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Laboratory note

Synthesis of 4-*N*,*N*-dialkylaminoethyl-2-indolones as potential dopamine agonists†

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Summary — A set of fourteen 4-{2-[*N*-propyl-*N*-alkyl-(or alkylaryl-) amino]ethyl}-2-indolone analogues of dopamine were synthesized in 15 steps and evaluated for their affinities towards the D_2 receptor using [^{3}H]sulpiride or [^{3}H]spiperone as radioligands. Six analogues displayed D_2 agonist activities comparable (K_i = 450–650 nM) to Ropinirole or SK&F 101468. The functionalized amino side chain introduced in the 4-position can be used to modulate the lipophilicity of the analogues without significantly affecting D_2 activity.

lactam / indolone / rigid dopamine analogue / D_2 receptor binding

Introduction

It has been reported that dopamine **I** (fig 1) and DA_2 agonists and antagonists could lower intraocular pressure [1], but there are no dopaminergic drugs in clinical use for the treatment of ocular hypertension and glaucoma.

In the course of our research on new dopaminergic agents for ophthalmological applications, we synthesized a series of 3-*N*,*N*-dipropylamino-2-chromanone derivatives **IV**, as isosteric analogues of aminotetralins **II** and aminochromanes **III** [2] (Benoit-Guyod *et al*, manuscript submitted). None of these lactones displayed potent DA_2-binding affinities. It thus appeared that the lactone strategy was not as fruitful as we hoped. We indicated several structural features that could explain this lack of potency with structural arguments invoking lower pK_a values due to H bonding or electrostatic interactions between the NH^+ and C=O groups coupled with low stability due to the presence of a lactone group.

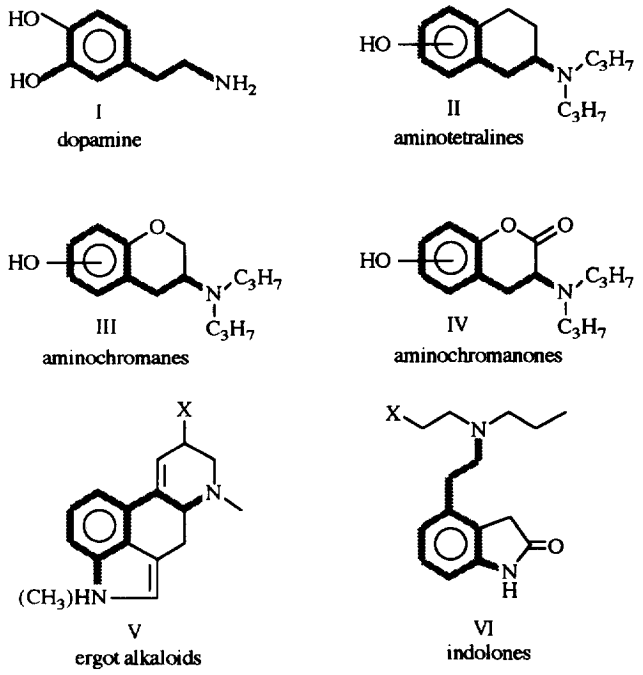

Fig 1. Chemical structures of dopamine analogues.

A new set of targets **VI** was then considered, bearing in mind our initial goal, *ie* a potent DA_2 agonist which could be delivered topically and which would be devoid of CNS side effects. The indolones

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VI bear some resemblance to ergot derivatives **V**. The NH-CO group *meta* to the aminoethyl chain can be considered as an isostere of the *meta* OH group of catecholamines. In our design we used the more stable lactam group instead of the lactone group. One of the most important reasons for examining the indolones as dopaminergic agonists was the hypothesis that an indolone would be less prone to the rapid and variable metabolic degradations that make true catechols undesirable. Additionally, we introduced a distal labile functionality into our analogues which would be susceptible to hydrolysis by enzyme esterases. Hydrolysis of the distal group in each molecule should lead to compounds polar enough to prevent the crossing of the blood–brain barrier, and thus not give rise to CNS-mediated side effects. Investigations of indolones for use in the treatment of cardiovascular disorders by Gallagher and DeMarinis [3–5] led to the synthesis of 4-[2-(dipropylamino)ethyl]-2-indolone, SK&F 101468 and Ropinirole [6] (**VI**, X = CH_3, compound **18** in this paper). Ropinirole is now in phase III trials for the treatment of Parkinson's disease. Our purpose was thus to prepare derivatives of **VI** bearing both an *N*-propyl substituent and a side chain bearing a suitable X group.

The 4-position of the side chain was reported as the most active [7]. Moreover, it could be predicted that the 4-position of the ethylamino chain would preclude any intramolecular H-bond formation thus giving a normal pK_a for the amine (Benoit-Guyod *et al*, manuscript submitted). Such indolones also fit the D_2 receptor model described by Hibert *et al* [8].

Chemistry

The key 2-indolone (or 2-oxindole) **17** was obtained in 15 steps as described in figure 2. The 4-[2-(*N*-propyl-*N*-alkyl amino)ethyl]-2-indolones **18–24** were further prepared in one step from **17** by means of two methods which also gave five secondary products **25–29** (fig 3).

Commercially available 2-methyl 3-nitrobenzoic acid **1** was converted into acyl chloride **2** by thionyl chloride. The smooth reduction of **2** by $NaBH_4$ in tetrahydrofuran led to the nitroalcohol **3** in an excellent yield. Compound **1** could also be converted to **3** in one step by treatment with B_2H_6 in THF [3]. However, this method was less convenient for large quantities. The hydroxyl group of **3** was substituted by a chlorine atom using thionyl chloride in pyridine. The phenacyl chloride **7** was obtained from halide **4** by substitution with KCN followed by hydrolysis to the corresponding acid **6** and then conversion to chloride **7**. On the other hand, *N*-propylbenzamide **9** was obtained by reaction of propylamine with benzoyl chloride **8** and reduction of the CO-N group to amine

