



3-(1-Piperazinyl)-4,5-dihydro-1*H*-benzo[*g*]indazoles: High Affinity Ligands for the Human Dopamine D₄ Receptor with Improved Selectivity over Ion Channels

Ian Collins,^{a,*} Michael Rowley,^a William B. Davey,^a Frances Emms,^a Rosemarie Marwood,^a Shil Patel,^a Smita Patel,^a Alan Fletcher,^a Ian C. Ragan,^a Paul D. Leeson,^a Ann L. Scott^b and Theodore Broten^b

^a*Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, UK*

^b*Merck Research Laboratories, West Point, PA., USA*

Received 18 October 1997; accepted 5 December 1997

Abstract—3-(4-Piperidinyl)-5-arylpyrazoles, such as **1**, were selective for the cloned human dopamine D₄ receptor (hD₄), but also showed affinity at voltage sensitive calcium, sodium and potassium ion channels. A combination of substituent changes to reduce the basicity of the piperidine nitrogen and conformational restriction to give 4,5-dihydro-1*H*-benzo[*g*]indazoles reduced this ion channel affinity at the expense of selectivity for hD₄ over other dopamine receptors. Incorporation of piperazine into the 4,5-dihydro-1*H*-benzo[*g*]indazoles in place of piperidine gave a novel series of high affinity, selective, orally bioavailable hD₄ ligands, such as **16**, with improved selectivity over ion channels. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

Schizophrenia is a serious mental illness characterised by episodes of disordered thought, hallucinations, delusions, social withdrawal and other estranging behaviours.¹ Classical neuroleptic drugs for the treatment of the disorder are presumed to act by the unselective blockade of D₂-like dopamine receptors.² Although these are effective for the treatment of positive symptoms, there is a great need for more selective treatments that reduce or eliminate the often severe movement disorders³ and hyperprolactinaemia⁴ associated with these drugs, and that also show greater efficacy in the treatment of the negative symptoms of the illness. Recent advances in molecular biology have identified five cloned human subtypes of dopamine receptor, divided

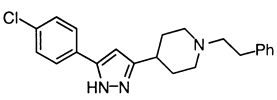
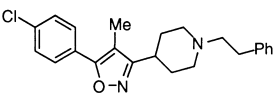
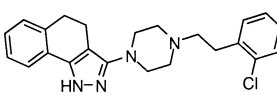
pharmacologically into two classes: D₁-like (D₁ and D₅) and D₂-like (D₂, D₃ and D₄).^{5–9} The atypical neuroleptic clozapine,¹⁰ which does not provoke the movement disorders, shows, amongst many other actions, some selectivity for the human D₄ (hD₄) subtype.^{8,11} Additionally, there have been reports that hD₄ receptors are located preferentially in the areas of the brain involved with antipsychotic activity,¹² and that hD₄ receptor density may be elevated in post-mortem schizophrenic brain,^{13–15} although this latter finding is disputed.^{16,17}

For these reasons, we^{18–20} and others^{21–25} have described the development of novel, selective hD₄ receptor antagonists with the aim of determining the role of the hD₄ receptor in psychosis. In particular, we recently reported the discovery of the pyrazolopiperidine (**1**) (Table 1) and its elaboration to the very highly selective antagonist **2**.^{18,19} Further characterisation of these ligands has revealed that, although they are selective with respect to other central nervous system G-protein coupled receptors, they exhibit moderately high affinities at voltage sensitive sodium, calcium and

Key words: 4,5-1*H*-Benzo[*g*]indazoles; selective dopamine receptor ligands.

*Corresponding author: Tel: 01279440419; Fax: 01279440187; E-mail: ian_collins@merck.com

Table 1. Binding^a and physicochemical properties of the lead compounds

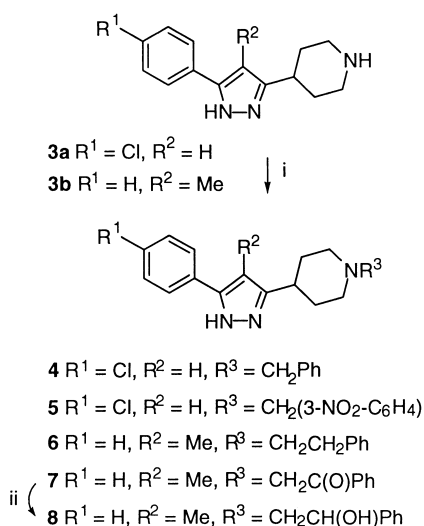
No.	1	2	16
Structure			
hD ₂ K _i (nM)	644	> 1700	> 1500
hD ₃ K _i (nM)	> 4000	770	> 4100
hD ₄ K _i (nM)	5.8	3.5	4.3
Ca channel K _i (μM)	1.4	0.82	58% @ 10 μM
Na channel K _i (μM)	0.56	1.9	33% @ 10 μM
I _{Kr} channel EC ₂₅ (μM)	0.40	n.d. ^b	> 30
pK _a	> 7.5 ^c	> 7.4 ^c	6.55
log P (pH 7.4)	4.2	4.5	> 4

^aSee footnotes to Table 2 for definition of binding parameters.^bn.d., not determined.^cPoor solubility prevented accurate measurement.

potassium ion channels (Table 1). This represents a potential bar to the eventual use of these compounds as investigational tools in the clinic. In this paper we describe the evolution of ligands related to **1** to produce the title compounds: high affinity, selective hD₄ ligands with reduced ion channel activities and good oral bio-availability.

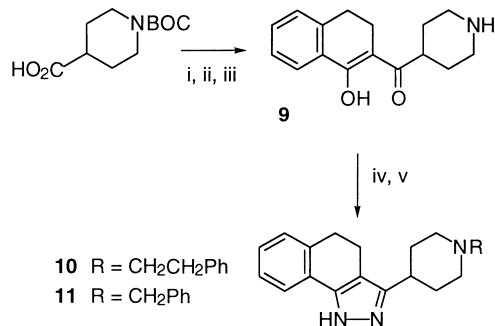
Chemistry

The pyrazolopiperidines (**3a**, **3b**, and **4**; Scheme 1) were prepared by the general procedure described previously.¹⁹ Alkylation of **3a** gave the analogue (**5**) and

**Scheme 1.** Reagents: (i) RBr, DMF, ⁱPr₂NEt, 60 °C, 25–46%; (ii) NaBH₄, EtOH, rt, 43%.

alkylation of **3b** gave the compounds **6** and **7**. The ketone (**7**) was reduced with sodium borohydride to give the alcohol (**8**). 3-(4-Piperidiny)-4,5-dihydro-1*H*-benzo[*g*]indazoles (**10** and **11**; Scheme 2) were synthesised by an extension of the previously described route. Thus, the condensation of two equivalents of the lithium enolate of α-tetralone with protected isonipecotic acid, activated as the imidazolide, gave the diketopiperidine (**9**) in good yield after *N*-deprotection. Alkylation of **9** and subsequent condensation with hydrazine afforded the target tricyclic compounds (**10** and **11**).

