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5-, 6-, 7- And 8-amino-2-(*N*,*N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalenes: centrally acting DA and 5-HT_{1A} agonists

P Stjernlöf[1], T Elebring[2], B Andersson[1], A Svensson[2], K Svensson[3], A Ekman[1], A Carlsson[3], H Wikström[1,4]

[1]*Medicinal Chemistry Unit, Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg;*
[2]*Astra-Hässle AB, Kärragatan 5, S-431 83 Mölndal;*
[3]*Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg, Sweden;*
[4]*University Centre for Pharmacy, Department of Medicinal Chemistry, University of Groningen, Antonius Deusinglaan 2, NL-9713AW Groningen, The Netherlands*

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Summary — 5-, 6-, 7- and 8-Amino-2-(*N*,*N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene were synthesized and compared with the corresponding phenolic compounds *in vivo* and *in vitro* for their effects on central serotonergic (5-HT_{1A}) and dopaminergic (D_2) systems. The 5- and 8-amino isomers surprisingly showed a 100-fold lower affinity for D_2 and 5-HT_{1A} receptors, respectively, than their corresponding phenols. This was also reflected *in vivo*. The 6-amino- and hydroxy-isomers were equipotent, while the 7-amino compound showed *in vivo* effects both on dopaminergic and serotonergic systems, the latter not being noticed *in vitro*. Intermediates 8-bromo-2-(*N*,*N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene and 2-(*N*,*N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene-8-carboxylic acid methyl ester were also tested and found to be quite potent 5-HT_{1A} agonists.

synthesis / aminotetralins / anilines / serotonergic / dopaminergic / agonists / 5-HT_{1A} / D_2 binding / 5-HTP accumulation / DOPA-accumulation / CNS

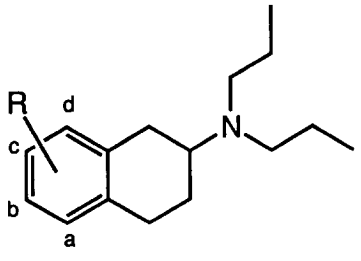
Introduction

The isomeric monohydroxylated aminotetralins **1a–d** (fig 1) have been extensively studied for their effects upon both central dopamine and serotonin receptors [1–11]. The 5-, 6- and 7-hydroxylated analogues (**1a–c**) were found to possess dopamine D_2 receptor agonist properties, the potency order being **1a** > **1c** > **1b**. These compounds showed no 5-HT_{1A} receptor agonism. The 8-substituted analog **1d**, also known as 8-OH-DPAT, was found to be a potent and selective 5-HT_{1A} agonist [1].

Compounds possessing a phenolic moiety are targets for metabolic inactivation *via* conjugation. This inactivation greatly reduces the oral bioavailability of such compounds. Bioisosteric analogues of phenols, which are less prone to be targets for metabolic inactivation by enzymes, may be of great interest with regard to the development of clinically useful drugs. One approach to solving this problem may be to use different types of heterocyclic compounds. A suitable starting material for the synthesis of, for example, indolic bioisosters may be the aniline moiety. The objectives of this investigation were to prepare anilines **2a–d** for such use and to investigate their action upon central monoaminergic receptors.

Chemistry

Different approaches have been adopted for the preparation of anilinic aminotetralins **2b–d** [12–18]. In addition, an attractive route for compound **2a** has

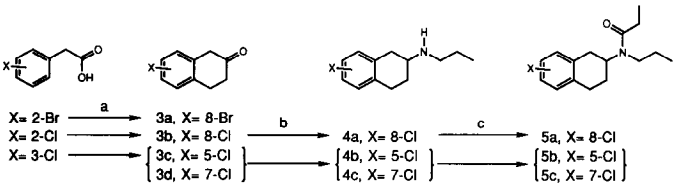


Compd	R
1(a-d)	OH
2(a-d)	NH_2

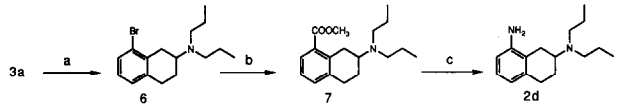
Fig 1. 5-, 6-, 7- and 8-OH- and -NH_2-DPAT (**1a–d** and **2a–d**, respectively).

recently been reported [19]. In the present study all the regioisomers were needed. Therefore, a general synthetic method leading to all 4 isomers would be attractive. An obvious route would be to synthesize the unsubstituted amide **5** (X = H), which after nitration and reduction would give all 4 isomers. Initial tests were made on this route, but the isomers were not easily separated on a silica column. Another straightforward route for the 8-NH_2 compound was investigated, where the key step was a Curtius rearrangement. Thus, starting from 2-bromophenylacetic acid (scheme 1) the corresponding 8-bromotetralone **3a** was synthesized according to the method of Burckhalter and Campbell [20] *via* Friedel–Crafts acylation of ethene followed by intramolecular alkylation in good yields. The ketone and dipropylamine were condensed (scheme 2) to give the enamine, which was reduced with cyanoborohydride resulting in the 8-bromo substituted aminotetralin **6** (scheme 2). Treatment of this compound with *n*-butyllithium followed by carbon dioxide afforded the corresponding carboxylic acid, which was readily converted into its methyl ester **7** by refluxing in methanol containing hydrochloric acid. The methyl ester was treated with conc sulfuric acid and sodium azide in refluxing dichloromethane to yield the desired 8-amino-2- (*N,N*-di-*n*-propylamino)tetralin **2d**.

In order to minimize the separation problems of the first-mentioned route and to avoid starting from scratch for each isomer as in the second route (which would also necessitate separation of bromotetralones) and other routes, a pathway was outlined (schemes 1, 3) which would lead to 2 isomers at a time. As mentioned above, nitration of an unsubstituted aminotetralin gives rise to all isomers. The following pathway utilizes the directive ability of a chlorine substituent to direct to the *ortho-* and *para*-positions in electrophilic aromatic substitution. After its use the chlorine functionality can be easily removed by reduction. Starting with 2-chlorophenyl acetyl chloride, 8-chloro-2-tetralone **3b** was prepared in the same manner as for **3a** and then further converted into the *n*-propylamine analog **4a** by reductive amination using sodium cyanoborohydride. The amine was then propionylated to **5a** and nitrated, giving a mixture of



Scheme 1. Reagents: a) 1. $SOCl_2$; 2. Ethene, $AlCl_3$; b) 1. *n*-$PrNH_2$, $NaBH_3CN$; 2. HCl; c) EtCOCl, TEA.



