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Synthesis and structure–activity relationships of a series of substituted 2-(1*H*-furo[2,3-*g*]indazol-1-yl)ethylamine derivatives as 5-HT$_{2C}$ receptor agonists

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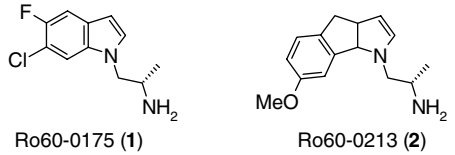
Abstract—A series of novel indazole derivatives were synthesized, and their structure–activity relationships examined in order to identify potent and selective 5-HT$_{2C}$ receptor agonists. Among these compounds, (*S*)-2-(7-ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)-1-methylethylamine (YM348) had a good in vitro profile, that is, high agonistic activity to the human 5-HT$_{2C}$ receptor subtype (EC_{50} = 1.0 nM) and high selectivity over 5-HT$_{2A}$ receptors. This compound was also effective in a rat penile erection model when administered po.

1. Introduction

5-Hydroxytryptamine (5-HT), an important neurotransmitter in the central and peripheral nervous systems (CNS and PNS, respectively), has been implicated in a variety of important physiological processes. At least 14 distinct serotonin receptor subtypes are expressed in the mammalian CNS, each of which is assigned to one of seven families, 5-HT$_1$ to 5-HT$_7$.[1] The 5-HT$_2$ receptor family currently consists of three subtypes termed 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors. Given their relative brain specificity, regional messenger RNA distribution in the brain,[2] and the results from a recent study using gene-knockout mice,[3] 5-HT$_{2C}$ receptors are considered to be attractive targets for the design of novel drugs for treatment of CNS-related diseases such as obesity, obsessive compulsive disorder, and sexual dysfunction.[4–6] Unfortunately, very few 5-HT$_{2C}$-selective agonists were known[7]; therefore, a program to develop selective 5-HT$_{2C}$ receptor agonists was initiated.

Only a few selective 5-HT$_{2C}$ agonists had been reported previously, such as Ro60-0175 (**1**), Ro60-0213 (**2**) (Fig. 1), and related compounds.[8,9] Therefore, in order to discover more potent and selective 5-HT$_{2C}$ agonists, focus was placed upon replacing the indole core with other heterocycles. Since the indazole ring system is known to be a viable bioisostere for the indole ring system,[10] its potential as an 5-HT$_{2C}$ agonist was investigated.



Ro60-0175 (**1**) Ro60-0213 (**2**)

Figure 1. Structures of Ro60-0175 and Ro60-0213.

Keywords: 5-HT$_{2C}$ receptor agonist; Binding affinity; Indazole; YM348.
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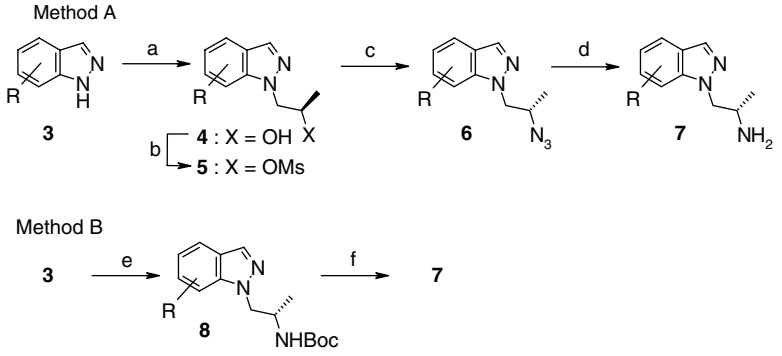
This paper reports on the synthesis and structure–activity relationships (SAR) of indazole derivatives when used as 5-HT_{2C} agonists [representative compound: YM348 (**7i**)].[11] In addition to the binding affinities for 5-HT_{2C} and 5-HT_{2A} receptors, the functional activities for 5-HT_{2C}, 5-HT_{2B}, and 5-HT_{2A} receptors and a further in vivo characterization of a 5-HT_{2C} receptor-mediated response, penile erection of YM348 (**7i**) are shown.

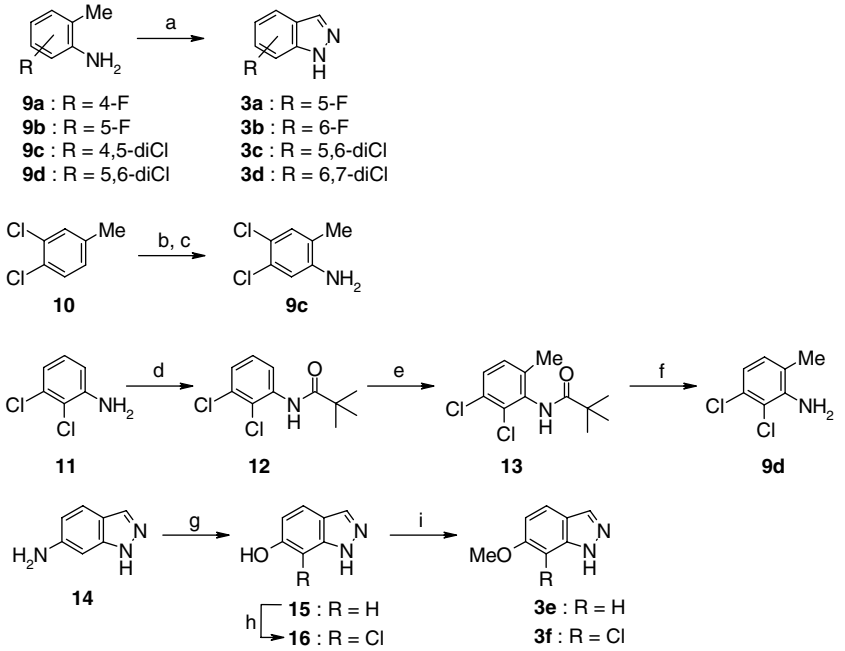
2. Chemistry

The desired substituted 2-(indazol-1-yl)-1-methylethylamines (**7**) were prepared starting from substituted indazoles **3** via two different routes (Scheme 1). Method A started with the deprotonation of the indazoles **3**, followed by alkylation with (*R*)-propylene oxide to afford the alcohols **4**. The S_N2 reaction of the corresponding mesylates **5** with sodium azide, and the subsequent reduction of the azide **6** with $LiAlH_4$ or PPh_3, produced the amines **7**. Alternatively, the amines **7** were also obtained via Method B, which started with N-alkylation of the indazoles **3** with *N*-Boc-*O*-Ts-L-alaninol[12] followed by Boc-deprotection with HCl.

Scheme 2 shows the syntheses of the substituted indazoles **3a**–**f**. A protocol developed by Bartsch and Yang[13] was adopted to synthesize the halogenated indazoles **3a**–**d**. The halogenated *o*-toluidines **9a**–**d** were diazotized with sodium nitrite in hydrochloric acid, followed by the addition of sodium tetrafluoroborate to yield benzenediazonium tetrafluoroborates as precipitates. The crude benzenediazonium tetrafluoroborates were treated with potassium acetate and 18-crown-6 in chloroform to give the halogenated indazoles **3a**–**d** in 20%, 19%, 49%, and 45% yield, respectively. The toluidine **9c** was obtained by nitration of 3, 4-dichlorotoluene (**10**), followed by reduction of the nitro group with $SnCl_2$. The regio-



Scheme 1. Synthetic route to compound **7**. Reagents: (a) NaH, (*R*)-propylene oxide, DMF; (b) MsCl, Et_3N, CH_2Cl_2; (c) NaN_3, DMF; (d) $LiAlH_4$, THF or PPh_3, H_2O, THF; (e) *N*-Boc-*O*-Ts-L–alaninol, Cs_2CO_3, DMSO; (f) HCl, AcOEt.



Scheme 2. Synthetic route to compound **3a**–**3f**. Reagents: (a) 1—$NaNO_2$, *c*-HCl then $NaBF_4$, H_2O; 2—AcOK, 18-crown-6, $CHCl_3$; (b) KNO_3, *c*-H_2SO_4; (c) $SnCl_2{\cdot}2H_2O$, *c*-HCl, EtOH; (d) PivCl, K_2CO_3, acetone; (e) BuLi, MeI, TMEDA, ^{t}BuOMe; (f) KOH, $HOCH_2CH_2OH$; (g) $NaNO_2$, H_2SO_4, then 10 M H_2SO_4; (h) NCS, dioxane; (i) MeI, K_2CO_3, DMF.

isomer of the toluidine **9c**, **9d** was prepared from 2,3-dichloroaniline (**11**). *o*-Lithiation of the pivaloyl-protected derivative **12** generated an aryllithium intermediate, which was trapped with methyl iodide in a moderate yield. The obtained **13** was then deprotected to afford the toluidine **9d**. The methoxy indazoles **3e**, **3f** were prepared from a commercially available 6-aminoindazole (**14**). The hydroxyindazole **15** was obtained by hydrolyzing the diazonium sulfate derivative of **14**.[14] The synthesis of **16** was carried out by chlorinating **15** using the *N*-chlorosuccinimide (NCS). The hydroxy groups in **15** and **16** were reacted with methyl iodide to afford **3e** and **3f**.

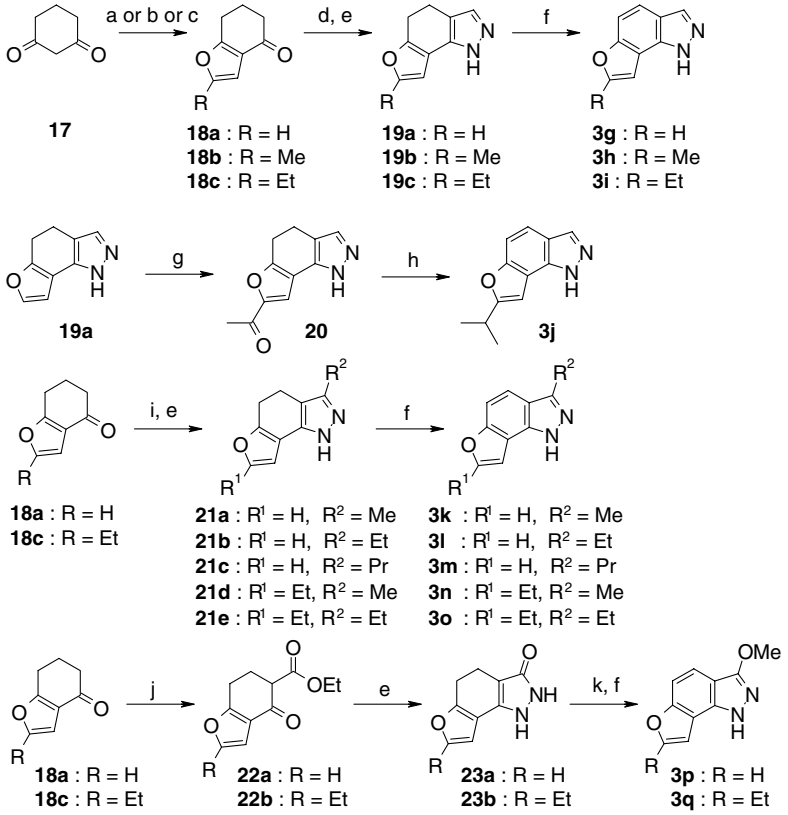
Scheme 3 shows the syntheses of the furan-fused indazoles **3g**–**q**. 1,3-Cyclohexanedione (**17**) was reacted with chloroacetaldehyde to give 6,7-dihydrobenzofuran-4(5*H*)-one (**18a**)[15] in 60% yield. Subsequent α-formylation of **18a** was performed using ethyl formate and *t*-BuOK, followed by the addition of hydrazine to afford 4, 5-dihydro-1*H*-furo[2,3-*g*]indazole (**19a**) in 73% yield. Finally, dehydration with DDQ provided 1*H*-furo[2,3-*g*] indazole (**3g**) in 40% yield. The 7-methyl analogue **3h** and 7-ethyl analogue **3i**[16] were prepared from the corresponding dihydrobenzofuranones **18b**, **18c** using the method outlined above. The 7-isopropyl analogue **3j** was derived from **19a** first by the acetylation using acetic acid and trifluoroacetic anhydride, followed by methylation and dehydration. The 3-alkyl analogues **3k**–**o** were prepared from dihydrobenzofuranones **18a**, **18c** by utilizing the aforementioned synthetic methods with minor modifications. The 3-methoxy analogues **3p**, **3q** were also derived from **18a** or **18c** first by introducing the ethoxycarbonyl group followed by cyclization, O-methylation, and aromatization.

Scheme 4 shows the syntheses of the thiophene-fused indazole **3r** and the oxazole-fused indazole **3s**. The thiophene-fused analogue **3r** was prepared from commercially available **24** according to the procedure for synthesizing **3g**. The oxazole-fused analogue **3s** was synthesized from 6-hydroxyindazole (**15**) by nitration at the 7-position, followed by reduction and cyclization using triethyl orthoformate in three steps and an overall yield of 77%.

