

SAR Study of 1-Aryl-4-(phenylarylmethyl)piperazines as Ligands for Both Dopamine D₂ and Serotonin 5-HT_{1A} Receptors Showing Varying Degrees of (Ant)agonism. Selection of a Potential Atypical Antipsychotic

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The syntheses of several 1-aryl-4-(arylpyridylmethyl)piperazines (4) and their affinities for dopamine D₂ and serotonin 5-HT_{1A} receptors are described. The compounds were evaluated both *in vitro* and *in vivo*, resulting in the identification of the drug candidate SLV313 (4e) with equipotent and full D₂ receptor antagonism and 5-HT_{1A} receptor agonism. Minor structural modifications in SLV313 revealed the possibility of designing compounds possessing varying degrees of partial agonism on one or both target receptors.

Key words SLV313; *N*-phenylpiperazines; biaryl; (partial) dopamine D₂ receptor antagonist; (partial) serotonin 5-HT_{1A} receptor agonist; atypical antipsychotic

Schizophrenia¹⁾ is a disease of which the etiology is unknown. The disease is characterized by the so-called positive and negative symptoms. Positive symptoms include hallucinations and paranoia. The most characteristic negative symptoms are social withdrawal and flattening of the personality. In addition, both cognitive as well as depressive symptoms and anxiety may occur.

The most frequently used antipsychotic haloperidol (**1**) (Fig. 1), a dopamine D₂ receptor antagonist, only alleviates the positive symptoms presumably by attenuating the dopaminergic neurotransmission system in the mesolimbic area of the brain, leaving the negative symptoms untreated. Therapy with this type of compounds is frequently accompanied by extrapyramidal side effects (EPS), resulting from a blockade of dopaminergic activity within the (extrapyramidal) motor areas of the brain. This type of compounds is referred to as "typical" antipsychotics. There is a strong need for compounds that will treat all types of symptoms and will not induce EPS. An example of such an "atypical" antipsychotic is clozapine (**2**) (Fig. 1), a D₂ receptor antagonist with modest potency (69 nM, see Fig. 1). Clozapine (**2**) shows higher affinity for several other receptors, especially for serotonin receptor subtypes, which may account for the beneficial effect against negative symptoms.^{2,3)} Combining dopaminergic and serotonergic activity may be a valid approach to de-

velop atypical antipsychotics.⁴⁾

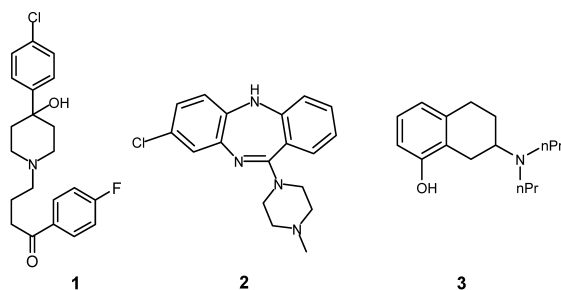
The rationale behind the combination of a D₂ receptor antagonist and a 5-HT_{1A} receptor agonist is based on several preclinical data, supporting the hypothesis that selective 5-HT_{1A} receptor agonists are capable of preventing D₂ receptor antagonist induced EPS in animal models. The 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*N*-propylamino) tetralin (**3**) (8-(OH)-DPAT, Fig. 1) is capable of antagonizing haloperidol (**1**) induced catalepsy in rats and dystonia in non human primates,⁵⁾ and reduces the forelimb retraction time in the paw test.⁶⁾ Furthermore, 5-HT_{1A} receptor agonists are active in the forced swimming test (FST), a preclinical model predictive of antidepressant activity.⁷⁾

This report focusses on compounds of type (**4**) (Fig. 2) which share affinity for dopamine D₂ as well as serotonin 5-HT_{1A} receptors. Compound (**4e**) of this series possessed the desired profile (full dopamine D₂ receptor antagonism and full serotonin 5-HT_{1A} receptor agonism) and was selected as a clinical candidate.

In this paper we like to demonstrate that compounds (**4**) behave quite differently compared to our previously published¹⁾ series of compounds (**5**) when examining their functional behavior on both dopamine D₂ and serotonin 5-HT_{1A} receptors.