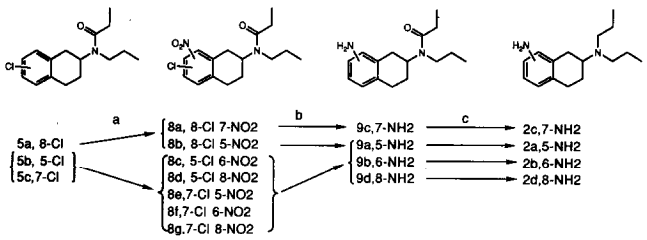
Scheme 2. Reagents: a) 1. $(n\text{-}Pr)_2NH$, *p*-TosOH; 2. $NaBH_3CN$; 3. HCl; b) 1. *n*-BuLi, CO_2; 2. MeOH, HCl; c) H_2SO_4, NaN_3.

the 5- and 7-nitro derivatives **8a** and **8b**. Chromatographic separation on silica yielded the pure isomers, which were independently reduced in 2 steps. First, catalytic hydrogenation yielded the aniline-amides **9a** and **9c** in turn, followed by reduction with lithium aluminium hydride to give the desired 5- and 7-NH_2-substituted 2-(*N,N*-di-*n*-propylamino)tetralins **2a** and **2c**. A similar route was outlined for the 2 other isomers using 3-chlorophenyl acetic acid as starting material, which in the cyclization step gave the 5- and the 7-chlorotetralones **3c** and **3d**. Without separation, the cyclic ketones were further converted *via* reductive amination to **4b** and **4c**. Acylation and nitration yielded an isomeric mixture, presumably containing **8c–g** which after hydrogenation and chromatographic separation furnished the 6- and 8-NH_2-substituted 2-(*N*-propyl-*N*-propionylamino)tetralins **9b** and **9d**, but also a minor amount of the 5-NH_2-substituted isomer **9a**. Obviously some of the 7-chloro compounds must have been nitrated in the 5-position, *meta* to the chlorine substituent. The compounds **9b** and **9d** were reduced as above using lithium aluminium hydride to the corresponding amines **2b** and **2d**. The identities of the isomers were assigned by ^{1}H-NMR and simplified by the fact that the 8-isomer **2d** was made by 2 different routes.

Pharmacology

Biochemistry

The *in vivo* biochemical test utilizes the well-established phenomenon of receptor mediated feed-



Scheme 3. Reagents: a) HNO_3, H_2SO_4; b) HCO_2 NH_2, Pd/C; c) $LiAlH_4$.

back inhibition of the presynaptic neuron [21]. DA and noradrenaline (NA) have the same general biosynthetic pathway, and the synthesis rate of the catecholamines DA and NA is decreased by agonists (and increased by antagonists) at dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT receptor agonists [22, 23]. The 5-HTP accumulation, following decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD 1015), was used as an indicator of the 5-HT synthesis rate in 3 different brain areas (table I). In addition, the DOPA accumulation was used as an indicator of DA synthesis rate in the DA-rich areas (*ie* limbic system and corpus striatum) and the NA synthesis rate in the NA-rich hemispheres (mainly the cortex). For this study we used reserpine-pretreated rats (5 mg/kg sc, 18 h), in which the synthesis rate of DOPA in particular was raised *via* feedback regulation. This behavioural and biochemical model was designed to detect directly-acting agonists at central monoamine receptors.

Locomotor activity and behaviour

Postsynaptic agonistic effects of the test compounds were assessed by the increase in locomotor activity (reversal of reserpine-induced hypokinesia). DA receptor agonists induce locomotor stimulation and at high doses also stereotyped behaviour, such as sniffing and licking. Selective 5-HT_{1A} receptor agonists induce the so called 5-HT syndrome (flat body posture and reciprocal forepaw treading).

Motor activity recordings were carried out as previously described with the use of motility meters (table II) [3]. The behaviour of the animals could be observed through semi-transparent glass windows.

In vitro binding

The ability of the test compounds to displace the radioactively-labelled ligands, [^{3}H]-spiperone and [^{3}H]-8-OH-DPAT, from D_2 and 5-HT_{1A} receptor sites respectively in homogenized rat brain tissue was assessed *in vitro* (table II) [24].

Results and discussion

As can be seen in table II, compounds **2a–2d** showed a very poor binding at both 5-HT_{1A} and D_2 receptors. There was a striking difference between these anilines and the corresponding phenolic compounds. The 5-anilino compound **2a** had ≈ 80-fold lower affinity, as compared to 5-OH-DPAT **1a** at D_2 sites. There was a similar relationship between 8-NH_2-DPAT **2d** and 8-OH-DPAT **1d**, *ie* **2d** had a 50-fold lower affinity for 5-HT_{1A} sites than **1d**. The trend was similar for the 7-substituted compounds **1c** and **2c**, where the difference in D_2 receptor binding was ≈ 30-fold. The lower potency of these anilinic compounds was also reflected in the DOPA and 5-HTP accumulation assays (table I). Here the 5-anilino compound **2a** showed only weak responses, especially when compared to **1a**. The 8-anilino compound **2d** had a clear-cut 5-HT_{1A} agonist profile, although with low

Table I. Effects on brain DA and 5-HT synthesis rates *in vivo* (sc administration).

Compound	*Subst*	*ED_{50} (μmol/kg (sc))*					
		DOPA accumulation[a]			*5-HTP accumulation*[a]		
		Limb	*Stri*	*Hem*	*Limb*	*Stri*	*Hem*
1a	5-OH	0.011[b]	0.009[b]	I[c] (13.5)	I (13.5)[b]	I (13.5)[b]	I (13.5)[b]
2a	5-NH_2	P[d] (3.1)	P (3.1)	I (50.0)	P (3.1)	P (12.5)	P (12.5)
1b	6-OH	0.18[b]	0.17[b]	I (11.3)	I (11.3)[b]	I (11.3)[b]	I (11.3)[b]
2b	6-NH_2	P (12.5)	1.1	P (12.5)	P (12.5)	P (12.5)	P (12.5)
1c	7-OH	0.027[b]	0.03[b]	I (11.0)	I (11.0)[b]	I (11.0)[b]	I (11.0)[b]
2c	7-NH_2	0.8	2.3	P (12.5)	0.8	0.8	0.8
1d	8-OH	P (45.0)	P (45.0)	P (45.0)	0.052	0.063	0.052
2d	8-NH_2	P (50.0)	3.0	I (50.0)	13.3	16.6	4.6
6	8-Br	13.5	12.0	I (50.0)	11.0	14.0	18.0
7	8-COOMe	I (50.0)	P (50.0)	I (50.0)	3.3	2.4	1.4

