Development of Novel 1,2,3,4-Tetrahydroisoquinoline Derivatives and Closely Related Compounds as Potent and Selective Dopamine D_3 Receptor Ligands

Ulrich R. Mach,[a] Anneke E. Hackling,[a] Sylvie Perachon,[b] Sandrine Ferry,[b] Camille G. Wermuth,[c] Jean-Charles Schwartz,[d] Pierre Sokoloff,[d] and Holger Stark*[a]

Based on N-*alkylated 1,2,3,4-tetrahydroisoquinoline derivatives, which are structurally related to the partial agonist BP 897, a series of novel, selective dopamine D_3 receptor antagonists has been synthesised. Derivatisation included changes in the arylamide moiety and the tetrahydroisoquinoline substructure leading to compounds with markedly improved selectivities and affinities in the low nanomolar concentration range. From the 55 structures presented here, (*E*)-3-(4-iodophenyl)-*N*-(4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butyl)acrylamide (**51**) has high affinity ($K_i(hD_3) = 12$ nM) and a 123-fold preference for the D_3 receptor relative to the D_2 receptor subtype. Its pharmacological profile offers the prospect of a novel radioligand as a tool for various dopamine D_3-receptor-related in vitro and in vivo investigations.*

Introduction

Classification of dopamine receptor subtypes distinguishes two G-protein-coupled receptor families: the D_1-like receptors, including D_1 and D_5 receptor subtypes, which activate adenylyl cyclase; and the D_2-like receptors comprising D_2, D_3 and D_4 receptor subtypes, which inhibit adenylyl cyclase.[1] Within the D_2-like receptors, the D_2 and D_3 subreceptors bear the highest amino acid sequence homology resulting in a pronounced likeness in binding behaviour.[2]

Dopamine receptor subtypes show distinct localisations in the central nervous system (CNS); this suggests specific functions for each subtype.[3] It has been shown that most clinically effective antipsychotic agents such as haloperidol (**1**) or pimozide (**2**) share high affinities for D_2 and D_3 receptor subtypes, indicating their prominent therapeutic relevance in this pathological process (although the atypical antipsychotic clozapine (**3**) shows a high affinity at D_4 receptors, clinical testing of D_4-receptor-selective ligands has brought about mainly unpromising results) (Scheme 1).[4–6] Typical antipsychotics have a number of serious adverse side effects, which are thought to be promoted by the blockade of dopamine receptors in the striatum where the D_2 receptor subtypes are predominantly located.[7] The dopamine D_3 receptor, however, is found in high abundance in the limbic system where blockade of dopamine receptors is incidental with a loss of acute schizophrenic symptoms. Additionally, this brain region is associated with other psychiatric or neurological disorders, such as Parkinson's disease or drug abuse.[8] A more profound knowledge of the pathological characteristics of these conditions requires the development of dopamine D_3-receptor-selective ligands, which primarily might be beneficial as pharmacological tools but also in the therapy of these diseases.[9, 10] Some antagonists with varying D_3 receptor preference have been identified, for example SB-277011 (**4**).[11] More recently, the antagonist phenylpiperazine derivative FAUC 365 (**5**) was reported, which has a remarkable 7200-fold selectivity for D_3 over D_2 receptors.[12, 13]

The aim of this study was the development of antagonist analogues of BP 897 (**6**), which is a partial agonist at dopamine D_3 receptors (Scheme 1).[8] To facilitate the determination of structure–activity relationships, we differentiated three elements in the key structure: 1) the lipophilic basic or amine

[a] Dr. U. R. Mach, A. E. Hackling, Prof. Dr. H. Stark
Institut für Pharmazeutische Chemie, Johann Wolfgang Goethe-Universität
Marie Curie Straße 9, 60439 Frankfurt am Main (Germany)
Fax: (+49) 69-798-29258
E-mail: h.stark@pharmchem.uni-frankfurt.de

[b] Dr. S. Perachon, Dr. S. Ferry
Laboratoire Bioprojet
30 rue des Francs-Bourgeois, 75003 Paris (France)

[c] Prof. Dr. C. G. Wermuth
Faculté de Pharmacie (CNRS), Université Louis Pateur
74 route de Rhin, 67401 Illkrich (France)

[d] Prof. Dr. J.-C. Schwartz, Dr. P. Sokoloff
Unité de Neurobiology et Pharmacologie Moléculaire
Centre Paul Broca de l'INSERM (U. 573)
2 ter rue d'Alésia, 75015 Paris (France)

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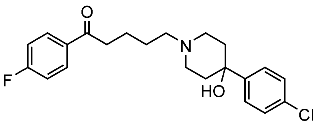
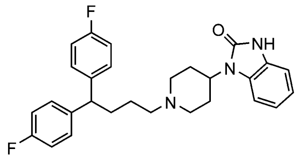
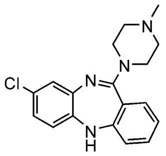
  DOI: 10.1002/cbic.200300784 ChemBioChem 2004, 5, 508–518



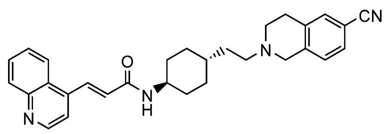
haloperidol (**1**)



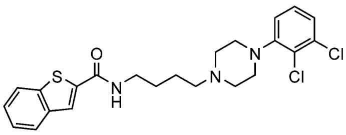
pimozide (**2**)



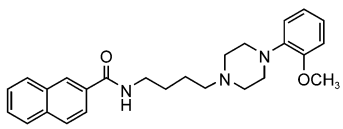
clozapine (**3**)



SB-277011 (**4**)



FAUC 365 (**5**)



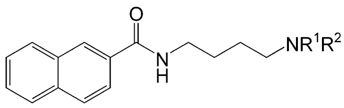
BP 897 (**6**)

moiety, a phenylpiperazine in BP 897, 2) the spacer, usually a linear tetramethylene chain, and 3) the hydrophobic residue, often connected through an amide bond, which has proven to be favourable for high receptor affinity and also allows various facile derivatisation reactions.

In order to evaluate structural requirements for high-affinity binding, the amine element was structurally reduced to the essential requirements of a basic nitrogen connected to an aryl group through an aliphatic linker. This phenylalkylamine scaffold was further diversified by introducing higher degrees of rigidity with varying geometry and hydrogen-bonding capabilities (**7** – **15**, Table 1).

Within this series, several structures displayed dopamine D_3 receptor affinities in the low nanomolar concentration range. 2-Aminoindane compounds have been reported as ligands with strongly diverging intrinsic activities,[14, 15] whereas 1,2,3,4-tetrahydroisoquinolines demonstrated mostly antagonist properties.[11, 16] Therefore, the 1,2,3,4-tetrahydroisoquinoline ring was chosen as the lead core structure for antagonist development.

