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Substituted Pyrazoles as Novel Selective Ligands for the Human Dopamine D_4 Receptor

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Abstract—Two novel series of 3-(heterocyclylmethyl)pyrazoles have been synthesised and evaluated as ligands for the human dopamine D_4 receptor. Compounds in series I (exemplified by **8k**) have a phenyl ring joined to the 4-position of the pyrazole while those in series II (exemplified by **15j**) have a 5-phenyl ring linked by a saturated chain to the 4-position of the pyrazole. Both series supplied compounds with excellent affinity for the human D_4 and good selectivity over other dopamine receptors. Excellent selectivity over calcium, sodium, and potassium ion channels was also achieved.

Introduction

Dopamine has long been known to be implicated in schizophrenia. As early as 1960[1] scientists discovered that abnormally low quantities of dopamine were present in the brains of schizophrenic patients. Considerable efforts have since been made to find a cure for this debilitating illness.[2]

Current medications that have been successfully used in the clinic are not devoid of side effects. The typical antipsychotics such as haloperidol[3] (**1**), which treat the positive symptoms of the illness, induce extrapyramidal side effects,[4] tardive dyskinesia and hyperprolactinaemia.[5] The atypical antipsychotic clozapine[6] (**2**), which treats both positive and negative symptoms, has been found to induce agranulocytosis,[7] a fatal blood disorder, in a small number of patients. Even though the mechanism of action of these drugs is not entirely clear they are believed to exert their antipsychotic activity via blockade of D_2-like receptors.[8]

Before the emergence of molecular cloning, only two types of dopamine receptors acting through G-proteins had been defined: the D_1 receptor which mediates the activation of adenylyl cyclase[9] and the D_2 receptor which mediates its inhibition.[10] Over the past 5 years, molecular biologists have cloned a total of five dopamine receptors, grouped into two families: the D_1 group (D_1[11] and D_5[12]) and the D_2 group (D_2,[13] D_3,[14] and D_4[15]). The typical and atypical antipsychotic drugs were subsequently tested against these new human dopamine receptors. Clozapine, amongst its other activities, has a sevenfold higher affinity for the human D_4 (hD_4) receptor compared to the human D_2 (hD_2) receptor.[15] In view of this result, it has been proposed that the atypical antipsychotic activity observed with clozapine is due to its high affinity for the hD_4 receptor, rather than to its affinity for the hD_2 receptor.

In order to determine if a selective hD_4 receptor ligand would show antipsychotic activity with a reduced side effect profile, a program was initiated to identify novel dopamine receptor ligands, which would be selective for the hD_4 receptor. Our approach to finding such ligands began with the application of a topological similarity model (TOPOSIM)[16,17] to known nonselective dopamine

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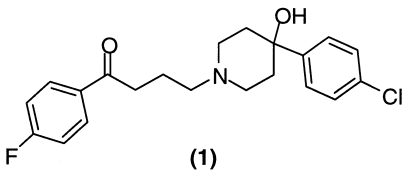
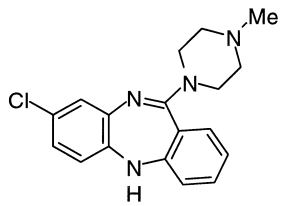
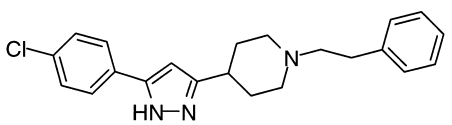
antagonists. As a result of this work, the pyrazole (**3**) was identified within our laboratories[18,19] as a highly selective hD_4 ligand. This paper describes the synthesis and biological evaluation of an alternative series that led to the identification of **15j**, a high affinity hD_4 receptor ligand with excellent selectivity over the hD_2 and hD_3 dopamine receptors and reduced ion channel activity compared to the lead compound (**3**).



(1)



(2)



(3)

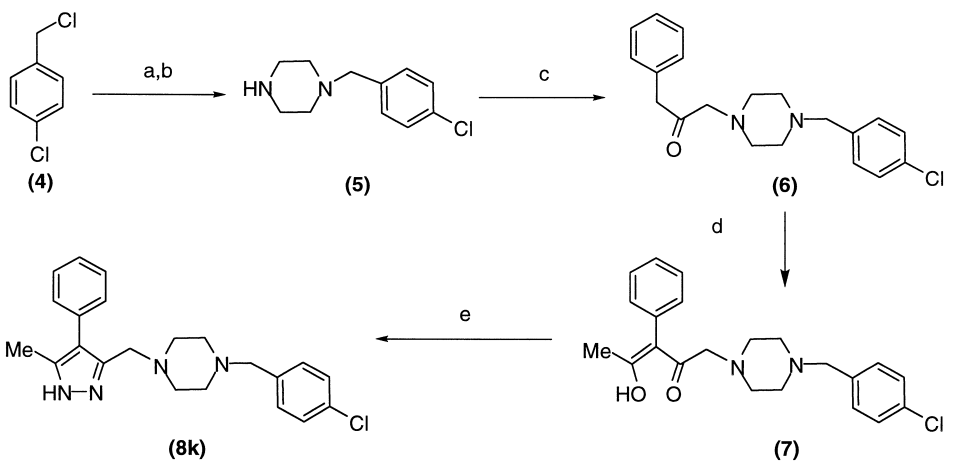
Chemistry

Scheme 1 illustrates the procedure used to synthesise a series of 4-phenyl pyrazole analogues (series I, **8a–n**). BOC-Piperazine was coupled with 4-chlorobenzyl chloride (**4**) in ethanol to give 4-chlorobenzyl BOC-piperazine, which was deprotected with trifluoroacetic acid in dichloromethane to yield 4-chlorobenzyl piperazine (**5**). Coupling of **5** with 1-chloro-3-phenyl-2-propanone gave the amino ketone (**6**), which on deprotonation with lithium bis(trimethylsilyl)amide and reaction with the activated ester of acetic acid yielded the β-diketone (**7**). Construction of the pyrazole ring was achieved by reaction of the crude diketone with hydrazine hydrate in methanol to give 1-(4-chlorobenzyl)-4-(5-methyl-4-phenyl-1H-pyrazol-3-ylmethyl)-piperazine (**8k**).

Tricyclic pyrazole analogues (series II) were prepared following the procedures highlighted in Schemes 2–4. Scheme 2 illustrates the synthesis of dihydrobenzo[g]indazoles (**15a–h**). The lithium anion derived from α-tetralone (**9**) was condensed with the activated ester of BOC-sarcosine to give the β-diketone (**10**), from which the pyrazole (**11**) was obtained by treatment with hydrazine hydrate. The protected amine was converted to the quaternary ammonium salt (**14**) and subsequent displacement with 4-(4-methoxyphenyl)piperazine gave the final 3-[4-(4-methoxyphenyl)-piperazin-1-ylmethyl]-4,5-dihydro-1H-benzo[*g*]indazole (**15a**).

Scheme 3 exemplifies the preparation of the 3-[4-(4-methoxyphenyl)-piperazin-1-ylmethyl]-1,4-dihydro-indeno[1,2-c]pyrazole (**15i**). The lithium anion produced from 1-indanone (**16**) was coupled with the activated ester of (4-(4-methoxyphenyl)-piperazin-1-yl) acetic acid to give the β-diketone (**17**). Subsequent treatment with hydrazine hydrate in the presence of triethylamine yielded the dihydroindeno[1,2-*c*]pyrazole (**15i**).