[a]Abbreviations: limb : limbic system; stri : corpus striatum; hem : hemispheres; [b]data from [1]; [c]I : inactive at the highest dose tested (""); [d]P : partial effects at the doses tested.

potency. The *in vivo* potency of compound **2c** in reserpinized rats was, however, relatively high. Compound **2c** showed activity at both the D_2 and the 5-HT_{1A} receptors. This result was supported by the mixed behavioural effects observed (table II). The 7-OH-analog **1c** also showed dopaminergic effects, but no 5-HT behavioural effects could be seen. This discrepancy for **2c** in the *in vitro* and *in vivo* assays may be due to an active metabolite, but this needs to be further evaluated. The difference in affinity for the 6-isomers was not that dramatic. The 6-anilinotetralin **2b**, which showed low affinity at both D_2 and 5-HT_{1A} sites, had an agonistic profile in reserpinized rats which was quite similar to the corresponding phenolic compound **1b**.

In addition to the NH_2-substituted 2-aminotetralins some intermediates were tested. The 8-bromo-compound **6** showed affinity for both D_2 and 5-HT_{1A} binding sites, with a preference for 5-HT_{1A} sites. It was active in both the DOPA and the 5-HTP accumulation biochemical assays. In the behavioural assay a 5-HT syndrome was seen. The 8-substituted ester **7** acted as a 5-HT_{1A} agonist with a profile similar to that of 8-OH-DPAT, although less potent. This is in accordance with the recent binding results of Liu *et al* [25].

Experimental protocols

Chemistry

Magnetic resonance spectra were achieved on a Varian VXR4000 300 MHz spectrometer using tetramethylsilane as the internal standard. ^{13}C-NMR spectra were assigned in most of the cases by the use of the Attached Proton Test (APT). In any questionable case the assignment was omitted. The numerous resonance peaks in ^{1}H- and ^{13}C-NMR in the amide compounds were due to the rotamers. No attempts (heating, etc) were made to simplify these spectra. Mass spectra were recorded on a HP5970A Mass Selective Detector at 70 eV and interfaced with an HP 5700A gas chromatograph. Elemental analyses (C, H, N) for new and biologically tested substances were within 0.4% of theoretical values. Melting points are uncorrected. All physical data (except for mp and elemental analysis) on amines were performed on the free bases. Yields were not optimized. 5-,6-,7- and 8-Hydroxy-2-*N*,*N*-dipropylamino-1,2,3,4-tetrahydronaphthalenes **1a–1d** were previously synthesized in our laboratory [1].

8-Bromo-1,2,3,4-tetrahydronaphthalene-2-one ***3a***

A solution of thionyl chloride (2.5 g, 21.2 mmol) in dichloromethane (5 ml) was added to a solution of 3.65 g (16.9 mmol) 2-bromophenylacetic acid in dichloromethane (10 ml). After 1.5 h reflux, the solution was cooled and the solvent and excess thionyl chloride were removed by evaporation. The resulting acid chloride was dissolved in dichloromethane (10 ml) and slowly added to a cooled (–5°C) slurry of 9.2 g (68.9 mmol) aluminium trichloride in dichloromethane (200 ml). Ethene was added to the solution in a gentle stream for 2 h. The resulting mixture was cautiously poured on ice-water (75 ml). After separation, the organic phase was washed with 10% hydrochloric acid followed by a saturated solution of sodium hydrogen carbonate. The organic solution was dried (magnesium sulfate), filtered and evaporated to obtain a residue of 5.9 g. This material was dissolved in ethanol and subjected to a solution of 4.1 g (21.4 mmol) sodium bisulfite in a small amount of water. The precipitated bisulfite adduct was filtered off, washed with acetone and air-dried (5.0 g). Prior to use, the adduct was dissolved in water and basified (5 M sodium hydroxide). The aqueous phase was extracted 3 times

Table II. *In vitro* binding and *in vivo* behavioural data.

Compound	*Subst*	*In vitro binding, K_i*[a]		*Motor activity*		
		5-HT_{1A} (nM)	*D_2 (nM)*	*Dose (sc) (μmol/kg)*	*Counts*[d] *30 min*	*Behavioral observation*
1a	5-OH	1040[b]	10.8 ± 2.3	0.08	59 ± 24	DA
2a	5-NH_2	1280	828 ± 225	50.0	326 ± 72	DA
1b	6-OH	3260[b]	339[b]	3.5	160 ± 23	DA
2b	6-NH_2	4000[b]	580 ± 65	12.5	109 ± 46	DA
1c	7-OH	2810[b]	54 ± 12	3.5	170 ± 7	DA
2c	7-NH_2	530[b]	1629 ± 135	12.5	11 ± 2	DA, 5-HT
1d	8-OH	8.7 ± 5.8	1357 ± 275	0.02	55 ± 17	5-HT
2d	8-NH_2	162 ± 63	1620[b]	12.5	89 ± 28	5-HT
6	8-Br	30 ± 11	316[b]	50	95 ± 29	5-HT
7	8-COOMe	8.9[b]	1691 ± 208[c]	3.1	69 ± 25	5-HT

[a]Inhibition constants (K_i) of the various compounds were calculated as described in the *Experimental protocols*, based on 3 determinations in triplicate unless otherwise stated. The deviations are given as SEM values; [b]single determination in triplicate; [c]2 determinations in triplicate; [d]value with SEM ($n = 4$).

with diethyl ether, dried (magnesium sulfate), filtered and evaporated to yield 2.4 g (64%) of a brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 2.60 (t, 2H), 3.10 (t, 2H), 3.65 (s, 2H), 7.08 (t, J = 7.7 Hz, 1H), 7.18 (d, J_1 = 7.5 Hz, 1H), 7.48 (d, J_2 = 7.3 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 29.18 (CH_2), 38.42 (CH_2), 44.45 (CH_2), 124.21 (C), 126.93 (CH), 127.97 (CH), 130.86 (CH), 133.05 (C), 138.60 (C); MS *m/e* 224 (65, M^+), 226 (65, M^+ + 2), 182 (100), 184 (95), 115 (82), 103 (74), 117 (53), 57 (41).

