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1-(1-Phenethylpiperidin-4-yl)-1-phenylethanols as Potent and Highly Selective 5-HT_{2A} Antagonists

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*The discovery of a novel class of highly potent and selective 5-HT_{2A} antagonists is reported herein. Selectivity for the serotonin 5-HT_{2A} receptor was optimized, decreasing the affinity of these antagonists toward the adrenergic α_1 and dopaminergic D_2 receptors, and especially to the 5-HT_{2C} receptor. A series of corresponding 7-substituted indoles is described for the first time as serotonergic ligands. The enantiomer R-(+)-1-(4-fluorophenyl)-1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl} ethanol (R-(+)-**74**) was identified to have superior affinity for the serotonergic 5-HT_{2A} receptor [IC_{50} = 0.37 nM] and selectivity toward the dopaminergic D_2- [IC_{50} = 2300 nM], adrenergic α_1- [IC_{50} = 1000 nM] and 5-HT_{2C} receptors [IC_{50} = 490 nM].*

Introduction

The ubiquitous biogenic amine serotonin (5-hydroxytryptamine, 5-HT) and its biological targets are probably among the best studied in the field of medicinal chemistry.[1] The control of 5-HT function by three different quaternary structures (transporters, ligand-gated ion channels, and G-protein-coupled receptors), the further accuracy of receptor discrimination (structural, operational, and transductional characteristics of seven major families 5-HT_{1-7}),[2] together with the localization of the targets in human tissue constituted the platform for decades of research.[3,4] The role of 5-HT_{2A} receptors in the regulation of a number of processes of the CNS (such as mood, appetite, sexual behavior, learning, and memory) and their dysfunctions (such as psychosis, depression, and anxiety) has been well documented.[5] In this context it should be mentioned that all atypical neuroleptics on the market possess intrinsic 5-HT_{2A} activity, but the importance of this property has been difficult to examine because of the lack of appropriately selective compounds (vide infra).[6] Furthermore, it has also been shown that 5-HT_2 ligands can influence the day–night rhythm and represent potential treatments for sleep disorders.[7,8]

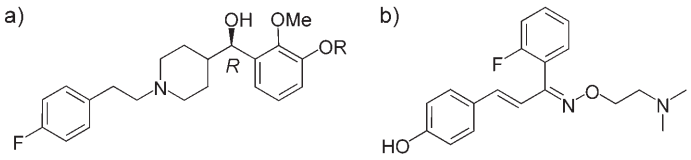

Figure 1. Established 2-HT_{2A} ligands: a) MDL-100907: R = Me, MDL-105725: R = H; b) eplivanserin.

Notably, 5-HT_2 receptor subtypes naturally have different and sometimes opposite effects that depend on the degree of receptor activation or deactivation. This was documented for the antipsychotic action of the first-described selective 5-HT_{2A} antagonist MDL-100907 (Figure 1 a).[9] The compound binds 5-HT_{2A} with affinity in the sub-nanomolar range in vitro and has 104-fold selectivity over the 5-HT_{2C} receptor.[9–11]

The apparent antipsychotic action of the 5-HT_{2A} antagonist MDL-100907 in mice treated with dizocilpine[12] was counteracted markedly by the 5-$HT_{2A,2C}$ receptor antagonist ritanserin.[13] Clearly, the more pronounced inhibition of the 2C subtype by ritanserin reverses the antipsychotic effect of 2A subtype antagonism. This oppositional action of 5-HT_{2C} antagonism on the outcome of 5-HT_{2A} blockage is supported by an explorative study performed with MDL-100907.[14] In this initial report of clinical activity of MDL-100907, the dose–response curves for activity assessment[15] did not show a steady increase, but a roughly "U-shaped" curve progression with a climax at the medium daily dosage (20 mg) with a decrease in efficacy at maximum daily dosage (40 mg). This suggests that at higher concentrations the 5-HT_{2C} activity of the drug comes into play and decreases the desired effect against 5-HT_{2A}. It can be speculated that this activity toward the 2C subtype is the reason behind the insufficient efficacy of MDL-100907 in trials for the treatment of psychosis,[16] even though high receptor occupancy was demonstrated in PET labeling studies.[17] Subsequently MDL-100907 has been reported in further clinical

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examinations to determine its potential to improve sleep quality.[18]

Another example of a potent and selective 5-HT_2 receptor antagonist is eplivanserin (Figure 1 b).[19] This oxime ether showed good selectivity for dopaminergic, α-adrenergic, and histaminergic receptors and differentiation to the 5-HT_1 receptors, but the compound is equally potent at the 5-HT_{2A} and 5-HT_{2C} receptor subtypes. The development of this drug candidate for schizophrenia and anxiety disorders has been reported and it is under clinical evaluation for chronic insomnia.[20]

These two examples, together with numerous nonselective compounds on the market (such as clozapine and olanzapine),[21] clearly indicate that it is difficult to establish selectivity between the 5-HT receptor subtypes 2A and 2C within one compound. As discussed above, however, and corroborated by more experimental results, a pronounced difference in receptor affinity at these targets appears to be essential because a ligand with equal potency at both serotonergic receptors 5-HT_{2A} and 5-HT_{2C} could lead to the disappearance of desired receptor effects.[22]

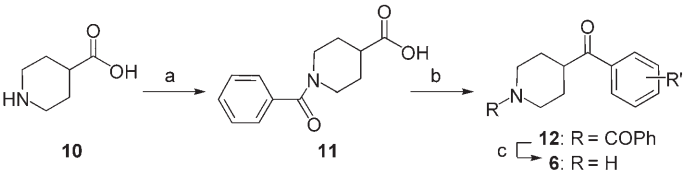
To thoroughly elucidate the meaning of 5-HT_{2A} selectivity and to confirm the hypothesis that selective 5-HT_{2A} receptor blockade alone is sufficient for antipsychotic efficacy,[23] we decided that a drug candidate should have at least a 1000-fold difference in affinity between the 5-HT receptor subtypes 2A and 2C. The MDL scaffold appeared quite promising for this challenge, and we used it as a starting point. Unfortunately no detailed structure–activity relationship has been reported yet for this compound class. We describe herein the optimization of the structure and the discovery of a selective 5-HT_{2A} antagonist that could serve as a useful tool for the understanding of serotonergic receptor functions.

Chemistry

The reference compound **26** (MDL-100907) and its *S* enantiomer **27** were synthesized and separated as described previously.[24] The syntheses of the compounds from Tables 1 and 2 were performed analogously to those depicted in Schemes 1 and 2. The piperidine ketones were prepared by two different routes. Either an aryl nitrile was transferred into the ketone with a piperidine Grignard reagent (Scheme 1) or a piperidine acid chloride was arylated in a Friedel–Crafts manner (Scheme 2).

After activation of benzoic acid **1** with $SOCl_2$ the resulting acid chloride[25] was transformed into the carboxamide **2**,[26] which was subsequently dehydrated to the cyano compound **3**.[26] The nucleophilic attack of 1-methylpiperidin-4-yl magnesium chloride at the cyano group gave, after hydrolysis of the resulting imine, the corresponding ketone **4**.[27] The N-methyl group was removed in a standard two-step sequence. First, the methyl moiety was exchanged to give the 2,2,2-trichloroethyl carbamate **5**, which was subsequently cleaved by reduction to the amine **6**. Commercially available 2-arylethanol compounds were converted into the corresponding mesylates **7**, and the basic nitrogen atom of **6** displaced the methylsulfonate group of **7** to give ketone **8**. The carbonyl carbon was reduced to the alcohol **9** with sodium borohydride.

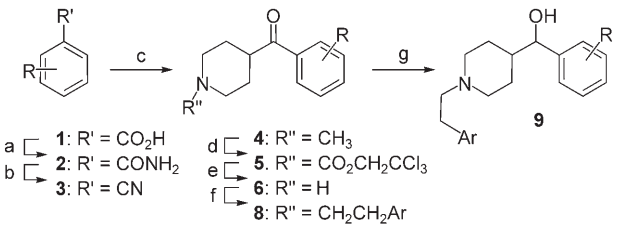
In an alternative approach to the arylpiperidine ketones, potassium piperidin-4-carboxylate **10** was N-acylated with benzoyl chloride to the corresponding benzamide **11** (Scheme 2).