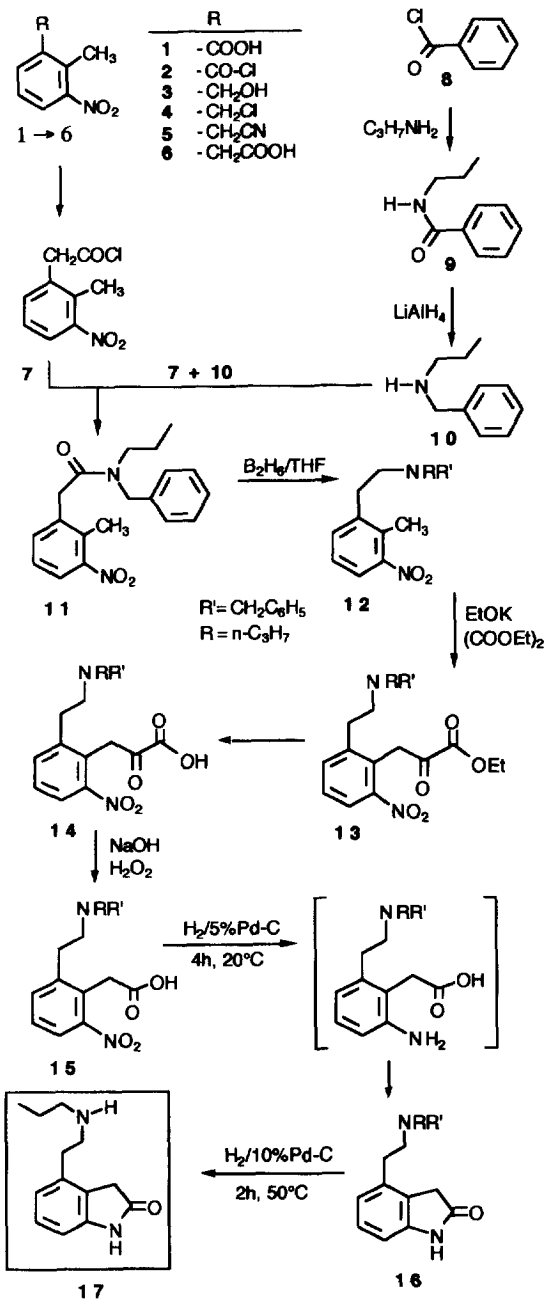


Fig 2. Reaction scheme for indolones **16–17**.

10 by $LiAlH_4$ in diethyl ether. The benzylamine **10** was coupled with the acyl chloride **7** to give the tertiary amide **11**, which was reduced to the corresponding amine **12**. Under the conditions of the Claisen condensation, the stabilized benzylic carbanion of **12** and diethyl oxalate gave benzyl pyruvate **13**.

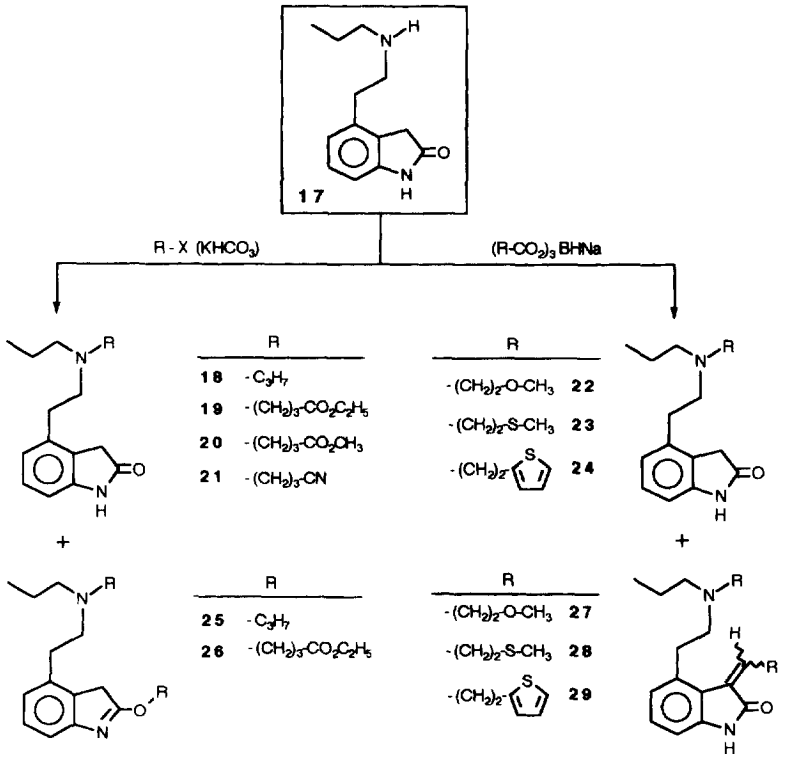


Fig 3. Reaction scheme for *N,N*-disubstituted indolones **18–29**.

Saponification of **13** with $NaOH/H_2O$ instead of $FeSO_4/H_2O$, which is used classically in the Reissert method [9], gave the crude ketoacid **14** which was cleaved to **15** by hydroperoxide and aqueous sodium hydroxide. Catalytic hydrogenation of the nitro aromatic group with 5% palladium on charcoal at room temperature most likely led to the amino group (non-isolated), which cyclized to the oxindole **16**. A similar cyclization was reported by Askam and Deeks in the 4-methyloxindole synthesis [10]. *N*-Debenzylation was accomplished catalytically under more drastic conditions to give indolone **17**. In this manner, reduction, cyclization and deprotection were all carried out in a one-pot reaction.

Indolone **18** and all *N,N*-disubstituted indolones were obtained from **17** (fig 3). Our strategy was thus to prepare large quantities of the intermediate indolone **17** and alkylate the secondary amine function of **17** to obtain the tertiary amines **18–21**. The direct alkylation *(Method A)* with alkylhalides in basic medium gave secondary *O*-alkylated products, *ie* 25% of **25** along with 40% of **18** when 1-bromopropane was used as alkyl halide. $KHCO_3$ in DMF (12 h at 60°C) gave the best results in comparison with other basic media or solvents (K_2CO_3, triethylamine, *N*-methylmorpholine in DMSO or toluene). *Method B*, which was used in other work on chromanones (Benoit-Guyod *et al*, manuscript submitted), called for the reductive alkylation of **17** with sodium triacyloxyborohydride. This method proved successful when the direct alkylation failed, but secondary C-alkylated products **27–29** were also formed (18–24% yield) along with the expected indolones **22–24** (40–60%). In **17**, the nucleophilic reaction can occur both at the nitrogen atom or the C_3 position. This can be explained by the fact that both NH and C_3-H groups have similar pK_a values [11]. Consequently both direct alkylation *(Method A)* and reductive alkylation *(Method B)* on **17** led to a mixture of two products. One of these is monoalkylated at the nitrogen while the other has two alkyl groups, one on the nitrogen and one on the C_3 carbon.

The chemical structures of all compounds were consistent with spectral data. Moreover, an NMR conformational study of the sterically hindered amide **11** showed the presence of *Z* and *E* isomers in a 3:2 ratio in DMSO indicating that conformation *Z* with the two aromatic rings in a *trans* position was prevailing [12].

The structures of **25** and **26** were assigned by spectroscopic methods. ^{1}H-NMR spectra showed the methylene CH_2O as a triplet at δ = 4.15 ppm (sextet at 1.80, triplet at 1.06 due to the propoxy group). ^{1}H decoupling at δ = 1.80 ppm ($OCH_2CH_2CH_3$) confirmed unambiguously the structure of **25**. The *O*-alkylation reaction was in accordance with the stability of the enolic aromatic amide group of oxindole.

The NMR spectrum of **26** (table I) showed the presence of two functionalized chains at the N and O positions. Furthermore, no N-H frequencies could be observed in the spectrum, thus confirming that this analogue is the *O*-alkyl and not the *N*-alkyl substituted indolone. These NMR assignments were obtained from the ^{1}H-^{13}C COSY spectrum.

