New (Sulfonyloxy)piperazinyldibenzazepines as Potential Atypical Antipsychotics: Chemistry and Pharmacological Evaluation

Yi Liao,* Bastiaan J. Venhuis, Nienke Rodenhuis, Wia Timmerman, and Håkan Wikström

Department of Medicinal Chemistry, University of Groningen, A. Deusinglaan 1, NL-9713 AV Groningen, The Netherlands

Eddie Meier

Lundbeck A/S, Ottilliavej 9, DK-2500 Copenhagen-Valby, Denmark

Gerd D. Bartoszyk, Henning Böttcher, and Christoph A. Seyfried

Preclinical Pharmaceutical Research, Merck KGaA, D-64271 Darmstadt, Germany

Staffan Sundell

Department of Medical Biochemistry, University of Göteborg, Box 440, SE-405 30 Göteborg, Sweden

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A series of 2- or 8-trifluoromethylsulfonyloxy (TfO) and 2- or 8-methylsulfonyloxy (MsO) 11-piperazinyldibenzodiazepines, -oxazepines, and -thiazepines were synthesized and evaluated in pharmacological models for their potential clozapine-like properties. In receptor binding assays, the 2-TfO analogues (**18a**, GMC2-83; **24**, GMC3-06; and previously reported GMC1-169, **9a**) of the dibenzazepines have profiles comparable to that of clozapine, acting on a variety of CNS receptors except they lack M_1 receptor affinity. Introduction of 2-TfO to clozapine leads to compound **9e** (GMC61-39) which has a similar binding profile as that of clozapine including having M_1 receptor affinity. Interestingly, the MsO analogues, as well as the 8-TfO analogues, have no or weak dopaminergic and serotonergic affinities, but all 8-sulfonyloxy analogues do have M_1 affinities. In behavioral studies performed to indicate the potential antipsychotic efficacy and the propensity to induce EPS, 2-TfO analogues blocked effectively the apomorphine-induced climbing in mice in a dose-dependent manner with ED_{50} values (mg/kg) of 2.1 sc for **9a**, 1.3 po for **18a**, 2.6 sc for **24**, and 8.2 sc for **9e**. On the other hand, they showed a clear dose separation with regard to their ED_{50} values (mg/kg) for indicating catalepsy in rats (>44 sc for **9a**, 28 po for **18a**, 30 sc for **24**, and >50 sc for **9e**, respectively), thus implicating a more favorable therapeutic ratio (*K*/*A*, ED_{50} climbing/ED_{50} catalepsy) in comparison with typical neuroleptics such as haloperidol and isoclozapine. Furthermore, compound **18a** was also demonstrated to be an orally potent DA antagonist with an ED_{50} value of 0.7 mg/kg po in the ex vivo L-DOPA accumulation model. The present study contributes to the SAR of 11-piperazinyldibenzazepines, and the 2-TfO analogues of 11-piperazinyldibenzazepines are promising candidates as clozapine-like atypical antipsychotics with low propensity to induce EPS.

Introduction

The neuroleptic 11-piperazinyldibenzazepines formed a valuable chemical class for structure−activity relationship (SAR) studies.[1] Some well-established representatives of this class of compounds in the clinical studies and practice, e.g., loxapine (**1**), clothiapine (**2**), and isoclozapine (**3**), are known to be typical neuroleptics such as haloperidol (**5**) and chloropromazine (**6**), while clozapine (**4**) is an effective atypical neuroleptic or antipsychotic (Chart 1).[1−3] The typical neuroleptics that are used to treat schizophrenia are generally potent dopamine (DA) receptor antagonists, especially at the DA D_2 receptor subtype, with high propensity to induce acute or chronic motor disturbances (extrapyramidal side effects, EPS). Other disadvantages of the typical neuroleptics include the lack of clinical efficacy in the negative symptoms of schizophrenia and, moreover, the lack of clinical efficacy in up to 30% of the therapy-resistant patients. The atypical antipsychotic clozapine couples a low incidence of EPS with an improved efficacy in relief of both positive and negative symptoms as well as an improved efficacy against treatment-resistant schizophrenia.[4−8] Still, the use of clozapine is limited due to its propensity to induce agranulocytosis and other side effects.[9−13] For several decades, research has been focused on studying the atypical nature of clozapine and on developing new clozapine-like antipsychotic agents without or with minimal EPS and other disturbing side effects. This remains to be a great challenge today.

Some new classes of compounds, from either a chemical or pharmacological point of view, as new antipsychotics were generated, such as remoxipride, a benzamide as a selective D_2 antagonist;[8,14] risperidone, a D_2/5-HT_2 antagonist;[15] and sertindole, with limbic selectivity.[16] However, the tricyclic piperazinyldibenzazepine remains to be an interesting chemical class with

* Corresponding author: Dr. Yi Liao. Tel: +31-50-3633302. Fax: +31-50-3636908. E-mail: y.liao@farm.rug.nl.

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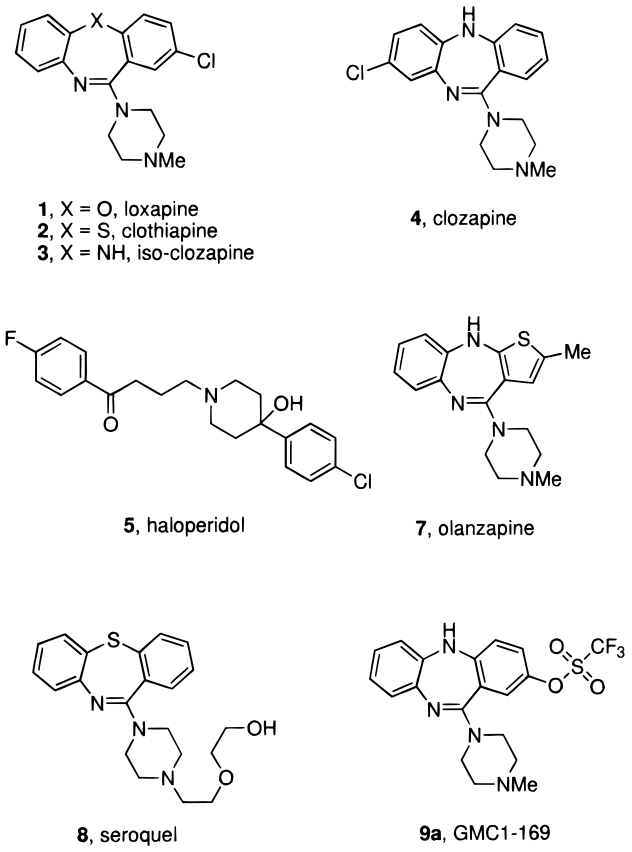
Chart 1. Structures of Some Antipsychotics



regard to developing new potential atypical antipsychotics. A small modification of the structure can provide very different pharmacological profiles.[3,17,18] Among the newer antipsychotics that have emerged from this approach are olanzapine (**7**), in which a benzene ring of the dibenzodiazepine has been replaced by a methylated thiophene ring,[19] and seroquel (**8**), which is a dibenzothiazepine derivative.[20] Olanzapine (**7**) has a receptor binding profile most similar to that of clozapine. Interestingly, compounds such as **7** and **8** with similar multireceptor interactions to clozapine are efficacious and well-tolerated antipsychotics.[5]

It has been demonstrated that a substituent, such as a chlorine atom, in an aromatic ring (especially in 2-position) of the tricyclic dibenzazepine system promoted neuroleptic activity. Fluorine was used in flumezapine and fluperlapine,[21,22] assuming to reduce the metabolism of these drugs since some metabolites could frequently play a role in the toxicological problems of this class of compounds. Indeed, the halogen substituent in different antipsychotic diarylazepine analogues has been considered as an important structural element for the recognition in the drug−receptor interaction.[23] Its favorable influence might be related not only to the electron-withdrawing effect but also to the increased lipophilicity.[17]