8-Chloro-1,2,3,4-tetrahydronaphthalene-2-one ***3b***
In a manner analogous to that for **3a**, 2-chlorophenylacetic acid (41 g, 240 mmol) was converted *via* bisulfite workup to yield 29.8 g (69%) of the desired tetralone. ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 2.60 (t, 2H), 3.10 (t, 2H), 3.67 (s, 2H), 7.15 (m, 2H), 7.3 (m, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 29.00, 38.41, 41.60, 126.26, 127.56, 127.62, 131.39, 133.64, 138.39, 208.96; MS *m/e* 182 (15, M^+), 180 (43, M^+–2), 138 (100), 115 (34), 103 (33), 140 (32).

5- and 7-Chloro-1,2,3,4-tetrahydronaphthalene-2-one ***3c*** *and* ***3d***
In a manner analogous to that of **3a** and **3b**, 3-chlorophenylacetic acid (10.0 g, 56.8 mmol) was converted *via* bisulfite workup to yield 10.2 g of the isomeric mixture (30/70, not assigned). This material was used in the next step without further purification.

8-Chloro-2-(N-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***4a***
Acetic acid (14 ml), propyl amine (15.6 g, 17 ml, 263 mmol) and sodium cyanoborohydride (40 g, 624 mmol) was added consecutively to a solution of 47 g (263 mmol) 8-chloro-1,2,3,4-tetrahydronaphthalene-2-one **3b** in methanol (400 ml). After standing overnight at room temperature, water was added followed by 10% hydrochloric acid. The mixture was stirred for a few h in a well-ventilated hood allowing hydrogen cyanide to vaporize, and then evaporated to a residue which was suspended in water, basified (2 M sodium hydroxide) and extracted twice with diethyl ether and twice with dichloromethane. The combined organic extracts were dried (sodium sulfate), filtered and evaporated to a crude product which contained a smaller amount of starting material. Purification on silica (dichloromethane/methanol, 19:1) yielded 29 g (50%) of the pure product as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.95 (t, 3H), 1.60 (sixt, 2H), 2.10 (m, 1H), 2.50 (dd, 1H), 2.74 (t, 2H), 2.86 (m, 2H), 2.98 (m, 2H), 3.20 (dd, 1H), 7.0 (m, 2H), 7.18 (d, 1H); ^{13}C-NMR (75.4 MHz, ∂ 11.68 (CH_3), 22.21 (CH_2), 22.78 (CH_2), 27.78 (CH_2), 28.45 (CH_2), 33.00 (CH_2), 53.59 (CH), 126.55 (CH), 126.59 (CH), 127.00 (CH), 132.54 (C), 134.48 (C), 138.20 (C); MS *m/e* 225 (13, M^+), 223 (38, M^+–2), 165 (100), 194.93, 129 (45), 128 (33).

5- and 7-Chloro-2-(N-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***4b*** *and* ***4c***
The isomeric mixture of tetralones **3c** and **3d** (10.0 g, 55.4 mmol) was subjected to reductive amination as above to give 5.0 g (40%) of the isomeric propylamines. The mixture was used in the next step without further purification.

8-Chloro-2-(N-n-propyl-N-propionyl-amino)-1,2,3,4-tetrahydronaphthalene ***5a***
Propionyl chloride (12.0 g, 12.0 ml, 129 mmol) was added dropwise to a solution of 8-chloro-2-(*N-n*-propylamino)-1,2,3,4-tetrahydronaphthalene **4a** (29.0 g, 129 mmol) and triethylamine (18 ml) in dichloromethane (300 ml) and left at room temperature for 10 min. The reaction mixture was washed with aqueous (10%) sodium carbonate followed by 10% hydrochloric acid, dried (magnesium sulfate), filtered and evaporated to yield 36.0 g (100%) of the desired material as an oil pure enough for further synthesis. ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.95 (q, 3H), 1.20 (q, 3H), 1.65 (m, 2H), 1.90 (m, 2H), 2.40 (m, 2H), 2.2–3.3 (m:s, 6H), 4.05 (m, 0.4 H), 4.65 (m, 0.6 H), 6.9–7.1 (m, 2H), 7.1–7.25 (m, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.61 (CH_3), 9.67 (CH_3), 11.38 (CH_2), 11.61 (CH_2), 22.94 (CH_2), 24.56 (CH_2), 26.85 (CH_2), 26.91 (CH_2), 27.20 (CH_2), 28.09 (CH_2), 30.05 (CH_2), 30.10 (CH_2), 30.70 (CH_2), 31.89 (CH_2), 43.74 (CH_2), 46.22 (CH_2), 51.27 (CH), 53.59 (CH), 126.4–127.0 (5 peaks, CH), 127.63 (C), 132.75 (C), 133.52 (C), 134.42 (C), 137.42 (C), 138.00 (C), 173.19 (C), 173.88 (C); MS *m/e* 281(0.4, M^+), 279 (1.1, M^+–2), 116 (100), 129 (48), 164 (41), 165 (18).

5- and 7-Chloro-2-(N-n-propyl-N-propionyl-amino)-1,2,3,4-tetrahydronaphthalene ***5b*** *and* ***5c***
The isomeric propylamines **4b** and **4c** (5.0 g, 22.3 mmol) were treated with propionic acid chloride as above and after the usual workup yielded 5.7 g (91%) of the isomeric mixture of desired amides, which was not further purified.

8-Bromo-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***6***
A solution of 8-bromo-1,2,3,4-tetrahydronaphthalene-2-one **3a** (2.0 g, 8.8 mmol), dipropyl amine (7.7 ml, 5.7 g, 56.3 mmol) and *p*-toluene sulfonic acid (0.17 g) in benzene (100 ml) was refluxed for 2 d using a Dean–Stark apparatus to separate condensed water. The progress in reaction was monitored on GLC. After cooling, the mixture was evaporated to a residue which was redissolved in methanol (100 ml). Sodium cyanoborohydride (8.3 g, 0.132 mol) was added and the resulting mixture stirred for 3 h. The mixture was evaporated, redissolved in dichloromethane and stirred together with 10% hydrochloric acid for several h in order to remove hydrogen cyanide (utilizing a well-ventilated hood). The aqueous phase was basified (15% sodium hydroxide) and extracted 3 times with dichloromethane. The combined organic phases were dried (magnesium sulfate), filtered and evaporated to obtain a residue of 2.48 g (91%) sufficiently pure for synthesis. Further purification by chromatography on silica could be carried out using acetone or ethyl acetate as eluant. Prior to biological testing the compound was converted into the HCl-salt by dissolution in HCl-saturated ethanol followed by evaporation and recrystallization from ethanol/diethyl ether. Mp: 158–161°C (HCl-salt); ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.90 (t, 6H), 1.50 (sext, 4H), 1.56 (m, 1H), 2.00 (m, 1H), 2.50 (t, 4H), 2.55 (m, 1H), 2.80–3.5 (m:s, 4H), 6.88 (t, J = 7.6 Hz, 1H), 7.04 (d, J_1 = 6.8 Hz, 1H), 7.38 (d, J_2 = 7.8 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 11.91 (CH_3), 22.21 (CH_2), 25.54 (CH_2), 30.64 (CH_2), 32.81 (CH_2), 52.67 (CH_2), 57.12 (CH), 126.05 (C), 126.71 (CH), 127.67 (CH), 129.75 (CH), 136.23 (C), 139.30 (C); MS *m/e* 309 (6, M^+), 311 (5, M^+ + 2), 130 (100), 280 (73), 282 (66),129 (46), 209 (28), 211 (26). Anal $C_{16}H_{25}BrClN$ (C, H, N).