Table 1. *Structures and receptor binding of compounds with amine variations.*



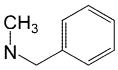
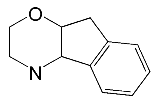
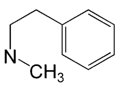
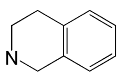
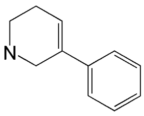
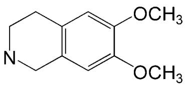
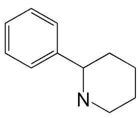
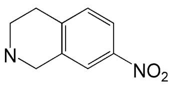
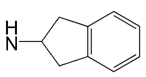
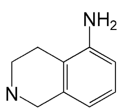
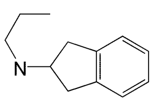
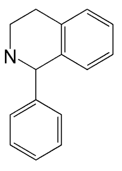
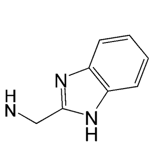
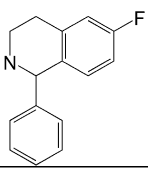
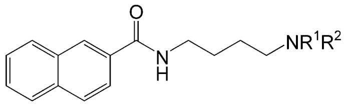
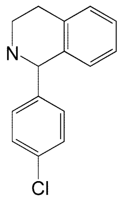
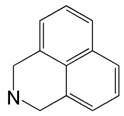
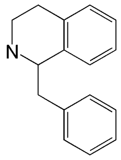
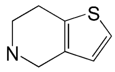
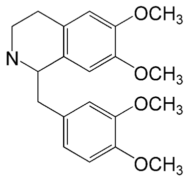
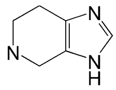
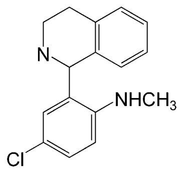
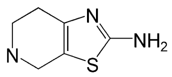
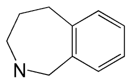
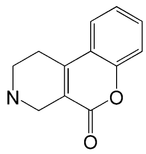
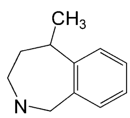
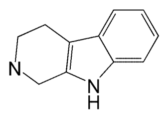
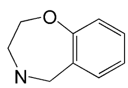
No.	NR^1R^2	Binding K_i ($\bar{x} \pm$ SEM)[a] [nM] D_2[b]	D_3[c]	$K_i(D_2)/K_i(D_3)$	No.	NR^1R^2	Binding K_i ($\bar{x} \pm$ SEM)[a] [nM] D_2[b]	D_3[c]	$K_i(D_2)/K_i(D_3)$
7		5000	6000	1	**14**		8400	10000	1
8		612 ± 84	123 ± 23	5	**15**		2200	98	23
9		540 ± 10	177 ± 16	3	**16**		840 ± 30	44 ± 7	19
10		1300 ± 110	1200 ± 170	1	**17**		1000	413 ± 84	3
11		1000 ± 400	70 ± 11	16	**18**		830 ± 93	42.7 ± 4.7	19
12		78 ± 32	5.7 ± 1.3	14	**19**		4500	2500	2
13		5500	1500 ± 300	4	**20**		8400	5600	2

Table 1. *(cont.)*



No.	NR^1R^2	Binding K_i ($\bar{x} \pm$ SEM)[a] [nM] D_2[b]	D_3[c]	$K_i(D_2)/K_i(D_3)$	No.	NR^1R^2	Binding K_i ($\bar{x} \pm$ SEM)[a] [nM] D_2[b]	D_3[c]	$K_i(D_2)/K_i(D_3)$
21		5000	5000	1	**28**		1000	1000	1
22		700 ± 250	500 ± 100	1	**29**		1200 ± 300	180 ± 40	7
23		3000	2500	1	**30**		2500	2300 ± 1100	1
24		20000	8400	2	**31**		2200 ± 800	840 ± 140	3
25		4000	110 ± 200	4	**32**		2500	93 ± 20	27
26		4200 ± 251	1016 ± 143	4	**33**		610 ± 20	74 ± 75	8
27		3630	831	4					

[a] Mean ± SEM values were determined by at least three separate experiments. [b] K_i values for D_2 receptors were measured on human D_{2L} receptors by using $[^{125}I]$iodosulpiride. [c] K_i values for D_3 receptors were measured on human D_3 receptors by using $[^{125}I]$iodosulpiride.

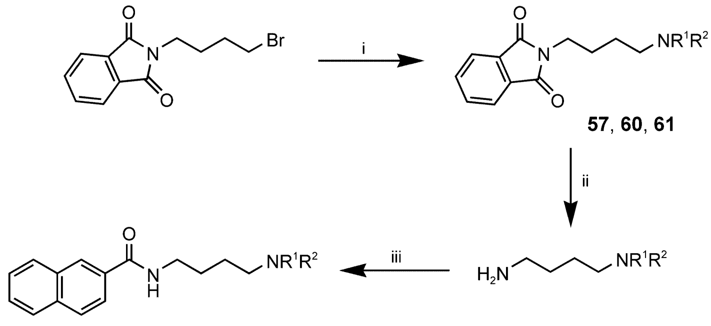
Hence, two pathways of derivatisations were selected: 1) the 1,2,3,4-tetrahydroisoquinoline structure was varied with regard to aryl substitution, enlargement or substitution of the aliphatic ring, change in geometry and flexibility or exchange of the aryl moiety by other potential bioisosteric groups; 2) the arylcarboxamide residue was varied (e.g. by aryl substitution). Replacement of the naphthamide group by diversely substituted (*E*)-cinnamide residues resulted in enhanced affinity and preference for the D_3 receptor, as for ST 198 (**43**), which is a useful pharmacological tool for D_3-receptor-related investigations in vitro and in vivo.[17–19] Additionally, a number of iodinated compounds have been prepared as potential dopamine D_3 receptor-selective radioligands, for example, applicable in single-photon emission computed tomography (SPECT) investigation.[20] Here, the *para*-

substituted cinnamide derivative **51** has low nanomolar affinity (K_i = 12.2 nM) and more than 120-fold preference for the D_3 receptor. (*Z*)-Cinnamide isomers were not taken into consideration in this study, since comparable *Z* isomers were reportedly less effective for dopamine D_3 receptor affinity than their corresponding *E* isomers.[21]

Results and Discussion

Two synthetic routes were chosen as key pathways for most of the compounds described, depending on whether the amine moiety was to be varied or a modification of the hydrophobic residue was desired.

A linear strategy (Scheme 2) involved alkylation of the appropriate secondary amines with *N*-(4-bromobutyl)phthalimide. Quaternary ammonium compounds, which were obtained from tertiary, pyridine-derived amines, were reduced to the tertiary amines. Subsequent cleavage of the phthalimide group with hydrazine led to primary amine compounds which, on treatment with naphthalene-2-carboxylic acid chloride, resulted in the corresponding amides **7**–**10**, **17**–**24** and **32**.

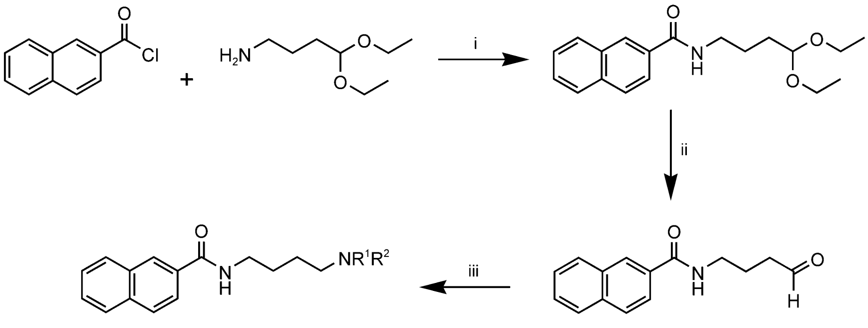


57, **60**, **61**

7-10, **17-24**, **32**

Scheme 2. *Reagents: i) a) H_3CCN, K_2CO_3, appropriate nitrogen-containing compound (in case of pyridine derivatives: a) and then b) MeOH, $NaBH_4$); ii) H_2N-NH_2, EtOH; iii) naphthalene-2-carboxylic acid chloride, CH_2Cl_2, K_2CO_3.*

A second approach (Scheme 3) started with naphthalene-2-carboxylic acid chloride and 4-aminobutyl diethylacetal and gave the corresponding amide in high yield. Mild acid hydrolysis of the acetal group resulted in the deprotected aldehyde, which served as one of the substrates for reductive amination to afford the final products **11**–**16**, **25**–**31** and **33**.