Scheme 4 illustrates the preparation of the oxygenated analogues of dihydrobenzo[g]indazoles (**15j–l**). 4-Chro-



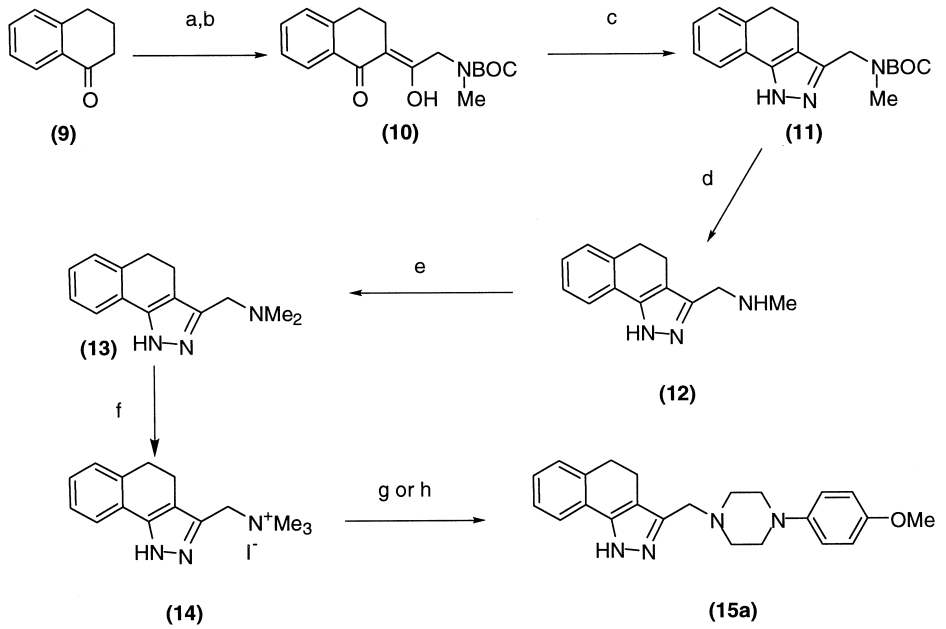
(4) (5) (6) (8k) (7)

Scheme 1. Reagents: (a) BOC-Piperazine, K_2CO_3, EtOH, 95%; (b) TFA, CH_2Cl_2, 99%; (c) 1-Chloro-3-phenyl-2-propanone, Et_3N, CH_2Cl_2, 99%; (d) *N*,*N*′-Carbonyl diimidazole, AcOH, LiHMDS, THF, 18%; (e) Hydrazine hydrate, MeOH, 90%.

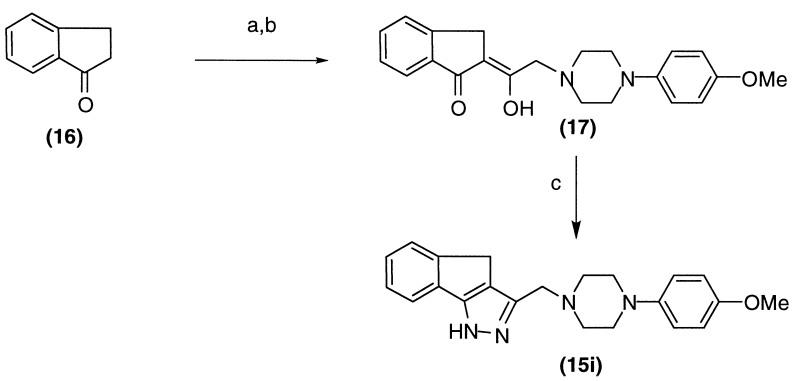
manone (**19**) was deprotonated with sodium bis(trimethylsilyl)amide in THF at −78 °C and treated with diethyl oxalate to give the β-diketone (**20**). Reaction with hydrazine hydrate followed by reduction with lithium aluminium hydride in THF and subsequent treatment with oxalyl chloride/dimethylformamide gave the chloromethyl pyrazole (**22**). Displacement of the chlorine by 4-(4-methoxyphenyl)piperazine gave 3-[4-(4-methoxyphenyl)-piperazin-1-ylmethyl]-1,4-dihydro-5-oxa-1,2-diazacyclopenta[*a*]naphthalene (**15j**).

Results and Discussion

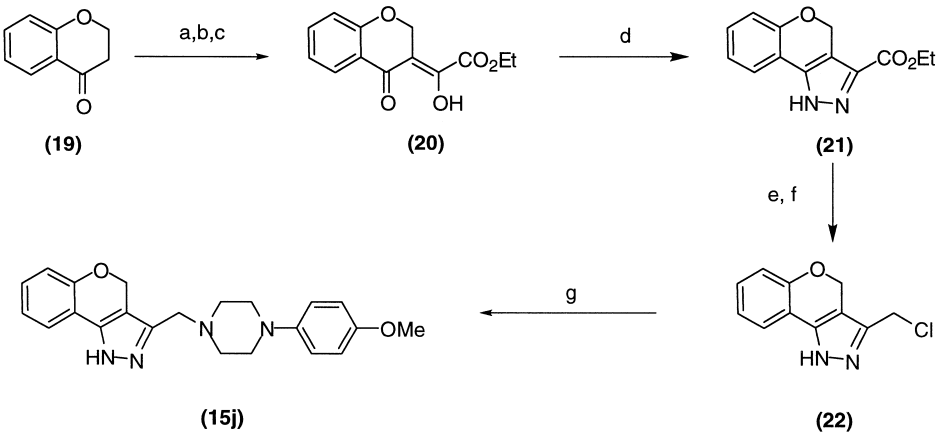
The novel compounds and reference drugs such as haloperidol (**1**) and clozapine (**2**) were tested in vitro for their abilities to displace [^{3}H]-spiperone from dopamine cloned human receptors (D_2 being stably expressed in CHO cells[20] and D_3 and D_4 in HEK293 cells[21]). Each inhibition constant (K_i) was an average of at least two experiments. Binding to voltage-sensitive ion channels was evaluated in rat for the sodium (Na^+) channel,[22] in



Scheme 2. Reagents: (a) Lithium diisopropylamide, THF; (b) BOC-Sarcosine, *N*,*N*′-carbonyl diimidazole, THF, 61% (from 9); (c) Hydrazine hydrate, MeOH, 89%; (d) HCl in EtOAc, 97%; (e) Formaldehyde, sodium cyanoborohydride, acetic acid, MeOH, 96%; (f) Methyl iodide, EtOH, 88%; (g) 4-(4-Methoxyphenyl)piperazine, butyllithium, THF, 42%; (h) 4-(4-Methoxyphenyl) piperazine, Hunig's base, DMF, 35%.



Scheme 3. Reagents: (a) Lithium diisopropylamide, THF; (b) (4-(4-Methoxyphenyl)-piperazin-1-yl)-acetic acid, *N*,*N*′-carbonyl diimidazole, THF-DMF, 23% (from 16); (c) Hydrazine hydrate, triethylamine, MeOH-DMF, 29%.



Scheme 4. Reagents: (a) Sodium bis(trimethylsilyl)amide, THF; (b) Diethyl oxalate; (c) Aqueous HCl, 97% (from **19**); (d) Hydrazine monohydrochloride, EtOH, 95%; (e) $LiAlH_4$, THF; (f) Oxalyl chloride, CH_2Cl_2, DMF, 88% (from **21**); (g) 1-(4-Methoxyphenyl) piperazine, K_2CO_3, DMF, 53%.

rabbit for the calcium (Ca^{2+}) channel,[23] and in ferret for the potassium (IK_R) channel.[24]

As previously disclosed by our co-workers,[18,19] optimisation of the topological similarity model led to the discovery of (**3**), a high affinity and selective hD_4 ligand. The aim of the current study was to develop a new series of selective analogues with comparable hD_4 affinity to **3**, but with reduced ion channel activity. These novel series have a cyclic amine linked to the pyrazole ring via a methylene spacer. The compounds prepared fall into two discrete series. Compounds in series I (exemplified by **8k**) have a phenyl ring joined to the 4-position of the pyrazole, while compounds in series II (illustrated by **15a** and **15j**) have a 5-phenyl ring linked by a saturated chain to the 4-position of the pyrazole. The structure–activity relationships (SAR) of the two series is discussed separately below as it was found not to be transferable.

SAR of series I

Influence of the piperazine substituent, R (Table 1). Simple alkyl substitution (e.g. **8a**) is not tolerated at the hD_4 receptor and introduction of a phenyl ring (**8b**) only marginally improves the affinity. However, addition of a methylene spacer separating the nitrogen and the aromatic ring substantially improves the affinity and the selectivity at the hD_4 receptor. The benzyl piperazine (**8c**) has now comparable hD_4 receptor affinity to the reference compound **3**. Extension of the alkyl chain linker, such as in **8d**, is detrimental both for binding and selectivity. These results presumably reflect the importance of the lipophilicity in this region of the molecule as well as its relative position in space.

Alternative pyrazole-4-phenyl substituents, X (Table 1). Introduction of a *para*-chloro atom on the C4-phenyl ring is detrimental in this series suggesting that the aromatic rings of **3** and **8e** do not interact with the hD_4 receptor in the same manner. Introduction of an *ortho*-methyl substituent (**8f**) leads to comparable hD_4 affinity compared to **8c** with a threefold improvement in selectivity over the hD_2 receptor.

