhydrazine and amino ketone, which are capable of reacting again in acidic media to give hydrazone with its subsequent rearrangement into indole (Scheme 7).

In the case of arylhydrazone **1** containing the phenyl substituent, its decomposition in an acidic medium leads to the protonated forms of phenylhydrazine and the cyclic imine. Apparently, their reaction leading to the starting arylhydrazone is strongly impeded by the Coulomb repulsion (see Scheme 7). For the same reason, the pyridine amino ketone undergoes no cyclization in an acidic medium since this should produce a dication with two close positively charged centers (the protonated pyridine ring and the imine N atom).

Arylhydrazones prepared from aminohexanones or seven-membered cyclic imines decompose into stable aminohexanones, which undergo no cyclization in an acidic medium (regardless of the presence of the phenyl or pyridine substituent) and enter into the Fischer reaction.

We assumed that the cyclization of amino ketones into imines and the decomposition of their arylhydrazones can be prevented by introduction of an electron-withdrawing substituent, which makes the terminal aliphatic N atom less nucleophilic. Indeed, we found[20] that amido ketones (synthesized from five-membered cyclic imines) easily enter into the Fischer reaction. With HCl in AcOH as a catalyst, the yields of the corresponding melatonin derivatives were from good to almost quantitative (Scheme 8). On the whole, there are no limitations on the structure of the amido ketone or arylhydrazine used in this reaction.

Thus, we discovered a new aspect of the Fischer reaction: the nature of the substituent and the length of the aminoalkyl fragment at the carbonyl C atom are decisive for the rearrangement of amino ketone arylhydrazones. The use of cyclic imines and amino ketones (including N-protected amino ketones) allowed us to develop a new versatile method for the synthesis of indolylalkylamines containing substituents not only in the benzene ring of the indole system but also in the pyrrole ring.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 with Me_4Si as the internal standard. Chemical shifts are given to within 0.01 ppm. TLC analysis was performed on Silufol UV-254 plates (spots were visualized with an acidified solution of $KMnO_4$, with a solution of ninhydrin in chloroform, with the iodine vapor, and under UV light). Arylhydrazines were synthesized by reduction of diazonium salts (prepared from the corresponding commercial anilines ("Aldrich", "Acros") and 1-(4-aminophenyl)adamantane[25]) with $SnCl_2$.[23a] 2-Hydrazino-5-trifluoromethylpyridine was prepared from 2-chloro-5-trifluoromethylpyridine.[23b]

Synthesis of arylhydrazones from amino carbonyl compounds (general procedure). Arylhydrazine hydrochloride (10 mmol) was mixed with amino ketone or cyclic imine hydrochloride (10 mmol) in water (3 mL). The mixture was heated to boiling and cooled in a refrigerator for 30 min. The precipitate of hydrazone hydrochloride was filtered off, repeatedly washed with ether, and dried.

4-Amino-1-phenylbutan-1-one phenylhydrazone hydrochloride (1). The yield was 95%, m.p. 172 °C. Found (%): C, 66.68; H, 7.15. $C_{16}H_{20}ClN_3$. Calculated (%): C, 66.31; H, 6.96. ^{1}H NMR, δ: 1.76—1.86 (m, 2 H, CH_2—C<u>H</u>$_2$—CH_2—NH_3^+); 2.95—2.99 (m, 4 H, C<u>H</u>$_2$—CH_2—C<u>H</u>$_2$—NH_3^+); 6.75 (t, 1 H, $H_{Ar}(4)$, ^3J = 7.6 Hz); 7.18—7.83 (m, 9 H, H_{Ar}); 8.23 (br.s, 3 H, NH_3^+); 9.79 (br.s, 1 H, NH). ^{13}C NMR, δ: 22.6, 23.5, 38.6 (CH_2—CH_2—CH_2—NH_3^+); 112.7 ($C_{Ar}(2)$, $C_{Ar}(6)$); 118.8 ($C_{Ar}NH(4)$); 125.1 (C_{Ar}—C=N(3), C_{Ar}—C=N(5)); 127.4 ($C_{Ar}NH(3)$, $C_{Ar}NH(5)$); 128.3 ($C_{Ar}C$=N(2), $C_{Ar}C$=N(6)); 128.8 ($C_{Ar}C$=N(4)); 138.0 ($C_{Ar}(1)$); 141.8 ($C_{Ar}C$—NH(1)); 146.0 (Ph—NH—N=C).