11-16, **25-31**, **33**

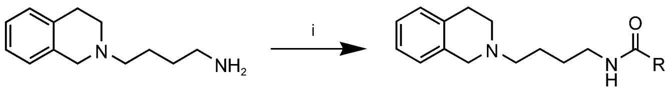
Scheme 3. *Reagents: i) CH_2Cl_2, K_2CO_3; ii) EtOH, HCl, HOAc; iii) $ClCH_2CH_2Cl$, HNR^1R^2, HOAc, $NaBH(OCOCH_3)_3$.*

Starting with the primary amine **34**, synthesised according to Scheme 2, a number of variations in the arylcarboxamide structure were performed as shown in Scheme 4. Treatment with the appropriate carboxylic acid chlorides resulted in the desired amides **35**–**41** and **43**–**54**.

Scheme 5 shows a possible route to [^{125}I]- or [^{123}I]-radiolabelled ligands. The iodo substituent of compound **51** is easily exchanged by a trialkylstannyl group in the presence of a palladium catalyst.[22] The stannylated compound **55** can be reversibly transformed with radioactive iodine, which is generated in situ from radiolabelled NaI and chloramine T, to give the corresponding radiolabelled derivative of compound **51**.[23]

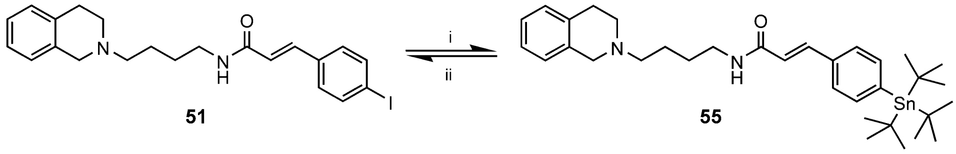
Additionally, compounds **56** (by using *N*-(3-bromopropyl)-phthalimide), **57**, **60** and **61** were prepared according to Scheme 2. Compound **58** was prepared by treatment of **34** with methyl-2-isothiocyanatobenzoate in a tandem ring-closure reaction. Comparable reaction conditions with the oxygen analogue methyl-2-isocyanatobenzoate led to acyclic compound **42**. Further treatment with potassium hydroxide in methanol afforded the ring-closed product **59**. Structure **62** was synthesised according to the final step in Scheme 2 by using (*E*)-cinnamoyl chloride for amidation.

Secondary aliphatic amines that were not commercially available were prepared by various methods. The precursor of **17** was prepared as described in the literature;[24] the 1-substituted 1,2,3,4-tetrahydroisoquinolines **63**–**66**, which are precursors for compounds **19**–**22**, were prepared according to the Bischler–Napieralski procedure as shown in Scheme 6.[25]



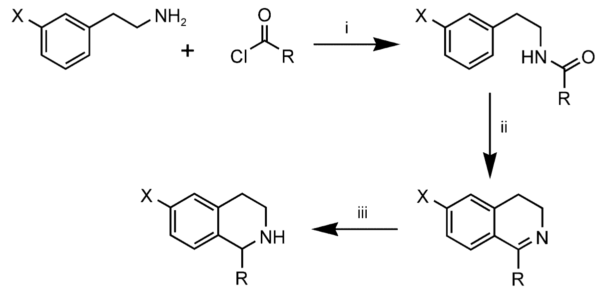
34 **35-41, 43-54**

Scheme 4. *Reagents: i) CH_2Cl_2, RCOCl, K_2CO_3.*



51 **55**

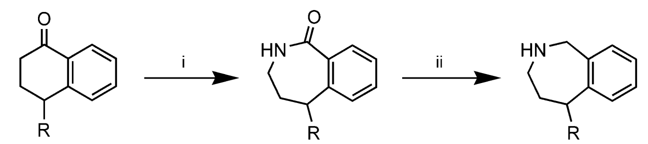
Scheme 5. *Reagents: i) (tBu_3Sn)$_2$, $Pd(PPh_3)_4$; ii) NaI, chloramine T.*



63: X=H, R=phenyl
64: X=F, R=phenyl
65: X=H, R=4-chlorophenyl
66: X=H, R=benzyl

Scheme 6. *Reagents: i) 2 N KOH; ii) toluene, $ZnCl_2$, $POCl_3$; iii) ThF, $NaBH_4$.*

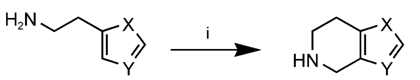
Tetrahydrobenzo[*c*]azepines **67** and **68**, which are precursors for **25** and **26**, respectively, were prepared by modified Schmidt reactions on α-tetralones (Scheme 7).[26]



67: R=H
68: R=CH_3

Scheme 7. *Reagents: i) conc. HCl, NaN_3; ii) THF, $LiAlH_4$.*

Tetrahydrobenzo[*f*][1,4]oxazepine, required for compound **27**, was prepared by amidation of 2-methoxybenzylamine with chloroacetic acid chloride, subsequent ether cleavage with boron tribromide and ring closure under mild basic conditions, followed by metal hydride reduction as described above. The heteroaromatic derivatives **69** and **70**, which are precursors for compounds **29** and **30**, respectively, were obtained by modified Pictet–Spengler reactions (Scheme 8).[27, 28] The aminothiazole scaffold, a proposed phenol bioisostere in compound **31**,[29] was available by Hantzsch thiazole synthesis.[30]



69: X=S, Y=CH
70: X=NH, Y=N

Scheme 8. *Reagents: i) 0.01 M HCl, $H_2C(OEt)_2$, reflux.*

From the series of substituted 1,2,3,4-tetrahydroisoquinolines derivatives (Table 1), compounds **19**–**24** had negative effects on affinity relative to 1-unsubstituted compounds. Despite the similarity between the phenyl- and benzyl-substituted fragments and apomorphine, an agonist with considerable affinity for dopamine D_2-like receptors, these rather bulky substituents were not tolerated by the receptor. Different substitution patterns on the aromatic moieties had only minor influence on binding behaviour. Thus, separation of enantiomers was not considered.

Substitution with electron donors on the aryl moiety of the 1,2,3,4-tetrahydroisoquinoline structure (**16**, **18**) led to slightly enhanced affinities for the D_3 receptor relative to that of compound **15** and a maintained preference for the D_3 receptor. In contrast, substitution with an electron-withdrawing nitro group (**17**) resulted in deteriorated affinity.

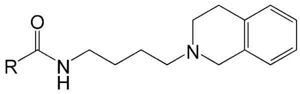
Compounds with a more rigid, seven-membered ring (**25**–**27**) suffered a decreased affinity for the D_3 receptor, possibly as a result of an unfavourable orientation of the nitrogen atom in relation to the aromatic residue. Replacement of the phenyl substructure by other aryl structures led to diverse binding profiles. The heterocyclic analogue **29**, which features thiophene as a potential bioisostere of the phenyl ring, has a slightly decreased affinity. Replacement by a basic imidazole resulted in a complete loss of binding (**30**). Unexpectedly, the 2-aminothiazole analogue **31**, which bears the same heteroaromatic moiety as the D_3 receptor agonist pramipexole, displayed a clear decline of affinity by one order of magnitude relative to the parent 1,2,3,4-tetrahydroisoquinoline compound **15**. Longitudinal enlargement of the aromatic moiety seems to be well tolerated as indicated by compounds **32** and **33**, although only in a restricted manner, as shown with the bulky naphthalene derivative **28**.