Influence of pyrazole substitution, $R_{1,2}$ (Table 1). The pyrazole-5-methyl substituent is optimum in this series. The hydrogen analogue (**8g**) has fivefold lower affinity at the hD_4 receptor than **8c** and homologation to an ethyl group (**8h**) is similarly detrimental for binding. Methyl substitution on either of the nitrogen atoms of the pyrazole (**8i** and **8j**) results in a marked reduction of hD_4 receptor affinity. This is presumably due to a steric effect and not to the removal of the hydrogen bonding capability as other heterocycles, such as isoxazole, have been reported to have high affinity to the hD_4 receptor.[18]

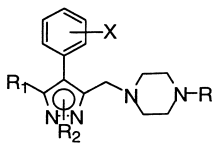
Effect of benzylpiperazine substitution (Table 1). Addition of a *para*-chloro atom to the benzyl moiety maintains the high hD_4 affinity and selectivity (**8k**, K_i: hD_4 2.6 nM; hD_2 430 nM; hD_3 1700 nM) seen with **8c**. Other substitution such as *meta*-chloro (**8l**) and *para*-methoxy (**8m**) results in a fourfold to sevenfold reduction in affinity. The *ortho*-methyl analogue (**8n**) has comparable affinity and selectivity to **8c** and **8k**.

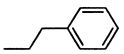
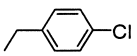
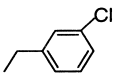
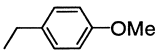
SAR of series II

Influence of the piperazine substituent, R (Table 2). The benzo[*g*]indazole **15b** has tenfold lower affinity for both

the hD_4 and hD_2 receptors compared to its analogue **8c**. However, this reduction in hD_4 receptor affinity can be reversed by variation of the piperazine substituent. For example the isoquinoline (**15d**) has a 16-fold higher affinity for the hD_4 receptor compared to **15b** and is at least 250-fold selective over the other dopamine receptors (**15d**, K_i: hD_4 3.0 nM; hD_2 750 nM; hD_3 1500 nM). Substituents such as *para*-methoxyphenyl also confer high hD_4 affinity to the molecule (**15a**) with even lower hD_2 affinity, whereas the 5-chloro-pyridyl-2-yl anologue (**15e**) has similar hD_4 affinity but increased hD_2 binding. These results suggest that in this small group of compounds of series II the distal piperazine nitrogen does not have to be protonated to obtain high hD_4 binding affinity.

Table 1. Series I. 1-substituted-4-(4-aryl pyrazol-3-ylmethyl)-piperazines



Number	R	R_1	R_2	X	K_i (nM)[a]		
					hD_2	hD_3	hD_4
Haloperidol **1**					1.4	2.0	2.3
Clozapine **2**					7.4	200	10
3					440	3600	2.3
8a	Me	Me	H	H	> 1650 (14%)	> 4300 (34%)	> 3100 (33%)
8b		Me	H	H	> 1690 (26%)	> 4480 (33%)	1200
8c		Me	H	H	440	2200	5.9
8d		Me	H	H	370	870	120
8e		Me	H	p-Cl	360	1100	20
8f		Me	H	o-Me	830	650	3.5
8g		H	H	H	930	2400	27
8h		Et	H	H	640	1400	31
8i[b]		H	1-Me	H	1140	2750	190
8j[b]		H	2-Me	H	> 1900 (28%)	4300	83
8k		Me	H	H	430	1700	2.6
8l		Me	H	H	320	2000	11
8m		Me	H	H	590	215	19
8n		Me	H	H	610	1300	7.4

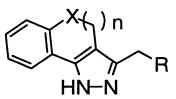
[a]Affinities at the cloned human dopamine receptors expressed in cell lines. Results are the mean of at least two determinations.
[b]Regiochemistry determined by NOE experiments.

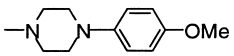
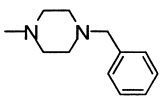
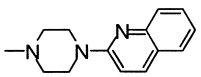
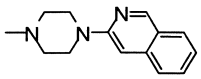
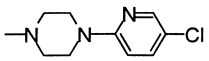
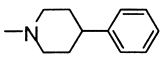
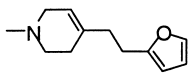
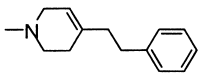
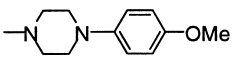
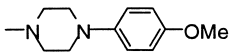
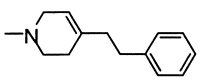
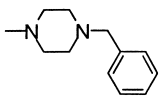
Piperazine replacement (Table 2). Replacement of the piperazine moiety with either piperidine (**15f**) or tetrahydropyridine (**15g** and **15h**) leads to compounds with high hD_4 affinity, but reduced selectivity against the hD_2 receptor. The 4-phenyl piperidine analogue **15f** has 5 nM affinity at the hD_4 receptor, but is nonselective (K_i; hD_2 5.4 nM; hD_3 12 nM). The furylethyltetrahydropyridine (**15g**) has subnanomolar affinity at the hD_4 receptor but is only 60-fold selective over the hD_2 receptor, and the phenethyltetrahydropyridine (**15h**) has slightly lower hD_4 affinity with no improvement in selectivity. These results suggest that the piperazine can be successfully replaced by cyclic monoamines without compromising hD_4 affinity, although at the expense of receptor subtype selectivity.

Influence of the saturated linker group, *n*, X (Table 2). The 1,4-dihydroindeno[1,2-*c*]pyrazole (**15i**) analogue of **15a** has a high affinity for the hD_4 receptor, but with a somewhat lower selectivity over the hD_2 and hD_3 receptors.

The 5-oxa-1,2-diazacyclopenta[*a*]naphthalene analogue (**15j**) (K_i: hD_4 2.6 nM; $hD_2 > 980$ nM; $hD_3 > 2900$ nM)

Table 2. Series II: Benzo[*g*]indazoles, pyrano[4,3-*c*]pyrazoles and 1,2-diaza-cyclopenta[*a*]naphtalenes.



Number	R	X	*n*	K_i (nM)[a]		
				hD_2	hD_3	hD_4
15a		CH_2	1	> 1700 (33%)	> 4400 (20%)	7.3
15b		CH_2	1	1800	800	49
15c		CH_2	1	154	220	19
15d		CH_2	1	750	1500	3
15e		CH_2	1	730	3000	7.4
15f		CH_2	1	5.4	12	5
15g		CH_2	1	34	290	0.5
15h		CH_2	1	190	470	3.3
15i		CH_2	0	220	430	1.5
15j		O	1	> 980 (29%)	> 2900 (22%)	2.6
15k		O	1	330	3300	0.95
15l		O	1	> 1850 (30%)	2550	35

[a]Affinities at the cloned human dopamine receptors expressed in cell lines. Results are the mean of at least two determinations.

has a slightly higher hD_4 receptor affinity compared to its benzo[*g*]indazole analogue (**15a**) with a good hD_2 selectivity profile.

Compound **15k**, analogue of **15h**, has high hD_4 affinity (K_i; hD_4 0.95 nM); but in contrast to the benzo[*g*]indazole series, the selectivity over the hD_2 receptor is improved ($hD_2/hD_4 = 350$).

The benzyl analogue (**15l**) has a similar hD_4 receptor affinity compared to **15b** but with a slight increase in selectivity over the hD_2 receptor. These results show that replacing the benzo[*g*]indazole skeleton by a 5-oxa-1,2-diazacyclopenta[*a*]naphthalene group provides analogues with the best selectivity profile.

Ion channel profile

Ion channel activity especially at the Ca^{2+} and IK_R channel is considered to be responsible for cardiovascular imbalance.[25] Further evaluation of the pyrazole lead (**3**) showed that it has affinity at Ca^{2+}, IK_R, and Na^+ channels (Table 3). Consequently, selective high affinity hD_4 ligands from series I and II were evaluated at these three channels. Compound **8k** has no affinity for the IK_R channel, modest affinity for the Ca^{2+} channel, and has an affinity of 1 μM at the Na^+ channel. The benzyl analogue **8c**, which is also inactive at the IK_R channel, has reduced affinity at the Ca^{2+} channel but still has affinity for the Na^+ channel. The 5-oxa-1,2-diazacyclopenta[*a*]naphthalene **15k** has moderate affinity at both the Ca^{2+} and the Na^+ channels; whereas, the *para*-methoxyphenylpiperazine analogue (**15j**) is devoid of affinity at Na^+, Ca^{2+}, and IK_R ion channels. Affinity at other G-protein receptors was also investigated with **15j** being inactive (K_i: > 10 μM) at $5HT_2$, $5HT_{1A}$, and Sigma receptors.

