Pyridobenzoxazepine and Pyridobenzothiazepine Derivatives as Potential Central Nervous System Agents: Synthesis and Neurochemical Study

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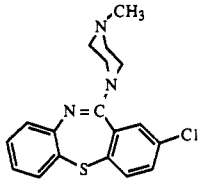
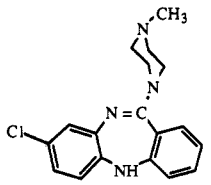
In order to characterize the pharmacological profile of the different chemical classes of pyridobenzazepine derivatives, a series of *N*-methylpiperazinopyrido[1,4]- and -[1,5]- benzoxa- and benzothiazepine derivatives were prepared. The affinities for D_2, D_1, 5-HT_2, and cholinergic (M) receptors were measured. In comparison to dibenzazepine reference compounds, a strong decrease of the affinities was observed, less pronounced, however, for the substituted analogues. Oxazepine and thiazepine analogues like clozapine (except 8-chloro-6-(4-methylpiperazin-1-yl)-pyrido[2,3-*b*][1,4]benzoxazepine (**9**) and 8-chloro-6-(4-methylpiperazin-1-yl)pyrido[2,3-*b*][1,4]-benzothiazepine (**11**)) were found to be inactive against apomorphine stereotypies. In the open-field test in rats, different molecules showed a high disinhibitory activity as observed with anxiolytic drugs. Moreover, 8-chloro-5-(4-methylpiperazin-1-yl)pyrido[2,3-*b*][1,5]benzoxazepine (**14**) presented a clozapine-like profile that was confirmed in the behavioral model in dogs and showed most of the behavioral characteristics described for antipsychotic drugs. Its neurochemical profile, in particular the 5-HT_2/D_2 ratio, was also compatible with atypical antipsychotic activity.

Introduction

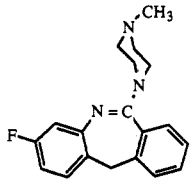
Dibenzazepine derivatives have represented and still represent today an interesting and exciting field of investigation in medicinal chemistry.[1-16] A slight modification of the tricyclic structure leads to a profound alteration of the activity profile. Indeed, clothiapine (**1**) is a typical neuroleptic[17] with a strong propensity to induce extrapyramidal symptoms (EPS), while clozapine (**2**) and fluperlapine (**3**) show an atypical antipsychotic profile[18-21] and produce only minimal EPS. Clozapine, although



clothiapine (**1**)



clozapine (**2**)



fluperlapine (**3**)

possessing clear antipsychotic activity, has also revealed some disinhibitory or anxiolytic effects not only in animals[22-23] but also in humans.[24-25] The mixed 5-HT_2/D_2 antagonism of clozapine could be implicated in these bivalent activities since either the 5-HT_2 antagonism or a combination of the 5-HT_2 and D_2 affinities seems particularly important to improve the negative symptoms of schizophrenia.[26-28] Moreover, it is well known that the 5-HT_2 antagonism is also characteristic of some anxiolytics like ritanserin. The 5-HT_2/D_2 concept has been widely developed and has contributed to the development of many works.[29-33]

Although clozapine represents a great advance in the treatment of psychiatric disorders, the induction of severe toxic effects (granulocytopenia, agranulocytosis,[34-36] and seizures,[37] etc.) has stimulated the search for an alternative to clozapine. This challenge is currently the focus of the most active efforts in contemporary neuropharmacology.[21,38] This context led us to synthesize and evaluate a series of *N*-methylpiperazinopyrido[1,4]- and -pyrido[1,5]-benzazepine derivatives. The study of *N*-methylpiperazinopyridobenzodiazepines has already demonstrated[16] that diarylazepine structural modifications could lead to new promising clozapine-like drugs. Parallel to this study, an investigation of an analogous series of pyridobenzoxazepines and pyridobenzothiazepines was undertaken, the results of which are reported below. Biological studies were conducted through *in vitro* or *in vivo* models.

The ability to interact with dopaminergic (D_2 and D_1), serotonergic (5-HT_2), and muscarinic (M) receptors, frequently invoked as potential targets of clozapine and other atypical neuroleptics,[21,26,38] was evaluated in comparison with different tricyclic reference compounds. Compounds were studied *in vivo* using the antagonism of an apomorphine-induced stereotypies test to evaluate their antidopaminergic potential. An open-field test in rats and a complex operant-conditioning schedule in dogs, successfully employed in previous studies to discriminate between acutely[23] or chronically[43] administered typical and atypical antipsychotic drugs, were used to evaluate the newly synthesized and previously reported pyridobenzazepine analogues.[44]

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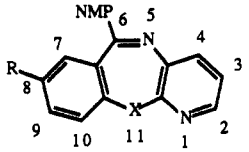
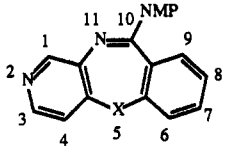
Table 1. *N*-Methylpiperazinopyrido[1,4]- and *N*-Methylpiperazinopyrido[1,5]benzothiazepines and -Oxazepines



8-11



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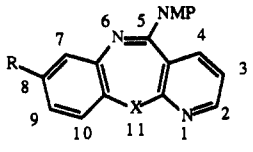
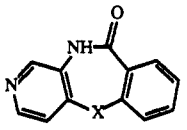


13-16

	X	R	formula	anal.	mp, °C	% yield
8	O	H	$C_{17}H_{18}N_4O$, $C_4H_4O_4$	C, H, N	182–184[a]	30–35
9	O	Cl	$C_{17}H_{17}ClN_4O$, $C_4H_4O_4$	C, H, N	249–251[a]	20–25
10	S	H	$C_{17}H_{18}N_4S$	C, H, N, S	133–134	45–50
11	S	Cl	$C_{17}H_{17}ClN_4S$, $C_4H_4O_4$	C, H, N, S	197–199[a]	30–35
12	S		$C_{17}H_{18}N_4S$	C, H, N, S	143–145	34–40
13	O	H	$C_{17}H_{18}N_4O$, $C_4H_4O_4$	C, H, N	205–207[b]	45–50
14	O	Cl	$C_{17}H_{17}ClN_4O$, $C_4H_4O_4$	C, H, N	259–261[a]	55–60
15	O	CH_3	$C_{18}H_{20}N_4O$, $C_4H_4O_4$[c]	C, H, N	234–236[a]	35–40
16	S	H	$C_{17}H_{18}N_4S$	C, H, N, S	126–128	40–45

[a] $C_4H_4O_4$ represents fumaric acid. [b] $C_4H_4O_4$ represents maleic acid. [c] $0.5C_2H_5OH$.

