Behavioral Approach to Nondyskinetic Dopamine Antagonists: Identification of Seroquel

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A great need exists for antipsychotic drugs which will not induce extrapyramidal symptoms (EPS) and tardive dyskinesias (TDs). These side effects are deemed to be a consequence of nonselective blockade of nigrostriatal and mesolimbic dopamine D2 receptors. Nondyskinetic clozapine (**1**) is a low-potency D2 dopamine receptor antagonist which appears to act selectively in the mesolimbic area. In this work dopamine antagonism was assessed in two mouse behavioral assays: antagonism of apomorphine-induced climbing and antagonism of apomorphine-induced disruption of swimming. The potential for the liability of dyskinesias was determined in haloperidol-sensitized Cebus monkeys. Initial examination of a few close cogeners of **1** enhanced confidence in the Cebus model as a predictor of dyskinetic potential. Considering dibenzazepines, **2** was not dyskinetic whereas **2a** was dyskinetic. Among dibenzodiazepines, **1** did not induce dyskinesias whereas its *N*-2-(2-hydroxyethoxy)ethyl analogue **3** was dyskinetic. The emergence of such distinctions presented an opportunity. Thus, aromatic and N-substituted analogues of 6-(piperazin-1-yl)-11*H*-dibenz[*b,e*]azepines and 11-(piperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepines and -oxazepines were prepared and evaluated. 11-(4-[2-(2-Hydroxyethoxy)ethyl]-piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (**23**) was found to be an apomorphine antagonist comparable to clozapine. It was essentially nondyskinetic in the Cebus model. With **23** as a platform, a number of N-substituted analogues were found to be good apomorphine antagonists but all were dyskinetic.

Introduction

The use of conventional antipyschotic drugs in the treatment of schizophrenia is associated with the occurrence of involuntary movements termed extrapyramidal symptoms (EPS) and tardive dyskinesias (TDs). These drugs share a common pharmacological action. As dopamine antagonists they diminish the functioning of dopamine neurons.

Clozapine[1] (**1**) emerged as an effective antipsychotic which does not induce TDs, is relatively free of other EPS, and has superior efficacy[2] in patients which are refractory to other antipsychotic drugs. It is referred to as an atypical antipsychotic. A significant obstacle to a wider use of clozapine, however, is the increased risk of agranulocytosis.[3,4]

The weak antidopaminergic effects of **1** tend to undermine the hypothesis of a hyperdopaminergic state in schizophrenia. For example, in rats **1** does not antagonize[5] apomorphine-induced stereotypy, a behavior which constitutes a classical assay[6] for dopamine antagonists. In fact, **1** was observed to antagonize apomorphine-induced climbing in mice while, at the same time, eliciting gnawing.[7,8] The ability of **1** to influence striatal dopamine neurons differs from that of typical antipsychotics. Chronic dosing of rats with **1** does not result in tolerance to increases in dopamine metabolites (DOPAC and HVA), nor is there an increase in the number of D2 receptors.[9] However, in common with typical antipsychotics, **1** on chronic dosing in rats induces depolarization inactivation of dopamine A10 cells, a specific effect observed with all clinically effective antipsychotics.[10,11]

Since a mechanism other than dopamine blockade for the efficacy of **1** has not been elaborated, our initial approach to an antipsychotic with minimal or no liability to produce TDs or EPS was to identify novel compounds[12] which, comparably to **1**, potentiated gnawing in mice while inhibiting apomorphine-induced climbing.[13] As a measure of the potential for such compounds to induce dyskinesias, a neurochemical assessment of striatal dopamine D2 receptor upregulation following chronic administration to rats was made. Here, we experienced a dichotomy. The identified antagonists were well-tolerated, and high doses could be used unlike the dosage of **1** which was limited by toxicity. At these high doses, increases in striatal D2 receptor numbers were observed whereas no increases occurred at the highest "tolerated" dose of **1**. This amibiguity was resolved with the haloperidol-sensitized Cebus monkey dykinesia model[14] where comparable doses of the compounds of interest and clozapine could be administered. *Only **1** proved to be nondyskinetic* in the Cebus model, and we concluded that the nondyskinetic characteristic of **1** was not associated with its ability to potentiate apomorphine stereotypy.

In this paper, we present the results of our subsequent behavioral approach to identify nondyskinetic

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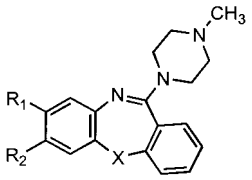
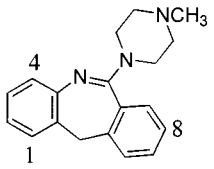
Table 1. Activity of 4-Methylpiperazin-1-yl Analogues



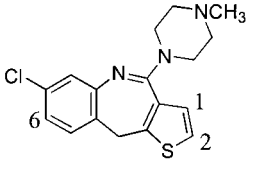
							dose (mg/kg)						
compd	X	R_1	R_2	test	route	veh + apo	2.5	5	10	20	40	80	D2 affinity[d]
2	CH_2	H	H	climbing[a]	ip	22	9**	9**	7**	0**			IC_{50} 2700 nM
					po	23		20	9**	2**			
					po + SKF525A	23		24	20 ns	16*			
4	O	H	H	climbing	ip	23	19	13**	2**	0	3**		27%
				climbing	po	22	19	13**	10**	3**	3**		
					po + SKF525A	24	25	19	24	18	19		
5	S	H	H	climbing	ip	23	21	14**	3**	0**			35%
					ip + SKF525A	23	23	21	18 ns	3**			
					po	22		21	8**	0**			
					po + SKF525A	22		23	18 ns	9**			
6	CH_2	Cl	H	climbing	ip	25					24	25	40%
7	O	Cl	H	climbing	ip	23					20	14	48%
8	S	Cl	H	climbing	ip	22						18	46%
9	CH_2	H	OH	climbing	ip	21	19	7**	0**	2**			
				swimming[b]	ip	0.5	1	7**	20**	42**			
10	S	H	OH	climbing	ip	23	18	13**	1**	1**			IC_{50} 49 nM
				swimming	ip	0	3	10**	34**	32**			
				Cebus monkey[c]	po				3/3				
11	S	H	F	climbing	ip	21			18	13	5**	1**	IC_{50} 963 nM
				swimming	ip	0			1	2	3	9**	

[a] Antagonism of apomorphine-induced climbing in mice, $N = 20$; score = mean rung height of a possible 27 rungs. [b] Antagonism of apomorphine-induced disruption of swimming in mice, $N = 20$; score = mean number of 180° swims. [c] Number of monkeys showing dyskinesias/number of monkeys tested. [d] D2 affinity: % displacement of spiropiperidone at 1000 nM unless otherwise indicated. IC_{50} values were determined using a minimum of five concentrations of each compound in triplicate. Each value represents the mean from two replicate experiments which differ by ±5% or less. Statistics: comparison of means (drug-treated to vehicle-treated) made using Student's *t*-test $*p < 0.05$, $**p < 0.01$.

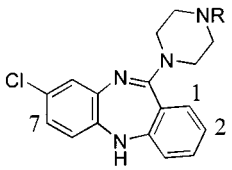
dopamine antagonists which led to the discovery of the antipsychotic seroquel (**23**).[15] The potential for the liability of dyskinesias in this program was determined in haloperidol-sensitized Cebus monkeys.[16,17] Our confidence in the Cebus model as a predictor of dyskinetic potential was strengthened upon examination of a few known close congeners of **1**. Perlapine (**2**), a clinical predecessor of **1**, was reported to have practically no antipsychotic efficacy.[18] However, Wilks and Stanley[19] found that **2** elevated the dopamine metabolite HVA in rats and suggested that it be reevaluated in the clinical setting. In the Cebus model, we found that **2** did not induce any dyskinesias.



2



2a



1, R = CH_3

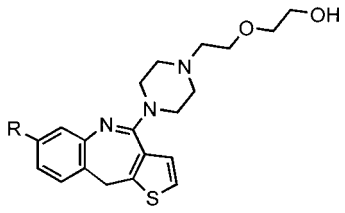
3, R = -$(CH_2)_2O(CH_2)_2OH$

2a was reported to be a clinically effective antipsychotic[20] but prone to the induction of seizures. When given to two Cebus monkeys at 20 mg/kg po, **2a** induced dyskinesias in both monkeys. Thus, in the "dibenzazepine" class of potential antipsychotics, there exists a dyskinetic and a nondyskinetic agent. The potential antipsychotic **3**[21] produced severe dyskinesias in three of six monkeys given 40 mg/kg po. So, in the "dibenzodiazepine" class there is the nondyskinetic **1** and dyskinetic **3**. Since such distinctions exist and can be determined by the Cebus model, an opportunity was presented for the further identification of nondyskinetic dopamine antagonists in the aforementioned chemical classes.