2-(N,N-Di-n-propylamino)-1,2,3,4-tetrahydronaphthalene-8-carboxylic acid methyl ester ***7***
8-Bromo-2-(*N,N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene **6** (1.8 g, 5.8 mmol) was dissolved in dry diethyl ether (100 ml) and cooled to –78°C in a nitrogen atmosphere. *n*-Butyllithium (12 ml 1.6 M in hexane, 17 mmol) was added and the resulting mixture stirred for 2 h and then poured into a mixture of dry CO_2–ice in diethyl ether. After 1 h, water was added and the resulting mixture stirred for 0.5 h. The aqueous phase was separated and evaporated. The residue was redissolved in methanol, filtered and evaporated to yield 1.5 g of the intermediate carboxylic acid. Gaseous hydrogen chloride was bubbled through a solution of this material in dry methanol

(100 ml) for 30 min. The mixture was refluxed for 24 h and evaporated to yield 1.60 g (95%) of a raw product, which was chromatographed on silica (dichloromethane/methanol, 19:1) to yield 0.56 g pure product (30%). Analytical samples were recrystallized from methanol/diethyl ether, mp: 139–141°C (HCl-salt); Lit[25] 148–150°C (*R*-enantiomer) ^{1}H-NMR (300 MHz, $CDCl_3$) δ, 0.90 (t, 6H), 1.50 (sext, 4H), 1.65 (m, 1H), 2.05 (br d, 1H), 2.50 (t, 4H), 2.70–3.1 (m:s, 4H), 3.25 (q, 1H), 3.90 (s, 3H), 7.10 (d of d, J_1, J_2 = 7.6 Hz, 1H), 7.23 (d, J_2 = 7.6 Hz, 1H), 7.67 (d, J = 7.8, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 11.9 (CH_3), 22.1 (CH_2), 25.4 (CH_2), 29.7 (CH_2), 30.5 (CH_2), 51.8, 52.7 (CH_2), 57.0, 125.2 (CH), 128.0 (CH), 130.4 (C), 132.5 (CH), 137.9 (C), 138.2 (C), 168.4 (C); MS *m/e* 289 (M^+, 7), 260 (100), 157 (59), 129 (30), 128 (25), 189 (22). Anal $C_{18}H_{28}ClNO_2$ (C, H, N).

*8-Chloro-7-nitro-2-(N-n-propyl-N-propionylamino)-1,2,3,4-tetrahydronaphthalene **8a** and 8-chloro-5-nitro-2-(N-n-propyl-N-propionylamino)-1,2,3,4-tetrahydronaphthalene **8b***

To an ice-cooled solution of 8-chloro-2-(*N-n*-propyl-*N*-propionylamino)-1,2,3,4-tetrahydronaphthalene **5a** (36.0 g, 129 mmol) in nitromethane (250 ml) was added dropwise 150 ml nitrating acid (6.3 vol% nitric acid, 80.6 vol% sulfuric acid and 13.1 vol % water) until all starting material was consumed (monitored with gas chromatography after basification and extraction of analytical samples). Ice-water/diethyl ether was added and the mixture shaken and separated. The aqueous phase was basified (5 M sodium hydroxide) and extracted 3 times with diethyl ether. The combined organic extracts were dried (sodium sulfate), filtered and evaporated to obtain a residue of 46 g. The resulting residue was chromatographed by flash chromatography on silica column using petroleum ether/diethyl ether 1:2 as eluant and yielded 17 g (41%) of 8-chloro-7-nitro-2-(*N-n*-propyl-*N*-propionylamino)-1,2,3,4-tetrahydronaphthalene **8b** and 13 g (31%) of 8-chloro-5-nitro-2-(*N-n*-propyl-*N*-propionylamino)-1,2,3,4-tetrahydronaphthalene **8a** in mentioned order. **8a**: ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.90 (two t, 3H), 1.20 (t, 3H), 1.60 (m, 2H), 2.00 (m, 2H), 2.40 (q, 2H), 2.70–2.90 (m, 1H), 2.95–3.30 (m, 7H), 4.05 (m, 0.25H), 4.50 (sept, 0.75H), 7.10 (d+d, 1H), 7.55 (d+d, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.60 (CH_3), 11.36 (CH_3), 11.62 (CH_3), 23.00 (CH_2), 24.47 (CH_2), 26.39 (CH_2), 26.93 (CH_2), 27.40 (CH_2), 30.30 (CH_2), 30.39 (CH_2), 31.09 (CH_2), 32.29 (CH_2), 43.76 (CH_2), 46.72 (CH_2), 51.31 (CH), 53.03 (CH), 122.27 (CH), 122.57 (CH), 126.61 (CH), 127.28 (CH), 127.42 (CH), 135.80 (C), 136.72 (C), 141.80 (C), 142.53 (C), 146.77 (C), 173.00 (C), 174.00 (C); MS *m/e* 326 (0.9, M^+), 324 (2.3, M^+ – 2), 116 (100), 239 (20), 209 (16), 128 (16). **8b**: ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.95 (t, 3H), 1.20 (t, 3H), 1.65 (m, 2H), 2.00 (m, 2H), 2.40 (q, 2H), 2.75–2.95 (m, 1H), 3.00–3.30 (m, 7H), 4.10 (m, 0.25H), 4.50 (sept, 0.75H), 7.34 (d, 0.75H), 7.40 (d, 0.25H), 7.70 (d, 0.75H), 7.75 (d, 0.25H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.60 (CH_3), 11.39 (CH_3), 11.64 (CH_3), 23.05 (CH_2), 24.48 (CH_2), 26.30 (CH_2), 26.98 (CH_2), 27.35 (CH_2), 27.51 (CH_2), 31.55 (CH_2), 32.74 (CH_2), 43.65 (CH_2), 46.83 (CH_2), 50.90 (CH), 52.35 (CH), 122.93 (CH), 123.31 (CH), 127.26 (CH), 127.58 (CH), 132.90 (C), 133.16 (C), 136.00 (C), 136.85 (C), 139.57 (C), 148.14 (C), 173.00 (C), 173.99 (C); MS *m/e* 326 (4, M^+), 324 (15, M^+–2), 192 (10), 239 (63), 194 (40), 164 (20).

