SAR Study of 1-Aryl-4-(phenylarylmethyl)piperazines as Ligands for Both Dopamine D_2 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 D_2 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 D_2 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 D_2 receptor antagonist; (partial) serotonin 5-HT_{1A} receptor agonist; atypical antipsychotic

Schizophrenia[1] 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 D_2 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 D_2 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 actitivity may be a valid approach to develop atypical antipsychotics.[4]

The rationale behind the combination of a D_2 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 D_2 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 D_2 as well as serotonin 5-HT_{1A} receptors. Compound (**4e**) of this series possessed the desired profile (full dopamine D_2 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 published[1] series of compounds (**5**) when examining their functional behavior on both dopamine D_2 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-

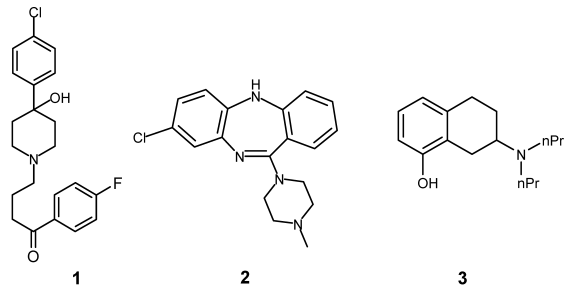

Fig. 1. Structures and Affinities (K_i, nM) on Dopamine D_2 and Serotonin 5-HT_{1A} Receptors of Haloperidol (**1**), Clozapine (**2**) and 8-(OH)-DPAT (**3**)

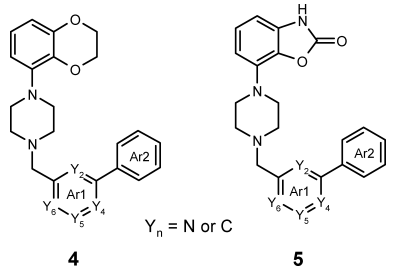

Fig. 2. General Structures of Compounds **4** and **5**

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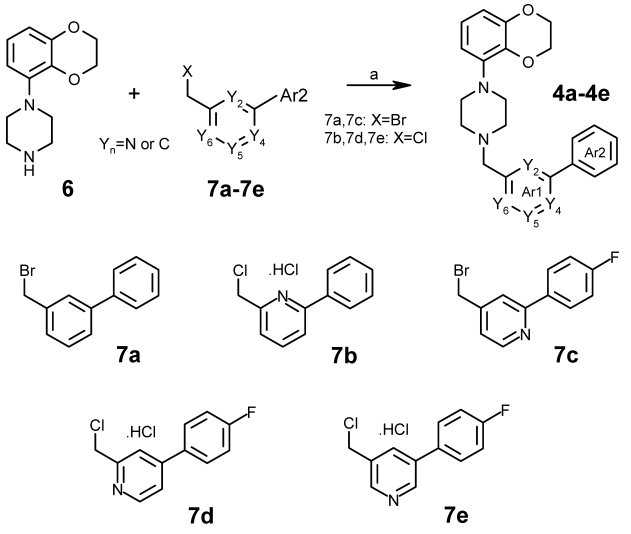


Reagents and conditions: (a) Et(*i*-Pr)$_2$N, KI, CH_3CN, reflux.

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

prazine (**6**) and a biarylmethyl halide (**7**) in the presence of Et(*i*-Pr)$_2$N 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 D_2 and the serotonin 5-HT_{1A} receptors were measured using [^{3}H]-spiperone[10] and [^{3}H]-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 D_2 receptor affinity lowering effect if the nitrogen atom was introduced on position Y_2: 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 Y_4, Y_6 and Y_5 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 D_2 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 D_2 receptors than series (**4**) compounds, with the exception of compound (**5a**). This effect is most pronounced when comparing (**4d**) to (**5d**). Affinity for serotonin 5-HT_{1A} receptors in series (**4**) increases when comparing (**5a**) to (**4a**) and (**5d**) to (**4d**). Introduction of a nitrogen atom on position Y_4 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 D_2 receptor antagonism—inhibition of the apomorphine-induced climbing behavior (CB) in mice[12]—, and for antipsychotic activity—the suppression of the conditioned avoidance response (CAR) in rats[13]—. 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 1. Structures and Affinities (K_i, nM) of Compounds **4** and **5** on Dopamine D_2 and Serotonin 5-HT_{1A} Receptors, Respectively