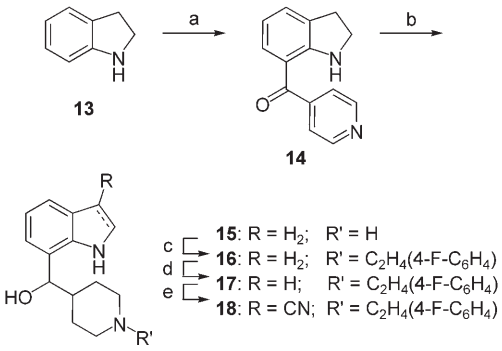
Scheme 2. a) K_2CO_3, H_2O, 0 °C, then benzoyl chloride, 0 °C→room temperature; b) $SOCl_2$, CH_2Cl_2, 40 °C, then $AlCl_3$, substituted benzene, CH_2Cl_2, 40 °C; c) HCl, H_2O, 100 °C. (For R and R′, see Tables 2 and 4).

The activated acid function of **11** was used in an aluminum chloride catalyzed Friedel–Crafts reaction with the appropriately substituted benzene derivatives to yield ketone **12**. The *N*-benzoyl protecting group of **12** was removed under acidic conditions to afford amine **6**, which was transformed further as described above for Scheme 1.

The corresponding indolyl compounds listed in Table 3 were prepared from an amino borane as described previously (Scheme 3).[28]



Scheme 1. a) $SOCl_2$, 80 °C, then NH_3/H_2O, toluene, room temperature; b) $SOCl_2$, 80 °C; c) 4-(1-methylpiperidine)magnesium chloride, THF, 60 °C; d) 2,2,2-trichloroethyl chloroformate, K_2CO_3, toluene, 110 °C; e) NH_4Cl, Zn, THF, room temperature; f) $ArCH_2CH_2OSO_2CH_3$ **7**, MeCN, $NaHCO_3$, 80 °C; g) $NaBH_4$, MeOH, room temperature. (For R and Ar, see Tables 1 and 2).

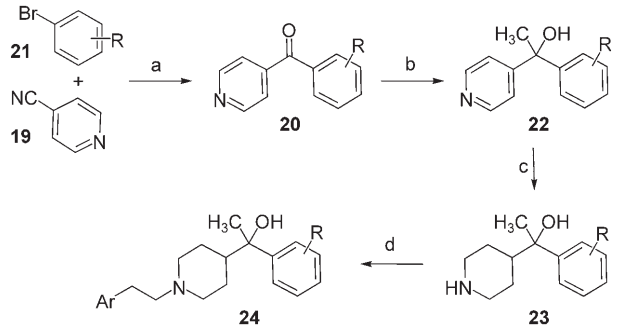


Scheme 3. a) MeCN, BCl_3, 4-CN-pyridine, $AlCl_3$, 0 °C→80 °C, then HCl, H_2O, 100 °C; b) H_2/Pd-C; c) 4-F-$(C_6H_4)CH_2CH_2OSO_2CH_3$, MeCN, $NaHCO_3$, 80 °C; d) MnO_2, H_2O; e) $POCl_3$, NH_4OH.

Indoline **13** was activated with boron trichloride and reacted with 4-cyanopyridine to the indolinyl-pyridinylmethanone **14**. The pyridine ring of this intermediate was hydrogenated selectively, and the carbonyl group was reduced simultaneously in one step with hydrogen at a Pd–charcoal contact to give the indolinyl-piperidinylmethanol **15**.[29] The N-alkylation of the piperidinyl group with 2-(4-fluorophenyl)ethyl mesylate proceeded to **16** as described above. The indole **17** was prepared by oxidation of the indoline with manganese(IV)oxide in water. Cyano substitution at position 3 of the indole to give **18** was carried out according to published methods.[30]

The tertiary alcohols listed in Table 6 were prepared starting from commercially available 4-cyano-pyridine **19** (Scheme 4).

Isonicotinic nitrile **19** was converted into the benzoyl pyridine **20** in an initial Grignard reaction with **21** followed by acidic hydrolysis of the intermediate imine. The carbonyl carbon atom of ketone **20** was attacked by methyl magnesium iodide to give 1,1-diarylethanol **22**. Selective hydrogenation of the pyridine moiety delivered a piperidine group with a basic nitrogen atom in **23**, which was further alkylated with phenethyl residues to afford **24** as described above.

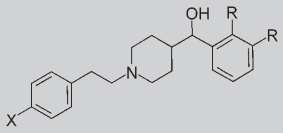


Scheme 4. a) Mg, THF; b) methyl magnesium iodide, ether; c) Pd-C, H_2; d) $NaHCO_3$, acetonitrile, $ArCH_2CH_2OSO_2CH_3$ **7** (for R and Ar, see Tables 5 and 6).

Results and Discussion

The receptor-binding profile of the unsubstituted racemic scaffold **25** (MDL-11939, glemanserin)[31] already showed some desired selectivity. The compound has affinity for 5-HT$_{2A}$ in the nanomolar range, only micromolar-range dopaminergic D_2 potential, and is ≈60-fold less potent toward the 5-HT$_{2C}$ receptor. The fluorine-substituted enantiomers **26** (MDL-100907) and **27** share similar receptor profiles, with the *R* enantiomer **26** being more potent and selective than the *S* enantiomer **27** at the serotonergic receptors. Dopaminergic D_2 and adrenergic α_1 receptor affinity is negligible for both antipodes (IC_{50} values: **26** = 1.5 μM, **27** = 1.0 μM; Table 1). Clearly the introduction of the electron-donating residues at the benzyl ring and the electron-withdrawing fluorine group at the phenethyl moiety improves potency toward both 5-HT receptor subtypes 2A and 2C equally; it therefore has no influence on the selectivity profile. In addition to the small amount of SAR information available for MDL-100907,[32] we prepared derivatives to gain insight into the compound class (Table 1).

Table 1. Receptor binding data for the fundamental scaffold with functional group variations at the phenethyl moiety.



			Receptor				
Compd	R	X	5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	D_2[a]	α_1[a]	2C/2A[b]
25	H	H	6.5 ± 2	400 ± 3	> 1000	ND	61
26 (*R*) MDL-100907	OMe	F	0.57 ± 0.2	35 ± 8	28000	1510 ± 268	61
27 (*S*) MDL-100907	OMe	F	15.6 ± 10	750 ± 86	> 10000	1000 ± 173	48
28	OMe	CN	73 ± 1	ND	ND	ND	ND
29	OMe	$CONH_2$	> 100	ND	> 10000	ND	ND

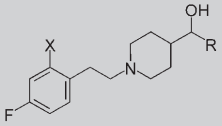
[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$). ND = not determined.

An initial comparison of *para* substitutions on the phenethyl group (compounds **25**–**29**) in Table 1 already indicates the subtle SAR at the 5-HT$_2$ receptors. A switch from the *para*-fluoro substituent to the bioisosteric 4-cyano residue in **28**[33] effects a decrease in 5-HT$_{2A}$ affinity by a factor of ≈130. This trend continues with the 4-carboxamide **29** and explains our emphasis on the modification of the benzylpiperidine moiety to optimize selectivity further.

Rigidifying the methoxy residues of **26** to the benzodioxane head group led to conservation of serotonergic activity (**30** and **31** in Table 2). The affinity for 5-HT$_{2A}$ is maintained upon substitution of the benzodioxane group with the bicyclic aromatic system naphthalene (compound **32**) and is decreased only slightly if the attachment position of the naphthyl group is moved one carbon unit from position 1 to position 2 (compound **33**). A decrease in the size of the aryl moiety and introduction of fluorine (compounds **34** and **35**) does not influence potency toward 5-HT$_{2A}$, but has an effect on the receptor profile. The 2C/2A subtype selectivity ratio of the fluoroaryl compound **35** is threefold higher than of **26**. We found that the introduction of electron-deficiency at the benzyl group decreases α-adrenergic receptor potential, as **34** shows an IC_{50} value of 3 μM at this target. Other heterocycles like thiophene in **36** or pyridine in **37** and **38** do not help in further optimization of 5-HT$_{2A}$ receptor affinity.

The aza heterocycles **39**–**42** listed in Table 3 show that this modification has some potential.[8,34,35] Interestingly, indoline **39** is not as selective as the oxidized indole analogue **40**,

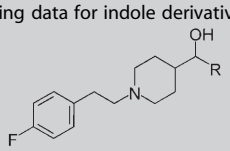
Table 2. Receptor binding data for substitutions at the benzyl ring of secondary alcohols.



Compd	R	X	Receptor 5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	D$_2$[a]	2C/2A[b]
30	benzodioxan-5-yl	H	3.8 ± 1.1	200 ± 58	> 1000	52
31	benzodioxan-5-yl	F	3.2 ± 0.6	28 ± 0.6	> 1000	8
32	1-naphthyl	H	3.8 ± 1.8	ND	ND	ND
33	2-naphthyl	H	9 ± 4	ND	1600 ± 305	ND
34	4-fluorophenyl	H	6.4 ± 1.9	> 1000	> 20000	ND
35	4-fluorophenyl	F	3.2 ± 0.4	1000 ± 121	> 10000	312
36	2-thienyl	H	3.9 ± 0.6	ND	> 15000	ND
37	4-pyridinyl	H	5.8 ± 1.9	1000 ± 153	> 1000	172
38	4-pyridinyl	F	9.1 ± 5.9	300 ± 100	> 1000	32

[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$). ND = not determined.