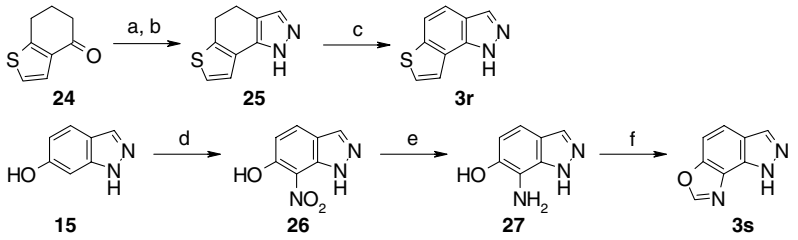
3. Results and discussion

3.1. In vitro binding assay

The synthesized compounds were evaluated for their 5-HT_{2C} and 5-HT_{2A} receptor binding affinities, which were determined using the displacement of agonist ([^{3}H]5-HT) radioligand binding to human 5-HT_{2C} and 5-HT_{2A} receptor sites in CHO cell membranes. The structure–activity relationships of the novel indazole derivatives are summarized in Tables 1–4.

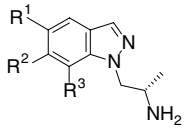


Scheme 3. Synthetic route to compounds **3g**–**3q**. Reagents: (a) $ClCH_2CHO$, $NaHCO_3$, H_2O; (b) 1—2,3-dibromopropene, Triton B, MeOH, H_2O; 2—$HClO_4$, HCO_2H; (c) 1-bromo-2-butanone, $NaHCO_3$, MeOH, H_2O; (d) ^{t}BuOK, HCO_2Et, THF; (e) $H_2NNH_2{\cdot}H_2O$, EtOH; (f) DDQ, dioxane or Pd–C, diethyl fumarate, ethylene glycol; (g) AcOH, TFAA; (h) 1—MeMgCl, THF; 2—I_2, benzene; (i) R^2CO_2Et, KH, NaH, DME; (j) KHMDS, $ClCO_2Et$, THF; (k) CH_2N_2, dioxane, MeOH.



Scheme 4. Synthetic route to compound **3r** and **3s**. Reagents: (a) HCO_2Et, ^tBuOK, THF; (b) $H_2NNH_2{\cdot}H_2O$, EtOH; (c) DDQ, dioxane; (d) KNO_3, H_2SO_4; (e) H_2, Pd–C, AcOH; (f) $HC(OEt)_3$.

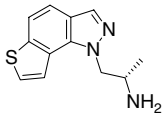
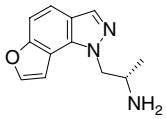
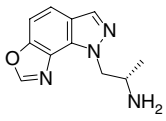
Table 1. Affinities of compounds **1** and **7a-7f** for 5-HT_{2C} and 5-HT_{2A} receptors



Compound	R^1	R^2	R^3	K_i[a] (nM)		Selectivity[b]
				5-HT_{2C}	5-HT_{2A}	5-HT_{2A}/5-HT_{2C}
1				26	39	2
7a	F	H	H	43	89	2
7b	H	F	H	32	82	3
7e	H	OMe	H	16	37	2
7f	H	OMe	Cl	140	1200	9
7c	Cl	Cl	H	7.5	11	1
7d	H	Cl	Cl	4.0	9.1	2

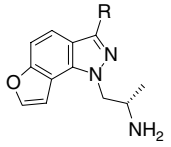
[a] K_i for [^{3}H]5-HT binding; human 5-HT_{2C} and 5-HT_{2A} receptors expressed in CHO cells.
[b] Selectivity = 5-HT_{2A} value/5-HT_{2C} value.

Table 2. Affinities of compounds **7g**, **7r**, and **7s** for 5-HT_{2C} and 5-HT_{2A} receptors

Compound		K_i[a] (nM)		Selectivity[b]
		5-HT_{2C}	5-HT_{2A}	5-HT_{2A}/5-HT_{2C}
7d		4.0	9.1	2
7r		1.4	6.7	5
7g		0.2	0.78	4
7s		59	47	1

[a] Refer to Table 1.
[b] Refer to Table 1.

Table 3. Affinities of compounds **7k**, **7l**, **7m**, and **7p** for 5-HT_{2C} and 5-HT_{2A} receptors



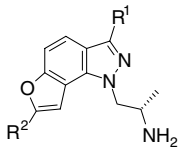
Compound	R	K_i[a] (nM)		Selectivity[b]
		5-HT_{2C}	5-HT_{2A}	5-HT_{2A}/5-HT_{2C}
7g	H	0.20	0.78	4
7k	Me	13	17	1
7l	Et	2.5	11	4
7m	Pr	25	64	3
7p	OMe	0.51	8.7	17

[a] Refer to Table 1.
[b] Refer to Table 1.

The replacement of the Ro60-0175 indole ring (**1**) with the indazole ring was examined first. As shown in Table 1, the binding of the indazole derivative **7a** to the 5-HT_{2C} and 5-HT_{2A} receptors (K_i = 43 and 89 nM, respectively) was almost equipotent to that of **1** (K_i = 26 and 39 nM, respectively). This result indicated that the replacement of the indole ring system with the indazole ring system was acceptable.

3.1.1. Indazole ring substituents. The 6-fluoro derivative **7b** was found to be as potent as **7a** (K_i = 43 vs 32 nM). The 6-methoxy derivative **7e** was more potent (K_i = 16 nM) than the 5-fluoro derivative **7a** and the 6-fluoro derivative **7b**. However, the introduction of the chloro group at the 7-position of the compound **7e** led to a loss of binding affinity for the 5-HT_{2C} receptors (K_i = 140 nM). The dihalogenated compounds **7c**, **7d**

Table 4. Affinities of compounds **7h**–**7j**, **7n**, **7o**, and **7q** for 5-HT_{2C} and 5-HT_{2A} receptors



Compound	R^1	R^2	K_i[a] (nM)		Selectivity[b]
			5-HT_{2C}	5-HT_{2A}	5-HT_{2A}/5-HT_{2C}
7g	H	H	0.20	0.78	4
7h	H	Me	0.30	2.1	7
7i	H	Et	0.89	13	15
7j	H	^{i}Pr	20	87	4
7n	Me	Et	5.0	46	9
7o	Et	Et	2.7	51	19
7q	OMe	Et	12	38	3

[a] Refer to Table 1.
[b] Refer to Table 1.

were examined next. Although the 5, 6-dichloro derivative **7c** had a higher affinity for the 5-HT_{2C} receptors (K_i = 7.5 nM) than the fluoro derivatives **7a**, **7b**, this compound **7c** had poor 2A/2C selectivity (1-fold). Among the compounds evaluated, the 6,7-dicholoro derivative **7d** had the highest affinity for the 5-HT_{2C} receptors (K_i = 4.0 nM).

The 6,7-dichloro derivative **7d** showed high binding affinity (K_i = 4.0 nM), which indicated that the introduction of substituents at the 6- and 7-positions was tolerated. Therefore, fused-heteroaromatics were put in place at the 6- and 7-positions (results shown in Table 2). The affinity of the thiophene-fused analogue **7r** (K_i = 1.4 nM) for the 5-HT_{2C} receptors was greater than that of the 6,7-dichloroindazole derivative **7d**. The furan-fused analogue **7g** was identified as the most potent of the fused analogues, with a K_i value of 0.20 nM at 5-HT_{2C} receptors; however, its selectivity for 5-HT_{2A} receptors was poor (4-fold). The oxazole-fused analogue **7s** had a significantly lower affinity (K_i = 59 nM) for 5-HT_{2C} receptors compared to those of the thiophene-fused **7r** and furan-fused analogue **7g**. The 1*H*-furo[2,3-*g*]indazole derivative **7g** was considered to be the preferable template because of its affinity for 5-HT_{2C} receptors; thus optimization of the substituents on this ring was chosen for further improvement of the selectivity for 5-HT_{2A} receptors.

The data in Table 3 show the binding affinities for the 3-substituted furoindazole analogues. Compounds with methyl (**7k**), ethyl (**7l**), or propyl (**7m**) substitutions at the 3-position showed decreased affinities for 5-HT_{2C} receptors (K_i = 13, 2.5, and 25 nM, respectively) compared to the non-substituted derivative **7g** (K_i = 0.20 nM). In contrast, the 3-methoxy derivative **7p** had high 5-HT_{2C} affinity (K_i = 0.51 nM) with a 10-fold decrease in affinity for 5-HT_{2A} receptors, which resulted in high 2A/2C selectivity (17-fold).

The substituents at the 7-position were investigated next (Table 4). The introduction of a methyl (**7h**) or ethyl group (**7i**) resulted in a slight loss of 5-HT_{2C} affinity (K_i = 0.30 and 0.89 nM, respectively), and the isopropyl group (**7j**) caused a significant drop (K_i = 20 nM). Compared to the non-substituted derivative **7g**, the ethyl derivative **7i** showed a slight loss of 5-HT_{2C} binding affinity (K_i = 0.89 vs 0.20 nM) and a significant drop in 5-HT_{2A} affinity (K_i = 13 vs 0.78 nM). As a result, this compound **7i** showed high 2A/2C selectivity (15-fold). Thus, out of the substituents introduced at the 7-position, the ethyl group was the best. Next, substituents were introduced at the 3-position while the 7-ethyl group remained. Introduction of a methyl (**7n**) or ethyl group (**7o**) at the 3-position of the compound **7i** resulted in a reduction of the 5-HT_{2C} binding affinity (K_i = 5.0 and 2.7 nM, respectively). As was the case with compound **7p**, the introduction of the methoxy group (**7q**) was expected to decrease the affinity for 5-HT_{2A} receptors and improve the 2A/2C selectivity. However, the introduction of the methoxy group (**7q**) led to a substantial decrease in 5-HT_{2C} receptor affinity, which resulted in a decrease in 2A/2C selectivity (K_i = 12 nM, 2A/2C = 3-fold).

In view of its affinity for 5-HT_{2C} receptors and selectivity for 5-HT_{2A} receptors, the ethyl derivative **7i** was considered to be the most promising compound of those examined. Therefore compound **7i** was subjected to further evaluation.

3.2. In vitro agonist activity

The functional activities of YM348 (**7i**) and known 5-HT_{2C} agonists (5-HT, mCPP, and Ro60-0175) of human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors were determined by measuring the myo-[^{3}H] inositol turnover in CHO or HEK 293-EBNA cells. The results are summarized in Table 5.

The non-selective 5-HT_{2C} receptor agonist, mCPP, had a potency for 5-HT_{2C} receptors (EC_{50} = 120 nM) that was 6-fold lower than that of 5-HT. Its efficacy for 5-HT_{2C} receptors was also relatively weak (E_{max} = 63%). The potency of mCPP for 5-HT_{2A} and 5-HT_{2B} receptors was also relatively weak (EC_{50} = 150 and 93 nM, respectively). Their efficacy was also low (E_{max} = 18% and 21%, respectively). The potency of Ro60-0175 (**1**) for 5-HT_{2C} receptors was 2-fold lower (EC_{50} = 52 nM) than that of 5-HT, but it did have full agonist activity (E_{max} = 88%). For 5-HT_{2A} receptors, the potency of Ro60-0175 (**1**) was 6-fold lower (EC_{50} = 400 nM) than that of 5-HT, but it did show full efficacy (E_{max} = 91%). For 5-HT_{2B} receptors, the potency of Ro60-0175 (**1**) was 2-fold higher (EC_{50} = 2.4 nM) than that of 5-HT, and it showed full efficacy (E_{max} = 130%). Meanwhile, YM348 (**7i**) exhibited high 5-HT_{2C} potency (EC_{50} = 1.0 nM), and its E_{max} value for 5-HT_{2C} receptors was 76%. For 5-HT_{2A} receptors, YM348 (**7i**) showed a similar potency (EC_{50} = 93 nM) and efficacy (E_{max} = 97%) to 5-HT. For 5-HT_{2B} receptors, YM348 (**7i**) showed a similar potency (EC_{50} = 3.2 nM) and efficacy (E_{max} = 110%) to 5-HT. When YM348 (**7i**) was compared with Ro60-0175 (**1**), it was about 50-fold more potent for 5-HT_{2C} receptors (1.0 vs 52 nM) and had excellent functional selectivity

Table 5. Functional activities of **7i** and known 5-HT_2 agonists for the cloned human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors

Compound	5-HT_{2C}		5-HT_{2A}		5-HT_{2B}		Selectivity	
	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)	2A/2C	2B/2C
5-HT	24	100	70	100	5.8	97	2.9	0.24
mCPP	120	63	150	18	93	21	1.3	0.78
Ro60-0175 (**1**)	52	88	400	91	2.4	130	7.7	0.05
YM348 (**7i**)	1.0	76	93	97	3.2	110	93	3.2

E_{max} indicates intrinsic activity and is expressed as the percentage of maximal stimulation produced by 10 μM 5-HT.

for 5-HT_{2C} over 5-HT_{2A} (93-fold vs 7.7-fold). Moreover, YM348 (**7i**) showed higher selectivity than Ro60-0175 (**1**) for 5-HT_{2B} over 5-HT_{2C} receptors (0.05-fold vs 3.2-fold).