Table 2. Pyridobenzoxazepinones and Pyridobenzothiazepinones



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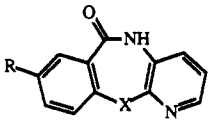
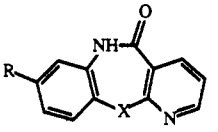


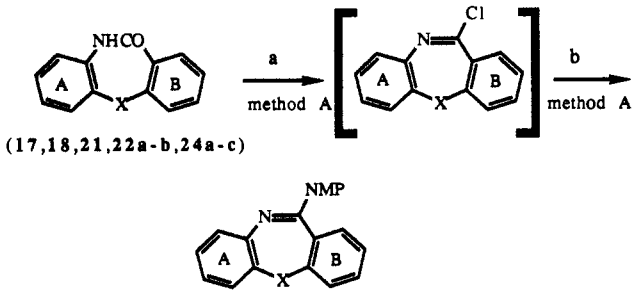
18,21,22a,22b



24b,24c

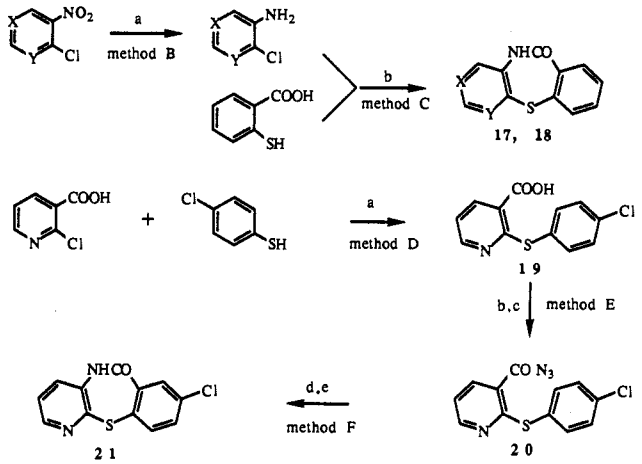
	X	R	formula	anal.	mp, °C	% yield
17	S		$C_{12}H_8N_2OS$	C, H, N, S	244–246	40–50
18	S	H	$C_{12}H_8N_2OS$	C, H, N, S	205–206	30–40
21	S	Cl	$C_{12}H_7ClN_2OS$	C, H, N, S	310–314	20–30
22a	O	H	$C_{12}H_8N_2O_2$	C, H, N	268–269	30–40
22b	O	Cl	$C_{12}H_7ClN_2O_2$	C, H, N	313–314	15–20
24b	O	Cl	$C_{12}H_7ClN_2O_2$	C, H, N	285–286	55–65
24c	O	CH_3	$C_{13}H_{10}N_2O_2$	C, H, N	199–201	40–50

Scheme 1[a]



[a] Key: (a) $OPCl_3$; (b) *N*-methylpiperazine, toluene, Δt. A,B: benzene or pyridine. X = O, S. NMP: *N*-methylpiperazin-1-yl.

Scheme 2[a,b]



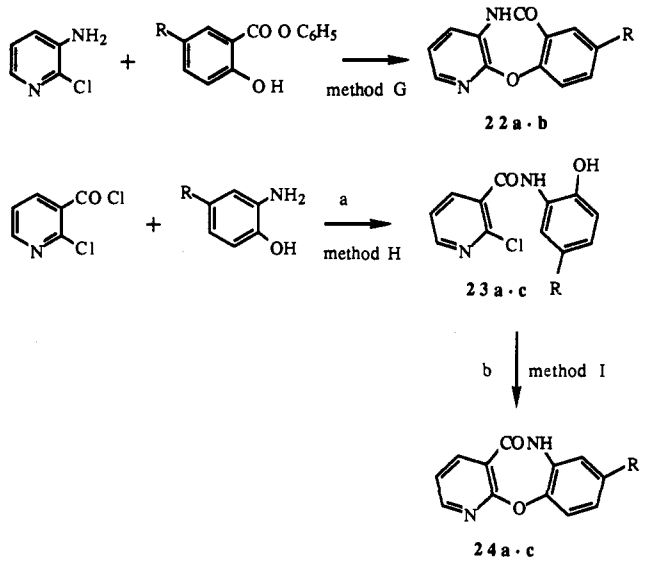
[a] Key: (a) $SnCl_2 \cdot 2H_2O$, HCl; (b) *o*-DCB, Δt. 17: X = N, Y = CH. 18: X = CH, Y = N. [b] Key: (a) NaH, propylene glycol, Δt; (b) $SOCl_2$; (c) NaN_3; (d) *o*-DCB, Δt; (e) $AlCl_3$, Δt.

Chemistry

The lateral benzene rings in the reference dibenzazepine compounds were alternatively replaced by a pyridine, thus determining the preparation of two series of derivatives: *N*-methylpiperazinopyrido[1,4]- and -pyrido[1,5]benzazepines. The synthesis of the amidine derivatives **8–16** was conducted according to the same procedure reported in Scheme 1. The lactams (**17**, **18**, **21**...) were transformed into an imino chloride by the action of phosphorus oxychloride (method A). The crude product directly gave amidines **8–16** (Table 1) by reaction with an excess of *N*-methylpiperazine (method A). Compounds **10**, **12**, and **16** were isolated as a free base. Compounds **8**, **9**, **11**, **14**, and **15** and compound **13** were crystallized as fumarate and maleate salts, respectively. The lactams (Table 2) were obtained by different synthetic pathways which are summarized below.

5*H*-Pyrido[2,3-*b*][1,4]benzothiazepin-6-one derivatives were prepared by two procedures. For the nonsubstituted analogues, the appropriate 3-aminochloropyridine directly reacted with thiosalicylic acid to give lactams **17** and **18** (Scheme 2a, method C). 3-Amino-4-chloropyridine was prepared from 4-chloro-3-nitropyridine (method B) according to the method of Delarge and Lapière.[45] The 8-chlorothiazepinone analogue **21** was obtained following the procedure illustrated in Scheme 2b. In the first step,

Scheme 3[a,b]



[a] Key: Δt, 1,2,4-$Cl_3C_6H_3$. R = H (**22a**), Cl (**22b**). [b] Key: (a) THF, Δt; (b) EtONa, DMF, Δt. R = H (**23a**, **24a**), Cl (**23b**, **24b**), CH_3 (**23c**, **24c**).

2-chloronicotinic acid reacted with 4-chlorothiophenol to provide 2-[(4-chlorophenyl)thio]nicotinic acid (**19**) (method D). The corresponding acid chloride was transformed to an acyl azide, **20**, by reaction with NaN_3 (method E). The anhydrous product, by thermal decomposition, yields the corresponding isocyanate (method F). In the presence of Lewis acids such as aluminum chloride, the isocyanate group, by an electrophilic attack of the adjacent benzene ring, yields lactam **21**.