Results and Discussion

Target compounds are shown in Tables 1−4. The assessment of dopamine antagonism was made in rodent models. The primary assays entailed antagonism of the effects of apomorphine in mice (see the Experimental Section). Initially, this involved the antagonism of apomorphine-induced climbing behavior. Mice treated with apomorphine will climb to near the top of the climbing cages and remain there during most of the observation period. This climbing can be antagonized in a dose-related manner with dopamine antagonists. Later in the program, the antagonism of apomorphine-induced disruption of swimming was also used. Mice will normally score 16−20 swims around a circular tank in 2 min. Apomorphine-treated mice fail to swim and remain in place, pawing the walls of the swimming chamber, or make abortive swims. Dopamine antago-

Table 2. Activity of Thieno[3,2-*c*][1]benzazepines



compd	R	test	route	veh + apo	dose (mg/kg) 2.5	5	10	20	40	80	D2 affinity[c]
12	Cl	climbing[a]	ip	23			20	1**	2**	3**	60% at 250 nM
		Cebus monkey[b]	po					1/2			
13	H	climbing	ip	24					21	7**	

[a] Antagonism of apomorphine-induced climbing in mice, $N = 20$; score = mean rung height of a possible 27 rungs. [b] Number of monkeys showing dyskinesias/number of monkeys tested. [c]D2 affinity: % displacement of spiropiperidone at 1000 nM unless indicated otherwise. Statistics: comparison of means (drug-treated to vehicle-treated) made using Student's *t*-test $*p < 0.05$, $**p < 0.01$.

nists will "normalize" the swimming behavior of such mice. We believe this new test to be more predictive of potential antipsychotic activity in humans. The climbing test lacks specificity since nonantipsychotics agents can antagonize it (sedation, toxicity).

Actives in the above tests were administered at various doses to haloperidol-sensitized Cebus monkeys which were observed over a 6−7-h period for dyskinesias. With compounds prone to dykinesias, the dose which generally evoked the most frequent reactions was 20 mg/kg po. The antagonists were also characterized by ancillary neurochemical[22] and electrophysiological[23] methods. The former included the displacement of labeled spiroperidol for D2 affinity, and the latter invoked the reversal of amphetamine-suppression of spontaneous cell firing.

The ability of *N*-methylpiperazines of the dibenz[*b*,*e*]-azepine, dibenz[*b*,*f*][1,4]oxazepine, and dibenzo[*b*,*f*][1,4]-thiazepine classes to antagonize apomorphine-induced climbing in mice is shown in Table 1. Prominent here were **2**, **4**, and **5**, all of which bear unsubstituted aromatic rings. The chlorinated analogues **6**−**8** are substituted analogously to **1** and **2a** but are essentially inactive in the apomorphine model. These results suggested the possibility that in vivo metabolites of **2**, **4**, and **5** could be the active agents, formation of which is inhibited by chlorination. From metabolic studies on loxapine,[24] it is known that the 7- and 8-positions are hydroxylated in the rat. In mice pretreated with SKF 525A (a cytochrome P450 inhibitor),[25] the ability of **2** and **4** to antagonize apomorphine-induced climbing was essentially suppressed and that of **5** was considerably attenuated (Table 1). After oral administration of **2** to rats, a major metabolite was observed in extracts of blood and urine by HPLC and the same substance was also the major drug-related extractable component in rat brain tissue (Kirkland, unpublished information). This metabolite proved to be **9** (2-hydroxy **2**, synthesis of which is described herein) which antagonized apomorphine-induced effects to the same degree as **2**. Thus, it appears likely that **2** requires metabolism to **9** for effective dopamine antagonism in rodents. If mammals do not metabolize **2** to **9**, then the perlapine/dopamine hypothesis story requires reevaluation. We did not undertake Cebus experiments to clarify this situation.

The activity of **5** in mice treated with SKF 525A appeared not to have been completely blocked, suggesting that unmetabolized **5** might have intrinsic activity. This intrinsic level of activity was somewhat approached by that of the 7-fluoro analogue **11** (D2 IC_{50} 960 nM). However, much of the activity of **5** must still be attributed to a metabolite since **10** (7-hydroxy **5**, D2 IC_{50} 49 nM) was just as potent in the behavioral mouse assays. Three monkeys treated with **10** at 10 mg/kg po exhibited dyskinesias.

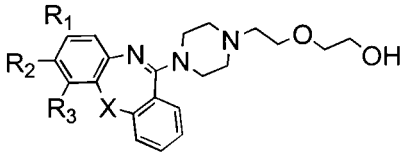
Replacement of the *N*-methyl in the thieno[3,2-*c*][1]-benzazepine **2a** by a 2-(2-hydroxyethoxy)ethyl moiety gave **12** (Table 2) which was a good antagonist of apomorphine-induced climbing but was also dyskinetic. The deschloro analogue **13** was a much weaker antagonist.

Replacement of the *N*-methyl in **2** by a 2-(2-hydroxyethoxy)ethyl moiety gave **14** which lacked potency but was efficacious at 80 mg/kg ip (Table 3). It produced long-lasting sedation without dyskinesias in nine sensitized Cebus monkeys at 80 mg/kg po. The 2-hydroxy analogue **15** was also only active at 80 mg/kg ip, considerably weaker than **9**, and was dyskinetic. The 3-chloro analogue **16** displayed better activity in antagonizing apomorphine-induced climbing. In contradistinction to the thieno[3,2-*c*][1]benzazepine **12**, seven monkeys treated with **16** at 80 mg/kg po showed no dyskinesias and were clearly sedated. Interest in this series waned, however, when lethality was observed in rats upon chronic dosing.

Of the corresponding dibenz[*b*,*f*][1,4]oxepines **17** and **18**, only **17** antagonized apomorphine-induced climbing at 40 mg/kg ip and two of three monkeys given 20 mg/kg po exhibited moderate dyskinesias.

Replacement of the *N*-methyl of the inactive 8-chlorodibenzo[*b*,*f*][1,4]thiazepine **8** by a 2-(2-hydroxyethoxy)-ethyl moiety gave **19** which by the ip route exhibited the same degree of apomorphine antagonism as **16**. No dyskinesias was induced when **19** was administered at 20, 40, and 80 mg/kg po. At the highest dose, six monkeys were clearly sedated and six were slightly sedated. Also, **19** in rats reversed the amphetamine suppression of A10 firing, 0.87 mg/kg iv being the minimal effective dose to cause a 50% or greater reversal compared to 0.50 mg/kg iv for clozapine. Despite these good prognostications, **19** in mice by oral administration did not antagonize the effects of apomorphine and in rats at 40 mg/kg po only marginally increased DOPAC and HVA.

Table 3. Activity of 4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl Analogues



								dose (mg/kg)				
compd	X	R_1	R_2	R_3	test	route	veh + apo	10	20	40	80	D2 affinity[d]
14	CH_2	H	H	H	climbing[a]	ip	23		21	17	2**	22%
						po	23		24	17	10**	
					swimming[b]	po	1		1	1	3**	
					Cebus monkey[c]	po					0/9	
15	CH_2	H	OH	H	climbing	ip	26			22	1**	25%
					swimming	ip	0.4			5	14**	
					Cebus monkey	po			2/3			
16	CH_2	Cl	H	H	climbing	ip	23		19	6**	2**	IC_{50} 1000 nM
						po	25			26	1**	
					swimming	po	0.4			1	2**	
					Cebus monkey	po			0/2	0/2	0/7	
17	O	Cl	H	H	climbing	ip	23		17	0**		54% at 250 nM
					swimming	ip	1.4		2	4		
					Cebus monkey	po			2/3			
18	O	H	H	H	climbing	ip	23			17	11**	16%
					swimming	ip	0			1	8**	
19	S	Cl	H	H	climbing	ip	23	20	12**	8**	0**	58%
						po	23		25	24	16*	
					swimming	po	1.2		1	1	1	
					Cebus monkey	po			0/2	0/4	0/12	
20	S	F	H	H	climbing	ip	24		16	14*	6**	34%
					Cebus monkey	po			0/2	0/4	0/2	
21	S	H	F	H	climbing	ip	20	14	9**	8**	2**	IC_{50} 560 nM
						po	23				23	
					swimming	ip	1	1	1	8**	18**	
						po	0				2	
					Cebus monkey	po		1/5	3/12	0/2		
22	S	H	H	F	climbing	ip	24				22	0%
					swimming	ip	0				0	
23	S	H	H	H	climbing	ip	23		15	2**	0**	IC_{50} 330 nM
						po	18	19	18	14	8**	
					swimming	po	1.6	3	3	11*	18**	
					Cebus monkey	po		1/13	2/13	0/4		
24	S	H	OH	H	climbing	ip	25	27	5**	0**		IC_{50} 166 nM
					swimming	ip	0.3	5**	17**	31**		
					Cebus monkey	po		5/6				
25	S	OH	H	H	climbing	ip	25				24	24%
					swimming	ip	0				0	
26	SO	H	H	H	climbing	ip	22				23	
					swimming	ip	0				0	
27	SO_2	H	H	H	climbing	ip	24				23	
					swimming	ip	0				0	
clozapine					climbing	po	18	23	19	5**	0**	IC_{50} 132 nM
					swimming	po	1.6	4	3	13**	15**	
					Cebus monkey	po		0/13	0/13	0/11		

[a] Antagonism of apomorphine-induced climbing in mice, $N = 20$; score = mean rung height of a possible 27 rungs. [b] Antagonism of apomorphine-induced disruption of swimming in mice, $N = 20$; score = mean number of 180° swims. [c] Number of monkeys showing dyskinesias/number of monkeys tested. Statistics: comparison of means (drug-treated to vehicle-treated) made using Student's *t*-test *$p < 0.05$, **$p < 0.01$. [d] D2 affinity: % displacement of spiropiperidone at 1000 nM unless otherwise indicated. IC_{50} values were determined using a minimum of five concentrations of each compound in triplicate. Each value represents the mean from two replicate experiments which differ by ±5% or less.

