Recl. Trav. Chim. Pays-Bas **112**, 143–150 (1993) 0165–0513/93/02143–08$06.00

Monoamine re-uptake inhibiting 1-[2-[(phenoxyphenyl)methoxy]ethyl]-piperazines as potential antidepressants

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(Received August 3, 1992)

Abstract. A series of 1-[2-[(2-phenoxyphenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines **17–50** (Figure 1) were prepared and tested as inhibitors of biogenic amine re-uptake. In our search for antidepressants, the relationship between their *in vitro* and *in vivo* activity as dopamine-re-uptake inhibitors is described quantitatively by using Retention Index values determined by reversed-phase liquid chromatography.

Introduction

Inhibitors of neuronal re-uptake of monoamine neurotransmitters have been of interest since the recognition that re-uptake mechanisms are important in terminating the actions of released neurotransmitters.
First-generation antidepressants, such as amitriptyline, imipramine, and their descendants, maprotiline, clomipramine, desmethylimipramine, doxepine and amoxapine are said to derive their antidepressant effects from more or less selective inhibition of noradrenaline and serotonin re-uptake. However, all of these compounds show equal or higher affinity for, and functional antagonism at neurotransmitter receptors for histamine and serotonin, the α_1-adrenergic receptor and (to a lesser extent) acetylcholine receptor[1].
The second generation of antidepressants derived its therapeutic success mainly from improvements in side-effect profiles, which in turn were mediated predominantly by this neurotransmitter receptor antagonism[2].
These improvements were realised by retaining a more selective neurotransmitter antagonistic profile, thereby creating safer compounds with a desired sedative clinical profile (*e.g.*, mianserin and setiptiline, which lack antagonism towards acetylcholine receptors).
Another approach was to create a full selectivity for the neurotransmitter carriers to the detriment of all receptor antagonism, thereby creating a neutral to slightly stimulating clinical profile.
In the latter case, effective antidepressants with re-uptake inhibitory subspecificity were discernible. A major effort was made by the pharmaceutical industry towards selective inhibitors of serotonin re-uptake, exemplified by zimelidine (withdrawn), fluoxetine and the more recent sertraline, fluvoxamine, citalopram and paroxetine. Compounds with selective inhibition of noradrenaline and dopamine re-uptake were developed, exemplified by nomifensine and bupropion. In this area, induced by the early withdrawal of nomifensine due to severe side effects and the modest impact of bupropion, additional efforts to generate structurally unrelated antidepressants with a similar mechanism of action seemed justified.
Among the various series of compounds displaying high affinity for the dopamine-re-uptake carrier, an outstanding position is taken by those synthesised around GBr 12909 (see Figure 1)[3].
The apparent limited specificity of this compound and its congeners for noradrenaline and dopamine-re-uptake inhibition (see Table II and Refs. 3 and 4) triggered our effort to design a series of related compounds using an unusual and novel bioisosteric replacement of substituted diphenylmethyl groups by substituted phenoxyphenyl groups (Figure 2). The synthetic feasibility, in combination with the possibility to avoid the introduction of chirality in the case of single aromatic substitution, made this effort worthwhile.
We describe in this paper the synthesis[5] and biochemical evaluation of a novel series of dopamine-re-uptake inhibitors: viz. 1-[2-[(2-phenoxyphenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines and derivatives thereof, viz., **17–50**.

Chemistry

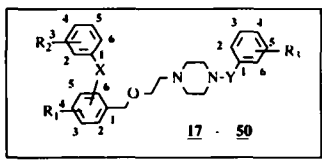
Several major synthetic routes, illustrated in the following schemes (Schemes 1–4), were used for the synthesis of our target compounds (Table I). The choice of a specific synthetic route was guided by the availability of starting materials.

Route 1

The route mainly used for the synthesis of the derivatives **17–45** (Figure 1 and Scheme 1), started with the treatment of acid **1** with thionyl chloride. Subsequent reaction of the resulting acid chloride with an excess of piperazine

† Deceased.

Table I Compounds investigated.

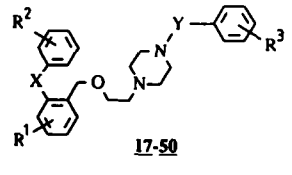


X = O,S,CH_2, OCH_2, NMe
Y = N-$CH_2CH_2CH_2$-Ar = A
N-CH_2CH_2-Ar = B
N-$CH_2C{\equiv}C$-Ar = C
N-CH_2CH=CH-Ar(Z) = D
N-CH_2CH=CH-Ar(E) = E

Compd.	X	Y	R^1	R^2	R^3	M.p(°C)	Mol. formula[a]	Route
17	2-O	A	4-Cl	H	H	225	$C_{28}H_{33}ClN_2O_2$ 2HCl[T]	1
18	2-O	A	H	H	H	216	$C_{28}H_{34}N_2O_2$ 2HCl[T]	1
19	2-O	A	4-F	4-F	H	216	$C_{28}H_{32}F_2N_2O_2$ 2HCl[#]	1
20	2-O	A	4-F	3-F	H	220	$C_{28}H_{32}F_2N_2O_2$ 2HCl[#]	1
21	3-O	A	H	H	3-Cl	212	$C_{28}H_{33}ClN_2O_2$ 2HCl[T]	1
22	3-O	A	H	H	4-Me	221	$C_{29}H_{36}N_2O_2$ 2HCl[T]	1
23	3-O	A	H	H	3-OMe	208	$C_{29}H_{36}N_2O_3$ 2HCl[T]	1
24	3-O	A	H	H	2-Cl	218	$C_{28}H_{33}ClN_2O_2$ 2HCl[T]	1
25	2-O	A	H	H	3-OMe	187	$C_{29}H_{36}N_2O_3$ 2HCl[T]	1
26	2-O	A	H	H	4-Me	225	$C_{29}H_{36}N_2O_2$ 2HCl[T]	1
27	3-O	A	H	H	H	216	$C_{28}H_{34}N_2O_2$ 2HCl[#]	1
28	2-O	A	H	H	2-Cl	200	$C_{28}H_{33}ClN_2O_2$ 2HCl[T]	1
29	3-O	A	H	H	2-OMe	195	$C_{29}H_{36}N_2O_3$ 2HCl[T]	1
30	2-S	A	H	H	H	213	$C_{28}H_{34}N_2OS$ 2HCl[#]	1
31	2-OCH_2	A	H	H	H	206	$C_{29}H_{36}N_2O_2$ 2HCl[T]	1
32	2-O	A	H	H	3-Cl	199	$C_{28}H_{33}ClN_2O_2$ 2HCl[T]	1
33	4-O	A	H	H	3-Cl	212	$C_{28}H_{33}ClN_2O_2$ 2HCl[#]	1
34	4-O	A	H	H	4-Me	218	$C_{29}H_{36}N_2O_2$ 2HCl[T]	1
35	2-OCH_2	A	H	H	4-Me	195	$C_{30}H_{38}N_2O_2$ 2HCl[#]	1
36	4-O	A	H	H	2-OMe	201	$C_{29}H_{36}N_2O_3$ 2HCl[T]	1
37	2-S	A	H	H	2-OMe	186	$C_{29}H_{36}N_2O_2S$ 2HCl[T]	1
38	2-OCH_2	A	H	H	2-OMe	191	$C_{30}H_{38}N_2O_3$ 2HCl[T]	1
39	2-O	A	H	H	2-OMe	186	$C_{29}H_{36}N_2O_3$ 2HCl[#]	1
40	2-CH_2	A	H	H	H	209	$C_{29}H_{36}N_2O$ 2HCl[#]	1
41	4-O	A	H	H	H	210	$C_{28}H_{34}N_2O_2$ 2HCl[#]	1
42	2-NMe	A	H	H	H	220	$C_{29}H_{37}N_3O_2$ 2HCl[T]	1
43	2-O	A	H	H	3-NH_2	182	$C_{28}H_{35}N_3O_2$ 3HCl[#]	1
44	2-O	A	H	H	2-OH	217	$C_{28}H_{34}N_2O_3$ 2HCl[T]	1
45	2-O	B	H	H	H	221	$C_{27}H_{32}N_2O_2$ 2HCl[#]	1
46	3-O	C	H	H	H	195	$C_{28}H_{30}N_2O_2$ 2HCl[T]	2
47	2-O	C	H	H	H	200	$C_{28}H_{30}N_2O_2$ 2HCl[T]	2
48	3-O	D	H	H	H	197	$C_{28}H_{32}N_2O_2$ 2HCl[#]	3
49	2-O	D	H	H	H	201	$C_{28}H_{32}N_2O_2$ 2HCl[#]	3
50	2-O	E	H	H	H	221	$C_{28}H_{32}N_2O_2$ 2HCl[T]	4