*5- and 7-Chloro-6- and 8-nitro-2-(N-n-propyl-N-propionylamino)-1,2,3,4-tetrahydronaphthalene **8c–g***

The amides **5b** and **5c** (5.6 g, 20.0 mmol) from the previous step were nitrated as described above to give a crude mixture (7.1 g, > 100%) of isomers.

*7-Amino-2-(N-n-propyl-N-propionylamino)-1,2,3,4-tetrahydronaphthalene **9c***

To solution of 13.0 g (40.2 mmol) 8-chloro-7-nitro-2-(*N-n*-propyl-*N*-propionylamino)-1,2,3,4-tetrahydronaphthalene **8a** and ammonium formate (70 g, 1.1 mol) in ethanol (300 ml) was added Pd/C (3.0 g) under a nitrogen atmosphere. After stirring overnight the reaction was complete. The mixture was filtered on Celite and the solvent evaporated. The residue was taken up in 10% sodium carbonate and dichloromethane and extracted. The aqueous solution was extracted 2 additional times with dichloromethane and the combined organic extracts were dried (magnesium sulfate), filtered and evaporated to yield 10.5 g (100%) crude product sufficiently pure for further synthesis. An analytical sample was recrystallized from diisopropyl ether. Mp: 90–95°C; ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.9 (q, 3H), 1.15 (q, 3H), 1.6 (br q, 2H), 2.9 (m, 2H), 2.35 (m, 2H), 2.65–3.0 (m, 4H), 3.15 (m, 3H), 3.55 (br s, 2H), 4.0 (sept, 0.5H), 4.6 (sept, 0.5H), 6.4 (d, 1H), 6.5 (t, 1H), 6.9 (d, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.70 (CH_3), 9.75 (CH_3), 11.4 (CH_3), 11.7 (CH_3), 22.9 (CH_2), 24.6 (CH_2), 26.9 (CH_2), 27.0 (CH_2), 28.1 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 33.0 (CH_2), 34.3 (CH_2), 43.7 (CH_2), 46.1 (CH_2), 51.3 (CH), 51.4 (CH), 53.8 (CH), 113.5–113.9 (5 peaks, CH), 115.0–115.4 (5 peaks, CH), 125.1 (C), 125.8 (C), 129.3–129.7 (6 peaks, CH), 135.6 (C), 136.4 (C), 144.1 (C), 144.4 (C), 173.3 (C), 173.8 (C); MS *m/e* 260 (M^+, 2),145 (100), 144 (36), 146 (14), 130 (10). Anal $C_{16}H_{24}N_2O$ (C, H, N).

*5-Amino-2-(N-n-propyl-N-propionylamino)-1,2,3,4-tetrahydronaphthalene **9a***

In a manner similar to that given above, 8-chloro-5-nitro-2-(*N-n*-propyl-*N*-propionylamino)-1,2,3,4-tetrahydronaphthalene **8b** (4.0 g, 12.3 mmol) was converted to 2.8 g (88%) of the desired material. Mp: 98–101°C; ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.9 (q, 3H), 1.15 (two t:s, 3H), 1.6 (m, 2H), 1.85–2.15 (m, 2H), 2.35 (q, 2H), 2.50–2.85 (m, 3H), 2.85–3.05 (m, 1H), 3.2 (m, 2H), 3.55 (br s, 2H), 4.0 (t of t, 0.55H), 4.6 (t of t, 0.45H), 6.55 (m, 2H), 6.95 and 6.98 (two t:s, J = 7.6 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.7 (CH_3), 9.8 (CH_3), 11.4 (CH_3), 11.7 (CH_3), 23.0 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 26.95 (CH_2), 27.05 (CH_2), 27.5 (CH_2), 28.4 (CH_2), 33.4 (CH_2), 34.7 (CH_2), 43.5 (CH_2), 46.0 (CH_2), 50.9 (CH), 53.2 (CH), 112.5 (CH), 112.7 (CH), 119.5 (CH), 119.6 (CH), 119.8 (C), 120.4 (C), 126.4 (CH), 126.8 (CH), 135.8 (C), 136.6 (C), 144.1 (C), 144.2 (C), 173.3 (C), 173.9 (C). Anal $C_{16}H_{24}N_2O$ (C, H, N).

*6-and 8-Amino-2-(N-n-propyl-N-propionylamino)-1,2,3,4-tetrahydronaphthalene **9b** and **9d***

Pd/C (1.0 g) was added to a solution of the nitrated material **5c–f** (6.9 g, 21.3 mmol) and triethylamine (15 ml) in methanol (150 ml) under a nitrogen atmosphere. The mixture was then hydrogenated in a Parr apparatus for 2 d. The mixture was filtered through Celite and evaporated to obtain a residue of 6 g containing the 2 desired isomers (according to GLC). Purification on silica (diethyl ether) yielded 1.25 g of the pure 6-amino isomer **9b** and 1.19 g of an isomeric mixture which was subjected to a semi-preparative HPLC–silica column (250 x 2.0 mm Kromasil, EKA, Bohus, Sweden) using hexane/ethylacetate/ethanol (75:20:5) as eluant. Several injections of 80 mg each afforded a total of 340 mg of the 8-isomer **9d** but also 90 mg of the 5-isomer **9a** (for physical data see **9a**) and 75 mg of mixed fractions. **9b**: mp: 85–87°C; ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.90 (q (two t), 3H), 1.15 (q (two t), 3H), 1.60 (m, 2H), 1.90 (m, 2H), 2.35 (m, 2H), 2.6–3.0 (m, 4H), 3.15 (m, 2H), 3.55 (br s, 2H), 4.0 (m, 0.5H), 4.6 (m, 0.5H),