Chemistry

The synthesis of compounds (**4**) is depicted in Chart 1. The compounds (**4a—e**) were prepared by reacting elto-



K_i (nM) D₂/5-HT_{1A}: 1.4 / 2800

69 / 270

2200 / 2.5

Fig. 1. Structures and Affinities (K_i, nM) on Dopamine D₂ and Serotonin 5-HT_{1A} Receptors of Haloperidol (**1**), Clozapine (**2**) and 8-(OH)-DPAT (**3**)

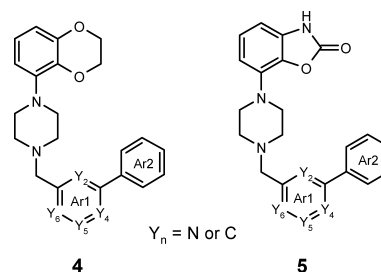
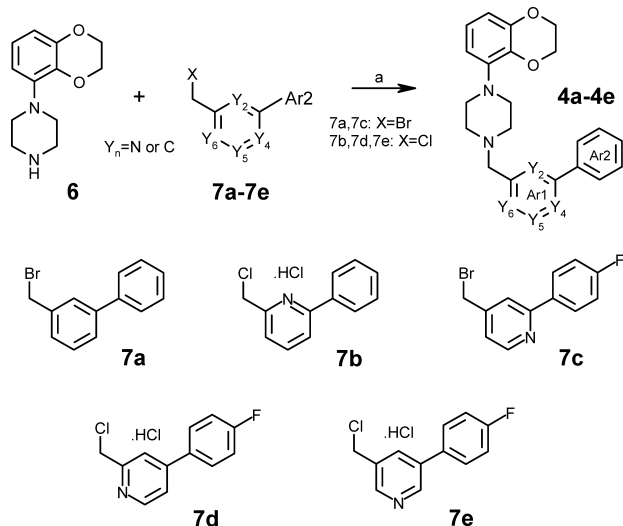


Fig. 2. General Structures of Compounds **4** and **5**

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Reagents and conditions: (a) Et(*i*-Pr)₂N, KI, CH₃CN, reflux.

Chart 1. Synthesis Scheme of Compounds **4**

prazine (**6**) and a biarylmethyl halide (**7**) in the presence of Et(*i*-Pr)₂N and KI in acetonitrile at reflux temperature. Yields of **4a–e** ranged from 38 to 83%. Some of the compounds (**4**) were converted into their mono- or di-HCl salts by treatment with HCl/EtOH. The intermediates (**7a–e**) were synthesized according to the procedures described in the references given in the experimental part.

The syntheses of compounds (**5**) are described in the literature.^{1,8} In Table 1 the relevant compounds (**4**) and (**5**) are depicted.

Biological Evaluation and Discussion

The affinities of compounds (**1–5**) for dopamine D₂ and the serotonin 5-HT_{1A} receptors were measured using [³H]-spiperone¹⁰ and [³H]-8-OH-DPAT respectively.¹¹ Both assays make use of rat receptors. In Fig. 1, the K_i values are given (calculated from at least three independent experiments) for compounds (**1**), (**2**) and (**3**). In Table 1, the affinities of **4** and **5** expressed as K_i values for both receptors are listed.

Within the series (**4**), replacement of a carbon atom by a nitrogen atom in the aromatic ring Ar1 was studied in order to improve pharmacokinetic properties. This had a dopamine D₂ receptor affinity lowering effect if the nitrogen atom was introduced on position Y₂: affinity drops from 1.7 nM (**4a**) to 26 nM for compound (**4b**). The affinities for compounds (**4c**), (**4d**) and (**4e**) in which carbon to nitrogen replacement is on positions Y₄, Y₆ and Y₅ respectively, remain almost unaltered. The presence of a fluorine atom in compounds (**4c**), (**4d**) and (**4e**) did not seem to play a crucial role for dopamine D₂ receptor affinity. Considering the serotonin 5-HT_{1A} receptor affinities in series (**4**), compounds (**4b**) and (**4c**), in contrast to (**4d**) and (**4e**), show a drop in affinity compared to (**4a**).