4-Amino-1-(3-pyridyl)butan-1-one phenylhydrazone hydrochloride (2). The yield was 97%, m.p. 201 °C (*cf.* Ref. 26: m.p. 201.5 °C). Found (%): C, 66.74; H, 6.81. $C_{15}H_{19}ClN_4$. Calculated (%): C, 66.96; H, 6.59. ^{1}H NMR, δ: 1.74—1.86 (m, 2 H, CH_2—C<u>H</u>$_2$—CH_2—NH_3^+); 2.92—3.05 (m, 4 H, C<u>H</u>$_2$—CH_2—C<u>H</u>$_2$—NH_3^+); 6.77 (t, 1 H, $H_{Ar}(4)$, ^3J = 7.0 Hz); 7.22 (t, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, ^3J = 7.0 Hz); 7.37 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, ^3J = 7.0 Hz); 7.41 (m, 1 H, H_{Ar}(Py-5)); 8.12—8.23 (m, 4 H, Py-4 and NH_3^+); 8.48 (m, 1 H, H_{Ar}(Py-2)); 9.00 (m, 1 H, H_{Ar}(Py-6)); 9.95 (br.s, 1 H, NH). ^{13}C NMR, δ: 22.6, 23.4, 38.8 (CH_2—CH_2—CH_2—NH_3^+); 113.7 ($C_{Ar}(2)$, $C_{Ar}(6)$); 120.0 ($C_{Ar}(4)$); 124.3 (C_{Ar}(Py-2)); 129.6 ($C_{Ar}(3)$, $C_{Ar}(5)$); 133.3 (C_{Ar}(Py-4)); 134.4 ($C_{Ar}(1)$); 140.2 (C_{Ar}(Py-3)); 146.5 (Ph—NH—N=C); 147.1 (C_{Ar}(Py-2)); 148.7 (C_{Ar}(Py-6)).

Synthesis of indolylalkylamines 4—28. ***A.*** A two-neck 250-mL flask fitted with a Würtz adapter, a reflux condenser, and a dropping funnel was charged with an arylhydrazine or its salt (10 mmol), amino ketone or cyclic imine hydrochloride (10 mmol), and 5 *M* HCl (20 mL). The mixture was heated in an air bath until a viscous mass formed, its drying being not allowed. Then 5 *M* HCl (40 mL) was slowly added through the dropping funnel at such a rate that the reaction mixture remained equally viscous throughout the reaction (monitoring by TLC with MeCN—25% NH_3 (100 : 5) as the eluent).

B. An arylhydrazine salt (10 mmol) was mixed with amino ketone or cyclic imine hydrochloride (10 mmol) in glacial acetic acid (15 mL), conc. HCl (1.5 mL) was added, and the mixture was refluxed to the completion of the reaction (monitoring by TLC with MeCN—25% NH_3 (100 : 5) as the eluent).

C. An arylhydrazine salt (10 mmol) was mixed with amino ketone or cyclic imine hydrochloride (10 mmol) in glacial acetic acid (15 mL) and the mixture was refluxed to the completion of the reaction (monitoring by TLC with MeCN—25% NH_3 (100 : 5) as the eluent). The reaction products were isolated as follows: the mixture was evaporated to dryness, diluted with water (10 mL), concentrated again, recrystallized from ethanol (1 mL)—water (4 mL), and washed with methanol—ether (1 : 10, 2×5 mL) to give dihomotryptamine hydrochlorides. If the hydrochlorides were well soluble in water, oxalate were obtained instead: after the reaction was completed, the reaction mixture was evaporated to dryness, dissolved in water (15 mL), and alkalified with 50% KOH to pH 10. The product was extracted with CH_2Cl_2 (2×20 mL) and the combined extracts were washed with warm water (2×40 mL), dried with Na_2SO_4, concentrated, and dissolved in methanol (5 mL). A solution of oxalic acid dihydrate (1 equiv. in hot methanol (5 mL)) was added. If the precipitate did not form within 5 min, the solution was heated to boiling and concentrated by half. The mixture was cooled to room temperature; after 20 min, ether (30 mL) was added and the precipitate was filtered off, washed successively with acetone (15 mL), ether—methanol (9 : 1, 2×10 mL), and ether, and dried to give indolylalkylammonium oxalates.

^{1}H and ^{13}C NMR data for compounds **4—28** are given in Tables 3 and 4, respectively.

2-[2-(2-Pyridyl)-1*H*-indol-3-yl]ethyl-1-amine oxalate monohydrate (4). The yield was 94% (method ***A***), m.p. 166—167 °C. Found (%): C, 59.32; H, 5.65. $C_{17}H_{19}N_3O_5$. Calculated (%): C, 59.12; H, 5.55.