Table 3. Ion channel activity

Number	Ca^{2+} [a]	Na^+ [b]	IK_R [c]	hD_4 [d]
3	1.4	0.56	0.4	2.3
8c	> 1	72% at 10	> 10	5.9
8k	65% at 10	46% at 1	> 10	2.6
15j	> 10	> 10	> 10	1.5
15k	59% at 10	56% at 10	n. d.	0.95

[a]Inhibition of specific binding of [^{3}H] diltiazem to rabbit skeletal muscle (IC_{50}, μM).
[b]Inhibition of specific binding of [^{3}H] batrachotoxin to rat cortex (IC_{50}, μM).
[c]Concentration of drug required to increase the effective refractory period 25% over baseline measurements (EC_{25}, μM).
[d]Affinities at the cloned human dopamine receptors stably expressed in cell lines (K_i, nM).

Conclusions

Two new series of 3-(heterocyclylmethyl)pyrazoles were synthesised and evaluated for their ability to bind selectively at the hD_4 receptor. Both series provided compounds with high hD_4 receptor binding and good selectivity over the hD_2 and hD_3 receptors. In series I, it was shown that a piperazine *N*-benzyl substituent is necessary for high hD_4 receptor binding; whereas, in series II, the second basic nitrogen is not essential. Compound **15j** has no measurable affinity for ion channels such as Ca^{2+}, Na^+, and IK_R, nor for $5HT_2$, $5HT_{1A}$, and Sigma receptors. The overall profile of **15j** makes it a suitable candidate to test the pharmacology of the hD_4 receptor.

Experimental

Biochemical methods

[^{3}H]-Spiperone binding studies.[20,21] Clonal cell lines expressing the human dopamine D_2, D_3, and D_4 receptor subtypes were harvested in PBS (phosphate buffered saline) and then lysed in 10 mM Tris-HCl (pH 7.4) buffer containing 5 mM $MgSO_4$ 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 $CaCl_2$, 5 mM $MgCl_2$, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid at 20 mg wet weight/mL (human D_4 HEK cells), 10 mg wet weight/mL (human D_2 CHO cells and human D_3 HEK cells). Incubations were carried out for 120 min at ambient temperature (22 °C) in the presence of 0.2 nM [^{3}H]-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.[22–24] Binding to the voltage-sensitive sodium channel was evaluated by displacement of [^{3}H]-batrachotoxin (30–60 Ci/mmol, NEN, USA) binding to rat cerebral cortex. Activity at the voltage sensitive calcium channel (diltiazem allosteric site) was evaluated by displacement of [^{3}H] diltiazem (60–87 Ci/mmol, NEN, USA) binding to rabbit skeletal muscle. Binding to the voltage sensitive potassium channels (particularly IK_R channels) was estimated by measurement of the

effective refractory period (ERP) in the ferret papillary muscle.

Chemistry

All melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 360 (360 MHz) or AC250 (250 MHz) spectrometer with TMS as an internal standard. Chemical shifts were measured in ppm and coupling constants in Hertz. Mass spectra were obtained using a VG Quattro (55 eV) spectrometer. Microanalysis were carried out in the Analytical Department of Butterworth Laboratories, Teddington, Middlesex. Reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel plates from E. Merck (Kieselgel 60 F_{254}). Column chromatography was performed on Fluka silica gel 60 (220–440 mesh).

1-(4-Chlorobenzyl)-piperazine (5). To a solution of 4-chlorobenzyl chloride (1.73 g, 10.7 mmol) in EtOH (30 mL) was added *tert*-butyl 1-piperazinecarboxylate (2 g, 10.7 mmol) and K_2CO_3 (3 g, 21.4 mmol). The mixture was heated at reflux overnight and the solvent removed. The residue was partitioned between water and CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated to give the required carbamate as an oil. To a solution of the oil in CH_2Cl_2 (30 mL) was added TFA (7.7 mL, 97 mmol). The solution was stirred at ambient temperature overnight, evaporated, and the residue partitioned between EtOAc and a 10% solution of K_2CO_3 in water. The organic layer was decanted and the aqueous phase was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated to give the title product as a solid (2 g, 91%). ^{1}H NMR δ ($CDCl_3$) 2.46–2.62 (4H, m), 2.99–3.12 (4H, m), 3.51 (2H, s), 7.20–7.35 (9H, m).

1-(4-(4-Chlorobenzyl)piperazin-1-yl)-3-phenyl-propan-2-one (6). To a solution of 1-chloro-3-phenyl-propan-2-one (1 g, 5.9 mmol) in CH_2Cl_2 (30 mL) was added **5** (1.25 g, 5.9 mmol) and Et_3N (0.82 mL, 5.9 mmol). The yellow solution was stirred overnight at ambient temperature and water was added. The organic phase was decanted, washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica using petroleum ether (60–80)/EtOAc as eluent to afford **6** as a yellow oil (1.88 g, 99%). ^{1}H NMR ($CDCl_3$) δ 2.36–2.56 (8H, m), 3.20 (2H, s), 3.48 (2H, s), 3.72 (2H, s), 7.15–7.37 (9H, m).

1-(4-(4-Chlorobenzyl)piperazin-1-yl)-3-phenyl-pentan-2,4-dione (7). AcOH (0.36 mL, 6.2 mmol) was added to a stirred solution of *N*,*N*′-carbonyldiimidazole (1.02 g, 6.2 mmol) in dry THF (25 mL). After 30 min at ambient temperature, a solution of **6** (1 g, 3.1 mmol) in dry THF (25 mL) was added. The solution was cooled to −78 °C and lithium bis(trimethylsilyl)amide (6.2 mL, 1 M in THF) was added dropwise. The resulting mixture was stirred for 45 min at −78 °C, then overnight at room temperature, and quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica using petroleum ether (60–80)/EtOAc to afford **7** as an oil (210 mg, 18%). ^{1}H NMR ($CDCl_3$) δ 1.86 (3H, s), 2.40–2.58 (8H, m), 2.99 (2H, s), 3.48 (2H, s), 7.12–7.40 (9H, m).

1-(4-Chlorobenzyl)-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-yl-methyl)-piperazine (8k). To a solution of **7** (200 mg, 0.52 mmol) in MeOH (5 mL) was added hydrazine hydrate (0.2 mg, 6.2 mmol). The solution was stirred at room temperature for 1 h and evaporated. CH_2Cl_2 and 10% aq NaOH solution were added to the residue. The organic layer was separated and the aqueous extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to give the free base as a gum (180 mg, 90%). The bis hydrogen oxalate salt had a mp 217–219 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.23 (3H, s), 2.60–2.92 (8H, m), 3.74 (2H, s), 3.84 (2H, s), 7.24–7.46 (9H, m). MS, CI$^+$ $m/z = 381$ for $(M+H)^+$. Found: C, 53.62; H, 5.27; N, 9.64. $C_{22}H_{25}N_4Cl{\cdot}2(CO_2H)_2{\cdot}H_2O$ requires C, 53.93; H, 5.40; N, 9.68%.

The following compounds were prepared in the same manner as **8k** using the appropriate piperazine.

1-Methyl-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8a). The hydrogen oxalate salt had a mp 196–197 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.24 (3H, s), 2.50–2.80 (4H, m), 2.70 (3H, s), 3.0–3.20 (4H, m), 3.47 (2H, s), 7.22–7.44 (5H, m). MS, CI$^+$ $m/z = 271$ for $(M+H)^+$. Found: C, 54.59; H, 6.37; N, 13.40. $C_{16}H_{22}N_4{\cdot}1.5(CO_2H)_2{\cdot}0.7H_2O$ requires C, 54.53; H, 6.56; N, 13.03%.

1-Phenyl-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8b). The hydrogen oxalate salt had mp 185–188 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.25 (3H, s), 2.76–2.90 (4H, m), 3.12–3.32 (4H, m), 3.82 (2H, s), 6.76–7.44 (10H, m). MS, CI$^+$ $m/z = 333$ for $(M+H)^+$. Found: C, 64.02; H, 6.31; N, 12.98. $C_{21}H_{24}N_4{\cdot}(CO_2H)_2{\cdot}0.5H_2O$ requires C, 64.20; H, 6.10; N, 13.16%.