3.3. In vivo activity

The compounds mentioned above were tested for efficacy in the induction of penile erection in rats. This is a symptom of the serotonin syndrome, which is a reflection of 5-HT_{2C} receptor activation in rodents.[17] The results are presented with MED values [minimum effective dose; that is, the lowest dose that significantly ($p < 0.05$ as compared with vehicle) affected penile erections] in Table 6.

First, the in vivo profile of the non-selective 5-HT_{2C} receptor agonist, mCPP, which has been shown to induce penile erection in rats,[18] was evaluated. Indeed, subcutaneous (sc) and oral (po) administration of mCPP did induce penile erections. The MED values for sc and po administration were 0.1 and 3 mg/kg, respectively. sc administration of Ro60-0175 (**1**) induced penile erections at an activity level 3-fold lower than that of mCPP (MED = 0.3 vs 0.1 mg/kg sc). Compound **7p**, which had a high affinity for 5-HT_{2C} receptors and high 2A/2C selectivity, induced penile erections via sc administration (MED = 0.1 mg/kg sc), but not via po administration. This was probably due to the metabolic weakness of the methoxy group. On the other hand, YM348 (**7i**) showed high 5-HT_{2C} potency and induced penile erections when administered via both sc and po (MED = 0.03 and 0.3 mg/kg, respectively). These effects were completely inhibited by the selective 5-HT_{2C} receptor antagonist, SB242084,[19] which indicates that 5-HT_{2C} activation was the mechanism by which YM348 (**7i**) induced penile erection.

Table 6. Effects of representative indazole derivatives and known 5-HT_{2C} agonists on penile erections in rats after sc or po administration

Compound	MED[a]	
	sc (mg/kg)	po (mg/kg)
mCPP	0.1	3
Ro60-0175 (**1**)	0.3	NT[b]
7p	0.1	NE[c]
YM348 (**7i**)	0.03	0.3

[a] The lowest dose that significantly ($p < 0.05$ as compared with vehicle) affected penile erections was considered to be the minimum effective dose (MED).
[b] Not tested.
[c] Not effective.

4. Conclusion

As part of the search for novel 5-HT_{2C} receptor agonists, a series of indazole derivatives were synthesized and evaluated to determine their in vitro and in vivo 5-HT_{2C} agonist activities. YM348 (**7i**), (*S*)-2-(7-ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)-1-methylethylamine, showed high affinity ($K_i = 0.89$ nM) and potency ($EC_{50} = 1.0$ nM) for the 5-HT_{2C} receptors. Though its functional selectivity over the 5-HT_{2B} receptors was not enough (3.2-fold), it had high functional selectivity over the 5-HT_{2A} receptors (93-fold). YM348 (**7i**) showed excellent oral agonistic activity in the induction of penile erection in rat. Further refined analogs with high 5-HT_{2B} selectivity have potential for use in therapy for CNS-related diseases such as obesity, obsessive compulsive disorder, and sexual dysfunction.

5. Experimental

5.1. Chemistry

Melting points were determined with a Yanaco MP-500D or a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 or a JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard (in NMR description, s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet). Mass spectra were recorded on a Hitachi M-80 or a JEOL JMS-LX2000 spectrometer. Elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and a Yokogawa IC-7000S ion chromatographic analyzer (halogens), and the results were within ±0.4% of theoretical values.

5.1.1. 5-Fluoro-1*H*-indazole (3a). To a mixture of **9a** (6.3 g, 50 mmol), H_2O (13 mL), and concd HCl (13 mL) was added a solution of $NaNO_2$ (3.5 g, 50 mmol) in H_2O (10 mL) at −10 °C, and the resulting mixture was stirred for 0.5 h at 0 °C. The insoluble material was removed by filtration, and to the filtrate was added a solution of $NaBF_4$ (7.7 g, 70 mmol) in H_2O (20 mL). The resulting precipitate was collected by filtration and washed with 5% $NaBF_4$ aq, cold MeOH, and Et_2O, after which it was air-dried. This process yielded 7.86 g of 4-fluoro-2-methylbenzenediazonium tetrafluoroborate as a slightly violet solid that was used in the next step without further purification.

A mixture of 4-fluoro-2-methylbenzenediazonium tetrafluoroborate (7.86 g, 35 mmol), AcOK (6.9 g, 70 mmol), 18-crown-6 (0.48 g, 1.8 mmol), and $CHCl_3$ (500 mL) was stirred at room temperature for 3 h. The insoluble material was removed by filtration, after which the filtrate was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/toluene = 1:8 to 1:4) to yield **3a** (1.36 g, 20%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.21–7.27 (1H, m), 7.53–7.54 (1H, m), 7.55–7.57 (1H, m), 8.06 (1H, s); EI-MS *m*/*z* 136 [M^+].

5.1.2. 6-Fluoro-1*H*-indazole (3b). Compound **3b** was prepared from **9b** using a procedure similar to that described for **3a**, in 19% yield as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 6.95–7.04 (1H, m), 7.28–7.35 (1H, m), 7.80 (1H, dd, J = 5.1, 8.7 Hz), 8.09 (1H, s), 13.12 (1H, br s); EI-MS *m*/*z* 136 [M^+].

5.1.3. 5,6-Dichloro-1*H*-indazole (3c). Compound **3c** was prepared from **9c** using a procedure similar to that described for **3a**, in 49% yield as a pale yellow solid.^{1}H NMR ($CDCl_3$) δ 7.86 (1H, s), 8.10–8.11 (2H, m), 13.35 (1H, br s); EI-MS *m*/*z* 186 [M^+].

5.1.4. 6,7-Dichloro-1*H*-indazole (3d). Compound **3d** was prepared from **9d** using a procedure similar to that described for **3a**, in 45% yield as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 7.32 (1H, d, J = 8.8 Hz), 7.78 (1H, d, J = 8.8 Hz), 8.22 (1H, d, J = 1.2 Hz), 13.75 (1H, br s); EI-MS *m*/*z* 186 [M^+].

5.1.5. 6-Methoxy-1*H*-indazole (3e). To a mixture of **15** (1.90 g, 14.2 mmol), K_2CO_3 (2.35 g, 17.0 mmol), and DMF (20 mL) was added MeI (1.06 mL, 17.0 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 15 h. To the mixture was added H_2O, which was then extracted with AcOEt and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:2) to yield **3e** (1.02 g, 48%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 3.81 (3H, s), 6.71–6.76 (1H, m), 6.88–6.92 (1H, m), 7.60 (1H, d, J = 8.7 Hz), 7.92 (1H, s), 12.80 (1H, br s); FAB-MS *m*/*z* 147 [$(M-H)^+$].

5.1.6. 7-Chloro-6-methoxy-1*H*-indazole (3f). Compound **3f** was prepared from **16** using a procedure similar to that described for **3e**, in 56% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 3.94 (3H, s), 7.09 (1H, d, J = 9.0 Hz), 7.71 (1H, d, J = 9.0 Hz), 8.08 (1H, s), 13.24 (1H, br s); FAB-MS *m*/*z* 183 [$(M+H)^+$].

5.1.7. 1*H*-Furo[2,3-*g*]indazole (3g). To a mixture of **19a** (8.50 g, 53 mmol) and dioxane (150 mL) was added DDQ (13.4 g, 58.5 mmol), and the resulting mixture was heated at reflux for 2 h. After cooling, the insoluble material was removed by filtration. To the filtrate was added saturated aqueous $NaHCO_3$, which was then extracted with $CHCl_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 30:1) to yield **3g** (3.63 g, 40%) as a yellow solid.^{1}H NMR (DMSO-d_6) δ 7.16 (1H, dd, J = 0.7, 2.2 Hz), 7.41 (1H, d, J = 8.8 Hz), 7.66 (1H, d, J = 8.8 Hz), 8.06 (1H, d, J = 2.2 Hz), 8.14 (1H, d, J = 1.5 Hz), 13.39 (1H, br s); FAB-MS *m*/*z* 159 [$(M+H)^+$].

5.1.8. 7-Methyl-1*H*-furo[2,3-*g*]indazole (3h). Compound **3h** was prepared from **19b** using a procedure similar to that described for **3g**, in 33% yield as a pale yellow solid.^{1}H NMR (DMSO-d_6) δ 2.51 (3H, s), 6.78 (1H, s), 7.31 (1H, d, J = 8.7 Hz), 7.55 (1H, d, J = 8.7 Hz), 8.09 (1H, d, J = 1.5 Hz), 13.29 (1H, br s); FAB-MS *m*/*z* 173 [$(M+H)^+$].

5.1.9. 7-Ethyl-1*H*-furo[2,3-*g*]indazole (3i). To a solution of **19c** (500 mg, 2.66 mmol) in ethylene glycol (5 mL) were added diethyl fumarate (0.44 mL, 2.66 mmol) and 5% Pd on carbon, after which the mixture was heated at reflux for 5 h. After cooling, the mixture was diluted with MeOH (50 mL). The catalyst was removed by filtration. The filtrate was concentrated in vacuo, after which brine was added to the residue. The resulting aqueous solution was extracted with AcOEt/toluene (1:3), the organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:5) to yield **3i** (391 mg, 79%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.5 Hz), 2.87 (2H, dq, J = 0.9, 7.5 Hz), 6.60 (1H, d, J = 0.9 Hz), 7.32 (1H, dd, J = 0.8, 8.7 Hz), 7.54 (1H, d, J = 8.7 Hz), 8.15 (1H, s), 10.85 (1H, br s); FAB-MS *m*/*z* 187 [$(M+H)^+$].

5.1.10. 7-Isopropyl-1*H*-furo[2,3-*g*]indazole (3j). To a solution of **20** (1.70 g, 8.41 mmol) in THF (50 mL) was added MeMgCl (8.40 mL, 3 M in THF) at 0 °C, and then the mixture was stirred for 0.5 h at room temperature. The resulting mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 100:1 to 50:1) to yield yellow amorphous solid (2.36 g).

To this product (2.36 g) was added benzene (20 mL) and I_2 (10 mg), and the resulting mixture was heated at reflux for 2 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/AcOEt = 10:1) to yield **3j** (539 mg, 32%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.34 (6H, d, J = 6.8 Hz), 3.08–3.22 (1H, m), 6.74 (1H, s), 7.33 (1H, d, J = 8.4 Hz), 7.56 (1H, d, J = 8.4 Hz), 8.09 (1H, d, J = 1.6 Hz), 13.27 (1H, br s); FAB-MS *m*/*z* 201 [$(M+H)^+$].

5.1.11. 3-Methyl-1*H*-furo[2,3-*g*]indazole (3k). Compound **3k** was prepared from **21a** using a procedure similar to that described for **3g**, in 44% yield as a slightly yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.63 (3H, s), 6.97–7.01 (1H, m), 7.35–7.40 (1H, m), 7.54 (1H, d, J = 8.7 Hz), 7.71 (1H, d, J = 2.1 Hz); FAB-MS *m*/*z* 173 [$(M+H)^+$].

5.1.12. 3-Ethyl-1*H*-furo[2,3-*g*]indazole (3l). Compound **3l** was prepared from **21b** using a procedure similar to that described for **3g**, in 26% yield as a pale purple solid. ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, J = 7.5 Hz), 3.06 (2H, q, J = 7.5 Hz), 6.98 (1H, dd, J = 0.9, 2.4 Hz), 7.36 (1H, dd, J = 0.9, 8.7 Hz), 7.57 (1H, d, J = 8.7 Hz), 7.70 (1H, d, J = 2.1 Hz); FAB-MS m/z 187 [$(M+H)^+$].

5.1.13. 3-Propyl-1*H*-furo[2,3-*g*]indazole (3m). Compound **3m** was prepared from **21c** using a procedure similar to that described for **3g**, in 13% yield as a purple solid. ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.5 Hz), 1.82–1.95 (2H, m), 3.00 (2H, t, J = 7.5 Hz), 6.98 (1H, dd, J = 1.2, 2.4 Hz), 7.36 (1H, dd, J = 0.6, 9.0 Hz), 7.57 (1H, d, J = 9.0 Hz), 7.70 (1H, d, J = 2.4 Hz); FAB-MS m/z 201 [$(M+H)^+$].

5.1.14. 7-Ethyl-3-methyl-1*H*-furo[2,3-*g*]indazole (3n). Compound **3n** was prepared from **21d** using a procedure similar to that described for **3i**, in 34% yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.5 Hz), 2.68 (3H, s), 2.87 (2H, q, J = 7.5 Hz), 6.69 (1H, s), 7.33 (1H, d, J = 9.0 Hz), 7.46 (1H, d, J = 9.0 Hz); FAB-MS m/z 201 [$(M+H)^+$].

5.1.15. 3,7-Diethyl-1*H*-furo[2,3-*g*]indazole (3o). Compound **3o** was prepared from **21e** using a procedure similar to that described for **3g**, in 33% yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.5 Hz), 1.47 (3H, t, J = 7.5 Hz), 2.87 (2H, dq, J = 0.9, 7.5 Hz), 3.11 (2H, q, J = 7.5 Hz), 6.70 (1H, d, J = 0.9 Hz), 7.33 (1H, dd, J = 0.9, 9.0 Hz), 7.50 (1H, d, J = 9.0 Hz); FAB-MS m/z 215 [$(M+H)^+$].