Reductive alkylation of the *N*-propylaminoethyl chain by various carboxylic acid and $NaBH_4$ *(Method B)* gave *N*-substituted indolones **22–24**, respectively, together with their respective secondary products **27–29** (18–24% yield). The IR spectrum of **29** showed a large band at 1630 cm^{-1} (C=C) and two straight bands at 1705 and 1700 cm^{-1} (C=O lactam) consistent with *Z/E* isomers. The presence of the two isomers was further confirmed by the ^{1}H-NMR spectrum, which showed two distinct NH frequencies in a 3:2 ratio. The ^{13}C-NMR spectrum was also consistent with such an interpretation. The structure of **29** was also confirmed by mass spectrometry.

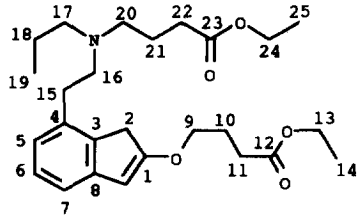
Biological results and discussion

Binding experiments on rat brain striatum membranes using either 0.6 nM of tritiated spiperone or sulpiride indicated that the unsubstituted indolones have dopaminergic affinities lower than those of dopamine or bromocriptine (table II). Similar results were obtained by Gallagher [3] and DeMarinis [4, 5] in related series. Indeed these indolones had *ca* 5–10 times smaller affinities than dopamine itself (EC_{50} = 70 nM). However, our work clearly showed that the introduction of function on the amino side chain was compatible with a DA_2 activity. Tertiary amine is favorable and at least one propyl substituent was required for activity. The second propyl substituent can be replaced by a functionalized chain containing ester, nitrile, thiophene or benzyl functions. Based on the fact that 7-OH Ropinirole showed a 50-fold increased activity on D_2 receptors *versus* Ropinirole, a similar approach was planned in our series. However, the moderated affinities obtained were considered not promising enough to deserve further development in the ophthalmological domain.

Conclusion

We have demonstrated that the introduction of ester, nitrile, thiophene or benzyl functions on the side chain

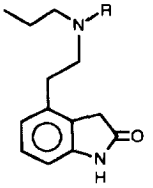
Table I. ^{13}C-NMR chemical shifts (δ ppm) for compound **26** in $CDCl_3/Me_4Si$ (at 303K) at 200 MHz[a].



Carbon	δ	*Carbon*	δ
19	11.21	16	54.32
25 or 14	14.14	24 or 13	60.52
25 or 14	14.18	24 or 13	61
18	16.90	9	75
22 or 23	18.2	7	106.39
22 or 23	23.66	8	119.51
22 or 11	26.63	5	123.03
22 or 11	30.45	6	128.95
2	32.84	4	132.59
15	45.84	3	142.24
20 or 17	51.09	1	169
20 or 17	52.37	12 and 23	172; 172.72

[a]Numbering of carbon atoms does not follow the rules of the nomenclature but is used to simplify the assignment of chemical displacements.

Table II. Biological results on rat brain for synthesized indolones.



Compound	*R*	*Radioligand*	K_i *(nM)*
Bromocriptine		[^{3}H]sulpiride	9[a]
16	-$CH_2C_6H_5$	[^{3}H]sulpiride	640[b]
17	-H	[^{3}H]sulpiride	> 1000[c]
18a	-$CH_2CH_2CH_3$	[^{3}H]sulpiride	400[a]
19	-$(CH_2)_3COOC_2H_5$	[^{3}H]sulpiride	450[b]
20	-$(CH_2)_3COOCH_3$	[^{3}H]sulpiride	650[b]
21	-$(CH_2)_3CN$	[^{3}H]sulpiride	560[b]
22	-$CH_2CH_2OCH_3$	[^{3}H]spiperone	> 1000[c]
23	-$CH_2CH_2SCH_3$	[^{3}H]spiperone	> 1000[c]
24	-CH_2CH_2(2-thienyl)	[^{3}H]spiperone	476[c]

[a]DeMarinis and Hieble (personal communication); [b]Kyba, Alcon Laboratories, Fort Worth, TX (personal communication); [c]binding studies, see *Experimental protocols*.

of *N,N*-dialkylaminoethyl-2-indolones does not significantly alter their affinity to the dopaminergic receptor. Indeed the compounds retained binding values comparable to that of dopamine. The functionalized amino side chain introduced in the 4-position can be used to modify the lipophilicity of the analogs without significantly affecting D_2 activity.

Experimental protocols

Chemistry

All organic chemicals were purchased from Aldrich, France, and other organic chemicals from Prolabo, France. The following instruments were used: CCM: Merck 60 F 254; melting point (mp): Kofler bench; IR: Philips Pye Unicam SP3-100; NMR: Bruker AC 200, AM 300 (chemical shift δ in ppm with internal reference and coupling constants in Hz); analyses: Laboratoire de microanalyse, CNRS, Vernaison, France.

2-Methyl-3-nitrophenylethanoyl chloride 7

Compound **6** [10] (30 g; 0.15 mol) was added in portions to a stirred solution of thionyl chloride (57 g; 0.48 mol). The solution was refluxed for 3 h and evaporated to dryness *in vacuo*. The resulting crude solid **7** was used in the next step without further purification (96%) mp: 50–52°C (lit [11], no mp given). IR (KBr): 2980, 1780, 1700, 1520, 1360, 1220, 960, 740, 620 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 2.40 (3H, 1s, CH_3); 4.29 (2H, 1s, CH_2); 7.34 (1H, 1t, C_5-*H*); 7.46 (1H, d, C_6H); 7.78 (1H, 1d, C_4H).

N-Propyl-N-benzylamine 10

This compound was prepared in 89% yield by $LiAlH_4$ reduction of *n*-propylbenzamide [13]. The amine **10** was converted into its hydrochloride, mp: 186–188°C (lit [14] = 184°C). IR (KBr): 2990, 2800, 1560, 1460, 1420, 1005, 860, 700 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.92 (3H, t, CH_3); 1.62 (2H, m, CH_2CH_3); 2.71 (2H, m, $CH_3CH_2CH_2$); 4.01 (2H, t, $ArCH_2$); 7.34–7.62 (5H, m, Ar-*H*).