Several applications of the aromatic triflate functionality in medicinal chemistry have recently been presented.[24−30] An aromatic triflate group induces less oxidative metabolism in comparison with a hydroxy or methoxy group due to its electron-withdrawing effect and lipophilicity. We reported previously the introduction of the triflate substituent to the intact dibenzodiazepine skeleton of clozapine, aiming at maintaining the interesting pharmacological profile of clozapine while possibly avoiding some aspects of metabolism of clozapine. It had been documented that clozapine and/or its metabolites can cause a sometimes fatal agronulocytosis.[31] GMC1-169 (**9a**) was indicated from the preclinical pharmacological evaluation to be an atypical antipsychotic agent. It has a profile similar to that of clozapine both in vitro and in vivo; however, it lacks anticholinergic properties.[24,5] GMC1-169 also retains the DA D_1 and D_2 partial agonist-like properties of clozapine, which may underline the atypical clinical profile of clozapine.[32,33] Therefore, we were encouraged to carry out a further SAR study to evaluate the trifluoromethylsulfonyloxy (TfO)- or methylsulfonyloxy (MsO)-substituted derivatives of 11-piperazinyldibenzazepine, including not only its diazepine subclass but also the oxazepine and thiazepine subclasses. We report here that several 2-TfO analogues of dibenzazepines appear to be interesting as potential clozapine-like atypical antipsychotics.

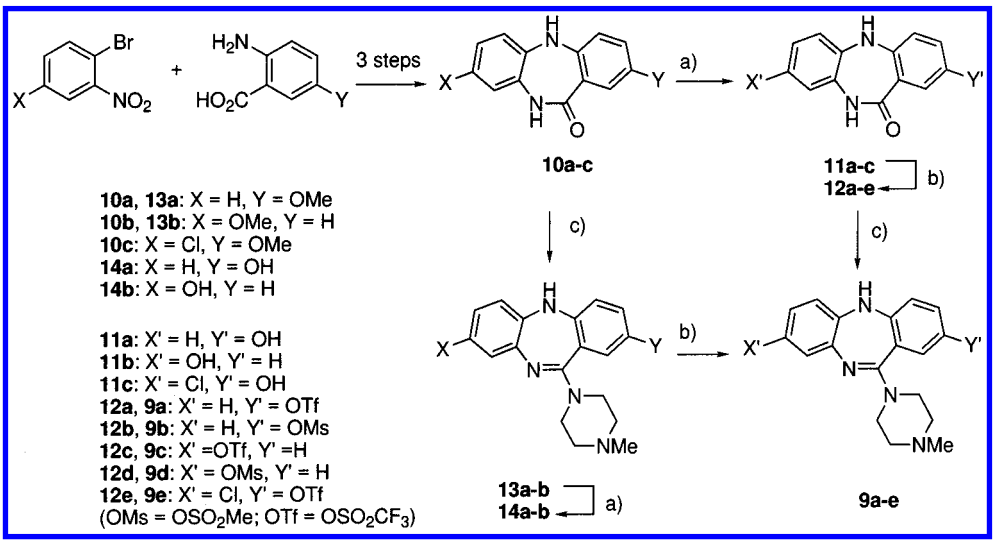
Chemistry

As reported previously,[24] the lactam intermediates **10a**−**c** and 2- or 8-methoxydibenzodiazepine derivatives **13a**,**b** were made by following the conventional synthesis of the tricyclic dibenzodiazepines with some modifications in practice.[34,35] *O*-Demethylation of compounds **10a**−**c** and **13a**,**b** by aluminum chloride in ethylmercaptan at room temperature allowed us to obtain 2- or 8-hydroxylactam intermediates **11a**−**c** and 2- or 8-hydroxydibenzazepine analogues **14a**,**b**, respectively. Furthermore, intermediates **11a**−**c** were converted by the appropriate agents to their sulfonic esters **12a**−**e**, which were eventually converted to the (sulfonyloxy)dibenzodiazepine derivatives **9a**−**e** (Scheme 1). Among them, compounds **9a**,**c** were reported before.[24] Alternatively, compounds **14a,b** also led to **9a**−**d** by the formation of the sulfonic esters. It is more efficient to convert first the methoxylactam intermediates **10a**−**c** to their (sulfonyloxy)lactam derivatives **11a**−**c** before the formation of the imide intermediates and then the corresponding 11-piperazinyldiazepines **9a**−**e**.

The syntheses of 2-TfO- and 2-MsO-11-(4-methylpiperazinyl)dibenz[*b*,*f*][1,4]oxazepine (**18a**,**b**) are outlined in Scheme 2. 2-Methoxylactam intermediate **15** was prepared according to a four-step protocol from 2-chloronitrobenzene and 2-hydroxy-4-methoxybenzaldehyde.[36] Again, *O*-demethylation by aluminum chloride in ethylmercaptan of **15** gave its hydroxy derivative **16**, which was converted to the corresponding lactam **17a** or **17b**. Treatment of **17a** or **17b** with $POCl_3$ in reluxing toluene formed the corresponding imino chloride intermediate, which was converted to the final product **18a** or **18b**, respectively.

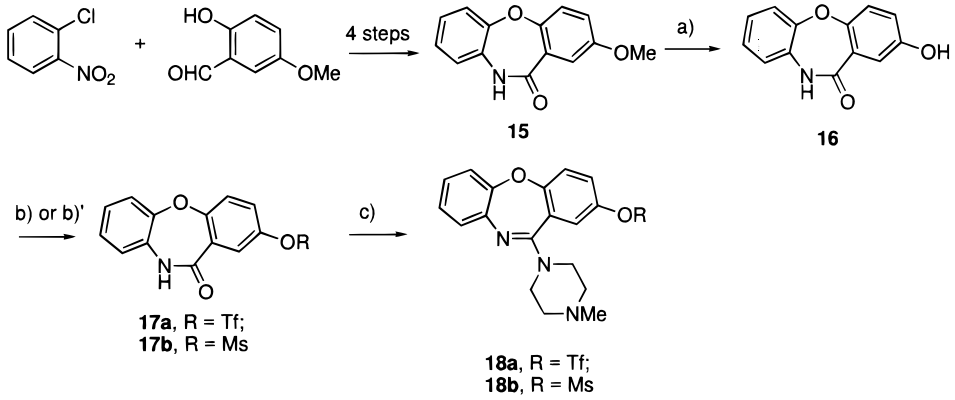
The synthesis of 2-TfO-11-(4-methylpiperazinyl)-dibenzo[*b*,*f*][1,4]thiazepine (**24**) is outlined in Scheme 3. 4-Iodoanisole reacted with 2-carboxythiophenol to form acid intermediate **19**,[37] which was converted to its azide derivative **20**. First, the one-pot treatment of **20** with aluminum chloride in 1,3-dichlorobenzene under heating was conducted to generate **22** directly but in only 13−30% yield. Later, not a one-pot but two-step treatment was carried out to improve the total yield (from **20** to **22**) up to 80%; that is, heating of **20** alone

Scheme 1[a]



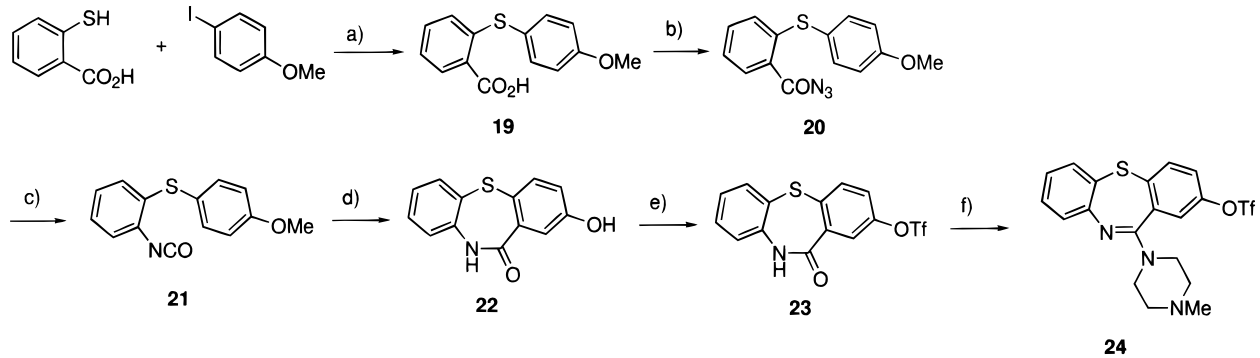
[a] Reagents and conditions: (a) $AlCl_3$, EtSH, rt, 4 h; (b) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, rt, overnight; or MsCl or Tf_2O, Et_3N, −78 °C; (c) i. $POCl_3$, toluene, *N*,*N*-di-Me-aniline, reflux, 3 h, ii. *N*-Me-piperazine, toluene, reflux, 3 h.