5.1.16. 3-Methoxy-1*H*-furo[2,3-*g*]indazole(3p). To a mixture of 40% aqueous NaOH (15 mL) and Et_2O (30 mL) was added portionwise *N*-methyl-*N*-nitrosourea (4.21 g, 10.2 mmol) at 0 °C. After stirring for 0.5 h at this temperature, the ether layer was decanted, and added to a solution of **23a** (1.50 g, 8.51 mmol) in dioxane (10 mL) and MeOH (20 mL) at 0 °C. After stirring at room temperature for 15 min, AcOH was added until the solution became colorless, after which it was evaporated in vacuo. The residue was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 30:1:0.1) to yield 3-methoxy-4, 5-dihydro-1*H*-furo[2,3-*g*]indazole (0.80 g, 49%).

To this product were added dioxane (50 mL) and DDQ (1.41 g, 6.23 mmol), and the resulting mixture was stirred at 60 °C for 0.5 h. After cooling, the insoluble material was removed by filtration. To the filtrate was added saturated aqueous $NaHCO_3$, which was then extracted with $CHCl_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to yield **3p** (0.66 g, 85%) as a yellow solid.^{1}H NMR (DMSO-d_6) δ 4.01 (3H, s), 7.08–7.10 (1H, m), 7.29 (1H, dd, J = 1.2, 8.8 Hz), 7.45 (1H, d, J = 8.8 Hz), 8.03 (1H, d, J = 2.0 Hz); FAB-MS m/z 189 [$(M+H)^+$].

5.1.17. 7-Ethyl-3-methoxy-1*H*-furo[2,3-*g*]indazole (3q). Compound **3q** was prepared from **23b** using a procedure similar to that described for **3p**, in 30% yield as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.30 (3H, d, J = 7.5 Hz), 2.85 (2H, q, J = 7.5 Hz), 4.00 (3H, s), 6.70 (1H, d, J = 0.9 Hz), 7.22 (1H, dd, J = 0.9, 8.8 Hz), 7.36 (1H, d, J = 8.8 Hz), 12.16 (1H, br s); FAB-MS m/z 217 [$(M+H)^+$].

5.1.18. 1*H*-Thieno[2,3-*g*]indazole (3r). Compound **3r** was prepared from **25** using a procedure similar to that described for **3g**, in 78% yield as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 7.66–7.73 (2H, m), 7.83 (1H, d, J = 5.6 Hz), 7.87 (1H, d, J = 5.6 Hz), 8.16 (1H, s), 13.62 (1H, br s); EI-MS m/z 174 [M^+].

5.1.19. 1*H*-[1,3]Oxazolo[5,4-*g*]indazole (3s). A mixture of **27** (360 mg, 2.41 mmol) and $HC(OEt)_3$ (10 mL) was heated at reflux for 2 h. After cooling, the solvent was removed and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 50:1) to yield **3s** (310 mg, 81%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 7.55 (1H, d, J = 8.7 Hz), 7.82 (1H, d, J = 8.7 Hz), 8.23 (1H, s), 8.83 (1H, s), 13.85 (1H, br s); FAB-MS m/z 160 [$(M+H)^+$].

5.1.20. (2*R*)-1-(5-Fluoro-1*H*-indazol-1-yl)propan-2-ol (4a). To a mixture of 60% NaH (0.48 g, 12 mmol) and DMF (15 mL) were added **3a** (1.5 g, 11 mmol) at room temperature, and the mixture was stirred for 0.5 h. To the reaction mixture was added (*R*)-propylene oxide (0.89 mL, 13 mmol) at 0 °C, and it was stirred at room temperature for 17 h. The mixture was poured into water and extracted with AcOEt. The extracts were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (AcOEt/toluene = 1:4 to 1:2) to yield **4a** (0.87 g, 41%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J = 6.4 Hz), 3.18 (1H, d, J = 4.0 Hz), 4.20–4.25 (1H, m), 4.29–4.39 (2H, m), 7.15–7.20 (1H, m), 7.33–7.40 (2H, m), 7.97 (1H, d, J = 0.8 Hz); FAB-MS m/z 195 [$(M+H)^+$].

5.1.21. (2*R*)-1-(6-Fluoro-1*H*-indazol-1-yl)propan-2-ol (4b). Compound **4b** was prepared from **3b** using a procedure similar to that described for **4a**, in 40% yield. ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J = 6.4 Hz), 3.18 (1H, d, J = 4.0 Hz), 4.15–4.21 (1H, m), 4.30–4.38 (2H, m), 6.92–6.97 (1H, m), 7.07–7.10 (1H, m), 7.68 (1H, dd, J = 5.2, 8.8 Hz), 8.00 (1H, s); FAB-MS m/z 195 [$(M+H)^+$].

5.1.22. (2*R*)-1-(5,6-Dichloro-1*H*-indazol-1-yl)propan-2-ol (4c). Compound **4c** was prepared from **3c** using a procedure similar to that described for **4a**, in 43% yield.^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d, J = 5.9 Hz), 4.00–4.08 (1H, m), 4.30–4.32 (2H, m), 4.85 (1H, d, J = 4.9 Hz), 8.04–8.08 (3H, m); EI-MS m/z 244 [M^+].

5.1.23. (2*R*)-1-(6,7-Dichloro-1*H*-indazol-1-yl)propan-2-ol (4d). Compound **4d** was prepared from **3d** using a procedure similar to that described for **4a**, in 24% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (3H, d, J = 5.4 Hz),

4.01–4.12 (1H, m), 4.50–4.57 (1H, m), 4.69–4.76 (1H, m), 4.88 (1H, d, J = 5.2 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 8.4 Hz), 8.20 (1H, m); FAB-MS m/z 245 [M^+].

5.1.24. (2*R*)-1-(6-Methoxy-1*H*-indazol-1-yl)propan-2-ol (4e). Compound **4e** was prepared from **3e** using a procedure similar to that described for **4a**, in 45% yield. ^{1}H NMR (DMSO-d_6) δ 1.06 (3H, d, J = 6.0 Hz), 3.83 (3H, s), 4.05–4.16 (1H, m), 4.10–4.30 (2H, m), 4.85 (1H, d, J = 5.2 Hz), 6.73 (1H, dd, J = 2.0, 8.8 Hz), 7.08–7.11 (1H, m), 7.58 (1H, d, J = 8.8 Hz), 8.22 (1H, s); FAB-MS m/z 207 [(M+H)$^+$].

5.1.25. (2*R*)-1-(7-Chloro-6-methoxy-1*H*-indazol-1-yl)propan-2-ol (4f). Compound **4f** was prepared from **3f** using a procedure similar to that described for **4a**, in 57% yield. ^{1}H NMR (DMSO-d_6) δ 1.00 (3H, d, J = 6.0 Hz), 3.94 (3H, s), 4.04–4.09 (1H, m), 4.46–4.50 (1H, m), 4.65–4.70 (1H, m), 4.84 (1H, d, J = 5.5 Hz), 7.10 (1H, d, J = 9.0 Hz), 7.71 (1H, d, J = 9.0 Hz), 8.06 (1H, s); FAB-MS m/z 241 [(M+H)$^+$].

5.1.26. (2*R*)-1-(1*H*-Furo[2,3-*g*]indazol-1-yl)propan-2-ol (4g). Compound **4g** was prepared from **3g** using a procedure similar to that described for **4a**, in 51% yield. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, d, J = 6.3 Hz), 3.99–4.18 (2H, m), 4.38–4.58 (2H, m), 4.50 (1H, d, J = 5.1 Hz), 7.39–7.44 (1H, m), 7.45–7.48 (1H, m), 7.63 (1H, d, J = 8.7 Hz), 8.08–8.12 (2H, m); FAB-MS m/z 217 [(M+H)$^+$].

5.1.27. (2*R*)-1-(7-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-ol (4i). Compound **4i** was prepared from **3i** using a procedure similar to that described for **4a**, in 49% yield. ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, d, J = 6.0 Hz), 1.39 (3H, t, J = 7.8 Hz), 2.88 (2H, q, J = 7.8 Hz), 4.40–4.60 (3H, m), 6.68 (1H, s), 7.30 (1H, d, J = 8.7 Hz), 7.51 (1H, d, J = 8.7 Hz), 8.04 (1H, s); FAB-MS m/z 245 [(M+H)$^+$].

5.1.28. (2*R*)-1-(3-methyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-ol (4k). Compound **4k** was prepared from **3k** using a procedure similar to that described for **4a**, in 49% yield. ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, J = 5.0 Hz), 3.32 (3H, s), 4.07–4.10 (3H, m), 4.30–4.36 (1H, m), 4.40–4.46 (1H, m), 4.91 (1H, d, J = 5.0 Hz), 7.37 (1H, d, J = 10 Hz), 7.42 (1H, s), 7.56 (1H, d, J = 10 Hz), 8.07 (1H, s); FAB-MS m/z 226 [(M+H)$^+$].

5.1.29. (2*R*)-1-(3-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-ol (4l). Compound **4l** was prepared from **3l** using a procedure similar to that described for **4a**, in 30% yield. ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, J = 6.3 Hz), 1.41 (3H, t, J = 7.8 Hz), 3.00 (2H, q, J = 7.8 Hz), 4.32–4.42 (2H, m), 4.47-4.55 (1H, m), 7.06 (1H, dd, J = 0.9, 2.4 Hz), 7.33 (1H, dd, J = 0.9, 9.0 Hz), 7.53 (1H, d, J = 9.0 Hz), 7.72 (1H, d, J = 2.4 Hz); FAB-MS m/z 245 [(M+H)$^+$].

5.1.30. (2*R*)-1-(3-Propyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-ol (4m). Compound **4m** was prepared from **3m** using a procedure similar to that described for **4a**, in 28% yield. ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, J = 7.5 Hz), 1.30 (3H, d, J = 6.0 Hz), 1.79–1.91 (2H, m), 2.96 (2H, t, J = 7.5 Hz), 4.34–4.42 (2H, m), 4.48–4.58 (1H, m), 7.07 (1H, d, J = 2.1 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.54 (1H, d, J = 9.0 Hz), 7.72 (1H, d, J = 2.1 Hz); FAB-MS m/z 259 [(M+H)$^+$].

5.1.31. (2*R*)-1-(3-Methoxy-1*H*-furo[2,3-*g*]indazol-1-yl) ropan-2-ol (4p). Compound **4p** was prepared from **3p** using a procedure similar to that described for **4a**, in 44% yield. ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, J = 6.3 Hz), 3.57 (1H, s), 4.09 (3H, s), 4.19–4.44 (3H, m), 7.01 (1H, dd, J = 0.9, 2.1 Hz), 7.27 (1H, dd, J = 0.9, 8.7 Hz), 7.51 (1H, d, J = 8.7 Hz), 7.70 (1H, d, J = 2.1 Hz); FAB-MS m/z 247 [(M+H)$^+$].

5.1.32. (2*R*)-1-(1*H*-Thieno[2,3-*g*]indazol-1-yl)propan-2-ol (4r). Compound **4r** was prepared from **3r** using a procedure similar to that described for **4a**, in 15% yield. ^{1}H NMR (DMSO-d_6) δ 1.10 (3H, d, J = 6.4 Hz), 4.03–4.17 (1H, m), 4.45–4.56 (1H, m), 4.60–4.73 (1H, m), 5.02 (1H, d, J = 5.2 Hz), 7.70–7.80 (2H, m), 7.91 (1H, d, J = 5.2 Hz), 8.04 (1H, d, J = 5.2 Hz), 8.25 (1H, s); FAB-MS m/z 233 [(M+H)$^+$].

5.1.33. (2*R*)-1-(1*H*-[1,3]Oxazolo[5,4-*g*]indazol-1-yl)propan-2-ol (4s). Compound **4s** was prepared from **3s** using a procedure similar to that described for **4a**, in 28% yield. ^{1}H NMR (DMSO-d_6) δ 1.05 (3H, d, J = 8.0 Hz), 4.20–4.33 (1H, m), 4.52–4.61 (1H, m), 4.63–4.74 (1H, m), 4.92 (1H, d, J = 8.1 Hz), 7.56 (1H, d, J = 9.0 Hz), 7.80 (1H, d, J = 9.0 Hz), 8.21 (1H, s), 8.87 (1H, s); FAB-MS m/z 218 [(M+H)$^+$].

5.1.34. 1-[(2*S*)-2-Azidopropyl]-5-fluoro-1*H*-indazole (6a). To a solution of **4a** (0.80 g, 4.1 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.7 mL, 12.3 mmol) and MsCl (0.47 mL, 6.2 mmol) at room temperature, and it was stirred at this temperature for 2 h. The mixture was poured into water and extracted with $CHCl_3$. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to give the crude **5a**.

The residue was dissolved in DMF (15 mL) without further purification. To this solution was added NaN_3 (0.78 g, 12 mmol), and the mixture was stirred at 70 °C for 17 h. After cooling to room temperature, the mixture was poured into water and extracted with Et_2O. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to yield **6a** (0.83 g, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, J = 6.8 Hz), 4.07–4.15 (1H, m), 4.29–4.40 (2H, m), 7.17–7.22 (1H, m), 7.35 (1H, dd, J = 2.0, 8.6 Hz), 7.41 (1H, dd, J = 4.0, 9.0 Hz), 8.00 (1H, d, J = 0.8 Hz); FAB-MS m/z 220 [(M+H)$^+$].