Table 3. Receptor binding data for indole derivatives.



Compd	R	Receptor 5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	2C/2A[b]
39	7-indolinyl	27 ± 19	180 ± 35	6
40	7-indolyl	2.2 ± 0.9	560 ± 182	254
41	3-(2,2,2-trisfluoroacetyl)indol-7-yl	31 ± 8	400 ± 87	12
42	3-cyanoindol-7-yl	9 ± 5.6	450 ± 29	50

[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$).

which has equal selectivity to that of **35**. The two indoles with electron-withdrawing groups in position 3 (compounds **41** and **42**) are less selective and less potent than the unsubstituted derivative **40**.

Besides the discussed modifications of substituents at the benzyl group, we addressed the stabilization of a certain conformation of the arylpiperidine linkage to further improve receptor affinity and selectivity. Because the ketones of the corresponding alcohols were available from the syntheses as outlined above, we determined the receptor binding for the carbonyl derivatives (Table 4).

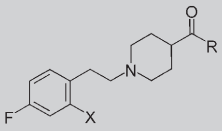
The benzyl residues previously mentioned such as those in **25**, **26**, **30**–**33**, **35**, **40**, and **42** (see **43**–**48**, **53**, **57**, and **58**) and some additional modifications (**49**–**52**, **55**, **56**) were evaluated as the corresponding ketones. In general, 5-HT$_{2A}$ activity decreases slightly upon a switch from the alcohol to the ketone forms by factors ranging from ≈2 (for **44** versus **26**) to ≈4 (for **43** versus **25**). The indole couples **40**/**57** and **42**/**58** are an interesting comparison. In these two cases, the loss in activity is much higher than for the other compounds; the activity of **57** is 55-fold less than that of **40**, and a 16-fold decrease is observed for **58** relative to **42**. For some explicit examples from this series, dopaminergic D$_2$ receptor binding was determined and found to be only moderate. The most potent 5-HT$_{2A}$ ligand **44** has affinity for the D$_2$ receptor in the micromolar range and an IC_{50} value of 300 nM at the α-adrenergic receptor subtype 1. The D$_2$ receptor affinity of the compound with the highest 2C/2A ratio of IC_{50} values in this series, **56**, is also negligible.

Another alternative to the carbonyl bridge for the introduction of higher barriers of rotational energy between the aryl and the piperidinyl moiety is possible through the conversion of the secondary alcohol into a tertiary alcohol. The previously described (in compounds **59**–**63**) and some new aryl residues (in compounds **64**–**73**) were considered for the analysis of the affinity of corresponding tertiary alcohols (Table 5).

Interestingly, many compounds of the entire series have affinity for 5-HT$_{2A}$ in the single-digit nanomolar (**61**–**63**, **65**, **66**, **69**, **72**) or even sub-nanomolar ranges (**59**, **64**), and for selected entries we show that the dopaminergic potential is negligible. The permutation of fluorine at the phenyl group (**67**–**73**) does not improve the affinity for the 2A subtype; therefore, these derivatives were not examined further. It is clear that the introduction of a methyl group does not improve the affinity for 5-HT$_{2A}$ in general and that it has only marginal effects on the 2C/2A selectivity in comparison with the secondary alcohol analogues listed in Table 2. At this point, compound **35** was the most promising derivative, and thus we decided to prepare the tertiary analogue **74** (Table 6). For this case as well, the receptor profile was not much better than that of our benchmark compound **26**. Nevertheless, we decided to examine the 1-(4-fluorobenzyl)ethanol derivatives in more detail and to cross-check the inverted electronic properties of the benzyl ring relative to **26** to determine whether they influence the SAR around the substitution pattern of the phenethyl moiety (Table 6).

With regard to 5-HT$_{2A}$ activity and 2C/2A selectivity, the 4-chloro derivative **75** represents an approximate 6-fold improvement over **26**, **35**, and **74**. All other derivatives **76**–**99** are either less selective or have potencies in agreement with the results listed in Table 4. Clearly dual *ortho* substitutions on the phenethyl moiety are not well-tolerated by the 5-HT$_{2A}$ receptor, as shown with the chlorofluoro derivative **87** (IC_{50} = 110 nM) and the fluoro trifluoromethyl derivative **96** (IC_{50} = 330 nM). Single *ortho* substitution is tolerated, as shown by the fluorinated **77** (IC_{50} = 0.7 nM), the chlorinated **79** (IC_{50} = 0.6 nM), and even the trifluoromethylated **92** (IC_{50} = 1.7 nM). Two small fluo-

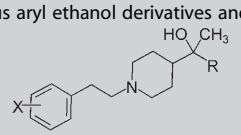
Table 4. Receptor binding data for ketones.



Compd	R	X	Receptor 5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	D$_2$[a]	2C/2A[b]
43	phenyl	H	24 ± 13	ND	ND	ND
44	2,3-dimethoxyphenyl	H	0.9 ± 0.05	70 ± 9	3800 ± 389	75
45	2,3-dihydrobenzo[1,4]dioxin-5-yl	H	8.6 ± 2.9	300 ± 52	> 1000	34
46	2,3-dihydrobenzo[1,4]dioxin-5-yl	F	6.8 ± 0.7	100 ± 15	3000 ± 299	14
47	1-naphthyl	H	6.3 ± 2	ND	ND	ND
48	2-naphthyl	H	21 ± 12	ND	560 ± 58	ND
49	4-methoxyphenyl	H	21 ± 3	ND	ND	ND
50	2-amino-4-fluorophenyl	H	4.4 ± 3	100 ± 41	260 ± 32	22
51	2-formamido-4-fluorophenyl	H	16 ± 10	100 ± 50	3500 ± 279	6
52	4-chlorophenyl	H	24 ± 6	ND	ND	ND
53	4-fluorophenyl	H	9 ± 4	600 ± 104	590 ± 120	66
54	2,4-difluorophenyl	H	8.7 ± 2.8	ND	ND	ND
55	2-hydroxy-4-phenyl	H	24 ± 13	ND	ND	ND
56	2-methoxy-4-fluorophenyl	H	3.7 ± 1	700 ± 234	1200 ± 301	189
57	7-indolyl	H	120 ± 31	> 1000	ND	ND
58	3-cyanoindol-7-yl	H	140 ± 89	> 1000	ND	ND

[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$). ND = not determined.

Table 5. Receptor binding data for various aryl ethanol derivatives and fluorine atom positions.



Compd	R	X	Receptor 5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	D$_2$[a]	2C/2A[b]
59	phenyl	4-F	0.7 ± 0.15	30 ± 8	> 1000	44
60	2,3-dimethoxyphenyl	4-F	11 ± 7	60 ± 5	1800 ± 458	5
61	1-naphthyl	4-F	5.2 ± 1.8	ND	ND	ND
62	2,3-dihydrobenzo[1,4]dioxin-5-yl	4-F	3.7 ± 0.2	15 ± 6	1800 ± 376	4
63	4-chlorophenyl	4-F	2.1 ± 0.3	70 ± 16	2100 ± 297	33
64	2-methoxy-5-fluorophenyl	4-F	0.8 ± 0.09	ND	980 ± 158	ND
65	4-OCF$_3$-phenyl	4-F	2 ± 0.9	ND	ND	ND
66	4-OCF$_3$-phenyl	2,4-F$_2$	4.3 ± 1.9	ND	ND	ND
67	4-CF$_3$-phenyl	4-F	2.9 ± 0.6	300 ± 62	1520 ± 199	101
68	4-CF$_3$-phenyl	3-F	11 ± 5	ND	ND	ND
69	4-CF$_3$-phenyl	2-F	1.9 ± 0.8	ND	ND	ND
70	4-CF$_3$-phenyl	2,3-F$_2$	29 ± 13	ND	ND	ND
71	4-CF$_3$-phenyl	3,4-F$_2$	29 ± 9	ND	ND	ND
72	4-CF$_3$-phenyl	2,4-F$_2$	2 ± 0.7	ND	ND	ND
73	4-CF$_3$-phenyl	2,6-F$_2$	64 ± 19	ND	ND	ND

[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$). ND = not determined.