[a] Compounds marked with ([T]) or ([#]) gave satisfactory microanalyses for C, H and N and satisfactory exact *m/z* data, respectively.

in acetic acid gave the monoacylated piperazine **2** in 70–92% yield. The monoalkyl piperazine derivatives **3** were obtained in 67–92% yield by lithium aluminium hydride reduction of the amides **2**. Treatment of **3** with chloroacetyl chloride gave **4** in 57–100% yield. The coupling of **4** with the benzyl alcohol derivatives **6**, prepared by lithium-aluminium-hydride reduction from commercial available benzoic acid derivatives **5**, was troublesome and was only possible in moderate yields of **7** (35–51%) and when freshly prepared chloroacetamides **4** were used. Finally, reduction of the amide function of **7** using lithium aluminium hydride gave the desired piperazine derivatives **17–45** in 60–78% yield. In order to improve the water solubility of the compounds, all derivatives were converted into their hydrochloride salts (see also Table I and Experimental).



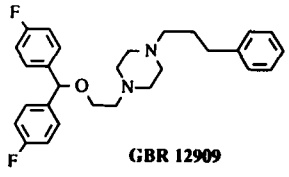
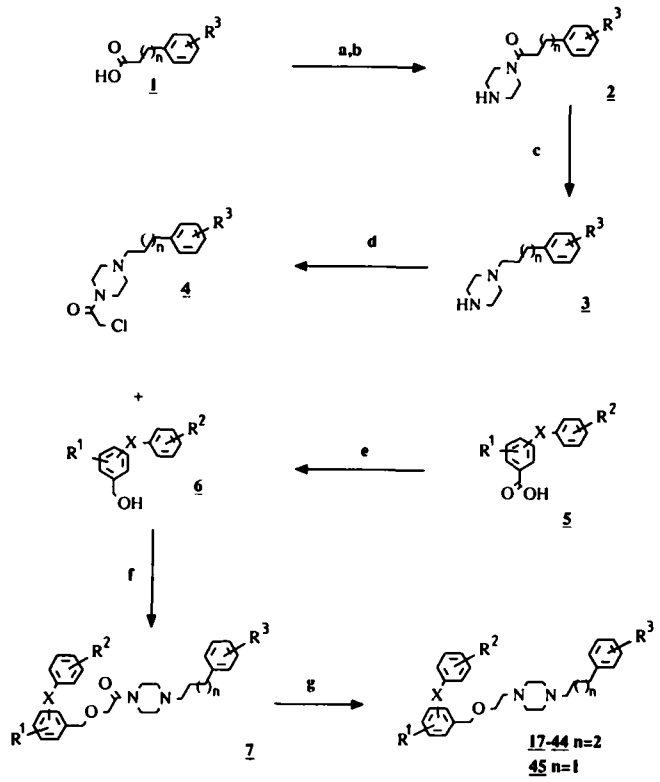
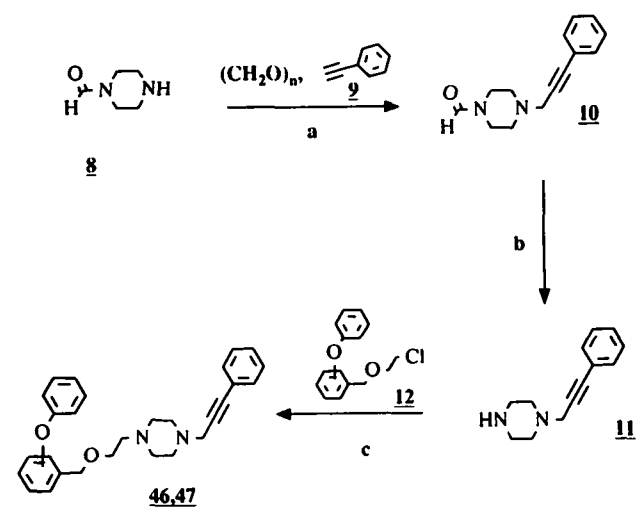


Figure 1.



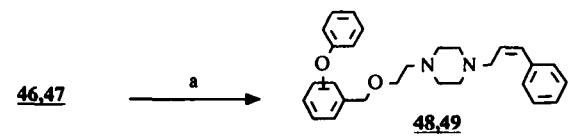
Scheme 1. Route 1: a) $SOCl_2$; b) piperazine; c) $LiAlH_4$, diethyl ether; d) chloroacetyl chloride; e) $LiAlH_4$, diethyl ether; f) 33% NaOH; g) $LiAlH_4$, diethyl ether.



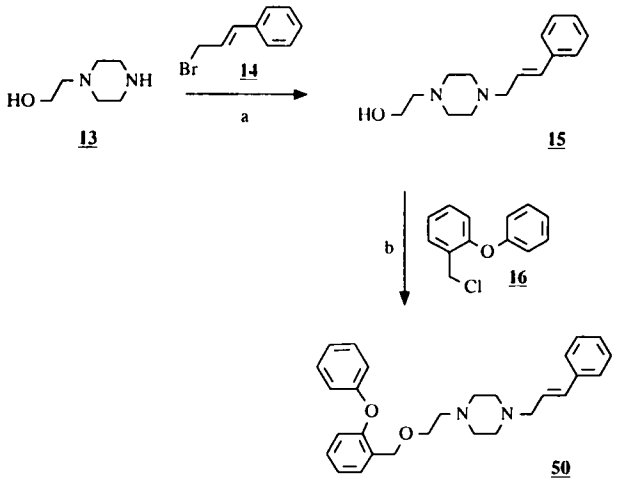
Scheme 2. Route 2: a) dioxane, reflux; b) 4N NaOH; c) K_2CO_3 / KI, 4-methyl-2-butan one.

Route 2

For synthesis of the alkyne derivatives **46** and **47** (Scheme 2), we chose phenylacetylene (**9**) as starting material. Mannich reaction of 1-piperazinecarboxaldehyde (**8**) with paraformaldehyde and **9** in dioxane using a catalytic amount of copper(II) acetate gave the desired piperazine derivative **10** in 88% yield. Removal of the protecting formyl group gave **11** (95%). The coupling of **11** with **12**, prepared from benzyl-alcohol derivatives **6** in a one-step process using published procedures in the presence of



Scheme 3. Route 3: a) Lindlar catalyst, H_2.



Scheme 4. Route 4: a) $NaHCO_3$, dioxane, 85°C; b) $KOC(CH_3)_3$, DME, 40°C.

potassium carbonate and a catalytic amount of potassium iodide in refluxing 4-methyl-2-pentanone, gave derivatives **46**, **47** in 43% yield.

Route 3

The synthesis of alkene derivatives was then attempted. Two routes were investigated: one for the (*Z*)-alkenes (Route 3) and another for the (*E*)-alkenes (Route 4). Thus, hydrogenation of the alkyne derivatives **46**, **47** with Lindlar's catalyst in a Parr apparatus (Scheme 3) gave access to (*Z*)-alkene derivatives **48**, **49** (67% yield).

Route 4

For the preparation of a (*E*)-phenylpropene derivative **50**, 1-piperazineethanol (**13**) and (*E*)-cinnamyl bromide (**14**) were chosen as starting materials (Scheme 4). The coupling reaction of **13** and **14** using $NaHCO_3$ as base gave **15** in 76% yield. Subsequent coupling of **15** with 2-phenoxybenzyl chloride (**16**) using potassium tert-butoxide as base gave the desired (*E*)-alkene derivative **50** in 14% yield.