Scheme 2[a]



[a] Reagents and conditions: (a) $AlCl_3$, EtSH, rt, 4 h; (b) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, rt, overnight; (b)′ $MeSO_2Cl$ or Tf_2O, Et_3N, −78 °C 2 h; (c) i. $POCl_3$, toluene, *N*,*N*-di-Me-aniline, reflux, 3 h, ii. *N*-Me-piperazine, toluene, reflux, 3 h.

Scheme 3[a]



[a] Reagents and conditions: (a) heat; (b) i. $SOCl_2$, reflux 0.5 h, ii. NaN_3; (c) 120 °C (oil bath), 20 min; (d) $AlCl_3$, 1,3-dichlorobenzene, 150 °C, 20 min; (e) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, rt, overnight; (f) i. $POCl_3$, toluene, *N*,*N*-di-Me-aniline, reflux, 3 h, ii. *N*-Me-piperazine, toluene, reflux, 3 h.

generated first the isocyanate intermediate **21**, which was further treated with aluminum chloride under heating at 150 °C (oil bath) in 1,3-dichlorobenzene for only 20 min to give 2-hydroxylactam derivative **22**. It was assumed that the ring closure and *O*-demethylation happened simultaneously. The final product **24** was synthesized in a similar manner as described above for its dibenzoxazapine analogue **18a**.

The physicochemical properties in the lipophilicity or hydrophobicity aspect of these dibenzazepines are indicated by their calculated log *P* (logarithm of a partition coefficient) values (Table 1). The smaller the log *P* value as an important index of lipophilicity, the less lipophilic a molecule. The MsO analogues and the compounds with electron-donating substituents, like methoxy or hydroxy, have smaller log *P* values in comparison with

Table 1. Calculated log *P* Values[a] and Binding Affinities (IC_{50} Values, nM)[b] to Various CNS Receptors of Haloperidol and the Tested Dibenzazepine Analogues[c]

compd	log *P*	D_1	D_2	hD_2	hD_3	$hD_{4.2}$	5-HT_{2A}	5-HT_{2C}	H_1	α_1	hM_1
5	3.98	36	7.5	4.9	10	6.5	55[d]	>1000	>1000	18	5500
4	3.48	130	330	260	450	52	12 (7.8[d])	11	23	9.2	9.4
3	3.48	11	13	34	120	110	12[d]	2.9	NT	64	6.0
1	3.67	NT[e]	NT	54	22	14	6	NT	NT	NT	NT
9a	3.58	64	31	140	53	120	43 (8[d])	34	47	12	>1000
9b	1.80	2100	920	NT	NT	NT	880[d]	1200	NT	160	1000
9c	3.58	930	8100	NT	NT	NT	550[d]	620	720	>1000	35
9d	1.80	22000	33000	NT	NT	NT	4900[d]	7400	NT	8700	38
9e	4.30	200	43	30	52	490	23	13	NT	7.1	54
13a	2.71	550	68	NT	NT	NT	12[d]	21	NT	120	39
13b	2.71	7400	4300	NT	NT	NT	160[d]	86	NT	240	19
14a	2.21	550	1300	NT	NT	NT	35[d]	81	NT	260	37
14b	2.21	9800	6400	NT	NT	NT	310[d]	440	NT	1200	27
18a	3.76	66	40	52	29	150	48	100	120	27	490
18b	1.98	NT	NT	>1000	350	>1000	230	NT	NT	NT	NT
24	4.04	100	32	23	8	570	110	280	NT	3.6	460

[a] The log *P* values of the neutral species of compounds in *n*-octanol/water system were calculated by Pallas 2.1 (CompuDrug Chemistry Ltd.). [b] Results of receptor binding assays are expressed as IC_{50} values in nM (logarithmic means). For the method descriptions and data calculations, see the Experimental Section. [c] Binding affinities of compounds **3**−**5**, **9a,c**, **13, and 14** are partly reported previously; see ref 24. [d] Previously reported data from a different source; see refs 24 and 43 for methodology. [e] NT, not tested.

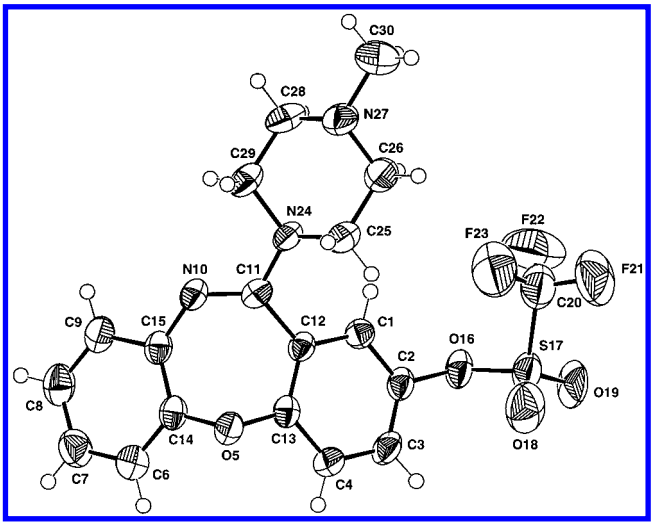


Figure 1. Molecular structure of compound **18a**, showing 50% probability thermal ellipsoids for the non-H atoms and the atom-numbering scheme.

the TfO or Cl analogues. 2-TfO-8-Cl-dibenzodiazepine **9e** has a slightly increased log *P* value (4.30) as compared to that of clozapine (**4**) and GMC1-169 (**9a**) (log *P* = 3.48 and 3.58, respectively). Although the TfO- or Cl-substituted dibenzazepines are more lipophilic and thus less aqueous soluble than their MsO, methoxy, or hydroxy analogues with smaller log *P* values, their calculated log *P* values are all below 5, which is important for them to avoid absorption-permeability alerting according to the "rule of 5" for estimating solubility and permeability of drugs.[53]

To study how a triflate substituent will affect the molecular conformation of 11-piperazinyldibenzazepines, the molecular structure of compound **18a** was determined by single-crystal X-ray analysis. To our knowledge, this is the first reported single-crystal X-ray analysis of an aryl triflate. The observed conformation of compound **18a** is shown in Figure 1. The central seven-membered ring of **18a** is in a boat conformation, like that of loxapine (**1**), isoclozapine (**3**), and clozapine (**4**).[1,38] However, the dihedral angle between the planes of the two benzene rings was found to be 124°, which is slightly greater than 114° for **1**, 117.5° for **3**, and 115° for **4**. For observing the orientation of the piperazine ring with respect to the dibenzodiazepine skeleton, compound **18a** was compared to the molecular structures of compounds **1** and **4** in the Cambridge Structures Database (CSD).[38] It was found that the orientation of the piperazine ring was approximately the same in all cases. Thus, it seems that the triflate group has little or negligible influence on the 11-piperazinyldibenzazepine conformation. However, it might be that the triflate group stabilizes this seemingly preferred conformation. As calculated by MOPAC, the slightly negatively charged fluorine atom F23 (carrying a charge of −0.20) makes contact (distance of H···F < 2.8 Å) with four slightly positively charged H atoms (the charges range from 0.13 to 0.25) on piperazine residue. Thus, there is a favorable electrostatic interaction between the triflate group and piperazine group. The further analysis of the energetics of the molecule will help decide the exact role of a triflate group. The detailed information of compound **18a** in the crystal are given as Supporting Information.