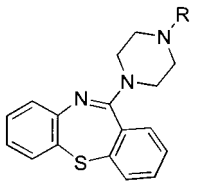
As measured in mouse climbing, the 8-fluorinated **20** was an antagonist comparable to **19**. The profile of the 7-fluorinated **21** (D2 IC_{50} 560 nM; A10 MED_{50} 0.75 mg/kg iv) was similar to that of **19**, but it was dyskinetic. The 6-fluorinated **22** was not active.

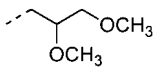
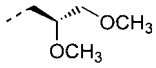
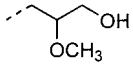
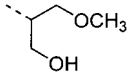
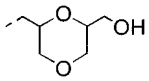
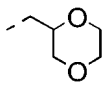
Since the dibenz[*b*,*e*]azepine **14** without aromatic substitutions had efficacy but lacked potency, the analogous dibenzo[*b*,*f*][1,4]thiazepine **23** was synthesized. As shown in Table 3, **23** (D2 IC_{50} 330 nM) by the oral route had comparable activity in the swimming paradigm to that of clozapine. Moreover, this compound was essentially nondyskinetic. Two of 13 monkeys treated at 20 mg/kg po showed dyskinesias of weak intensity which lasted 10 s in one and 20 min in the other. The hydroxylated analogues **24** and **25** were also evaluated. As in the case of **10**, the 7-hydroxylated **24** was a potent antagonist (D2 IC_{50} 166 nM) which induced dyskinesias in five of six monkeys at 20 mg/kg po. The 8-hydroxylated **25** was not a dopamine antagonist.

The sulfoxide **26** and the sulfone **27** also were not behavioral dopamine antagonists.

Following on the activity of **23**, other N-substituted analogues were investigated. Piperazines with N-substituents derived from various ethers, cyclic ethers,

Table 4. Activity of N-Substituted Analogues



					dose (mg/kg)						
compd	R	test	route	veh + apo	2.5	5	10	20	40	80	D2 affinity[d]
28	$-CH_2CH_2OH$	climbing[a]	ip	24			24	6**	1**		IC_{50} 1330 nM
		swimming[b]	ip	0.4			3	18**	28**		
		Cebus monkey[c]	po				2/3				
29	$-(CH_2)_2O(CH_2)_2O(CH_2)_2OH$	climbing	ip	19				20	14	3**	IC_{50} 1394 nM
		swimming	ip	0.3				2	3**	12**	
30	$-CH(CH_2OCH_3)_2$	climbing	ip	22						19	4%
		swimming	ip	0						0	
31		climbing	ip	21	18	5**	1**	2**	0**		IC_{50} 795 nM
		swimming	ip	0.3	5**	9**	17**	28**	33**		
		Cebus monkey	po				1/2	1/2			
32		climbing	ip	22					19	1**	10%
		swimming	ip	0.2					3	13**	
33	$-CH_2CH_2CH(OCH_3)CH_2OCH_3$	climbing	ip	23		21	5**	0**	0**		IC_{50} 293 nM
		swimming	ip	0		2	8**	20**	32**		
		Cebus monkey	po			0/5		5/5			
34		climbing	ip	21	21	19	8**	2**	1**		IC_{50} 755 nM
		swimming	ip	0.4	0	2	6**	22**	32**		
		Cebus monkey	po				2/2				
35		climbing	ip	24						21	IC_{50} 1640 nM
		swimming	ip	0						0	
36		climbing	ip	21				18	7**	0**	4%
		swimming	ip	0				0	8**	27**	
		Cebus monkey	po						4/4		
37		climbing	ip	22	14**	6**	1**	0**	2**		50%
		swimming	ip	0	8**	13**	20**	20**	30**		
		Cebus monkey	po			2/3					
38		climbing	ip	19		21	9**	2**	7**	1**	IC_{50} 417 nM
		swimming	ip	0		1	7**	16**	26**	37**	
		Cebus monkey	po					2/2			

[a] Antagonism of apomorphine-induced climbing in mice, $N = 20$; score = mean rung height of a possible 27 rungs. [b] Antagonism of apomorphine-induced disruption of swimming in mice, $N = 20$; score = mean number of 180° swims. [c] Number monkeys showing dyskinesias/number of monkeys tested. [d] D2 affinity: % displacement of spiropiperidone at 1000 nM unless otherwise indicated. IC_{50} values were determined using a minimum of five concentrations of each compound in triplicate. Each value represents the mean from two replicate experiments which differ by ±5% or less. Statistics: comparison of means (drug-treated to vehicle-treated) made using Student's *t*-test $*p < 0.05$, $**p < 0.01$.

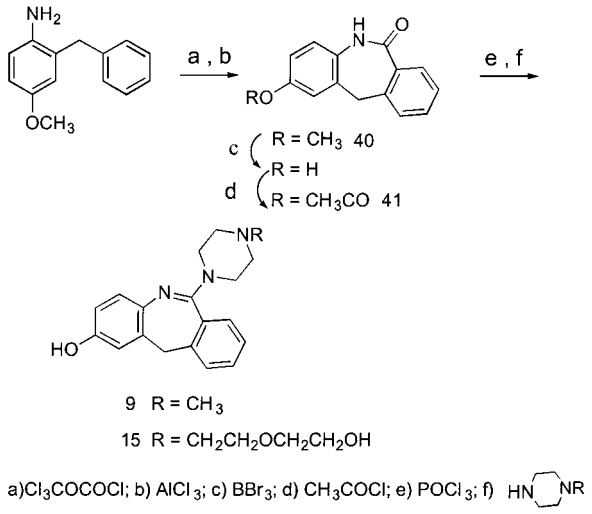
alcohols, and combinations thereof, were prepared and incorporated into compounds shown in Table 4. While many of these exhibited good potency as apomorphine antagonists, none was nondyskinetic. Some structure–activity (SAR) features could be discerned. Branching at the α-carbon as in **30** and **35** resulted in loss of activity. Ethers and alcohols could be equipotent as in **31** and **34**. Chiral **32** was much weaker than racemic **31**, indicating a preference for the *R*-configuration.

Chemistry

All of the targeted compounds are amidines. Most were obtained by reacting the requisite imino chloride with the appropriate piperazine. The imino chlorides were derived from the corresponding lactams following literature precedents using phosphorus oxychloride and were used as either toluene or xylene extracts or were isolated prior to dissolution. A few amidines were prepared from imino thioethers which were obtained by reacting the lactam with Lawsson's reagent followed by S-methylation with dimethyl sulfate.

The lactams in Schemes 1 and 2 were prepared from isocyanates which were derived from anilines using trichloromethyl chloroformate. Those in Scheme 3 were

Scheme 1



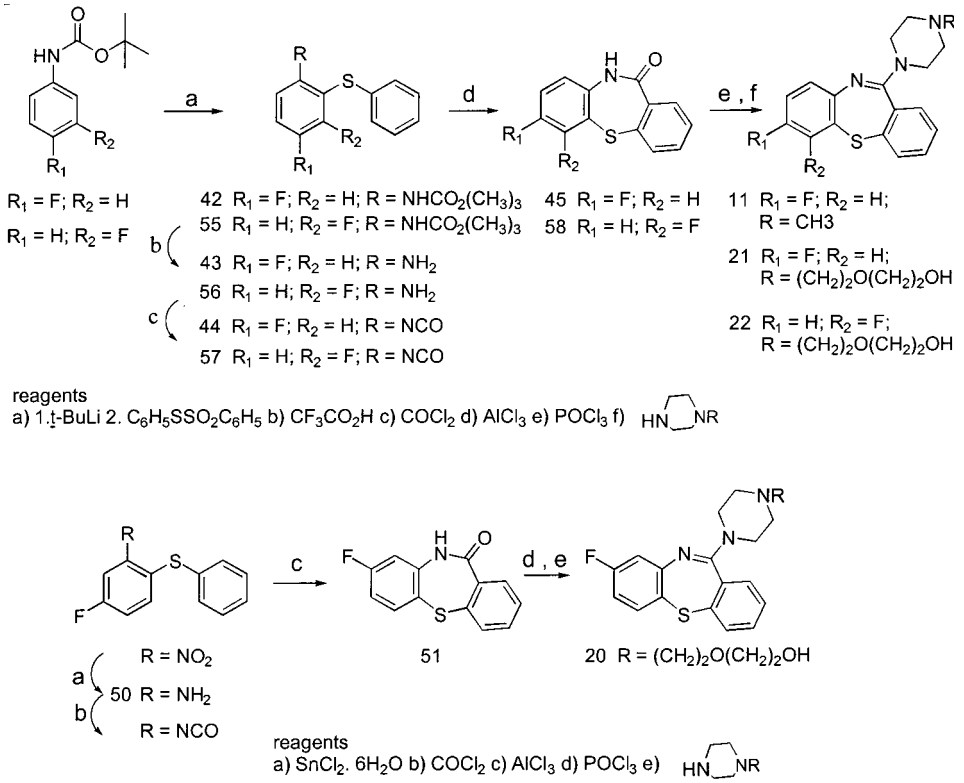
prepared by intramolecular aminolysis of anilino esters. In the preparation of the 2-hydroxydibenzazepines **9** and **15** (Scheme 1), the precursor phenolic lactam was converted to the acetate **41** prior to reaction with $POCl_3$. Subsequent reaction with the piperazines gave the amidines with concurrent removal of the acetyl.