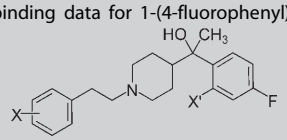
rine substituents in both *ortho* positions lead to a decrease in affinity (**86**: IC_{50} = 32 nM). The CF_3 substituent warrants further detailed discussion. Direct attachment at the *para* position (compounds **91**, **93**, and **94**) or as the ether (compound **84**) is not well-tolerated by the 5-HT$_{2A}$ receptor, and neither is substitution at the *meta* position (compound **97**). Derivatives **92** and **95** indicate that single substitution with CF_3 in the *ortho* position is tolerated for 5-HT$_{2A}$ binding. These findings confirm the observations concerning the subtle structure–activity relationship around the phenethyl moiety which were given above in the discussion of Table 1. The introduction of further fluorine substitutions in the benzyl ring does not substantially influence the discussed profile as shown by **97**.

Methylation of the OH function of **74** to the methyl ether 1-[2-(4-fluorophenyl)ethyl]-4-[1-(4-fluorophenyl)-1-methoxyethyl]piperidine resulted in some loss of affinity toward receptor subtype 2A, as expected (IC_{50} = 12 nM).

At this point, we had a couple of compounds in hand which showed interesting affinities to the serotonergic receptors but their selectivity was not much better than that of **26**. However, this is for the comparison of racemic mixtures with the enantiomerically pure benchmark, and as mentioned above, the configuration of the benzyl carbon atom is known to be important for target interactions.[24b] Therefore, we decided to separate the enantiomers of some of these compounds by chiral HPLC. The results for a selection of compounds (**30**, **63**, **67**, **74**, and **98**) are shown in Table 7.

For all examples, the dextrorotatory enantiomers are more active and selective than the levorotatory antipodes. The separation of enantiomers does not result in the gain or loss of activity by a factor of two for the examined targets. The measured affinity has a dramatic effect on the selectivity of the compounds: The 2C/2A IC_{50} ratio for the benzodioxane isomer (+)-**30** is roughly one order of magnitude better than that of the racemic mixture **30**. In contrast, the optically pure (+)-**63** and (+)-**67** show selectivities that are only within the range of their respective racemates. This trend is reversed for the other two derivatives **74** and **98**. We cannot explain why the racemic mixture of **98** is 25-fold more selective than the enantiomeri-

Table 6. Receptor binding data for 1-(4-fluorophenyl)ethanol derivatives.



Compd	X	X′	Receptor 5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	D$_2$[a]	2C/2A[b]
74	4-F	H	1.3 ± 0.3	100	8100 ± 580	76
75	4-Cl	H	1 ± 0.6	400 ± 127	4600 ± 408	400
76	3-F	H	7 ± 4.7	500 ± 104	> 1000	71
77	2-F	H	0.7 ± 0.3	45 ± 9	> 1000	64
78	2-OMe	H	2.5 ± 0.2	ND	ND	ND
79	2-Cl	H	0.6 ± 0.2	20 ± 11	310 ± 99	32
80	2-Br	H	1 ± 0.6	10 ± 2.9	970 ± 102	10
81	4-CN	H	27 ± 9	ND	ND	ND
82	4-OH	H	4.2 ± 0.8	ND	ND	ND
83	2-Me	H	1.4 ± 0.3	35 ± 9	> 1000	25
84	4-OCF$_3$	H	110 ± 18	ND	ND	ND
85	2,4-F$_2$	H	0.8 ± 0.1	20 ± 4	> 1000	24
86	2,6-F$_2$	H	32 ± 12	ND	ND	ND
87	2-F-6-Cl	H	110 ± 64	ND	ND	ND
88	3,4-F$_2$	H	4.5 ± 0.2	200 ± 41	> 13 000	44
89	2,3-F$_2$	H	7.2 ± 1.9	400 ± 87	7600 ± 156	55
90	2,4-Cl$_2$	H	2 ± 0.3	ND	1900 ± 203	ND
91	4-CF$_3$	H	32 ± 15	ND	ND	ND
92	2-CF$_3$	H	1.7 ± 0.5	30 ± 9	> 1000	17
93	3-F-4-CF$_3$	H	> 100	ND	ND	ND
94	2-F-4-CF$_3$	H	44 ± 17	ND	ND	ND
95	4-F-2-CF$_3$	H	9.8 ± 4.7	ND	ND	ND
96	2-F-6-CF$_3$	H	330 ± 58	ND	ND	ND
97	3-F-5-CF$_3$	F	> 100	ND	ND	ND
98	4-F	F	0.7 ± 0.1	910 ± 84	> 1000	1300
99	2-F	F	1.1 ± 0.7	100 ± 21	2300 ± 252	90

[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$). ND = not determined.

Table 7. Receptor binding data for purified enantiomers of selected compounds.

Compd	Receptor 5-HT$_{2A}$[a]	5-HT$_{2C}$[a]	D$_2$[a]	α_1[a]	2C/2A[b]
(−)-**30**	15	200	ND	ND	13
(+)-**30**	1.8	> 1000	ND	700	> 500
(−)-**63**	110	ND	ND	ND	ND
(+)-**63**	0.78	40	1200	1000	51
(−)-**67**	30	ND	2900	ND	ND
(+)-**67**	1.2	100	830	2000	83
(−)-**74**	57	> 1000	> 1000	2500	> 17
(+)-**74**	0.37	490	2450	1000	1324
(−)-**98**	22	700	> 1000	1000	31
(+)-**98**	0.85	45	2300	1000	52

[a] Values of IC_{50} [nM] ± SEM were obtained from 5–10 different concentrations of the compound, each in triplicate. [b] Ratio of IC_{50} (5-HT$_{2C}$) over IC_{50} (5-HT$_{2A}$). ND = not determined.

cally pure dextrorotatory isomer. Nevertheless, the antipode (+)-**98** has equal potency to the racemate in 5-HT$_{2A}$ binding.

We made a breakthrough with (+)-**74**, and discovered a compound with a four-digit ratio of selectivity between the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. This compound shows sub-nanomolar range affinity in 5-HT$_{2A}$ binding and such a weak interaction with the 5-HT$_{2C}$ receptor subtype that the selectivity ratio is greater than 1300. We observed an improvement by a factor of ≈18 after separation of the racemic mixture and finally obtained the exact profile for which we had been aiming at the start of the optimization program.

Comparison of the binding data of the racemic mixtures with the enantiomerically pure antipodes emphasizes that there is more gained from the separation of the mixture than just a factor of two. It is likely that subtle interactions between the enantiomers and the receptor are responsible for these results, which are hardly predictable.

To verify that the rotational direction of the optical activity and the absolute configuration of (+)-**74** correlate with the absolute configuration of **26**, we conducted an X-ray crystallographic analysis (Figure 2).[36] Chiral, enantiomerically pure 1-(4-fluorophenyl)-1-piperidin-4-yl-ethanol[37] of unknown absolute configuration was crystallized with a chiral, enantiomerically pure phosphonic acid[38] with known absolute configuration at the asymmetric center. The results of the single-crystal diffraction analysis show that the applied 1-(4-fluorophenyl)-1-piperidin-4-yl-ethanol has the *S* configuration at the asymmetric center. Accordingly, we could reason that the absolute configuration of the building block in the preparation of (+)-**74** has the *R* configuration; we conclude that the orientation of the alcohol function of (+)-**74** is directly comparable with that of **26**.

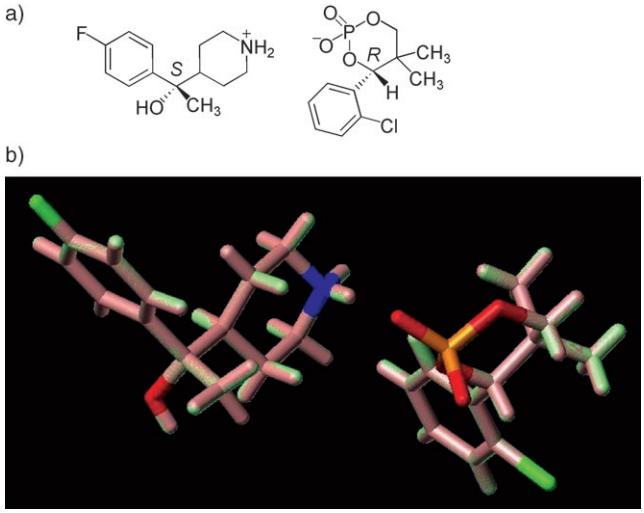


Figure 2. a) Structures and b) stick representation of the results of the X-ray crystallographic analysis of enantiomerically pure 1-(4-fluorophenyl)-1-piperidin-4-yl-ethanol (left) crystallized with enantiomerically pure phosphonic acid (right).