The piperazine (**12**; Table 2) was prepared as described previously.¹⁹ The analogous 3-(1-piperazinyl)-4,5-dihydro-1*H*-benzo[*g*]indazoles (**14**, **15**, and **16**; Scheme 3) were synthesised from α-tetralone, starting with a condensation with carbon disulfide under basic conditions, followed by double *S*-methylation with methyl iodide. The resulting dithioketeneacetal was refluxed with *N*-

**Scheme 2.** Reagents: (i) *N,N*-carbonyldiimidazole, solvent, rt; (ii) α-tetralone, LDA, THF, −78 °C; (iii) HCl, EtOAc, rt, 48% (three steps); (iv) RBr, ⁱPr₂NEt, DMF, rt–70 °C, 47–49%; (v) NH₂NH₂·H₂O, MeOH, rt, 55–81%.

BOC-piperazine in acetonitrile to yield the mono-substitution product (**13**). The regiochemistry of **13** was demonstrated by the observation of an NOE between the *S*-methyl group and the proximal bridging methylene. Further substitution of the remaining thiomethyl group of **13** with hydrazine was accompanied by ring closure to introduce the pyrazole ring. The syntheses of **14**, **15**, and **16** were completed by *N*-deprotection and alkylation in poor to moderate yield. For the analogous 7-membered ring compound (**18**; Scheme 4) a variation of this route was used, starting from 1-benzosuberone, in which the *N*-substituted piperazine was introduced

complete in a single step to give **17**, albeit in low yield. Elaboration of **17** as before gave the target (**18**).

The *N*-methylated analogues (**21** and **22**; Scheme 5) were prepared from **13** by condensation with *N*-methylhydrazine to give a mixture of **19** and **20** (1.7:1), which were separated by flash column chromatography. The regiochemistry of **19** was demonstrated by the observation of a reciprocal NOE between the pyrazole methyl group and the neighbouring aromatic proton. The two compounds were taken on separately as before to give **21** and **22**.

Table 2. Variation of the substituent on the basic nitrogen

No.	Structure	K_i^a (nM)			Inhibition (at 10 μ M) ion channels	
		hD ₂	hD ₃	hD ₄	Ca ^b	Na ^c
4		125	160	9.1	80%	n.d. ^d
5		400	1500	40	52%	4%
6 ^e		140	1800	1.2	77%	100%
7		450	970	38	33%	61%
8		660	> 4400	4.4	77%	n.d.
10		41	908	0.40	71%	n.d.
11		14	55	4.5	62%	n.d.

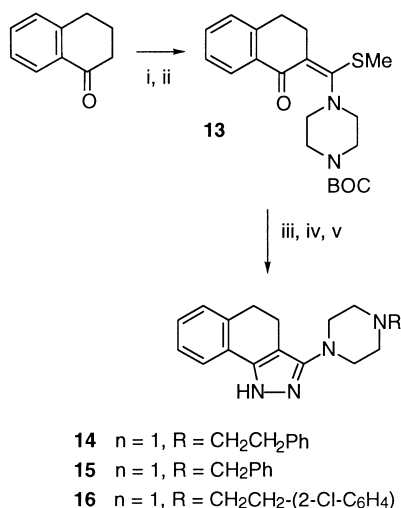
^aAffinities at cloned human dopamine receptors stably expressed in cell lines. Results are the mean of two or more determinations.

^bInhibition of specific binding of [³H] diltiazem to rabbit skeletal muscle at 10 μ M concentration of test compound. Results are the mean of two or more determinations.

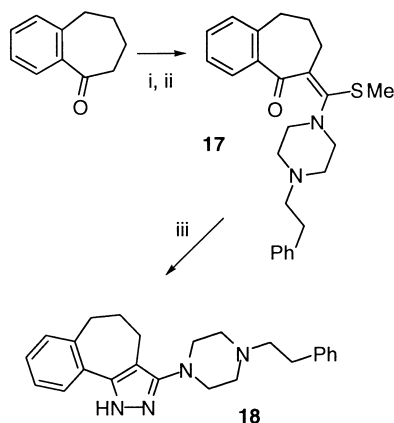
^cInhibition of specific binding of [³H] batrachotoxin to rat cortex at 10 μ M concentration of test compound. Results are the mean of two or more determinations.

^dn.d., not determined.

^eAffinities are the result of a single determination only.



Scheme 3. Reagents: (i) NaH, CS_2 , MeI, THF, rt, 59%; (ii) *N*-tert-butoxycarbonylpiperazine, MeCN, reflux, 49%; (iii) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, rt, 80%; (iv) $\text{CF}_3\text{CO}_2\text{H}$, rt; (v) RBr, $^i\text{Pr}_2\text{NEt}$, DMF, rt–60 °C, 7–51% (two steps).



Scheme 4. Reagents: (i) NaH, CS_2 , MeI, THF, rt, 65%; (ii) phenethylpiperazine trifluoroacetate, $^i\text{Pr}_2\text{NEt}$, MeCN, reflux, 13%; (iii) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, rt, 71%.

Results and Discussion

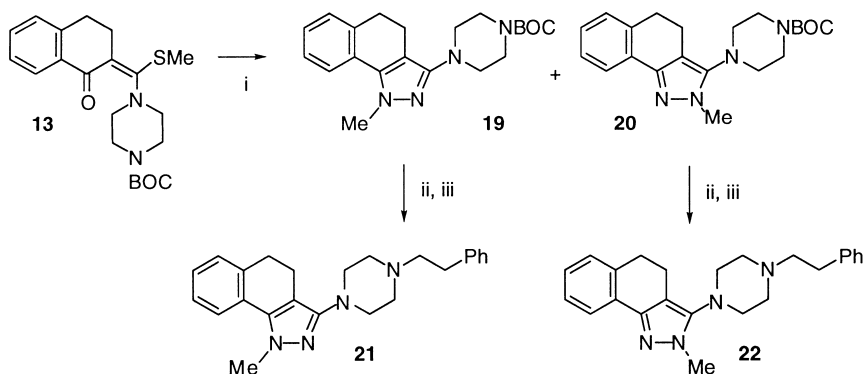
The compounds prepared were tested *in vitro* for their ability to displace [^3H]-spiperone from cloned human dopamine receptors (hD_2 stably expressed in CHO cells²⁶ and hD_3 and hD_4 in HEK293 cells²⁷). Each inhibition constant (K_i) was the mean of at least two experimental determinations: errors in the mean were within twofold of the mean. Binding to voltage sensitive ion channels was evaluated *in vitro* in rat cerebral cortex for the sodium (Na) channel²⁸ and in rabbit skeletal muscle for the calcium (Ca) channel.²⁹ Values obtained

were expressed as the percentage inhibition of radiolabel binding at a fixed test compound concentration of 10 μM and were the mean of at least two determinations. Binding to voltage sensitive potassium channels (mainly IK_R) was estimated *in vitro* by the measurement of prolongation of effective refractory period (ERP) in ferret papillary muscle.³⁰