Preparations of the monofluorinated dibenzothiazepines **11** and **20**−**22** are indicated in Scheme 2. The 7-fluorodibenzothiazepines **11** and **21** were obtained from 4-fluoroaniline. Ortholithiation of the *tert*-butoxy carbamate using *tert*-butyllithium followed by sulfenylation with *S*-phenyl benzenethiosulfonate gave carbamate **42** and subsequently aniline **43**. 6-Fluorodibenzothiazepine **22** was obtained by the same process starting from 3-fluoroaniline. Sulfenylation at the 2-position gave **55** and ultimately the aniline **56**. Reaction of 2-chloro-5-fluoronitrobenzene with thiophenoxide followed by reduction of the nitro functionality gave aniline **50** which was processed to the lactam **51**.

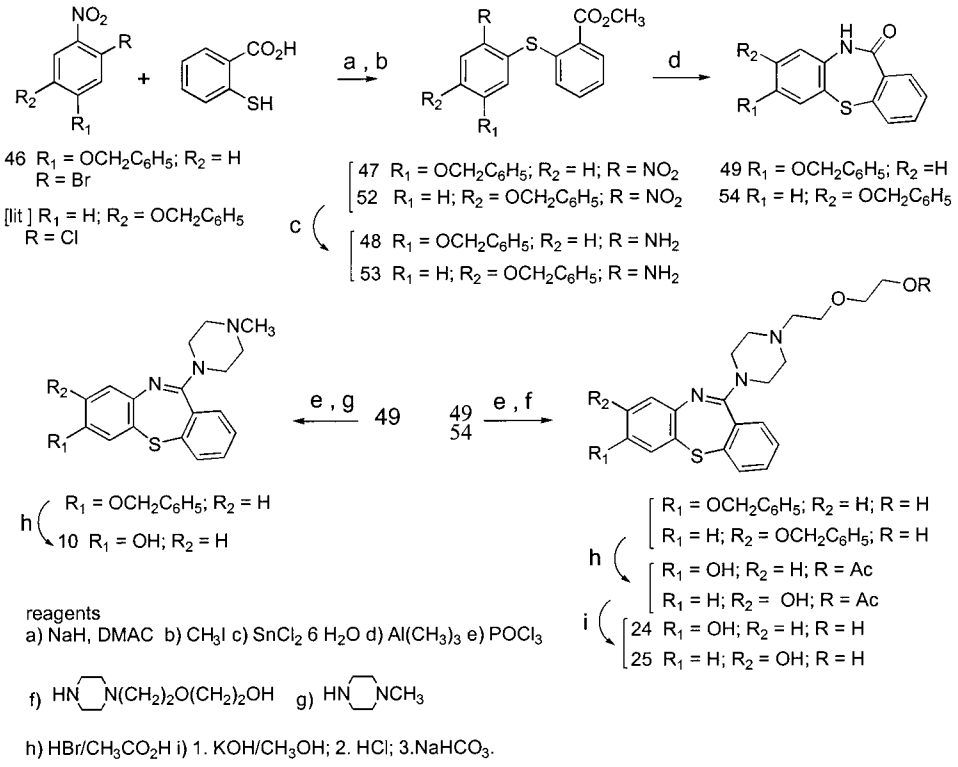
The preparation of the hydroxydibenzothiazepines **10**, **24**, and **25** from appropriately substituted nitrobenzenes is shown in Scheme 3. Reaction of 4-benzyloxy-2-bromonitrobenzene (**46**) with thiosalicylic acid using sodium hydride in dimethylacetamide followed by treatment with iodomethane gave the nitro ester **47.** An alternate procedure, in which the disodium salt of thiosalicylic acid was generated from sodium methoxide in methanol, taken to dryness, and then reacted with **46** in DMAC, resulted in a byproduct (10%) from ipso displacement of the benzyloxy by sodium methoxide. The nitro ester **52** was prepared by the sodium methoxide route. Reduction of these nitro esters with stannous chloride gave the anilino esters **48** and **53** which were converted to the lactams **49** and **54** using trimethylaluminum. The imino chloride from 7-benzyloxy lactam **49** was reacted with *N*-methylpiperazine and debenzylated with HBr in acetic acid to **10**. It was also reacted with 1-[2-(2-hydroxyethoxy)ethyl]piperazine and debenzylated with HBr in acetic acid which resulted in concomitant acetylation of the alcohol functionality. Following the sequence of hydrolysis with KOH, acidification with HCl, and basification with bicarbonate, **24** was obtained. It exhibited poor solubility, requiring a large volume of chloroform for extraction. The 8-benzyloxy lactam **54** was also reacted with 1-[2-(2-hydroxyethoxy)ethyl]piperazine via the imino chloride. Following the debenzylation and hydrolysis sequence as used for **24**, there was obtained **25** which was readily soluble in chloroform.

The other N-substituted piperazines used in our studies were prepared from either *N*-benzylpiperazine

Scheme 2



Scheme 3



or *N*-carbethoxypiperazine as shown in Scheme 4. With the exception of **61** which has the *S*-absolute configuration, all the piperazines were racemates. **67** is a single diastereomer of the *cis*-configuration.

Periodate oxidation of **23** gave sulfoxide **25** as two conformational entities (TLC R_f's 0.10 and 0.30). Heating this mixture in toluene resulted in the lower R_f material being converted to the higher, presumably through resonance involving the piperazine nitrogen.

Conclusion

It is our belief that the sensitized Cebus monkey model is currently the most predictive test for EPS and possibly TDs of neuroleptics. **1** does not produce dyskinesias in this model. We were struck by the fact that nearly all of our apomorphine antagonists induced unacceptable dyskinesias. Only **23** emerged with a profile most closely resembling that of **1**, and it was progressed through additional tertiary behavioral assays.[26] It must be noted that this behavioral profile translated to a neurochemical[22] and electrophysiological[23] profile like that of **1**, both compounds showing a prediliction for blockade of the mesolimbic (A10) D2 dopamine receptors. As shown, even the use of **23** as a platform resulted in only dyskinetic analogues.

A nondyskinetic compound being a rarity may imply that it is such by virtue of another pharmacological property. Chronic administration of **1** and **23** resulted in much smaller increases in ΔFosB-like immunoreactivity in the striatum than produced by haloperidol (dramatic increase).[27] It has also been shown[28] that the acute increase of striatal Fos expression by haloperidol can be significantly *attenuated* by pretreatment with **1**. Indeed, the proposal[29] has been made that **1** is an *antidyskinetic* agent since it shows marked efficacy in TDs of all types and there is no rebound occurrence upon withdrawal. It remains to be determined if the same can be said for **23**. The *atypicality* of **23** has been demonstrated by its ability to elict long-term improvement in psychotic symptoms in Parkinson's disease patients without causing a deterioration of the motor symptoms.[30] A particular clinical advantage of **23** over other antipyschotics is the freedom from EPS and lack of plasma prolactin elevation over its entire antipsychotic dose range.[31]