N-Benzyl-N-propyl-(2-methyl-3-nitrophenyl)acetamide 11

A solution of **7** (29.25 g; 0.15 mol) in thionyl chloride (57.10 g; 0.48 mol) was refluxed for 3 h. After excess of thionyl chloride was evaporated, toluene (2 x 100 mL) was added and then evaporated to dryness. The crude product was solubilized in toluene (200 mL) and was added dropwise to 400 mL of a cold solution of water/toluene (v/v), containing Na_2CO_3 (36 g; 0.34 mol) and **10** (18.00 g; 0.17 mol). After standing 2 h at room temperature the organic layer was successively washed with 5% $NaHCO_3$, 1 N HCl and water. The toluene phase was dried, filtered and evaporated. Compound **11** was induced to crystallize with diethyl ether; yield 90%, mp: 49–51°C. IR (KBr): 3000, 2900, 2840, 1640, 1520, 1350, 1220, 1120, 1080, 940, 900, 800, 740, 700 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.90 (3H, t, $CH_3CH_2CH_2$); 0.93 (3H, t, $CH_3CH_2CH_2$); 1.63 (4H, sext, $CH_3CH_2CH_2$); 2.26 (3H, s, CH_3Ar); 2.38 (3H, s, CH_3Ar); 3.24 (2H, t, $CH_3CH_2CH_2$-); 3.42

(2H, t, $CH_3CH_2CH_2N$); 3.71 (2H, s, $ArCH_2CO$); 3.83 (2H, s, $ArCH_2CO$); 4.60 (2H, s, $ArCH_2$); 4.63 (2H, s, $ArCH_2N$); 7.20–7.67 (16H, m, Ar*H*). $C_{19}H_{22}N_2O_3 \cdot 0.25H_2O$ (330.89). Anal C, H, N, O.

N-Benzyl-N-propyl-2-(2-methyl-3-nitrophenyl)ethylamine ***12***

A portion of 20 mL 1 M B_2H_6 in anhydrous THF was added dropwise under nitrogen to a solution of compound **11** (35 g; 0.11 mol) in 250 mL anhydrous THF. The reaction was heated under reflux for 12 h followed by 12 h at room temperature (TLC). Anhydrous methanol was added slowly and then the solution was evaporated. The residue was dissolved in 40 mL 6 N HCl heated under reflux for 1 h, cooled, treated with 40% NaOH until pH 10 was obtained and extracted with diethyl ether. Compound **12** was purified on a silica gel column chromatography using cyclohexane/ethyl acetate 8:2. The oily amine was converted into its hydrochloride: colorless crystals; yield 70%, mp: 151–153°C. IR (KBr): 3000, 2950, 2800, 1600, 1500, 1440, 1340, 1110, 1060, 1020, 800, 740, 700 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.93 (3H, t, CH_3CH_2); 1.54 (2H, m, CH_3CH_2); 2.28 (3H, s, CH_3Ar); 2.54 (2H, m, $CH_3CH_2CH_2N$); 2.62 (2H, m, $ArCH_2CH_2$-); 2.86 (2H, m, $ArCH_2CH_2$); 3.65 (2H, s, $ArCH_2N$); 7.19–7.32 (8H, m, Ar*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.75 ($CH_3CH_2CH_2N$); 14.39 ($ArCH_3$); 20.39 ($CH_3CH_2CH_2N$); 31.60 ($ArCH_2CH_2N$); 53.80 ($CH_3CH_2CH_2N$); 56.07 ($ArCH_2CH_2N$); 58.61 ($CH_2C_6H_5$); 121.62 (ArC_4); 125.84 (C4, phenyl); 128.03 (C2, C6, phenyl); 128.06 (ArC5); 128.50 (C3, -C5, -phenyl); 129.94 (ArC2); 133.53 (ArC6); 139.64 (C1, phenyl); 141.74 (ArC1); 151.27 (ArC3). MS ([FAB(+)], *meta*-nitrobenzylic alcohol); M = 312; *m/e* = 313 ([M + H]$^+$, 26). $C_{19}H_{24}N_2O_2 \cdot HCl$. Anal C, H, N, O, Cl. M 348.86.

Ethyl 2-Nitro-6-[2-(N-benzyl-N-propylaminoethyl)phenyl]pyruvate ***13***

To a suspension of potassium (0.39 g; 0.01 g/at) in 10 mL diethyl ether at 0°C, anhydrous ethanol (0.6 mL, 0.01 mol) was added slowly under stirring until complete solubilization. Diethyl oxalate was added (1.46 g; 0.01 mol). The yellow mixture obtained was stirred for 10 min and then a solution of amine **12** (3.12 g; 0.01 mol) in 5 mL of anhydrous ether was added dropwise under stirring. The solution was left overnight under argon. After ether evaporation the crude product was solubilized in 52 mL water and was extracted with ethyl acetate. The organic layer was dried, evaporated and the crude product was purified by silica gel column chromatography using ethyl acetate (yield 48% as an oil). IR (film): 3000, 2975, 2850, 2800, 1725, 1720, 1600, 1520, 1400, 1340, 1250, 1050, 840, 800, 780, 730, 700 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.94 (3H, t, $CH_3CH_2CH_2$); 1.21 (3H, t, CH_3CH_2O); 1.48 (2H, m, $CH_3CH_2CH_2N$); 2.61–2.76 (4H, m, $ArCH_2CH_2N$); 3.59 (2H, t, s, $ArCH_2CO$); 4.16 (2H, s, $ArCH_2N$); 4.37 (2H, m, CH_3CH_2O); 7.18–7.82 (8H, m, Ar*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.32 ($CH_3CH_2CH_2N$); 14.01 (CH_3CH_2O); 20.30 ($CH_3CH_2CH_2N$); 31.63 ($ArCH_2CH_2N$); 38.79 ($ArCH_2CO$); 54.46 ($CH_3CH_2CH_2N$); 56.21 ($ArCH_2CH_2N$); 58.63 (NCH_2 phenyl); 60.28 (CH_3CH_2O); 126.96 (C4, phenyl); 127.07 (ArC2); 135.30 (C1, phenyl); 142.93 (ArC1); 149.65 (ArC3); 160.48 (CO, ester); 189.47 (CO). MS ([FAB(+)], glycerol); M = 412: *m/e* = 413 ([M + H]$^+$, 100). $C_{23}H_{18}N_2O_5$. M 418.48.

2-Nitro-6-[2-(N-benzyl-N-propylaminoethyl)]phenylpyruvic acid ***14***

Compound **13** was solubilized in 10 ml of 1 N NaOH and refluxed for 30 min. The cold solution was acidified by 1 N HCl and extracted with chloroform (70%, mp: 116–120°C). IR (KBr): 3400, 2980, 2500, 1720, 1630, 1600, 1520, 1450, 1360, 1340, 1060, 810, 740, 700 cm^{-1}. ^{1}H-NMR (200 MHz; CD_3OD): δ 0.92 (3H, t, CH_3CH_2); 1.85 (2H, m, CH_3CH_2); 3.15 (2H, m, $CH_3CH_2CH_2N$); 3.30 (4H, m, $ArCHCH_2$); 4.40 (2H, $ArCH_2CO$); 4.63 (2H, s, $ArCH_2N$); 7.52–7.64 (8H, m, Ar*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.15 ($CH_3CH_2CH_2N$); 18.28 ($CH_3CH_2CH_2N$); 28.60 ($ArCH_2CH_2N$); 54.16 ($CH_3CH_2CH_2N$); 55.94 ($ArCH_2CH_2N$); 58.66 (NCH_2 phenyl); 123.09 (ArC4); 124.75 (C4, phenyl); 129.57 (ArC5); 130.55 (C2, C6, phenyl); 130.85 (ArC2); 131.28 (ArC6); 132.06 (C3, C5, phenyl); 135.62 (ArC1); 152.41 (ArC3); 180.36 (CO, acid); 227.12 (CO). MS ([FAB(+)], glycerol), M = 412: *m/e* = 413 ([M + H]$^+$, 40); 384 ([M – C_2H_5]$^+$, 10); 368 ([M – OC_2H_5]$^+$, 5). MS ([FAB (–)], glycerol negative ions); M = 412: *m/e* = 411 ([M – H]$^-$, 40); 311 ([M – $COCO_2C_2H_5$], 25); 366 ([M – OC_2H_5]$^-$, 10). $C_{21}H_{24}N_2O_5$. M 384.44.