Efforts to introduce a larger window between the hD_4 affinity and ion channel activities began by varying the substitution, and consequently the basicity, of the piperidine nitrogen of **1** (Table 2). The introduction of *N*-benzyl in **4** as a replacement for the *N*-phenethyl group of **1**, previously found to be optimal for selectivity at hD_4 receptors over hD_2 and hD_3 ,¹⁹ produced the expected decrease in selectivity for hD_4 over the other dopamine subtypes whilst little change in calcium channel activity was observed. Substitution by the more electron withdrawing 3-nitrobenzyl group did produce a compound (**5**) with significantly decreased activity at both calcium and sodium ion channels. However, this change also reduced affinity at the hD_4 receptor by sevenfold, suggesting that modulation of the basicity of the nitrogen atom alone would not be sufficient to achieve the desired selectivity over the ion channels.

Earlier studies had shown that a 4-methyl substituent on the central pyrazole ring of ligands related to **1** was beneficial for hD_4 affinity,¹⁹ possibly as a result of introducing a conformational bias in the relative orientation of the aromatic heterocycle and the two substituent rings. Also, removal of the 4-chloro substituent from the pendant 5-phenyl ring did not reduce affinity for the hD_4 receptor.¹⁹ Thus the 4-methylpyrazole (**6**) had fivefold improved affinity at hD_4 and the same selectivity as **1** with regard to hD_2 . Again, gradual reduction of the basicity of the piperidine nitrogen, this time by substitution on the ethylene linker to give the alcohol (**8**) and ketone (**7**), produced a progressive decline in hD_4 affinities. The ketone (**7**) had a similar profile to the nitrobenzyl analogue (**5**) in terms of dopamine receptor affinities and calcium ion channel activity. However, the difference in sodium channel activities between **5** and **7** indicated that the ion channels had divergent structure–activity relationships (SAR) in this series of compounds and, furthermore, that these SAR were not wholly dominated by the pK_a of the piperidine.

The 4-methyl substituent on the pyrazole (**6**) was extended to create an ethylene bridge to the 5-aryl ring, providing compound (**10**), with the intention of restricting the rotation of the aromatic ring whilst providing a similar conformational bias with regard to the piperidine as the original 4-methyl group. A significant increase in affinity at all dopamine subtypes was



Scheme 5. Reagents: (i) MeNHNH₂, EtOH, temp, 30%, (19)/(20) 1.7/1; (ii) CF₃CO₂H, rt; (iii) PhCH₂CH₂Br, ⁱPr₂NEt, DMF, 60 °C, 37–41% (two steps).

observed on making these changes, leading to sub-nanomolar affinity at hD₄ for **10** with reduced selectivity over hD₂. There was also a marginal reduction in calcium ion channel activity. The increase in affinity associated with the planar tricyclic 4,5-dihydro-1*H*-benzo[*g*]indazole system meant the analogue (**11**) retained good hD₄ activity when *N*-benzyl was substituted for *N*-phenethyl. Although this combination of changes also reduced calcium channel activity, this was at the expense of the selectivity for hD₄ over the other dopamine receptors.

An alternative approach to finding more selective compounds was based on piperazine analogues of the piperidine lead **1** (Table 2). The piperazine (**12**; p*K_a* 7.2), which was somewhat less basic than **1** (p*K_a* > 7.5), had lower hD₄ affinity than **1**, but represented a better lead profile than the modified piperidines such as **5** and **7**. In particular, good selectivity over hD₂ and hD₃ subtypes was maintained and a significant reduction in calcium and sodium ion channel activity was associated with only a modest drop in hD₄ affinity. The piperazine (**12**) also had improved selectivity over the potassium channels (IK_R EC₂₅ 5.8 μM) compared to the piperidine (**1**; Table 1).

Replacement of the phenylpyrazole moiety of **12** with the 4,5-dihydro-1*H*-benzo[*g*]indazole structure, which had led to increased hD₄ affinity in the piperidine series, now gave the high affinity compound (**14**) which retained the high selectivity over hD₂ and hD₃ expected from the *N*-phenethyl substitution. The small decrease in calcium channel activity associated with the change from phenylpyrazole to 4,5-dihydro-1*H*-benzo[*g*]indazole, previously observed in the comparison of **6** with **10**, was apparently additive to that associated with the change from piperidine to piperazine. Thus **14** had negligible activity at the calcium ion channel, and was now

also inactive at potassium channels (IK_R EC₂₅ > 30 μM). Regrettably, despite an otherwise promising profile, compound **14** remained active at the sodium channel.

Replacement of the *N*-phenethyl group of **14** by *N*-benzyl to yield **15** was not tolerated either in terms of affinity or selectivity at dopamine receptors. Several analogues of **14** bearing simple substituents on the aromatic ring of the *N*-phenethyl group were prepared—for example; 4-Cl, 2-NO₂ and 2-, 3-, and 4-OMe—but were generally significantly less active than the parent (**14**) at dopamine receptors (hD₄ K_i > 20 nM). An exception was the 2-chloro substituted derivative (**16**) which showed slightly improved hD₄ binding. More importantly, **16** had a much improved sodium ion channel profile (33% inhibition at 10 μM) whilst remaining inactive at potassium channels (EC₂₅ > 30 μM). Although the activity of **16** at calcium channels was more than **14**, this still represented a satisfactory improvement on the lead piperidines **1** and **2**.