2-[2-(3-Pyridyl)-1*H*-indol-3-yl]ethyl-1-amine oxalate monohydrate (5). The yield was 79% (***A***), m.p. 232 °C. Found (%): C, 59.39; H, 5.87. $C_{17}H_{19}N_3O_5$. Calculated (%): C, 59.12; H, 5.55.

2-[2-(4-Pyridyl)-1*H*-indol-3-yl]ethyl-1-amine oxalate (6). The yield was 97% (***A***), m.p. 244—245 °C. Found (%): C, 62.61; H, 5.11. $C_{17}H_{17}N_3O_4$. Calculated (%): C, 62.38; H, 5.23.

2-[2-(3-Quinolinyl)-1*H*-indol-3-yl]ethyl-1-amine oxalate monohydrate (7). The yield was 73% (***A***), m.p. 255—256 °C.

Table 3. ^{1}H NMR spectra (DMSO-d_6, δ, *J*/Hz) of compounds **4—7** and **9—28**

Compound	CH_2—$(CH_2)_n$—CH_2 (n = 0, 1, 2)	Ar	NH_3^+ (br.s, 3 H)	NH (1 H, indole)
4	3.10—3.41 (m, 4 H)	7.05—8.69 (m, 8 H)	8.10	11.55
5	3.04—3.18 (m, 4 H)	7.05—8.86 (m, 8 H)	8.16	11.51
6	3.03—3.26 (m, 4 H)	7.07—7.68 (m, 6 H); 8.68 (d, 2 H, J = 4.0)	8.15	11.60
7	3.06—3.28 (m, 4 H)	7.05—8.58 (m, 10 H)	9.20	11.65
9	1.88—1.96 (m, 2 H); 2.85—2.93 (m, 4 H)	7.02—8.88 (m, 8 H)	7.98	11.41
10	1.60—1.71 (m, 4 H); 2.75 (t, 2 H, C<u>H</u>$_2$—CH_2—CH_2—CH_2—NH_3^+, J = 7.0); 2.85 (t, 2 H, —CH_2—CH_2—CH_2—C<u>H</u>$_2$—NH_3^+, J = 7.0)	6.95—7.65 (m, 9 H)	7.94	11.21

(*to be continued*)

Table 3 (*continued*)