Pharmacological Results and Discussion

In Vitro Binding Study. The newly synthesized compounds **9b**,**d**,**e**, **18a**,**b**, and **24** were tested in vitro for their ability to bind to the different CNS receptors (D_1, D_2, 5-HT_{2A}, 5-HT_{2C}, H_1, α_1, and M_1) and were compared with our previously reported compounds (**9a**,**c**, **13a,b**, and **14a,b**) and the reference compounds haloperidol (**5**), clozapine (**4**), isoclozapine (**3**), and loxapine (**1**). Furthermore, compounds **9a**,**e**, **18a,b**, and **24** were tested in binding assays in vitro for their affinities to human cloned DA D_2, D_3, and $D_{4.2}$ receptors and were compared with above-mentioned reference compounds (Table 1).

From the binding profiles of the dibenzodiazepines, it is seen that 2-substituted analogues generally show more potent dopaminergic and serotonergic activities than their corresponding 8-substituted analogues. The typical neuroleptic haloperidol (**5**) was shown to have high affinities at D_2 and α_1 receptors (IC_{50} = 7.5 and 18 nM), intermediate affinities at 5-HT_{2A} and D_1 receptors (IC_{50} = 55 and 36 nM), and low affinities at 5-HT_{2C},

Table 2. Effects on Behavioral Models Indicative for Antipsychotic Activity or EPS[a]

drug	apomorphine-induced climbing (ED_{50}, mg/kg)	catalepsy (ED_{50}, mg/kg)	K/A[b]	ΔED_{50}[c] (mg/kg)
haloperidol (**5**)	0.27 po	1.5 po	5.5	1.23 po
	0.10 sc	0.25 sc	2.5	0.15 sc
clozapine (**4**)	17 po	>100 po	>5.8	>83 po
	5.6 sc	>32.6 sc[e]	>5.8	>26.8 sc
loxapine (**1**)	0.04 po	<1.0 po	<25	<0.96 po
	0.04 (0.07[d]) sc	0.35 sc[d]	8.8 (or 5[d])	0.31 sc
clotiapine (**2**)	0.27 sc[d]	0.72 sc[d]	2.7	0.45 sc
isoclozapine (**3**)	1.7 sc[d]	2.0 sc (1.8 sc[d])	1.1	0.3 sc
GMC1-169 (**9a**)	11 po	>100 po	>9	>89 po
	2.1 sc	>44 sc	>20	>41.9 sc
GMC2-83 (**18a**)	1.3 po	28 po	21.5	26.7 po
	2.2 sc	(100 po, 32%)[f]		
		20 sc	9	17.8 sc
GMC3-06 (**24**)	2.6 sc	30 sc	11.5	27.4 sc
GMC61-39 (**9e**)	8.2 sc	>50 sc	>6.1	>41.8 sc

[a] Inhibition of apomorphine-induced climbing effects in mice and catalepsy in rats was measured; see the Experimental Section and refs 39 and 40 for details. [b] K/A (therapeutic ratio) = quotient ED_{50} catalepsy/ED_{50} climbing. [c] $\Delta ED_{50} = ED_{50}$ catalepsy − ED_{50} climbing. [d] Data from ref 1. [e] Data from ref 24. [f] Catalepsy score percent at an extremely high dose of 100 mg/kg po.

H_1, and M_1 receptors (IC_{50} > 1000 nM). Isoclozapine (**3**) has high affinities at both DA (D_1 and D_2) and serotonin (5-HT_{2A} and 5-HT_{2C}) receptors. Clozapine (**4**) showed moderate affinities at DA (D_1 and D_2) receptors but high affinities at 5-HT_{2A} and 5-HT_{2C} receptors. Compounds **9a**,**e**, **13a**, **18a**, and **24** showed comparable profiles to **3** and **4** in these respects. It is noteworthy that both clozapine (**4**) and isoclozapine (**3**) showed high affinities for M_1 receptor (IC_{50} = 9.4 and 6.0 nM, respectively). The analogues with an electron-donating group at the 2- or 8-position, like compounds **13a,b** and **14a,b**, kept this anticholinergic activity. Interestingly, the analogues with electron-withdrawing groups at the 2-position, like **9a**,**b**, displayed no affinities at M_1 receptors (IC_{50} >1000 nM), but those at the 8-position, like **9c**,**d**, showed good affinities at M_1 receptor (IC_{50} = 38 and 35 nM, respectively). As a matter of fact, the 8-MsO (**9d**) and 8-TfO (**9c**) analogues are inactive at all the tested receptors except for M_1 receptors. Comparably, the 2-MsO analogue **9b** showed improved but still weak affinities to D_2, 5-HT_{2A}, and α_1 receptors. The 2-TfO analogue **9a**, however, showed a very promising binding profile like those of clozapine and isoclozapine except for lacking M_1 affinity. It is also noteworthy that the 2-HO analogue **14a** showed very good serotonergic over dopaminergic affinities, and in addition, this compound had a moderate α_1 binding affinity and potent M_1 binding affinity. The disubstituted analogue, 2-(trifluoromethylsulfonyloxy)clozapine (**9e**), like compound **9a**, also showed a promising clozapine-like binding profile. Interestingly, this compound had the M_1 affinity (IC_{50} = 54 nM), although this affinity is weaker than that of clozapine.

The 2-TfO-dibenzoxapine analogue **18a** showed a similar binding profile as its diazepine analogue **9a**. This compound had good affinities at the DA D_1 and D_2, 5-HT_{2A}, 5-HT_{2C}, and α_1 receptors. Interestingly, the 2-MsO analogue **18b** lost dopaminergic affinities and showed only low affinity at 5-HT_{2A} receptor (IC_{50} = 230 nM). Furthermore, the 2-TfO-dibenzothiazepine analogue **24** showed high affinities at D_2 and α_1 receptors (IC_{50} = 32 and 3.6 nM for D_2 and α_1 receptors, respectively) but comparably lower 5-HT_{2A} and 5-HT_{2C} binding affinities (IC_{50} = 110 and 280 nM, respectively). It is noteworthy that, after introducing 2-TfO group, both **18a** and **24** are also lacking M_1 binding affinity as does the diazepine analogue **9a**.

In binding assays at human cloned DA hD_2, hD_3, and $hD_{4.2}$ receptors, compound **9a** showed a similar profile as clozapine (**4**), while compound **18a** showed a similar binding profile as loxapine (**1**), except for a slightly lower $hD_{4.2}$ binding affinity, as compared to those of clozapine (**4**) and loxapine (**1**). Compound **9a** showed a higher binding affinity at the hD_3 receptor than did clozapine. Compared to clozapine, compound **9e** has improved hD_2 and hD_3 binding affinities but a lower affinity at the $hD_{4.2}$ receptor. Compound **24** showed potent binding affinities at hD_2 and hD_3 receptors but not at the $hD_{4.2}$ receptor.

In other binding assays, compound **18a** showed intermediate affinity at histamine H_1 receptors (IC_{50} = 120 nM), in comparison with 23 and 47 nM for clozapine and compound **9a**, respectively. Compounds **18a** and **9a** were found to have weak and negligible affinities at H_3 receptors (K_i > 20 μM)[39] and also at 5-HT_{1A} and 5-HT_{1B} receptors (data not shown). Interestingly, compounds **9a** and **18a** were found to have high affinities in binding assays at 5-HT_6 and 5-HT_7 receptors (data not shown; to be published by Unelius et al.).