Among the series of modifications on the aryl structure at the carboxamide element (Table 2), compounds with differently substituted aryl (**35**–**39**) or heteroaromatic residues (**40**–**42**) directly connected to the carbonyl group display binding values comparable to those of **15**. While the dopamine D_3 receptor preference of compound **39** is as good as that of compound **15**, the former has lower K_i values. This series may suggest that improved binding can be incidental with an elongated and rigid geometry of the arylcarboxamide residue, leading to the cinnamide derivatives **43**–**55**. This derivatisation proves to be most favourable with the compounds described here, since binding values in the low nanomolar concentration range can be achieved, especially for cinnamides sharing a linear conjugated structure. Compound **43** (ST 198) not only has strongly enhanced affinity and a noticeably higher preference for the dopamine D_3 receptor relative to compound **15**, but also displays low affinities for other human dopamine receptor subtypes and a variety of non-dopaminergic receptors.[19] Substituents in the α-position are tolerated (**45**), although their maximum size seems to be rather limited (**46**).

The series of substituted cinnamides confirms that elongated residues provide improved affinities, whereas in most cases increased bulkiness or additional hydrogen bonding is accompanied by a decrease in affinity (**54**). However, compound **55** maintains a remarkable nanomolar affinity considering the bulky trialkylstannyl substituent. While structure **51** proves to have the wanted pharmacological affinity profile with a low nanomolar K_i value and over 120-fold selectivity towards the D_3 receptor, the chloro analogue **49** possesses a comparable affinity accompanied by a lower dopamine D_3 receptor preference.

More divergent modifications were performed on compounds **56**–**61** (Table 3) with phthalimide and structurally related

Table 2. Structures and receptor binding of arylcarboxylic acid derivatives.



No.	R	Binding K_i ($\bar{x} \pm$ SEM)[a] [nM] D_2[b]	D_3[c]	$K_i(D_2)/K_i(D_3)$
35	6-bromonaphth-2-yl	1000	105 ± 20	10
36	6-cyanonaphth-2-yl	260 ± 33	47 ± 1	6
37	4-acetylphenyl	500 ± 100	48 ± 8	10
38	4-(phenylcarbonyl)phenyl	700 ± 300	60.5 ± 3.5	12
39	4-iodophenyl	630 ± 230	28 ± 3	22
40	2-oxochromen-3-yl	650 ± 100	93 ± 20	7
41	3-methyl-1*H*-inden-2-yl	800	93 ± 18	9
42	2-(methoxycarbonyl)anilino	70 ± 13	65 ± 6	1
43	(*E*)-cinnamyl	780 ± 30	12 ± 0.5[d]	62
44	*trans*-2-phenylcyclopropyl	1600 ± 200	158 ± 7.8	10
45	(*E*)-2-fluoro-3-phenylacryl	189 ± 22	12.1 ± 2.5	16
46	(*E*)-2-methyl-3-phenylacryl	920 ± 110	26 ± 2	35
47	phenylethinyl	165 ± 1	17 ± 1.5	10
48	2-phenylethyl	910 ± 70	190 ± 22	5
49	(*E*)-3-(4-chlorophenyl)acryl	293 ± 61	11 ± 2	26
50	(*E*)-3-(4-nitrophenyl)acryl	290 ± 76	38 ± 11	8
51	(*E*)-3-(4-iodophenyl)acryl	1500 ± 400	12.2 ± 0.6	123
52	(*E*)-3-(3-iodophenyl)acryl	1700	34 ± 7	50
53	(*E*)-3(2-iodophenyl)acryl	1100 ± 650	150 ± 50	7
54	(*E*)-3-(3-iodo-4,5-dimethoxyphenyl)acryl	800	400	2
55	(*E*)-3-(4-(tBu$_3$stannyl)phenyl)acryl	910 ± 103	255 ± 5	4

[a] Mean ± SEM values were determined by at least three separate experiments. [b] K_i values for D_2 receptors were measured on human D_{2L} receptors using [^{125}I]iodosulpiride. [c] K_i values for D_3 receptors were measured on human D_3 receptors using [^{125}I]iodosulpiride. [d] pA_2 7.5 determined by Schild plot with quinpirole.[19]

groups. Some of these groups are known elements in other ligands with remarkable affinities for dopamine D_2-like receptors.[31] Although affinity could be improved (**56** → **57** → **58** → **59**), the low selectivity ratios were discouraging for further development. Compound **62** presents another new promising lead for further development, since its D_3 receptor affinity is even higher than that of compound **43**, but it possesses a lower selectivity ratio (cf. also 2-naphthalene derivative **12**).

Exemplary functional mitogenesis assays on compounds **15**, **16** and **43** verified **15** and **43**[19] as full antagonists, since quinpirole-induced mitogenesis was completely blocked by these compounds, whereas the dimethoxylated tetrahydroisoquinole derivative **16** had a low intrinsic activity of 20%, demonstrating partial agonist properties.

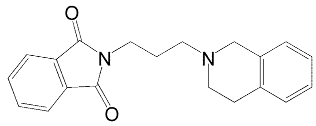
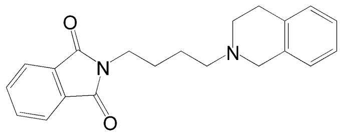
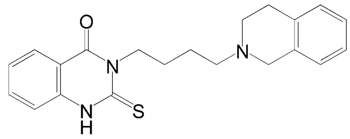
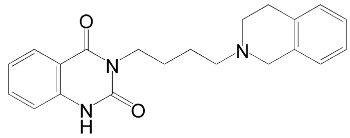
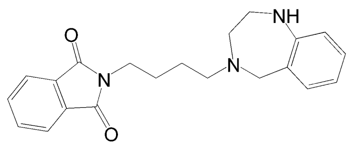
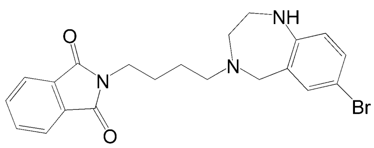
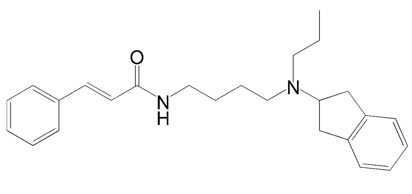
Conclusion

Possibilities for derivatisation of *N*-(4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butyl)arylcarboxamides that simultaneously maintain high affinity and D_3 receptor subtype preference appear to be rather limited. In this study, potent dopamine D_3 receptor antagonists with K_i values in the low nanomolar concentration range and up to 120-fold preference for the D_3 receptor subtype were designed and synthesised. These compounds are suitable as pharmacological tools.[17, 18] A new iodinated compound (**51**, ST 283) was developed and a convenient and facile method for its radiolabelling was applied.[23] Based on the lead structure **15** (ST 80), remarkable improvements in affinity and selectivity were achieved mainly by alterations of the arylamide residue to cinnamide derivatives. Compound **43** (ST 198) has already proven to be a valuable tool for pharmacological investigations concerning the dopamine D_3 receptor in vitro and in vivo.[17–19] Further modifications and alterations will concern compounds **32**, **33** and **62**, since their binding values indicate that their basic substructures are interesting bioisosteres of the 1,2,3,4-tetrahydroisoquinoline scaffold.