Compound	$CH_2-(CH_2)_n-CH_2$ (n = 0, 1, 2)	Ar	NH_3^+ (br.s, 3 H)	NH (1 H, indole)
11	1.53—1.80 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.40 (s, 3 H, Me); 2.71—2.92 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.91—7.74 (m, 8 H)	7.42	11.14
12	1.57—1.71 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.77 (t, 2 H, $C\underline{H}_2-CH_2-CH_2-CH_2-NH_3^+$, J = 7.0); 2.87 (t, 2 H, $-CH_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$, J = 7.0)	7.01—8.29 (m, 7 H)	7.54	11.30
13	1.61—1.79 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.69—2.91 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$); 3.83 (s, 3 H, MeO)	6.88—7.61 (m, 8 H)	7.44	11.22
14	1.51—1.70 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.73—2.86 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.99—7.66 (m, 8 H)	7.54	11.21
15	1.62—1.70 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.73—2.85 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.72—7.75 (m, 8 H)	6.94	11.23
16	1.62—1.76 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.75—3.23 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.95—7.70 (m, 8 H)	7.90	11.37
17	1.55—1.75 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.77 (t, 2 H, $C\underline{H}_2-CH_2-CH_2-CH_2-NH_3^+$, J = 6.7); 2.85 (t, 2 H, $-CH_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$, J = 7.3)	7.01—8.84 (m, 8 H)	7.93	11.36
18	1.41—1.48 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.72—2.81 (m, 4 H, $C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.81 (m, 1 H); 7.26 (m, 2 H); 7.31—8.62 (m, 5 H)	7.98	9.84
19	1.62—1.71 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.73—2.94 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.97—7.62 (m, 7 H)	7.89	11.31
20	1.57—1.71 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.72—2.85 (m, 4 H, $C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	7.15—7.97 (m, 8 H)	7.92	11.48
21	1.57—1.72 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.75 (t, 2 H, $C\underline{H}_2-CH_2-CH_2-CH_2-NH_3^+$, J = 7.0); 2.85 (t, 2 H, $-CH_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$, J = 7.0; 3.79 (s, 3 H, MeO)	6.71—7.62 (m, 8 H)	7.96	11.04
22	1.57—1.67 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.32 (s, 3 H, 6-Me); 2.60 (s, 3 H, 4-Me); 2.71—2.77 (m, 2 H, $C\underline{H}_2-CH_2-CH_2-CH_2-NH_3^+$); 2.81—2.87 (m, 2 H, $CH_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.56, 6.97 (both s, 1 H each); 7.34—7.56 (m, 5 H)	8.02	10.99
23	1.55—1.75 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.72—2.85 (m, 4 H, $C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.93 (t, 1 H, $H_{Ar}(6)$, $J_{H,F}$ = 9.0); 7.23 (d, 1 H, $H_{Ar}(4)$, $J_{H,F}$ = 8.0); 7.35—7.95 (m, 5 H)	8.07	11.67
24	0.91 (t, 3 H, $C\underline{H}_3-CH_2-CH_2-CH_2$, J = 7.4); 1.28—1.38 (m, 2 H, $CH_3-C\underline{H}_2-CH_2-CH_2$); 1.61—1.71 (m, 6 H, $Me-CH_2-C\underline{H}_2-CH_2$, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.63—2.66 (m, 2 H, $C\underline{H}_2-CH_2-CH_2-Me$); 2.73—2.77 (m, 2 H, $C\underline{H}_2-CH_2-CH_2-CH_2-NH_3^+$); 2.80—2.84 (m, 2 H, $CH_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	6.92—7.62 (m, 8 H)	7.99	11.06
25	1.62—2.10 (m, 19 H, 1-$AdC_{10}\underline{H}_{15}$, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.72—2.79 (m, 2 H, $C\underline{H}_2-CH_2-CH_2-CH_2-NH_3^+$); 2.87—2.95 (t, 2 H, $-CH_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$, J = 7.3)	7.25—9.07 (m, 7 H)	8.06	11.66
26	1.55—1.70 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.74—2.85 (m, 4 H, $C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$); 5.12 (s, 2 H, $PhC\underline{H}_2$)	6.85—8.81 (m, 12 H)	7.89	11.20
27	1.55—1.70 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.72—2.87 (m, 4 H, $C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$)	7.25—8.85 (m, 6 H)	7.97	11.81
28	1.53—1.75 (m, 4 H, $CH_2-C\underline{H}_2-C\underline{H}_2-CH_2-NH_3^+$); 2.73—2.82 (m, 4 H, $-C\underline{H}_2-CH_2-CH_2-C\underline{H}_2-NH_3^+$); 3.70 (t, 2 H, $C\underline{H}_2-CH_2-N$, J = 7.0); 4.52 (t, 2 H, $CH_2-C\underline{H}_2-N$, J = 7.0)	6.88—8.77 (m, 7 H)	7.86	—

Table 4. ^{13}C NMR spectra (DMSO-d_6, δ) of compounds **4**—**7** and **9**—**28**