In Vivo Pharmacology. Compounds **9a**,**e**, **18a**, and **24** were studied and compared to the reference compounds **1**−**5** in the in vivo behavioral models for their ability to inhibit apomorphine-induced climbing effects in mice and, additionally, their cataleptogenic activity in rats (Table 2). Typical antipsychotics, haloperidol (**5**), loxapine (**1**), clothiapine (**2**), and isoclozapine (**3**), showed the greatest antipsychotic potential on inhibition of apomorphine-induced climbing in mice at quite low doses under sc or po administrations. However, they also produced catalepsy at low doses. The dose separation of these two effects, indicated by the therapeutic ratio (K/A, quotient ED_{50} catalepsy/ED_{50} climbing), is determined to be small, e.g., K/A (sc) to be 5, 2.7, 1.1, and 2.5 for compounds **1**−**3** and **5**, respectively. In contrast, the atypical antipsychotic clozapine (**4**), at higher doses, effectively blocked apomorphine-induced climbing effects in mice (ED_{50} = 5.6 sc and 17 po mg/kg) and induced no catalepsy in rats up to 100 po and

Table 3. Accumulation of L-DOPA Measured ex Vivo in the Striatum of Rats

	haloperidol (**5**)	clozapine (**4**)	GMC2-83 (**18a**)
ED_{50}, mg/kg po	0.1	17	0.7

32.6 sc mg/kg. Thus, clozapine displayed a good EPS separation ($K/A > 5.8$ sc or po). It is worthy to note that the therapeutic ratio discussed here is just a preliminary indication, since the differences in pharmacokinetics in different testing species may have an influence on the therapeutic index of a drug.

Like clozapine (**4**), our previously reported compound **9a** (GMC1-169) showed no cataleptogenic activity at either sc or po administration up to 44 sc and 100 po mg/kg doses but inhibited effectively the apomorphine-induced climbing effects in mice at much lower doses (ED_{50} = 11 po and 2.1 sc mg/kg). Compound **18a** was shown to be a potent DA antagonist, which has very high potency for inhibition of apomorphine-induced climbing effects in mice, and moreover, it is orally active (ED_{50} = 1.3 mg/kg po). At an extremely high dose of 100 mg/kg po administration, it has only marginal cataleptogenic capacity (scoring 32%), but surprisingly and interestingly, this compound showed a cataleptogenic activity (57%) at 30 mg/kg po in rats. ED_{50} values for its cataleptogenic activities were eventually determined to be 28 po and 20 sc mg/kg. Nevertheless, these are still quite high doses (at least 21.5- and 9-fold, respectively, for po and sc administration) as compared to those necessary for its antipsychotic effect. Therefore, its therapeutic ratio (K/A) is more favorable than that for the typical antipsychotics including compound **1**. The 2-TfO-thiazepine analogue **24** has ED_{50} values of 2.6 and 30 mg/kg sc for inhibition of apomorphine-induced climbing effects in mice and catalepsy in rats, respectively, therefore, also a favorable K/A ratio (11.5). Compound **9e**, a 2-TfO analogue of clozapine itself, showed the antipsychotic activity comparable to clozapine (**4**) (ED_{50} climbing = 8.2 and 5.6 mg/kg sc for **9e** and **4**, respectively) and no cataleptogenic activity at up to the extremly high dose of 50 mg/kg sc.

Ex Vivo Biochemistry. Accumulation of the dopamine precursor L-DOPA was measured ex vivo in the striatum of rats after po administration of compound **18a**, as compared to clozapine (**4**) and haloperidol (**5**). In intact rats treated with the DOPA decarboxylase inhibitor NSD1015 (*m*-hydroxybenzylhydrazine), compound **18a** increased L-DOPA accumulation in a dose-dependent manner with ED_{50} values of 0.7 mg/kg po. Compounds **4** and **5** had ED_{50} values of 17 and 0.1 mg/kg po, respectively (Table 3). As drugs that mimic the action of endogenous transmitters decrease turnover, increased turnover indicates receptor blockade. Compound **18a** is thus demonstrating to be an orally potent DA antagonist in this ex vivo biochemical model.

In summary, the pharmacological evaluation of this new series of 2- or 8-sulfonyloxylated 11-piperazinyldibenzodiazepines, -oxazepines, and thiazepines has shown that the monosubstituted 2-TfO analogues (**9a**, GMC1-169; **18a**, GMC2-83; and **24**, GMC3-06) have multireceptor binding profiles comparable to those of clozapine and/or other parent neuroleptic diazepines. However, there is one important difference: i.e., they lack anticholinergic properties. The disubstituted 8-Cl-2-TfO analogue **9e** (GMC61-39) has a binding profile comparable to that of clozapine including M_1 affinity. Interestingly, the MsO analogues, as well as the 8-TfO analogues, have no or weak dopaminergic and serotonergic affinities, but all 8-sulfonyloxy analogues do have M_1 affinities. However, to postulate that the 2-TfO analogues are potential atypical antipsychotics solely based on their receptor binding profiles can be misleading as, for instance, isoclozapine also has a binding profile comparable to that of clozapine but still behaves as a typical antipsychotic in functional studies.

In behavioral studies performed to indicate their potential antipsychotic efficacy, the 2-TfO analogues blocked the apomorpine-induced climbing effects in mice effectively and in a dose-dependent manner like DA antagonists, and in particular, compounds **9a**, **18a**, and **24** are more potent in this respect than clozapine. It is noteworthy that compound **18a** is orally very potent in this in vivo model and also in the biochemical ex vivo model. On the other hand, compounds **9a**,**e**, **18a**, and **24** all displayed a clear dose separation with regard to their ED_{50} values for causing catalepsy in rats versus the ED_{50} values for showing presumed antipsychotic efficacy, thus implicating a favorable therapeutic ratio (K/A). Since catalepsy in rats is regarded as a measure indicative of EPS in humans, and D_2 receptor antagonistic properties are associated with antipsychotic action, these 2-TfO analogues (**9a,e**, **18a**, **24**) with widely divergent cataleptogenic versus DA antagonistic activities may be of clinical interest as clozapine-like atypical antipsychotics with a low potential to induce EPS. Since this unique series of compounds are structurally closely related to clozapine but differ in binding affinities for receptors allegedly important for antipsychotic action and/or side effects (e.g., D_2, 5-HT_{2A}, M_1), clinical study on these compounds would help elucidate which preclinical in vitro, ex vivo, and in vivo properties best predict clozapine-like atypical antipsychotic activity.

Experimental Section

Chemistry. Melting points were determined on an Electrothermal digital melting point apparatus and are not corrected. IR spectra were obtained on a ATI-Mattson spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 NMR spectrometer. Chemical shifts are given in δ units (ppm) and relative to TMS or deuterated solvent. Coupling constants (J) are given in Hz. Mass spectra were obtained on a Unicam 610/Automass 150 GC−MS system or on a Finnegan 3300 system. Elemental analyses were performed in the Microanalytic Laboratory, University of Groningen, and were within 0.4% of theoretical values. Merck silica gel (Kieselgel 60, 70−230 mesh) was used for flash chromatography. Chemicals used were either commercially available (Aldrich) and used without further purification or prepared according to the references indicated.