Conclusions

Herein, we show that phenethylpiperidine aryl methanol is a suitable platform for the identification and optimization of highly potent and selective 5-HT$_{2A}$ antagonists relative to MDL-100907. The phenethyl moiety could not be further optimized, and the *para*-fluoro substitution was confirmed to be best

suited within this scaffold as is already the case for **26**. Modification of the second aryl group allowed improvement and the bis-(fluorophenyl) compound **35** was found to be highly potent and more selective than **26**. The bridging area between the piperidine and this second aryl group seems to have a strong influence on compound attributes.[34] In the ketone derivative series (Table 4), the same substitution pattern as that of **35** with one fluorine atom on each aryl moiety (compound **53**) showed the same selectivity as the benchmark **26**. Methylation of the benzyl carbon atom in conjunction with the two fluorophenyl residues led to the most potent (sub-nanomolar binding affinity for 5-HT_{2A}) and selective (2C/2A > 1300) derivative in this series (*R*-(+)-**74**; IC_{50} values [nM]: 5-HT_{1A}, 3.6 μM; 5-HT_{1D}, > 10 μM; 5-HT_3, > 10 μM; 5-HT_4, > 10 μM; 5-HT_6, > 1 μM; D_3, 6.1 μM; D_4, 1.6 μM; H_1, 1.13 μM; α_2, 1.6 μM). Notably, the SAR around **26** and *R*-(+)-**74** can hardly be compared, although the molecules look quite similar at first glance. Racemate **60**, the tertiary alcohol analogue of the secondary alcohol **26**, shows much weaker 5-HT_{2A} affinity and much stronger 5-HT_{2C} affinity than the unmethylated parent compound **26**, resulting in a selectivity ratio of 5. Clearly the change from a secondary to a tertiary alcohol reverses the electronic demands of the benzyl moiety. The introduction of two electron-donating methyl ethers has no influence on the 2A/2C selectivity ratio of **26** in comparison with **25**, but for the tertiary alcohol, the electron-withdrawing fluorine atom gave much more potent and selective compounds (for example, **60** versus **74** and **26** versus **74**).

The development compound **26** is metabolized to the 3-desmethyl derivative MDL-105725 (Figure 1).[39] Furthermore, it can be speculated that oxidation of the secondary alcohol function could represent another route in the metabolism of this drug. The compound optimization described herein should contribute to metabolic stability of the scaffold. The enzymatic transformations of **26** cannot take place with *R*-(+)-**74** and the two electron-deficient aryl moieties should be more resistant to oxidative cytochrome P metabolism than the methoxy-substituted benzene group of **26**. Our efforts to prepare even more potent and selective 5-HT_{2A} antagonists without a stereogenic center through the introduction of an amide bridge between the basic nitrogen atom and the benzyl group have been described elsewhere.[34,35]

Experimental Section

Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. IR, ^{1}H NMR and MS data are in agreement with the structures and were recorded on a Bruker IFS 48 IR spectrophotometer, a Bruker AMX 250 MHz or DRX 500 MHz NMR spectrometer (with trimethylsilane (TMS) as an internal standard), and Vacuum Generators VG 70-70 or 70-250 (MS) at 70 eV. Elemental analyses (obtained with a Perkin–Elmer 240 BCHN analyzer) for the final products were within 0.4% of calculated values if not otherwise stated. All reactions were followed by TLC carried out on Merck KGaA F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure.

General reaction procedures:

Methanesulfonic acid 2-(4-fluorophenyl)ethyl ester: Commercially available 2-(4-fluorophenyl)ethanol (50.0 g, 0.35 mol) was dissolved in dichloromethane (1 L) and cooled to 0 °C. Methanesulfonyl chloride (34.3 mL, 0.44 mol) was added slowly followed by triethylamine (74.8 mL, 0.54 mol). After 1 h, the suspension was poured into 1 L ice-cold water. The aqueous phase was extracted with dichloromethane, and the combined organic layers were dried over sodium sulfate, filtered, and evaporated to give a yellow oil (76.0 g, 99%), which was used without further purification.

*4-(2-{4-[(2,3-Dimethoxyphenyl)hydroxymethyl]piperidin-1-yl}ethyl)benzonitrile (**28**):* Commercially available 2-(4-aminophenyl)ethan-1-ol (35.6 g, 0.26 mol) was dissolved in water (140 mL) and HCl (44 mL, conc. aq.). The solution was cooled to 0 °C, and sodium nitrite (18.4 g) in water (44 mL) were added slowly. After 5 min, sodium carbonate was added to bring the reaction mixture to pH 7.

In a second vessel, CuCN (28.7 g, 0.3 mol) and KCN (41.7 g, 0.6 mol) were dissolved in water (130 mL) and toluene (150 mL). This solution was cooled to 0 °C and the afore-prepared reaction mixture was added quickly. After stirring for 30 min at 0 °C, the cooling bath was removed and stirring was continued for a further 4 h. The mixture was then added to ethyl ester (800 mL) and the resulting solution was washed sequentially with 1 N NaOH, H_2O, 1 N HCl, and H_2O. The organic phase was dried over magnesium sulfate, filtered, and evaporated to give a crude red oil (26.3 g), which was transferred into the corresponding mesylate without further purification.

The alcohol (26.3 g, 0.2 mol) was dissolved in dichloromethane (1 L) and cooled to 0 °C. First methanesulfonyl chloride (15.3 mL, 0.2 mol) and then triethylamine (30.1 mL, 0.2 mol) were added. After 45 min, the reaction mixture was poured into ice-cold water (1 L). The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with water, dried over sodium sulfate, filtered, and evaporated to dryness to give a crude oil (39 g), which was used without further purification.

The mesylate (11.3 g, 50 mmol), 4-(2,3-dimethoxyphenyl)piperidin-4-yl-methanone hydrochloride (14.3 g, 50 mmol) and triethylamine (13.9 mL, 0.1 mol) were dissolved in acetonitrile (450 mL). After the addition of $NaHCO_3$ (8.4 g, 0.1 mmol) the suspension was heated at reflux for 12 h. After cooling to room temperature the solvent was evaporated, and the crude residue was dissolved in water and ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. After purification over silica gel, the free base was isolated (7.5 g). The base (2.0 g) was dissolved in acetone (40 mL) and HCl in ethanol was added to bring the solution to pH 2. Addition of ethyl ether caused the hydrochloride to precipitate to give brownish crystals (1.8 g) 4-{2-[4-(2,3-dimethoxybenzoyl)piperidin-1-yl]ethyl}benzonitrile; mp: 206–208 °C; Anal. ($C_{23}H_{26}N_2O_3$·HCl) C; H; N; Cl.

The ketone (5.2 g, 14 mmol) was dissolved in methanol (180 mL), and $NaBH_4$ (2.6 g, 69 mmol) was added in portions. After the addition was complete, the suspension was stirred for an additional 30 min. The reaction mixture was then evaporated to dryness, and the crude residue was dissolved in water and ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and evaporated to give a colorless oil (6.1 g). The oil was dissolved in acetone, and HCl in ethanol was added to bring the solution to pH 2. Addition of ethyl ether caused the hydrochloride to precipitate, giving colorless crystals of **28** (3.9 g, 67%); mp: 184–186 °C; ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 10.48 (br s, 1H), 7.80 (d, 2H, J = 8.2 Hz), 7.48 (d, 1H, J = 8.2 Hz), 7.09–6.92 (m, 3H), 5.24 (br s, 1H), 4.65 (br s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.53 (m, 1H), 3.46 (m, 1H), 3.18 (m,

4H), 2.84 (m, 2H), 1.92 (m, 1H), 1.71 (m, 3H), 1.39 ppm (br m, 1H); Anal. ($C_{23}H_{28}N_2O_3$·HCl) Cl; C: calcd 66.2, found 65.4; H: calcd 7.0, found 6.1; N: calcd 6.7, found 5.9; EI MS [M^+]: *m/z* 380.

*4-(2-{4-[(2,3-Dimethoxyphenyl)hydroxymethyl]piperidin-1-yl}ethyl)benzamide (**29**):* Nitrile **28** (0.8 g, 2 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF, 20 mL), and DMSO (0.5 mL, 7 mmol) and H_2O_2 (1.3 mL, 30%, 10 mmol) were added. Potassium carbonate (1.4 g, 10 mmol) was added, and the suspension was stirred for 2 h at room temperature. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate. The organic phase was dried, filtered, and evaporated to dryness after checking for peroxide with MerckoQuant 10011. The resulting oil was transferred into the corresponding hydrochloride as described above to give yellowish crystals of **29** (0.1 g, 12%); mp: 221–223 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 10.30$ (br s, 1H), 7.93 (br s, 1H), 7.83 (d, 2H, $J = 8.2$ Hz), 7.32 (d, 1H, $J = 8.2$ Hz), 7.29 (br s, 1H), 7.09–6.92 (m, 3H), 5.25 (br s, 1H), 4.65 (d, 1H, $J = 5.1$ Hz), 3.80 (s, 3H), 3.73 (s, 3H), 3.51 (m, 2H), 3.19 (m, 2H), 3.10 (m, 2H), 2.84 (m, 2H), 1.92 (m, 1H), 1.71 (m, 2H), 1.42 ppm (m, 1H); Anal. ($C_{23}H_{30}N_2O_4$·HCl) H; Cl; N; C: calcd 63.5, found 62.4; EI MS [M^+]: *m/z* 399.