5.1.35. 1-[(2*S*)-2-Azidopropyl]-6-fluoro-1*H*-indazole (6b). Compound **6b** was prepared from **4b** using a procedure similar to that described for **6a**, in 97% yield. ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, J = 7.2 Hz), 4.08–4.16 (1H, m), 4.23–4.36 (2H, m), 6.92–6.97 (1H, m), 7.09–7.12 (1H,

m), 7.67 (1H, dd, J = 5.6, 8.8 Hz), 8.01 (1H, d, J = 1.2 Hz); EI-MS m/z 219 [M^+].

5.1.36. 1-[(2*S*)-2-Azidopropyl]-6-methoxy-1*H*-indazole (6e). Compound **6e** was prepared from **4e** using a procedure similar to that described for **6a**, in 80% yield. ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, d, J = 6.6 Hz), 3.83 (3H, s), 4.06–4.19 (1H, m), 4.42–4.46 (2H, m), 6.77 (1H, dd, J = 2.1, 9.0 Hz), 7.18–7.21 (1H, m), 7.61 (1H, d, J = 9.0 Hz), 7.98 (1H, s); FAB-MS m/z 232 [(M+H)$^+$].

5.1.37. 1-[(2*S*)-2-Azidopropyl]-7-chloro-6-methoxy-1*H*-indazole (6f). Compound **6f** was prepared from **4f** using a procedure similar to that described for **6a**, in 60% yield. ^{1}H NMR (DMSO-d_6) δ 1.23 (3H, d, J = 6.6 Hz), 3.95 (3H, s), 4.03–4.10 (1H, m), 4.73–4.76 (2H, m), 7.14 (1H, d, J = 9.0 Hz), 7.75 (1H, d, J = 9.0 Hz), 8.14 (1H, s); FAB-MS m/z 266 [(M+H)$^+$].

5.1.38. 1-[(2*S*)-2-Azidopropyl]-7-methyl-1*H*-furo[2,3-*g*]indazole (6h). To a mixture of 60% NaH (213 mg, 5.34 mmol) and DMF (10 mL) was added **3h** (835 mg, 4.85 mmol) at 0 °C, and it was stirred at this temperature for 0.5 h. To the reaction mixture was added (*R*)-propylene oxide (0.41 mL, 5.82 mmol) at 0 °C, and it was stirred at room temperature for 70 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3) to yield a mixture of **3h** and **4h** (700 mg).

This mixture was dissolved with $CHCl_3$ (25 mL). To the solution were added triethylamine (1.26 mL, 9.12 mmol) and MsCl (0.35 mL, 4.56 mmol) at 0 °C, and it was stirred at room temperature for 1 h. The mixture was poured into water and extracted with $CHCl_3$. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to give the crude **5h** which was used in the next step without further purification.

The crude **5h** was dissolved in DMF (15 mL). To this solution was added NaN_3 (0.98 g, 15 mmol), and the mixture was stirred at 80 °C for 15 h. After cooling to room temperature, the mixture was poured into water and extracted with Et_2O. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to yield the crude product, which was purified by column chromatography on silica gel (AcOEt/hexane = 1:10) to give **6h** (510 mg, 41% from **3h**) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.30 (3H, d, J = 6.9 Hz), 2.52 (3H, s), 4.05–4.20 (1H, m), 4.50–4.75 (2H, m), 7.15 (1H, s), 7.36 (1H, d, J = 8.7 Hz), 7.57 (1H, d, J = 8.7 Hz), 8.15 (1H, s); FAB-MS m/z 256 [(M+H)$^+$].

5.1.39. 1-[(2*S*)-2-Azidopropyl]-7-ethyl-1*H*-furo[2,3-*g*]indazole (6i). Compound **6i** was prepared from **4i** using a procedure similar to that described for **6a**, in 76% yield. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J = 6.6 Hz), 1.37 (3H, t, J = 7.8 Hz), 2.85 (2H, q, J = 7.8 Hz), 4.05–4.22 (1H, m), 4.43–4.56 (2H, m), 6.64 (1H, s), 7.28 (1H, d, J = 8.7 Hz), 7.47 (1H, d, J = 8.7 Hz), 8.03 (1H, s); FAB-MS m/z 270 [(M+H)$^+$].

5.1.40. 1-[(2*S*)-2-Azidopropyl]-3-methyl-1*H*-furo[2,3-*g*]indazole (6k). Compound **6k** was prepared from **4k** using a procedure similar to that described for **6a**, in 68% yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6.3 Hz), 2.58 (3H, s), 4.07–4.20 (1H, m), 4.43 (1H, d, J = 6.3 Hz), 7.03 (1H, d, J = 2.1 Hz), 7.32 (1H, d, J = 8.7 Hz), 7.46 (1H, d, J = 8.7 Hz), 7.69 (1H, d, J = 2.1 Hz); FAB-MS m/z 256 [(M+H)$^+$].

5.1.41. 1-[(2*S*)-2-Azidopropyl]-3-ethyl-1*H*-furo[2,3-*g*]indazole (6l). Compound **6l** was prepared from **4l** using a procedure similar to that described for **6a**, in 81% yield. ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, J = 6.6 Hz), 1.41 (3H, t, J = 7.5 Hz), 3.02 (2H, q, J = 7.5 Hz), 4.08–4.24 (1H, m), 4.48 (2H, d, J = 6.6 Hz), 7.07 (1H, dd, J = 0.9, 2.1 Hz), 7.34 (1H, dd, J = 0.9, 8.7 Hz), 7.54 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 2.1 Hz); FAB-MS m/z 270 [(M+H)$^+$].

5.1.42. 1-[(2*S*)-2-Azidopropyl]-3-propyl-1*H*-furo[2,3-*g*]indazole (6m). Compound **6m** was prepared from **4m** using a procedure similar to that described for **6a**, in 81% yield. ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, J = 7.5 Hz), 1.32 (3H, d, J = 6.6 Hz), 1.79–1.93 (2H, m), 2.97 (2H, t, J = 7.5 Hz), 4.09–4.20 (2H, m), 4.48 (2H, d, J = 6.6 Hz), 7.07 (1H, dd, J = 0.9, 2.4 Hz), 7.34 (1H, dd, J = 0.9, 8.7 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 2.4 Hz); FAB-MS m/z 284 [(M+H)$^+$].

5.1.43. 1-[(2*S*)-2-Azidopropyl]-3-methoxy-1*H*-furo[2,3-*g*]indazole (6p). Compound **6p** was prepared from **4p** using a procedure similar to that described for **6a**, in 88% yield. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J = 6.4 Hz), 4.10 (3H, s), 4.11–4.60 (1H, m), 4.28–4.38 (1H, m), 6.99–7.03 (1H, m), 7.26 (1H, dd, J = 1.2, 8.8 Hz), 7.50 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 2.0 Hz); FAB-MS m/z 272 [(M+H)$^+$].

5.1.44. 1-[(2*S*)-2-Azidopropyl]-1*H*-thieno[2,3-*g*]indazole (6r). Compound **6r** was prepared from **4r** using a procedure similar to that described for **6a**, in 88% yield. ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, d, J = 6.6 Hz), 3.98–4.08 (1H, m), 4.10–4.24 (1H, m), 4.69–4.88 (2H, m), 7.70–7.78 (2H, m), 7.94 (1H, d, J = 5.4 Hz), 8.06 (1H, d, J = 5.4 Hz), 8.20 (1H, s); FAB-MS m/z 258 [(M+H)$^+$].

5.1.45. 1-[(2*S*)-2-Azidopropyl]-1*H*-[1,3]oxazolo[5,4-*g*]indazole (6s). Compound **6s** was prepared from **4s** using a procedure similar to that described for **6a**, in 56% yield. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, d, J = 8.8 Hz), 4.24–4.32 (1H, m), 4.77–4.83 (2H, m), 7.61 (1H, d, J = 9.0 Hz), 7.84 (1H, d, J = 9.0 Hz), 8.29 (1H, s), 8.90 (1H, s); EI-MS m/z 242 [M^+].

5.1.46. (2*S*)-1-(5-Fluoro-1*H*-indazol-1-yl)propan-2-amine (7a). To a stirred suspension of $LiAlH_4$ (218 mg, 5.74 mmol) in THF (10 mL) was added a solution of **6a** (630 mg, 2.87 mmol) in THF (5 mL) at 0 °C, and it was stirred at room temperature for 1 h. The excess reagent was quenched by the addition of MeOH, followed

by the addition of water (0.22 mL), 15% aqueous NaOH (0.22 mL), and water (0.66 mL). After stirring for 1 h, the resulting mixture was filtered through Celite and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to yield **7a** (393 mg; 72%). This compound was subsequently converted to its hydrochloride to yield a white solid (mp 185–186 °C). ^{1}H NMR (DMSO-d_6) δ 1.19 (3H, d, J = 6.4 Hz), 3.63–3.74 (1H, m), 4.54–4.75 (2H, m), 7.33–7.39 (1H, m), 7.58 (1H, dd, J = 2.0, 9.2 Hz), 7.86 (1H, dd, J = 4.4, 9.2 Hz), 8.15 (1H, s), 8.36 (3H, br s); FAB-MS m/z 194 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{12}N_3F$·HCl: C, 52.29; H, 5.70; N, 18.29; Cl, 15.44; F, 8.27. Found: C, 52.18; H, 5.72; N, 18.27; Cl, 15.25; F, 8.41.

5.1.47. (2*S*)-1-(6-Fluoro-1*H*-indazol-1-yl)propan-2-amine (7b). Compound **7b** was prepared from **6b** using a procedure similar to that described for **7a**, in 65% yield. This compound was subsequently converted to its hydrochloride to yield a white solid (mp 160–161 °C). ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, d, J = 6.4 Hz), 3.43–3.47 (1H, m), 4.50–4.70 (2H, m), 7.04–7.09 (1H, m), 7.72 (1H, dd, J = 2.4, 9.8 Hz), 7.84 (1H, dd, J = 4.8, 9.0 Hz), 8.18 (1H, s), 8.34 (3H, br s); EI-MS m/z 193 [M$^+$]. Anal. Calcd for $C_{10}H_{12}N_3F$·HCl: C, 52.29; H, 5.70; N, 18.29; Cl, 15.44; F, 8.27. Found: C, 52.46; H, 5.68; N, 18.11; Cl, 15.36; F, 8.47.

5.1.48. (2*S*)-1-(5,6-Dichloro-1*H*-indazol-1-yl)propan-2-amine (7c). To a solution of **4c** (468 mg, 1.91 mmol) in CH_2Cl_2 (20 mL) were added triethylamine (1.06 mL, 7.64 mmol) and MsCl (438 mg, 3.82 mmol) at 0 °C, and it was stirred at room temperature for 0.5 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to give the crude **5c** which was used in the next step without further purification.

The crude **5c** was dissolved in DMF (10 mL), to which NaN_3 (373 g, 5.73 mmol) was added. This mixture was then stirred at 80 °C for 8 h. After cooling to room temperature, the mixture was poured into water and extracted with AcOEt. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. Removal of the solvent gave the crude **6c** which was used in the next step without further purification.

To a stirred suspension of $LiAlH_4$ (144 mg, 3.82 mmol) in THF (5 mL) was added a solution of the crude **6c** in THF (10 mL) at 0 °C, and it was stirred at room temperature for 0.5 h. The excess reagent was quenched by the addition of MeOH, followed by the addition of water (0.15 mL), 15% aqueous NaOH (0.15 mL), and additional water (0.45 mL). After stirring for 0.5 h, the mixture was filtered through Celite, and then concentrated in vacuo to yield the crude product, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 10:1:0.1) to yield **7c** (393 mg; 85% from **4c**). This compound was subsequently converted to its fumarate to yield a white solid (mp 157–160 °C). ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, d, J = 6.8 Hz), 3.50–3.61 (1H, m), 4.42–4.59 (2H, m), 6.49 (2H, s), 8.11 (1H, s), 8.16 (1H, s), 8.21 (1H, s); FAB-MS m/z 244 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{11}N_3Cl_2$·$C_4H_4O_4$: C, 46.68; H, 4.20; N, 11.67; Cl, 19.69. Found: C, 47.12; H, 4.05; N, 11.71; Cl, 18.17.

5.1.49. (2*S*)-1-(6,7-Dichloro-1*H*-indazol-1-yl)propan-2-amine (7d). Compound **7d** was prepared from **3d** using a procedure similar to that described for **7c**, in 57% yield. This compound was subsequently converted to its hemifumarate to yield a white solid (mp 183–185 °C). ^{1}H NMR (DMSO-d_6) δ 1.01 (3H, d, J = 6.4 Hz), 3.50–3.61 (1H, m), 4.58–4.73 (2H, m) 7.37 (1H, d, J = 8.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 8.25 (1H, s); FAB-MS m/z 244 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{11}N_3Cl_2$·0.5$C_4H_4O_4$: C, 47.70; H, 4.34; N, 13.91; Cl, 23.27. Found: C, 47.82; H, 4.15; N, 13.93; Cl, 23.27.