Experimental Section

General procedures: Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal Me_4Si as reference. ^{1}H NMR data are reported in the following order: multiplicity, approximate coupling constants in Hertz (Hz) and number of protons. Elemental analyses were measured on Perkin – Elmer 240 B or 240 C instruments and were within ±0.4% of theoretical values for all compounds (except **55**). Chromatographic purifications were done with Merck silica gel (43 – 60 μm) or by accelerated, rotary chromatography on a Chromatotron 7924T (Harrison research) and glass rotors with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck). All reactions were monitored by thin-layer chromatography (TLC), performed on silica gel PF_{254} plates (Merck). Spectral data and elemental analyses

Table 3. Structures and receptor binding of miscellaneous compounds.

No.	Structure	Binding K_i ($\bar{x} \pm$ SEM)[a] [nM] D2[b]	D3[c]	$K_i(D_2)/K_i(D_3)$
56		6500	5600	1.2
57		400 ± 80	233 ± 35	1.7
58		37 ± 6	77 ± 19	0.5
59		37 ± 3	42 ± 4	0.9
60		17280 ± 6410	4525 ± 940	4
61		2030 ± 5230	5230 ± 1225	0.4
62		326 ± 47	8.5 ± 1.3	38

[a] Mean ± SEM values were determined by at least three separate experiments. [b] K_i values for D_2 receptors were measured on human D_{2L} receptors by using [125I]iodosulpiride. [c] K_i values for D_3 receptors were measured on human D_3 receptors by using [125I]iodosulpiride.

are shown only for parent compounds, those describing different reactions or methods, and for the most potent compounds.

Method A: **General procedure preparation of arylcarboxylic acids (7–10, 17–24, 32, 35–54 and 62) by amidation**: A mixture of the appropriate amine (1.5 mmol), triethylamine (152 mg, 1.5 mmol) and dry CH_2Cl_2 (10 mL) was stirred and a solution of the arylcarboxylic acid chloride (1.8 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. Stirring was continued until no amine could be detected by TLC. The solvent was removed under reduced pressure and the products were obtained in 48–95% yield by crystallisation from ethanol or precipitation as salts of oxalic acid.

Method B: **General preparation of naphthoic acid amide derivatives by reductive amination (11–16, 25–31 and 33)**:[32] A mixture of the appropriate secondary amine (2 mmol) in dry $ClCH_2CH_2Cl$ (15 mL), glacial acetic acid (1.5 mL), $NaBH(OCOCH_3)_3$ (850 mg, 4 mmol) and *N*-(4-oxobutyl)naphthalene-2-carboxamide (1 g, 4 mmol) was stirred at room temperature under an argon atmosphere overnight. The mixture was carefully quenched with NaOH and the product extracted with CH_2Cl_2. The combined organic layers were treated with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude yellow oil obtained was purified by column chromatography and the corresponding salt precipitated in 4–34% yield on addition of oxalic acid.

***N*-(4-(*N*′-Benzyl-*N*′-methylamino)butyl)naphthalene-2-carboxamide (7)**: The title compound was prepared as a colourless solid by method A (48% yield for the last reaction step). M.p. 132–133 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.6$ (m, 2H), 1.85 (m, 2H), 2.6 (s, 3H), 2.95 (t, $J = 7.13$ Hz, 2H), 3.35 (dt, $J = 6.13$ Hz, 2H), 4.19 (s, 2H), 7.42 (m, 5H), 7.6 (m, 2H), 7.96 (m, 4H), 8,44 ppm (s, 1H); EI MS: *m/z*: 441.0 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(Indan-2-ylamino)butyl)-naphthalene-2-carboxamide (11)**: The title compound was prepared as a colourless solid by method B (10% yield for the last reaction step). M.p. 149–151 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.67$ (s, 4H), 3.05 (m, 4H), 3.31 (m, 4H), 4.02 (m, 1H), 7.2 (m, 4H), 7.60 (m, 2H), 8.01 (m, 4H), 8.45 (s, 1H), 8.71 ppm (s, 1H); EI MS: *m/z*: 358 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(*N*′-Indan-2-yl-*N*′-propylamino)butyl)naphthalene-2-carboxamide (12)**: The title compound was prepared as a colourless solid by method B (14% yield for the last reaction step). M.p. 65–67 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.92$ (t, $J = 7.2$ Hz, 3H), 1.08 (m, 2H), 1.71 (m, 4H), 5.99 (m, 6H), 5.52 (m, 4H), 4.21 (t, $J = 8.1$ Hz, 1H), 7.23 (m, 4H), 7.64 (m, 2H), 8.0 (m, 4H), 8.41 (s, 1H), 8.78 ppm (s, 1H); EI MS: *m/z*: 400 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl)naphthalene-2-carboxamide (15)**: The title compound was prepared as a colourless solid by method B (18% yield for the last reaction step). M.p. 163–164 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.71$ (t, $J = 6.95$ Hz, 2H), 1.85 (m, 2H), 3.1 (m, 4H), 3.42 (m, 4H), 4.3 (s, 2H), 7.2 (m, 4H), 7.6 (m, 2H), 7.95 (m, 4H), 8.45 (s, 1H), 8.7 ppm (t, $J = 5.14$ Hz, 1H); EI MS: *m/z*: 448.52 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(2,3,4,5-Tetrahydro-1*H*-benzo[*c*]azepino)butyl)naphthalene-2-carboxamide (25)**: The title compound was prepared as a colourless solid by method B (31% yield for the last reaction step). M.p. 125 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.54$ (m, 2H), 1.75 (m, 2H), 1.88 (s, 2H), 2.89 (s, 2H), 2.95 (s, 2H), 3.33 (m, 2H), 3.44 (m, 2H), 4.42 (s, 2H), 7.17 (m, 1H), 7.27 (m, 2H), 7.38 (d, $J = 7.3$ Hz, 1H), 7.60 (m, 2H), 7.98 (m, 4H), 8.44 (s, 1H), 8.71 ppm (t, $J = 5.4$ Hz, 1H); EI MS: *m/z*: 372 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-5-yl)butyl)naphthalene-2-carboxamide (29)**: The title compound was prepared as a colourless solid by method B (16% yield for the last reaction step). M.p. 195 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.69$ (brs, 2H), 1.85 (brs, 2H), 3.16 (s, 2H), 3.29 (brs, 2H), 3.42 (s, 2H), 3.57 (brs, 2H), 4.15 (s, 2H), 5.56 (brs,1H), 6.89 (d, $J = 5.1$ Hz, 1H), 7.42 (d, $J = 5.1$ Hz, 1H), 7.61 (m, 2H), 7.98 (m, 4H), 8.45 (s, 1H), 8.70 ppm (s, 1H); EI MS: *m/z*: 364 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(2-Amino-4,5,6,7-Tetrahydrothiazolo[5,4-*c*]pyridin-6-yl)butyl)naphthalene-2-carboxamide (31)**: The title compound was prepared as a colourless solid by method B (6% yield for the last reaction step). M.p. 56 – 58 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.00$ (m, 3H), 1.68 (m, 7H), 1.90 (m, 1H), 2.16 (m, 1H), 2.67 (m, 2H), 2.82 (m, 1H), 2.91 (m, 1H), 3.08 (m, 2H), 3.18 (m, 2H), 3.38 (m, 2H), 3.66 (m, 1H), 6.86 (brm, 2H), 7.61 (m, 2H), 7.98 (m, 4H), 8.44 (s, 1H), 8.68 ppm (m, 1H); EI MS: *m/z*: 380.50 [M^+]; elemental analysis: see Supporting Information.