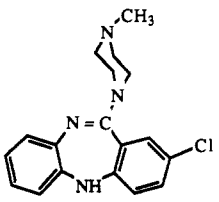
5*H*-Pyrido[2,3-*b*][1,4]benzoxazepin-6-one derivatives were prepared by a method previously described.[46,47] Lactams **22a,b** were obtained by direct condensation of phenyl salicylate or its 5-chloro analogue and 3-amino-2-chloropyridine (Scheme 3a, method G). Yields were poor due to problems of purification related to the presence of a byproduct such as pyridoxazole.[47]

The synthesis of 6*H*-pyrido[2,3-*b*][1,5]benzothiazepin-5-one derivatives was accomplished according to literature procedure.[48] The corresponding amidine derivative **16** has previously been described[49] but was prepared in order to examine its neurochemical and behavioral profile.

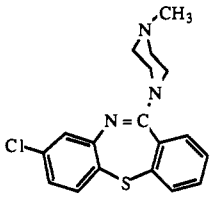
The preparation of the 6*H*-pyrido[2,3-*b*][1,5]benzoxazepin-5-one derivatives **24a–c** was achieved following the procedure of Hoffmann and Faure[48] (Scheme 3b). The reaction of 2-chloronicotinoyl chloride with an appropriate 2-aminophenol gave amides **23a–c** (method H). Ring closure was achieved with sodium ethoxide in DMF (160–170 °C) (method I).

Results and Discussion

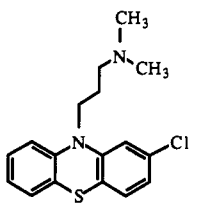
Hereby we report the biological evaluation of different *N*-methylpiperazinopyridobenzoxazepines and -benzothiazepines in comparison with some reference compounds. The binding affinities for D_1, D_2, 5-HT_2, and M receptors and their ratios compared to those of relevant reference compounds (isoclozapine (**4**), isoclothiapine (**5**), chlorpromazine (**6**), and haloperidol (**7**)) are reported in Table 3 along with the *in vivo* pharmacological data.



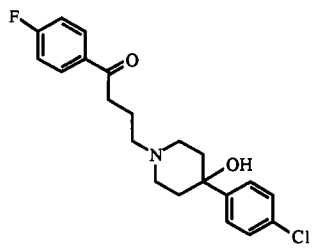
isoclozapine (**4**)



isoclothiapine (**5**)



chlorpromazine (**6**)



haloperidol (**7**)

Binding Profile of Oxa- and Thiazepines. In each series, either X = O or X = S, the introduction of a pyridine ring in the tricyclic structure reduced the affinities for each receptor site. Nonsubstituted derivatives (**8**, **10**, **13**, and **16**) were less potent than the substituted analogues in either the oxazepine or thiazepine series. A halogen substituent was more favorable as shown for **9** and **14** than a methyl group (**15**). Indeed, the halogen group in different antipsychotic diarylazepine analogues has been considered as an important structural element for the recognition

Table 3. Neurochemical Data: Binding Affinities and Ratio Values and Pharmacological Data of *N*-Methylpiperazinopyridobenzothiazepines, -Pyridobenzoxazepines, and Reference Compounds

	D_2[a]	D_1[a]	5-HT_2[a]	M[a]	5-HT_2/D_2[b]	D_2/M[b]	D_2/D_1[b]	apomorphine antagonism[c]	
8	4.96	5.04	4.65	6.07	0.94	0.82	0.98	0	
9	6.44	5.97	7.35	5.86	1.14	1.10	1.08	100	
10	5.18	5.09	5.94	6.13	1.15	0.84	1.02	0	
11	6.58	6.17	7.35	5.75	1.12	1.14	1.06	100	
12	5.64	4.81	6.55	6.68	1.16	0.84	1.17	0	
13	4.83	5.62	5.85	5.47	1.21	0.88	0.86	0	
14	5.92	6.52	7.19	5.65	1.21	1.05	0.91	0	
15	5.91	6.12	7.01	5.42	1.19	1.09	0.97	0	
16	5.39	5.79	6.29	5.61	1.17	0.96	0.93	0	
clozapine (**2**)	7.34	6.94	8.41	7.60	1.15	0.97	1.06	0	I*
isoclozapine (**4**)	7.90	7.55	8.75	7.68	1.11	1.03	1.05	NT	1.7*
clothiapine (**1**)	8.35	7.85	9.23	6.87	1.10	1.21	1.06	100	0.72*
isoclothiapine (**5**)	7.52	6.62	8.38	8.25	1.11	0.90	1.14	NT	I*
fluperlapine (**3**)	6.88	6.85	8.41	7.60	1.22	0.96	1.00	NT	
chlorpromazine (**6**)	8.70	7.45	8.48	7.22	0.97	1.20	1.17	NT	2.6*
haloperidol (**7**)	9.06	7.12	7.63	5.13	0.84	1.77	1.27	100	0.14*

[a] $-\log K_i$. [b] From $-\log K_i$. [c] Percent inhibition, by 20 mg/kg (sc) of drug, 1 h after apomorphine administration (2.5 mg/kg, sc). NT = not tested. * = from ref 1, ED_{50} in mg/kg, sc. I = inactive.

part of the receptor interaction.[50] Its favorable influence might be related not only to an electronic effect but also to the increased lipophilicity. The serotonergic affinity was consistently retained throughout these different modifications. The compounds evaluated in this study showed an evolution of the binding affinities similar to that of the pyridobenzodiazepine derivatives previously described.[16] Thus, for the isomers **10** and **16**, we observed two different evolutions of the binding profile. The isomer -[1,5]- (**16**) was more dopaminergic and serotonergic but less muscarinic than its isomer -[1,4]- (**10**). A similar evolution was noted for the oxazepine analogues **8** and **13** except for the D_2 affinity. Very few differences were noted between 8-chloro thiazepine **11** and 8-chloro oxazepine **9**. Compounds **9** and **11** showed a higher dopaminergic potential. Compound **12**, analogue of isoclothiapine, where the pyridine nitrogen replaced the C–Cl group, presented reduced dopaminergic (D_2 and D_1) affinities while serotonergic and muscarinic affinities were less modified. As previously reported,[20] this part of the molecule has a great influence on the cholinergic activity. Substituted compounds like **14** and **15** showed reduced dopaminergic and muscarinic potentials while serotonergic activity was retained. As previously mentioned, the pyridobenzazepine compounds were less potent than the dibenzazepine analogues[14,15] and thus constituted a new opportunity, in the group of diarylazepines, for the preparation of atypical antipsychotics.[16] This therapeutic class possessed the ability to reduce preferentially the activity of the mesolimbic dopaminergic system.[51,52] Moreover, interactions with nondopaminergic systems, such as 5-hydroxytryptamine, could also contribute to their activity.[53-56] A functional D_2 receptor blockade may be unnecessary for some atypical drugs to produce their antipsychotic effect[57] or to block some of the effects of DA agonists. It has been shown that at clinically effective doses, clozapine produced a lower occupancy at striatal D_2 receptors than classical antipsychotic drugs.[58] Moreover, clozapine is known to interact with other binding sites.[39-42] However, the implication of other receptors such as D_4 or 5-HT_{1C} in the atypical neuroleptic profiles remains to be confirmed.