5.1.50. (2*S*)-1-(6-Methoxy-1*H*-indazol-1-yl)propan-2-amine (7e). Compound **7e** was prepared from **6e** using a procedure similar to that described for **7a**, in 86% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 138–139 °C). ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, d, J = 6.4 Hz), 3.55–3.66 (1H, m), 3.85 (3H, s), 4.43 (1H, dd, J = 6.8, 14 Hz), 4.55 (1H, dd, J = 6.0, 14 Hz), 6.48 (2H, s), 6.77 (1H, dd, J = 2.0, 8.8 Hz), 7.23–7.25 (1H, m), 7.62 (1H, d, J = 8.8 Hz), 7.99 (1H, s); FAB-MS m/z 206 [(M+H)$^+$]. Anal. Calcd for $C_{11}H_{15}N_3O$·$C_4H_4O_4$·0.1H_2O: C, 55.76; H, 5.99; N, 13.00. Found: C, 55.76; H, 5.90; N, 12.96.

5.1.51. (2*S*)-1-(7-Chloro-6-methoxy-1*H*-indazol-1-yl)propan-2-amine (7f). To a solution of **6f** (260 mg, 0.98 mmol) in THF (20 mL) was added PPh_3 (308 mg, 1.18 mmol) at room temperature, and it was stirred at 50 °C for 5 h. To the mixture was added H_2O (0.5 mL), and it was stirred at 50 °C for 15 h. The resulting mixture was concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 30:1:0.1) to yield **7f** (222 mg; 95%). This compound was subsequently converted to its fumarate to yield a white solid (mp 166–168 °C). ^{1}H NMR (DMSO-d_6) δ 1.04 (3H, d, J = 6.4 Hz), 3.51–3.61 (1H, m), 3.95 (3H, s), 4.68–4.78 (2H, m), 6.47 (2H, s), 7.14 (1H, d, J = 9.2 Hz), 7.75 (1H, d, J = 9.2 Hz), 8.13 (1H, s); FAB-MS m/z 240 [(M+H)$^+$]. Anal. Calcd for $C_{11}H_{14}N_3OCl$·$C_4H_4O_4$·0.4H_2O: C, 49.63; H, 5.22; N, 11.58; Cl, 9.77. Found: C, 49.48; H, 4.97; N, 11.54; Cl, 9.73.

5.1.52. (2*S*)-1-(1*H*-Furo[2,3-*g*]indazol-1-yl)propan-2-amine (7g). Compound **7g** was prepared from **4g** using a procedure similar to that described for **7c**, in 47% yield. This compound was subsequently converted to its dihydrochloride to yield a white solid (mp 209–210 °C). ^{1}H NMR (DMSO-d_6) δ 1.11 (3H, d, J = 6.8 Hz), 3.65–3.78 (1H, m), 4.75–4.96 (2H, m), 7.48 (1H, d, J = 8.8 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.84 (1H, d, J = 2.0 Hz), 8.17 (1H, d, J = 2.0 Hz), 8.57 (3H, br s); FAB-MS m/z 216 [(M+H)$^+$]. Anal. Calcd for $C_{12}H_{13}N_3O$·2HCl·0.1C_2H_6O: C, 50.05; H, 5.37; N, 14.35; Cl, 24.22. Found: C, 50.06; H, 5.39; N, 14.28; Cl, 23.99.

5.1.53. (2*S*)-1-(7-Methyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7h). Compound **7h** was prepared from **6h** using a procedure similar to that described for **7f**, in 98% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 191–197 °C). ^{1}H NMR (DMSO-d_6) δ 1.05 (3H, d, J = 6.0 Hz), 2.52 (3H, s), 3.54–3.66 (1H, m), 4.55–4.63 (1H, m), 4.62–4.68 (1H, m), 6.51 (2H, s), 7.26 (1H, s), 7.37 (1H, d, J = 8.8 Hz), 7.57 (1H, d, J = 8.8 Hz), 8.14 (1H, s); FAB-MS m/z 230 [(M+H)$^+$]. Anal. Calcd for $C_{13}H_{15}N_3O{\cdot}C_4H_4O_4{\cdot}0.1H_2O$: C, 58.82; H, 5.57; N, 12.10. Found: C, 58.62; H, 5.57; N, 12.20.

5.1.54. (2*S*)-1-(7-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7i). Compound **7i** was prepared from **6i** using a procedure similar to that described for **7a**, in 89% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 191–193 °C). ^{1}H NMR (DMSO-d_6) δ 1.05 (3H, d, J = 6.8 Hz), 1.33 (3H, t, J = 8.0 Hz), 2.86 (2H, q, J = 8.0 Hz), 3.55–3.68 (1H, m), 4.61 (1H, dd, J = 8.0, 14 Hz), 4.76 (1H, dd, J = 6.0, 14 Hz), 6.50 (2H, s), 7.28 (1H, s), 7.38 (1H, d, J = 8.8 Hz), 7.58 (1H, d, J = 8.8 Hz), 8.15 (1H, s); FAB-MS m/z 244 [(M+H)$^+$]. Anal. Calcd for $C_{14}H_{17}N_3O{\cdot}C_4H_4O_4$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.13; H, 5.83; N, 12.60.

5.1.55. (2*S*)-1-(7-Isopropyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7j). Compound **7j** was prepared from **3j** using a procedure similar to that described for **7q**, in 17% yield. This compound was subsequently converted to its dihydrochloride to yield a white solid (mp 243–249 °C). ^{1}H NMR (DMSO-d_6) δ 1.10 (3H, d, J = 6.8 Hz), 1.37 (3H, d, J = 7.6 Hz), 3.10–3.22 (1H, m), 3.61–3.79 (1H, m), 4.77 (1H, dd, J = 8.8, 14 Hz), 4.92 (1H, dd, J = 6.4, 14 Hz), 7.40 (1H, d, J = 8.8 Hz), 7.52 (1H, s), 7.59 (1H, d, J = 8.8 Hz), 8.44 (1H, s), 8.68 (1H, br s), 10.29 (1H, br s); FAB-MS m/z 258 [(M+H)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O{\cdot}2HCl{\cdot}0.3H_2O$: C, 53.67; H, 6.49; N, 12.52; Cl, 21.12. Found: C, 53.96; H, 6.36; N, 12.50; Cl, 20.93.

5.1.56. (2*S*)-1-(3-Methyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7k). Compound **7k** was prepared from **6k** using a procedure similar to that described for **7f**, in 84% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 172–174 °C). ^{1}H NMR (DMSO-d_6) δ 1.07 (3H, d, J = 6.4 Hz), 3.17 (3H, s), 3. 56–3.68 (1H, m), 4.54–4.63 (1H, m), 4.65–4.75 (1H, m), 6.50 (2H, s), 7.42 (1H, d, J = 8.8 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.62–7.63 (1H, m), 8.12 (1H, d, J = 2.0 Hz); FAB-MS m/z 230 [(M+H)$^+$]. Anal. Calcd for $C_{13}H_{15}N_3O{\cdot}C_4H_4O_4{\cdot}H_2O$: C, 56.19; H, 5.82; N, 11.56. Found: C, 56.39; H, 5.81; N, 11.36.

5.1.57. (2*S*)-1-(3-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7l). Compound **7l** was prepared from **6l** using a procedure similar to that described for **7f**, in 61% yield. This compound was subsequently converted to its dihydrochloride to yield a white solid [mp >195 °C (dec)]. ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, d, J = 6.4 Hz), 1.34 (3H, t, J = 8.0 Hz), 2.97 (2H, q, J = 8.0 Hz), 3.62–3.75 (1H, m), 4.66–4.74 (1H, m), 4.78–4.86 (1H, m), 6.79 (2H, br s), 7.43 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 9.0 Hz), 7.78–7.79 (1H, m), 8.14 (1H, d, J = 2.0 Hz), 8.52 (3H, br s); FAB-MS m/z 244 [(M+H)$^+$]. Anal. Calcd for $C_{14}H_{17}N_3O{\cdot}1.9HCl{\cdot}0.8H_2O$: C, 51.42; H, 6.32; N, 12.85; Cl, 20.60. Found: C, 51.50; H, 6.34; N, 12.74; Cl, 20.65.

5.1.58. (2*S*)-1-(3-Propyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7m). Compound **7m** was prepared from **6m** using a procedure similar to that described for **7f**, in 48% yield. This compound was subsequently converted to its dihydrochloride to yield a white solid (mp 191–193 °C). ^{1}H NMR (DMSO-d_6) δ 0.95 (3H, d, J = 8.7 Hz), 1.11 (3H, t, J = 6.4 Hz), 1.73–1.82 (2H, m), 2.92 (2H, t, J = 8.7 Hz), 3.62–3.75 (1H, m), 4.65–4.73 (1H, m), 4.78–4.85 (1H, m), 5.74 (2H, br s), 7.43 (1H, d, J = 8.8 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.74–7.77 (1H, m), 8.15 (1H, d, J = 2.4 Hz), 8.47 (3H, br s); FAB-MS m/z 258 [(M+H)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O{\cdot}1.8HCl{\cdot}0.8H_2O$: C, 53.40; H, 6.69; N, 12.46; Cl, 18.92. Found: C, 53.19; H, 6.58; N, 12.49; Cl, 18.78.

5.1.59. (2*S*)-1-(7-Ethyl-3-methyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7n). Compound **7n** was prepared from **3n** using a procedure similar to that described for **7q**, in 42% yield. This compound was subsequently converted to its hydrochloride to yield a white solid [mp >245 °C (dec)]. ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, d, J = 6.6 Hz), 1.34 (3H, t, J = 7.5 Hz), 2.51 (3H, s), 2.87 (2H, q, J = 7.5 Hz), 3.60–3.75 (1H, m), 4.63 (1H, dd, J = 7.9, 14 Hz), 4.74 (1H, dd, J = 5.7, 14 Hz), 7.31–7.39 (2H, m), 7.53 (1H, d, J = 9.0 Hz), 8.39 (3H, br s); FAB-MS m/z 258 [(M+H)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O{\cdot}1.05HCl{\cdot}0.2H_2O$: C, 60.21; H, 6.89; N, 14.04; Cl, 12.44. Found: C, 60.29; H, 6.84; N, 14.03; Cl, 12.34.

5.1.60. (2*S*)-1-(3,7-Diethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7o). Compound **7o** was prepared from **3o** using a procedure similar to that described for **7q**, in 33% yield. This compound was subsequently converted to its hydrochloride to yield a white solid [mp >215 °C (dec)]. ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, d, J = 6.6 Hz), 1.33 (3H, t, J = 7.5 Hz), 1.35 (3H, t, J = 7.5 Hz), 2.87 (2H, q, J = 7.5 Hz), 2.94 (2H, q, J = 7.5 Hz), 3.60–3.76 (1H, m), 4.65 (1H, dd, J = 8.3, 14 Hz), 4.78 (1H, dd, J = 5.7, 14 Hz), 7.32–7.40 (2H, m), 7.55 (1H, d, J = 9.0 Hz), 8.46 (3H, br s); FAB-MS m/z 272 [(M+H)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O{\cdot}HCl{\cdot}0.3H_2O$: C, 61.35; H, 7.27; N, 13.42; Cl, 11.32. Found: C, 61.21; H, 7.14; N, 13.30; Cl, 11.41.

5.1.61. (2*S*)-1-(3-Methoxy-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7p). Compound **7p** was prepared from **6p** using a procedure similar to that described for **7f**, in 64% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 160–162 °C). ^{1}H NMR (DMSO-d_6) δ 1.13 (3H, d, J = 6.4 Hz), 3.60–3.71 (3H, m), 4.04 (1H, s), 4.53 (1H, dd, J = 8.0, 14 Hz), 4.63 (1H, dd, J = 6.0, 14 Hz), 6.55 (2H, s), 7.36 (1H, d, J = 8.8 Hz), 7.48 (1H, d, J = 8.8 Hz), 7.63 (1H, d, J = 2.0 Hz), 8.13 (1H, d, J = 2.0 Hz); FAB-MS

m/*z* 246 [(M+H)$^+$]. Anal. Calcd for $C_{13}H_{15}N_3O_2 \cdot C_4H_4O_4 \cdot 1.2H_2O$: C, 53.32; H, 5.63; N, 10.97;. Found: C, 53.25; H, 5.39; N, 10.74.

5.1.62. (2*S*)-1-(7-Ethyl-3-methoxy-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine (7q). To a solution of **3q** (295 mg, 1.36 mmol) in DMSO (10 mL) were added (2*S*)-2-[(*tert*-butoxycarbonyl)amino]propyl 4-methylbenzenesulfonate (674 mg, 2.04 mmol) and Cs_2CO_3 (889 mg, 2.72 mmol) at room temperature, and the mixture was stirred at 60 °C for 7 h. After cooling to room temperature, the mixture was poured into ice-water and extracted with AcOEt. The organic extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:5) to yield **8q**.