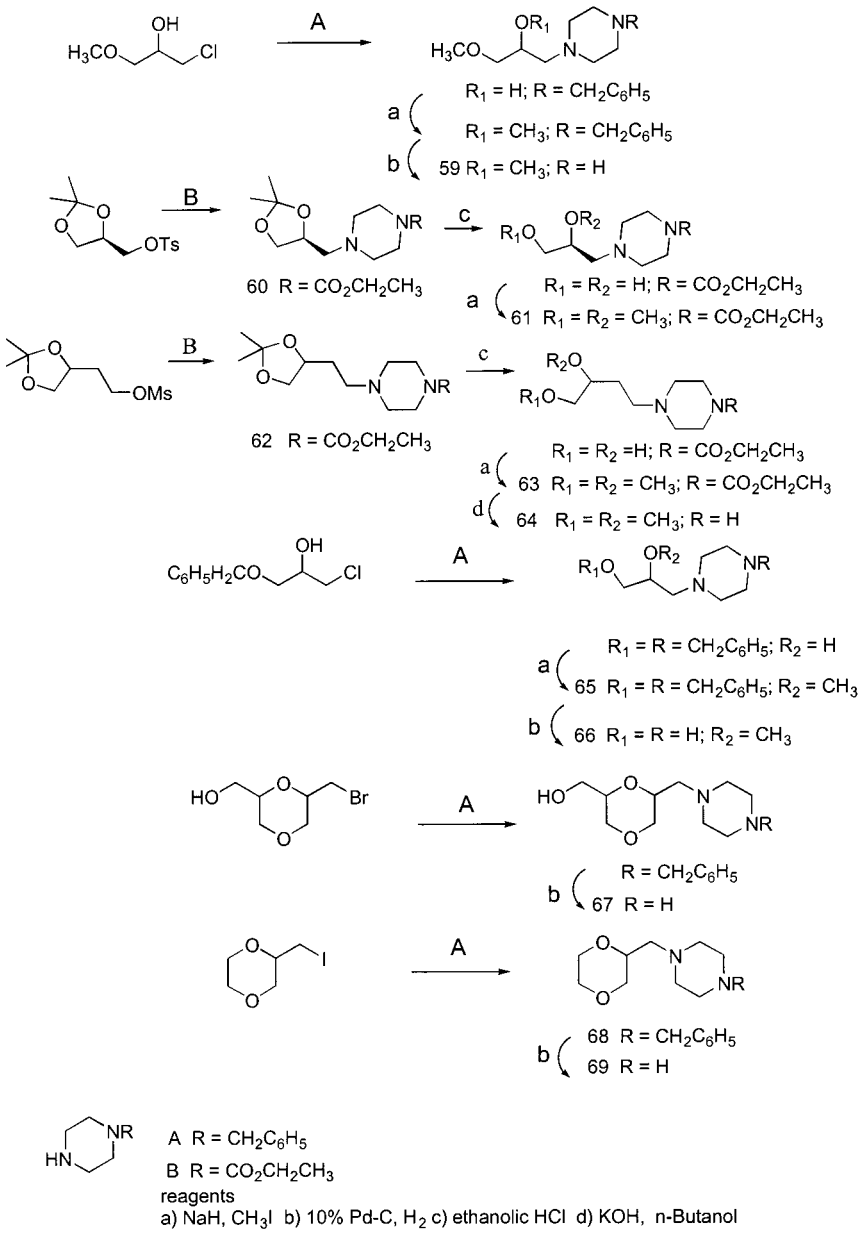
Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Brucker AM 300 (300 MHz), Brucker WM 250 (250 MHz), and Brucker N80 (80 MHz) instruments, and chemical shifts are reported in δ units with tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS-80 instrument. Combustion analysis were performed on a Perkin-Elmer 241 instrument. Chromatographic purification refers to flash chromatography conducted on Keiselgel 60 (230−400 mesh) supplied by E. Merck. Silica gel GHLF (250-μm) plates supplied by Analtech were used for thin-layer chromatography (TLC).

General Methods for the Preparation of Requisite Imino Chlorides. Intermediate imino chlorides were prepared by refluxing the appropriate lactam with $POCl_3$, removal of the excess $POCl_3$, and workup by one of two methods. In method A, the imino chloride was isolated by extraction, the solution was dried ($MgSO_4$), the solvent was removed, and the imino chloride was redissolved in an appropriate solvent for subsequent reaction with an appropriate piperazine. In method B, the extraction solvent (xylene or toluene) was dried ($MgSO_4$) and filtered, and the solvent was concentrated to an appropriate volume for use in the subsequent reaction.

Method A: 7-Benzyloxy-11-chlorodibenzo[*b*,*f*][1,4]thiazepine (see 10). A solution of **49**, 1.84 g (5.5 mmol), 10 drops of *N*,*N*-dimethyaniline and 20 mL of $POCl_3$ was stirred and heated in an oil bath at 125 °C. After 1 h, TLC analysis (2% $CH_3OH-CH_2Cl_2$) indicated the absence of **49** (R_f 0.33). Concentration in vacuo yielded a residue which was treated with

Scheme 4



ethyl acetate and ice, followed by dilution with water. The ethyl acetate extract was washed with brine and dried ($MgSO_4$). Remova1 of solvent in vacuo gave 1.67 g of the titled imino chloride; TLC analysis (ibid) indicated a single component, R_f 0.70.

Method B: 3,6-Dichlorodibenz[*b,e*]azepine (see 16). A solution of 4.0 g (16.5 mmol) of 3-chloro-5,6-dihydrodibenz-[*b,e*]azepin-6-one and 1.5 mL of *N,N*-dimethylaniline in 60 mL $POCl_3$ was refluxed for 8 h. After concentration in vacuo, the residue was partitioned between 125 mL xylene and ice/water. The organic extract was washed with 1 N HCl, water, saline and dried ($MgSO_4$). This solution was concentrated to 40 mL and used without further purification.

6-(4-Methylpiperazin-1-yl)-11*H*-dibenz[*b,e*]azepine (2). This compound was made by the procedure of Hunziker et al.:[32] mp 135−137 °C (lit. mp 136−138 °C). Anal. ($C_{19}H_{21}N_3$) C,H,N.

11-(4-Methylpiperazin-1-yl)dibenz[*b,f*][1,4]oxazepine (4). The base was made by the procedure of Schmutze et al.;[33] *m/z* 327. An ethereal solution of this base was treated with ethereal HCl to give a white hydroscopic solid which was dried at 60 °C at 10 mmHg: mp 160−170 °C. Anal. ($C_{18}H_{19}N_3O$·1.5HCl·1.5H_2O) C,H,N,Cl.

11-(4-Methylpiperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepine (5). This compound was made by the method of Schmutz et al.[33] The hydrochloride salt was prepared in ether with ethereal HCl: mp 169−171 °C. Anal. ($C_{18}H_{19}N_3S$·2HCl·0.25H_2O) C,H,N,Cl.

3-Chloro-6-(4-methylpiperazin-1-yl)-11*H*-dibenz[*b,e*]-azepine (6). This compound was made by the procedure of Hunziker et al.:[32] mp 200−201.5 °C (lit. mp 202−204 °C). Anal. ($C_{19}H_{20}ClN_3$) C,H,N.

8-Chloro-11-(4-methylpiperazin-1-yl)dibenz[*b,f*][1,4]-oxazepine (7). This compound was made by the procedure of Schmutze et al.:[33] mp 163.5−165 °C (lit. mp 165−166 °C); *m/z* 327. Anal. ($C_{18}H_{18}ClN_3O$) C,H,N.

8-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepine (8). This compound was made by the method of Schmutz et al.[33] and was isolated by column chromatography using 5% methanol−methylene chloride: mp 162−163 °C (lit. mp 166−167 °C). Anal. ($C_{18}H_{18}ClN_3S$) H,N,C: calcd, 62.87; found, 62.33.

2-Hydroxy-6-(4-methylpiperazin-1-yl)-11*H*-dibenz[*b,e*]-azepine (9). Lactam **41**, 0.85 g (3.18 mmol), 0.23 g of *N,N*-dimethylaniline and 6.4 mL of $POCl_3$ were heated to reflux for 2.5 h (method A, CH_2Cl_2) to give the imino chloride. TLC

analysis (2% $CH_3OH-CH_2Cl_2$) indicated a single component with R_f 0.65. This material was treated with 3.2 mL of xylene and 0.96 g (9.54 mmol) of *N*-methylpiperazine and the mixture was heated in an oil bath at 165 °C for 19 h. After cooling, the viscous residue was stirred with ether which was then decanted from an insoluble gum. After washing the ether extract with water, a solid began to separate and this was further promoted by cooling the extract in an ice bath. Filtration and drying gave 0.46 g of a tan solid, homogeneous by TLC (10% $CH_3OH-CH_2Cl_2$) with R_f 0.45.

The above solid, 220 mg, was dissolved in ethanol and treated with 84 mg (0.72 mmol) of fumaric acid whereupon a solid began to form. Cooling followed by filtration gave 170 mg of a white solid. This material was recrystalized from ethanol by effecting solution with 100 mL of hot ethanol and concentration to 20 mL where precipation began. The resulting solid was dried in a drying pistol over refluxing methanol at 10 mTorr: 122 mg; mp 258.5−259.5 °C; ^{1}H NMR (250 MHz, CH_3OH-d_4) 6.91−6.94 (1H, C*H*=C*H*). Anal. ($C_{19}H_{21}N_3O\cdot 0.5C_4H_4O_4\cdot 0.25H_2O$) C,H,N.

7-Hydroxy-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepine (10). The imino chloride was made from 1.00 g (3.0 mmol) of **49**, 10 drops of *N*,*N*-dimethylaniline and 8 mL of $POCl_3$ (method A, ethyl acetate). This solid was treated with 7 mL of xylene and 1.1 mL of *N*-methylpiperazine and the solution was heated in an oil bath at 140 °C under nitrogen for 19 h and paritioned between dilute K_2CO_3 and ethyl acetate which was then dried ($MgSO_4$). Removal of solvent in vacuo gave 1.25 g of a glass which by TLC (10% $CH_3OH-CH_2Cl_2$) showed a major component at R_f 0.50 and a minor impurity in the solvent front. This material was chromatographed on 42 g of silica gel using 10% methanol−methylene chloride: 1.11 g; *m*/*z* 416 $(M + H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) 2.33 (s, 3H, NC*H*$_3$), 4.96 (s, 2H, OC*H*$_2$Ar).