1-Benzyl-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8c). The bis hydrogen oxalate salt had mp 226–230 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.23 (3H, s), 2.62–2.80 (8H, m), 3.70–3.92 (4H, s), 7.26–7.47 (10H, m). MS, CI$^+$ $m/z = 347$ for $(M+H)^+$. Found: C,

58.80; H, 5.45; N, 10.33. $C_{22}H_{26}N_4 \cdot 2.1(CO_2H)_2$ requires C, 58.76; H, 5.68; N, 10.46%.

1-(2-Phenylethyl)-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8d). The hydrogen oxalate salt had mp 190–194 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.21 (3H, s), 2.55–2.65 (4H, m), 2.8–2.94 (8H, m), 3.59 (2H, s), 7.2–7.4 (10H, m). MS, CI$^+$ $m/z = 361$ for $(M+H)^+$. Found: C, 63.78; H, 6.43; N, 11.55. $C_{23}H_{28}N_4 \cdot 1.4(CO_2H)_2$ requires C, 63.69; H, 6.38; N, 11.52%.

1-(3-Chlorobenzyl)-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8l). The hydrogen oxalate salt had mp 233–235 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.24 (3H, s), 2.60–3.00 (8H, m), 3.71 (2H, s), 3.89 (2H, s), 7.26–7.48 (9H, m). MS, CI$^+$ $m/z = 381$ for $(M+H)^+$. Found: C, 54.45; H, 4.87; N, 9.52. $C_{22}H_{25}N_4Cl \cdot 2(CO_2H)_2 \cdot 0.5H_2O$ requires C, 54.79; H, 5.30; N, 9.83%.

1-(4-Methoxyphenyl)-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8m). The hydrogen oxalate salt had mp 222–224 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.23 (3H, s), 2.60–3.04 (8H, m), 3.64 (2H, s), 3.75 (3H, s), 3.97 (2H, s), 6.95–7.47 (9H, m). MS, CI$^+$ $m/z = 377$ for $(M+H)^+$. Found: C, 56.53; H, 5.82; N, 9.86. $C_{23}H_{28}N_4O \cdot 2(CO_2H)_2 \cdot H_2O$ requires C, 56.44; H, 5.86; N, 9.75%.

1-(2-Methylbenzyl)-4-(5-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8n). The hydrogen oxalate salt had mp 225–228 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.23 (3H, s), 2.31 (3H, s), 2.66–3.00 (8H, m), 3.69 (2H, s), 3.89 (2H, s), 7.13–7.47 (9H, m). MS, CI$^+$ $m/z = 361$ for $(M+H)^+$. Found: C, 59.79; H, 6.02; N, 10.32. $C_{23}H_{28}N_4 \cdot 2(CO_2H)_2$ requires C, 59.99; H, 5.96; N, 10.36%.

The following compounds were prepared in the same way as **8k** using benzyl piperazine and the appropriate 1-chloro-3-aryl-propanone.[26]

1-Benzyl-4-[4-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]-piperazine (8e). The bis hydrogen oxalate had a mp 232–233 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.33 (3H, s), 2.65–2.95 (8H, m), 3.68 (2H, s), 3.90 (2H, s), 7.35–7.50 (9H, m). MS, CI$^+$ $m/z = 381$ for $(M+H)^+$. Found: C, 54.97; H, 5.10; N, 9.74. $C_{22}H_{25}N_4Cl \cdot 2(CO_2H)_2 \cdot 0.4H_2O$ requires C, 54.96; H, 5.29; N, 9.56%.

1-Benzyl-4-[5-methyl-4-(2-methylphenyl)-1*H*-pyrazol-3-ylmethyl]-piperazine (8f). The bis hydrogen oxalate salt had a mp 220–221 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.00 (3H, s), 2.04 (3H, s), 2.60–2.9 (8H, m), 3.54–3.80 (2H, m), 3.79 (2H, s), 7.08–7.44 (9H, m). MS, CI$^+$ $m/z = 361$ for $(M+H)^+$. Found: C, 58.85; H, 6.00; N, 10.17. $C_{23}H_{28}N_4 \cdot 2(CO_2H)_2 \cdot 0.5H_2O$ requires C, 59.01; H, 6.05; N, 10.19%.

The following compounds were prepared in the same way as **8k** using benzyl piperazine and either formic or propionic acid to form the pentan-2,4-dione.

1-Benzyl-4-(4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8g). The bis hydrogen oxalate salt had a mp 226–228 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.66–3.05 (8H, m), 3.80 (2H, s), 4.02 (2H, s), 7.22–7.62 (10H, m), 7.94 (1H, s). MS, CI$^+$ $m/z = 333$ for $(M+H)^+$. Found: C, 57.34; H, 5.92; N, 10.29. $C_{21}H_{24}N_4 \cdot 2(CO_2H)_2 \cdot H_2O$ requires C, 57.50; H, 5.45; N, 10.41%.

1-Benzyl-4-(5-ethyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8h). The bis hydrogen oxalate salt had a mp 224–227 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 1.12 (3H, t, $J = 7.5$ Hz), 2.61 (2H, q, $J = 7.5$ Hz), 2.70–2.96 (8H, m), 3.76 (2H, s), 3.87 (2H, s), 7.26–7.48 (10H, m). MS, CI$^+$ $m/z = 360$ for $(M+H)^+$. Found: C, 58.80; H, 5.80; N, 9.93. $C_{23}H_{28}N_4 \cdot 2(CO_2H)_2 \cdot 0.5H_2O$ requires C, 59.01; H, 6.05; N, 10.19%.

The following compounds were prepared in the same manner as **8k** using benzyl piperazine, formic acid and methyl hydrazine in the last step.

1-Benzyl-4-(1-methyl-4-phenyl-1*H*-pyrazol-3-ylmethyl)-piperazine (8i). The bis hydrogen oxalate had a mp 222–225 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.66–3.02 (8H, m), 3.74 (2H, s), 3.85 (3H, s), 3.97 (2H, s), 7.22–7.57 (10H, m), 7.98 (1H, s). Selective irradiation of the ethyl group (3.74 ppm) led to enhancement of the phenyl ortho proton and the pyrazole methyl (3.85 ppm) signals. MS, CI$^+$ $m/z = 347$ for $(M+H)^+$. Found: C, 56.35; H, 5.75; N, 9.71. $C_{22}H_{26}N_4 \cdot 2(CO_2H)_2 \cdot 1.5H_2O$ requires C, 56.41; H, 6.01; N, 10.12%.

1-Benzyl-4-(2-methyl-4-phenyl-2*H*-pyrazol-3-ylmethyl)-piperazine (8j). The bis hydrogen oxalate had a mp 214–217 °C (From EtOH/Et_2O). ^{1}H NMR (DMSO) δ 2.50–3.10 (8H, m), 3.69 (2H, s), 3.88 (3H, s), 4.07 (2H, s), 7.23–7.48 (10H, m), 7.58 (1H, s). Selective irradiation of the hydrogen (7.58 ppm) led to enhancement of the phenyl ortho proton and the pyrazole methyl (3.88 ppm) signals. MS, CI$^+$ $m/z = 347$ for $(M+H)^+$. Found: C, 55.42; H, 5.51; N, 9.24. $C_{22}H_{26}N_4 \cdot 2.25(CO_2H)_2 \cdot 1.5H_2O$ requires C, 55.26; H, 5.86; N, 9.73%.

2-(1-Hydroxy-2-(*N*-*tert*-butyloxycarbonyl-*N*-methyl)amino-ethylidene)-3,4-dihydronapthalen-1-one (10). A solution of LDA was prepared by the addition of *n*-BuLi (43 mL,

2.5 M in hexane) to diisopropylamine (14.9 mL, 106 mmol) in THF (300 mL) at 0 °C under argon. The yellow solution was cooled to −78 °C and **9** (14.1 mL, 106 mmol) in THF (20 mL) was added dropwise, then stirred for 30 min. *N*,*N*′-Carbonyldiimidazole (8.6 g, 53 mmol) was added to a solution of *N*-BOC-sarcosine (10 g, 53 mmol) in THF (100 mL) at 0 °C under argon. After stirring for 15 min, the resulting solution was cannulated into the enolate solution. The mixture was stirred at −78 °C for 30 min, then warmed to room temperature. After a further 30 min, the thick brown gel was poured into saturated aq NH_4Cl. The two phases were separated and the aqueous layer was further extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Dry flash column chromatography on silica gel, eluting with petroleum ether (60–80)/EtOAc, gave **10** as a claret-coloured oil (10.3 g, 61%). ^{1}H NMR (DMSO, δ) Mixture of carbamate rotamers and two enol forms of diketone observed: 1.38 and 1.43 (9H, br s), 2.56–2.62 (2H, m), 2.80–2.92 (5H, m), 4.30–4.40 (2H, m), 7.26–7.40 (2H, m), 7.47 and 7.61 (1H, t, J = 6 Hz), 7.78–7.90 (1H, m), 15.50 and 15.70 (1H, br s). MS, CI$^-$ m/z = 317 for $(M+H)^+$.