Evaluation of biological results

In vitro activity

The pharmacological data given in Table II indicate that most of the compounds we have prepared are very potent inhibitors of dopamine-(DUP) and noradrenaline-(NUP) re-uptake *in vitro*, while serotonin-re-uptake (SUP) is less effectively inhibited.

The position of the Ar–X– group on the phenyl ring of the 2-(phenylmethoxy)ethyl chain is important for the *in vitro* profile. The most potent dopamine and noradrenaline-re-uptake inhibitors are obtained with the Ar–X– substituent at the 2-position. If this Ar–X– substituent is moved from the 2-position towards the 3- or 4-position, the DUP and NUP values are decreased to a higher extent than the SUP values. This can be concluded by comparing the data in Table II of the pairs of entries: **18**, **27**; **26**, 2h2; **25**, **23**; **28**, **24**; **39**, **29** (2-*vs.* 3-substitutions); **18**, **41**; **26**, **34**; **39**, **26** (2- versus 4-substitutions). Some 4-substituted derivatives, such as **33**, **34** and **36**, equally affect dopamine-, noradrenaline- and serotonin-re-uptake.

For the 2-substituted derivatives, the nature of the –X– group has little effect upon the *in vitro* profile: compare

Table II Pharmacological data; calculated log(P) values

Compd.	NUP[a] pKi	SUP[a] pKi	DUP[a] pKi	CIRC IPSI[b] LAD (mg/kg)	LOG(P)[c] calcd.
17	7.6	5.8	8.0	20	6.51
18	7.7	6.2	8.0	10	5.77
19	7.6	6.4	8.1	15	6.26
20	8.0	5.8	7.7	8	6.26
21	7.2	6.1	6.7	>32	7.06
22	6.9	5.9	7.3	>22	6.83
23	8.0	5.9	7.4	32	6.12
24	6.6	6.0	7.4	>32	5.33
25	8.5	6.4	8.0	25	5.91
26	7.5	6.1	7.5	25	6.37
27	7.2	6.4	7.5	>32	5.77
28	7.7	6.5	7.9	30	6.60
29	7.9	6.7	7.7	>32	6.34
30	7.9	6.1	8.1	15	6.63
31	6.8	6.3	7.7	>32	5.98
32	7.8	6.2	7.9	32	6.80
33	6.1	5.8	6.0	>32	6.80
34	6.0	5.7	6.1	>32	6.83
35	6.9	6.0	6.9	>32	6.52
36	6.5	6.5	6.4	>32	5.91
37	8.0	6.7	8.1	25	6.71
38	7.7	6.7	7.6	>32	6.06
39	8.3	6.9	8.2	15	6.37
40	7.6	6.0	8.2	7	6.44
41	6.5	5.9	6.7	>32	5.77
42	7.2	6.6	8.4	30	5.46
43	8.1	6.0	8.5	2.5	5.40
44	8.2	6.5	8.1	10	5.94
45	7.6	6.4	8.3	5	5.58
46	6.2	4.9	6.5	>32	5.56
47	6.9	5.5	8.0	30	5.56
48	6.6	5.9	7.4	30	6.25
49	7.3	6.3	8.0	15	6.25
50	6.7	6.1	7.4	10	5.98
GBR12909	7.1	6.6	7.85	10	5.87

[a] NUP: Noradrenaline-re-uptake inhibition
SUP: Serotonin-re-uptake inhibition
DUP: Dopamine-re-uptake inhibition
Specific re-uptake of radiolabelled transmitters is defined as the total amount of radioactivity taken up in tissue, corrected for the amount of radioactivity taken up in the presence of 10^{-4}M desipramine (for noradrenaline), 10^{-4}M nomifensis (for dopamine) and 10^{-4}M imipramine (for serotonin).
Data are expressed as pK_i values. The pK_i represents $-\log(K_i)$ and the K_i value is calculated from the IC_{50} value from inhibition curves, using the formula $K_i = IC_{50} - K_m/(K_m + C)$, with the IC_{50} representing the concentration of the compound showing 50% inhibition of specific re-uptake, with C representing the concentration of the ligand and with K_m as the Michaelis constant, calculated from Lineweave–Burke plots measured separately. [b] CIRC IPSI *LAD*: Lowest active dose in the ipsiversive circling test. [c] LOG(*P*) calcd: calculated log(*P*) values, using the *Rekker* system [8].

entries **18** (X = O), **30** (X = S), **31** (X = O–CH_2), **40** (X = CH_2) and **42** (X = N–CH_3).

Concerning the nature of –Y– (A, B, C, D and E), it is clear that the molecular variations used do not have a great impact upon the *in vitro* profile: compare **18** with **45**, **47**, **48** and **50** (all X = 2-O, $R^1 = R^2 = R^3 = H$).

Finally, the extent of dopamine-re-uptake inhibition of the 1-[2-(diphenylmethoxy)ethyl]piperazines described in *Van der Zee et al.*[3] and the values for 1-[2-[(2-phenoxyphenyl)methoxy]ethyl]piperazines described in this pa-

Figure 2.

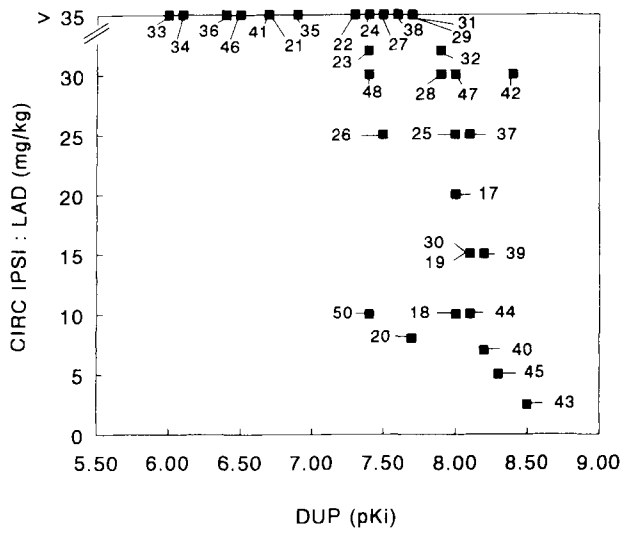


Figure 3.

per, are very similar. Therefore, the 2-(diphenylmethoxy) ethyl moiety **I** (Figure 2) and the 2-[(2-phenoxyphenyl)-methoxy]ethyl moiety **II** can be considered as bioisosters for recognition at the monoamine-re-uptake carriers.
Compared to GBR 12909, compound **47** has improved potency and selectivity as a dopamine-re-uptake inhibitor.

In vivo activity

In order to assess the *in vivo* efficacy, all derivatives were tested in the circling test in rats. In this test, dopamine-re-uptake inhibitors induce ipsiversive circling, i.e., circling towards the site of the unilateral lesion induced by 6-hydroxydopamine in the nigro-striatal dopaminergic pathway[6].
It is obvious from Table II that certain compounds, although being potent dopamine-re-uptake inhibitors *in vitro*, are only moderately active *in vivo* (*e.g.*, **32**, **37** and **42**). This phenomenon is illustrated further in Figure 3: the relationship between the *in vitro* (DUP: pK_i) and *in vivo* data (CIRC IPSI: *LAD*) is not straightforward.
These discrepancies might be related to differences in bio-availability for the title compounds. Therefore, we examined the lipophilicity of the prepared compounds by calculating log(*P*) values. It is generally accepted that log(*P*) values can be used as physicochemical parameters relevant for the bio-availability of drugs. An optimal log(*P*) value of 2.0–2.5 has been suggested for several classes of Central Nervous System (CNS) agents with divergent structures[7]. The log(*P*) values given in Table II have been calculated using the *Rekker* system[8]. The values obtained clearly indicate that all prepared compounds should be considered as being "over"-lipophilic.
Therefore, it is tempting to assume that these compounds probably pass the blood–brain barrier quickly, after which they preferentially diffuse into lipophilic areas in the brain. From these sites, re-diffusion into the central spinal fluid and, finally, into the central site responsible for activity is very slow, resulting in very low local concentrations. The possibility of initial diffusion into hydrophobic areas in the periphery may also play a role.
In order to describe these effects quantitatively, we have used the hypothesis that the *in vivo* activity of a drug is determined by its efficacy, on the one hand, and its local concentration, on the other [9]. This implies that, for a dopamine-re-uptake inhibitor, *in vivo* activity (CIRC IPSI: *LAD*) can be described as a common function of its efficacy (DUP: pK_i) and its ability to reach the site of