When series (**4**) are compared to series (**5**) it can be seen from Table 1 that series (**5**) compounds are slightly more potent on dopamine D₂ receptors than series (**4**) compounds, with the exception of compound (**5a**). This effect is most pronounced when comparing (**4d**) to (**5d**). Affinity for sero-

Table 1. Structures and Affinities (K_i, nM) of Compounds **4** and **5** on Dopamine D₂ and Serotonin 5-HT_{1A} Receptors, Respectively

Compounds		
	K _i (nM) D ₂ /5-HT _{1A}	
Y:	(4a) (2HCl) 1.7/1.1	(5a) (HOMs) 2.2/9.4
	(4b) (fb) 26/46	
	(4c) (2HCl) 5.8/20	(5c) (fb) 2.9/21
	(4d) (2HCl) 1.5/1.4	(5d) (2HCl) 0.47/16
	(4e) (HCl) 3.6/3.2	(5e) (fb) 1.6/2.1

Values are based on 3 assays, each using 4 to 6 concentrations in triplicate. fb: free base.

Table 2. *In Vivo* Test Results (ED₅₀ Values) in Inhibition of Apomorphine Induced Climbing Behavior (CB), Suppression of Conditioned Avoidance Behavior (CAR) and Lowerlip Retraction (LLR) of Compounds **1–5**

Compounds	CB (mg/kg)	CAR (mg/kg)	LLR (mg/kg)
	Mouse <i>p.o.</i>	Rat <i>p.o.</i>	Rat <i>p.o.</i>
1	0.2	0.3	
2	22	32	
3		>20	0.1 ^a
4a	6	<10	6
4b	>20 ^a		
4c	16		
4d	0.2	0.5	1.0
4e (SLV313)	0.5	2.6	1.8
5a	0.1	0.6	10

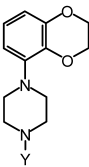
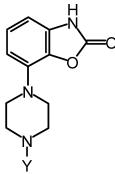
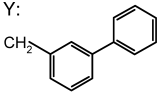
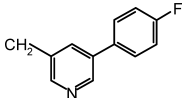
ED₅₀ values are based on at least 3 dose levels. ^a i.p. administration.

tonin 5-HT_{1A} receptors in series (**4**) increases when comparing (**5a**) to (**4a**) and (**5d**) to (**4d**). Introduction of a nitrogen atom on position Y₄ is unfavourable for the serotonin 5-HT_{1A} receptor affinity in the case of compound (**4c**) as well as for compound (**5c**).

The compounds of series (**4**) were tested in *in vivo* models relevant for D₂ receptor antagonism—inhibition of the apomorphine-induced climbing behavior (CB) in mice¹²—, and for antipsychotic activity—the suppression of the conditioned avoidance response (CAR) in rats¹³—. To determine the 5-HT_{1A} receptor agonistic component *in vivo*, the compounds were tested for the occurrence of the so called lower lip retraction in rats (LLR).¹⁴ The results are given in Table 2.

Considering the *in vivo* profiles of series (**4**), compound (**4b**) and (**4c**) turned out to be not potent enough in the CB

Table 3. Maximal Partial Agonistic Values (%) of Key Compounds (**4a**), (**4e**), (**5a**) and (**5e**) on Dopamine D₂ and Serotonin 5-HT_{1A} Receptors, Respectively^{15–17)}

Compounds		
	induces full D ₂ antagonism	induces partial D ₂ agonism
	Percentage agonism D ₂ /5-HT _{1A}	
Y: 	(4a) 9/65	(5a) 28/73
induces partial 5HT _{1A} agonism		
	(4e) 2/96	(5e) 24/96
induces full 5HT _{1A} agonism		

Values are based on 3 to 6 assays, measured at 1000 nM. When measuring (partial) agonism at even higher concentrations than 1000 nM, no higher percentages were found, indicating that the maximum degree of agonism is reached at 1000 nM.

test and were not investigated further. Compounds (**4d**) and (**4e**) both show an attractive *in vivo* profile: they are potent in the CB test and about equipotent with regard to the CAR and LLR test, which may lead to equal expression of the desired D₂- and 5-HT_{1A} mediated therapeutic actions at a given dose. Compound (**4a**) does show activity (*p.o.*) in the CB, CAR and LLR tests, but less potently than (**4d**) and (**4e**). After further preclinical profiling of the compounds (**4d**) and (**4e**), the latter was selected for further investigation.