*(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl} methanone (**45**) and (2,3-dihydrobenzo[1,4]dioxin-5-yl)-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl} methanol (**30**)*: Commercially available 2,3-dihydroxybenzoic acid (44 g, 0.3 mol) and KOH (46.5 g, 0.8 mol) were dissolved in water (250 mL) and ethanol (100 mL). 1,2-Dibromoethane (25 mL, 0.3 mol) was added, and the reaction mixture was heated at reflux for 20 h. The solution was poured over ice (300 g) and HCl (30 mL, 37%, aq.). The resulting precipitate was filtered and washed with water to give 35 g colorless crystals of 2,3-dihydrobenz[1,4]dioxine-5-carboxylic acid.[26] The acid (12 g; 61 mmol) was added to $SOCl_2$ (50 mL) and heated at reflux for 1.5 h. Excess $SOCl_2$ was distilled off, and toluene was used twice (100 mL each) for co-distillation. The crude acid chloride[25] was dissolved in toluene (50 mL), and ammonia (150 mL, 25% in water) was added at 10 °C. After 0.5 h stirring at room temperature the resulting precipitate was filtered and dried to give yellow crystals of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid amide (10.1 g);[26] mp: 130 °C.

The carboxamide (9.9 g, 55.2 mmol) was added to $SOCl_2$ (50 mL, 0.7 mol) and heated at reflux for 3 h. Excess $SOCl_2$ was distilled off, and the crude product was added to ice-cold water. The aqueous phase was extracted with ethyl ether, and the organic phase was washed with a saturated solution of $NaHCO_3$ and brine. After the usual procedure, the yellow oil (10 g) was crystallized with *tert*-butyl methyl ether to give colorless crystals of 2,3-dihydrobenzo-[1,4]dioxine-5-carbonitrile (8.4 g);[26] mp: 53 °C.

Magnesium (0.6 g, 24.6 mmol) was immersed in THF (5 mL), and iodomethane (50 μL) was added. When the solvent started boiling, commercially available 4-chloro-1-methylpiperidine (3.3 g, 24.6 mmol) dissolved in THF (25 mL) was added. After 1 h heating at reflux, the afore-prepared nitrile (3.4 g, 21 mmol) dissolved in THF (20 mL), was added at 30 °C. After the addition was complete the reaction mixture was heated at reflux for an additional 2 h. After cooling to room temperature the reaction mixture was poured into a saturated aqueous solution of ammonium chloride (20 mL) and extracted with *tert*-butyl methyl ether. The organic phase was washed with brine and evaporated to dryness. The resulting crude yellow oil was purified by flash chromatography over silica gel to give (2,3-dihydrobenzo[1,4]dioxin-5-yl)-(1-methylpiperidin-4-yl) methanone (2.7 g); mp: 195–200 °C.

The methyl piperidine (2.4 g, 9.2 mmol), commercially available 2,2,2-trichloroethyl chloroformate (4.0 g, 18.8 mmol) and potassium carbonate (1.9 g, 13.7 mmol) were dissolved in toluene (50 mL). The suspension was heated at reflux for 4 h, and methanol (3 mL) was added to the reaction mixture drop by drop. The solvent was evaporated very slowly and the resulting slurry was dissolved in ether and washed with water and brine. The organic phase was dried, filtered, and evaporated to dryness. The resulting crude product was crystallized from ether to give colorless crystals of 4-(2,3-dihydrobenzo[1,4]dioxine-5-carbonyl)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester (2 g); mp: 150 °C.

The carbamate (3.3 g, 6.2 mmol) was dissolved in THF (30 mL), and a solution of ammonium chloride (1 M, 5 mL) and Zn dust (4 g) were added. The suspension was stirred for 3 h at room temperature, filtered, washed with methanol, and evaporated to dryness. The resulting slurry was dissolved in *tert*-butyl methyl ether and washed with HCl (2 N, aq.) and an aqueous solution of NaOH (32%). After evaporation of the solvent the crude product was dissolved in ether, and HCl in ether was added to bring the solution to pH 2. Crystallization was induced with acetone to give colorless crystals of (2,3-dihydrobenzo[1,4]dioxin-5-yl)piperidin-4-yl methanone hydrochloride (240 mg); mp: 195 °C.

This secondary amine (570 mg, 2 mmol) was dissolved in acetonitrile (10 mL), and $NaHCO_3$ (400 mg, 4.8 mmol) and 2-(4-fluorophenyl)ethenyl mesylate (480 mg, 2.2 mmol) were added. The suspension was heated at 80 °C for 12 h and poured into water after cooling to room temperature. The aqueous phase was extracted with dichloromethane, and the combined organic phases were washed with water and brine. After drying over sodium sulfate, filtration, and evaporation, the resulting crude yellow oil (1.1 g) was dissolved in acetone, and methanol and HCl in ether were added to bring the solution to pH 2. The resulting colorless crystals were filtered and dried to give (2,3-dihydrobenzo[1,4]dioxin-5-yl)-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl} methanone (**45**) (467 mg, 63%); mp: 216–218 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 10.11$ (br s, 1H), 7.34 (d, 1H, $J = 5.7$ Hz), 7.31 (d, 1H, $J = 5.6$ Hz), 7.18 (t, 2H, $J = 8.8$ Hz), 7.08 (m, 2H), 6.92 (t, 1H, $J = 7.8$ Hz), 4.33 (m, 4H), 3.61 (m, 2H), 3.44 (m, 1H), 3.24 (m, 2H), 3.04 (m, 4H), 2.05 (m, 2H), 1.89–1.73 ppm (m, 2H); Anal. ($C_{22}H_{24}FNO_3$·HCl) C; H; Cl; F; N.

The ketone **45** (560 mg, 1.5 mmol) was dissolved in MeOH (10 mL), and $NaBH_4$ (80 mg) was added in portions. Further $NaBH_4$ (210 mg, 5 mmol) was added at intervals of 0.5 h. After the reaction was completed, the solvent was removed in vacuum, and the residue was dissolved in *tert*-butyl methyl ether and water. The aqueous phase was extracted with ether, and the combined organic phases were washed with water and brine, dried over sodium sulfate, filtered, and evaporated to dryness to give a yellow oil (527 mg, 94%). The oil (175 mg) was dissolved in acetone, and HCl in ether was added to bring the solution to pH 2. The precipitate was filtered and dried to give colorless crystals of **30** (103 mg, 58%); mp: 97 °C (foaming!) ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 9.91$ (br s, 1H), (7.31, d, 1H, $J = 5.7$ Hz), 7.28 (d, 1H, $J = 5.6$ Hz), 7.16 (t, 2H, $J = 8.9$ Hz), 6.93 (dd, 1H, $J = 1.7$ Hz and $J = 7.5$ Hz), 6.82 (t, 1H, $J = 7.9$ Hz), 6.73 (dd, 1H, $J = 1.7$ Hz and $J = 7.9$ Hz), 5.20 (br s, 1H), 4.69 (d, 1H, $J = 4.2$ Hz), 4.23 (s, 4H), 3.51 (m, 2H), 3.19 (m, 3H), 3.01 (m, 2H), 2.85 (m, 2H), 1.88–1.52 ppm (m, 6H); Anal. ($C_{22}H_{26}FNO_3$·HCl) H; N; C: calcd 64.8, found 62.5; Cl: calcd 8.7, found 10.0; EI MS [M^+]: *m/z* 371.