Atypical neuroleptics seem to possess a higher 5-HT_2/D_2 binding ratio than classical neuroleptics.[26] This concept is corroborated by different works.[29-31,33] In our series, all molecules, except **8** and **11**, presented a ratio superior to 1.12, considered as the critical value.[26] Nevertheless, as mentioned by Meltzer et al.,[26] some molecules of the diarylazepine class, like clothiapine, were not properly differentiated and remained just borderline. In our study, **11**, which, incidentally, behaved as an antidopaminergic in the apomorphine test, had a value near 1.12. Compound **9**, as previously reported for loxapine,[26] possessed a value superior to 1.12, but all other compounds, inactive in the apomorphine-antagonism test, had a value superior to 1.12. As reported by Meltzer et al.[26] D_2/D_1 ratios were presented as being less discriminant than 5-HT_2/D_2 ratio values. Moreover, in our study, they also appeared more markedly differentiated by the 5-HT_2/D_2 and D_2/M ratio values. For a long time, a correct balance of the antidopaminergic and anticholinergic activities appeared important to reveal an atypical neuroleptic profile.[1-3,8] If we examine the D_2/M binding ratio, it is interesting to note that among the reference compounds, a value superior to 1.0 was observed for the typical neuroleptic drugs (clothiapine, haloperidol, and chlorpromazine) while the atypical antipsychotics (clozapine and fluperlapine) presented a value inferior to 1.0. Some azepines such as **9** and **11** showed values more related to those of typical antipsychotic compounds. These compounds presented an activity in the apomorphine-antagonism test. The anticholinergic activity prevents the inhibition of nigrostriatal cell firing linked to the dopamine-mediated effects, but it is also known that 5-HT_2 antagonism attenuates the effects of the dopamine blockade.[55]

***In Vivo* Pharmacological Evaluation.** The study of atypical neuroleptics presents many problems related to the characterization of the antipsychotic effect. The biggest problem is to find analogy and/or homology between animal and human behaviors. The newly developed model by Bruhwyler et al.[23] has allowed the detection of potential antipsychotics and the discrimination between typical and atypical antipsychotic properties.[23,43] In this study, two supplementary models were used, the antagonism of apomorphine stereotypies and the open-field test in rats. With the exception of chloro-substituted analogues, pyridobenzoxa- and thiazepines did not inhibit apomorphine-mediated stereotypies in rats (Table 3). Compounds **9** and **11** decreased stereotypies in a similar manner to that of haloperidol and clothiapine.

In behavioral models such as the open-field test in rats or the temporal-conditioning procedure in dogs, **14** showed an antipsychotic potential similar to clozapine.[44] Results obtained in the open-field test with other derivatives reveal mainly disinhibitory properties characterized by a high increase in the total ambulation score and a decrease in the defecation score (unpublished data). As generally observed for this chemical class, the clinical activity is borderline between antidepressant and anxiolytic. In the temporal-conditioning schedule in dogs, different molecules appeared clearly as disinhibitors and, using a cluster analysis, different thiazepines (**10** and **12**) were classified among antidepressant compounds (unpublished data). Such activities should be confirmed using appropriate experiments like Porsolt's test. The most interesting compound seems to be **14**, which, like clozapine (up to 24 mg/kg, ip), did not significantly modify the total ambulation score[44] and did not induce catalepsy nor stereotypy/hyperkinesia but reduced all the motor effects. The conservation of the clozapine behavioral profile with a reduction of motor side effects and the complete disappearance of sialorrhea,[59] as we showed for some pyridobenzodiazepines,[16] could represent a significant progress in psychosis treatment. Compound **14** has been selected for further investigation.

Conclusion

In this study, we confirmed our previous results[16] and we showed that the proposed modulations of dibenzazepine structures led to interesting new compounds. Different pyridobenzazepine derivatives, although possessing reduced *in vitro* binding affinities compared to those of their dibenzazepine analogues, could be classified among neuroleptic drugs. Other molecules presented a disinhibitory activity that could be related to an anxiolytic potential.

Experimental Section

Melting points were determined with a Tottoli (Buchi) melting point apparatus in open capillary tubes and are uncorrected. All compounds were characterized by physical methods using IR (Perkin-Elmer Model 297 spectrophotometer) and ^{1}H NMR (Bruker AW 80 spectrometer with HMDS as the internal

standard). Column chromatography was carried out using silica gel 60, 230–400 mesh (Merck). Microanalyses were performed in house (Carlo Erba CHNS-O EA1108 elemental analyzer) and were within ±0.4% of the theoretical values.

Method A. General Method for the Preparation of Oxazepine and Thiazepine Derivatives. 10-(4-Methylpiperazin-1-yl)pyrido[4,3-*b*][1,4]benzothiazepine (12). Lactam **17** (2.28 g, 0.01 mol) was heated to reflux in the presence of an excess of phosphorus oxychloride (20 mL) and *N,N*-dimethylaniline (0.5 mL) for 20 h. The brown solution was dissolved in anhydrous toluene and evaporated under reduced pressure. The crude product was used without any further purification in the next step.

The crude imino chloride was dissolved in toluene (20 mL), and an excess of *N*-methylpiperazine (10 mL, 0.09 mol) was added. The mixture was heated to reflux for 2–4 h. The solvent was then evaporated under reduced pressure and the residue dissolved in $CHCl_3$ (100 mL) and washed with water (2 × 50 mL). The organic layer was clarified with Norit, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by liquid/solid chromatography on Kieselgel 60 (Merck) using acetone as eluent. Recrystallization in petroleum ether (100–140 °C) gave pale yellow crystals: yield 35–40%; mp 143–145 °C; IR (KBr) 1583, 1554, 1477, 1430, 1242, 1002, 823, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28 (s, HC(1)), 7.98 (d, HC(3)), 7.44–7.13 (m, benzene and HC(2)), 3.53 (m, $-CH_2CH_2-$), 2.40 (m, $-CH_2-CH_2-$), 2.26 (s, CH_3-). Anal. ($C_{17}H_{18}N_4S$) C, H, N, S.

Compounds **10** and **16** were prepared and isolated in a similar manner.

Compounds **8**, **9**, **11**, **14**, and **15** were isolated as fumarate salts. The organic layer was concentrated to give an oil. The oil was dissolved in hot ethanol (20 mL) and treated with an equivalent of fumaric acid in hot ethanol (10 mL). The product crystallized as a white solid and was recrystallized from methanol.

Compound **13** was isolated as a maleate salt. The organic layer was removed to leave the crude free base which was converted into the maleate salt and crystallized from ethyl methyl acetone–ether–acetone. Filtration gave the salt as a white powder.