Table III

Compd.	DUP[a] pK_i	*RI*[b]	1000 DUP/RI	CIRC IPSI[c] *LAD* (mg/kg)	*LAD* (μmol/kg)
18	8.0	1293	6.187	10	19.9
19	8.1	1295	6.255	15	27.8
25	8.0	1263	6.334	25	46.8
26	7.5	1368	5.482	25	48.3
28	7.9	1345	5.874	30	55.8
30	8.1	1361	5.952	15	28.9
32	7.9	1403	5.631	32	59.5
37	8.1	1350	6.000	25	45.5
39	8.2	1350	6.074	15	28.1
40	8.2	1323	6.198	7	14.0
43	8.5	1061	8.011	2.5	4.5
44	8.1	1180	6.864	10	19.2
45	8.3	1199	6.922	5	10.2
Nomifensine	7.05	759	9.290	2	5.7
GBR 12909	7.85	1212	6.477	10	19.1

DUP: Dopamine re-uptake inhibition (see legend Table II).
RI: Retention index on reversed-phase HPLC
CIRC IPSI *LAD*: lowest active dose in the ipsiversive circling test.

action (1/[log(*P*)], as the title compounds are over-lipophilic. Provided a low correlation exists between DUP: pK_i and log(*P*). As this seems largely to be the case ($R = 0.26$ for the relationship) DUP: pK_i versus log(*P*) for the derivatives given in Table II), we have examined the relationship between the activity in the ipsiversive circling model and DUP, corrected for over-lipophilicity, i.e., divided by log(*P*).
Information on the polarity of a given molecule can be easily obtained by reversed-phase liquid chromatography. A relative measure that was introduced some years ago is the retention index (*RI*)[10]. Therefore, we decided to concentrate on *RI* values as experimentally derived estimates of log(*P*). Numerous methods have been described for the determination of *RI* values[10]. In our work we used the method of *Baker* and *Ma*[11], which is based on a homologous series of 2-alkanones (for details, see Experimental).
In Table III, the data for the anticipated linear regression analysis are presented for those compounds whose *RI* value could be calculated. Figure 4 shows the results of this analysis, as well as the calculated linear regression curve, described by Eqn. 1. In view of the parabolic

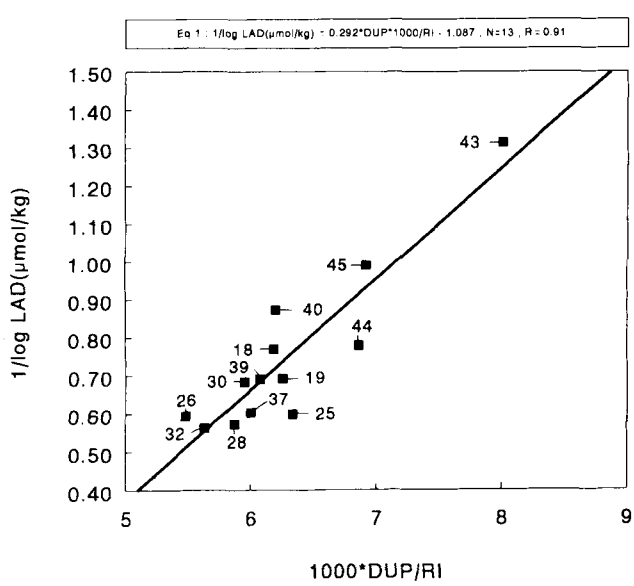


Figure 4.

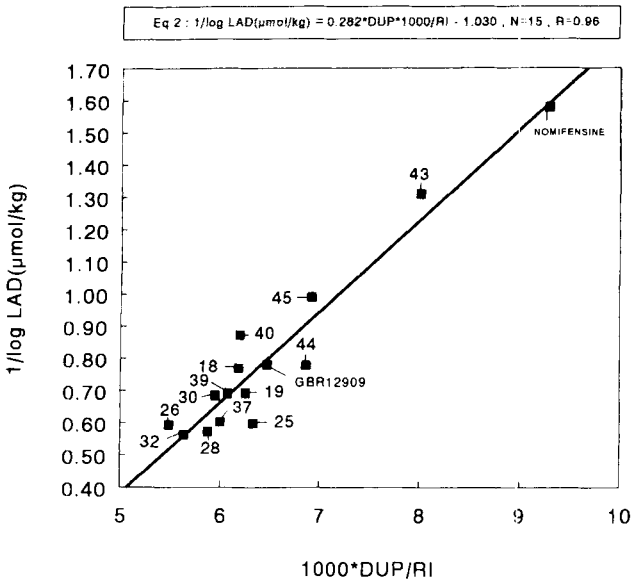


Figure 5.

relationship between log(*P*) and the CNS availability[7], and the over-lipophilic character of the title derivatives, Eqn. 1 only describes the *in vivo* activity of compounds with a log(*P*) value well above 2.0.

$$1/[\log[LAD(\mu\text{mol/kg})]] = 0.292 \cdot \text{DUP}(\text{p}K_i) \cdot 1000/RI - 1.087 \quad (n = 13,\ R = 0.91) \qquad (1)$$

Although the usefulness of physicochemical parameters in QSAR (Quantitative Structure–Activity Relationship) studies is sometimes limited to specific series of closely related compounds, the data of some reference compounds were added (see also Table III). The results given in Figure 5 are described by Eqn. 2.

$$1/\log[LAD(\mu\text{mol/kg})] = 0.282 \cdot \text{DUP}(\text{p}K_i) \cdot 1000/RI - 1.030 \quad (n = 15,\ R = 0.96) \qquad (2)$$

Taking into account the lipophilic character of the compounds described and Eqns. 1 and 2, we conclude that the factor $1/RI$ is an adequate, experimentally derived, physicochemical parameter to describe at least part of the pharmacokinetic profile.

Experimental

Chemistry, general

Melting points (m.p.) were taken on a Buechi capillary melting point apparatus and are uncorrected. The microanalytical values for C, H, and N reported were within 0.45 of the theoretical values. ^{1}H-NMR spectra were measured on a Bruker WP200, -AC200 or AM360 instrument (using standard conditions). Chemical shifts are reported as δ values (ppm) relative to Me_4Si as internal standard.

Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates (thickness 0.25 mm); R_f values between 0.35 to 0.5 were found; eluent system: toluene/ethanol, 8/2, v/v; (unless, stated otherwise). Spots were visualized with a UV hand lamp and Cl_2/tetramethylbenzidine. For column chromatography, Merck silica gel 60 was used. The retention index by reversed-phase liquid chromatography was determined as follows: the compounds were chromatographed on a reversed-phase C18 column using an eluent of methanol and buffer (50 mM tetramethylammonium hydroxide, pH 7.4 with concentrated phosphoric acid). The eluent composition was chosen to give a capacity factor (k') of the substance between 3 and 30. A series of 2-alkanones (preferably 3 to 5) was then injected. The *RI* values of the 2-alkanones are by definition $100 \cdot n$, in which n = the number of C atoms. From the linear graph of log(k') *vs.* *RI* of these 2-alkanones, the *RI* values of the derivatives examined were determined by interpolation.

Fast-Atom-Bombardment (FAB) mass spectra were recorded with a Finnigan MAT 90 mass spectrometer (Finnigan MAT, Bremen, FRG). Samples were dissolved in methanol and mixed with the matrix compounds on standard stainless-steel targets. Exact masses of the protonated molecular ions were determined with the peak-matching technique at a mass resolution of >8900 (10% valley definition) in the positive-ion mode using two reference masses either from poly(ethylene glycol), average molecular mass 400, or poly(propylene glycol), average molecular mass 425. Average exact masses were calculated from at least 10 computer-controlled measurements using the bracketing method.