Comparison of **6**, **10**, **14**, and **16** suggested that although a large component of the binding at ion channels was due to the basicity of the heterocycle in these series, there were more subtle effects in the structure–activity relationships arising from aromatic substitution on the *N*-substituent in the case of the sodium channel, and also more generally from the local conformation around the heteroaromatic ring. The strong influence of the latter property was demonstrated by the ring expanded analogue (**18**), where the longer propylene tether was expected to twist the pyrazole and 5-phenyl substituent out of coplanarity. This led to a large increase in the calcium channel activity compared to the more planar **14**. Similarly, methylation of the pyrazole nitrogen to give **21** also enhanced calcium channel activity. In this case, the buttressing effect of the methyl group and the

5-phenyl substituent may disrupt the planarity of the tricycle relative to the parent (**14**). This hypothesis was supported by the regioisomeric *N*-methyl pyrazole (**22**), where the conformation of the tricycle would again be more planar as the *peri* interaction is removed, which showed an ion channel profile more like that of **14**. The high affinity of both the *N*-methyl pyrazoles (**21** and **22**) suggested that neither the pyrazole N-H nor the lone pair on the pyrazole nitrogen were engaged in a direct

interaction with the receptor. This was consistent with earlier observations that the central pyrazole ring in ligands related to **1** could be replaced successfully by a variety of heterocycles and acyclic linkers.¹⁹ In view of the promising dopamine receptor and ion channel profile of **16** (Table 1), the pharmacokinetic properties of this compound were investigated in rats. The compound (**16**) was orally bioavailable (31%) with a plasma half-life of 1 h.

Table 3. Replacing the piperidine ring with piperazine

No.	Structure	K_i^a (nM)			Inhibition (at 10 μ M) ion channels	
		hD ₂	hD ₃	hD ₄	Ca ^b	Na ^c
12		> 1900	1200	23	32%	43%
14		> 1800	2000	5.3	17%	100%
15		270	810	22	14%	n.d. ^d
16		> 1500	> 4100	4.3	58%	33%
18		> 1800	700	3.9	72%	n.d.
21		480	400	7.9	78%	n.d.
22		250	1200	1.9	44%	76%

^aAffinities at cloned human dopamine receptors stably expressed in cell lines. Results are the mean of two or more determinations.

^bInhibition of specific binding of [³H] diltiazem to rabbit skeletal muscle at 10 μ M concentration of test compound. Results are the mean of two or more determinations.

^cInhibition of specific binding of [³H] batrachotoxin to rat cortex at 10 μ M concentration of test compound. Results are the mean of two or more determinations.

^dn.d., not determined.

Conclusions

A significant improvement in the selectivity for hD₄ receptors over ion channels in the series of heterocyclopipyrroles derived from **1** was achieved by a combination of three approaches. A general reduction in the basicity of the heterocycle on changing from piperidine to piperazine reduced affinity at the ion channels, but also at dopamine receptors. The hD₄ affinity was restored by conformational restriction of the pendant 5-phenyl group to produce the more planar, tricyclic 4,5-dihydro-1*H*-benzo[*g*]indazoles. Generally lower ion channel activities were also associated with this more planar structure, although the three ion channel types studied did not have identical structure–activity relationships. Appropriate aromatic substitution in the *N*-phenethyl group attached to the piperazine further improved selectivity over ion channels and allowed the identification of the high affinity, selective, orally bio-available hD₄ ligand (**16**).

Experimental

Biochemical methods

[³H]-Spiperone binding studies.^{26,27} Clonal cell lines expressing the human dopamine D₂, D₃ and D₄ receptor subtypes were harvested in PBS (phosphate buffered saline) and then lysed in 10 mM Tris–HCl pH 7.4 buffer containing 5 mM MgSO₄ for 20 min on ice. Membranes were centrifuged at 50,000 *g* for 15 min at 4 °C and the resulting pellets resuspended in assay buffer (50 mM Tris–HCl) pH 7.4 containing 5 mM EDTA, 1.5 mM CaCl₂, 5 mM MgCl₂, 5 mM KCl, 120 mM NaCl and 0.1% ascorbic acid) at 20 mg wet weight/mL (human D₄ HEK cells), 10 mg wet weight/mL human D₂ CHO cells and D₃ HEK cells). Incubations were carried out for 120 min at ambient temperature (22 °C) in the presence of 0.2 nM [³H]-spiperone for displacement studies and were initiated by the addition of 20–100 mg protein in a final assay volume of 0.5 mL. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI (polyethylenimine) and washed with ice-cold 50 mM Tris–HCl, pH 7.4. Specific binding was determined by 10 mM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by nonlinear least squares regression analysis, from which the inhibition constant K_i could be calculated for each test compound.

Ion channel activities.^{28–30} Activity at the voltage sensitive calcium channel (diltiazem allosteric site) was evaluated by displacement of [³H]-diltiazem (60–87 Ci mmol^{−1}, NEN, USA) binding to rabbit sketetal muscle. Binding to the voltage sensitive sodium channel

was evaluated by displacement of [³H]-batrachotoxin (30–60 Ci mmol^{−1}, NEN, USA) binding to rat cerebral cortex. Binding to the voltage sensitive potassium channels (particularly IK_R channels) was estimated by measurement of the prolongation of effective refractory period (ERP) in ferret papillary muscle.

Chemistry

Melting points were determined on a Reichert Thermo-var apparatus and are uncorrected. Proton NMR were measured on Bruker AM 360 or AC 250 spectrometers and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard, coupling constants are in Hertz. Chemical ionisation mass spectra were recorded on a VG70/250 spectrometer. Merck Kieselgel (230–400) mesh was used for column chromatography. For reactions, anhydrous solvents were used as purchased from Aldrich or Fluka. Organic solutions were dried with anhydrous magnesium sulfate or anhydrous sodium sulfate. Elemental analyses were performed by Butterworth Laboratories Ltd, Teddington, Middlesex, UK.

Compounds **5**, **6**, and **7** were prepared from the intermediates (**3a**) and (**3b**) according to the published procedure¹⁹ using the appropriate alkyl halide:

3-(1-(3-Nitrobenzyl)-4-piperidinyl)-5-(4-chlorophenyl)pyrazole (5). Pale-yellow needles, mp 174–176 °C (from EtOH); ¹H NMR (360 MHz, DMSO-*d*₆) δ 1.69 (2 H, dq, *J* = 2.8 and 12), 1.90 (2 H, br d, *J* = 12), 2.13 (2 H, dt, *J* = 2.1 and 10), 2.60–2.80 (1 H, m), 2.88 (2 H, br d, *J* = 10), 3.64 (2 H, s), 6.53 (1 H, s), 7.43 (2 H, d, *J* = 8), 7.64 (1 H, t, *J* = 8), 7.77–7.80 (3 H, m), 8.13 (1 H, d, *J* = 8), 8.18 (1 H, s), 12.69 (1 H, s); MS *m/z* 397 (M⁺ + H). Found: C, 63.85; H, 5.31; N, 14.10. C₂₁H₂₁N₄O₂Cl requires C, 63.55; H, 5.33; N, 14.12.