To this material in 5 mL of glacial acetic acid was added 5 mL of 30% HBr in acetic acid and the flask was stoppered. After stirring for 2 h, TLC analysis (10% $CH_3OH-CH_2Cl_2$) showed only a trace of starting material and a major component with R_f 0.20. The content of the flask was added to 200 mL of ether. The resulting solid was collected by filtration and dissolved in water which was made alkaline with $NaHCO_3$ and extracted with ethyl acetate. After drying, the solvent was removed in vacuo to give 0.90 g. Chromatography on 50 g silica gel with 10% methanol−methylene chloride elution gave 0.83 g of a light brown amorphous material which was triturated with ether and dried in a drying pistol over refluxing methanol at 5 mTorr: 0.64 g; mp 204−206 °C. Anal. ($C_{18}H_{19}NOS$) C,H,N.

7-Fluoro-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepine (11). The crude imino chloride was obtained from the reaction of 1.00 g (4.08 mmol) of lactam **45**, 0.30 g of *N*,*N*-dimethyaniline and 8.2 mL of $POCl_3$, following method B (toluene, 4 mL xylene). The residual xylene solution was treated with 1.23 g (12.2 mmol) of 1-methylpiperazine and refluxed for 17 h. The crude material was partioned between ether and water and the ether phase was extracted with 3 N HCl. This acidic aqueous phase was made alkaline with 20% sodium hydroxide, extracted with ether and dried ($MgSO_4$). Removal of solvent in vacuo gave 0.98 g of a foam. Addition of 4 mL of ethanol resulted in complete solution and the immediate formation of white solid which was collected by filtration and dried in vacuo in a drying pistol at 65 °C: 0.33 g; mp 127.5−128.5 °C. Anal. ($C_{18}H_{18}FN_3S$) C,H,N.

The ethanolic filtrate was treated with 5 mL of ethanolic HCl and this solution was added dropwise to ether, resulting in the formation of a white solid. This solid was collected by filtration and dried in a drying pistol at 65 °C at 10 mTorr: 0.52 g; mp 215−218 °C. Anal. ($C_{18}H_{18}FN_3S\cdot 2HCl\cdot 0.75H_2O$) C,H,N,Cl.

7-Chloro-4-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)-10*H*-thieno[3,2-*c*][1]benzazepine (12). Refluxing a solution of 1.68 g (6.73 mmol) of 7-chloro-5,10-dihydro-4*H*-thieno-[3,2-*c*][1]benzazepin-4-one[19] and 1.63 g (4.04 mmol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) in 38 mL toluene for 3 h gave the crude thiolactam (TLC, R_f 0.89, 3% MeOH−CH_2Cl_2), void of the starting lactam (TLC, R_f 0.24). Flash chromatography on silica gel with methylene chloride gave 1.30 g of an orange solid. To 0.66 g of this material in 7.4 mL dioxane was added 0.79 g of powdered KOH in 4.5 mL methanol. This solution was treated with 0.70 mL (7.44 mmol) of dimethyl sulfate and stirred at ambient temperature for 70 min. The solvent was removed in vacuo and the residue was partitioned between water and chloroform which was dried ($MgSO_4$). Concentration in vacuo gave 0.66 g of a brown solid, essentially homogeneous by TLC (20% ether−hexane, R_f 0.66): ^{1}H NMR (80 MHz, $CDCl_3$) 2.66 (3H, SC*H*$_3$).

The above imino thioether, 0.65 g (2.47 mmol), 1.23 g (7.08 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and 2 drops of acetic acid were held at 140 °C (oil bath) for 21 h and then partitioned between methylene chloride and water. The organic extract was washed well with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 0.90 g of a foam. Purification by silica gel column chromatography using 7% methanol−methylene chloride afforded 0.64 g of a yellow solid. Trituration with hot petroleum ether followed by filtration and drying in vacuo gave 0.54 g, homogeneous by TLC (8% $CH_3OH-CH_2Cl_2$, R_f 0.44): mp 107−109 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.55−2.70 (m, 6H), 3.60−3.80 (m, 12H), 6.85−7.20 (m, 5H). Anal. ($C_{20}H_{24}ClN_3O_2S$) C,H,N,Cl.

4-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)-10*H*-thieno[3,2-*c*][1]benzazepine (13). Refluxing a solution of 0.38 g (1.76 mmol) of 5,10-dihydro-4*H*-thieno[3,2-*c*][1]benzazepin-4-one[19] and 0.43 g (1.06 mmol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) in 10 mL toluene for 2.6 h gave the crude thiolactam (TLC, R_f 0.86, 3% $CH_3OH-CH_2Cl_2$), void of the starting lactam (TLC, R_f 0.29). Flash chromatography on silica gel with gradient ether−hexane (25, 50 and 100% ether) elution gave 0.28 g of a yellow solid, homogeneous by TLC (25% ether−hexane, R_f 0.34). To 0.27 g (1.17 mmol) of this material in 3.5 mL dioxane was added 0.33 g of powdered KOH in 2.1 mL methanol. This solution was treated with 0.33 mL (3.5 mmol) of dimethyl sulfate and stirred at ambient temperature for 90 min. The solvent was removed in vacuo and the residue was partitioned between water and chloroform which was dried ($MgSO_4$). Concentration in vacuo gave 0.29 g of a brown solid, essentially homogeneous by TLC (10% ether−hexane, R_f 0.53): ^{1}H NMR (80 MHz, $CDCl_3$) 2.60 (3H, SC*H*$_3$).

The above imino thioether, 0.28 g (1.14 mmol), 0.60 g (3.42 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and 2 drops of acetic acid were held at 140 °C (oil bath) for 4 h and then partioned between ether and water. The organic extract was washed well with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 0.39 g of a foam. Purification by silica gel column chromatography using 8% methanol−methylene chloride afforded 0.35 g of a yellow foam, homogeneous by TLC (8% $CH_3OH-CH_2Cl_2$, R_f 0.30). Trituration with a small amount of ether gave a solid which was collected by filtration and dried in vacuo: 0.22 g; mp 115−118 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.5−2.7 (m, 6H), 3.6−3.8 (m, 12H), 6.9−7.2 (m, 6H). Anal. ($C_{20}H_{25}N_3O_2S$) H,N,C: calcd, 64.66; found, 64.20.

6-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)-11*H*-dibenz[*b,e*]azepine (14). The imino chloride, 2.00 g (8.8 mmol) prepared by method B from 5,6-dihydrodibenz[*b*,*e*]-azepin-6-one,[32] and 4.6 g (28.8 mmol) of 1-[2-(2-hydroxyethoxy)-ethyl]piperazine in 100 mL xylene was refluxed overnight. Solvent was removed in vacuo. The residue was extracted with chloroform, washed with water, saline and dried ($MgSO_4$). Filtration and evaporation gave an oil which was purified by chromatography with 5% methanol−methylene chloride to give 1.98 g, homogeneous by TLC.

An ethereal solution of 1.60 g was treated with ethereal HCl to yield a salt which was dried in a drying pistol over refluxing methanol at 10 mTorr: 1.45 g; mp 140−142 °C; *m*/*z* 365. Anal. ($C_{22}H_{27}N_3O_2\cdot 2HCl\cdot H_2O$) C,H,N,Cl.

A fumarate was prepared by treating a solution of 0.74 g (2.02 mmol) of base in 8 mL of hot ethanol with 125 mg (1.01 mmol) of fumaric acid. After concentration to 4 mL and cooling,

crystallization was promoted by scratching. The solid was dried in a drying pistol over refluxing methanol at 5 mTorr: 0.75 g; mp 154−155 °C; ^{1}H NMR (250 MHz, DMSO-d_6) 6.61 (0.75H, C*H*═C*H*). Anal. ($C_{22}H_{27}N_3O_2 \cdot 0.75C_4H_4O_4$) C,H,N.

2-Hydroxy-6-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)-11*H*-dibenz[*b,e*]azepine (15). Lactam **41**, 1.30 g (4.86 mmol), 0.35 g of *N*,*N*-dimethylaniline and 10 mL of $POCl_3$ were refluxed for 5 h (method A, CH_2Cl_2). The crude imino chloride was dissolved with difficulty in 7 mL xylene and added to 2.54 g (14.58 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed for 20 h. The cooled residue was triturated with ether which was then decanted. Sodium bicarbonate solution was added to the remainder. Extraction with methylene chloride resulted in a solid separating at the interphase so the volume of methylene chloride was increased to effect solution and it was dried with $MgSO_4$. Removal of solvent gave 1.48 g of a brown residue, TLC analysis of which (10% $CH_3OH-CH_2Cl_2$) indicated a major component with R_f 0.50 and minor impurities at both higher and lower R_f values. This crude material in hot ethanol was treated with 0.45 g (3.88 mmol) of fumaric acid and concentrated to 20 mL. After cooling, crystallization was promoted by scratching The solid was collected by filtration and dried in a drying pistol over refluxing methanol at 10 mTorr: 1.16 g; mp 194−195.5 °C; *m*/*z* 381; ^{1}H NMR (250 MHz, CH_3OH-d_4) 6.92−6.96 (1H, C*H*═C*H*). Anal. ($C_{22}H_{27}N_3O_3 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$) C,H,N.