The syntheses of 2- or 8-methoxy-5,10-dihydro-11-oxodibenzo[*b*,*e*][1,4]diazepine (**10a**,**b**), 2- or 8-hydroxy-5,10-dihydro-11-oxodibenzo[*b*,*e*][1,4]diazepine (**11a**,**b**), 2- or 8-(trifluoromethylsulfonyloxy)-5,10-dihydro-11-oxodibenzo[*b*,*e*][1,4]diazepine (**12a**,**c**), 2-methoxy- or 2-hydroxy-11-(4-methylpiperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**13a** or **14a**), and 2- or 8-(trifluoromethylsulfonyloxy)-11-(4-methylpiperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**9a**,**c**) were described in a previous report.[24]

2-(Methylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (9b). Compound **11a** (226 mg, 1 mmol) in 10 mL of dichloromethane and 1 mL of triethylamine was cooled to −78 °C under N_2(g). To the solution was added methanesulfonyl chloride (0.082 mL, 1.2 mmol) in 10

mL of dichloromethane dropwise under stirring. Stirring was continued for 1 h to allow the temperature to come back to room temperature and stopped after the disappearance of **11a** (monitored by TLC in ethyl acetate). The reaction solution was washed with 2 N HCl (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography (SiO_2, 9:1 to 1:1 hexanes−ethyl acetate gradient) to afford 270 mg (89%) of intermediate **12b** as a light-yellow solid [MS (EI) *m/z* 304; R_f 0.8 in EtOAc], which was used in the next step without further characterization.

Intermediate **12b** (200 mg, 0.66 mmol), phosphorus oxychloride (3 mL), toluene (6 mL), and *N*,*N*-dimethylaniline (0.2 mL) were combined, heated to reflux for 3 h, and then evaporated under vacuum. The generated imino chloride intermediate was added to 10 mL of toluene and treated with 2 mL of *N*-methylpiperazine under refluxing for 3 h. After cooling to room temperature the solution was diluted with 30 mL of ethyl acetate, washed with 2 N NaOH (20 mL), and evaporated to dryness under vacuum. The residue was purified twice by flash chromatography (SiO_2, EtOAc then 9:1 dichloromethane−ethanol) and recrystallization from *n*-hexane/ethyl acetate (4:1) to afford 139 mg (54%) of compound **9b**: mp 188−190 °C; IR (KBr) 3341, 2937, 2795, 1607, 1466, 1366, 1161, 1144 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26−6.67 (m, 7 H), 5.03 (s, 1 H), 3.42 (m, 4 H), 3.11 (s, 3 H), 2.50 (m, 4 H), 2.36 (s, 3 H); MS (EI) *m/z* 386 (M^+). Anal. ($C_{19}H_{22}N_4SO_3$) C, H, N.

8-(Methylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (9d) was made from 8-hydroxy-5,10-dihydro-11-oxodibenzo[*b*,*e*][1,4]diazepine (**11b**) in three steps (total yield ca. 50−60%) in the same manner described for compound **9b**. **9d**: mp 155−7 °C; IR (KBr) 3352, 1599, 1561, 1463, 1373, 1181 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.24 (m, 2 H), 7.07−7.03 (m, 2 H), 6.99−6.67 (m, 3 H), 4.97 (s, 1 H), 3.47−3.41 (m, 4 H), 3.07 (s, 3 H), 2.47 (m, 4 H), 2.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.7, 152.4, 145.8, 141.9, 140.8, 131.9, 130.2, 123.3, 123.0, 120.1, 119.9, 119.7, 116.5, 54.8, 46.0, 45.9, 36.8; MS (EI) *m/z* 386 (M^+). Anal. ($C_{19}H_{22}N_4SO_3$) C, H, N.

Synthesis of Compound 9e. 2-Methoxy-8-chloro-11-oxo-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**10c**) was prepared in three steps in a similar manner as described for the syntheses of **10a**,**b** in the literature:[24,34] mp 213−216 °C (lit.[40] mp 215−217 °C).

2-Hydroxy-8-chloro-11-oxo-5*H*-dibenzo[*b*,*e*][1,4]diazepine (11c). Compound **10c** was *O*-demethylated with $AlCl_3$ in EtSH at room temperature in the same manner described for compounds **10a,b**:[24] mp 248−249 °C; IR (KBr) 3339, 3178, 1635, 1581 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.1 (s, 1 H), 6.6 (s, 2 H), 6.4−6.1 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 173.3, 156.7, 147.1, 145.0, 136.3, 131.4, 128.8, 128.7, 125.8, 125.5, 125.2, 122.2; MS (EI) *m/z* 260 (M^+). Anal. ($C_{13}H_9N_2O_2Cl$) C, H, N.

2-(Trifluoromethylsulfonyloxy)-8-chloro-11-oxa-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**12e**) was made from compound **10c** by triflation with $PhN(Tf)_2$ in a similar manner described for compounds **12a,c**:[24] mp 281−283 °C; IR (KBr) 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8 (d, 2 H), 7.6 (t, 3 H), 7.4−7.1 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 168.7, 149.2, 139.2, 139, 138.1, 133.6, 132.9, 130.8, 130.2, 128.8, 124.6, 123.1, 118.5 [d (121.7, 115.3), J = 321 Hz]; MS (EI) *m/z* 360 (M^+).

2-(Trifluoromethylsulfonyloxy)-8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (9e). Compound **9e** was made from intermediate **12e** in 75% yield in the same manner described previously for compounds **9b**,**d**: mp 121−123 °C; IR (KBr) 3636, 3281, 2941, 1611, 1567 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.6 (s, 1 H), 7.5 (dd, 1 H), 7.3 (d, 1 H), 7.2 (d, 1 H), 6.9 (s, 1 H), 3.3 (brs, 4 H), 2.4 (brs, 4 H), 2.2 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 161.2, 154.7, 144.1, 141.7, 127.6, 126.2, 125.4, 125.2, 124.5, 123.4, 123.1, 122.2, 121.3, 118.5 (d, 121.7, 115.3, J = 321.6 Hz), 54.2, 46.9, 30.6; MS (EI) *m/z* 474 (M^+). Anal. ($C_{19}H_{18}N_4O_3SF_3Cl$) H, N; C: calcd, 48.06; found, 48.81. HRMS (EI) *m/z* 474.0756 (found); calcd for $C_{19}H_{21}N_3O_4S$, 474.0740.

Synthesis of Compounds 18a/b. 2-Methoxydibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (**15**) was prepared in a four-step protocol according to ref 36: mp 168 °C (lit.[36] mp 168 °C).

2-Hydroxydibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (16). Compound **15** (1.2 g, 5.0 mmol) in 10 mL of EtSH and 10 mL of dichloromethane was treated with $AlCl_3$ (5.0 g) with stirring at room temperature for 6 h. The mixture was evaporated and quenched with 20 mL of ice−water and then 20 mL of 4 N aqueous HCl. White precipitate was collected, washed with water, dried under vacuum, and characterized as the desired product: 1.0 g, 88%; mp 233−235 °C (lit.[36] mp 228−230 °C); IR (KBr) 3281, 3192, 3057, 1672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.72 (s, 1 H), 7.25 (m, 1 H), 7.16−7.06 (m, 6 H), 6.93 (dd, 1 H, J = 3, 8 Hz); ^{13}C NMR (DMSO-d_6) δ 166.1, 154.8, 151.8, 131.5, 126.5, 126.0, 125.5, 121.9, 121.4, 121.2, 116.5; MS (EI) *m/z* 227 (M^+).

2-(Trifluoromethylsulfonyloxy)dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (17a). Compound **16** (1.0 g, 4.4 mmol) in 20 mL of dichloromethane and 5 mL of triethylamine was cooled to −78 °C and treated with triflic anhydride (1.54 mL, 7 mmol). The mixture was stirred for 3 h to allow the temperature to come back to room temperature, quenched with 3 mL of water, and concentrated. The residue was flash chromatographed on a silica gel column (hexane and ethyl acetate, 9:1 then 1:1, as eluents) to afford 1.1 g (70%) of the title compound as a white crystal: mp 164−166 °C; IR (KBr) 3186, 3057, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.87 (s, 1 H), 7.87 (d, 1 H, J = 3.2 Hz), 7.47−7.09 (m, 7 H); MS (EI) *m/z* 359 (M^+). Anal. ($C_{14}H_8NO_4SF_3$) C, H, N.