2-Nitro-6-[2-(N-benzyl-N-propylamino)ethyl]phenylacetic acid ***15***

H_2O_2 (30%, 1.34 ml; 13.11 mmol) was added dropwise to a cold solution (0°C) of **14** (3 g; 7.14 mmol) in 40 mL of 40% NaOH (0.02 mol). The solution was stirred for 2 h at room temperature, acidified with 3 N HCl, and then extracted with chloroform. Vacuum evaporation gave a yellow product which was recrystallized from water (68%, white solid, mp: 110–115°C). IR (KBr): 3400, 2980, 2500, 1720, 1600, 1520, 1450, 1350, 1210, 800, 740, 700 cm^{-1}. ^{1}H-NMR (200 MHz; CD_3OD): δ 0.94 (3H, t, CH_3CH_2); 1.85 (2H, m, CH_3CH_2); 3.11–3.39 (6H, m, $ArCH_2CH_2$ and $CH_3CH_2CH_2$); 3.87 (2H, s, $ArCH_2CO$); 4.45 (2H, s, $ArCH_2N$); 7.45–7.86 (8H, m, Ar*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.15 ($CH_3CH_2CH_2N$); 18.28 ($CH_3CH_2CH_2N$); 28.60 ($ArCH_2CH_2N$); 35.31 ($ArCH_2CO_2H$); 54.16 ($CH_3CH_2CH_2N$); 55.94 ($ArCH_2CH_2N$); 58.66 (NCH_2 phenyl); 123.09 (ArC4); 124.75 (C4, phenyl); 129.57 (ArC5); 130.55 (C2, C6, phenyl); 130.85 (ArC2); 131.28 (ArC6); 132.06 (C3, C5, phenyl); 135.62 (ArC1); 152.41 (ArC3); 173.90 (CO, acid). MS $C_{19}H_{25}N_2O_4Cl$. M 380.86.

4-[2-(N-Benzyl-N-propylamino)ethyl]-2-indolone ***16***

A solution of compound **15** (2.00 g; 5.02 mmol) in 100 mL of methanol, and 5% palladium–charcoal (0.2 g) was hydrogenated under atmospheric pressure for 4 h. The catalyst was removed by filtration on celite. The methanol was evaporated and the crude product was taken up in chloroform. The organic phase was washed with 5% $NaHCO_3$, dried and evaporated to dryness. The residue was purified by column chromatography with hexane/ethyl acetate 1:1 to give **16** which was dissolved into anhydrous ether and treated with HCl gas to give the hydrochloride as a white solid, recrystallized from ethanol/ether (60%, mp: 173–175°C). IR (KBr): 3200, 2950, 2900, 1720, 1700, 1600, 1450, 1250, 1180, 780, 760, 700 cm^{-1}. ^{1}H-NMR (200 MHz; CD_3OD): δ 0.96 (3H, t, CH_3CH_3); 1.85 (2H, m, CH_3CH_2); 3.19 (2H, m, $CH_3CH_2CH_2$); 3.29 (4H, m, $ArCH_2CH_2$); 3.45 (2H, s, $ArCH_2CO$); 4.47 (2H, s, $ArCH_2N$); 6.71 (1H, d, Ar*H*); 6.90 (1H, t, Ar*H*); 7.15 (1H, t, Ar*H*); 7.52 (5H, m, Ar*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.16 ($CH_3CH_2CH_2N$); 18.27 ($CH_3CH_2CH_2N$); 28.38 ($ArCH_2CH_2N$); 35.77 ($ArCH_2CO$); 53.33 ($CH_3CH_2CH_2N$); 55.69 ($ArCH_2CH_2N$); 58.48 (NCH_2 phenyl); 109.88 (ArC4); 123.45 (ArC6); 125.20 (C4, phenyl); 128.06 (ArC5); 129.69 (C2, C6, phenyl); 130.57 (C3, C5, phenyl); 130.83 (ArC1); 133.54 (ArC2); 145.03 (ArC3); 179.27 (CO, lactam). MS ([FAB(+)], thioglycerol), M = 308; *m/e* = 309 ([M + H]$^+$, 100). $C_{20}H_{24}N_2O \cdot HCl \cdot H_2O$. M = 362.89 (C, H, N).

4-[2-(N-Propylamino)ethyl]-2-indolone ***17***

A mixture of **16** (2 g; 5.02 mmol) in 100 mL methanol and 0.4 g of 10% palladium–charcoal was vigorously stirred at

room temperature under a normal pressure of hydrogen. The reaction was complete after 2 h at 50°C. The catalyst was removed by filtration through celite which was washed with hot methanol. After concentration of the solvent under reduced pressure, the solution was kept overnight at 0°C. The precipitate formed was filtered and recrystallized from methanol. The corresponding hydrochloride was prepared as before for compound **16** (40%, mp > 270°C). IR (KBr): 3200, 2950, 2750, 2500, 2440, 1680, 1600, 1460, 1260, 1020, 890, 780 cm^{-1}. ^{1}H-NMR (200 MHz; DMSO-d_6): δ 0.93 (3H, t, CH_3CH_2); 1.66 (2H, m, CH_3CH_2); 2.92 (4H, m, CH_2N); 3.13 (2H, m, $ArCH_2$); 3.54 (2H, s, CH_2CO); 6.81 (1H, d, ArH); 6.92 (1H, s, ArH); 7.20 (1H, t, ArH); 8.98 (1H, s, NH). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.16 ($CH_3CH_2CH_2N$); 18.22 ($CH_3CH_2CH_2N$); 28.38 ($ArCH_2CH_2N$); 35.77 ($ArCH_2CO$); 53.38 ($CH_3CH_2CH_2N$); 55.69 ($ArCH_2CH_2N$); 109.87 (ArC4); 123.44 (ArC6); 129.68 (ArC5); 130.83 (ArC1); 133.54 (ArC2); 143.12 (ArC3); 179.11 (CO, lactam). MS ([FAB(+)], thioglycerol) *M* = 218; *m/e* = 219 ($[M + H]^+$, 30); 241 ($[M + Na]^+$, 80) $C_{13}H_{18}N_2O$•HCl•0.25H_2O. M 259.25.