Method 1 (compounds 17–45)

1-[3-(2-Methoxyphenyl)-1-oxopropyl]piperazine (**2**). 3-(2-Methoxyphenyl)propionic acid chloride (55.75 g, 310 mmol; prepared quantitatively from 3-(2-methoxyphenyl)propionic acid (**1**) using thionyl chloride as reagent) was added dropwise to a stirred solution of piperazine (41.57 g; 483 mmol) in acetic acid (830 ml). After stirring for 16 h at 20°C, the crystals were filtered off and the solvent was evaporated. Ethanol (500 ml) was added to the residue, the suspension was filtered, and the solvent was then evaporated. The resulting material was partitioned between CH_2Cl_2 and an aqueous in HCl solution. The latter was separated, the pH adjusted to pH 9–10, saturated with NaCl and subsequently extracted with toluene. Evaporation of the dried organic layer gave **2** as an oil, which was homogeneous by TLC (R_f 0.3; butanol/acetic acid/water, 4/1/1, v/v/v) in 86% (60.5 g) yield. ^{1}H NMR ($CDCl_3$): δ 7.1–7.25, 6.8–6.9 (m, C_6H_4), 3.8 (s, OCH_3), 3.6 and 3.4 [2, t, $(CH_2)_2$], 2.5–3.0 (m, 8 piperazine Hs).

1-[3-(2-Methoxyphenyl)propyl]piperazine (**3**). A solution of piperazine amide **2** (60.5 g, 244 mmol) in dry diethyl ether (324 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (27.33 g, 718.8 mmol) in dry diethyl ether (979 ml) under nitrogen. After stirring for 3 h at 20°C, the reaction mixture was cooled to 0°C and water (109 ml) was added dropwise. The suspension was filtered and the solvent was evaporated to give **3** as an oil, which was homogeneous by TLC (R_f = 0.1; butanol/acetic acid/water, 4/1/1, v/v/v) in 77% (44 g) yield. ^{1}H NMR ($CDCl_3$): δ 7.1–7.25, 6.8–6.9 (m, C_6H_4), 3.8 (s, OCH_3), 1.7–2.9 (m, $-(CH_2)_3-$ + 8 piperazine Hs).

1-(2-Chloro-1-oxoethyl)-4-(3-[2-methoxyphenyl]propyl)piperazine (**4**). Chloroacetyl chloride (13.57 ml) was added dropwise to a cooled and stirred solution of **3** in (39 g, 166.7 mmol) and triethylamine (25.5 ml) under nitrogen. After stirring for 16 h at 20°C, the reaction mixture was poured into ice water and the extracted with CH_2Cl_2. The aqueous phase was then adjusted to pH 9–10, saturated with NaCl and extracted with toluene. Evaporation of the dried organic layer ($MgSO_4$) gave **4** as an oil in quantitative yield. ^{1}H NMR ($CDCl_3$): δ 6.8–7.25 (m, C_6H_4), 4.0 (s, CH_2), 3.75 (s, OCH_3), 3.6 (t, $ArCH_2$), 3.5 (t, CH_2–N), 2.35–2.65 (m, 8 piperazine Hs), 1.75 (m, C–CH_2–C).

1-[3-(2-Methoxyphenyl)propyl]-4-[1-oxo-2-[(2-phenoxyphenyl)methoxy]ethyl]piperazine (**7**). 2-Phenoxybenzylalcohol (**6**) (5.8 g, 29 mmol) was added to a suspension of **4** (9 g, 29 mmol) in an aqueous solution of NaOH (101.9 ml of a 33% solution). After stirring for 3 h at 60°C, the reaction mixture was cooled and diluted with water. Extraction of the aqueous phase with toluene, evaporation of the solvents and subsequent purification of the crude product by column chromatography (silica gel, eluent: ethyl acetate) gave **7** as an oil in 50% yield (6.9 g). ^{1}H NMR ($CDCl_3$): δ 6.8–7.25 (m, $C_6H_4 + C_6H_5$), 4.65 (s, OCH_2Ar) 4.15 (s, $COCH_2$), 3.8 (s, OCH_3), 3.6 (t, $ArCH_2$), 3.45 (t, CH_2–N), 2.35–2.65 (m, 8 piperazine Hs), 1.75 (m, C–CH_2–C).

1-[3-(2-Methoxyphenyl)propyl]-4-[2-[(2-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**39**). A solution of **7** (6.9 g, 14.6 mmol) in dry diethyl ether (200 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2.5 g, 58 mmol) in dry diethyl ether (100 ml) under nitrogen. After stirring for 2 h at 20°C, the reaction mixture was cooled to 5°C and water (8.8 ml) was added dropwise. The suspension was filtered and the solvent was evaporated. The crude product was dissolved in ethanol and a solution of HCl in ethanol (2.1 equivalent of HCl) was added. After evaporation of the solvent *in vacuo*, the solid product **39** was recrystallized from ethanol. Yield 5.1 g (65%). M.p. 186°C. ^{1}H NMR ($CDCl_3 + CD_3OD$): δ 6.8–7.6 (m, 13 aromatic Hs), 4.65 (s, Ar–CH_2–O), 3.91 (m, O–CH_2–C–N), 3.83 (s, OCH_3), 3.4–4.0 (br, s, 8 piperazine Hs), 3.47 (m, N–CH_2–C–O),

3.22 (m, N-CH_2-C-C-Ar), 2.72 (t, Ar-CH_2-C-C), 2.07 (m, Ar-C-CH_2-C).

Using the above procedure, the following derivatives were prepared:

1-[2-[(4-Chloro-2-phenoxy)methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (**17**). M.p. 225°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.55 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.5–4.0 (m, 8 piperazine Hs), 3.33 (m, N-CH_2-C-O), 3.05 (m, N-CH_2-C-C-Ar), 2.76 (t, Ar-CH_2-C-C), 2.12 (m, Ar-C-CH_2-C).

1-[2-(2-Phenoxyphenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride hemihydrate (**18**). M.p. 216°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 14 aromatic Hs), 4.57 (s, Ar-CH_2-O), 4.00 (m, O-CH_2-C-N), 3.5–4.0 (m, 8 piperazine Hs), 3.22 (m, N-CH_2-C-O), 2.98 (N-CH_2-C-C-Ar), 2.72 (t, Ar-CH_2-C-C), 2.15 (m, Ar-C-CH_2-C).

1-[2-[[4-Fluoro-2-(4-fluorophenoxy)phenyl]methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (**19**). M.p. 216°C. ^{1}H NMR ($CDCl_3$): δ 6.4–7.7 (m, 12 aromatic Hs), 4.58 (s, Ar-CH_2-O), 4.02 (m, O-CH_2-C-N), 3.4–3.9 (m, 8 piperazine Hs), 3.33 (m, N-CH_2-C-O), 3.03 (m, N-CH_2-C-C-Ar-), 2.72 (t, Ar-CH_2-C-C), 2.19 (m, Ar-C-CH_2-C).

1-[2-[[4-Fluoro-2-(3-fluorophenoxy)phenyl]methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (**20**). M.p. 220°C. ^{1}H NMR (CD_3OD): δ 6.7–7.6 (m, 12 aromatic Hs), 4.62 (s, Ar-CH_2-O), 3.95 (m, O-CH_2-C-N), 3.4–3.9 (m, 8 piperazine Hs), 3.49 (m, N-CH_2-C-O), 3.28 (m, N-CH_2-C-C-Ar), 2.75 (t, Ar-CH_2-C-C), 2.12 (m, Ar-C-CH_2-C).

1-[3-(3-Chlorophenyl)propyl]-4-[2-[(3-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**21**). M.p. 212°C. 1H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.52 (s, Ar-CH_2-O), 3.95 (m, O-CH_2-C-N), 3.5–4.1 (m, 8 piperazine Hs), 3.39 (m, N-CH_2-C-O), 3.09 (m, N-CH_2-C-C-Ar), 2.70 (t, Ar-CH_2-C-C), 2.18 (m, Ar-C-CH_2-C).