(4,5-Dihydro-1*H*-benzo[*g*]indazol-3-ylmethyl)-(*N*-*tert*-butyloxycarbonyl)-methylamine (11). A solution of **10** (6 g, 19 mmol) and hydrazine hydrate (5 mL, 161 mmol) in MeOH (50 mL) was stirred at room temperature under argon for 15 min. MeOH was removed by evaporation and the orange residual oil was partitioned between water and 10% MeOH–CH_2Cl_2. The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give **11** as an orange foam (5.25 g, 89%). ^{1}H NMR (DMSO, δ) a 1:1 mixture of two pyrazole tautomers was observed: 1.42 (9H, s), 2.58–2.68 (2H, m), 2.74 (3H, br s), 2.86–2.96 (2H, m), 4.38 (2H, br s), 7.16–7.28 (3H, m), 7.56–7.70 (1H, m), 12.58 and 13.04 (1H, br s). MS, CI$^+$ m/z = 314 for $(M+H)^+$.

(4,5-Dihydro-1*H*-benzo[*g*]indazol-3-yl[*g*]methyl)-methylamine (12). A saturated solution of HCl in EtOAc (100 mL) was added at room temperature to a solution of **11** (5.1 g, 16 mmol) in EtOAc (50 mL). The mixture was chilled for 90 min, then filtered to collect the salt. The salt was partitioned between 2 M aqueous Na_2CO_3 and EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give **12** as a yellow crystalline solid (3.36 g, 97%). ^{1}H NMR (DMSO) δ 2.27 (3H, s), 2.66 (2H, t, J = 7.7 Hz,), 2.85 (2H, t, J = 7.7 Hz), 3.33 (1H, br s), 3.63 (2H, s), 7.14–7.26 (3H, m), 7.63 (1H, d, J = 7.0 Hz) and 12.42 (1H, br s). MS, CI$^+$ m/z = 214 $(M+H)^+$.

(4,5-Dihydro-1*H*-benzo[*g*]indazol-3-ylmethyl)-dimethylamine (13). A solution of **12** (3.1 g, 14.5 mmol), $NaCNBH_3$ (1.1 g, 17.5 mmol), and AcOH (2 mL) in MeOH (50 mL) was cooled to 0 °C and formaldehyde solution (2 mL, 38% formaldehyde in MeOH) was added. The mixture was stirred at 0 °C for 90 min, with mild effervescence observed. The mixture was basified with 1 M aqueous NaOH, diluted with water, and saturated with NaCl before extracting twice with EtOAc. The organic phases were dried ($MgSO_4$), filtered, and concentrated to give **13** as an orange foam (3.17 g, 96%). ^{1}H NMR ($CDCl_3$) 2.35 (6H, s), 2.73 (2H, t, J = 7.7 Hz), 2.95 (2H, t, J = 7.7 Hz), 3.59 (2H, s), 7.17–7.26 (3H, m) and 7.77 (1H, d, J = 7 Hz). MS, CI$^+$ m/z = 228 for $(M+H)^+$.

(4,5-Dihydro-1*H*-benzo[*g*]indazol-3-ylmethyl)-trimethylammonium iodide (14). A solution of **13** (3.17 g, 13.9 mmol) and iodomethane (1.5 mL, 24.1 mmol) in 3:1 Et_2O/EtOH (40 mL) was stirred at room temperature under argon for 24 h. The solvent was evaporated to give a yellow residue, which was washed with Et_2O to give **14** as a cream-coloured solid (4.49 g, 88%). ^{1}H NMR (DMSO) δ 2.77 (2H, t, J = 7.8 Hz), 2.94 (2H, t, J = 7.8 Hz), 3.08 (9H, s), 4.53 (2H, s), 7.23–7.35 (3H, m), 7.66 (1H, d, J = 7 Hz) and 13.8 (1H, br s). MS, CI$^+$ m/z = 228 for $(M+H)^+$.

3-(4-(4-Methoxyphenyl)-piperazin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15a). *n*-BuLi (2.5 mL, 2.5 M in hexane) was added cautiously at 0 °C under argon to a stirred suspension of 1-(4-methoxyphenyl)-piperazine dihydrochloride (530 mg, 2 mmol) in THF (10 mL), giving vigorous effervescence and forming a yellow solution. The solution was added at room temperature to a stirred suspension of **14** (500 mg, 2.2 mmol) in THF (15 mL). The mixture was heated at reflux under argon for 30 min, then cooled, poured into water, and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give an orange solid which was recrystallised from EtOH to give **15a** (210 mg, 42%) as white granules, mp 207–208 °C. ^{1}H NMR (DMSO) δ 2.53 (4H, br s), 2.69 (2H, t, J = 7 Hz), 2.87 (2H, t, J = 7 Hz), 3.00 (4H, br s), 3.56 (2H, br s), 3.67 (3H, s), 6.78–6.87 (4H, m), 7.15–7.25 (3H, m), 7.60–7.70 (1H, m), 12.57 and 12.96 (1H, 2×br s). MS CI$^+$ m/z = 375 for $(M+H)^+$. Found: C, 73.5; H, 6.9; N, 14.7. $C_{23}H_{26}N_4O$ requires C, 73.8; H, 7.0; N, 15.0%.

3-(4-Benzylpiperazin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]-indazole (15b). (General method for the preparation of compounds **15c–h**.) A solution of **14** (500 mg, 2.2 mmol), 1-benzylpiperazine (0.20 mL, 1.1 mmol) and diisopropylethylamine (0.40 mL, 2.3 mmol) in DMF (10 mL) was heated under argon at 80 °C for 18 h. The mixture was cooled, poured into water, and extracted with 10% EtOAc/Et_2O. The extracts were dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography on

silica gel, eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:1) gave a white solid. This was recrystallised from hexane/EtOAc to yield **15b** (127 mg, 33%) as white granules, mp 158–160 °C. ^{1}H NMR δ (DMSO) 2.38 (8H, br s), 2.65 (2H, t, J = 7.6 Hz), 2.84 (2H, t, J = 7.6 Hz), 3.43 (2H, s), 3.49 (2H, br s), 7.14–7.32 (8H, m), 7.65 (1H, br s), 12.51 and 12.96 (1H, 2×br s). MS, CI$^+$ m/z = 359 for $(M+H)^+$. Found: C, 76.7; H, 7.2; N, 15.6. $C_{23}H_{26}N_4 \cdot 0.1(H_2O)$ requires C, 76.7; H, 7.3; N, 15.6%.

3-(4-Quinolin-2-yl-piperazin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15c). Coupling of **14** (400 mg, 1.8 mmol) with 1-(quinolin-2-yl)piperazine (230 mg, 1.1 mmol), as previously described for the preparation of **15b**, gave **15c**, crystallised as the oxalate salt from EtOH to give brown granules (26 mg, 5%), mp 154–155 °C. ^{1}H NMR δ (DMSO) 2.73 (2H, t, J = 7.7 Hz), 2.84 (4H, br s), 2.90 (2H, t, J = 7.7 Hz), 3.79 (4H, br s) 7.18–7.30 (5H, m), 7.51–7.59 (2H, m), 7.65 (1H, d, J = 7.6 Hz), 7.71 (1H, d, J = 7.9 Hz) and 8.06 (1H, d, J = 9.2 Hz). MS, CI$^+$ m/z = 396 for $(M+H)^+$. Found: C, 64.6; H, 5.5; N, 13.7. $C_{25}H_{25}N_5 \cdot 1.3(CO_2H)_2$ requires C, 64.7; H, 5.4; N, 13.7%.