3-(1-(2-Phenylethyl)-4-piperidinyl)-4-methyl-5-phenylpyrazole (6). White crystals, mp 154–157 °C (from EtOAc); ¹H NMR (360 MHz, DMSO-*d*₆) δ 1.76–1.82 (4 H, m), 2.00–2.15 (5 H, m), 2.53–2.57 (2 H, m), 2.60–2.70 (1 H, m), 2.77 (2 H, t, *J* = 7), 3.05 (2 H, d, *J* = 11), 7.18–7.57 (10 H, m), 12.47 (1 H, br s); MS *m/z* 346 (M⁺ + H). Found: C, 79.97; H, 7.78; N, 12.40. C₂₃H₂₇N₃ requires C, 79.96; H, 7.88; N, 12.16.

3-(1-(2-Oxo-2-phenylethyl)-4-piperidinyl)-4-methyl-5-phenylpyrazole (7). Pale-yellow crystals, mp 176–178 °C (from EtOAc); ¹H NMR (360 MHz, DMSO-*d*₆) δ 1.72–1.84 (4 H, m), 2.10 (3 H, s), 2.26 (2 H, t, *J* = 11), 2.58–2.68 (1 H, m), 3.01 (2 H, d, *J* = 11), 3.86 (2 H, s), 7.32 (1 H, t, *J* = 7), 7.42 (2 H, t, *J* = 7), 7.51–7.58 (4 H, m), 7.64 (1 H, t, *J* = 7), 8.02 (2 H, d, *J* = 8), 12.48 (1 H, s);

MS m/z 360 ($M^+ + H$). Found: C, 76.85; H, 6.91; N, 11.76. $C_{23}H_{25}N_3O$ requires C, 76.85; H, 7.01; N, 11.69.

3-(1-(2-Hydroxy-2-phenylethyl)-4-piperidiny)-4-methyl-5-phenylpyrazole (8). A mixture of the ketone (7) (0.081 g, 0.225 mmol) and sodium borohydride (0.017 g, 0.50 mmol) in ethanol (2 mL) was stirred at rt under nitrogen for 4 h. The solids were filtered off, washed with warm ethanol, and the filtrate was concentrated. The resulting white powder was dissolved in ethyl acetate and washed with water. The organic layer was dried and concentrated, and the residual white powder was recrystallised from ethanol to give **8** (0.035 g, 43%), mp 173–175 °C (from EtOH); 1H NMR (360 MHz, DMSO- d_6) δ 1.74–1.83 (4 H, m), 2.10–2.22 (5 H, m), 2.40–2.64 (3 H, m), 3.04 (2 H, t, $J=11$), 4.71–4.75 (1 H, m), 4.95 (1 H, s), 7.23 (1 H, t, $J=7$), 7.29–7.57 (9 H, m), 12.45 (1 H, s); MS m/z 362 ($M^+ + H$). Found: C, 76.07; H, 7.43; N, 11.31. $C_{23}H_{27}N_3O$ requires C, 76.42; H, 7.53; N, 11.62.

3-(1-(2-Phenylethyl)-4-piperidiny)-4,5-dihydro-1H-benzoglindazole (10). α -Tetralone (6.4 g, 44 mmol) in THF (15 mL) was added over 5 min to a solution of lithium diisopropylamide (45 mmol) in THF (150 mL) under nitrogen at $-78^\circ C$, then stirred for 45 min to give an orange solution. Meanwhile, carbonyldiimidazole (3.89 g, 24 mmol) was added to a solution of *N*-tert-butyloxycarbonyl isonipecotic acid (5 g, 22 mmol) in THF (100 mL) at rt under nitrogen. The mixture was stirred for 45 min, then cannulated into the above orange solution at $-78^\circ C$. After a further 40 min the mixture was warmed to rt, diluted with ethyl acetate, and washed sequentially with saturated sodium hydrogencarbonate solution, water and brine. The organic layer was dried and concentrated to give a yellow oil (13.1 g). The oil was dissolved in ethyl acetate (15 mL), then a saturated solution of HCl in ethyl acetate (40 mL) was added. When effervescence had stopped, the mixture was heated to boiling then cooled. The solid was collected, washed with ethyl acetate and dried to give 2-(4-piperidinocarbonyl)-3,4-dihydro-1-hydroxynaphthalene hydrochloride (**9**) (3.12 g, 48%) as an off-white amorphous solid, mp 257–259 °C. 1H NMR (360 MHz, DMSO- d_6) δ 1.80–2.00 (4 H, m), 2.67 (2 H, t, $J=8$), 2.86 (2 H, t, $J=8$), 2.90–3.00 (2 H, m), 3.10–3.20 (1 H, m), 3.31 (2 H, d, $J=12$), 7.30–7.40 (2 H, m), 7.49 (1 H, t, $J=8$), 7.81 (1 H, d, $J=8$).

A suspension of **9** (1.12 g, 3.8 mmol), diisopropylethylamine (1.49 mL, 8.6 mmol) and 2-phenylethyl bromide (0.63 mL, 4.6 mmol) in DMF (10 mL) was stirred at rt for 3 days, then at 70 °C for 17 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, then dried and concentrated. The crude product was purified by flash chromatography, eluting with

a gradient of 1% to 5% v/v methanol in dichloromethane containing 1% v/v triethylamine to give 2-(4-(1-(2-phenylethyl)) piperidinocarbonyl)-3,4-dihydro-1-hydroxynaphthalene (0.64 g, 47%) as off-white needles, mp 85–86 °C (from EtOH); 1H NMR (360 MHz, DMSO- d_6) δ 1.60–1.80 (4 H, m), 2.04 (2 H, t, $J=11$), 2.50–2.60 (2 H, m), 2.62 (2 H, t, $J=7$), 2.75 (2 H, t, $J=7$), 2.85 (2 H, t, $J=7$), 2.90–3.10 (3 H, m), 7.10–7.50 (8 H, m), 7.81 (1 H, d, $J=7$), 15.2 (1 H, br s); MS m/z 362 ($M^+ + H$). Found: C, 79.93; H, 7.47; N, 4.04. $C_{24}H_{27}NO_2$ requires C, 79.74; H, 7.53; N, 3.87.

2-(4-(1-(2-Phenylethyl))piperidinocarbonyl)-3,4-dihydro-1-hydroxynaphthalene (0.158 g, 0.44 mmol) was stirred with hydrazine hydrate (0.050 g, 1.6 mmol) in methanol (3 mL) under nitrogen for 17 h. The mixture was concentrated and the residue was dissolved in ethyl acetate, washed with water and brine, then dried, concentrated and recrystallised from ethanol to give **10** (0.086 g, 55%) as white needles, mp 151–152 °C (from EtOH); 1H NMR (360 MHz, DMSO- d_6) δ 1.70–1.80 (4 H, m), 2.00–2.10 (2 H, m), 2.50–2.60 (2 H, m), 2.60–2.70 (3 H, m), 2.75 (2 H, t, $J=7$), 2.85 (2 H, t, $J=7$), 3.02 (2 H, d, $J=11$), 7.10–7.30 (8 H, m), 7.60 (1 H, br s), 12.30 (1 H, br s); MS m/z 358 ($M^+ + H$). Found: C, 78.77; H, 7.53; N, 11.39. $C_{24}H_{27}N_3 \cdot 0.5(H_2O)$ requires C, 78.65; H, 7.70; N, 11.46.