1-[3-(4-Methylphenyl)propyl]-4-[2-[(3-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**22**). M.p. 221°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.51 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.5–4.1 (m, 8 piperazine Hs), 3.37 (m, N-CH_2-C-O), 3.04 (m, N-CH_2-C-C-Ar), 2.68 (t, Ar-CH_2-C-C), 2.31 (s, Ar-CH_3), 2.18 (m, Ar-C-CH_2-C).

1-[3-(3-Methoxyphenyl)propyl]-4-[2-[(3-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**23**). M.p. 208°C. ^{1}H NMR ($CDCl_3$): δ 6.7–7.4 (m, 13 aromatic Hs), 4.51 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.79 (s, OCH_3), 3.5–4.1 (m, 8 piperazine Hs), 3.35 (m, N-CH_2-C-O), 3.06 (m, N-CH_2-C-C-Ar), 2.69 (t, Ar-CH_2-C-C), 2.19 (m, Ar-C-CH_2-C).

1-[3-(2-Chlorophenyl)propyl]-4-[2-[(3-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**24**). M.p. 218°C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 6.9–7.4 (m, 13 aromatic Hs), 4.55 (s, Ar-CH_2-O), 3.95 (m, O-CH_2-C-N), 3.6–3.9 (m, 8 piperazine Hs), 3.41 (m, N-CH_2-C-O), 3.18 (m, N-CH_2-C-C-Ar), 2.87 (t, Ar-CH_2-C-C), 2.19 (m, Ar-C-CH_2-C).

1-[3-(3-Methoxyphenyl)propyl]-4-[2-[(2-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**25**). M.p. 187°C. ^{1}H NMR ($CDCl_3$): δ 6.7–7.4 (m, 13 aromatic Hs), 4.59 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.4–3.9 (m, 8 piperazine Hs), 3.26 (m, N-CH_2-C-O), 3.00 (m, N-CH_2-C-C-Ar), 2.68 (t, Ar-CH_2-C-C), 2.14 (m, Ar-C-CH_2-C).

1-[3-(4-Methylphenyl)propyl]-4-[2-[(2-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**26**). M.p. 225°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.59 (s, Ar-CH_2-O), 4.00 (m, O-CH_2-C-N), 3.3–3.9 (m, 8 piperazine Hs), 3.26 (m, N-CH_2-C-O), 2.96 (m, N-CH_2-C-C-Ar), 2.67 (t, Ar-CH_2-C-C), 2.32 (s, Ar-CH_3), 2.12 (m, Ar-C-CH_2-C).

1-[2-[(3-Phenoxyphenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (**27**). M.p. 216°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.51 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.5–4.1 (m, piperazine Hs), 3.35 (m, N-CH_2-C-O), 3.06 (m, N-CH_2-C-C-Ar), 2.72 (t, Ar-CH_2-C-C), 2.18 (m, Ar-C-CH_2-C).

1-[3-(2-Chlorophenyl)propyl]-4-[2-[(2-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**28**). M.p. 200°C. ^{1}H NMR $CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.59 (s, Ar-CH_2-O), 3.99 (m, O-CH_2-C-N), 3.4–3.9 (m, 8 piperazine Hs), 3.28 (m, N-CH_2-C-O), 3.06 (m, N-CH_2-C-C-Ar), 2.82 (t, Ar-CH_2-C-C), 2.15 (m, Ar-C-CH_2-C).

1-[3-(2-Methoxyphenyl)propyl]-4-[2-[(3-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**29**). M.p. 195°C. ^{1}H NMR ($CDCl_3$): δ 6.8–7.4 (m, 13 aromatic Hs), 4.51 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.82 (s, OCH_3), 3.5–4.1 (m, 8 piperazine Hs), 3.35 (m, N-CH_2-C-O), 3.06 (m, N-CH_2-C-C-Ar), 2.70 (t, Ar-CH_2-C-C), 2.16 (m, Ar-C-CH_2-C).

1-(3-Phenylpropyl)-4-[2-[[2-(phenylthio)phenyl]methoxy]ethyl]piperazine dihydrochloride (**30**). M.p. 213°C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.2–7.6 (m, 14 aromatic Hs), 4.72 (s, Ar-CH_2-O), 3.92 (m, O-CH_2-C-N), 3.5–4.0 (br.s, 8 piperazine Hs), 3.30 (m, N-CH_2-C-O), 3.25 (m, N-CH_2-C-C-Ar), 2.73 (t, Ar-CH_2-C-C), 2.14 (m, Ar-C-CH_2-C).

1-[2-[[2-(Phenylmethoxy)phenyl]methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (**31**). M.p. 206°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 14 aromatic Hs), 5.12 (s, Ar-CH_2-O-Ar), 4.61 (s, Ar-CH_2-O), 4.00 (m, O-CH_2-C-N), 3.2–4.0 (m, 8 piperazine Hs), 3.20 (m, N-CH_2-C-O), 2.92 (m, N-CH_2-C-C-Ar), 2.70 (t, Ar-CH_2-C-C), 2.11 (m, Ar-C-CH_2-C).

1-[3-(3-Chlorophenyl)propyl]-4-[2-[(2-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**32**). M.p. 199°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 4.58 (s, Ar-CH_2-O), 4.00 (m, O-CH_2-C-N), 3.4–4.0 (m, 8 piperazine Hs), 3.27 (m, N-CH_2-C-O), 3.03 (m, N-CH_2-C-C-Ar), 2.68 (t, Ar-CH_2-C-C), 2.12 (m, Ar-C-CH_2-C).

1-[3-(3-Chlorophenyl)propyl]-4-[2-[(4-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**33**). M.p. 212°C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.0–7.4 (m, 13 aromatic Hs), 4.54 (s, Ar-CH_2-O), 3.9 (m, O-CH_2-C-N), 3.6–4.0 (m, 8 piperazine Hs), 3.40 (m, N-CH_2-C-O), 3.15 (m, N-CH_2-C-C-Ar), 2.71 (t, Ar-CH_2-C-C), 2.18 (m, Ar-C-CH_2-C).

1-[3-(4-Methylphenyl)propyl]-4-[2-[(4-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**34**). M.p. 218°C. ^{1}H NMR ($CDCl_3$): δ 7.0–7.4 (m, 13 aromatic Hs), 4.52 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.5–4.1 (m, 8 piperazine Hs), 3.36 (m, N-CH2-C-O), 3.05 (m, N-CH_2-C-C-Ar), 2.68 (t, Ar-CH_2-C-C), 2.31 (s, Ar-CH_3), 2.18 (m, Ar-C-CH_2-C).

1-[3-(4-Methylphenyl)propyl]-4-[2-[[2-(phenylmethoxy)phenyl]methoxy]ethyl]piperazine dihydrochloride (**35**). M.p. 195°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs), 5.10 (s, Ar-CH_2-O-Ar), 4.59 (s, Ar-CH_2-O), 3.96 (m, O-CH_2-C-N), 3.3–3.9 (m, 8 piperazine Hs), 3.23 (m, N-CH_2-C-O), 2.92 (m, N-CH_2-C-C-Ar), 2.65 (t, Ar-CH_2-C-C), 2.31 (s, Ar-CH_3), 2.08 (m, Ar-C-CH_2-C).

1-[3-(2-Methoxyphenyl)propyl]-4-[2-[(4-phenoxyphenyl)methoxy]ethyl]piperazine dihydrochloride (**36**). M.p. 201°C. ^{1}H NMR ($CDCl_3$): δ 6.8–7.4 (m, 13 aromatic Hs), 4.51 (s, Ar-CH_2-O), 3.98 (m, O-CH_2-C-N), 3.80 (s, OCH_3), 3.5–4.1 (m, 8 piperazine Hs), 3.36 (m, N-CH_2-C-O), 3.06 (m, N-CH_2-C-C-Ar), 2.71 (t, Ar-CH_2-C-C), 2.16 (m, Ar-C-CH_2-C).