3-(4-Isoquinolin-3-yl-piperazin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15d). Coupling of **14** (400 mg, 1.8 mmol) with 4-isoquinolin-3-yl-piperazine dihydrochloride[27] (310 mg, 1.1 mmol), as previously described for the preparation of **15b**, gave **15d**, which was recrystallised twice from EtOAc/hexane, to give grey granules (38 mg, 9%)with a mp 228–230 °C. ^{1}H NMR (DMSO) δ 2.54–2.57 (4H, m), 2.71 (2H, t, J = 7 Hz), 2.88 (2H, t, J = 7 Hz), 3.50–3.57 (4H, m), 3.59 (2H, br s), 6.94 (1H, s), 7.15–7.28 (4H, m), 7.53 (1H, t, J = 7.8 Hz), 7.65 (2H, d, J = 8.2 Hz), 7.85 (1H, d, J = 8.1 Hz), 8.96 (1H, s), 12.56 and 12.96 (1H, 2×br s). MS, CI$^+$ m/z = 396 for $(M+H)^+$. Found: C, 75.0; H, 6.3; N, 17.3. $C_{25}H_{25}N_5 \cdot 0.25(H_2O)$ requires C, 75.0; H, 6.4; N, 17.5%.

3-(4-(5-Chloropyridin-2-yl)-piperazin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15e). Coupling of **14** (400 mg, 1.8 mmol) with 1-(5-chloropyridin-2-yl)-piperazine[28] (320 mg, 1.6 mmol), as previously described for the preparation of **15b**, gave a white solid which was recrystallised from CH_2Cl_2 to give **15e** (87 mg, 21%), mp 207–208 °C. ^{1}H NMR (DMSO) δ 2.45–2.50 (4H, m), 2.68 (2H, t, J = 7.4 Hz), 2.84 (2H, t, J = 7.4 Hz), 3.40–3.48 (4H, m), 3.56 (2H, br s), 6.84 (1H, d, J = 9.1 Hz), 7.15–7.24 (3H, m), 7.56 (1H, dd, J = 9.1 and 2.6 Hz), 7.60–7.70 (1H, m), 8.08 (1H, d, J = 2.6 Hz), 12.56 and 12.98 (1H, 2×br s). MS, CI$^+$ m/z = 380 for $(M+H)^+$. Found: C, 66.3; H, 5.8; N, 18.1. $C_{21}H_{22}N_5Cl$ requires C, 66.4; H, 5.8; N, 18.4%.

3-(4-Phenylpiperidin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]-indazole (15f). Coupling of **14** (300 mg, 1.3 mmol) with 4-phenylpiperidine (150 mg, 0.9 mmol) as previously described for the preparation of **15b**, gave **15f**, as a brown oil. This was crystallised as the half-oxalate salt from DMF/EtOH/EtOAc (45 mg, 12%), mp 228–230 °C. ^{1}H NMR (DMSO; 353 K) δ 1.70–1.92 (4H, m), 2.40–2.56 (2H, m), 2.58–2.64 (1H, m), 2.78 (2H, t, J = 7.5 Hz), 2.90 (2H, t, J = 7.5 Hz), 3.16 (2H, br d, J = 11 Hz), 3.82 (2H, s), 7.15–7.30 (8H, m) and 7.66 (1H, d, J = 7.7 Hz). MS, CI$^+$ m/z = 344 for $(M+H)^+$. Found: C, 73.85; H, 6.8; N, 10.8. $C_{23}H_{25}N_3 \cdot 0.55(CO_2H)_2$ requires C, 73.7; H, 6.7; N, 10.7%.

3-(4-(2-Furan-2-ylethyl)-1,2,5,6-tetrahydropyridin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15g). Coupling of **14** (420 mg, 1.8 mmol) with 4-(2-furan-2-ylethyl)-1,2,3,6-tetrahydropyridine[29] (200 mg, 1.1 mmol), as previously described for the preparation of **15b**, gave **15g** as a brown oil which was recrystallised as its half-oxalate salt from EtOH/hexane (83 mg, 18%), mp 205–208 °C. ^{1}H NMR (DMSO) δ 2.16 (2H, br s), 2.27 (2H, t, J = 7.7 Hz), 2.67–2.73 (4H, m), 2.86–2.90 (4H, m), 3.22 (2H, br s), 3.88 (2H, br s), 5.42 (1H, br s), 6.1 (1H, d, J = 3 Hz), 6.33 (1H, dd, J = 3 and 2 Hz), 7.18–7.29 (3H, m), 7.48 (1H, d, J = 2 Hz) and 7.64 (1H, d, J = 6.6 Hz). MS, CI$^+$ m/z = 360 for $(M+H)^+$. Found: C, 70.85; H, 6.5; N, 10.05. $C_{23}H_{25}N_3O \cdot 0.55(CO_2H)_2$ requires C, 70.78; H, 6.4; N, 10.27%.

3-(4-Phenethyl-1,2,5,6-tetrahydropyridin-1-ylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (15h). Coupling of **14** (400 mg, 1.8 mmol) with 4-phenethyl-1,2,5,6-tetrahydropyridine[30] (200 mg, 1.1 mmol) as previously described for the preparation of **15b**, gave a red solid which was recrystallised from EtOAc to give **15h** (100 mg, 25%), mp 173–174 °C. ^{1}H NMR ($CDCl_3$) δ 2.19 (2H, br s), 2.30 (2H, t, J = 8.3 Hz), 2.68–2.76 (6H, m), 2.95 (2H, t, J = 6.9 Hz), 3.09 (2H, br s), 3.71 (2H, br s), 5.38–5.42 (1H, m), 7.16–7.30 (8H, m) and 7.80 (1H, d, J = 7.4 Hz). MS, CI$^+$ m/z = 370 for $(M+H)^+$. Found: C, 80.8; H, 7.3; N, 11.3. $C_{25}H_{27}N_3 \cdot 0.2(H_2O)$ requires C, 80.5; H, 7.4; N, 11.3%.

Hydroxy-(4-oxo-chroman-3-ylidene)-acetic acid ethyl ester (20). A solution of sodium 1,1,1,3,3,3-hexamethyldisilylazide (35 mL, 1 M in THF) was added at −78 °C under nitrogen to a stirred solution of 4-chromanone (**19**) (5 g, 34 mmol) in dry THF (100 mL). The bright orange solution was stirred at −78 °C for 20 min, followed by addition of diethyl oxalate (4.75 mL, 35 mmol). The mixture was warmed to room temperature, becoming a thick red gel. The gel was diluted with 1 M HCl and extracted with EtOAc. The extract was dried ($MgSO_4$), filtered, and concentrated to give **20** (8.3 g, 97%) as a bright-yellow waxy solid; ^{1}H NMR (DMSO) δ 1.30 (3H, t, J = 7.5 Hz), 4.30 (2H, q, J = 7.5 Hz), 5.18 (2H, s), 7.04 (1H, d, J = 8.5 Hz), 7.12

(1H, dd, $J=8.5$ and 8.5 Hz), 7.58 (1H, dd, $J=8.5$ and 8.5 Hz) and 7.79 (1H, d, $J=8.5$ Hz). MS, CI^+ $m/z=249$ for $(M+H)^+$.

Ethyl benzo-[*b*]-2*H*-pyrano-[4,3-*c*]-1*H*-pyrazole-3-carboxylate (21). A solution of **20** (5.27 g, 21 mmol) and hydrazine monohydrochloride (1.5 g, 21 mmol) in EtOH (80 mL) was heated at reflux under nitrogen for 3 h. The mixture was cooled, then poured into water, and extracted with EtOAc. The extract was dried ($MgSO_4$), filtered, and concentrated to give **21** (4.93 g, 95%) as a yellow solid; ^1H NMR (DMSO) δ 1.32 (3H, t, $J=7.1$ Hz), 4.30 (2H, q, $J=7.1$ Hz), 5.46 (2H, s), 6.95 (1H, d, $J=8$ Hz), 7.02 (1H, dd, $J=8$ and 8 Hz), 7.23 (1H, dd, $J=8$ and 8 Hz), 7.62 (1H, d, $J=8$ Hz) and 14.1 (1H, br s). MS, CI^+ $m/z=245$ for $(M+H)^+$.