In order to establish the desired full dopamine D₂ receptor antagonism and full serotonin 5-HT_{1A} receptor agonism, some related compounds of series (**4**) and (**5**) were tested for their (ant)agonistic properties *in vitro*. This was accomplished by using CHO cells transfected with either the human dopamine D₂ receptor^{15,16)} or the human serotonin 5-HT_{1A} receptor.¹⁷⁾ In this type of experiments receptor agonists decrease forskolin induced levels of the tritium labeled second messenger [³H]-cAMP, giving the value of the intrinsic efficacy (ϵ) of the compound studied. A ligand not decreasing the cAMP level, is an antagonist ($\epsilon=0\%$), a compound bringing cAMP levels down to zero is a full agonist ($\epsilon=100\%$). Partial agonists have ϵ values between 0 and 100%. As can be seen from Table 3, it turned out that independent of the arylpiperazine chosen, the 3-(4-fluorophenyl)-pyridyl-5-yl-methyl moiety induces full 5-HT_{1A} agonism ((**4e**) $\epsilon=96\%$ and (**5e**) $\epsilon=96\%$). Furthermore, the benzodioxanyl piperazine moiety induces full D₂ antagonism, ((**4a**) $\epsilon=9\%$ and (**4e**) $\epsilon=2\%$), independently of the biaryl methyl part of the molecule. These structural tools enable to design all four possible combinations of D₂ antagonism/partial agonism and 5HT_{1A} full agonism/partial agonism.

Compound (**5a**) that was previously selected for clinical

Table 4. Calculated and Measured Properties of Compound (**4e**)

	4e SLV313	Criterion
H-Acceptors ^{a)}	5	≤ 10
H-Donors ^{a)}	0	≤ 5
MW ^{a)}	405	≤ 500
log P ^{a),#}	3.9	≤ 5
Rotable bonds ^{b)}	4	≤ 10
PSA (Å) ^{c)}	35	≤ 70
Pgp factor ^{d),#}	1.0	≤ 1.5
Membrane passage (%) ^{e),#}	33	≥ 20

a) Lipinski's "Rule of five",¹⁸⁾ log P was measured according to procedure described in ref. 19. b) Any acyclic single bond connecting non-terminal, non-hydrogen atoms.²⁰⁾ c) Calculated polar surface area.²¹⁾ d) P-Glycoprotein transport ratio, expressed as the ratio of the bottom to top transport and the top to bottom transport.²²⁾ e) Membrane passage expressed as the mean percentage of compound transported.²²⁾ # Experimentally determined values.

development¹⁾ shows partial agonism at both sites. Compound (**4e**) on the other hand displays full antagonism at dopamine D₂ receptors and full agonism at serotonin 5-HT_{1A} receptors and was therefore studied in more detail. Some calculated and measured physico-chemical properties that may be of relevance for pharmacokinetic behavior, are depicted in Table 4.

Favorable absorption may be predicted on the basis of the low number of H-donor and H-acceptor sites and the relatively low molecular weight, logP^{18,19)} and number of rotatable bonds.²⁰⁾ The low polar surface area²¹⁾ (PSA) and a P-gp factor²²⁾ around 1 indicate a favourable brain penetration. The measured high membrane passage further substantiates these expectations.

Indeed, a favorable bioavailability of 69% (dog)²³⁾ and brain/plasma ratio of 4 (rat)²⁴⁾ were measured. A more detailed publication describing the pharmacodynamic profile of SLV313 (**4e**) is in preparation.

Further clinical studies with (**4e**) may reveal if these pre-clinical properties also translate into a favorable therapeutic profile.