Method B. 3-Amino-4-chloropyridine. To a solution of 4-chloro-3-nitropyridine (4.1 g, 0.032 mol) in 12 N HCl (25 mL) was added dropwise under stirring a mixture of $SnCl_2 \cdot 2H_2O$ (30.2 g, 0.134 mol) and 12 N HCl (50 mL). The temperature was maintained between 50 and 60 °C. After addition, the suspension was heated to 90 °C for 5 min and then cooled at 0 °C for 2 h. The precipitate was collected by filtration and dissolved in water (200 mL). The solution was made basic with a 10% NaOH solution and extracted with $CHCl_3$ (4 × 200 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated after addition of petroleum ether (100–140 °C, 100 mL) under reduced pressure until crystallization. The product was collected by filtration, washed with petroleum ether (40–60 °C), and dried under reduced pressure: yield 55%; mp 58–59 °C; IR (KBr) 1640, 1570, 1558, 1486, 1416, 1328, 1244, 821, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (s, HC(1)), 7.80 (d, HC(6)), 7.07 (d, HC(5)), 4.18 (br s, H_2N). Anal. ($C_5H_5ClN_2$) C, H, N.

Method C. 11*H*-Pyrido[4,3-*b*][1,4]benzothiazepin-10-one (17). Thiosalicylic acid (1.62 g, 0.01 mol) and 3-amino-4-chloropyridine (1.28 g, 0.01 mol) in *o*-dichlorobenzene (20 mL) were heated to reflux for 2–3 h. After the reaction was complete, the solvent was eliminated and the residue was taken up in water (100 mL). The pH was adjusted to 5–6, and the mixture was extracted with $CHCl_3$ (4 × 50 mL) and dried over anhydrous $MgSO_4$. The organic layer was evaporated under reduced pressure, and the residue was taken up in a 10% $NaHCO_3$ solution. After the solution had stirred for 30 min, the product was collected by filtration, washed with water, and dried at room temperature: yield 40–50%; mp 244–246 °C; IR (KBr) 1662, 1590, 1559, 1474, 1398, 1383, 1286, 1188, 836, 743 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 10.76 (br s, HNCO), 8.41 (s, HC(1)), 8.21 (d, HC(3)), 7.65–7.31 (m, benzene and HC(4)). Anal. ($C_{12}H_8N_2OS$) C, H, N, S.

Method D. 2-[(4-Chlorophenyl)thio]nicotinic Acid (19). To 4-chlorothiophenol (28.8 g, 0.2 mol) and NaH (4.8 g, 0.2 mol) in propylene glycol (50 mL) was added 2-chloronicotinic acid (15.7 g, 0.1 mol). The mixture was heated to reflux until the starting materials were consumed, and the solvent was then evaporated under low pressure. The residue was dissolved in a 10% $NaHCO_3$ solution. The excess of thiophenol was extracted with $CHCl_3$ (4 × 50 mL). The solution was made acidic with 6 N aqueous HCl. The separated product was collected by filtration, washed with water, and dried at room temperature: yield 60%; mp 223–225 °C; IR (KBr) 1685, 1568, 1478, 1436, 1253, 1077, 822, 766, 716 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 9.81 (br s, H(OC=O), 8.32–8.12 (dd, dd, HC(6'), HC(4')), 7.47–7.23 (m, benzene), 7.09–6.93 (dd, HC(5')). Anal. ($C_{12}H_8ClNO_2S$) C, H, N, S.

Method E. 2-[(4-Chlorophenyl)thio]nicotinoyl Azide (20). **19** (5.3 g, 0.02 mol) in $SOCl_2$ (50 mL) and DMF (0.5 mL) was heated to reflux for 1 h. The excess of $SOCl_2$ was evaporated under reduced pressure, and the residue was dissolved in cold anhydrous acetone (30 mL) with vigorous stirring. The acid chloride was added dropwise to a cooled 30% NaN_3 solution. The solution was then diluted with water (200 mL) and allowed to stand for 2 h at 0 °C. The separated product was collected by filtration, washed with cold water, and dried under reduced pressure. The product was used without any further purification in the next step: yield 90–95%.

Method F. 8-Chloro-5*H*-pyrido[2,3-*b*][1,4]benzothiazepin-6-one (21). **20** (1 g, 0.0033 mol) in *o*-dichlorobenzene (15 mL) was added to a suspension of aluminum chloride (1.5 g, 0.011 mol) in *o*-dichlorobenzene (50 mL) and heated to 160–170 °C for 15 min. The solution was diluted with $CHCl_3$ (150 mL) and extracted three times with 2 N aqueous HCl. The aqueous acid solution was extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were concentrated under reduced pressure, and the residue was dissolved in acetone (30 mL). The product was collected by filtration, washed with acetone, and resuspended in 1 N aqueous HCl (30 mL). The precipitate was collected by filtration, washed with water, and dried at room temperature: yield 20–30%; mp 310–314 °C; IR (KBr) 1666, 1580, 1555, 1445, 1412, 1347, 1102, 828, 776 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 8.92 (br s, HNCO), 8.14–8.03 (m, pyridine), 7.35 (m, benzene), 7.17 (dd, HC(3)). Anal. ($C_{12}H_7ClN_2OS$) C, H, N, S.

Method G. 8-Chloro-5*H*-pyrido[2,3-*b*][1,4]benzoxazepin-6-one (22b). Phenyl 5-chlorosalicylate (12.4 g, 0.05 mol) and 3-amino-2-chloropyridine (12.8 g, 0.1 mol) in 1,2,4-trichlorobenzene (10 mL) were heated to reflux under N_2 for 1 h. The liberated phenol was distilled during the experiment, and HCl was absorbed in a 10% NaOH solution. The hot mixture was then poured into ethanol (100 mL). The separated product was collected by filtration, washed with ethanol, and dried. The product was recrystallized from methanol/DMF (6/1): yield 35–40%; mp 313–314 °C; IR (KBr) 1683, 1600, 1569, 1506, 1462, 1432, 1357, 1105, 827, 794 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.68 (br s, HNCO), 7.98 (dd, HC(2)), 7.68–7.50 (m, 3H), 7.37–7.17 (m, 2H). Anal. ($C_{12}H_7ClN_2O_2$) C, H, N.

Method H. *N*-(2-Hydroxy-5-chlorophenyl)-2-chloro-3-pyridinecarboxamide (23b). To a solution of 2-amino-4-chlorophenol (15.9 g, 0.1 mol) in THF (150 mL) was added dropwise a solution of 2-chloronicotinoyl chloride (17.5 g, 0.1 mol) in THF (100 mL). The solution was heated to reflux while stirring for 1 h. The mixture was diluted with water (1 L). The separated product was collected by filtration, washed with water, and air-dried; yield 75–80%. A sample was recrystallized from 2-propanol: mp 193–194 °C; IR (KBr) 1657, 1612, 1579, 1583, 1547, 1429, 1394, 1189, 805, 744 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 9.79 and 9.46 (br s, HO and HNCO), 8.42 (dd, HC(6')), 8.05–7.82 (m, benzene and HC(4')), 7.38 (dd, HC(5')), 6.86 (d, benzene). Anal. ($C_{12}H_8Cl_2N_2O_2$) C, H, N.