Compound	CH_2—$(CH_2)_n$—CH_2 (n = 0, 1, 2)	R	R´	Indole	COOH
4	22.8, 39.4	111.6 (C(3), Py); 122.7 (C(5), Py); 128.5 (C(4), Py); 149.2 (C(6), Py); 150.8 (C(2), Py)	—	109.9 (C(7)); 118.6 (C(4)); 119.1 (C(3)); 120.9 (C(5)); 121.9 (C(6)); 126.6 (C(3a)); 136.1 (C(7a)); 137.1 (C(2))	164.1
5	22.7, 39.4	123.9 (C(5), Py); 128.2 (C(4), Py); 128.4 (C(3), Py); 148.0 (C(6), C(2), Py)	—	108.0 (C(3)); 111.5 (C(7)); 118.6 (C(4)); 119.3 (C(6)); 122.3 (C(5))l 131.9 (C(3a)); 135.3 (C(7a)); 136.4 (C(2))	163.8
6	22.7, 39.4	121.7 (C(3), C(5), Py); 128.3 (C(4), Py); 150.1 (C(6), C(2), Py)	—	109.8 (C(3)); 111.7 (C(7)); 118.8 (C(4)); 119.4 (C(6)); 123.0 (C(5)); 131.6 (C(3a)); 136.4 (C(7a)); 139.4 (C(2))	164.65
7	22.7, 39.4	125.7 (C(6), Q*); 127.2 (C(3), Q); 127.5 (C(5), Q); 128.2 (C(4a), Q); 128.5 (C(8), Q); 128.7 (C(7), Q); 132.0 (C(4), Q); 146.5 (C(2), Q); 149.8 (C(8a), Q)	—	108.5 (C(3)); 111.5 (C(7)); 118.6 (C(5)); 119.3 (C(4)); 122.3 (C(6)); 129.8 (C(3a)); 134.0 (C(7a)); 136.5(C(2))	164.7
9	21.3, 28.7 38.8	124.0 (C(5), Py); 128.3 (C(4), Py); 136.4 (C(3), Py); 148.0 (C(2), Py) 148.2 (C(6), Py)	—	111.4 (C(3)); 112.1 (C(7)); 118.9 (C(4)); 119.0 (C(6)); 122.1 (C(5)); 128.9 (C(3a)); 130.8 (C(7a)); 135.1 (C(2))	163.2
10	23.9, 27.3, 27.6, 38.7	127.2 (C(1), Ph); 127.7 (C(2), C(6), Ph); 128.6 (C(4), Ph); 128.7 (C(3), C(5), Ph)	—	111.2 (C(3)); 111.5 (C(7)); 118.6 (C(4)); 118.7 (C(6)); 121.4 (C(5)); 133.0 (C(3a)); 133.9 (C(7a)); 136.0 (C(2))	—
11	24.0, 27.4, 27.7, 38.9	124.9 (C(2), Ph); 127.9 (C(6), Ph); 128.7 (C(5), Ph); 133.0 (C(4), Ph); 134.1 (C(1), Ph); 137.8 (C(3), Ph)	21.2 (Me)	111.2 (C(3)); 111.4 (C(7)); 118.6 (C(5)); 118.7 (C(4)); 121.4 (C(6)); 128.3 (C(3a)); 136.0 (C(2)); 137.9 (C(7a))	—
12	23.7, 27.1, 27.2, 38.7	127.6 (C(6), Ph); 128.4 (C(2), Ph); 129.5 (C(1), Ph); 130.8 (C(4), Ph); 131.1 (C(5), Ph); 131.4 (C(3), Ph)	—	111.2 (C(3)); 113.0 (C(7)); 118.8 (C(5)); 118.9 (C(4)); 122.1 (C(6)); 129.0 (C(3a)); 133.6 (C(2)); 136.1 (C(7a))	164.3
13	24.1, 27.4, 27.7, 38.8	111.2 (C(2), Ph); 113.1 (C(4), Ph); 120.0 (C(6), Ph); 129.9 (C(5), Ph); 133.8 (C(1), Ph); 159.5 (C(3), Ph)	55.2 (MeO)	111.7 (C(3)); 113.0 (C(7)); 118.6 (C(5)); 118.7 (C(4)); 121.6 (C(6)); 128.7 (C(3a)) 134.4 (C(2)); 136.0 (C(7a))	164.9
14	24.2, 28.0, 28.1, 39.2	129.0 (C(2), C(6), Ph); 129.7 (C(3), C(5), Ph) 132.2 (C(4), Ph); 133.3 (C(1), Ph)	—	111.5 (C(3)); 112.5 (C(7)); 119.0 (C(4)); 119.1 (C(5)); 122.1 (C(6)); 129.0 (C(3a)); 132.9 (C(3)); 136.4 (C(7a))	169.3
15	23.9, 27.5, 27.6, 38.9	122.4 (C(4), Ph); 130.3 (C(2), C(6), Ph); 132.3 (C(3), C(5), Ph); 132.9 (C(1), Ph)	—	111.8 (C(3)); 112.8 (C(7)); 119.3 (C(5)); 119.4 (C(4)); 121.0 (C(6)); 129.3 (((3a)); 133.4 (C(2)); 136.9 (C(7a))	166.0
16	23.8, 27.0, 27.3, 38.8	114.8 (C(3), Py); 122.4 (C(5), Py); 132.0 (C(4), Py); 149.3 (C(6), Py); 151.4 (C(2), Py)	—	111.5 (C(7)); 118.7 (C(4)); 119.0 (C(3)); 120.7 (C(5)); 121.4 (C(6)); 128.8 (C(3a)); 136.0 (C(7a)); 136.8 (C(2))	164.2
17	23.8, 27.21, 27.5, 38.7	121.9 (C(3), Py); 128.4 (C(4), Py); 130.8 (C(5), Py); 148.0 (C(2), Py); 148.2 (C(6), Py)	—	111.3 (C(3)); 112.8 (C(7)); 118.8 (C(5)); 118.9 (C(4)); 123.8 (C(6)); 129.0 (C(3a)); 135.0 (C(7a)); 136.3 (C(2))	163.8

(*to be continued*)

Table 4 (*continued*)