1-[3-(2-Methoxyphenyl)propyl]-4-[2-[[2-(phenylthio)phenyl]methoxy]ethyl]piperazine dihydrochloride (**37**). M.p. 186°C. ^{1}H NMR ($CDCl_3$): δ 6.8–7.5 (m, 13 aromatic Hs), 4.65 (s, Ar-CH_2-O), 4.00 (m, O-CH_2-C-N), 3.81 (s, OCH_3), 3.4–4.0 (m, 8 piperazine Hs), 3.26 (m, N-CH_2-C-O), 3.03 (m, N-CH_2-C-C-Ar), 2.69 (t, Ar-CH_2-C-C), 2.14 (m, Ar-C-CH_2-C).

1-[3-(2-Methoxyphenyl)propyl]-4-[2-[2-(phenylmethoxy)phenyl]methoxy]ethyl]piperazine dihydrochloride (**38**). M.p. 191°C. ^{1}H NMR ($CDCl_3$): δ 6.8–7.4 (m, 13 aromatic Hs), 5.11 (s, Ar-CH_2-O-Ar), 4.61 (s, Ar-CH_2-O), 4.00 (m, O-CH_2-C-N), 3.82 (s, OCH_3), 3.2–4.0 (m, 8 piperazine Hs), 3.2 (m, N-CH_2-C-O), 2.93 (m, N-CH_2-C-C-Ar), 2.69 (t, Ar-CH_2-C-C), 2.07 (m, Ar-C-CH_2-C).

1-[2-[[2-(Phenylmethyl)phenyl]methoxy]ethyl]-4-(3-phenoxypropyl)piperazine dihydrochloride (**40**). M.p. 209°C. ^{1}H NMR ($CDCl_3$): δ 7.0–7.4 (m, 14 aromatic Hs), 4.51 (s, Ar-CH_2-O), 4.04 (s, ar-CH_2-

Ar), 3.85 (m, O-CH_2-C-N), 3.4–4.0 (br.s, 8 piperazine Hs), 3.08 (m, N-CH_2-C-O), 3.05 (m, N-CH_2-C-C-Ar), 2.70 (t, Ar-CH_2-C-C), 2.16 (m, Ar-C-CH_2-C).

1-[2-[(4-Phenoxyphenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (**41**). M.p. 210°C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.0–7.4 (m, 14 aromatic Hs), 4.54 (s, Ar-CH_2-O), 3.95 (m, O-CH_2-C-N), 3.6–4.0 (br.s, 8 piperazine Hs), 3.30 (m, N-CH_2-C-O), 3.12 (m, N-CH_2-C-C-Ar), 2.74 (t, Ar-CH_2-C-C), 2.19 (m, Ar-C-CH_2-C).

N-Methyl-N-phenyl-2-[[2-[4-(3-phenylpropyl)-1-piperazinyl]ethoxy]methyl]benzenamine dihydrochloride (**42**). M.p. 220°C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 6.55 (m, 2 aniline *o*-Hs), 6.72 (tt, aniline *p*-H), 7.1–7.5 (m, 13 other aromatic Hs), 4.46 (s, Ar-CH_2-O), 3.90 (m, O-CH_2-C-N), 3.4–3.9 (m, 8 piperazine Hs), 3.49 (s, NCH_3), 3.29 (m, N-CH_2-C-O), 3.08 (m, N-CH_2-C-C-Ar), 2.73 (t, Ar-CH_2-C-C), 2.16 (m, Ar-C-CH_2-C).

3-[3-[4-[(2-Phenoxyphenyl)methoxy]ethyl]-1-piperazinyl]propyl]benzenamine trihydrochloride (**43**). M.p. 182°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.5, (m, 13 aromatic Hs), 4.61 (s, Ar-CH_2-O), 3.96 (m, O-CH_2-C-N), 3.6–3.9 (m, 8 piperazine Hs), 3.36 (m, N-CH_2-C-O), 3.16 (m, N-CH_2-C-C-Ar), 2.76 (t, Ar-CH_2-C-C), 2.16 (m, Ar-C-CH_2-C).

2-[3-[4-[2-[(2-Phenoxyphenyl)methoxy]ethyl]-1-piperazinyl]propyl]phenol dihydrochloride (**44**). M.p. 217°C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 6.8–7.5 (m, 13 aromatic Hs), 4.62 (s, Ar-CH_2-O), 3.96 (m, O-CH_2-C-N), 3.4–3.9 (m, 8 piperazine Hs), 3.33 (m, N-CH_2-C-O), 3.10 (m, N-CH_2-C-C-Ar), 2.70 (t, Ar-CH_2-C-C), 2.10 (m, Ar-C-CH_2-C).

1-[2-[(2-Phenoxyphenyl)methoxy]ethyl]-4-(2-phenylethyl)piperazine dihydrochloride (**45**). M.p. 221°C. ^{1}H NMR (CD_3OD): δ 6.9–7.6 (m, 14 aromatic Hs), 4.67 (s, Ar-CH_2-O), 3.91 (m, O-CH_2-C-N), 3.5–3.9 (br.s, 8 piperazine Hs), 3.50 (m, 4 other N-CH_2's), 3.13 (m, Ar-CH_2).

Method 2 (compound **46**, **47**)

4-(3-Phenyl-2-propynyl)piperazine-1-carboxaldehyde (**10**) Copper(II) acetate (0.25 g) was added to a solution of paraformaldehyde (2.5 g) and piperazinecarboxaldehyde (**15**) (6.3 g, 55 mmol) in dry dioxane. The resulting mixture was heated to 100°C and a solution of phenylacetylene (**9**) (5.85 g, 57 mmol) in dry dioxane (10 ml) was added dropwise. After 3 h, the reaction mixture was cooled to 20°C. The resulting suspension was then filtered and the solvent was evaporated. The crude product was purified by column chromatography (silica gel, eluent: toluene/ethanol, 9/1, v/v) to give **10** as an oil in 83% yield (10.4 g). R_f 0.4 (toluene/ethanol, 9/1, v/v). ^{1}H NMR ($CDCl_3$): δ 8.05 (s, COH), 7.25–7.5 (m, C_6H_5), 3.6 (s, CH_2), 3.6–3.7, 3.4–3.5, 2.6–2.7 (m, 8 piperazine Hs).

4-(3-Phenyl-2-propynyl)piperazine (**11**). **10** (9.5 g) was added to a aqueous 4 N NaOH solution (100 ml) and refluxed. After ½ h, the reaction mixture was cooled to 20°C and extracted with dichloromethane. The organic layer was washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gas **11** quantitatively as an oil. R_f 0.6 (toluene/ethanol, 8/2, v/v). ^{1}H NMR ($CDCl_3$) δ 7.25–7.5 (m, C_6H_5), 3.5 (s, CH_2), 2.8–2.9, 2.6–2.7 (m, 8 piperazine Hs).

1-[2-[(3-Phenoxyphenyl)methoxy]ethylchloride (**12**). Conc. sulfuric acid (0.55 ml) was added to a mixture of 2-chloroethanol (6.22 g, 77.5 mmol) and 3-phenoxybenzyl alcohol (10 g, 50 mmol). After stirring for 20 h at 100°C, the reaction mixture was cooled, water was added and the aqueous layer was extracted with toluene. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was subjected to column chromatography (silica gel, eluent: hexane/ethanol, 98/2, v/v) to yield 4.5 g (35%) of **12** as an oil, which was homogeneous on TLC (R_f 0.6; hexane/ethyl-acetate, 8/2, v/v). ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 9 aromatic Hs), 4.55 (s, CH_2), 3.6–3.8 [m, $(CH_2)_2$].