Method I. 8-Chloro-6*H*-pyrido[2,3-*b*][1,5]benzoxazepin-5-one (24b). Compound **23b** (26.2 g, 0.1 mol) and NaOEt (6.8 g, 0.1 mol) in DMF (100 mL) were heated to reflux for 3–4 h. The mixture was concentrated under reduced pressure, and the product was collected by filtration, washed with cold methanol, and recrystallized from methanol/DMF (4/1): yield 65%; mp 285–286 °C; IR (KBr) 1686, 1596, 1573, 1498, 1423, 1384, 818, 780 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 10.67 (br s, HNCO), 8.42 (dd, HC(2)), 8.22 (dd, HC(4)), 7.37 (dd, HC(3)), 7.27–6.98 (m, benzene). Anal. ($C_{12}H_7ClN_2O_2$) C, H, N.

Radioligand Binding Study. Experiments on receptor preparations were performed following classical methods previously described, D_1,[60,61] D_2,[62] 5-HT_2,[63] and M.[64] Specific binding was defined as the difference between total and nonspecific

binding (with and without [^{3}H] drug). K_i values were calculated according to the Cheng–Prusoff equation:[65] $K_i = IC_{50}/(1 + L/K_d)$ with L the concentration and K_d the apparent dissociation constant of the [^{3}H] ligand obtained from Scatchard analysis of saturation experiments. Each K_i value was determined at least in duplicate with nine concentrations of the drug in triplicate. The mean coefficient of variation for duplicate determinations of the K_i value for the four types of binding sites was 15.3 ± 3.8% (SD). The pK_i (−log K_i) values are reported in Table 3 and were used in the calculation of binding ratios.

Apomorphine-Antagonism Test in the Rat. Experiments were performed following the classical method previously described.[66]

Open-Field Test in the Rat. Experiments were performed following the classical method previously described.[22]

Temporal-Regulation Schedule in the Dog. Experiments were performed following the previously described procedure.[23,43,44]

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References

(1) Bürki, H. R.; Sayer, A. C.; Ruch, W.; Asper, H. Effects of Clozapine and other Dibenzo-Epines on Central Dopaminergic and Cholinergic Systems. Structure-Activity Relationships. *Arzneim.-Forsch.* **1977**, *27*, 1561–1565.

(2) Chakrabarti, J. K.; Hotten, T. M.; Pullar, I. A.; Steggles, D. J. Synthesis and Pharmacological Evaluation of CNS Activities of [1,2,3]Triazolo[4,5-*b*][1,5]-, Imidazolo[4,5-*b*][1,5]-, and Pyrido-[2,3-*b*][1,5]benzodiazepines. 10-Piperazinyl-4*H*-1,2,3-triazolo[4,5-*b*][1,5]benzodiazepines with Neuroleptic Activity. *J. Med. Chem.* **1989**, *32*, 2375–2381.

(3) Chakrabarti, J. K.; Hotten, T. M.; Pullar, I. A.; Tye, N. C. Synthesis and Pharmacological Evaluation of a series of 4-Piperazinylpyrazolo[3,4-*b*]- and -[4,3-*b*][1,5]benzodiazepines as Potential Anxiolytics. *J. Med. Chem.* **1989**, *32*, 2573–2582.

(4) Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Fanshawe, W. J.; Day, I. P.; Greenblatt, E. N.; Safir, S. R. 10-(Alkylamino)-4*H*-thieno-[3,4-*b*][1,5]benzodiazepines. A Novel Class of Potential Neuroleptic Agents. *J. Med. Chem.* **1979**, *22*, 725–731.

(5) Chakrabarti, J. K.; Horsman, L.; Hotten, T. M.; Pullar, I. A.; Tupper, D. E.; Wright, F. C. 4-Piperazinyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepines as Potential Neuroleptics. *J. Med. Chem.* **1980**, *23*, 878–884.

(6) Hunzicker, F.; Fischer, R.; Kipfer, P.; Schmutz, J.; Bürki, H. R.; Eichenberger, E.; White, T. G. Neuroleptic Piperazinyl Derivatives of 10*H*-Thieno[3,2-*c*][1]benzazepines and 4*H*-Thieno[2,3-*c*][1]-benzazepines. *Eur. J. Med. Chem.* **1981**, *16*, 391–398.

(7) Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Day, I. P.; Greenblatt, E. N.; Safir, S. R. Thiophene systems. 5. Thieno[3,4-*b*][1,5]-benzoxazepines, Thieno[3,4-*b*][1,5]benzothiazepines, and Thieno-[3,4-*b*][1,4]benzodiazepines as Potential Central Nervous System Agents. *J. Med. Chem.* **1981**, *24*, 154–159.

(8) Chakrabarti, J. K.; Hotten, T. M.; Morgan, S. E.; Pullar, I. A.; Rackham, D. M.; Risius, F. C.; Wedley, S.; Chaney, M. O.; Jones, N. D. Effects on Conformationally Restricted 4-Piperazinyl-10*H*-thienobenzodiazepine Neuroleptics on Central Dopaminergic and Cholinergic Systems. *J. Med. Chem.* **1982**, *25*, 1133–1140.

(9) Rupard, J. H.; de Paulis, T.; Janowsky, A.; Smith, H. E. Sterically Hindered 5,11-Dicarbo Analogues of Clozapine as Potential Chiral Antipsychotic Agents. *J. Med. Chem.* **1989**, *32*, 2261–2268.

(10) Davis, D. A.; de Paulis, T.; Janowsky, A.; Smith, H. E. Chloro-Substituted, Sterically Hindered 5,11-Dicarbo Analogues of Clozapine as Potential Chiral Antipsychotic Agents. *J. Med. Chem.* **1990**, *33*, 809–814.

(11) Kovac, T.; Oklobdzija, M.; Comisso, G.; Decorte, E.; Fajdiga, T.; Moimas, F.; Angeli, C.; Zonno, F.; Toso, R.; Sunjic, V. New Synthesis of 11-Acyl-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and Related Studies. *J. Heterocycl. Chem.* **1983**, *20*, 1339–1349.

(12) Oklobdzija, M.; Comisso, G.; Decorte, E.; Fajdiga, T.; Gratton, G.; Moimas, F.; Toso, R.; Sunjic, V. Novel Synthesis of 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and Related Studies. *J. Heterocycl. Chem.* **1983**, *20*, 1329–1334.

(13) Engel, W. W.; Eberlein, W. G.; Mihm, G.; Hammer, R.; Trummlitz, G. Tricyclic Compounds as Selective Muscarinic Receptor Antagonists. 3. Structure-Selectivity Relationships in a Series of Cardioselective (M_2) Antimuscarinics. *J. Med. Chem.* **1989**, *32*, 1718–1724.

(14) Bartl, V.; Metysova, J.; Protiva, M. Neurotropic and Psychotropic Agents. LXI. Derivatives of 6-Piperazinobenzo[*b*]pyrido[3,2-*f*]-thiepin. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1693–1699.