3-(1-Benzyl-4-piperidiny)-4,5-dihydro-1H-benzoglindazole (11). This was prepared in the same way as **10** from the intermediate (**9**) using benzyl bromide as the alkylating agent (49%). The final product was purified by preparative thin layer chromatography, eluting with 3% methanol and 1% v/v triethylamine in dichloromethane, to give **11** as a white foam (0.081 g, 16%); 1H NMR (360 MHz, DMSO- d_6) δ 1.70–1.80 (4 H, m), 2.00–2.10 (2 H, m), 2.70–2.80 (3 H, m), 2.90–3.00 (4 H, m), 3.49 (2 H, s), 7.00–7.70 (9 H, m), 12.40 (1 H, br s); MS m/z 344 ($M^+ + H$). Found: C, 77.97; H, 7.33; N, 11.78. $C_{23}H_{25}N_3 \cdot 0.6(H_2O)$ requires C, 77.98; H, 7.45; N, 11.86.

3-(4-(2-Phenylethyl)piperazin-1-yl)-4,5-dihydro-1H-benzoglindazole (14). Sodium hydride (60% in oil, 35 g, 880 mmol) was added with care to a solution of α -tetralone (54 g, 370 mmol), carbon disulfide (27 mL, 443 mmol) and methyl iodide (52 mL, 810 mmol) in THF (400 mL) at 0 °C. The mixture was stirred at rt overnight, giving a yellow solution with a white precipitate. Saturated aqueous ammonium chloride solution and ethyl acetate were added and the mixture was separated. The organic layer was washed with water and brine, dried and concentrated. The resulting solid was recrystallised from ethyl acetate-hexanes to give 2-(bis-methylthiomethylene)-4,5-dihydro-2H-naphthalen-1-one (67 g, 59%) as yellow cubes, mp 54–56 °C; 1H NMR (360 MHz, $CDCl_3$) δ 2.43 (6 H, br s), 2.98 (2 H, t, $J=7$),

3.26 (2 H, t, $J=7$), 7.22 (1 H, d, $J=8$), 7.32 (1 H, t, $J=8$), 7.43 (1 H, dt, $J=1$ and 8), 8.10 (1 H, dd, $J=1$ and 8).

2-(Bis-methylthiomethylene)-4,5-dihydro-2*H*-naphthalen-1-one (11.56 g, 46 mmol) and 1-*tert*-butyloxycarbonyl-piperazine (10.3 g, 55 mmol) were refluxed in acetonitrile (300 mL) for 24 h. The mixture was cooled, water (500 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried and concentrated. The resulting oil was purified by flash chromatography, eluting with dichloromethane then dichloromethane:methanol (97:3 v/v) to give 2-(methylthio[4-(*tert*-butyloxycarbonyl)-1-piperazinyl]methylene)-4,5-dihydro-2*H*-naphthalen-1-one (**13**) (8.75 g, 49%) as a foam; ^1H NMR (360 MHz, CDCl_3) δ 1.49 (9 H, s), 3.31 (3 H, s), 2.86–2.94 (4 H, m), 3.3–3.5 (8 H, m), 7.18 (1 H, d, $J=8$), 7.30 (1 H, t, $J=8$), 7.37 (1 H, dt, $J=1$ and 8), 8.10 (1 H, dd, $J=1$ and 8). Irradiation of the singlet at 3.31 ppm gave a positive NOE to the signal at 2.86–2.94 ppm.

The intermediate (**13**) (5.3 g, 14 mmol) and hydrazine hydrate (3.4 g, 69 mmol) were stirred in ethanol (100 mL) at rt for 16 h. The mixture was concentrated and the resulting oil was purified by flash chromatography, eluting with dichloromethane:methanol (95:5 v/v) to give 3-(4-(*tert*-butyloxycarbonyl)-1-piperazinyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (3.9 g, 80 %) as a yellow oil; ^1H NMR (360 MHz, CDCl_3) δ 1.48 (9 H), 2.72 (2 H, t, $J=8$), 2.95 (2 H, t, $J=8$), 3.13 (4 H, t, $J=5$), 3.53 (4 H, t, $J=5$), 7.20–7.40 (4 H, m).

3-(4-(*tert*-Butyloxycarbonylpiperazin-1-yl)-4,5-dihydro-1*H*-benzo[*g*]indazole (1.65 g, 4.8 mmol) was dissolved in trifluoroacetic acid (10 mL) at rt. After 30 min the solvent was evaporated in vacuo to give 3-(1-piperazinyl)-4,5-dihydro-1*H*-benzo[*g*]indazole bis-trifluoroacetate (2.64 g), which still contained an excess amount of trifluoroacetic acid, as a light brown solid; (360 MHz, $\text{DMSO}-d_6$) δ 2.66 (2 H, t, $J=7$), 2.95 (2 H, t, $J=7$), 3.22 (4 H, br s), 3.30 (4 H, br s), 7.20–7.30 (3 H, m), 7.56 (1 H, d, $J=7$), 8.8 (2 H, br s).

This crude material (0.416 g, 1.1 mmol), diisopropylethylamine (0.59 mL, 3.3 mmol) and 2-phenethyl bromide (0.168 mL, 1.23 mmol) were heated in DMF (3 mL) at 60 °C for 4 h. The mixture was cooled, diluted with water (20 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. The resulting light brown oil was dissolved in ethanol (2 mL), heated to boiling, and oxalic acid (1.3 mL of a 1M solution in ethanol) was added. After cooling to room temperature the resulting solid was collected, washed with ethanol, and recrystallised from DMF:ethanol (1:9 v/v) to give the oxalate salt of **14**

(0.098 mg, 30% over two steps) as white needles, mp 216–219 °C (from DMF-EtOH); ^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 2.66 (2 H, t, $J=8$), 2.87 (2 H, t, $J=8$), 2.88 (2 H, t, $J=7$), 3.10–3.20 (6 H, m), 3.2–3.40 (4 H, m), 7.10–7.40 (8 H, m), 7.55 (1 H, d, $J=7$); MS m/z 359 ($\text{M}^+ + \text{H}$). Found: C, 66.55; H, 6.32; N, 12.30. $\text{C}_{23}\text{H}_{24}\text{N}_4\cdot\text{C}_2\text{H}_2\text{O}_4$ requires C, 66.94; H, 6.29; N, 12.49.