***N*-(4-(1,2,3,4-Tetrahydro-5-oxo-5*H*-chromeno[3,4-*c*]pyridin-2-yl)-butyl)naphthalene-2-carboxamide (32)**: The title compound was prepared as a colourless solid by method A (60% yield for the last reaction step). M.p. 177 – 178 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.65$ (m, 4H), 3.17 (m, 4H), 3.37 (d, $J = 5.6$ Hz, 2H), 3.71 (s, 2H), 7.42 (m, 2H), 7.59 (m, 3H), 7.74 (d, $J = 7{,}8$ Hz, 1H), 7.97 (m, 4H), 8.43 (s,1H), 8.66 ppm (s, 1H); EI MS: *m/z*: 426.51 [M^+]; elemental analysis: see Supporting Information.

(*E*)-*N*-(4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl)cinnamide (43): The title compound was prepared as a colourless solid by method A (72% yield for the last reaction step). M.p. 163 – 164 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.54$ (m, 2H), 1.73 (m, 2H), 3.05 (m, 4H), 3.22 (m, 2H), 3.37 (m, 2H), 4.25 (s, 2H), 6.62 (d, $J = 15.9$ Hz 1H), 7.22 (m, 4H), 7.40 (m, 4H), 7.55 (d, $J = 7.0$ Hz, 2H), 8.18 ppm (t, $J = 5.4$ Hz, 1H); EI MS: *m/z*: 334.46 [M^+]; elemental analysis: see Supporting Information.

(*E*)-3-(4-Iodophenyl)-*N*-(4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butyl)acrylamide (51): The title compound was prepared as a colourless solid by method A (82% yield for the last reaction step). M.p. 148 – 149 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.53$ (m, 2H), 1.75 (m, 2H), 3.03 (m, 4H), 3.35 (s, 2H), 4.25 (s, 2H), 6.66 (d, $J = 15.9$ Hz, 1H), 7.18 (m, 4H), 7.36 (m, 3H), 7.76 (m, 2H), 8.23 ppm (t, $J = 5.48$ Hz, 1H); EI MS: *m/z*: 460.36 [M^+]; elemental analysis: see Supporting Information.

(*E*)-3-(4-(Tri(*tert*-butylstannyl)phenyl)-*N*-(4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butyl)acrylamide (55): A mixture of the 4-iodo derivative **51** (124 mg, 0.27 mmol) and dry 1,4-dioxane (10 mL) was treated with hexa(*tert*-butyl)ditin (240 mg, 0.41 mmol) and a catalytic amount of tetrakis(triphenylphosphine)palladium and heated at reflux under an argon atmosphere in the absence of light for 18 h. After cooling to room temperature, the mixture was filtered and the filter washed with ethyl acetate. The combined filtrates were evaporated under vacuum and purified by chromatotron chromatography ($CHCl_3/NH_3$) to afford the title compound (50% yield) as a yellow oil. ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.81$ (m, 9H), 1.04 (m, 6H), 1.28 (m, 7), 1.49 (m, 11H), 2.6 (m, 2H), 2.77 (m, 2H), 3.18 (m, 2H), 3.50 (m, 2H), 6.59 (d, $J = 15.78$ Hz, 1H), 7.06 (m, 4H), 7.35 (d, $J = 15.84$ Hz, 1H), 7.45 (m, 4H), 8.12 ppm (m, 1H); EI MS: peaks of isotopic distribution were resolved by using the peak match method; all peaks uniquely resolved; main peak *m/z*: 624.3 [M^+]; average *m/z*: 623.5.

***N*-(4,4-Di(ethoxy)butyl)naphthalene-2-carboxamide**: A mixture of 4-aminobutyldiethyl acetal (16.1 g, 100 mmol) and K_2CO_3 (27.6 g, 200 mmol) in dry CH_2Cl_2 (80 mL) was treated with naphthalene-2-carboxylic acid chloride (19 g, 100 mmol) dissolved in dry CH_2Cl_2 (40 mL) under basic conditions and stirred for 3 h. After the solvent was evaporated in vacuo, water (100 mL) was added. The mixture was vigorously stirred until the entire product precipitated as a colourless solid in 97% yield. M.p. 65 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.1$ (t, $J = 7.0$ Hz, 6H), 1.6 (m, 4H), 3.31 (m, 2H), 3.45 (m, 2H), 3.57 (m, 2H), 4.50 (brs, 1H), 7.58 (m, 2H), 7.98 (m, 4H), 8.43 (s, 1H), 8.61 ppm (t, $J = 5.47$ Hz, 1H).

***N*-(4-Oxobutyl)naphthalene-2-carboxamide**: Glacial acetic acid (5 mL) and HCl (2 M, 5 mL) were added to a mixture of *N*-(4,4-di(ethoxy)butyl)naphthalene-2-carboxamide (1.26 g, 4 mmol) in ethanol (10 mL). After stirring at room temperature for 2 h, the mixture was concentrated in vacuo, water was added and the product extracted into CH_2Cl_2. The organic layers were treated with brine, dried over Na_2SO_4 and evaporated to dryness to afford the title compound (90% yield) as a colourless oil. The product was used straightaway in following reactions without further purification.

Coupling of 2-(4-bromobutyl)isoindole-1,3-dione with secondary amines (57, 60 and 61): The appropriate secondary amine (2.7 mmol) was dissolved in dimethylformamide. 2-(4-Bromobutyl)-isoindole-1,3-dione (762 mg, 2.7 mmol) and K_2CO_3 (746 mg, 5.4 mmol) were added and the mixture was heated at reflux for 2 h. The hot suspension was filtered and the residue was washed with acetone. The filtrate was evaporated to dryness and purified by column chromatography (CH_2Cl_2, 10% MeOH) to afford the product as a colourless oil in 56 – 70% yield.

Cleavage of phthalimide protecting group (preparation of 34):[33] Phthalimide **57** (2.7 g, 8 mmol) was dissolved in methanol (50 mL), hydrazine hydrate (0.5 g, 10 mmol) was added and the solution was heated to reflux. After 2 h, HCl (6 M, 5 mL) was added to the hot solution and the heating at reflux was continued for 1 h more. After cooling down to room temperature the mixture was filtered, the residue was washed with cold methanol and the volatiles were evaporated under vacuum. The product was purified by column chromatography ($CHCl_3$, 1% $MeOH/NH_3$) to give the title compound as a slightly yellow oil in 86% yield.

2,3,4,5-Tetrahydrobenzo[*c*]azepine derivatives

2,3,4,5-Tetrahydro-1H-benzo[c]azepan-1-one:[26] Sodium azide (2.6 g, 40 mmol) was added to a stirred solution of α-tetralone (2.9 g, 20 mmol) in ice-cooled concentrated HCl (50 mL). The mixture was allowed to warm to room temperature and stirring was continued overnight. After completion of the reaction, the mixture was poured onto ice. Basic pH was accomplished by addition of K_2CO_3. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product obtained was purified by chromatotron chromatography (petroleum ether (PE)/CH_2Cl_2 1:1) to afford the title compound (84% yield) as a slightly yellow oil. ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.88$ (m, 2H), 2.74 (t, $J = 7.1$ Hz, 1H), 2.90 (q, $J = 6.3$ Hz, 2H), 7.25 (d, $J = 7.4$ Hz, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.4$ Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 8.01 ppm (s, 1H); EI MS: *m/z*: 161.20 [M^+]; elemental analysis: see Supporting Information.

2,3,4,5-Tetrahydro-5-methylbenzo[c]azepan-1-one: The title compound was prepared in 77% yield from 3,4-dihydro-4-methylnaphthalen-1-one (3.2 g, 20 mmol) by using the method described for 2,3,4,5-tetrahydrobenzo[*c*]azepan-1-one.