Compound	$CH_2—(CH_2)_n—CH_2$ (n = 0, 1, 2)	R	R´	Indole	COOH
18	24.8, 25.7, 26.9, 38.6	129.0 (C(3), C(5), Py); 134.3 (C(4), Py); 149.2 (C(6), C(2), Py)	—	99.5 (C(3)); 113.3 (C(7)); 119.5 (C(4)); 119.8 (C(6)); 124.5 (C(3a)); 140.3 (C(5)); 145.3 (C(7a)); 145.9 (C(2))	164.65
19	24.0, 27.2, 27.3, 38.9	111.9 (C(4), Th**); 125.5 (C(3), Th); 127.6 (C(5), Th); 136.0 (C(2), Th)	—	110.9 (C(7)); 118.5 (C(5)); 118.8 (C(4)); 121.9 (C(3)); 124.6 (C(6)); 128.2 (C(3a)); 128.6 (C(2)); 134.5(C(7a))	—
20	23.7, 27.2, 27.5, 38.6	123.9 (C(1), Ph); 127.8 (C(2), C(6), Ph); 128.6 (C(4), Ph); 128.8 (C(3), C(5), Ph)	—	111.2 (C(3)); 111.3 (C(5)); 113.2 (C(7)); 120.8 (C(4)); 127.6 (C(6)); 132.5 (C(3a)); 134.6 (C(7a)); 135.5 (C(2))	—
21	23.9, 27.2, 27.4, 38.7	127.1 (C(1), Ph); 127.6 (C(2), C(6), Ph); 128.1 (C(3), C(5), Ph); 129.0 (C(4), Ph)	55.4 (MeO)	100.7 (C(4)); 111.3 (C(3)); 111.5 (C(7)); 111.8 (C(6)); 131.2 (C(3a)); 133.2 (C(7a)); 134.6 (C(2)); 153.1 ($CH_3O\underline{C}$)	—
22	25.0, 27.1, 30.3, 38.7	127.1 (C(1), Ph); 128.1 (C(2), C(6), Ph); 128.6 (C(3), C(5), Ph); 129.2 (C(4), Ph)	19.8 (Me-4); 21.2 (Me-6)	109.0 (C(3)); 112.3 (C(7)); 122.5 (C(5)); 124.5 (C(3a)); 130.2 (C(4)); 133.4 (C(6)); 133.6 (C(7a)); 136.9 (C(2))	—
23	23.6, 27.3, 27.4, 38.7	128.0 (C(1), Ph); 128.4 (C(2), C(6), Ph); 128.8 (C(3), C(5), Ph); 132.1 (C(4), Ph)	—	96.5 (dd, C(6), $J_{C,F}$ = 30.2, $J_{C,F}$ = 21.2); 99.8 (dd, C(4), $J_{C,F}$ = 22.7, $J_{C,F}$ = 3.6); 113.1 (C(3)); 120.6 (d, C(7a), $J_{C,F}$ = 12.6); 131.3 (dd, C(3a), $J_{C,F}$ = 10.8, 7.2); 137.5 (C(2)); 148.2 (dd, C(5), $J_{C,F}$ = 246.0, $J_{C,F}$ = 14.4); 155.8 (dd, C(7), $J_{C,F}$ = 234.0, $J_{C,F}$ = 10.2)	164.2
24	24.0, 27.3, 27.6, 38.7	127.1 (C(1), Ph); 127.7 (C(2), C(6), Ph); 128.7 (C(3), C(5), Ph); 132.4 (C(4), Ph)	13.9, 21.9, 33.9, 35.5 ($CH_3—CH_2—CH_2—CH_2$)	111.0 (C(3)); 111.1 (C(7)); 117.6 (C(4)); 122.4 (C(6)); 132.6 (C(3a)); 133.2 (C(7a)); 134.0 (C(5)); 134.6 (C(2))	—
25	23.6, 27.1, 27.4, 38.6	126.7 (C(3), Py); 128.1 (C(4), Py); 135.1 (C(5), Py); 141.3 (C(2), Py); 142.2 (C(6), Py)	28.5 ($\underline{C}$H—Ad-3, $\underline{C}$H—Ad-5, $\underline{C}$H—Ad-7); 35.6 ($\underline{C}$—Ad-1); 36.3 ($\underline{C}H_2$—Ad-4, $\underline{C}H_2$—Ad-6, $\underline{C}H_2$—Ad-10); 43.2 ($\underline{C}H_2$—Ad-2, $\underline{C}H_2$—Ad-8, $\underline{C}H_2$—Ad-9)	111.2 (C(3)); 114.3 (C(7)); 115.5 (C(4)); 120.9 (C(6)); 127.8 (C(3a)); 131.6 (C(2)); 140.9 (C(5)); 141.1 (C(7a))	—
26	23.8, 27.2, 27.4, 38.8	123.8 (C(5), Py); 131.7 (C(4), Py); 148.0 (C(3), Py); 148.2 (C(2), Py); 152.3 (C(6), Py)	69.9 (MeO); 127.7 (C(3), C(5), Ph); 128.4 (C(2), C(4), C(6), Ph); 134.9 (C(1), Ph)	102.5 (C(4)); 112.0 (C(3)); 112.7 (C(6)); 112.7 (C(7)); 129.0 (C(3a)); 131.9 (C(7a)); 149.1 (C(2)); 153.3 ($\underline{C}$—OBn)	163.9