1-[2-[(3-Phenoxyphenyl)methoxy]ethyl]-4-(3-phenyl-2-propynyl)piperazine dihydrochloride (**46**). A stirred suspension of **11** (0.91 g, 4.54 mmol), potassium carbonate (0.35 g), a catalytic amount of potassium iodide (0.03 g) and **12** (1.19 g, 4.5 mmol) in dry 4-methyl-2-pentanone were refluxed for 18 h. The reaction mixture was then cooled to 20°C. The resulting suspension was filtered and the solvent was evaporated in vacuo. The crude material was purified by column chromatography (silica gel, eluent: toluene/ethanol, 8/2, v/v). The product was dissolved in ethanol and a 5 N solution of HCl in ethanol (1 ml) was added, causing the product to crystallize. The HCl salt was recrystallized twice from ethanol/diethyl ether. Yield 79% (0.91 g) of **46**. M.p. 195°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.6 (m, 14 aromatic Hs), 4.55 (s, Ar-CH_2-O), 4.32 (s, N-CH_2≡C), 3.96 (m, O-CH_2-C-N), 3.6–4.1 (m, 8 piperazine Hs), 3.45 (m, N-CH_2-C-O).

Using the above procedure, the following other derivative was prepared:

1-[2-[(2-Phenoxyphenyl)methoxy]ethyl]-4-(3-phenyl-2-propynyl)piperazine dihydrochloride (**47**). M.p. 200°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.6 (m, 14 aromatic Hs), 4.60 (s, Ar-CH_2-O), 4.14 (s, N-CH_2-C≡C), 4.01 (m, O-CH_2-C-N), 3.4–4.2 (m, 8 piperazine Hs), 3.24 (m, N-CH_2-C-O).

Method 3 (compounds **48**–**49**)

(Z)-1-[2-[(3-Phenoxyphenyl)methoxy]ethyl]-4-(3-phenyl-2-propenyl)piperazine dihydrochloride (**48**). Lindlar catalyst (0.25 g) was added to a solution of **46** (2.1 g, 5 mmol) in toluene. The resulting suspension was treated for 2 h with hydrogen in a Parr apparatus (P 25 psi) at room temperature. Filtration and evaporation of the solvent was followed by column chromatography (silica gel, eluent: toluene/ethanol, 9/1, v/v). Addition of 2.1 equivalent HCl in ethanol and evaporation gave white solid material which was recrystallized to give 1.67 g of **48** (67% yield). M.p. 197°C. R_f 0.5 (toluene/ethanol, 8/2, v/v). ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 13 aromatic Hs + Ar-CH=C), 6.08 (dt, Ar-C=CH), 4.52 (s, Ar-CH_2O), 4.00 (m, O-CH_2-C-N), 3.98 (d, N-CH_2-C=C), 3.5–4.1 (m, 8 piperazine Hs), 3.30 (m, N-CH_2-C-O).

Using the above procedure also the following derivative was prepared:

(Z)-1-[2-[(2-1Phenoxyphenyl)methoxy]ethyl]-4-(3-phenyl-2-propenyl)piperazine dihydrochloride (**49**). M.p. 201°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.4 (m, 14 aromatic Hs + Ar-CH=C), 6.03 (dt, Ar-C=CH), 4.58 (s, Ar-CH_2-O), 4.0 (m, O-CH_2-C-N + N-CH_2-C=C), 3.3–3.9 (m, 8 piperazine Hs), 3.25 (m, N-CH_2-C-O).

Method 4 (compound **50**)

(E)-4-(3-Phenyl-2-propenyl)-1-piperazineethanol (**15**). Cinnamyl bromide (**14**) (9.9 g, 65 mmol) in dioxane (15 ml) was added dropwise to a suspension of *N*-(2-hydroxyethyl)piperazine (8.5 g, 65 mmol) (**13**) and $NaHCO_3$ (6.5 g) in dioxane (15 ml). The reaction mixture was stirred for 16 h at 85°C. The reaction mixture was then cooled to room temperature, filtered and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (silica gel, eluent: toluene/ethanol, 9/1, v/v) to yield 8.82 g (55%) of **15** as an oil. R_f 0.4, CH_2Cl_2/MeOH, 8/1, v/v. ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, C_6H_5), 6.55 (d, C_6H_5-CH=C), 6.2–6.5 (m, Ar-CH=CH), 3.6 (t, CH_2OH), 3.2 (dd, C=CH-CH_2N), 2.5–2.7 (m, NCH_2 and piperazine Hs).

(E)-1-[2-[(2-Phenoxyphenyl)methoxy]ethyl]4-(3-phenyl-2-propenyl)piperazine dihydrochloride (**50**). A solution of 2-phenoxybenzyl chloride (**16**) (7.82 g, 35.8 mmol) in dry 1,2-dimethoxyethane (8 ml) was added dropwise to a stirred solution of **15** (8.82 g, 35.8 mmol) and potassium tert-butoxide (4.4 g) in dry 1,2-dimethoxyethane (125 ml) at room temperature. After stirring for 3 days at 40°C, the reaction mixture was cooled to 20°C. The suspension was then filtered and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, eluent: toluene/ethanol, 9/1, v/v). The HCl salt of **50** was recrystallized twice from ethanol. Yield 2.4 g (14%). M/o. 199°C. ^{1}H NMR ($CDCl_3$): δ 6.8–7.4 (m, 14 aromatic Hs), 6.77 (d, Ar-CH=C), 6.37 (dt, Ar-C-CH), 4.59 (s, Ar-CH_2-O), 4.03 (m, O-CH_2-C-N), 3.4–3.9 ppm (m, 8 piperazine Hs), 3.23 ppm (m, N-CH_2-C-O).

Pharmacology

Re-uptake studies of monoamines. Male Wistar rats (Hsd/Cpb:WU), weighing between 150–200 g, were killed by decapitation and the brains were rapidly removed. Corpora striata and hypothalami were dissected out; weighed and homogenized using a Potter-Elvehjem homogenizer (with a total clearance of 0.25 mm; 10 strokes up and down at 850 rpm) in 20 volumes (w/v) of ice-cold solution containing 0.32M sucrose and 0.01M glucose, adjusted to pH 7.4 with 0.05M Tris-HCl. A crude mitochondrial pellet (P_2) was obtained by cen-

trifugation for 30 min at 11500 g and was used for re-uptake experiments. Further details are described by *Nickolson* and *Wieringa*[12]. Synaptosomes from the hypothalamus were used to measure the re-uptake of [^{3}H]noradrenaline, and synaptosomes from the striatum were employed for re-uptake experiments with [^{14}C]dopamine and [^{3}H]serotonin.

Ipsiversive circling. Male rats (Hsd/Cpb:WU), weighing between 350–550 g were lesioned under methohexital sodium (Brietal sodium) (80 mg/kg) anaesthesia, by infusion over a 5-min period of 4 μl of a freshly prepared solution of 6-hydroxydopamine HCl (2.5 mg/ml), NaCl 0.9% and ascorbic acid (0.1 mg/ml) in water, into the left median forebrain bundle using a stereotactic frame. The coordinates of the injection point were $A = 4.5$, $L = 1.7$, $H = 1.5$ according to the atlas of *Paxinos* and *Watson*[13]. Over a recovery period of at least 3 weeks, the rats were selected for having been successfully denervated by injecting them twice with apomorphine HCl (0.1 mg/kg s.c.) and once with SKF 38393 (2 mg/kg s.c.) with an interval of at least 5 days. Only those rats that showed 200 complete circlings per 60 min after apomorphine and 400 complete circlings per 120 min after SKF 38393 treatment were selected for drug testing. Drugs were injected subcutaneously and, immediately thereafter, a belt was fitted around the chest of the rat, after which it was placed in a perspex hemispherical bowl (40 cm diameter) in which it could move freely. A thin steel wire, connected to the belt, transferred the movements of the rat to a device which detected left and right circlings. 10 Rats were measured simultaneously in a battery of 10 bowls.

The results are expressed as the mean total number of circlings over a period of 60 min +/− S.E.M. The final result was given as the threshold dose indicating the lowest dose of the compound that induced at least 50 circlings in at least 50% of the animals within the group treated with this dose.

Acknowledgements

We wish to thank Dr. *C. Funke* for recording and interpretation of the NMR spectra, Mr. *G. Schmeits* for recording and interpretation of the (FAB)-mass spectra, Dr. *H. Hindriks* for determination of *RI* values and Dr. *C. Broekkamp* and Dr. *H. Berendsen* for their advice concerning *in vivo* testing.

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