To a solution of **8q** in AcOEt (5 mL) was added 4 M HCl–AcOEt (5 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. After removal of the solvent, to the residue was added saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 30:1:0.1) to yield **7q** (201 mg, 66%). This compound was subsequently converted to its fumarate to yield a white solid (mp 202–205 °C). ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, d, J = 6.4 Hz), 1.32 (3H, t, J = 7.6 Hz), 2.85 (2H, q, J = 7.6 Hz), 3.50–3.66 (1H, m), 4.02 (1H, s), 4.43 (1H, dd, J = 7.6, 14 Hz), 4.55 (1H, dd, J = 6.0, 14 Hz), 6.50 (2H, s), 7.21 (1H, s), 7.27 (1H, d, J = 8.8 Hz), 7.39 (1H, d, J = 8.8 Hz); FAB-MS *m*/*z* 274 [(M+H)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4$: C, 58.60; H, 5.95; N, 10.79;. Found: C, 58.44; H, 5.86; N, 10.79.

5.1.63. (2*S*)-1-(1*H*-Thieno[2,3-*g*]indazol-1-yl)propan-2-amine (7r). Compound **7r** was prepared from **6r** using a procedure similar to that described for **7f**, in 71% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 179–181 °C). ^{1}H NMR (DMSO-d_6) δ 1.05 (3H, d, J = 6.4 Hz), 3.50–3.66 (1H, m), 4.65–4.80 (2H, m), 6.49 (2H, s), 7.69–7.79 (2H, m), 7.95 (1H, d, J = 6.0 Hz), 8.13 (1H, d, J = 5.2 Hz), 8.19 (1H, s); FAB-MS *m*/*z* 232 [(M+H)$^+$]. Anal. Calcd for $C_{12}H_{13}N_3S \cdot 1.1C_4H_4O_4 \cdot 0.25H_2O$: C, 54.19; H, 4.96; N, 11.56; S, 8.82. Found: C, 53.95; H, 4.67; N, 11.54; S, 8.82.

5.1.64. (2*S*)-1-(1*H*-[1,3]Oxazolo[5,4-*g*]indazol-1-yl)propan-2-amine (7s). Compound **7s** was prepared from **6s** using a procedure similar to that described for **7f**, in 78% yield. This compound was subsequently converted to its fumarate to yield a white solid (mp 160–162 °C). ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, d, J = 6.4 Hz), 3.74–3.86 (1H, m), 4.78–4.86 (2H, m), 6.49 (2H, s), 7.61 (1H, d, J = 8.8 Hz), 7.84 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.91 (1H, s); FAB-MS *m*/*z* 217 [(M+H)$^+$]. Anal. Calcd for $C_{11}H_{12}N_4O \cdot 1.2C_4H_4O_4 \cdot 0.1H_2O$: C, 53.11; H, 4.80; N, 15.68. Found: C, 53.10; H, 5.16; N, 15.51.

5.1.65. 4,5-Dichloro-2-methylaniline (9c). To a mixture of 3, 4-dichlorotoluene **10** (16.1 g, 100 mmol) and conc. H_2SO_4 (160 mL) was added portionwise KNO_3 (7.0 g, 126 mmol) at 5 °C, and the resulting mixture was stirred at room temperature for 2 h. After cooling to 0 °C, the mixture was poured into ice-water. The resulting precipitate was collected with filtration and dried in vacuo to yield an orange solid. This orange solid was dissolved in Et_2O, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:100) to yield 3, 4-dichloro-6-nitrotoluene (17.8 g, 86%) as a slightly yellow solid.

To a mixture of 3, 4-dichloro-6-nitrotoluene (9.20 g, 44.7 mmol), conc. HCl (40 mL), and EtOH (40 mL) was added a solution of $SnCl_2 \cdot 2H_2O$ (50 g, 222 mmol) in concd HCl (40 mL), and the mixture was stirred at room temperature for 17 h. The reaction was quenched with aqueous NaOH solution and extracted with $CHCl_3$. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **9c** (7.0 g, 88%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, s), 3.63 (2H, br s), 6.73 (1H, s), 7.09 (1H, s); EI-MS *m*/*z* 175 [M$^+$].

5.1.66. 5,6-Dichloro-2-methylaniline (9d). To a mixture of **13** (6.55 g, 25.2 mmol) and ethylene glycol (200 mL) was added KOH (7.0 g, 126 mmol), and the resulting mixture was heated at 170 °C for 7 h. After cooling to room temperature, the mixture was poured into water and extracted with AcOEt. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/toluene = 1:10) to yield **9d** (4.23 g, 95%) as pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 2.12 (3H, s), 5.36 (2H, s), 6.70 (3H, d, J = 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz); EI-MS *m*/*z* 175 [M$^+$].

5.1.67. *N*-(2,3-Dichlorophenyl)-2,2-dimethylpropanamide (12). To a mixture of 2,3-dichloroaniline **11** (25.0 g, 154 mmol) and K_2CO_3 (44 g, 318 mmol) in acetone (600 mL) was added pivaloyl chloride (19.5 g, 162 mmol), and the resulting mixture was refluxed for 8 h. The mixture was cooled to room temperature and then filtered through Celite. The filtrate was concentrated in vacuo and diluted with AcOEt. This solution was washed with 1 M aqueous HCl, H_2O, and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 3:1) to yield **12** (13.6 g, 37%) as a white solid. ^{1}H NMR (DMSO-d_3) δ 1.24 (9H, s), 7.35 (1H, t, J = 8.4 Hz), 7.46 (1H, dd, J = 1.6, 8.4 Hz), 7.50 (1H, dd, J = 1.6, 8.4 Hz), 9.16 (1H, s); FAB-MS *m*/*z* 246 [(M+H)$^+$].

5.1.68. *N*-(2,3-Dichloro-6-methylphenyl)-2,2-dimethylpropanamide (13). To a mixture of **12** (10.22 g, 38.7 mmol) and TMEDA (3.15 mL, 27.1 mmol) in *t*-BuOMe (100 mL) was added BuLi (62 mL, 1.55 M in hexane) over 20 min at −20 °C. After stirring at this temperature for 1 h, a solution of MeI (4.82 mL, 77.4 mmol) in *t*-BuOMe (10 mL) was added over 1 h at −20 °C. The reaction was quenched with ice-water

and the aqueous phase was extracted with Et_2O. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude product. This was then washed with *i*-Pr_2O to yield **13** (5.92 g, 59%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.37 (9H, s), 2.20 (3H, s), 7.08 (1H, d, J = 8.7 Hz), 7.15–7.23 (1H, m), 7.27 (1H, d, J = 8.7 Hz); FAB-MS *m*/*z* 260 [(M+H)$^+$].

5.1.69. 1*H*-Indazol-6-ol (15). To a mixture of **14** (2.13 g, 16.0 mmol), H_2SO_4 (16 mL), and H_2O (20 mL) was added dropwise a solution of $NaNO_2$ (1.21 g, 17.5 mmol) in H_2O (5 mL) at 0 °C. After stirring at this temperature for 0.5 h, the mixture was cautiously poured into boiling 10 M aqueous H_2SO_4 (70 mL). After boiling for 10 min, the mixture was diluted with water and cooled to room temperature. The resulting solution was extracted with AcOEt and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 1.78 g of crude product as brown solid. This crude product was recrystallized from *i*-PrOH–Et_2O to yield **15** (885 mg, 41%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 6.40 (1H, dd, J = 2.0, 8.4 Hz), 6.75–6.78 (1H, m), 7.52 (1H, d, J = 8.4 Hz), 7.86 (1H, s), 9.52 (1H, s), 13.42 (1H, br s); FAB-MS *m*/*z* 135 [(M+H)$^+$].

5.1.70. 7-Chloro-1*H*-indazol-6-ol (16). To a solution of **15** (2.50 g, 18.7 mmol) in dioxane (100 mL) was added NCS (2.74 g, 20.5 mmol), and the resulting mixture was heated at 60 °C for 12 h. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 30:1) to yield **16** (1.70 g, 54%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 6.84 (1H, d, J = 8.8 Hz), 7.51 (1H, d, J = 8.8 Hz), 7.97–7.99 (1H, m), 10.25 (1H, s), 13.08 (1H, br s); FAB-MS *m*/*z* 168 [(M+H)$^+$].

5.1.71. 6,7-Dihydro-1-benzofuran-4(5*H*)-one (18a). To a mixture of chloroacetaldehyde (40 mL, 40% in water) and $NaHCO_3$ (20 g, 240 mmol) in H_2O (160 mL) was added a solution of 1,3-cyclohexanedione **17** (22.4 g, 200 mmol) in H_2O (230 mL) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 70 h. Following the addition of AcOEt (200 mL), to the mixture was added H_2SO_4 in order to adjust the pH of the aqueous layer to 1. After 1 h, the mixture was extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to yield **18a** (16.4 g, 60%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.12–2.20 (2H, m), 2.57 (2H, t, J = 6.9 Hz), 2.78 (2H, t, J = 6.9 Hz), 6.42 (1H, d, J = 1.5 Hz), 7.56 (1H, d, J = 1.5 Hz); EI-MS *m*/*z* 136 [M$^+$].

5.1.72. 2-Methyl-6,7-dihydro-1-benzofuran-4(5*H*)-one (18b). To a solution of **17** (10.0 g, 89.2 mmol) in H_2O (45 mL) was added a solution of Triton B (37.9 mL, 40% in MeOH), followed by the addition of 2,3-dibromopropene (21.4 g, 107 mmol). This reaction mixture was stirred at room temperature for 6 days, and then diluted with water, followed by extraction with AcOEt. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by crystallization from *i*-Pr_2O to yield 2-(2-bromoprop-2-en-1-yl)cyclohexane-1,3-dione (10.5 g, 48%) as a white solid.

HCO_2H (300 mL) and $HClO_4$ (30 mL) were added to this product, and then the solution was stirred at 80 °C for 4 h. After cooling and removal of the solvent, to the residue was added H_2O, after which it was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:5) to yield **18b** (4.70 g, 70%) as pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 2.02–2.09 (2H, m), 2.26 (3H, s), 2.34–2.38 (2H, m), 2.82 (2H, t, J = 6.4 Hz), 6.25 (1H, d, J = 1.6 Hz); FAB-MS *m*/*z* 151 [(M+H)$^+$].

5.1.73. 2-Ethyl-6,7-dihydro-1-benzofuran-4(5*H*)-one (18c). To a mixture of 1-bromobutan-2-one (25.0 g, 166 mmol) and $NaHCO_3$ (55.8 g, 332 mmol) in MeOH (250 mL) and H_2O (500 mL) was added a solution of 1,3-cyclohexanedione **17** (37.1 g, 332 mmol) in H_2O (500 mL) dropwise at 0 °C. The resulting mixture was stirrred at room temperature for 65 h. Subsequently, 1 M aqueous HCl (500 mL) was added and the crude mixture was extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. To the crude residue was added H_2SO_4 (150 mL) dropwise at −20 °C. After stirring at room temperature for 15 min, the mixture was poured onto ice and extracted with AcOEt. The extracts were washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to yield **18c** (13.6 g, 50%) as pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.8 Hz), 2.10–2.21 (2H, m), 2.43–2.51 (2H, m), 2.63 (2H, q, J = 7.8 Hz), 2.83 (2H, t, J = 6.3 Hz), 6.25 (1H, s); FAB-MS *m*/*z* 165 [(M+H)$^+$].

5.1.74. 4,5-Dihydro-1*H*-furo[2,3-*g*]indazole (19a). To a suspension of *t*-BuOK (16.5 g, 146 mmol) in THF (200 mL) was added a solution of **18a** (10 g, 73 mmol) and HCO_2Et (23.7 mL, 292 mmol) in THF (150 mL) dropwise at 0 °C, and the resulting mixture was stirred at this temperature for 2 h. To the reaction mixture was added hydrazine monohydrate (3.9 mL, 81 mmol) and 1 M aqueous HCl (150 mL) at 0 °C, and it was stirred for 20 h at room temperature. The reaction mixture was extracted with AcOEt, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 30:1) to yield **19a** (8.51 g, 73%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.84–2.86 (4H, m), 6.63 (1H, d, J = 2.2 Hz), 7.43 (1H, s), 7.58 (1H, d, J = 1.8 Hz); EI-MS *m*/*z* 160 [M$^+$].

5.1.75. 7-Methyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (19b). Compound **19b** was prepared from **18b** using a procedure similar to that described for **19a** (59%). ^{1}H NMR (DMSO-d_6) δ 2.27 (3H, s), 2.77–2.83 (4H, m), 6.23

(1H, s), 7.40 (1H, s), 12.20 (1H, br s); FAB-MS *m*/*z* 175 [(M+H)$^+$].

5.1.76. 7-Ethyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (19c). To a suspension of *t*-BuOK (35.3 g, 314 mmol) in THF (400 mL) was added a solution of **18c** (25.8 g, 157 mmol) and HCO_2Et (50.6 mL, 628 mmol) in THF (300 mL) dropwise at 0 °C. The mixture was then stirred at this temperature for an additional 1.5 h. Subsequently, 1 M aqueous HCl (350 mL) was added, and the crude mixture was extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Without further purification the residue was dissolved in EtOH (600 mL). This solution was added dropwise to a solution of hydrazine monohydrate (9.08 mL, 187 mmol) in EtOH (600 mL) over a period of 1 h and then stirred at room temperature for an additional 17 h. After removal of the solvent, the residue was diluted with AcOEt and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to yield **19c** (23.5 g, 80%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.5 Hz), 2.66 (2H, q, J = 7.5 Hz), 2.88–2.94 (4H, m), 6.27 (1H, s), 7.27 (1H, s); FAB-MS *m*/*z* 189 [(M+H)$^+$].