Alternatively, compound **16** (250 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was treated with *N*-phenyltrifluoromethanesulfonimide (540 mg, 1.5 mmol) in the presence of Et_3N (1 mL) with stirring overnight at room temperature. After evaporation the residue was purified by flash chromatography in the same manner described above to afford the product in 85−90% yield.

2-(Trifluoromethylsulfonyloxy)-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine (**18a**)**.** Compound **17a** (1.0 g, 2.8 mmol), phosphorus oxychloride (5 mL), toluene (10 mL), and *N*,*N*-dimethylaniline (1.0 mL) were combined and heated to reflux for 3 h. The mixture was evaporated under vacuum to afford the imino chloride intermediate, which was used in the next step without further purification.

The above imino chloride in 10 mL of toluene was treated with 5 mL of *N*-methylpiperazine under refluxing for 3 h. After evaporation the residue was purified by flash chromatography (SiO_2, 9:1 hexane and ethyl acetate then pure ethyl acetate as eluents) and recrystallization from *n*-hexane/ethyl acetate (10:1) to afford 1.01 g (82%) of the title compound: mp 117−118 °C; IR (KBr) 3070, 2941, 2793, 1610, 1566 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54−7.20 (m, 7 H), 3.74 (brs, 4 H), 2.77 (brs, 4 H), 2.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.9, 158.2, 151.4, 145.6, 139.8, 127.2, 125.9, 125.3, 125.1, 124.7, 123.0, 120.0, 118.4 (d, 120.7, 116.1, CF_3, J = 337.5 Hz), 54.7, 47.3, 46.0; MS (EI) *m/z* 441 (M^+). Anal. ($C_{19}H_{18}N_3O_4SF_3$) C, H, N.

2-(Methylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-dibenz[*b*,*f*][1,4]oxazepine (18b). Compound **16** (130 mg) in 20 mL of CH_2Cl_2 and 2 mL of triethylamine was treated with methanesulfonyl chloride (0.4 mL) at −78 °C for 2 h. The mixture was quenched with 4 N NaOH, extracted with dichloromethane (2 × 20 mL), washed with 4 N HCl and brine, dried over $MgSO_4$, filtered, and evaporated to give the crude lactam intermediate (**17b**) as a beige solid residue. The lactam **17b** was converted to the product **18b** in the same manner as described previously for **18a**. **18b**: mp 140−142 °C; IR (KBr) 1601, 1572, 1368, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 3 H), 7.20−6.90 (m, 4 H), 3.60 (brs, 4 H), 3.15 (s, 3 H), 2.60 (brs, 4 H), 2.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.4, 151.6, 145.0, 127.1, 125.9, 125.8, 124.6, 123.4, 122.6, 120.0, 54.4, 46.9, 45.7, 37.3; MS (EI) *m/z* 387 (M^+). HRMS (EI) *m/z* 387.1233 (found); calcd for $C_{19}H_{21}N_3O_4S$, 387.1252.

Synthesis of Compound 24. 2-[(4-Methoxyphenyl)thio]-benzoic acid (**19**) was prepared from 2-carboxythiophenol and 4-iodoanisole according to Pelz et al.[37]

2-[(4-Methoxyphenyl)thio]benzoyl Azide (20). Compound **19** (14 g, 53.8 mmol) was treated with 50 mL of $SOCl_2$ and 1 mL of DMF at refuxing for 1 h. The mixture was evaporated under vacuum, and the solid residue was dissolved

into dry acetone (100 mL). The resulting solution was added dropwise to a cooled 30% aqueous NaN_3 (60 mL) during 30 min. The suspension was stirred at 0 °C for 1 h, diluted with water (400 mL), filtered, washed well with water, and dried overnight under vacuum to afford 14 g of the title compound as a fine solid: mp 72−74 °C; IR (KBr) 3294, 2995, 2937, 2843, 2137, 1675, 1588, 1224 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.7−7.5 (m, 8 H), 3.8 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 137.6, 133.8, 133.4, 131.5, 131.3, 127.8, 126.5, 126.1, 124.8, 123.7, 115.3, 115.0, 55.2; MS (EI) *m*/*z* 257 ($M^+ - N_2$). Anal. ($C_{14}H_{11}N_3SO_2$) C, H.

2-Hydroxydibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one (22): Method A. compound **19** (1.4 g, 4.7 mmol) in 20 mL of dichlorobenzene was added to a suspension of $AlCl_3$ (2.7 g) in *o*-dichlorobenzene (50 mL) with stirring. The mixture was heated to reflux for 15 min, cooled to room temperature, added to 150 mL of $CHCl_3$, and extracted with 4 N aqueous HCl (2 × 50 mL). The organic layer was concentrated under vacuum, and the residue was purified by flash chromatography (SiO_2, ethyl acetate as eluent) and recrystallization from ethanol/*n*-hexane to afford 240 mg (21%) of the title compound: mp 298 °C; IR (KBr) 3147, 3015, 1630, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.8−7.5 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 168.7, 158.3, 140.3, 139.4, 133.3, 132.5, 130.3, 129.9, 125.6, 125.4, 123.5, 119.3, 117.8; MS (EI) *m*/*z* 243 (M^+). Anal. ($C_{13}H_9NSO_2$) C, H, N.

Method B. 2-[(4-Methoxyphenyl)thio]benzoyl azide (2.85 g, 10 mmol) was dissolved in 100 mL of 1,3-dichlorobenzene and heated with a preheated oil bath at 120 °C for 30 min with stirring. After oil bath was removed, the mixture was first cooled to room temperature and then to −20 °C. $AlCl_3$ (5.35 g, 40 mmol) was added slowly to it, and the temperature was then allowed to rise to room temperature. The mixture was further heated at 150 °C for 20 min. After cooling to room temperature, 100 mL of HCl saturated THF solution was added and stirring was continued for 5 min. Water (3 mL) was added dropwise, and the mixture was filtered. The filtrate was evaporated, and the residue was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc gradient) to yield 1.94 g (80%) of the desired product.

2-(Trifluoromethylsulfonyloxy)dibenzo[*b*,*f*][1,4]-thiazepin-11(10*H*)-one (23). Compound **22** (100 mg, 0.41 mmol) was triflated with *N*-phenyltrifluoromethanesulfonimide in the same manner described above for compound **17a** to afford 130 mg (84%) of the title compound which was recrystallized from ethyl acetate/*n*-hexane: mp 301 °C dec; IR (KBr) 3043, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8 (d, 1 H), 7.6 (m, 3 H), 7.1−7.4 (m, 4 H), 6.9 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.2, 149.2, 138.8, 138.1, 133.6, 133.0, 130.2, 129.8, 126.4, 124.8, 124.6, 123.0, 118.5 (d, 121.7, 115.3, J = 320 Hz, CF_3); MS (EI) *m*/*z* 375 (M^+). Anal. ($C_{14}H_9NO_4SF_3$) C, H, N.

2-(Trifluoromethylsulfonyloxy)-11-(4-methyl-1-piperazinyl)dibenzo[*b*,*f*][1,4]thiazepine (24). Compound **23** (80 mg), phosphorus oxychloride (1 mL), toluene (1 mL), and *N*,*N*-dimethylaniline (0.1 mL) were combined and heated to reflux for 3 h. The mixture was evaporated under vacuum to afford the imino chloride intermediate, which was used in the next step without further purification.

The above imino chloride in 1 mL of toluene was treated with 1 mL of *N*-methylpiperazine under refluxing for 3 h. After evaporation the residue was purified by flash chromatography (SiO_2, 9:1 hexane and ethyl acetate then pure ethyl acetate as eluents) and recrystallization from hexane to afford 33 mg of the title compound: mp 117 °C; IR (KBr) 3063, 2951, 1604, 1559 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70−7.60 (m, 7 H), 3.48 (brs, 4 H), 2.45 (brs, 4 H), 2.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.1, 158.7, 149.0, 148.3, 140.2, 135.8, 133.8, 132,2, 129.5, 126.0, 125.5, 123.3, 122.0; 118.8 (d, 121.7, 115.8, J = 297 Hz), 54.5, 45.6; MS (EI) *m*/*z* 457 (M^+). Anal. ($C_{19}H_{18}N_3O_3S_2F_3$) C, H, N.