The following compounds were prepared in the same way as **14** from the intermediate (**13**) using the appropriate alkyl halide:

3-(4-Benzyl-1-piperazinyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15**)**. Characterised as the oxalate salt, white microcrystalline solid, mp 254–256 °C (from EtOH); ^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 2.63 (2 H, t, $J=8$), 2.86 (2 H, t, $J=8$), 2.96 (4 H, br s), 3.26 (4 H, br s), 4.04 (2 H, s), 7.10–7.30 (3 H, m), 7.40–7.50 (5 H, m), 7.54 (1 H, d, $J=7$); MS m/z 345 ($\text{M}^+ + \text{H}$). Found: C, 65.71; H, 6.04; N, 12.40. $\text{C}_{22}\text{H}_{24}\text{N}_4\cdot\text{C}_2\text{H}_2\text{O}_4\cdot 0.25(\text{H}_2\text{O})$ requires C, 65.66; H, 6.08; N, 12.76.

3-(4-(2-(2-Chlorophenyl)ethyl)-1-piperazinyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (16**)**. Characterised as the oxalate salt, pale-yellow plates, mp 134–136 °C (from EtOH); ^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 2.66 (2 H, t, $J=8$), 2.88 (2 H, t, $J=8$), 3.03–3.07 (8 H, m), 3.20–3.36 (4 H, m), 7.19–7.35 (5 H, m), 7.41–7.47 (2 H, m) and 7.55 (1 H, d, $J=7$); MS m/z 393 ($\text{M}^+ + \text{H}$). Found: C, 61.58; H, 5.61; N, 11.33. $\text{C}_{23}\text{H}_{25}\text{N}_4\text{Cl}\cdot(\text{COOH})_2\cdot 0.2(\text{H}_2\text{O})$ requires C, 61.71; H, 5.68; N, 11.51.

3-(4-(2-Phenylethyl)-1-piperazinyl)-1,4,5,6-tetrahydro-1,2-diazabenz[*e*]azulene (18**)**. 1-Benzosuberone (10 g, 63 mmol) was treated with carbon disulfide (5.7 g, 75 mmol), methyl iodide (21.3 g, 150 mmol) and sodium hydride (60% in oil, 6 g, 150 mmol) according to the method described in the synthesis of **13** to give 6-(bis-methylthiomethylene)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (10.7 g, 65%) as yellow cubes, mp 63–64 °C (from EtOAc-hexanes); ^1H NMR (250 MHz, CDCl_3) δ 2.00 (2 H, quintet, $J=7$), 2.40 (6 H, s), 2.70–2.80 (4 H), 7.17 (1 H, d, $J=8$), 7.32 (1 H, t, $J=8$), 7.44 (1 H, t, $J=8$), 7.88 (1 H, d, $J=8$).

6-(Bis-methylthiomethylene)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (1.06 g, 4 mmol), phenethylpiperazine trifluoroacetate (2.2 g, 5.3 mmol) and diisopropylethylamine (2 mL, 11 mmol) were refluxed in acetonitrile (10 mL) for 24 h. The mixture was cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried and concentrated. The crude product was purified by flash chromatography, eluting with dichloromethane:methanol (92:8 v/v) to give 6-(methylthio-(4-phenethylpiper-

azin-1-yl)methylene)-6,7,8,9-tetrahydrohydrobenzocyclohepten-5-one (**17**) (0.208 g, 13%) as a yellow oil; ^1H NMR (360 MHz, CDCl_3) δ 1.95 (2 H, quintet, $J=7$), 2.25 (3 H, s), 2.50–2.90 (16 H, m), 7.10 (1 H, d, $J=8$), 7.10–7.40 (7 H, m), 7.73 (1 H, d, $J=8$).

A solution of **17** (0.208 g, 0.52 mmol) and hydrazine hydrate (0.5 mL, 10 mmol) in ethanol (3 mL) was stood for 16 h at rt. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried, concentrated and recrystallised to give **18** (0.132 g, 71%) as white needles, mp 147–148 °C (from EtOAc-hexanes); ^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 1.89 (2 H, quintet, $J=5$), 2.55–2.7 (10 H, m), 2.76–2.82 (2 H, m), 3.00–3.05 (2 H, m), 3.25–3.35 (2 H, m), 7.10–7.25 (8 H, m), 7.69 (1 H, d, $J=7$), 12.1 (1 H); MS m/z 373 ($\text{M}^+ + \text{H}$). Found: C, 76.56; H, 7.62; N, 14.80. $\text{C}_{24}\text{H}_{28}\text{N}_4 \cdot 0.2(\text{H}_2\text{O})$ requires C, 76.64; H, 7.61; N, 14.90.

3-(4-(2-Phenylethyl)-1-piperazinyl)-4,5-dihydro-1-methyl-1H-benzog[l]indazole (21) and **3-(4-(2-phenylethyl)-1-piperazinyl)-4,5-dihydro-2-methyl-2H-benzog[l]indazole (22)**. A solution of **13** (3.2 g, 8.2 mmol) and methylhydrazine (5 mL, 94 mmol) in ethanol (30 mL) was stood at rt for 4 days. Water (150 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. Purification by flash column chromatography, eluting with hexane:ethyl acetate (4:1 v/v) gave 3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-4,5-dihydro-1-methyl-1H-benzog[l]indazole (**19**) (0.342 g, 11%) as a colourless oil; ^1H NMR (360 MHz, CDCl_3) δ 1.52 (9 H, s), 2.67 (2 H, $J=7.3$), 2.94 (2 H, t, $J=7.3$), 3.15 (4 H, t, $J=5$), 3.61 (4 H, t, $J=5$), 4.15 (3 H, s), 7.22–7.34 (3 H, m), 7.55 (1 H, d, $J=7.7$). Irradiation at δ 4.15 gave a positive NOE to the doublet at δ 7.55, and the reverse. Further elution gave 3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-4,5-dihydro-2-methyl-2H-benzog[l]indazole (**20**) (0.561 g, 19%) as a white solid; ^1H NMR (360 MHz, CDCl_3) δ 1.54 (9 H, s), 2.86 (2 H, t, $J=8$), 2.95 (2 H, t, $J=8$), 3.08 (4 H, t, $J=5$), 3.60 (4 H, t, $J=5$), 7.20–7.30 (3 H, m), 7.83 (1 H, d, $J=8$).