3-Chloro-6-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)-11*H*-dibenz[*b,e*]azepine (16). A solution of 4.0 g (16.5 mmol) of 3-chloro-5,6-dihydrodibenz[*b*,*e*]azepin-6-one[34] and 1.5 mL of *N*,*N*-dimethylaniline in 60 mL $POCl_3$ was refluxed for 8 h. Workup followed method B. This xylene solution was concentrated to 40 mL, 7.19 g (41 mmol) of 1-[2-(2-hydroxyethyl)ethyl]piperazine was added and refluxed for 8 h. The cooled solution was treated with water, 10% NaOH and extracted with ether. The ether extract was washed with water and extracted three times with 1 N HCl. This acidic aqueous extract was made alkaline with dilute NaOH and extracted with ether which was washed with water, saline and dried ($MgSO_4$). Concentration in vacuo gave 6.16 g of a brown oil which was purified by chromatography using 5% methanol−methylene chloride to give 4.40 g of an oil, homogeneous by TLC.

This oil in ether was treated with ethereal HCl to give 4.2 g of a solid. Recrystallization from acetonitrile and drying gave 3.81 g: mp 192−195 °C. Anal. ($C_{22}H_{26}ClN_3O_2 \cdot 2HCl \cdot 0.5H_2O$) C,H,N.

A fumarate salt was prepared by treating a solution of 830 mg (2.08 mmol) of the base in 8 mL of ethanol with 242 mg (2.08 mmol) of fumaric acid. This solution was warmed to reflux, concentrated to 4 mL and left at ambient temperature. The resulting solid was collected by filtration and dried in a drying pistol over refluxing methanol at 10 mTorr: 830 mg; mp 115−117 °C; *m*/*z* 400 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) 6.61 (2H, C*H*═C*H*). Anal. ($C_{22}H_{26}ClN_3O_2 \cdot C_4H_4O_4$) C,H,N.

8-Chloro-11-(4-[2-(2-hydroxyethoxy)ethy]piperazin-1-yl)dibenz[*b,f*][1,4]oxazepine (17). Refluxing a solution of 0.94 g (3.82 mmol) of 8-chloro-10,11-dihydrodibenz[*b*,*f*][1,4]-oxazepin-11-one[34] and 0.93 g (2.3 mmol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) in 20 mL toluene for 1.5 h gave 1.0 g of the crude thiolactam (TLC, R_f 0.31, 12% ether−hexane). To this material in 12 mL dioxane was added 1.08 g of powdered KOH in 7 mL methanol. The clear yellow solution was treated with 1.1 mL (11.58 mmol) of dimethyl sulfate and stirred at ambient temperature for 40 min. The solvent was removed in vacuo and the residue was partitioned between water and chloroform which was dried ($MgSO_4$). Concentration in vacuo gave an oil which solidified on standing. TLC analysis (7% ether−hexane) indicated a major component with R_f 0.63 and several less mobile impurities. The material was purified by column chromatography to give 0.79 g (74%) of the imino thioether as white solid, homogeneous by TLC: ^{1}H NMR (250 MHz, $CDCl_3$) 2.56 (3H, SCH_3).

The above imino thioether, 0.78 g (2.83 mmol) and 1.48 g (8.5 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and 5 drops of acetic acid were held at 140 °C (oil bath) for 23 h and then partioned between methylene chloride and water. The organic extract was washed well with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 1.19 g of a foam. Purification by column chromatography using 5% methanol−methylene chloride afforded 0.93 g, homogeneous by TLC (same solvent), R_f 0.30. An ethereal solution of this base was treated with ethereal HCl to give a salt which was dried in a drying pistol over refluxing methanol at 10 mTorr: 0.69 g; mp 150 °C dec; *m*/*z* 402 $(M + H)^+$. Anal. ($C_{21}H_{24}ClN_3O_3 \cdot HCl \cdot H_2O$) C,H,N,Cl: calcd, 15.54; found, 14.95.

11-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)dibenz-[*b,f*][1,4]oxazepine (18). The crude imino chloride, from 2.49 g (11.8 mmol) of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-11-one (Aldrich), 1.0 g of *N*,*N*-dimethyaniline and 43 mL of $POCl_3$ (method B, xylene), in 70 mL xylene was treated with 2.2 g (12.6 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed for 10 h. On cooling, the solution was made alkaline with 2N NaOH, diluted with ethyl acetate and the organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 1.52 g. Column chromatography afforded 1.39 g of an oil which in ether was treated with ethereal HCl to give a white precipitate which was collected by filtration (hygroscopic) and dried in vacuo: mp 135−140 °C dec; *m*/*z* 368. Anal. ($C_{21}H_{25}N_3O_3 \cdot 1.5HCl \cdot 1.0H_2O$) C,H,N,Cl.

8-Chloro-11-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (19). The imino chloride from 3.0 g (11.46 mmol) of 8-chloro-10(*H*)-dibenz[*b*,*f*][1,4]azepin-11-one,[33] 0.83 mL of *N*,*N*-dimethylaniline and 22 mL of $POCl_3$ (method B) in 20 mL xylene was treated with 6.0 g (34.3 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed for 16.5 h. The cooled solution was partitioned between ether and water and this extract was washed well with water and dried ($MgSO_4$). Removal of solvent left 4.48 g of a crude oil. Column chromatography with 5% methanol−methylene chloride gave 2.77 g of clear viscous material. Using the same solvent, TLC analysis exhibited R_f 0.31.

A portion, 0.87 g (2.08 mmol), and 0.24 g of fumaric acid were dissolved in 8 mL of ethanol with heating, concentrated to 4 mL and left at ambient temperature. The resulting solid was collected by filtration and dried in a drying pistol over refluxing methanol at 10 mTorr: 0.91 g; mp 133−135 °C; *m*/*z* 418 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) 6.62 (s, 2H, C*H*═C*H*). Anal. ($C_{21}H_{24}ClN_3O_2S \cdot C_4H_4O_4$) C,H,N.

8-Fluoro-11-(4-[2-(2-hydroxyethyl)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (20). The crude imino chloride, from the reaction of 6.00 g (24.4 mmol) of lactam **43** and 1 mL of *N*,*N*-dimethyaniline with 35 mL of $POCl_3$ (method B), in 30 mL of xylene was treated with 12.78 g (73.3 mmol) of 1-[2-(2-hydroxyethyl)ethyl]piperazine and refluxed overnight. The crude material was partitioned between ether and water and the ether phase was extracted with 3 N HCl. This acidic aqueous phase was made alkaline with 20% sodium hydroxide, extracted with ether and dried ($MgSO_4$). Removal of solvent in vacuo gave 8.39 g which by TLC (5% $CH_3OH-CH_2Cl_2$) comprised a single component with R_f 0.50. This material in 50 mL of ethanol was treated with 1.30 g (11.2 mmol) of fumaric acid. After stirring for 30 min, the resulting white solid was collected by filtration and dried in a drying pistol at 60 °C at 20 mTorr: 8.20 g; mp 156−157 °C; *m*/*z* 401. Anal. ($C_{21}H_{24}FN_3O_2S \cdot 0.50C_4H_4O_4$) C,H,N.

7-Fluoro-11-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (21). The crude imino chloride from 4.00 g (16.31 mmol) of lactam **45**, 1.18 g of *N*,*N*-dimethylaniline and 32 mL of $POCl_3$ (method B, toluene, 16 mL xylene) in residual xylene was treated with 8.52 g (48.93 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed for 19 h. After partitioning between ether and water, the ether phase was extracted with 3 N HCl. This acidic aqueous phase was made alkaline with 20% sodium hydroxide, extracted with ether and dried ($MgSO_4$). Removal of solvent in vacuo gave 4.85 g of a foam which by TLC (5% $CH_3OH-CH_2Cl_2$) comprised

a major component with R_f 0.24. This material was chromatographed on silica gel using 5% methanol-methylene chloride to give 4.52 g which was dissolved in 10 mL of ethanol and 10 mL of ethanolic HCl and stirred overnight, resulting in the formation of a white solid. The content of the flask was added to ethyl ether and the solid was collected by filtration and dried in a drying pistol at 65 °C at 10 mTorr: 4.77 g; mp 213.5−215.5 °C. Anal. ($C_{21}H_{24}FN_3O_2S$·2HCl) C,H,N,Cl.

6-Fluoro-11-(4-[2-(2-hydroxyethyl)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (22). The crude imino chloride, from 0.30 g (1.22 mmol) of lactam **58**, 0.09 g of *N*,*N*-dimethyaniline and 25 mL of $POCl_3$ (method B, toluene, 2 mL xylene), in the residual xylene was treated with 0.64 g (3.66 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed for 17 h. After partionioning between ether and water, the ether phase was extracted with 3 N HCl. This acidic phase was made alkaline with 20% sodium hydroxide, extracted with ether and dried ($MgSO_4$). Removal of solvent in vacuo gave 0.23 g of a foam. This material was chromatographed on silica gel using 5% methanol−methylene chloride to give 0.20 g of a pale yellow oil, homogeneous by TLC (5% $CH_3OH-CH_2Cl_2$) with R_f 0.35: ^{1}H NMR (250 MHz, $CDCl_3$) 2.56−2.66 (m, 6H, N[CH_2]$_3$), 3.60−3.72 (m, 10H, N[CH_2]$_2$ and CH_2OCH_2CH_2O), 6.68−6.71 (1H), 6.82−6.86 (1H), 7.03−7.12 (1H), 7.26−7.36 (3H), 7.54−7.58 (1H).