6.35–6.55 (m, 2H), 6.75 (t (two d), 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.6 (CH_3), 11.3 (CH_3), 11.5 (CH_3), 22.8 (CH_2), 24.5 (CH_2), 26.75 (CH_2), 26.85 (CH_2), 27.7 (CH_2), 28.5 (CH_2), 29.5 (CH_2), 32.0 (CH_2), 33.3 (CH_2), 43.6 (CH_2), 45.9 (CH_2), 51.4 (CH), 53.9 (CH), 113.2 (CH), 113.3 (CH), 114.6 (CH), 124.3 (C), 125.2 (C), 129.8 (CH), 135.7 (C), 136.2 (C), 144.2 (C), 144.6 (C), 173.1 (C), 173.7 (C). Anal $C_{16}H_{24}N_2O$ (C, H, N). **9d**: mp: 87–89°C; ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.9 (q, 3H), 1.15 (q, 3H), 1.6 (m, 2H), 1.9 (m, 2H), 2.2–2.7 (m:s, 4H), 2.9 (m, 2H), 3.0–3.2 (m, 1.5H), 3.3 (m, 0.5H), 3.55 (br s, 2H), 4.05 (m, 0.55H), 4.65 (m, 0.45H), 6.5 (two d, J_1 = 10.2, J_2 = 7.8 Hz, 2H), 6.97 and 6.99 (two t:s, J = 7.8 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 9.7 (CH_3), 11.4 (CH_3), 11.7 (CH_3), 23.1 (CH_2), 24.6 (CH_2), 27.0 (CH_2), 27.3 (CH_2), 27.9 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 30.1 (CH_2), 43.8 (CH_2), 46.3 (CH2), 51.9 (CH), 54.0 (CH), 112.3 (CH), 112.5 (CH), 118.9 (CH), 119.6 (C), 120.4 (C), 126.3 (CH), 126.8 (CH), 136.0 (C), 136.5 (C), 144.4 (C), 173.2 (C), 173.9 (C); MS *m/e* 260 (M^+, 0.3),145 (100), 144 (36), 130 (16), 146 (16). Anal $C_{16}H_{24}N_2O$ (C, H, N).

7-Amino-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***2c***

To a suspension of lithium aluminium hydride (8.0 g, 211 mmol) in dry diethyl ether (300 ml) was slowly added a solution of 2-(*N*-*n*-propyl-*N*-propionyl-amino)-7-amino-1,2,-3,4-tetrahydronaphthalene **9c** (10.0 g, 38.5 mmol) in 100 ml diethyl ether at room temperature. After stirring overnight, water (8 ml), 15% sodium hydroxide (8 ml) and water (24 ml) were added consecutively and stirred for 10 min. The solid material was filtered off and the etheric solution was washed with water, dried (magnesium sulfate), filtered and evaporated to obtain a residue of 8.2 g yellow oil. Purification on silica (petroleum ether/ethylacetate/triethyl amine) afforded 7.5 g (91.7%) pure material. Prior to biological testing, the compound was dissolved together with an equimolar amount of fumaric acid in methanol, evaporated and recrystallized from ethanol/diethylether. Mp: 150–153°C (fum salt); ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.9 (t, 6H), 1.45 (sext, 4H), 1.55 (m, 1H), 1.95 (br d, 1H), 2.45 (t, 4H), 2.5–2.8 (m, 4H), 2.95 (m, 1H), 3.5 (br s, 2H), 6.40 (s, 1H), 6.45 (d of d, J_1 = 8.0 Hz, J_2 = 2.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 11.9 (CH_3), 22.2 (CH_2), 26.2 (CH_2), 29.1 (CH_2), 32.2 (CH_2), 52.7 (CH_2), 56.9 (CH), 113.3 (CH), 115.6 (CH), 126.7 (C), 129.3 (CH), 137.7 (C), 143.9 (C); MS *m/e* 246 (M^+, 24), 146 (100), 217 (70), 144 (36), 119 (32). Anal $C_{20}H_{30}N_2O_4$ (C, H, N).

5-Amino-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***2a***

In a manner similar to that for compound **2c**, 2-(*N*-*n*-propyl-*N*-propionylamino)-5-amino-1,2,3,4-tetrahydronaphthalene **9a** (2.8 g, 10.8 mmol) was reduced to give 2.4 g (90%) of the desired compound. Prior to biological testing the HCl-salt was formed by dissolution in HCl-saturated ethanol, evaporation and recrystallization from ethanol/diethyl ether. Mp: 235–240°C (dec; di-HCl-salt); ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.90 (t, 6H), 1.45 (sext, 4H), 1.63 (oct, 1H), 2.10 (m, 1H), 2.45 (t + m, 5H), 2.55–3.00 (m, 4H), 3.55 (s, 2H), 6.5 (dd, 2H), 6.96 (t, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 11.87 (CH_3), 22.10 (CH_2), 24.88 (CH_2), 25.88 (CH_2), 32.28 (CH_2), 52.53 (CH_2), 56.19 (CH), 112.09 (CH), 119.81 (CH), 121.13 C, 126.23 (CH), 137.74 (C), 143.99 (C); MS *m/e* 246 (M^+, 11), 146 (100), 217 (43), 144 (23), 130 (16). Anal $C_{16}H_{28}Cl_2N_2$ (C, H, N).

6-Amino-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***2b***

2-(*N*-*n*-Propyl-*N*-propionylamino)-6-amino-1,2,3,4-tetrahydronaphthalene **9b** (1.9 g, 7.3 mmol) was reduced with lithium aluminium hydride as described above and after usual workup yielded 1.56 g (87%) of the desired aniline. Prior to biological testing the HCl-salt was formed by dissolving in HCl-saturated ethanol, evaporation and recrystallization from ethanol/diethyl ether. Mp: 160–165°C (di-HCl-salt); ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.90 (t, 6H), 1.45 (q, 4H), 1.60 (m, 1H), 1.95 (br d, 1H), 2.45 (t, 4H), 2.5–3.0 (m, 5H), 3.4 (br s, 2H), 6.40 (s, 1H), 6.45 (d, 1H), 6.85 (d, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 12.0 (CH_3), 22.2 (CH_2), 26.1 (CH_2), 30.1 (CH_2), 31.4 (CH_2), 52.7 (CH_2), 57.2 (CH), 113.2 (CH), 114.9 (CH), 126.8 (C), 130.1 (CH), 137.2 (C), 143.9 (C); MS *m/e* 246 (M^+, 10), 146 (100), 217 (30), 119 (25), 130 (15). Anal $C_{16}H_{28}Cl_2N_2$ (C, H, N).