Compounds **19** and **20** were taken on separately according to the procedure described in the synthesis of **14** to give:

Compound 21: (37% over 2 steps from **19**) characterised as the oxalate salt, mp 225–226 °C (from EtOH) ^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 2.56 (2 H, t, $J=8$), 2.83 (2 H, t, $J=8$), 2.95 (2 H, t, $J=8$), 3.10–3.20 (6 H, m), 3.25–3.35 (4 H, m), 3.95 (3 H, s), 7.20–7.40 (8 H, m), 7.63 (1 H, d, $J=7$); MS m/z 373 ($\text{M}^+ + \text{H}$). Found: C, 67.04; H, 6.66; N, 11.92. $\text{C}_{24}\text{H}_{28}\text{N}_4 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 0.2(\text{H}_2\text{O})$ requires C, 66.99; H, 6.57; N, 12.01.

Compound 22: (41% over 2 steps from **20**) characterised as the oxalate salt, mp 244–245 °C (from EtOH) ^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 2.80–2.90 (4 H, m), 2.90–2.95 (2 H, m), 3.10–3.20 (6 H, m), 3.20–3.25 (4 H, m), 3.69 (3 H, s), 7.10–7.40 (8 H, m), 7.61 (1 H, d, $J=8$); MS m/z 373 ($\text{M}^+ + \text{H}$). Found: C, 66.94; H, 6.42; N, 11.71. $\text{C}_{24}\text{H}_{28}\text{N}_4 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 0.2(\text{H}_2\text{O})$ requires C, 66.99; H, 6.57; N, 12.02.

Acknowledgements

We would like to thank S. Thomas for NMR experiments and K. Locker for the measurement of pharmacokinetic data on **16**.

References

- Diagnostic and Statistical Manual of Mental Disorders IVth Edition; First, M. B., Ed.; American Psychiatric Association: Washington DC, 1994; pp 273–290.
- Snyder, S. H. *Am. J. Psych.* **1981**, *138*, 461.
- Baldessarini, R. J.; Tarsy, D. *Annu. Rev. Neurosci.* **1980**, *3*, 23.
- Ben-Jonathon, N. *Endocr. Rev.* **1985**, *6*, 564.
- Dearry, J. R.; Gingrich, J. A.; Falardeau, R. T.; Freneau, R. T.; Bates, M. D.; Caron, M. *Nature (London)* **1990**, *347*, 72.
- Grandy, D. K.; Marchionni, M. A.; Makam, H.; Stofko, R. E.; Alfano, M.; Frothingham, L.; Fischer, J. B.; Burk-Howie, K. J.; Bunzow, J. R.; Sewer, A. C.; Civelli, O. *Proc. Natl. Acad. Sci. U. S. A.* **1989**, *86*, 9762.
- Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. *Nature (London)* **1990**, *347*, 146.
- Van Tol, H. H. M.; Bunzow, J. R.; Guan, H.-C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. *Nature (London)* **1991**, *350*, 610.
- Sunahara, R. K.; Laurier, L. G.; Ng, G.; George, S. R.; Torchia, J.; Van Tol, H. H. M.; Niznik, H. B. *Nature (London)* **1991**, *350*, 614.
- Fitton, A.; Heel, R. *Drugs* **1990**, *40*, 722.
- Seeman, P.; Corbett, R.; Van Tol, H. H. M. *Neuropsychopharmacology* **1997**, *16*, 93.
- Matsumoto, M.; Hidaka, K.; Tada, S.; Tasaki, Y.; Yamaguchi, T. *Mol. Brain. Res.* **1995**, *29*, 157.
- Seeman, P.; Guan, H.-C.; Van Tol, H. H. M. *Nature (London)* **1993**, *365*, 441.
- Murray, A. M.; Hyde, T. M.; Knable, M. B.; Herman, M. M.; Bigelow, L. B.; Carter, J. M.; Weinberger, D. R.; Kleinman, J. E. *J. Neurosci.* **1995**, *15*, 2186.
- Sumiyoshi, T.; Stockmeier, C. A.; Overholser, J. C.; Thompson, P. A.; Meltzer, H. Y. *Brain Res.* **1995**, *681*, 109.
- Reynolds, G. P.; Mason, S. L. *J. Neurochem.* **1994**, *63*, 1576.
- Mulcrone, J.; Kerwin, R. W. *Neurosci. Lett.* **1996**, *219*, 163.
- Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Freedman, S.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1943.

19. Rowley, M.; Collins, I.; Broughton, H. B.; Davey, W. D.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Freedman, S. B.; Leeson, P. D. *J. Med. Chem.* **1997**, *40*, 2374.
20. Kulagowski J. K.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1941.
21. Boyfield, I.; Brown, T. H.; Coldwell, M. C.; Cooper, D. G.; Hadley, M. S.; Hagan, J. J.; Healy, M. A.; Johns, A.; King, R. J.; Middlemiss, D. N.; Nash, D. J.; Riley, G. J.; Scott, E. E.; Smith, S. A.; Stemp, G. *J. Med. Chem.* **1996**, *39*, 1946–48.
22. Boyfield, I.; Coldwell, M. C.; Hadley, M. S.; Healy, M. A.; Johns, A.; Nash, D. J.; Riley, G. J.; Scott, E. E.; Smith, S. A.; Stemp, G.; Wilson, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1227.
23. TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schleachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435.
24. Kula, N. S.; Baldessarini, R. J.; Kebebian, J. W.; Bakthavachalam, V.; Xu, L. *Eur. J. Pharmacol.* **1997**, *331*, 333.
25. Wright, J. L.; Gregory, T. F.; Heffner, T. G.; MacKenzie, R. G.; Pugsley, T. A.; Vander Meulen, S.; Wise, L. D. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1377.
26. Freedman, S. B.; Patel, S.; Marwood, R.; Emms, F.; Seabrook, G. R.; Knowles, M. R.; McAllister, G. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 417.
27. McAllister, G.; Knowles, M. R.; Wrad-Booth, S. M.; Sinclair, H. A.; Patel, S.; Marwood, R.; Emms, F.; Patel, S.; Smith, G. R.; Seabrook, G. R.; Freedman, S. B. *J. Recept. Sig. Trans. Res.* **1995**, *15*, 267.
28. Catterall, W. A.; Morrow, C. S.; Daly, J. W.; Brown, G. B. *J. Biol. Chem.* **1981**, *256*, 8922.
29. Reynolds, I.; Snowman, A. M.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* **1986**, *237*, 731.
30. Baskin, E. P.; Serik, C. M.; Wallace, A. A.; Brookes, L. M.; Selnik, H. G.; Claremon, D. A.; Lynch, J. J. *J. Cardiovasc. Pharmacol.* **1991**, *18*, 406.