*4-[2-(Dipropylamino)ethyl]-2-indolone **18** (Method A)*
1-Bromopropane (0.95 g; 7.80 mmol) was added dropwise to a mixture of **17** (hydrochloride 1.00 g; 3.9 mmol) and $KHCO_3$ (0.39 g; 3.9 mmol) in 10 mL of anhydrous DMF. The mixture was kept under argon at 50°C for 12 h. The solvent was removed under reduced pressure and the residue taken up in dichloromethane was washed with 1 N HCl. The aqueous solution was alkalinized with 5% $KHCO_3$ and extracted to afford the free base. This base was purified by silica gel column chromatography with ethyl acetate/cyclohexane 1:1. The base was converted by HCl into the hydrochloride, and recrystallized from acetonitrile to give pure **18-HCl** (41% of a white powder), mp: 240–242°C (lit [11] = 241–243°C). ^{1}H-NMR (200 MHz; CD_3OD): δ 1.03 (6H, t, CH_3CH_2); 1.78 (4H, s, CH_3CH_2); 3.02–3.40 (10H, m, CH_2N, $ArCH_2$); 8.79 (1H, d, ArH); 6.96 (1H, d, ArH); 7.17 (1H, t, ArH). MS ([FAB(+)], thioglycerol), M = 260: *m/e* = 261 ($[M + H]^+$, 50). $C_{16}H_{24}N_2O$•HCl. M 293.02.

*Ethyl 4-(N-propyl-{2-[4-(2-oxy-3H-indolyl)]}ethylamino)butanoate **19***
Compound **19** was prepared as for **18** from 4-bromoethyl butanoate (1.78 g; 9.16 mmol), **17** (hydrochloride 1.00 g; 3.9 mmol) and $KHCO_3$ (0.39 g; 3.9 mmol) in 10 mL of anhydrous toluene. Usual work up and silica-gel column chromatography with ethyl acetate/hexane 7:3, gave **19**. The base was converted to the hydrochloride (48% of a white powder, mp: 119–121°C, from acetonitrile). IR (KBr): 3200, 2950, 2940, 1720, 1700, 1600, 1450, 1380, 1250, 1180, 1160, 780 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.98 (3H, t, $CH_3CH_2CH_2$); 1.20 (3H, t, CH_3CH_2O); 1.43 (2H, m, $CH_3CH_2CH_2$); 1.75 (2H, m, $CH_2CH_2CH_2$); 2.26 (2H, t, CH_2CO); 2.29–2.54 (6H, m, CH_2CH_2N); 2.66 (2H, s, $ArCH_2CO$); 3.48 (2H, s, $ArCH_2N$); 4.10 (2H, m, CH_2O); 6.71 (1H, d, ArH); 6.82 (1H, d, ArH); 7.13 (1H, t, ArH); 9.84 (1H, s, NHCO). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.85 ($CH_3CH_2CH_2N$); 14.21 (CH_3CH_2O); 20.36 ($CH_3CH_2CH_2N$); 22.47 ($NCH_2CH_2CH_2CO_2$); 31.91 ($NCH_2CH_2CH_2CO_2$); 31.91 ($ArCH_2CH_2N$); 35.04 ($ArCH_2CON$); 53.05 ($CH_3CH_2CH_2N$); 54.09 ($NCH_2CH_2CH_2CO_2$); 56.02 ($ArCH_2CH_2N$); 60.23 (CH_3CH_2O); 107.45 (ArC4); 122.81 (ArC6); 123.94 (ArC1); 127.96 (ArC5); 137.09 (ArC2); 142.33 (ArC3); 173.62 (CO, acid); 177.37 (CO, lactam). MS (EI); M = 332; *m/e* = 333 ($[M + 1]^+$, 40); 303 ([M – Et], 10); 287 ([M – OEt], 60). Anal $C_{19}H_{28}N_2O_3$•HCl. M 368.89.

*Methyl 4-(N-propyl-{2-[4-(2-oxy-3H-indolyl)]}ethylamino)butanoate **20** (Method B)*
Ethyl monosuccinate (7.80 g; 78 mmol) was obtained by treating succinic anhydride in refluxing methanol and was dissolved in 50 mL auhydrous toluene under nitrogen. The solution was stirred and cooled at 0°C while $NaBH_4$ (0.74 g; 19.7 mmol) was added by portions under stirring below 10°C until the end of hydrogen evolution. A solution of compound **17-HCl** (1.00 g; 3.94 mmol) into 10 mL toluene was added dropwise and the mixture was refluxed until the reaction was complete (4 h, TLC). The mixture was cooled and washed with 2 N NaOH, extracted with organic solvent, dried over $MgSO_4$, evaporated under reduced pressure, and purified on a silica-gel column with ethyl acetate/hexane 8:2. Compound **20** was solubilized in anhydrous ether and the hydrocholoride was obtained by bubbling HCl gas (48%, white powder, mp: 157–159°C from acetonitrile). IR (KBr): 3400, 2950, 2600, 1720, 1700, 1600, 1450, 1240, 1200, 1180, 880, 780 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 1.027 (3H, t, CH_3CH_2); 1.85 (2H, m, CH_3CH_2); 2.16 (2H, m, $CH_2CH_2CH_2$); 2.32 (2H, t, CH_2CH_2CO); 3.18 (8H, m, $ArCH_2CH_2$ and CH_2N); 3.51 (2H, s, $ArCH_2CO$); 3.69 (3H, s, CH_3CO); 6.64 (2H, 2d, ArH); 7.14 (1H, t, ArH); 8.89 (1H, s, NH). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.21 ($CH_3CH_2CH_2N$); 16.49 ($NCH_2CH_2CH_2CO_2$); 18.43 ($CH_3CH_2CH_2N$); 26.80 ($ArCH_2CH_2N$); 27.10 ($NCH_2CH_2CH_2CO_2$); 34.59 ($ArCH_2CON$); 51.04 ($CH_3CH_2CH_2N$); 51.99 ($ArCH_2CH_2N$); 52.30 ($NCH_2CH_2CH_2CO_2$); 54.27 (CH_3O); 108.90 (ArC4); 122.02 (ArC6); 124.58 (ArC1); 128.63 (ArC5); 132.22 (ArC2); 143.10 (ArC3); 172.58 (CO, acid); 176.28 (CO, lactam). MS ([FAB(+)], thioglycerol); M = 318; *m/e* = 319 ($[M + H]^+$, 100); 303 ($M - CH_3^+$, 5). Anal $C_{18}H_{26}N_2O_3$•HCl•0.25H_2O. M 359.37.