5.1.77. 1-(4,5-Dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanone (20). To a solution of **19a** (5.0 g, 31.2 mmol) in AcOH (5 mL) was added TFAA (26.2 g, 125 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h, and then concentrated in vacuo. The residue was diluted with 15% aqueous NaOH and extracted with AcOEt. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 100:1 to 10:1), and then was washed with hot ethanol to yield **20** (1.74 g, 28%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.42 (3H, s), 2.85–3.02 (4H, m), 7.51 (1H, s), 7.61 (1H, s); FAB-MS *m*/*z* 203 [(M+H)$^+$].

5.1.78. 3-Methyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (21a). To a suspension of 35% KH (1.35 g, 11.8 mmol) and 60% NaH (9.12 g, 228 mmol) in DME (300 mL) was added a solution of **18a** (6.20 g, 45.6 mmol) in DME (300 mL) at 0 °C. The resulting mixture was stirred at this temperature for 0.5 h, followed by addition of AcOEt (13.4 mL, 137 mmol). The resulting mixture was refluxed for 3 h. After cooling, it was diluted with AcOEt, and then washed with saturated aqueous NH_4Cl, water, and brine. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:10) to yield a pale yellow oil. To this compound were added EtOH (50 mL) and hydrazine monohydrate (3.60 mL, 74 mmol), and it was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with AcOEt, washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:5) to yield **21a** (2.32 g, 29%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s), 2.77–2.84 (2H, m), 2.89–2.97 (2H, m), 6.66 (1H, d, J = 1.8 Hz), 7.31–7.34 (1H, m); FAB-MS *m*/*z* 175 [(M+H)$^+$].

5.1.79. 3-Ethyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (21b). To a suspension of 35% KH (420 mg, 3.67 mmol) and 60% NaH (7.36 g, 184 mmol) in DME (200 mL) was added a solution of **18a** (5.0 g, 36.7 mmol) in DME (30 mL) at 0 °C. The resulting mixture was stirred at this temperature for 0.5 h, followed by the addition of ethyl propionate (12.7 mL, 111 mmol). The resulting mixture was refluxed for 1 h. After cooling, it was diluted with AcOEt, washed with saturated aqueous NH_4Cl, water, and brine. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:7) to yield a yellow oil. To this compound were added EtOH (50 mL) and hydrazine monohydrate (5.10 mL, 104 mmol), and it was stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo, diluted with AcOEt, washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3) to yield **21b** (5.85 g, 85%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.8 Hz), 2.63 (2H, q, J = 7.8 Hz), 2.80–2.96 (4H, m), 6.66 (1H, d, J = 2.4 Hz), 7.32 (1H, d, J = 2.4 Hz); FAB-MS *m*/*z* 189 [(M+H)$^+$].

5.1.80. 3-Propyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (21c). To a suspension of 35% KH (420 mg, 3.67 mmol) and 60% NaH (7.36 g, 184 mmol) in DME (200 mL) was added a solution of **18a** (5.0 g, 36.7 mmol) in DME (30 mL) at 0 °C. The resulting mixture was stirred at this temperature for 0.5 h, followed by addition of ethyl butyrate (14.5 mL, 111 mmol). The resulting mixture was refluxed for 2 h. After cooling, it was diluted with AcOEt, washed with saturated aqueous NH_4Cl, water, and brine. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to yield a yellow oil. To this compound was added EtOH (50 mL) and hydrazine monohydrate (7.13 mL, 147 mmol), and it was stirred for 12 h at room temperature. The reaction mixture was concentrated in vacuo, diluted with AcOEt, washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to yield **21c** (6.30 g, 85%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7.5 Hz), 1.58–1.70 (2H, m), 2.57 (2H, t, J = 7.5 Hz), 2.79–2.96 (4H, m), 6.58–6.62 (1H, m), 7.33 (1H, d, J = 2.1 Hz); FAB-MS *m*/*z* 203 [(M+H)$^+$].

5.1.81. 7-Ethyl-3-methyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (21d). Compound **21d** was prepared from **18c** using a procedure similar to that described for **21a**, in 16% yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.5 Hz), 2.25 (3H, s), 2.65 (2H, q, J = 7.5 Hz), 2.75–2.94 (4H, m), 6.26 (1H, s), 8.53 (1H, br s); FAB-MS *m*/*z* 203 [(M+H)$^+$].

5.1.82. 3,7-Diethyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (21e). Compound **21e** was prepared from **18c** using a procedure similar to that described for **21b**, in 14% yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.5 Hz), 1.26 (3H, t, J = 7.5 Hz), 2.60–2.70 (4H, m), 2.78–2.94 (4H, m), 6.25 (1H, s), 8.59 (1H, br s); FAB-MS m/z 217 [(M+H)$^+$].

5.1.83. Ethyl 4-oxo-4,5,6,7-tetrahydro-1-benzofuran-5-carboxylate (22a). To a solution of KHMDS (11.0 g, 55.1 mmol) in THF (100 mL) was added dropwise a solution of **18a** (3.00 g, 22.0 mmol) and THF (50 mL) at −40 °C, and it was stirred for 10 min. To the reaction mixture was added dropwise ethyl chloroformate (2.32 mL, 24.2 mmol) at −40 °C. It was stirred at this temperature for 0.5 h, and then at room temperature for 2 h. The reaction mixture was poured into ice-water, added 1 M HCl (200 mL), and then extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (AcOEt/toluene = 1:10) to yield **22a** (3.88 g, 85%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, J = 7.2 Hz), 2.14–2.62 (2H, m), 2.81–3.14 (2H, m), 3.45–3.53 (1H, m), 4.22 (1H, q, J = 7.2 Hz), 6.69 (1H, d, J = 2.1 Hz), 7.34 (1H, d, J = 2.1 Hz); FAB-MS m/z 209 [(M+H)$^+$].

5.1.84. Ethyl 2-ethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-5-carboxylate (22b). Compound **22b** was prepared from **18c** using a procedure similar to that described for **22a**, in 37% yield. ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 1.28 (3H, t, J = 7.2 Hz), 2.29–2.38 (1H, m), 2.49–2.58 (1H, m), 2.63 (1H, q, J = 7.2 Hz), 2.79–2.88 (1H, m), 2.97–3.06 (1H, m), 3.43–3.48 (1H, m), 4.22 (1H, q, J = 7.2 Hz), 6.26 (1H, s); FAB-MS m/z 237 [(M+H)$^+$].

5.1.85. 1,2,4,5-Tetrahydro-3*H*-furo[2,3-*g*]indazol-3-one (23a). To a solution of hydrazine monohydrate (0.78 mL, 15.9 mmol) in EtOH (30 mL) was added dropwise a solution of **22a** (3.00 g, 14.4 mmol) in EtOH (20 mL), and it was stirred for 14 h at room temperature. After removal of the solvent, the residue was washed with EtOH to yield **23a** (2.08 g, 82%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.66 (3H, t, J = 8.4 Hz), 2.83 (1H, d, J = 8.4 Hz), 6.54 (1H, s), 7.56 (1H, s); FAB-MS m/z 177 [(M+H)$^+$].

5.1.86. 7-Ethyl-1,2,4,5-tetrahydro-3*H*-furo[2,3-*g*]indazol-3-one (23b). Compound **23b** was prepared from **22b** using a procedure similar to that described for **23a**, in 84% yield as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.17 (3H, t, J = 7.5 Hz), 2.55–2.69 (4H, m), 2.72–2.81 (2H, m), 6.14 (1H, s), FAB-MS m/z 205 [(M+H)$^+$].

5.1.87. 4,5-Dihydro-1*H*-thieno[2,3-*g*]indazole (25). Compound **25** was prepared from **24** using a procedure similar to that described for **19a**, in 78% yield as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.80 (2H, t, J = 7.6 Hz), 2.94 (2H, t, J = 7.6 Hz), 7.26 (1H, d, J = 4.8 Hz), 7.36 (1H, d, J = 4.8 Hz), 7.50 (1H, s), 12.41 (1H, br s); EI-MS m/z 176 [M$^+$].

5.1.88. 7-Nitro-1*H*-indazol-6-ol (26). To a mixture of **15** (500 mg, 3.37 mmol) and H_2SO_4 (5.0 mL) was added KNO_3 (375 mg, 3.71 mmol) portionwise at 0 °C, and it was stirred at this temperature for 0.5 h. To the reaction mixture was added ice (70 g), and it was stirred at 0 °C for 1 h. The resulting precipitate was collected by filtration and rinsed with water to yield **26** (575 mg, 95%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 6.94 (1H, d, J = 8.4 Hz), 8.06 (1H, d, J = 8.4 Hz), 8.18 (1H, s), 11.60 (1H, br s); FAB-MS m/z 180 [(M+H)$^+$].

5.1.89. 7-Amino-1*H*-indazol-6-ol (27). To a solution of **26** (460 mg, 2.56 mmol) in AcOH (30 mL) was added Pd on carbon (10%, 50 mg). The mixture was stirred for 20 h under H_2 at 40 psi. The catalyst was removed by filtration through Celite and the solvent was removed in vacuo. The resulting residue was washed with *i*-Pr_2O to yield **27** (380 mg, 100%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 4.51 (2H, br s), 6.66 (1H, d, J = 8.4 Hz), 6.83 (1H, d, J = 8.4 Hz), 7.79 (1H, s), 8.40 (1H, br s), 12.24 (1H, br s); FAB-MS m/z 148 [(M+H)$^+$].

6. Biological procedures

6.1. Receptor binding assay

The membrane preparation was washed once with 50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$ just before it was used for the binding assays. The 5-HT_{2C} and 5-HT_{2A} receptor binding assays with [^{3}H]5-HT were carried out using the methods of Pazos et al.[20] with a slight modification; reaction medium [50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$, 10 μM pargyline, and 0.1 mg/mL L-(+)-ascorbic acid] containing [^{3}H]5-HT, membrane preparation, and test compounds was incubated at 37 °C for 30 min. Non-specific binding was determined in the presence of 10 μM 5-HT, and specific binding was calculated as total binding minus non-specific binding. After incubation, 4 mL of 50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$ was added, and the medium was filtered under vacuum through Whatman GF/B glass filter pre-treated with 0.1% polyethyleneimine. The filter was washed with the same buffer solution (4× 3 mL). The GF/B glass filter was immersed in 6 mL of liquid scintillator (Packard, Aquasol-2), and the radioactivities were measured with a liquid scintillation counter (Packard, Tri-Carb-2500TR). The amounts of protein were measured according to the method established by Lowry et al.[21] Dissociation constants (K_d value) were obtained by Scatchard analysis using SAS (ver. 6.11) together with an application software developed by our company (5-HT_{2C}; 1.6 nM and 5-HT_{2A}; 9.8 nM). Concentrations of compounds showing 50% inhibition of receptor binding, IC_{50} values, were obtained by non-linear analysis using SAS (ver. 6.11) together with an application software developed by our company. K_i values indicating affinity for receptors were calculated by using a formula developed by Cheng and Prussoff.[22]

6.2. PI hydrolysis assay

PI hydrolysis assay was carried out using the methods of Aramori and Nakanishi [23] with a slight modification. CHO cells expressing human 5-HT_{2C} or 5-HT_{2A} receptors and HEK 293-EBNA cells expressing 5-HT_{2B} receptors were seeded onto a 24-well plate (approximately 1×105 cells/well), and cultured for 1 day. After the addition of myo-[^{3}H]inositol (3 μCi/mL), they were incubated for 24 h for labeling. After the cells were washed two times with phosphate buffered saline (PBS), they were incubated with PBS for 20 min, and then further incubated with PBS–LiCl solution for 20 min. After 20 min incubation with PBS–LiCl solution containing the test compound, the reaction was terminated by adding 0.2 M PCA, after which the reaction mixture was allowed to stand at 4 °C for 1–3 h. After 2 M KOH and 100 mM EDTA-2Na solution were added, the plate was centrifuged (2000 rpm, 5 min). The supernatant (1 mL) was added to a Bio-Rad AG1-X8 column, and washed with GPI solution (5 mM disodium tetraborate, 60 mM sodium formate) (3.5× 2 mL), and eluted with 4 mL of IP3 solution (0.1 M formate, 1 M ammonium formate). The elute was added to a liquid scintillator (Aquasol-2) and measured with the liquid scintillation counter. EC_{50} values and E_{max} (%) were calculated by non-linear analysis using SAS (ver.6.11) together with an application software developed by our company. E_{max} (%) indicated intrinsic activity and the response produced by 10 μM 5-HT was defined as 100%.

6.3. Behavioral studies

All experiments were carried out during 13:00–19:00. Rats were placed individually in transparent acrylic plastic cages to count the number of penile erections. A penile erection was defined as previously described[24]: repeated pelvic thrusts immediately followed by assuming an upright position (on hind limbs), an emerging, engorged penis, and licking it. The number of penile erections was observed for 30 min immediately after test compounds sc or po administration.

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