*2,3,4,5-Tetrahydro-1H-benzo[c]azepine (**67**)*: A solution of the benzazepanone (2.4 g, 15 mmol) in dry THF (25 mL) was added to an ice-cooled, stirred suspension of lithium aluminium hydride ($LiAlH_4$, 2 g, 52.5 mmol) in dry THF (70 mL). The mixture was stirred at room temperature for 30 min and then heated at reflux for 2 h. Remaining $LiAlH_4$ was hydrolysed with H_2O under ice cooling and separated by filtration. The product was extracted with ether and the solvent was removed in vacuo. Purification was accomplished by column chromatography (CH_2Cl_2, MeOH/NH_3 9:1) to afford the title compound (45% yield) as a yellow oil. ^1H NMR ([D_6]DMSO): $\delta = 1.61$ (t, $J = 4.5$ Hz, 2H), 2.86 (t, $J = 5.1$ Hz, 2H), 3.02, (t, $J = 5.0$ Hz, 1H), 3.78 (s, 2H), 7.11 ppm (m, 4H); EI MS: *m/z*: 147.22 [M^+]; elemental analysis: see Supporting Information.

*2,3,4,5-Tetrahydro-5-methyl-1H-benzo[c]azepine (**68**)*: The title compound was prepared in 39% yield from 2,3,4,5-tetrahydro-5-methylbenzo[*c*]azepan-1-one (2.6 g, 15 mmol) by using the method described for **67**.

2-Bromo-*N*-(2-methoxybenzyl)acetamide: A solution of 2-bromoacteyl bromide (8.9 g, 44 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to stirred mixture of 2-methoxybenzylamine (6 g, 44 mmol) and triethylamine (4.45 g, 44 mmol) in dry CH_2Cl_2 (80 mL) and the stirring was continued for 1 h. Solids were removed by filtration. The volatiles were evaporated under vacuum to afford the title compound (95% yield) as an orange solid, which was used in the next step without further purification. ^1H NMR ($CDCl_3$): $\delta = 3.85$ (s, 2H), 3.90 (s, 3H), 4.46 (d, $J = 5.88$ Hz, 2H), 6.90 (m, 2H), 7.10 (m, 1H), 7.30 ppm (m, 2H).

2-Bromo-*N*-(2-hydroxybenzyl)acetamide: A solution of 2-bromo-*N*-(2-methoxybenzyl)acetamide (5.16 g, 20 mmol) in dry CH_2Cl_2 (100 mL) was cooled to $-78\,^\circ C$. A solution of BBr_3 in CH_2Cl_2 (1 M, 20 mL, 20 mmol) was added dropwise at a temperature maintained below $-70\,^\circ C$. The solution was allowed to warm to room temperature and was stirred for 24 h. To quench the reaction, the solution was again cooled down to $-78\,^\circ C$ and dry methanol (20 mL) was added. The mixture was then allowed to warm up to room temperature, the volatiles were evaporated in vacuo and the oily residue was purified by column chromatography (MeOH/ CH_2Cl_2 9:1) to afford the title compound (88% yield). ^1H NMR ($CDCl_3$): $\delta = 3.88$ (s, 2H), 4.37 (d, $J = 6.54$ Hz, 2H), 6.90 (m, 2H), 7.23 (m, 2H), 7.32 ppm (brs, 1H).

2,4-Dihydro-1*H*-benzo[*f*][1,4]oxazepin-3-one:[34] A mixture of 2-bromo-*N*-(2-hydroxybenzyl)acetamide (4.86 g, 20 mmol) and K_2CO_3 (5.5 g, 40 mmol) in dry acetonitrile (80 mL) was stirred at $60\,^\circ C$ for 48 h. Solids were separated by filtration and the mixture was dried under vacuum. The residue was partitioned between CH_2Cl_2 and water. Evaporation of the organic layer yielded the pure product (60% yield). ^1H NMR ($CDCl_3$): $\delta = 4.37$ (s, 2H), 4.68 (s, 2H), 7.16 (m, 2H), 7.22 (m, 1H), 7.28 ppm (m, 1H).

1,2,3,4-Tetrahydrobenzo[*f*][1,4]oxazepine:[35] A solution of 2,4-dihydro-1*H*-benzo[*f*][1,4]oxazepan-3-one (1.62 g, 10 mmol) in dry THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (1.4 g, 37 mmol) in dry THF (20 mL). The mixture was heated at reflux for 12 h. Remaining $LiAlH_4$ was hydrolysed with water under ice cooling and separated by filtration. The product was extracted with ether and the solvent was removed in vacuo. Purification of the residue by column chromatography (CH_2Cl_2, MeOH/NH_3 9:1) afforded the title compound (54% yield) as a dark yellow oil. ^1H NMR ($CDCl_3$): $\delta = 3.10$ (t, $J = 4.29$ Hz, 2H), 3.84 (s, 2H), 3.93 (m, 2H), 6.96 (m, 2H), 7.08 ppm (m, 2H).

2-Phenylpiperidine:[36] Platinum oxide (PtO_2, 0.9 g, 4 mmol) was added to a solution of 2-phenylpyridine (9.9 g, 6.4 mmol) in methanol (30 mL) and glacial acetic acid (5 mL) and the mixture was hydrogenated at 10 bar for 62 h. The solution was separated from the solids by filtration and then evaporated in vacuo. On addition of diethyl ether, inorganic salts were precipitated and separated. After evaporation, remaining traces of phenylpyridine were removed by trituration with hexane to afford the title compound (80% yield) as a yellow oil.

4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine:[28] 2-Thien-2-ylethanamine (0.64 g, 5 mmol) was dissolved in propan-2-ol (10 mL) and HCl (1 M, 0.6 mL). After the addition of formaldehyde diethyl acetal (0.83 g, 8 mmol), the mixture was heated at reflux for 2.5 h. Precipitation from the hot solution was completed in an ice bath to afford the product (84% yield) as colourless crystals. M.p. $218\,^\circ C$; ^1H NMR ([D_6]DMSO): $\delta = 3.04$ (t, $J = 5.9$ Hz, 2H), 3.42 (t, $J = 6.0$ Hz, 2H), 4.16 (s, 2H), 6.93 (d, $J = 5.2$ Hz, 1H), 7.45 ppm (d, $J = 5.2$ Hz, 1H); EI MS: *m/z*: 139 [M^+]; elemental analysis: see Supporting Information.

4,5,6,7-Tetrahydro-3*H*-imidazo[4,5][*c*]pyridine:[27] Histamine dihydrochloride (0.74 g, 5 mmol) was dissolved in HCl (0.01 M, 40 mL). After the addition of formaldehyde diethyl acetal (0.52 g, 5 mmol), the mixture was heated at reflux overnight. More formaldehyde diethyl acetal (0.21 g, 2 mmol) was added and reflux was continued for 6 h to complete the reaction. The mixture was evaporated to dryness. The solid obtained was stirred in ethanol overnight to give pure product (96% yield) as colourless crystals. M.p. $270.0\,^\circ C$; ^1H NMR ([D_6]DMSO): $\delta = 2.96$ (t, $J = 5.5$ Hz, 2H), 3.41 (t, $J = 5.8$ Hz, 2H), 4.27 (s, 2H), 9.01 (s, 1H), 10.14 (brs, 2H), 13.22 – 15.67 ppm (br, 1H); EI MS: *m/z*: 123 [M^+]; elemental analysis: see Supporting Information.