*4-(N-Propyl-{2-[4-(2-oxy-3H-indolyl)]}ethylamino)butanenitrile **21***
Compound **21** was prepared as for **18** from 4-bromobutyronitrile (1.17 g; 7.90 mmol) and **17-HCl** (2.00 g; 7.18 mmol) in 10 mL anhydrous toluene and $KHCO_3$ (1.44 g; 14.36 mmol). Further purification and chromatography with ethyl acetate/hexane 6:4 gave **21**. The base was converted to the hydrochloride (35% of a pale yellow powder, mp: 126–128°C, from isopropanol/methanol 6:4). IR (KBr): 3400, 3200, 2980, 2220, 1700, 1620, 1460, 1320, 1260, 780 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.91 (3H, t, CH_3); 1.68 (2H, m, CH_3CH_2); 2.01 (2H, m, CH_2CH_2CN); 2.65 (2H, t, CH_2CN); 2.96–3.36 (8H, m, $5CH_2$); 3.54 (2H, s, $ArCH_2CO$); 6.69 (1H, d, ArH); 6.68 (1H, d, ArH); 7.17 (1H, t, ArH); 10.43 (1H, s, CONH); 11.50 (1H, s, NH). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 10.82 ($CH_3CH_2CH_2N$); 13.93 (CH_2CN); 16.34 ($NCH_2CH_2CH_2CN$); 19.11 ($CH_3CH_2CH_2N$); 26.76 ($ArCH_2CH_2N$); 34.56 ($ArCH_2CON$); 49.99 ($CH_3CH_2CH_2N$); 51.77 ($NCH_2CH_2CH_2CN$); 53.16 ($ArCH_2CH_2N$); 107.73 (ArC4); 119.74 (ArC6, CN); 123.94 (ArC1); 127.75 (ArC5); 132.85 (ArC2); 143.72 (ArC3); 176.09 (CO, lactam). MS (CI, NH_3 + isobutane) M = 285; *m/e* = 286 ($[M + 1]^+$, 100); 571 ($[2M + 1]^+$, 5]. Anal $C_{17}H_{23}N_3O$•HCl•H_2O. M 339.85.

*4-[2-(N-Propyl-N-(2-methoxyethyl)amino)ethyl]-2-indolone **22***
Compound **22** was prepared as for **20** from 2-methoxyethanoic acid (2.10 g; 23.34 mmol) in 100 mL anhydrous benzene, $NaBH_4$ (0.3 g; 7.81 mmol), and **17-HCl** (0.4 g; 1.56 mmol) in 10 mL toluene (reflux 2 h). Ethyl acetate/hexane 7:3 eluted the free base which was converted in its hydrochloride (40%, white crystals mp: 176–178°C from acetonitrile). IR (KBr): 3400, 2950, 1700, 1660, 1460, 1320, 1250, 1120, 800 cm^{-1}. ^{1}H-NMR

(200 MHz; DMSO-d_6): δ 0.89 (3H, t, CH_3CH_2); 1.54 (2H, m, CH_3CH_2); 2.97–3.37 (8H, m, $4CH_2$); 3.51 (2H, s, $ArCH_2CO$); 6.69–7.12 (3H, 2d + 1t, s, Ar*H*); 10.44 (1H, s, N*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 10.91 ($CH_3CH_2CH_2N$); 16.44 ($CH_3CH_2CH_2N$); 26.80 ($ArCH_2CH_2N$); 34.59 ($ArCH_2CON$); 51.04 ($CH_3CH_2CH_2N$); 52.31 ($ArCH_2CH_2N$); 53.88 ($NCH_2CH_2OCH_3$); 58.25 (CH_3O); 66.21 ($NCH_2CH_2OCH_3$); 107.78 (ArC4); 121.68 (ArC6); 125.03 (ArC1); 127.83 (ArC5); 133.04 (ArC2); 143.76 (ArC3); 176.15 (CO, lactam). MS ([FAB(+)], glycerol) M = 276; ([M + H]$^+$, 100). Anal $C_{16}H_{24}N_2O_2HCl{\cdot}0.75H_2O$. M 326.34.

4-[2-(N-Propyl-N-(2-thiomethylethyl)amino)ethyl]-2-indolone ***23***

Compound **23** was prepared as for **20** from 3-thiabutanoic acid (1.86 g; 17.55 mmol) in 100 mL anhydrous benzene, $NaBH_4$: (0.22 g; 5.85 mmol). Ethyl acetate/hexane 1:1 eluted the free base, which was converted to its hydrochloride (55%, white powder, mp: 190–192°C recrystallized twice from methanol/ether 6:4 and then from acetonitrile). IR (KBr): 3200, 2950, 2600, 1710, 1620, 1460, 1240, 950, 840 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.89 (3H, t, CH_3); 1.50 (2H, m, CH_3CH_2); 2.12 (3H, s, CH_3S); 2.48–2.70 (8H, m, $4CH_2$); 3.5 (2H, s, $ArCH_2CO$); 6.71–7.15 (3H, 2d + 1t, Ar*H*); 8.4 (1H, s, N*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11. 84 ($CH_3CH_2CH_2N$); 15.86 (CH_3S); 20.37 ($CH_3CH_2CH_2N$); 31.06 ($ArCH_2CH_2N$); 31.87 ($NCH_2CH_2SCH_3$); 35.03 ($ArCH_2CON$); 53.69 ($CH_3CH_2CH_2N$); 54.36 ($ArCH_2CH_2N$); 56.06 ($NCH_2CH_2S-CH_3$); 107.46 (ArC4); 122.85 (ArC6); 125.03 (ArC1); 128.06 (ArC5); 136.95 (ArC2); 142.20 (ArC3); 177.05 (CO, lactam). MS (CI, NH_3^+) M = 292: *m/e* = 293 ([M + 1]$^+$, 100). Anal $C_{16}H_{24}N_2OS{\cdot}HCl{\cdot}0.25H_2O$ (C, H, N, O, S, Cl). M 333.40.