Experimental

¹H- and ¹³C-NMR spectra were recorded on a Varian UN400 instrument (400 MHz for ¹H-NMR, 100 MHz for ¹³C-NMR), using DMSO-*d*₆ or CDCl₃ with (CH₃)₄Si as an internal standard, as solvents. Chemical shifts are given in ppm (δ scale). Thin-layer chromatography was performed on Merck pre-coated 60 F₂₅₄ plates, and spots were visualised with UV light. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). Melting points were recorded on a Büchi B-545 melting point apparatus and are uncorrected. Mass spectra were recorded with a Micromass GCT or Kratos Concept 1S instrument.

1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazine Hydrochloride (6) This compound was synthesized according to the procedure described in patent EP 0189612.²⁵⁾

1-Biphenyl-3-yl-methyl-4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazine (4a) Under a nitrogen atmosphere 4.9 g (19.0 mmol) of 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazine (**6**) hydrochloride and 4.8 g (19.5 mmol) of 1-bromomethyl-3-phenyl benzene (**7a**) were suspended in 250 ml of dry acetonitrile. While stirring 10.5 ml (60 mmol) of diisopropylethylamine were added and the mixture was brought to reflux temperature for 16 h. After cooling to room temperature the reaction mixture was concentrated *in vacuo*, the residue was purified by flash column chromatography (SiO₂, eluent CH₂Cl₂/MeOH 99/1). The product containing fraction was concentrated *in vacuo*, the residue taken up in methanol to which 2 eq of HCl (1 N HCl/MeOH) were added. Concentration *in vacuo* yielded 7.0 g (80%) of (**4a**) as the dihydrogenchloride salt. mp 223–225 °C. ¹H-NMR (CDCl₃) δ : 3.10 (pseudo t, 2H), 3.62–3.40 (cluster, 6H), 4.18–4.28 (cluster, 4H), 4.32 (s, 2H), 6.51 (dd, *J*=8, 2 Hz, 1H), 6.63 (dd, *J*=8, 2 Hz, 1H), 6.76 (t, *J*=8 Hz, 1H), 7.37 (mp, 1H), 7.47 (m, 2H), 7.53 (t, *J*=8 Hz, 1H),

7.62—7.72 (cluster, 4H), 7.88 (pseudo s, 1H), 12.9 (s broad, NH^+ , 1H). HR-EI-MS m/z : 387.2073 (Calcd for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_2$: 387.2072). Anal. ($\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$): Calcd (%): C: 65.4, H: 6.1, N: 6.1, Found (%): C: 65.3, H: 6.0, N: 6.0.

1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-(6-phenyl-pyridin-2-yl-methyl)-piperazine (4b) 0.95 g (4.0 mmol) of (7b) and 1.08 g (4.2 mmol) of (6) hydrochloride were suspended in 30 ml of acetonitrile after which 4.2 ml (25 mmol) of diisopropylethylamine were added and the mixture was brought to reflux temperature for 2 h. After cooling to room temperature the reaction mixture was concentrated *in vacuo*, to the residue water was added, after which extraction took place with CH_2Cl_2 . The combined organic fractions were dried on Na_2SO_4 . After removal of the drying agent by filtration and solvent by concentration *in vacuo*, the obtained residue was subjected to flash column chromatography (SiO_2 , eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97/3). The product containing fraction was concentrated *in vacuo*, the residue suspended in petroleum ether to which some diethyl ether was added. Stirring yielded 0.73 g (45%) of a white solid containing the free base of (4b), mp 125—126 °C.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.79 (t, 4H), 3.14 (t, 4H), 3.85 (s, 2H), 4.20—4.35 (cluster, 4H), 6.55 (dd, $J=8$, 2 Hz, 1H), 6.59 (dd, $J=8$, 2 Hz, 1H), 6.77 (t, $J=8$ Hz, 1H), 7.36 (cluster, 4H), 7.59 (d, $J=8$ Hz, 1H), 7.72 (t, $J=8$ Hz, 1H), 8.00 (m, 2H). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ : 50.9, 53.4, 63.9, 64.3, 64.7, 110.7, 111.8, 118.7, 120.6, 121.3, 127.0, 128.7, 128.8, 136.5, 137.0, 139.6, 141.9, 144.1, 156.8, 158.6. HR-EI-MS m/z : 388.2044 (Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_2$: 388.2025). Anal. ($\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0.4\text{H}_2\text{O}$): Calcd (%): C: 73.0, H: 6.6, N: 10.6, Found (%): C: 73.0, H: 6.3, N: 10.4.