3-Chloromethyl-benzo-[*b*]-2*H*-pyrano[4,3-*c*]-1*H*-pyrazole (22). A solution of $LiAlH_4$ (3 mL, 1 M in THF) was added to a stirred solution of **21** (360 mg,1.5 mmol) in THF (20 mL) at 0 °C under nitrogen. After 3 h, the reaction was quenched by cautious addition of water, then extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. A solution of oxalyl chloride in CH_2Cl_2 (0.9 mL, 2 M in CH_2Cl_2) was diluted with CH_2Cl_2 (10 mL) and cooled to 0 °C with stirring. DMF (0.14 mL, 1.8 mmol) was added dropwise, giving vigorous effervescence after a brief induction period. The mixture was stirred at 0 °C for 10 min, then warmed to room temperature, forming a white suspension. The suspension was cooled to 0 °C and a solution of the crude yellow solid in DMF (2 mL) was added. The yellow solution was heated at reflux for 2 h, then cooled and poured into brine. The mixture was extracted with Et_2O. The extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was further partitioned between water and Et_2O. The ethereal solution was dried ($MgSO_4$), filtered, and concentrated to give **22** (285 mg, 88%) as a yellow oil; ^1H NMR (DMSO) δ 4.78 (2H, s), 5.30 (2H, s), 6.93–7.05 (2H, m), 7.22 (1H, ddd, $J=8$, 8 and 2 Hz) and 7.57 (1H, d, $J=8$ Hz).

3-(4-(4-Methoxyphenyl)-piperazin-1-ylmethyl)-1,4-dihydro-5-oxa-1,2-diazacyclopenta[*a*]naphthalene (15j). A suspension of **22** (280 mg, 1.3 mmol), 1-(4-methoxyphenyl)piperazine (25 mg, 0.77 mmol) and K_2CO_3 (200 mg, 1.4 mmol) in DMF (10 mL) was stirred at room temperature under nitrogen for 48 h. The mixture was diluted with water and extracted with 10% EtOAc/Et_2O. The extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid, which was recrystallised from EtOH to give **15j** (241 mg, 53%) as cream-coloured granules, mp 190–192 °C (From EtOH). ^1H NMR (DMSO) δ 2.51 (4H, br s), 3.01 (4H, br s), 3.58 (2H, br s), 3.67 (3H, s), 5.20–5.36 (2H, m), 6.79–6.93 (5H, m), 6.98 (1H, dd, $J=8$ and 8 Hz), 7.17 (1H, dd, $J=8$ and 8 Hz), 7.52–7.62 (1H, m), 12.84 and 13.14 (1H, 2×br s). MS, CI^+ $m/z=377$ for $(M+H)^+$. Found: C, 69.9; H, 6.4; N, 14.5. $C_{22}H_{24}N_4O_2$ requires C, 70.2; H, 6.4; N, 14.9%.

3-(4-Phenethyl-3,6-dihydro-2*H*-pyridin-1-ylmethyl)-1,4-dihydro-5-oxa-1,2-diazacyclopenta[*a*]naphthalene (15k). Coupling of **22** (250 mg, 1.1 mmol) with 4-phenethyl-1,2,5,6-tetrahydropyridine (210 mg, 1.1 mmol), as previously described for the preparation of **15j**, gave an oil which was purified by preparative TLC on silica, eluting with EtOAc/hexane (2:1). The brown solid (300 mg) was recrystallised from EtOAc/hexane to give **15k** (47 mg, 11%) as pale pink granules, mp 177–179 °C. ^1H NMR ($CDCl_3$) δ 2.04 (2H, br s), 2.29 (2H, t, $J=8$ Hz), 2.62 (2H, apparent t, $J=6$ Hz), 2.73 (2H, t, $J=8$ Hz), 3.02 (2H, br s), 3.61 (2H, s), 5.26 (2H, s), 5.39 (1H, br s), 6.94–7.02 (2H, m), 7.16–7.22 (4H, m), 7.26–7.30 (2H, m) and 7.71 (1H, dd, $J=8$ and 2 Hz). MS, CI^+ $m/z=372$ for $(M+H)^+$. Found: C, 76.75; H, 6.67; N, 10.96. $C_{24}H_{25}N_3O{\cdot}0.2(H_2O)$ requires C, 76.85; H, 6.83; N, 11.20%.

3-(4-Benzylpiperazin-1-ylmethyl)-1,4-dihydro-5-oxa-1,2-diazacyclopenta[*a*]naphthalene (15l). Coupling of **22** (250 mg, 1.1 mmol) with 1-benzylpiperazine (200 mg, 1.1 mmol) as previously described for the preparation of **15j** gave a yellow oil which solidified on trituration to give **15l** (360 mg, 88%), characterised as the bis hydrogen oxalate. White granules, mp 234–236 °C (From DMF). ^1H NMR (DMSO) δ 2.64–3.00 (8H, m), 3.78 (2H, br s), 3.97 (2H, s), 5.30 (2H, s), 6.93 (1H, d, $J=8$ Hz), 6.99 (1H, dd, $J=8$ and 8 Hz), 7.20 (1H, ddd, $J=8$, 8 and 2 Hz), 7.38–7.40 (5H, m) and 7.58 (1H, dd, $J=8$ and 2 Hz). MS, CI^+ $m/z=361$ for $(M+H)^+$. Found: C, 56.60; H, 5.00; N, 9.92. $C_{22}H_{24}N_4O{\cdot}2(CO_2H)_2{\cdot}0.5(H_2O)$ requires C, 56.83; H, 5.32; N, 10.20%.

2-(1-Hydroxy-2-(4-(4-methoxyphenyl)-piperazin-1-yl)-ethylidene)-indan-1-one dihydrochloride (17). A solution of LDA was prepared at room temperature by the addition of *n*-BuLi (6.5 mL, 2.5 M in THF) to diisopropylamine (2.25 mL, 62 mmol) in dry THF (100 mL) under argon. The yellow solution was cooled to −78 °C and a solution of **16** (2.12 g, 16 mmol) in dry THF (10 mL) was added dropwise. The resulting yellow solution was stirred at −78 °C for 40 min. *N*,*N*′-Carbonyldiimidazole (1.3 g, 8 mmol) was added portionwise to a stirred solution of (4-(4-methoxyphenyl)-piperazin-1-yl)-acetic acid (2 g, 8.4 mmol) in 3:1 THF/DMF (40 mL) at room temperature. After 15 min, the solution was cannulated into the previously prepared solution of **16** in LDA. The resulting grey–green slurry was stirred at −78 °C for 15 min, then warmed to room temperature and poured into dilute aq NH_4Cl. The mixture was

extracted with EtOAc. The extract was dried ($MgSO_4$), filtered, and concentrated to give a brown oil. The oil was redissolved in EtOAc and a saturated solution of HCl in EtOAc was added. After cooling at 0 °C for 24 h, the brown precipitate was collected to give **17** (820 mg, 23%). ^{1}H NMR ($CDCl_3$) δ 3.20–3.70 (8H, m), 3.62 (2H, s), 3.71 (3H, s), 4.70 (2H, s), 6.88 (2H, d, J = 9 Hz), 7.03 (2H, d, J = 9 Hz), 7.45 (1H, d, J = 7 Hz), 7.62–7.59 (2H, m) and 8.14 (1H, br d, J = 7 Hz).

3-(4-(4-Methoxyphenyl)-piperazin-1-ylmethyl)-1,4-dihydro-1-indeno[1,2-*c*]pyrazole (15i). A suspension of **17** (300 mg, 0.82 mmol), hydrazine hydrate (1 mL, 20 mmol), and Et_3N (0.3 mL, 2 mmol) in 1:1 MeOH/DMF (10 mL) was stirred at room temperature under argon for 24 h. The solution was poured into water and extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography on silica gel, eluting with 2% MeOH/CH_2Cl_2, gave a yellow solid which was recrystallised from EtOH/water to give **15i** (70 mg, 29%) as yellow crystals, mp 176–178 °C (from EtOH/H_2O); ^{1}H NMR (DMSO) δ 2.55–2.58 (4H, m), 3.01–3.04 (4H, m), 3.27 (2H, s), 3.58 (2H, s), 3.67 (3H, s), 6.79 (2H, d, J = 9.2 Hz), 6.87 (2H, d, J = 9.2 Hz), 7.24 (1H, dd, J = 7.4 and 7.4 Hz), 7.32 (1H, dd, J = 7.4 and 7.4 Hz), 7.51 (1H, d, J = 7.4 Hz), 7.59 (1H, br d, J = 7.4 Hz) and 12.58 (1H, br s). MS, CI^+ m/z = 361 for $(M+H)^+$. Found: C, 71.0; H, 6.5; N, 14.9. $C_{22}H_{24}N_4O{\cdot}0.6(H_2O)$ requires C, 71.2; H, 6.8; N, 15.1%.

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