(15) Bartl, V.; Metysova, J.; Protiva, M. Neurotropic and Psychotropic Agents. LXV. 8-Chloro and 8-Isopropyl-6-piperazinobenzo[*b*]-pyrido[3,2-*f*]thiepin. *Collect. Czech. Chem. Commun.* **1973**, *38*, 2778–2787.

(16) Liégeois, J.-F.; Bruhwyler, J.; Damas, J.; Nguyen, T. P.; Chleide, E.; Mercier, M.; Rogister, F.; Delarge, J. New Pyridobenzodiazepine Derivatives as Potential Antipsychotics: Synthesis and Neurochemical Study. *J. Med. Chem.* **1993**, *36*, 2107–2114.

(17) Baldessarini, R. J. Drugs and the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics*, 8th ed.; Goodman Gilman, A., Rall, T. W., Nies, A. S., Taylor, P., Eds.; Pergamon Press: New York, 1990; pp 383–435.

(18) De Maio, D. Clozapine, a Novel Tranquilizer. *Arzneim.-Forsch.* **1972**, *22*, 919.

(19) Gross, H.; Langner, E. Effect Profile of a Chemically New Broad Spectrum Neuroleptic of the Dibenzo-diazepine Group. *Wien. Med. Wochenschr.* **1966**, *116*, 814–816.

(20) Baldessarini, R. J.; Frankenburg, F. R. Clozapine. A Novel Antipsychotic Agent. *N. Engl. J. Med.* **1991**, *324*, 746–754.

(21) Deutch, A. Y.; Moghaddam, B.; Innis, R. B.; Krystal, J. H.; Aghajanian, G. K.; Bunney, B. S.; Charney, D. S. Mechanisms of Action of Atypical Antipsychotic Drugs. Implication for Novel Therapeutic Strategies for Schizophrenia. *Schizophr. Res.* **1991**, *4*, 121–156.

(22) Bruhwyler, J.; Chleide, E.; Liégeois, J.-F.; Delarge, J.; Mercier, M. Anxiolytic Potential of Sulpiride, Clozapine and Derivatives in the Open-Field Test. *Pharmacol. Biochem. Behav.* **1990**, *36*, 57–61.

(23) Bruhwyler, J.; Chleide, E. Comparative Study of the Behavioural, Neurophysiological, and Motor Effects of Psychotropic Drugs in the Dog. *Biol. Psychiatry* **1990**, *27*, 1264–1278.

(24) Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H. Clozapine for the Treatment-Resistant Schizophrenic. A Double-Blind Comparison with Chlorpromazine. *Arch. Gen. Psychiatry* **1988**, *45*, 789–796.

(25) Claghorn, J.; Honigfeld, G.; Abuzzahab, F.; Wang, R.; Steinbook, R.; Tuason, V.; Klerman, G. The Risks and Benefits of Clozapine versus Chlorpromazine. *J. Clin. Psychopharmacol.* **1987**, *7*, 377–384.

(26) Meltzer, H. Y.; Matsubara, S.; Lee, J. C. Classification of Typical and Atypical Antipsychotic Drugs on the Basis of Dopamine D-1, D-2 and Serotonin$_2$ pKi Values. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238–246.

(27) Niemegeers, C. J. E.; Awouters, F.; Janssen, P. A. J. Involvement of Serotonin in the Action of Antipsychotic Drugs. Recent Evidence with Ritanserin and Risperidone. *Encephale* **1990**, *16*, 147–151.

(28) Gelders, Y. G.; Thymosthenic Agents, A Novel Approach in the Treatment of Schizophrenia. *Br. J. Psychiatry* **1989**, *155*(S5), 33–36.

(29) Perregaard, J.; Arnt, J.; Bøgesø, K. P.; Hyttel, J.; Sanchez, C. Noncataleptogenic, Centrally Acting D-2 and Serotonin 5-HT2 Antagonists within a Series of 3-Substituted 1-(4-Fluorophenyl)-1*H*-indoles. *J. Med. Chem.* **1992**, *35*, 1092–1101.

(30) Andersen, K.; Perregaard, J.; Arnt, J.; Nielsen, J. B.; Begtrup, M. Selective, Centrally Acting Serotonin 5-HT2 Antagonists. 2. Substituted 3-(4-Fluorophenyl)-1*H*-indoles. *J. Med. Chem.* **1992**, *35*, 4823–4831.

(31) Leysen, J. E.; Gommeren, W.; Eens, A.; De Chaffoy de Courcelles, D.; Stoof, J. C.; Janssen, P. A. J. Biochemical Profile of Risperidone, a New Antipsychotic. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 661–670.

(32) Peuskens, J.; Claus, A.; DeCuyper, H.; Bollen, J.; Eneman, M.; Wilms, G. Risperidone: A New Approach in the Treatment of Schizophrenia. *Abstr. VIII World Congresss Psychiat.*, Excerpta Medica International Congress Series 899, Athens, Greece; Elsevier: Amsterdam, 1989; p 347.

(33) Mewshaw, R. E.; Silverman, L. S.; Mathew, R. M.; Kaiser, C.; Sherril, R. G.; Cheng, M.; Tiffany, C. W.; Karbon, E. W.; Bailey, M. A.; Borosky, S. A.; Ferkany, J. W.; Abreu, M. E. Bridged γ-Carbolines and Derivatives Possessing Selective and Combined Affinity for 5-HT2 and D2 receptors. *J. Med. Chem.* **1993**, *36*, 1488–1495.

(34) Lieberman, J. A.; Johns, C. A.; Kane, J. M.; Rai, K.; Pisciotta, A. V.; Saltz, B. L.; Howard, A. Clozapine-Induced Agranulocytosis: Non-Cross Reactivity with other Psychotropic Drugs. *J. Clin. Psychiatry* **1988**, *49*, 271–277.

(35) Grohmann, R.; Schmidt, L. G.; Spieb-Kiefer, C.; Rüther, E. Agranulocytosis and Significant Leucopenia with Neuroleptic Drugs: Results from the AMÜP Program. *Psychopharmacology* **1989**, *99*, S109–S112.

(36) Pisciotta, A. V. Drug Induced Agranulocytosis Peripheral Destruction of Polymorphonuclear Leukocytes and their Marrow Precursors. *Blood Rev.* **1990**, *4*, 226–237.

(37) Haller, E.; Binder, R. L. Clozapine and Seizures. *Am. J. Psychiatry* **1990**, *147*, 1069–1071.