Pharmacology. 1. In Vitro Receptor Binding Assays. Dopamine D_1 receptors: Inhibition by drugs of the binding of 0.20 nM [^{3}H]SCH23390 to dopamine D_1 receptors in membranes from rat corpus striatum was determined as described by Hyttel et al.[41]

Dopamine D_2 receptors: Inhibition by drugs of the binding of 0.50 nM [^{3}H]spiperone to dopamine D_2 receptors in membranes from rat corpus striatum was described by Hyttel.[42,43]

h-Dopamine D_2 receptors: Incubations were carried out in 50 mM Tris-HCl buffer, pH 7.35, containing 120 mM NaCl, 5 mM $MgCl_2$, and 1 mM EDTA. The assay contained in a total volume of 1 mL: 0.15 nM [^{3}H]spiperone, specific radioactivity 3.6 TBq/mmol, and membranes of A9L cells expressing the human D_2 dopamine receptor (40−60 μg of protein/assay). Incubations were run for 15 min at 37 °C and terminated by rapid filtration on Whatman GF/B filters and 3 washes with ice-cold 50 mM Tris-HCl buffer, pH 7.35 (without salts and EDTA). Nonspecific binding was determined in the presence of 1 mM (+)-butaclamol. Membranes containing the cloned receptor were purchased from Receptor Biology Inc., 10000 Virginia Manaor Rd, Suite 360, Beltsville, MD 20705. Under these conditions total binding amounted to 4000−6000 dpm/filter and nonspecific binding to 170−300 dpm/filter; variability of triplicates run in parallel was <10%.

h-Dopamine D_3 receptors: A CHO cell expressing the human dopamine D_3 receptor was bought from INSERM, Paris (P. Sokoloff). Preparation of cell membranes: Pelleted cells (about 0.1−0.3 mL) were homogenized with a Polytron homogenizer for about 4 s at 80% of the maximal speed in 2 mL of 10 mM Tris-HCl buffer, pH 7.4, containing 5 mM $MgSO_4$. The homogenate was diluted 5-fold in the same buffer and centrifuged at 50000*g* for 15 min. The resulting pellet was resuspended by gentle sonication in incubation buffer in such a way that the amount of membranes per assay corresponded to about 70 μg of protein. Otherwise, the procedure of hD_2 receptor binding is followed, resulting in a total binding of ∼4000 dpm/filter and a nonspecific binding of ∼250 dpm/filter; variability of triplicates run in parallel was <10%.

h-Dopamine $D_{4.2}$ receptors: The procedure is identical to the one used for the hD_2 receptor assay except that the amount of membranes was slightly higher, i.e., corresponding to about 100 μg of protein/assay. Membranes of CHO-K1 cells, expressing the human $D_{4.2}$ receptor, were purchased from Receptor Biology Inc. (address as above). Under these conditions, total binding amounted to 4000−6000 dpm/filter and nonspecific binding to 400−800 dpm/filter; variability of triplicates run in parallel was <10%.

Serotonin 5-HT_{2A} receptors: Affinity at 5-HT_{2A} receptors in membranes from rat frontal cortex was determined using [^{3}H]ketanserin (0.5 nM) as radioligand as described by Klockow et al.[44]

Serotonin 5-HT_{2C} receptors: Inhibition by drugs of the binding of 0.50 nM [^{3}H]mesulergine to cloned rat 5-HT_{2C} receptors expressed in membranes from 3T3 cells was determined as described by Bøgesø et al.[45]

α_1 adrenoceptors: Inhibition by drugs of the binding of 0.25 nM [^{3}H]prazosin to α_1 adrenoceptors in rat brain membranes was determined as described by Arnt et al.[46]

Muscarinic cholinergic M_1 receptors: Inhibition by drugs of the binding of 1.0 nM [^{3}H]pirenzepine to cloned human M_1 receptors expressed in membranes from CHO-K1 cells was estimated as described by Meier et al.[47]

Histamine H_1 receptors: Inhibition by drugs of the binding of 2.0 nM [^{3}H]mepyramine to histamine H_1 receptors in rat brain membranes was determined as described by Hall et al.[48]

Data calculations: Results on receptor binding study were given as IC_{50} values (nM). Two complete concentration−response curves were determined by using five concentrations of the test drugs in triplicate (covering 3 decades). IC_{50} values were estimated from hand-drawn log concentration−response curves or computer-assisted log−logit analysis. In a series of *n* determinations the variance of the log ratio (VAR_R) between the double determinations is determined according to the formula: $VAR_R = \Sigma (\log R_1)^2/2n$, where R_1 is the ratio and *n* is the number of observations. The VAR_R is equivalent to the square of the standard deviation of the log ratio (SD_R^2). In case the ratio is greater than corresponding to 2 × SD_R (95% confidence interval), further determinations were performed and outliers discarded. For the binding analysis, the following

SD_R's were obtained: D_1, 1.5 ($n = 100$); D_2, 1.5 ($n = 100$); 5-HT_{2A}, 1.4 ($n = 30$); 5-HT_{2C}, 1.3 ($n = 100$); H_1, 1.5 ($n = 100$); α_1, 2.0 ($n = 76$); M_1, 1.4 ($n = 91$).[16,24]

2. Behavioral Experiments.[49] General procedure and statistics: All experiments were performed using coded solutions. Animals were randomized at the aid of permutation tables for treatment with drugs. The tied rank test by Krauth (1971) was used for all models in the following test. ED_{50} values were calculated from the dose−response curves using the statistical program RS/1.

Animals: Male mice (NMRI, 20−35 g for climbing test) obtained from Ivanovas (Kisslegg, Germany) and rats (Wistar, 182−381 g for catalepsy test) from Merck (Darmstadt) or C.D.L. (Groningen) were used. Animals were housed under standard laboratory conditions (22 ± 2 °C; 55% ± 15% relative humidity; 12-h light−dark cycle, on 6 a.m.). Food and water remained available ad libitum except during the actual experiments.

Catalepsy in rats:[50] After 1 h po or sc administration of drugs, the testing was carried out with 4−6 rats for each dose and respective placebo group. Catalepsy was assessed every 5 min over 30 min by placing a hindpaw of the rat on a wooden block (3 cm in height) and measuring the time the rat retained this forced posture and the overall mobility and stiffness of the hindpaw. The scoring system was as follows: (0) <3 s, (1) 3−10 s, (2) 10−15 s with reduced mobility and moderate stiffness, (3) >15 s with immobility and strong stiffness (maximal score: 18).

Inhibition of apomorphine-induced climbing effects in mice[51] (functional DA antagonism): Climbing was induced by injection of 1.25 mg/kg apomorphine and 2 min later was assessed in cylindrical wire mesh cages (11.5 cm in diameter, 15 cm in height) by scoring every 2 min for a period of 20 min as follows: (0) no climbing behavior, (1) at least two forelimbs on the wire mesh, (2) all four forelimbs on the wire mesh and climbing for at least 30 s (maximal score: 20). Drugs were administered sc or po 1 h before apomorphine. The tests were performed with 6−10 rats in a group for each dose (in mg/kg).

3. Biochemistry. Accumulation of L-DOPA by the tested drugs was measured ex vivo in the striatum of rats according to the reported method.[52] ED_{50} values were calculated from the dose−response curves using the statistical program RS/1.

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Supporting Information Available: Single-crystal X-ray diffraction data of compound **18a** collected at 293 K on a Siemens SMART CCD diffractometer at the University of Göteborg. This material is available free of charge via the Internet at http://pubs.acs.org.

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