Compounds		K_i (nM) D_2/5-HT_{1A}	
	Y: CH_2	(**4a**) (2HCl) 1.7/1.1	(**5a**) (HOMs) 2.2/9.4
	CH_2	(**4b**) (fb) 26/46	
	CH_2	(**4c**) (2HCl) 5.8/20	(**5c**) (fb) 2.9/21
	CH_2	(**4d**) (2HCl) 1.5/1.4	(**5d**) (2HCl) 0.47/16
	CH_2	(**4e**) (HCl) 3.6/3.2	(**5e**) (fb) 1.6/2.1

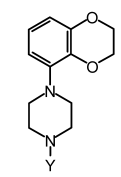
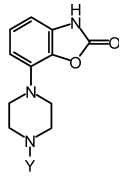
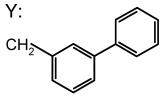
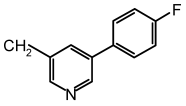
Values are based on 3 assays, each using 4 to 6 concentrations in triplicate. fb: free base.

Table 2. *In Vivo* Test Results (ED_{50} Values) in Inhibition of Apomorfine 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 *p.o.*	Rat *p.o.*	Rat *p.o.*
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

ED_{50} values are based on at least 3 dose levels. *a*) i.p. administration.

Table 3. Maximal Partial Agonistic Values (%) of Key Compounds (**4a**), (**4e**), (**5a**) and (**5e**) on Dopamine D_2 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}	
 induces partial 5HT_{1A} agonism	(**4a**) 9/65	(**5a**) 28/73
 induces full 5HT_{1A} agonism	(**4e**) 2/96	(**5e**) 24/96

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 D_2- 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 D_2 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 D_2 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 [^{3}H]-cAMP, giving the value of the intrinsic efficacy (ε) of the compound studied. A ligand not decreasing the cAMP level, is an antagonist (ε=0%), a compound bringing cAMP levels down to zero is a full agonist (ε=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**) ε=96% and (**5e**) ε=96%). Furthermore, the benzodioxanyl piperazine moiety induces full D_2 antagonism, ((**4a**) ε=9% and (**4e**) ε=2%), independently of the biarylmethyl part of the molecule. These structural tools enable to design all four possible combinations of D_2 antagonism/partial agonism and 5HT_{1A} full agonism/partial agonism.

Compound (**5a**) that was previously selected for clinical development[1)] shows partial agonism at both sites. Compound (**4e**) on the other hand displays full antagonism at dopamine D_2 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.

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.

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 area[21)] (PSA) and a P-gp factor[22)] 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 preclinical properties also translate into a favorable therapeutic profile.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a Varian UN400 instrument (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR), using DMSO-d_6 or $CDCl_3$ with $(CH_3)_4Si$ as an internal standard, as solvents. Chemical shifts are given in ppm (δ scale). Thin-layer chromatography was performed on Merck precoated 60 F_{254} 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 (SiO_2, eluent CH_2Cl_2/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. ^{1}H-NMR ($CDCl_3$) 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 $C_{25}H_{26}N_2O_2$: 387.2072). *Anal.* ($C_{25}H_{26}N_2O_2 \cdot 2HCl$): 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 CH_2Cl_2/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}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}C-NMR (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 $C_{24}H_{25}N_3O_2$: 388.2025). *Anal.* ($C_{24}H_{25}N_3O_2 \cdot 0.4H_2O$): 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: CH_2Cl_2/MeOH/NH_4OH (25%) 92/7.5/0.5 v/v/v), yielding 0.48 g of a brown siruppy 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: CH_2Cl_2/MeOH/NH_4OH (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}H-NMR (DMSO-d_6/$CDCl_3$ 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_{HF}=8 Hz, 2H), 8.26 (dd, J_{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}C-NMR (DMSO-d_6/$CDCl_3$ 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 $C_{24}H_{24}FN_3O_2$: 406.1931). *Anal.* ($C_{24}H_{24}FN_3O_2 \cdot 2H_2O \cdot 2HCl$): 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: CH_2Cl_2/MeOH/NH_4OH(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}H-NMR (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}C-NMR (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 $C_{24}H_{24}FN_3O_2$: 406.1931). *Anal.* ($C_{24}H_{24}FN_3O_2 \cdot 0.3H_2O \cdot 2HCl$): 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 (CH_2Cl_2/MeOH/NH_4OH (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}H-NMR (400 MHz, DMSO-d_6/$CDCl_3$, 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}C-NMR (DMSO-d_6/$CDCl_3$ 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 $C_{24}H_{24}FN_3O_2$: 406.1931). *Anal.* ($C_{24}H_{24}FN_3O_2 \cdot 0.5H_2O \cdot HCl$): 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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