1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[2-(4-fluoro-phenyl)-pyridin-4-yl-methyl]-piperazine (4c) 0.63 g (2.37 mmol) of bromide (7c) and 0.61 g (2.38 mmol) of the hydrochloride of (6) together with 1.0 ml (5.7 mmol) of diisopropylethylamine were suspended/dissolved in 20 ml of dry acetonitrile. A little potassium iodide was added and the reaction mixture was stirred and brought to 80 °C, under a nitrogen atmosphere. After 16 h the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (25%) 92/7.5/0.5 v/v/v), yielding 0.48 g of a brown sirupy oil. To the latter 20 ml of *tert*-butyl methyl ether was added upon which some precipitate formed which was removed by filtration. The filtrate was treated with 5 ml 1 N HCl/EtOH and the precipitate which formed was collected by filtration yielding 1.3 g of a light brown solid, which was again purified by column chromatography (SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (25%) 92/7.5/0.5 v/v/v), yielding a brown oil. The latter oil was dissolved in *tert*-butyl methyl ether and HCl (g) was led through the solution. The precipitate which formed was filtered, the residue washed with *tert*-butyl methyl ether and dried, yielding 0.36 g (32%) of the dihydrochloride of (4c), mp *ca.* 162 °C with decomposition.

$^1\text{H-NMR}$ ($\text{DMSO}-d_6/\text{CDCl}_3$ 4/1) δ : 3.22—3.58 (m, 8H), 4.20—4.28 (m, 4H), 4.63 (s, 2H), 6.50 (dd, $J=8$, 2 Hz, 1H), 6.55 (dd, $J=8$, 2 Hz, 1H), 6.74 (t, $J=8$ Hz, 1H), 7.37 (t, $J_{\text{HF}}=8$ Hz, 2H), 8.26 (dd, $J_{\text{HF}}=8$ Hz, 2H), 7.93 (d broad, $J=5$ Hz, 1H), 8.70 (s broad, 1H), 8.80 (d, $J=5$ Hz, 1H), 12.0—12.4 (broad band, NH^+ , 1H). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6/\text{CDCl}_3$ 4/1) δ : 46.7, 51.3, 57.3, 63.7, 63.9, 110.4, 112.1, 116.0, 120.3, 125.7, 129.8, 131.7, 136.1, 139.5, 143.9, 147.0, 153.8, 163.8. HR-EI-MS m/z : 406.1932 (Calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_2$: 406.1931). Anal. ($\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_2 \cdot 2\text{H}_2\text{O} \cdot 2\text{HCl}$): Calcd (%): C: 56.0, H: 5.9, N: 8.2, Found (%): C: 55.8, H: 5.5, N: 7.9.

1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[4-(4-fluoro-phenyl)-pyridin-2-yl-methyl]-piperazine (4d) To 50 ml of dry acetonitrile were added: 0.50 g (1.95 mmol) of the hydrochloride of (6), 0.50 g (1.94 mmol) of the hydrochloride of (7d), 0.80 ml (5.9 mmol) of triethylamine and 0.29 g (1.93 mmol) of sodium iodide. The resulting mixture was brought to reflux temperature for 3 h after which stirring was continued for 48 h at room temperature. To the reaction mixture some silicagel was added after which the mixture was concentrated *in vacuo*. The resulting powder was put on top of a flash chromatography column (SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (25%) 92/7.5/0.5 v/v/v), and elution was started. The collected product containing fractions were concentrated *in vacuo* yielding 0.72 g of a brown sirup. The latter was dissolved in some diethyl ether and 2 eq of 1 N HCl/EtOH were added. The formed precipitate was isolated by filtration and dried, giving 0.77 g (83%) of the dihydrochloride of (4d), mp 233 °C with decomposition.