4,5,6,7-Tetrahydrothiazolo[5,4-*c*]pyridin-2-amine:[30] An ice-cooled solution of 4-piperidone hydrate hydrochloride (1.5 g,10 mmol) in aqueous HBr (48%, 10 mL) was treated dropwise with bromine (1.6 g, 10 mmol). The mixture was stirred for 30 min, after which unreacted bromine was evaporated under vacuum. The remaining mixture of crystals and liquid was treated with thiourea (0.76 g, 10 mmol) and stirred for 1 h at reflux. After cooling down, the precipitated crystals were separated by filtration. On concentration of the filtrate, further product could be isolated to afford the title compound in 80% total yield.

1,2,3,4-Tetrahydro-7-nitroisoquinoline:[24] 1,2,3,4-Tetrahydroisoquinoline (1.33 g, 10 mmol) was dissolved in sulfuric acid (5 N, 2 mL) and then evaporated to dryness to afford a solid residue. This sulfate was added to a solution of potassium nitrate (1.26 g, 12.5 mmol) in sulfuric acid under ice cooling and stirred for 12 h at room temperature. The mixture was poured onto cooled aqueous ammonia and neutralised. The product was extracted with CH_2Cl_2 and the organic layers were treated with brine. Evaporation of the volatiles afforded a yellow oil, which was crystallised as the hydrochloride salt from ethanol/diethyl ether to give the title compound in 72% yield.

1,2,3,4-Tetrahydrochromeno[3,4-*c*]pyridin-5-one:[37] Water (3 mL) and concentrated sulfuric acid (12 mL) were added to a well-stirred mixture of phenol (4.34 g, 45 mmol) and ethyl-4-oxopiperidin-3-carboxylate (2.56 g, 15 mmol) under cooling conditions. After 3 h of stirring, the mixture was heated to $50\,^\circ C$ for 4 h and stirred for 10 h at room temperature. To complete the reaction, phenol (4.34 g, 45 mmol) was added and the mixture was heated to $60\,^\circ C$ for 8 h. The precipitated solids were separated by filtration, and the aqueous filtrate was adjusted to pH 10 by the addition of NaOH and then extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and evaporated to dryness. The remaining colourless crystals of the title compound (16% yield) were used in the next step without further purification.

1-Substituted 1,2,3,4-tetrahydroisoqinolines

N-*(2-Phenylethyl)benzamide*:[38] Phenethylamine (6.0 g, 50 mmol) was dissolved in KOH (2 N, 50 mL) and benzoyl chloride (8.43 g, 60 mmol) was added dropwise. The amide precipitated as a colourless solid and was separated from the solvent by filtration. The solid was washed with water until the filtrate was neutral. Recrystallisation from ethanol led to colourless crystals of the title compound (73% yield), which were used in the following step without further purification. ^{1}H NMR ([D$_6$]DMSO): $\delta = 2.82$ (t, $J = 7.8$ Hz, 2H), 3.47 (m, 2H), 7.23 (m, 5H), 7.47 (m, 3H), 7.79 (m, 2H), 8.56 ppm (t, $J = 5.2$ Hz, 1H).

3,4-Dihydro-1-phenylisoquinoline (Bischler – Napieralski cyclisation):[25] *N*-(2-Phenylethyl)benzamide (4.5 g, 20 mmol) was treated with zinc chloride (70 g, 70 mmol) and $POCl_3$ (21.5 g, 140 mmol) in toluene (50 mL) and heated at reflux for 8 h. The mixture was hydrolysed with NaOH (2 M) under ice cooling. The organic layer was separated and the aqueous phase was extracted three times with ether. The organic layers were evaporated to dryness to afford the title compound (52% yield) as a yellow oil, which was used in the next step without further purification. ^{1}H NMR ([D$_6$]DMSO): $\delta = 2.72$ (t, $J = 7.5$ Hz, 2H), 3.70 (t, $J = 7.2$ Hz, 2H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.31 (m, 3H), 7.43 (m, 3H), 7.52 ppm (m, 2H).

*1,2,3,4-Tetrahydro-1-phenylisoquinoline (**63**)*: 3,4-Dihydro-1-phenylisoquinoline (0.68 g, 3 mmol) was suspended in THF (10 mL) and added dropwise to $NaBH_4$ (0.45 g, 12 mmol) in THF (10 mL). The mixture was stirred for 30 min and heated at reflux for 1 h. After hydrolysis with water, the reaction mixture was extracted with THF. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The product crystallised spontaneously in 60% yield. ^{1}H NMR ([D$_6$]DMSO): $\delta = 2.72$ (m, 1H), 2.91 (m, 1H), 3.10 (m, 1H), 4.98 (s, 1H), 6.64 (d, $J = 7.7$ Hz, 1H), 7.00 (t, $J = 6.2$ Hz, 1H), 7.10 (m, 2H), 7.27 ppm (m, 5H).

Pharmacology

Binding studies: Human D_{2L} and D_3 receptors were expressed in stably transfected Chinese hamster ovary (CHO) cells.[9, 37] In brief, these cell lines were cultured in Dulbecco's Modified Eagle Medium supplement in 10% foetal calf serum in an atmosphere of 5% CO_2. Cells were harvested from culture dishes in the presence of 0.2% trypsin, centrifuged at 2000 *g* for 5 min and homogenised in 10 mM Tris-HCl, pH 7.4, containing 5 mM $MgCl_2$ by using a Polytron. The homogenate was centrifuged at 20000 *g* for 15 min at 4 °C and the pellet was resuspended by sonication in 50 mM Tris-HCl, pH 7.4, containing: NaCl, 120 mM; KCl, 5 mM; $CaCl_2$, 2 mM and $MgCl_2$, 8 mM incubation buffer. Membranes were used either immediately or after storage at −70 °C. Membranes (200 µL) diluted in incubation buffer supplemented with 0.2% bovine serum albumin were added to polystyrene tubes containing 0.1 nM [^{125}I]iodosulpiride and drug diluted in incubation buffer (100 µL). Nonspecific binding was determined in the presence of 1 µM enomapride. Incubations were run at 30 °C for 30 min. Reactions were stopped by vacuum filtration through Whatman GF/B glass-fibre filters coated in 0.3% polyethylenimine with automated cell harvester (Brandel – Beckman, Gaithersburg, MD/USA). Filters were rinsed three times with ice-cold incubation buffer (5 mL) and counted by liquid scintillation in 5 mL of ACS II (Amersham). K_i values were calculated from IC_{50} values according to the Cheng – Prusoff equation from at least three separate experiments and expressed as mean ± standard error of the mean (SEM).[39]

Functional receptor tests: NG 108-15 cells expressing the human D_3 receptor were cultured in Dulbecco's Modified Eagle Medium supplemented in 10% foetal calf serum in an atmosphere of 5% CO_2 and plated in collagen-coated 96-well plates. After a 24 h culture time, cells were washed twice with culture medium without foetal calf serum and incubated for 16 h with 1 µM forskoline and quinpirole in increasing concentrations, in the absence or presence of compounds at 1.5, 3, 30 or 300 nM. Then, [^{3}H]thymidine (1 µCi per well) was added for 2 h and cells were harvested by vacuum filtration through Whatman GF/C glass-fibre filters by using an automated cell harvester. The filters were rinsed 15 times with 200 µL of phosphate-buffered saline. Radioactivity was counted by liquid scintigraphy in 5 mL of ACS (Amersham).

Acknowledgements

This study was supported by a grant from the European Community (QLCG4-CT-1999-00075).

Keywords: antagonists · dopamines · radiopharmaceuticals · schizophrenia · tetrahydroisoquinoline

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Received: October 7, 2003 [F 784]