(38) Tricklebank, M. D.; Bristow, L. J.; Hutson, P. H. Alternative Approaches to the Discovery of Novel Antipsychotic Agents. In *Progress in Drug Research. Fortschritte der Arzneimittel Forschung*; Ersnst, J., Ed.; Birkhäuser Verlag: Basel, Boston, Berlin, 1992; Vol. 38, pp 299–336.
(39) Criswell, H. E.; Mueller, R. A.; Breese, G. A. Clozapine Antagonism of D_1 and D_2 Dopamine Receptor-Mediated Behaviors. *Eur. J. Pharmacol.* **1989**, *159*, 141–147.
(40) Watling, K. J.; Beer, M. S.; Stanton, J. A.; Newberry, N. R. Interaction of the Atypical Neuroleptic Clozapine with 5-HT_3 Receptors in the Cerebral Cortex and Superior Cervical Ganglion of the Rat. *Eur. J. Pharmacol.* **1990**, *182*, 465–472.
(41) Canton, H.; Verrièle, L.; Colpaert, F. C. Binding of Typical and Atypical Antipsychotics to 5-HT_{1C} and 5-HT_2 Sites: Clozapine Potently Interacts with 5-HT_{1C} Sites. *Eur. J. Pharmacol.* **1990**, *191*, 93–96.
(42) Van Tol, H. H. M.; Bunzow, J. R.; Guan, H. C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. Cloning of the Gene for a Human Dopamine D_4 Receptor with High Affinity for the Antipsychotic Clozapine. *Nature* **1991**, *350*, 610–614.
(43) Bruhwyler, J.; Chleide, E.; Houbeau, G.; Waegeneer, N.; Mercier, M. Differentiation of Haloperidol and Clozapine using a Complex Operant Schedule in the Dog. *Pharmacol. Biochem. Behav.* **1993**, *44*, 181–189.
(44) Bruhwyler, J.; Liégeois, J.-F.; Chleide, E.; Rogister, F.; Damas, J.; Delarge, J.; Mercier, M. Comparative Study of Typical Neuroleptics, Clozapine and New Synthesized Clozapine-Analogues: Correlations between Neurochemistry and Behaviour. *Behav. Pharmacol.* **1992**, *3*, 567–579.
(45) Delarge, J.; Lapière, C. L. Synthesis Using 4-Hydroxy-3-nitropyridine. Antimicrobial and Antiviral Activity. *Pharm. Helv. Acta* **1975**, *50*, 188–191.
(46) Dr. Karl Thomae G.m.b.H. Pyrido[2,3-b][1,4]benzoxazepines. Brit. Patent 1,050,565, 1966.
(47) Klunder, J. M.; Hargrave, K. D.; West, M. A.; Cullen, E.; Pal, K.; Behnke, M. L.; Kapadia, S. R.; MacNeil, D. W.; Wu, J. C.; Chow, G. C.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2. Tricyclic Pyridobenzoxazepinones and Dibenzoxazepinones. *J. Med. Chem.* **1992**, *35*, 1887–1897.
(48) Hoffmann, C.; Faure, A. Reactions of 2-Chloronicotinic Acid (I) Condensations with Aromatic Amines. *Bull. Soc. Chim. Fr.* **1966**, *196*, 2316–2319.
(49) Hoffmann, C.; Bouley, E. Benzothiazepine Compounds and Composition. U.S. Patent 4,163,785, 1979.
(50) Froimowitz, M.; Rämsby, S. Conformational Properties of Semirigid Antipsychotic Drugs: The Pharmacophore for Dopamine D-2 Antagonist Activity. *J. Med. Chem.* **1991**, *34*, 1707–1714.
(51) Chiodo, L. A.; Bunney, B. S. Typical and Atypical Neuroleptics: Differential Effects of Chronic Administration on the Activity of A9 and A10 Midbrain Dopaminergic Neurons. *J. Neurosci.* **1983**, *3*, 1607–1619.
(52) White, F. J.; Wang, R. Y. Differential Effects of Typical and Atypical Antipsychotic Drugs on A9 an A10 Dopamine Neurons. *Science* **1983**, *221*, 1054–1057.
(53) Leysen, J. E.; Niemegeers, C. J. E.; Tollenaere, J. P.; Laduron, P. Serotonergic Component of Neuroleptic Receptors. *Nature* **1978**, *272*, 168–171.
(54) Glennon, R. A. Central Serotonin Receptors as Targets for Drug Research. *J. Med. Chem.* **1987**, *30*, 1–12.
(55) Saller, C. F.; Czupryna, M. J.; Salama, A. I. 5-HT2 Receptor Blockade by ICI 169,369 and other 5-HT_2 Antagonists Modulates the Effects of D-2 Dopamine Receptor Blockade. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 1161–1170.
(56) Waldmeier, P. C.; Delini-Stula, A. A. Serotonin-Dopamine Interactions in the Nigrostriatal System. *Eur. J. Pharmacol.* **1979**, *55*, 363–373.
(57) Pugsley, T. A.; Coughenour, L. L.; Myers, S. L.; Shih, Y. H.; Courtland, G. G.; Berghoff, W.; Stewart, S. F. CI-943, a Potential Antipsychotic Agent. II. Neurochemical Effects. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 113–122.
(58) Farde, L.; Wiesel, F. A.; Nordström, A.-L.; Sedvall, G. D1- and D2-Dopamine Receptor Occupancy During Treatment with Conventional and Atypical Neuroleptics. *Psychopharmacology* **1989**, *99*, S28–S31.
(59) Copp, P. J.; Lament, R.; Tennent, T. G. Amitriptyline in Clozapine-Induced Sialorrhea. *Br. J. Psychiatry* **1991**, *159*, 166.
(60) Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L. C.; Barnett, A. Characterization of the Binding of ^{3}H-SCH 23390, a Selective D-1 Receptor Antagonist Ligand, in Rat Striatum. *Life Sci.* **1984**, *35*, 1885–1893.
(61) Faedda, G.; Kula, N. S.; Baldessarini, R. J. Pharmacology of Binding of ^{3}H-SCH 23390 to D-1 Dopaminergic Receptor Sites in Rat Striatal Tissue. *Biochem. Pharmacol.* **1989**, *38*, 473–480.
(62) Tecott, L. H.; Kwong, L. L.; Uhr, S.; Peroutka, S. J. Differential Modulation of Dopamine D_2 Receptors by Chronic Haloperidol, Nitrendipine, and Pimozide. *Biol. Psychiatry* **1986**, *21*, 1114–1122.
(63) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. [^{3}H]Ketanserin (R41468), a Selective ^{3}H-Ligand for Serotonin$_2$ Receptor Binding Sites. Binding Properties, Brain Distribution, and Functional Role. *Mol. Pharmacol.* **1982**, *21*, 301–314.
(64) Yamamura, H. I.; Snyder, S. H. Muscarinic Cholinergic Binding in Rat Brain. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 1725–1729.
(65) Cheng, Y.-C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_I) and the Concentration of Inhibitor which Causes 50 per Cent Inhibition (I_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
(66) Janssen, P. A. J.; Niemegeers, C. J. C.; Jagenau, A. H. M. Apomorphine-antagonism in rats. *Arzneim.-Forsch.* **1960**, *10*, 1003–1006.