(*to be continued*)

Table 4 (*continued*)

Compound	$CH_2—(CH_2)_n—CH_2$ (n = 0, 1, 2)	R	R´	Indole	COOH
27	23.6, 27.2, 27.5, 38.7	123.6 (C(4), Py); 127.8 (C(3), Py); 132.0 (C(5), Py); 148.9 (C(2), Py); 149.2 (C(6), Py)	—	114.1 (C(3)); 116.7 (C(4)); 117.5 (C(5)); 121.0 (C(6)); 123.7 (C(7)); 130.6 (C(3a)); 134.6 (C(7a)); 136.3 (C(2))	163.6
28	25.5, 27.3, 27.5, 38.7	121.4 (C(5), Py); 125.1 (C(4), Py); 128.4 (C(3), Py); 148.1 (C(2), Py); 148.2 (C(6), Py)	27.2 ($\underline{C}H_2—CH_2—N$); 49.5 ($CH_2—\underline{C}H_2—N$)	105.1 (C(3)); 115.6 (C(5)); 117.0 (C(4)); 120.0 (C(3a)); 120.9 (C(6)); 124.0 (C(7)); 135.5 (C(7a)); 148.6 (C(2))	164.5

* Quinolinyl.
** Thienyl.

Found (%): C, 63.45; H, 5.71. $C_{21}H_{21}N_3O_5$. Calculated (%): C, 63.79; H, 5.35.

3-[2-(3-Pyridyl)-1*H*-indol-3-yl]propyl-1-amine oxalate monohydrate (9). The yield was 80% (***B***), m.p. 221 °C. Found (%): C, 59.98; H, 5.72. $C_{18}H_{21}N_3O_5$. Calculated (%): C, 60.16; H, 5.89.

4-(2-Phenyl-1*H*-indol-3-yl)butyl-1-amine hydrochloride (10). The yield was 85% (***C***), m.p. 236 °C. Found (%): C, 72.04; H, 6.91. $C_{18}H_{21}ClN_2$. Calculated (%): C, 71.87; H, 7.04.

4-[2-(3-Methylphenyl)-1*H*-indol-3-yl]butyl-1-amine hydrochloride (11). The yield was 65% (***C***), m.p. 140—141 °C. Found (%): C, 72.04; H, 6.91. $C_{19}H_{23}ClN_2$. Calculated (%): C, 72.48; H, 7.36.

4-[2-(3,4-Dichlorophenyl)-1*H*-indol-3-yl]butyl-1-amine hydrochloride (12). The yield was 77% (***C***), m.p. 155—156 °C. Found (%): C, 58.27; H, 5.35. $C_{18}H_{19}Cl_3N_2$. Calculated (%): C, 58.48; H, 5.18.

4-[2-(3-Methoxyphenyl)-1*H*-indol-3-yl]butyl-1-amine hydrochloride (13). The yield was 57% (***C***), m.p. 138—139 °C. Found (%): C, 69.11; H, 6.95. $C_{19}H_{23}ClN_2O$. Calculated (%): C, 68.97; H, 7.01.

4-[2-(4-Chlorophenyl)-1*H*-indol-3-yl]butyl-1-amine hydrochloride (14). The yield was 72% (***C***), m.p. 224—225 °C. Found (%): C, 64.63; H, 6.22. $C_{18}H_{20}Cl_2N_2$. Calculated (%): C, 64.48; H, 6.01.

4-[2-(4-Bromophenyl)-1*H*-indol-3-yl]butyl-1-amine hydrochloride (15). The yield was 62% (***C***), m.p. 193—194 °C. Found (%): C, 57.05; H, 5.20. $C_{18}H_{20}BrClN_2$. Calculated (%): C, 56.93; H, 5.31.