8-Amino-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***2d***

Method A (scheme 2). To a solution of 2-(*N*,*N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene-8-carboxylic acid methyl ester hydrochloride **7b** (0.43 g, 1.32 mmol) in dichloromethane (25 ml) was added conc sulfuric acid (10 ml, 97%) followed by sodium azide (1.0 g, 15 mmol). The mixture was refluxed and the progress of reaction monitored by GLC. After 5 h, additional sodium azide (2.0 g, 30 mmol) was added and refluxing was continued. After stirring overnight the reaction was complete to 93% (GLC). More sodium azide (1.0 g, 15 mmol) was added. After refluxing 1 additional hour the mixture was cooled to ambient temperature and the organic solvent evaporated. The residue was diluted with water (150 ml) and basified with solid sodium carbonate. After extraction (dichloromethane) the organic phase was dried (magnesium sulfate), filtered and evaporated to obtain a crude product (0.31 g), which was purified on a silica column using dichloromethane/methanol (19:1) as eluant. A light yellow oil was obtained (200 mg, 62%). Prior to biological testing the HCl-salt was formed by dissolving in HCl-saturated ethanol, evaporation and recrystallization from ethanol/diethyl ether. Mp: 220–230°C (dec; di-HCl-salt); ^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 0.90 (t, 6H), 1.50 (sext, 4H), 1.55 (oct, 1H), 2.0 (m, 1H), 2.3–2.7 (t + m, 4 + 2), 2.8 (m, 2H), 3.0 (q of t, 1H), 3.55 (s, 2H), 6.5 (t, 2H), 6.95 (t, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) ∂ 11.9 (CH_3), 22.4 (CH_2), 25.0 (CH_2), 27.2 (CH_2), 30.5 (CH_2), 52.7 (CH_2), 57.1 (CH), 112.1 (CH), 118.9 (CH), 121.4 (C), 125.1 (CH), 137.5 (C), 144.5 (C). Anal $C_{16}H_{28}Cl_2N_2$ (C, H, N).

8-Amino-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphthalene ***2d***

Method B (scheme 3). In the same manner as for **2a–2c**, compound **2d** was synthesized from the corresponding amide **9d** (25 mg, 0.1 mmol) to yield 20 mg (85%) of the desired compound as free base. Physical data were identical to those obtained by *Method A*.

Pharmacology

Animals

Animals used in the biochemical and motor activity experiments were male rats of Sprague–Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. The rats were kept 5 per cage with free access to water and food for at least 1 wk since arrival until used in the experiments.

Materials
All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. Injection volumes were 5 ml/kg, and all solutions had neutral pH at the time of injection (except for the reserpine solutions; ≈ pH 4).

Biochemistry (table I)
The biochemical experiments and determinations of DOPA and 5-HTP *via* HPLC with electrochemical detection were performed according to a modification of a previously described method [26, 27]. Separate dose–response curves based on 4–6 dose levels (n = 4) for each substance (sc administration) and each brain area were constructed. From these curves, the dose of the drug yielding a half-maximal decrease (ED_{50} value graphically determined) in DOPA (the maximal effect, expressed as % of controls, was: limbic system = –65%, striatum = –80% and the hemispheres = –50%) and 5-HTP (the maximal effect, expressed as % of controls, was: limbic system, striatum and hemispheres = –50%) levels were estimated separately (table II). For 5-HTP control values were (ng/g, mean ± SEM, n = 10): limbic system = 192 ± 18, striatum = 129 ± 14 and the hemispheres 131 ± 14. For DOPA control values were (ng/g, mean ± SEM, n = 10): limbic system = 808 ± 56, striatum = 3653 ± 222 and the hemispheres = 156 ± 11.

Motor activity (table II)
The motor activity was measured *via* photocell recordings (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm) as previously described [3]. Eighteen h prior to motility testing (carried out between 9 am and 1 pm), the rats were injected sc in the neck region with reserpine (5 mg/kg). The different test compounds were also administered sc in the neck region (n = 4). Immediately after drug administration, the rats were placed in the test cages (1 rat/cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min (control values 3 ± 1 counts/30 min, mean ± SEM; n = 13) (table II). Observations of gross behaviour were made throughout the activity sessions through semi-transparent mirrors.

5-HT_{1A} radioligand binding (table II)
Male Sprague–Dawley rats (160–225 g) were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was rapidly removed, weighed and chilled in ice-cold 0.9% NaCl. Each brain was homogenized (Ultra-Turrax, 20 s) in 10 ml ice-cold 50 mM Tris buffer (pH 8.0 at 25°C) containing 120 mM NaCl, 4 mM $CaCl_2$ and 4 mM $MgCl_2$ and centrifuged at 20 000 g at 4°C for 10 min. Pellets were resuspended in 10 ml fresh buffer and preincubated for 10 min in a 37°C waterbath and then recentrifuged. Final pellets were homogenized in 100 vol (w/v). Tris buffer (as described above) containing 10 µM pargyline. The incubation tubes were kept on ice in triplicate and received 100 µl drug solution in water (or water for total binding) and 1000 µl membrane suspension (corresponding to 10 mg original tissue). The binding experiment was initiated by addition of 100 µl [^{3}H]-8-OH-DPAT (spec act 219–240 Ci/mmol) in ascorbic acid (the final incubation concentration was 1 nM [^{3}H]-8-OH-DPAT in 0.1% ascorbic acid). After incubation for 15 min at 37°C the reaction was terminated by separation of the free from the bound radioligand by rapid vacuum filtration using a cell harvester (OM Teknik, Denmark). The tubes were rinsed with 4 ml, and the filters (Whatman GF/F 25 mm) were washed twice with 4 ml ice-cold 0.9% NaCl.

The radioactivity of the filters was measured in a liquid scintillation counter (efficiency 41%) in 5 ml Ready Safe (Beckman). Specific binding (70–75% total binding) was defined as the radioactivity displaced by 10 µM 5-HT. IC_{50} value (the concentation of drug required to displace 50% of the labelled ligand) was calculated by semi-log plot and linear regression analysis. The inhibition constants (K_i) of the various compounds were calculated using the formula of Cheng and Prusoff [28]: $K_i = IC_{50}/(1 + [L/K_d])$, where L = concentration of labelled ligand and K_d = its affinity constant.

D_2 radioligand binding (table II)
Preparation of rat striatal membranes for [^{3}H]-spiperone (spec act 28 Ci/mmol) binding was carried out as described by Hyttel and Arnt [24]. The final pellets were homogenized in 1300 vol 50 mM K-phosphate buffer and the membrane suspension was incubated with 0.5 nM [^{3}H]-spiperone in a final vol of 4.2 ml (3 mg original tissue) for 10 min at 37°C. Specific binding was 70–80% of total binding and was obtained by adding 10 µM 6,7-ADTN to the membrane suspension.

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