*{1-[2-(2,4-Difluorophenyl)ethyl]piperidin-4-yl}-(2,3-dihydrobenzo-[1,4]dioxin-5-yl) methanone (**46**)*: The above-described (2,3-dihydrobenzo[1,4]dioxin-5-yl)piperidin-4-yl methanone (570 mg, 2 mmol) was dissolved in acetonitrile (10 mL), and methanesulfonic acid 2-(2,4-difluorophenyl)ethyl ester (620 mg, 2.4 mmol, 90% pure) and $NaHCO_3$ (400 mg, 4.8 mmol) were added; the suspension was refluxed for 12 h. After aqueous work-up and extraction with

dichloromethane, the combined organic phases were dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by chromatography to give the free base (709 mg, 91%). The base (198 mg) was dissolved in acetone and crystallized with HCl in ether to give white crystals of the title compound **46** (156 mg, 77%); mp: 221–223 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta =$ 10.11 (br s, 1H), 7.43 (q, 1H, $J = 8.6$ Hz), 7.26 (dt, 1H, $J = 2.5$ Hz and $J = 9.6$ Hz), 7.08 (m, 3H), 6.92 (t, 1H, $J = 7.8$ Hz), 4.33 (m, 4H), 3.63 (m, 2H), 3.45 (m, 1H), 3.24 (m, 2H), 3.13–2.99 (m, 4H), 2.06 (m, 2H), 1.89–1.72 ppm (m, 2H); Anal. ($C_{22}H_{23}F_2NO_3$·HCl) H; Cl; N; F; C: calcd 62.3, found 61.7; EI MS [M^+]: *m/z* 387.

*{1-[2-(2,4-Difluorophenyl)ethyl]piperidin-4-yl}-(2,3-dihydrobenzo-[1,4]dioxin-5-yl) methanol (**31**)*: Ketone **46** (511 mg, 1.3 mmol) and $NaBH_4$ (170 mg, 4.5 mmol) were suspended in methanol (30 mL) and stirred for 0.5 h at room temperature. The solvent was removed in vacuum, and the residue was dissolved in water and extracted with ether. After the usual drying and evaporation, the crude product was crystallized from acetone with HCl in ether to give pink crystals of **31** (324 mg, 58%); mp: 88–89 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 9.89$ (s, 1H), 6.92 (m, 2H), 6.82 (m, 2H), 6.73 (m, 2H), 5.21 (br d, 1H, $J = 4.1$ Hz), 4.69 (br s, 1H), 4.23 (s, 4H), 3.51 (m, 2H), 3.11 (m, 2H), 2.94–2.77 (m, 4H), 2.37 (m, 1H), 2.31 (m, 1H), 1.87–1.53 ppm (m, 4H); Anal. ($C_{22}H_{25}F_2NO_3$·HCl) H; Cl; F; N; C: calcd 62.0, found 59.8; EI MS [M^+]: *m/z* 389.

*(4-Fluorophenyl)-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl} methanol (**35**)*: Potassium carbonate (255 g, 1.8 mol) and piperidine-4-carboxylic acid (102 g, 0.8 mol) were dissolved in water (2.3 L) and cooled to 0 °C. At this temperature, benzoyl chloride (97 mL, 0.8 mol) was added within 0.5 h and after the addition was finished, stirring was continued for 30 min at 0 °C and then for 2.5 h at room temperature. For work-up, HCl (250 mL, 37%, aq.) was added carefully. After 12 h the precipitate was filtered off and dried to give colorless crystals of 1-benzoylpiperidine-4-carboxylic acid (169.8 g); mp: 132–135 °C.

The acid (168 g, 0.7 mol) was dissolved in dichloromethane (500 mL), and $SOCl_2$ (78.4 mL, 1.1 mol) was added dropwise. After the addition was complete, the reaction mixture was heated at reflux for 2 h. After cooling to room temperature, the solvent and reagent were distilled off, and the crude residue 1-benzoylpiperidine-4-carbonyl chloride was used without further purification.

The acid chloride (205.4 g, 0.7 mol) was dissolved in dichloromethane (320 mL) and stored in an addition funnel. In a three-necked flask, aluminum chloride (244.3 g, 1.8 mol) was suspended in dichloromethane (320 mL), and fluorobenzene (101 mL, 1.1 mol) was added quickly at room temperature. The acid chloride solution was added slowly at 0 °C within 30 min. After the addition was complete, stirring was continued for 2 h at room temperature. The reaction mixture was poured on ice (2 kg) and extracted with dichloromethane. The organic phase was washed with HCl (1 N, aq.), $NaHCO_3$ (saturated) and water, dried over sodium sulfate, and evaporated to dryness. The resulting residue was recrystallized from *tert*-butyl methyl ether to give colorless crystals of (1-benzoylpiperidin-4-yl)-(4-fluorophenyl) methanone (203.8 g); mp: 132–133 °C.

This carboxamide (203.8 g, 0.65 mol) was dissolved in HCl (700 mL, conc. aq.) and water (350 mL). The solution was heated at reflux for 7 h. After cooling to room temperature, it was extracted with *tert*-butyl methyl ether. The aqueous phase was cooled to 0 °C and treated with sodium hydroxide (700 mL, conc. aq.) and extracted with dichloromethane. The organic phase was washed with water and brine before drying over sodium sulfate and evaporating to dryness. The resulting slurry was dissolved in ethanol (250 mL), and the same amount of HCl in ether was added at 15 °C. Precipitation continued at this temperature for 12 h. The crystals were filtered off and dried to give (4-fluorophenyl)piperidin-4-yl methanone (66 g); mp: 225–227 °C.

The ketone (5 g, 0.02 mol) was dissolved in methanol (150 mL), and palladium on charcoal (2 g, 5%) was added before hydrogenation with H_2 (0.45 L) at 21 °C. The reaction mixture was filtered and evaporated before crystallization from ether to give (4-fluorophenyl)piperidin-4-yl-methanol (4.4 g); mp: 254–255 °C.

The alcohol (660 mg, 3 mmol), methanesulfonic acid 2-(2,4-difluorophenyl)ethyl ester (740 mg, 3 mmol), and $NaHCO_3$ (760 mg, 9 mmol) were dissolved in acetonitrile (10 mL) and heated at 75 °C for 24 h. The solvent was removed without work-up, and the residue was purified by chromatography. The crude product was dissolved in ethanol, and HCl in ether was added to give colorless crystals of the title compound **35** (290 mg, 25%); mp: 87–90 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 10.56$ (br s, 1H), 7.37–7.27 (m, 4H), 7.15 (dt, 4H, $J = 1.5$ Hz and $J = 8.9$ Hz), 5.46 (br d, 1H, $J =$ 3.6 Hz), 4.33 (br s, 1H), 3.50 (br ϕd, 2H), 3.15 (m, 2H), 3.06 (m, 2H), 2.84 (m, 2H), 1.93 (br ϕd, 2H), 1.65 (m, 2H), 1.41 ppm (br ϕd, 1H); Anal. ($C_{20}H_{23}F_2NO$·HCl·H_2O) Cl; F; N; C: calcd 62.3, found 63.5; H: calcd 6.8, found 6.3; EI MS [M^+]: *m/z* 331.

*(2,3-Dihydro-1H-indol-7-yl)pyridin-4-yl methanone (**15**)*: Indoline (10.7 g, 90 mmol) was dissolved in toluene (60 mL) and added dropwise to a solution of boron trichloride (100 mL, 102 mmol, 10% in xylene) at 0 °C. Pyridine-4-carbonitrile (11.5 g, 110 mmol) was added in portions to the reaction mixture at this temperature. Aluminum chloride (13.3 g, 102 mmol) was added at the same temperature. The slurry was heated at reflux for 12 h and cooled to 10 °C before the addition of water (20 mL). HCl (80 mL, 2 N, aq.) was then added, and the mixture was heated at reflux again for a further 4 h. After cooling the reaction to room temperature, the mixture was poured on ice, adjusted to pH 12 and extracted with ethyl acetate. The organic phase was evaporated, and the product crystallized form ethyl ether to yield fawn crystals (16 g, 79%).

*(2,3-Dihydro-1H-indol-7-yl)pyridin-4-yl methanol and 2,3-dihydro-1H-indol-7-yl)piperidin-4-yl methanol (**16**)*: Ketone **15** (4 g) was dissolved in methanol (80 mL). Platinum(IV)oxide hydrate (1.2 g) and H_2 (1.2 L) were used in the hydrogenation reaction. The crude product was fractioned on silica gel to give 1.3 g of the pyridine alcohol and 1.4 g of the piperidine alcohol **16**. The pyridine alcohol (1.2 g) was dissolved in methanol (40 mL), and the same catalyst (570 mg) and H_2 (560 mL) were used to give a further amount of the piperidine alcohol **16** (1 g) for a total of 2.4 g (60%).