4-[2-(N-n-Propyl-N-2-(2-thienylethyl)amino)ethyl]-2-3H-indolone ***24***

Compound **24** was prepared as for **20** from 2-thienyl ethanoic acid (4.16 g; 29.3 mmol) in 100 mL anhydrous benzene, $NaBH_4$ (0.37 g; 9.78 mmol) and **17-HCl** (0.50 g; 1.98 mmol) in 10 mL toluene (reflux 3 h). Ethyl acetate/hexane 6:4 eluted the free base, which was converted in its hydrochloride (61%, white powder, mp: 128–132°C from methanol/ether 6:4). IR (KBr): 3400, 3200, 2950, 2600, 1690, 1620, 1460, 1320, 1250, 800, 700 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.90 (t, 3H, CH_3); 1.49 (m, 2H, CH_3CH_2); 2.49–3.00 (m, 10H, $3CH_2N$, $ArCH_2$, thioCH_2); 3.48 (s, 2H, $ArCH_2CONH$); 6.74–7.19 (m, 6H, Ar*H*); 9.36 (1H, s, N*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): δ 11.68 ($CH_3CH_2CH_2N$); 20.41 ($CH_3CH_2CH_2N$); 27.97 (NCH_2CH_2CHS); 31.00 ($ArCH_2CH_2N$); 35.12 ($ArCH_2CON$); 54.21 ($CH_3CH_2CH_2N$); 55.88 ($ArCH_2CH_2N$); 55.99 ($NCH_2CH_2CH_2S$); 107.58 (ArC4); 122.76 (ArC6); 123.27 (C5, thienyl); 124.01 (C3, thienyl); 126.55 (C4, thienyl); 124.50 (ArC1); 127.97 (ArC5); 137.00 (ArC2); 142.46 (C2, thienyl); 142.90 (ArC3); 177.81 (CO, lactam). MS ([FAB(+)], *meta*-nitrobenzylic alcohol), M = 436; *m/e* = 437 ([M + H]$^+$, 100); 339 (M – $CH_2C_4H_3S$, 19). Anal $C_{19}H_{24}N_2OS{\cdot}HCl{\cdot}0.25H_2O$ (C, H, N, O, S, Cl). M 369.43.

2-Propoxy-4-[2(dipropylamino)ethyl]-2-3H-indole ***25***

Compound **25** was prepared as for **18** from 1-bromopropane (0.95 g; 7.80 mmol), **17-HCl** (1.00 g; 3.9 mmol) into 100 mL anhydrous toluene and $KHCO_3$ (0.59 g; 3.9 mmol). Usual work up and silica-gel column chromatography with ethyl acetate/cyclohexane 1:1 gave **25** which was converted to its hydrochloride (15% of a pale yellow powder, mp: 211–212°C, methanol/ether 6:4). ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.89 (6H, t, $2CH_3CH_2$ CH_2N); 1.06 (3H, t, $CH_3CH_2CH_2O$), 1.50 (4H, sext, 2 $CH_3CH_2CH_2N$); 1.80 (2H, sext, $CH_3CH_2CH_2O$); 2.40 (4H, m, 2 CH_2N); 2.66 (4H, m, $ArCH_2CH_2N$); 3.45 (2H, s, $ArCH_2C{=}N$); 4.15 (2H, t, CH_2O); 6.80–7.30 (3H, 2d and 1t, Ar*H*). MS ([FAB (+)], thioglycerol), M = 302; *m/e* = 303 ([M + H]$^+$, 25); 259 (M – C_3H_7, 50). $C_{19}H_{31}N_2OCl$. M 338.93.

Ethyl 4-(2-{[N-(ethyloxycarbonylpropyl)-N-propyl]amino}ethyl)-2-3H-indolyloxy butanoate ***26***

This compound was isolated during the preparation of **19**. Yield of hydrochloride 20%, white powder, mp: 94–98°C. IR (KBr): 3400, 2960, 2920, 2400, 1720, 1600, 1450, 1280, 1180, 1080, 1020, 860, 780 cm^{-1}. ^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.90 (3H, t, $CH_3CH_2CH_2$); 1.25 (3H, t, CH_3CH_2O); 1.26 (3H, t, CH_3CH_2O); 1.42 (2H, m, $CH_3CH_2CH_2$); 1.74 (4H, m, $CH_2CH_2CH_2$); 2.07 (2H, t, $OCH_2CH_2CH_2$); 2.26 (2H, t, $NCH_2CH_2CH_2$); 2.32–2.65 (6H, m, $ArCH_2CH_2$ and CH_2N); 3.44 (2H, s, $ArCH_2C(OR){=}N$); 4.17 (4H, m, CH_3CH_2O); 4.23 (2H, t, $CH_2CH_2CH_2O$); 6.78 (1H, d, Ar*H*); 6.87 (1H, Ar*H*); 7.22 (1H, t, Ar*H*). ^{13}C-NMR (200 MHz; $CDCl_3$): see table I. $C_{25}H_{40}N_2O_5Cl$. M 484.07.

3-[2-(2-Methoxymethyl)ethylidene]-4-{2-[N-(2-methoxymethyl)-N-propylamino]ethyl}-2-indolone ***27***

This compound was isolated during the preparation of **22** after elution with ethyl acetate/hexane 6:4. Yield of hydrochloride 18%, white powder, mp: 163–165°C, from acetonitrile. MS ([FAB(+)], glycerol); M = 332; *m/e* = 333 ([M + H]$^+$, 100); 317 (M – CH_3, 5); 301 (M – OCH_3, 10); 287 (M – CH_2OCH_3, 15). $C_{19}H_{29}N_2O_3Cl$. M 369.01.

3-[2-(2-Methylthiomethyl)ethylidene]-4-{2-[N-(2-methylthiomethyl)-N-propylamino]ethyl}-2-indolone ***28***

This compound was isolated during the preparation of **23** after elution with ethyl acetate/hexane 6:4. Yield of hydrochloride 19%, white powder, mp: 185–187°C, from acetonitrile. IR (KBr): 3200, 2950, 2900, 1700, 1660, 1620, 1540, 1460, 1340, 800, 740 cm^{-1}. MS ([FAB (+)], glycerol); M = 364; *m/e* = 365 ([M + H]$^+$, 100); 317 (M – CH_3S, 15); 303 (M – CH_2SCH_3, 20). $C_{19}H_{29}N_2OS_2Cl$. M 401.15.

3-[2-(2-Thienylmethyl)ethylidene]-4-{2-[N-(2-thienylmethyl)-N-propylamino]ethyl}-2-indolone ***29***

This compound was isolated during the preparation of **24** after elution with ethyl acetate/hexane 6:4. Yield of hydrochloride 24%; white powder soluble in toluene, mp: 150–152°C from methanol/ether. IR (KBr): 3400, 3100, 2950, 1720, 1620, 1460, 1410, 900, 860, 800, 700 cm^{-1}. MS ([FAB(+)], *meta*-nitrobenzylic alcohol); M = 436: *m/e* = 437 ([M + 1]$^+$ = 100); 339 (M – $CH_2C_4H_3S$, 19). $C_{25}H_{29}N_2OS_2Cl$. M 473.11.

Dopamine binding assays

D_2 dopamine receptor bindings were measured by using [^{3}H]-spiperone (spec act 90 Ci/mmol, Amersham) labeled D_2 site in homogenates of rat striata prepared with a Kontes-Duall homogenizer and diluted 1:50 [15]. Samples were incubated for 30 min at 37°C and then filtered over GF/B Whatman filters (pretreated with cold 50 mM Tris pH 7.7 buffer) and rinsed three times with 5 mL of 50 mM Tris pH 7.7 buffer. Filters were counted using standard liquid scintillation techniques. Specific D_2 binding was determined using [^{3}H]-spiperone (0.6 nM) with ketanserine for serotoninergic receptors inhibition (1 mM). IC_{50} values were calculated by log-probit analysis, using at least seven concentrations of the drug in triplicate. K_i values were calculated with the Cheng–Prusof relation.

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