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.36 (broad signal, 4H), 3.45 (broad signal, 4H), 4.23 (m, 4H), 4.72 (s, 2H), 5.1—5.7 (broad signal, H_2O , 2NH^+) 6.51 (dd, $J=8$, 2 Hz, 1H), 6.57 (dd, $J=8$, 2 Hz, 1H), 6.74 (t, $J=8$ Hz, 1H), 7.38 (t, 2H), 8.0—8.1 (cluster, 3H), 8.52 (d, $J=2$ Hz, 1H), 8.81 (d, $J=8$ Hz, 1H). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ : 47.4, 52.2, 58.7, 64.5, 64.7, 111.2, 112.8, 116.9, 117.2, 121.1, 122.9, 125.6, 130.4, 130.5, 133.0, 136.8, 140.6, 144.6, 148.5,

149.5, 149.9, 162.9, 165.4. HR-EI-MS m/z : 406.1948 (Calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_2$: 406.1931). Anal. ($\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_2 \cdot 0.3\text{H}_2\text{O} \cdot 2\text{HCl}$): Calcd (%): C: 59.6, H: 5.5, N: 8.7, Found (%): C: 59.3, H: 5.5, N: 8.5.

1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[5-(4-fluoro-phenyl)-pyridin-3-yl-methyl]-piperazine (4e) To a suspension of 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazine (6) hydrochloride (1.10 g, 4.3 mmol) in CH_3CN (40 ml) was added 3-chloromethyl-5-(4-fluoro-phenyl)-pyridinium chloride (7e) (1.0 g, 3.4 mmol) and diisopropylethylamine (2.45 g, 19.0 mmol). The mixture was stirred at reflux for 3 h. After cooling and evaporation of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2 , washed with 5% NaHCO_3 solution, saturated NaCl, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The resulting dark oil was purified by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (25%), 97.25/2.5/0.25 v/v/v) to give the free base of (4e) (0.91 g, 52%) as an oil. The product was converted to its monohydrochloride salt: the residue was dissolved in Et_2O and treated with 1 eq of ethanolic HCl. The product precipitated as a white solid. The solid hydrochloride of (4e) was collected by filtration and dried: mp 233—235 °C, dec. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6/\text{CDCl}_3$, 4/1) δ (ppm): 3.17 (m, 2H), 3.29 (m, 2H), 3.40—3.58 (cluster, 4H), 4.24 (cluster, 4H), 4.51 (s broad, 2H), 6.49 (dd, $J=8$, 2 Hz, 1H), 6.55 (dd, $J=8$, 2 Hz, 1H), 6.73 (t, $J=9$ Hz, 1H), 7.34 (cluster, 2H), 7.86 (cluster, 2H), 8.56 (broad, 1H), 8.77 (m, 1H), 8.95 (d, $J=2$ Hz, 1H), 11.7 (s broad, 1H, NH^+). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6/\text{CDCl}_3$ 4/1) δ : 46.8, 51.0, 56.1, 63.7, 63.9, 110.4, 111.9, 115.9, 120.3, 125.5, 129.1, 132.8, 134.4, 136.1, 137.6, 139.7, 143.9, 148.2, 150.5, 162.5. HR-EI-MS m/z : 406.1942 (Calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_2$: 406.1931). Anal. ($\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_2 \cdot 0.5\text{H}_2\text{O} \cdot \text{HCl}$): Calcd (%): C: 63.9, H: 5.8, N: 9.3, Found (%): C: 64.3, H: 5.6, N: 9.2.

Intermediates 1-Bromomethyl-3-phenylbenzene (7a): The synthesis of (7a) has been described in ref. 8.

2-Chloromethyl-6-phenylpyridine (7b): The synthesis of (7b) and precursors has been described in refs. 26, 27 and 29.

4-Bromomethyl-2-(4-fluoro-phenyl)pyridine (7c): The synthesis of (7c) and precursors has been described in refs. 26 and 30.

2-Chloromethyl-4-(4-fluoro-phenyl)pyridine (7d): The synthesis of (7d) and precursors has been described in refs. 26 and 31.

3-Chloromethyl-5-(4-fluoro-phenyl)pyridine (7e): The synthesis of (7e) and precursors has been described in refs. 26, 28, 32 and 33.

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References and Notes

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