4-[2-(2-Pyridyl)-1*H*-indol-3-yl]butyl-1-amine oxalate monohydrate (16). The yield was 87% (***C***), m.p. 215—216 °C. Found (%): C, 60.94; H, 6.35. $C_{19}H_{23}N_3O_5$. Calculated (%): C, 61.11; H, 6.21.

4-[2-(3-Pyridyl)-1*H*-indol-3-yl]butyl-1-amine oxalate monohydrate (17). The yield was 88% (***C***), m.p. 198 °C. Found (%): C, 61.35; H, 5.93. $C_{19}H_{23}N_3O_5$. Calculated (%): C, 61.11; H, 6.21.

4-[2-(4-Pyridyl)-1*H*-indol-3-yl]butyl-1-amine oxalate monohydrate (18). The yield was 82% (***C***), m.p. 134—135 °C. Found (%): C, 61.04; H, 6.16. $C_{19}H_{23}N_3O_5$. Calculated (%): C, 61.11; H, 6.21.

4-[2-(2-Thienyl)-1*H*-indol-3-yl]butyl-1-amine hydrochloride (19). The yield was 82% (***C***), m.p. 207—208 °C. Found (%): C, 62.39; H, 6.33. $C_{16}H_{19}ClN_2S$. Calculated (%): C, 62.63; H, 6.24.

4-(5-Bromo-2-phenyl-1*H*-indol-3-yl)butyl-1-amine hydrochloride (20). The yield was 78% (***C***), m.p. 242 °C. Found (%): C, 56.79; H, 5.24. $C_{18}H_{20}BrClN_2$. Calculated (%): C, 56.93; H, 5.31.

4-(5-Methoxy-2-phenyl-1*H*-indol-3-yl)butyl-1-amine hydrochloride (21). The yield was 80% (***C***), m.p. 241 °C. Found (%): C, 69.22; H, 6.87. $C_{19}H_{23}ClN_2O$. Calculated (%): C, 68.97; H, 7.01.

4-(4,6-Dimethyl-2-phenyl-1*H*-indol-3-yl)butyl-1-amine hydrochloride (22). The yield was 84% (***C***), m.p. 253 °C. Found (%): C, 73.08; H, 7.71. $C_{20}H_{25}ClN_2$. Calculated (%): C, 73.04; H, 7.66.

4-(5,7-Difluoro-2-phenyl-1*H*-indol-3-yl)butyl-1-amine oxalate (23). The yield was 57% (***B***), m.p. 207 °C. Found (%): C, 61.48; H, 5.21. $C_{20}H_{20}F_2N_2O_4$. Calculated (%): C, 61.53; H, 5.16.

4-(5-Butyl-2-phenyl-1*H*-indol-3-yl)butyl-1-amine hydrochloride (24). The yield was 85% (***C***), m.p. 235 °C. Found (%): C, 73.88; H, 8.11. $C_{22}H_{29}ClN_2$. Calculated (%): C, 74.03; H, 8.39.

4-[5-(1-Adamantyl)-2-(3-pyridyl)-1*H*-indol-3-yl]butyl-1-amine dihydrochloride tetrahydrate (25). The yield was 86% (***C***), m.p. 185 °C. Found (%): C, 59.76; H, 7.77. $C_{27}H_{43}Cl_2N_3O_4$. Calculated (%): C, 59.55; H, 7.96.

4-[5-Benzyloxy-2-(3-pyridyl)-1*H*-indol-3-yl]butyl-1-amine oxalate monohydrate (26). The yield was 75% (***C***), m.p. 207 °C. Found (%): C, 64.88; H, 6.31. $C_{26}H_{29}N_3O_6$. Calculated (%): C, 65.12; H, 6.10.

4-[5,7-Dichloro-2-(3-pyridyl)-1*H*-indol-3-yl]butyl-1-amine oxalate monohydrate (27). The yield was 66% (***B***), m.p. 216 °C. Found (%): C, 51.68; H, 4.71. $C_{19}H_{21}Cl_2N_3O_5$. Calculated (%): C, 51.60; H, 4.79.

4-[2-(3-Pyridyl)-4,5-dihydropyrrolo[3,2,1-*hi*]indol-1-yl]butyl-1-amine oxalate monohydrate (28). The yield was 77% (***C***), m.p. 190 °C. Found (%): C, 63.27; H, 6.44. $C_{21}H_{25}N_3O_5$. Calculated (%): C, 63.14; H, 6.31.

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