*1-{1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl}-1-(1H-indol-7-yl) methanol (**40**)*: Compound **16** (500 mg, 2 mmol), methanesulfonic acid 2-(2,4-difluorophenyl)ethyl ester (400 mg, 2 mmol), and *N*-ethyl diisopropylamine (0.7 mL) were dissolved in acetonitrile (50 mL) and heated at reflux for 24 h. After evaporation of the solvent, the residue was dissolved in ethyl ester, and water and NaOH (1 N, aq.) were added to bring the solution to pH 8. After exhaustive extraction, the crude product was purified by chromatography to give colorless crystals of **40** (200 mg, 28%); mp: 198–199 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 10.74$ (br s, 1H), 7.40 (d, 1H, $J = 7.6$ Hz), 7.26 (t, 1H, $J = 2.7$ Hz), 7.23 (d, 1H, $J = 5.7$ Hz), 7.21 (d, 1H, $J =$ 5.6 Hz), 7.06 (t, 2H, $J = 8.9$ Hz), 6.99 (d, 1H, $J = 6.7$ Hz), 6.94 (t, 1H, $J = 7.5$ Hz), 6.39 (dd, 1H, $J = 1.9$ Hz and $J = 2.9$ Hz), 5.23 (br d, 1H, $J = 3.8$ Hz), 4.69 (dd, 1H, $J = 4.0$ Hz and $J = 6.8$ Hz), 2.96 (br d, 1H), 2.84 (br d, 1H), 2.68 (m, 2H), 2.44 (br s, 2H), 1.85 (br d, 2H), 1.77 (br s, 2H), 1.63 (m, 1H), 1.38–1.26 (m, 2H), 1.17 ppm (m, 1H); Anal. ($C_{22}H_{25}FN_2O$) H; N; F; C: calcd 74.9, found 74.0; EI MS [M^+]: *m/z* 352.

*2,2,2-Trifluoro-1-[7-({1-[2-(4-fluorophenylethyl]piperidin-4-yl}hydroxy-methyl)-1H-indol-3-yl] ethanone (**41**)*: 40 (1 g, 3 mmol) was dissolved in trifluoroacetic acid anhydride (20 mL) and THF (10 mL). After 3 h, the reaction was evaporated to dryness and fractioned on silica gel to give 1.3 g of a fawn oil. $POCl_3$ (550 g, 3.6 mmol) was added slowly to DMF (10 mL) followed by the afore-prepared trifluoroacetic acid {1-[2-(4-fluorophenyl)-
ethyl]piperidin-4-yl}-(1H-indol-7-yl) methyl ester (1.3 g, 2.9 mmol) in DMF (10 mL). The mixture was heated at 125 °C for 1 h. Hydroxylamine hydrochloride (0.5 g, 6.5 mmol) in DMF (5 mL) was then added and the mixture was heated at 120 °C for 15 min. After usual work-up the residue was purified by chromatography and crystallized from acetone with HCl in ether to give **41** (600 mg, 43%); mp: 279–280 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 12.66$ (br d, 1H, $J = 3.0$ Hz), 10.21 (br s, 1H), 8.31 (d, 1H, $J = 1.6$ Hz), 8.11 (dd, 1H, $J = 2.6$ Hz and $J = 6.4$ Hz), 7.31 (m, 4H), 7.15 (m, 2H), 5.81 (br s, 1H), 4.94 (br d, 1H, $J = 4.1$ Hz), 3.51 (m, 2H), 3.15 (m, 2H), 3.01 (m, 2H), 2.84–2.73 (m, 2H), 1.93 (m, 2H), 1.78–1.55 ppm (m, 3H); Anal. ($C_{24}H_{24}F_4N_2O_2$·HCl) C; H; Cl; F; N.

*1-(4-Fluorophenyl)-1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl} ethanol (**74**)*: Magnesium (11.7 g, 0.5 mol) was mixed with I_2 (250 mg) and immersed in THF (50 mL). 1-Bromo-4-fluorobenzene (52.2 mL, 0.5 mol) in THF (350 mL) was added slowly to maintain smooth boiling. After 30 min a solution of pyridine-4-carbonitrile (41.6 g, 0.4 mol) in THF (400 mL) was added at room temperature. Stirring was continued for 12 h and the reaction mixture was poured into a saturated solution of aqueous NH_4Cl. After usual work-up the crude product was purified by chromatography and recrystallized from acetone to give (4-fluorophenyl)pyridin-4-yl methanone (54.1 g, 67%). The ketone was used in a second Grignard reaction:

Magnesium (5.8 g, 0.2 mol) was treated with iodomethane (15 mL, 0.2 mol) in ether (150 mL) to maintain smooth boiling. After 30 min a solution of the afore-prepared ketone (19 g, 80 mmol) in THF (150 mL) was added slowly at 0 °C. Stirring was continued for 1 h at room temperature and after usual work-up and chromatography, 1-(4-fluorophenyl)-1-pyridin-4-yl ethanol was obtained (11 g, 64%); mp: 161–163 °C.

The afore-prepared pyridine (2.2 g, 10 mmol) was hydrogenated at 0.5 g Pd on charcoal with H_2 (605 mL) in glacial acetic acid (50 mL) to give 1-(4-fluorophenyl)-1-piperidin-4-yl ethanol (1.6 g, 71%).

The piperidine (655 mg, 3 mmol) was coupled with methanesulfonic acid 2-(4-fluorophenyl)ethyl ester (670 mg, 3 mmol) as described to give **74** (350 mg, 34%); mp: 122–123 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 9.97$ (br s, 1H), 7.45 (d, 1H, $J = 5.6$ Hz), 7.42 (d, 1H, $J = 5.6$ Hz), 7.30 (d, 1H, $J = 5.7$ Hz), 7.27 (d, 1H, $J = 5.6$ Hz), 7.17 (d, 2H, $J = 3.7$ Hz), 7.11 (d, 1H, $J = 3.8$ Hz), 5.13 (br s, 1H), 3.52 (m, 1H), 3.45 (m, 1H), 3.16 (m, 2H), 3.00 (m, 2H), 2.81 (m, 2H), 1.93–1.71 (m, 2H), 1.66–1.51 (m, 3H), 1.45 ppm (s, 3H); Anal. ($C_{21}H_{25}F_2NO$) H; Cl; F; N; C: calcd 73.0, found 73.6; EI MS [M^+]: *m/z* 345.

Pharmacological Methods:

^{3}H-Ketanserin inhibition assay (5-HT$_{2A}$ receptor): The assay was performed as previously described.[40] For the human recombinant 5-HT$_{2A}$ receptor, a CHO-K1 cell line was used that stably expresses this receptor (Euroscreen S.A., Brussels, Belgium, cat. no. ES-313 M), and ≈15 μg membrane protein per assay was used. Alternatively, rat cortical membranes (1 mg protein per assay)[40] from male rats (IVA: WIWU, Kisslegg; weight range: 180–240 g) were used. The assay contained (final volume 1 mL): 0.5 nM 3H-ketanserin, 50 mM Tris-HCl (pH 7.4) and 10 μM methysergide for nonspecific binding. Incubations were carried out at 37 °C for 15 min.

^{3}H-Mesulergine inhibition assay (5-HT$_{2C}$ receptor): The procedure was adapted from Pazos et al.[41] Membranes from pig chorioid plexus were obtained from a local slaughter house and were incubated with 0.5 nM ^{3}H-mesulergine at 37 °C for 30 min. Nonspecific binding was determined in the presence of 1 μM serotonin. The assay with cells expressing the human 5-HT$_{2C}$ receptor was performed according to the method reported by Bonhaus et al.[42] Human 5-HT$_{2C}$ receptors expressed in CHO cells (Euroscreen) were used. The inhibition assay was performed in a total volume of 250 μL containing 1 nM ^{3}H-mesulergine and membrane suspension containing 50 μg protein. Incubations were carried out at 37 °C for 30 min and were stopped by rapid filtration on GFB filters (Whatman) presoaked for 2 h at 4 °C with 1% bovine serum albumin. Nonspecific binding was obtained in the presence of 1 μM mianserine.

^{3}H-Spiperone inhibition assay (cloned human D$_2$ receptors): Membrane preparations from cell lines expressing cloned dopamine D$_2$ receptor were purchased from Receptor Biology, Inc., Glen Echo, USA. The assay was performed as described for D$_2$ in rat striatal membranes[40] with the following modifications: human D$_2$ receptors expressed in A9L4 cells were used, and the inhibition assay was performed in a total volume of 1 mL containing 0.15 nM ^{3}H-spiperone and membrane suspension containing 40–60 μg protein.

^{3}H-Prazosin inhibition assay (α_1 receptor): The assay was performed as previously described[40] with rat cortical membranes (0.7 mg protein mL^{-1}) from male rats (IVA: WIWU, Kisslegg) with body weights in the range of 180–240 g. Rat cortical membranes (0.7 mg protein mL^{-1}) and 0.4 nM ^{3}H-prazosin were incubated in a total volume of 0.5 mL. The incubation was carried out at 25 °C for 1 h. Nonspecific binding was determined with 1 μM phentolamine.

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Keywords: insomnia · medicinal chemistry · neurotransmitters · schizophrenia · serotonin

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