This material in ether was treated with ethereal HCl to form the hydrochloride (hygroscopic) which was dried in a drying pistol over refluxing methylene chloride at 10 mTorr: 0.12 g; mp 150−160 °C dec; *m*/*z* 401. Anal. ($C_{21}H_{24}FN3O_2S$·1.6HCl·H_2O) C,H,N: calcd, 8.79; found, 8.13.

11-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo-[*b,f*][1,4]thiazepine (23). A solution of 3.0 g (13.2 mmol) of **39** and 0.5 mL of *N*,*N*-dimethylaniline in 20 mL $POCl_3$ was refluxed for 4 h (method B). The xylene extract was concentrated to 20 mL and treated with 3.2 g (18.6 mmol) of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed overnight. The cooled solution was treated with ether and this extract was washed well with water and extracted three times with 1 N HCl. This acidic aqueous extract was made alkaline with dilute NaOH and was extracted with ether and dried ($MgSO_4$). Removal of solvent left an oil which by TLC analysis (10% $CH_3OH-CH_2Cl_2$) showed a major component with R_f 0.50 and a more mobile impurity. Column chromatography with 10% methanol−ether gave 2.9 g of a brown oil.

A portion, 2.1 g (5.47 mmol), in 20 mL of ethanol was treated with 0.67 g (5.7 mmol) of fumaric acid. Upon heating, solution was effected for a few minutes after which a solid began to separate. After cooling, the solid was collected by filtration and dried in drying pistol over refluxing methanol at 10 mTorr: 2.4 g; mp 172−173 °C; *m*/*z* 383. Anal. ($C_{21}H_{25}N_3O_2S.0.5C_4H_4O_4$) C,H,N.

7-Hydroxy-11-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazapine (24). The lactam **49**, 1.84 g (5.5 mmol), 10 drops of *N*,*N*-dimethyaniline and 20 mL of phosphorus oxychloride were heated for 1 h after which time TLC analysis (2% $CH_3OH-CH_2Cl_2$) indicated the absence of **49**, R_f 0.33. Workup (method A, ethyl acetate) gave 1.67 g; TLC (ibid) indicated a single component, R_f 0.70.

1-[2-(2-Hydroxyethoxy)ethyl]piperazine, 2.50 g (14.5 mmol), was weighed directly into the flask containing the imino chloride, 15 mL of xylene was added, and the mixture was heated in an oil bath at 125 °C under nitrogen for 18 h. After partitioning between ethyl acetate and aqueous K_2CO_3, the organic phase was washed well with water, brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 1.99 g which was essentially a single component by TLC (5% $CH_3OH-CH_2Cl_2$), R_f 0.22.

To this material in 10 mL glacial acetic acid was added 10 mL of 30% HBr in acetic acid and the solution was stirred in a stoppered flask for 1 h. The content of the flask was added to ethyl ether and the orange HBr salt was collected by filtration, washed with ether and dissolved in 150 mL of water. This solution was made alkaline with $NaHCO_3$ and extracted with ethyl acetate which was washed with brine and dried ($MgSO_4$). Concentration in vacuo gave 1.93 g which by TLC (10% $CH_3OH-CH_2Cl_2$) was essentially a single component (R_f 0.42) with only minor impurities. Purification by column chromatography on 80 g silica gel and elution with 5% $CH_3OH-CH_2Cl_2$ gave 1.53 g of the acetate as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) 2.04 (s, 3H, CH_3), 4.18−4.21 (m, 2H, CH_2OAc).

This ester, 1.52 g (3.44 mmol), and 0.62 g (9.3 mmol) of KOH (powdered, 85%) in 16 mL of methanol was stirred at ambient temperature for 4 h. An aliquot was treated with ethereal HCl to yield the HCl salt which was dissolved in methanol and applied directly to a TLC plate. Development with 10% $CH_3OH-CH_2Cl_2$ exhibited a single component, R_f 0.30. The solvent was then removed in vacuo and the residual potassium salt was dissolved in 20 mL of water. Addition of 1 N HCl gave a precipitate which dissolved upon additon of 100 mL of water. The portionwise addition of $NaHCO_3$ resulted in the separation of a solid which required 850 mL of $CHCl_3$ to effect solution. After drying, evaporation of the solvent in vacuo gave **24** base, 1.39 g, as an amorphous solid, homogeneous by TLC (10% $CH_3OH-CH_2Cl_2$), R_f 0.33.

A 340-mg aliquot of this phenol was dissolved in 3 mL of ethanolic HCl and stirred at ambient temperature. After 40 min a fair amount of white solid had formed and 15 mL of ether was added and stirring continued for 4 h. The solid was collected by filtration, washed with ether and dried in a drying pistol over refluxing methanol at 5 mTorr: 313 mg; mp 219−221 °C; *m*/*z* 400 $(M + H)^+$. Anal. ($C_{21}H_{25}N_3O_3S$·2HCl·1.2H_2O) C,H,N,Cl.

To 0.99 g of **24** base in 25 mL of ethanol was added 10 mL of hot ethanol containing 0.40 g of fumaric acid. This solution was concentrated to 4 mL and allowed to cool to ambient temperature. Refrigeration for 3 days resulted in the formation of crystals which were collected by filtration, washed with ether and dried in a drying pistol over refluxing methanol at 10 mTorr: 1.04 g; mp 121−124 °C; ^{1}H NMR (300 MHz CH_3OH-d_4) 1.14−1.19 (t, CH_3CH$_2$OH), 6.69 (s, 2H, C*H*=C*H*). Anal. ($C_{21}H_{25}N_3O_3S$·$C_4H_4O_4$·0.33C_2H_5OH·0.5H_2O) C,H,N.

8-Hydroxy-11-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazapine (25). The lactam **54**, 1.50 g (4.52 mmol), 10 drops of *N*,*N*-dimethylaniline and 15 mL of phosporous oxychloride were heated in an oil bath at 120 °C. After 1 h, TLC analysis (2% $CH_3OH-CH_2Cl_2$) indicated the absence of **54**, R_f 0.38. Workup (method A, ethyl acetate) gave a brown oil; TLC (ibid) indicated a single component, R_f 0.75.

1-[2-(2-Hydroxyethoxy)ethyl]piperazine, 2.00 g (11.4 mmol), was weighed directly into the flask containing the imino chloride, 15 mL of xylene was added, and the mixture was heated in an oil bath at 140 °C under nitrogen for 17 h. After partitioning between ethyl acetate and aqueous K_2CO_3, the organic phase was washed well with water, brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 2.02 g which was essentially a single component by TLC (10% $CH_3OH-CH_2Cl_2$), R_f 0.50: *m*/*z* 490 $(M + H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) 4.98 (s, 2H, ArOCH_2).

To this material in 5 mL of glacial acetic acid was added 5 mL of 30% HBr in acetic acid and the solution was stirred in a stoppered flask for 1 h at which time TLC analysis (5% $CH_3OH-CH_2Cl_2$) indicated the absence of starting material (R_f 0.30). The contents of the flask was added to 200 mL of ethyl ether which resulted in an oil and suspended solid. Decantation with filtering recovered the solid which was dissolved in water and added back to the oily residue. This aqueous solution was made alkaline with $NaHCO_3$ and extracted with ethyl acetate which was washed with brine and dried ($MgSO_4$). Concentration in vacuo gave 1.74 g which by TLC (10% $CH_3OH-CH_2Cl_2$) was essentially a single component (R_f 0.62) with only minor impurities. Purification by column chromatography on 70 g silica gel and elution with 10% $CH_3OH-CH_2Cl_2$ gave 1.30 g of the acetate as an amorphous glass: ^{1}H NMR (300 MHz, $CDCl_3$) 2.03 (s, 3H, CH_3), 2.53−2.66 (m, 6H), 3.61−3.65 (m, 8H), 4.17−4.20 (m, 2H, CH_2OAc), 6.33−7.49 (m, 7H); *m*/*z* 442 $(M + H)^+$.

This acetate, 1.30 g (3.0 mmol), and 0.60 g (9.0 mmol) of KOH (powdered, 85%) in 20 mL of methanol was stirred at

ambient temperture for 5 h. An aliquot was treated with ethereal HCl to yield the HCl salt which was treated with dilute $NaHCO_3$ and extracted with $CHCl_3$. TLC analysis (10% $CH_3OH-CH_2Cl_2$) exhibited a single component, R_f 0.20. The solvent was then removed in vacuo and the residual potassium salt was dissolved in water. Addition of 1 N HCl gave a precipitate which would not completely dissolve by the addition of more water. After the portionwise addition of $NaHCO_3$, the solid readily dissolved in $CHCl_3$. After drying, evaporation of the solvent in vacuo gave **25**, 1.18 g, as an amorphous solid: *m/z* 400 $(M + H)^+$; ^1H NMR (300 MHz, CH_3OH-d_4) 2.55−2.67 (m, 6H, $N[CH_2]_3$), 3.28−3.66 (m, 11H, $N[CH_2]_2$, $CH_2OCH_2CH_2$-OH, CH_3OH), 6.35−6.47 (m, 2H), 7.14−7.50 (m, 5H).

To 1.17 g (3 mmol) of **25** base in 30 mL of ethanol was added 10 mL of hot ethanol containing 0.40 g (3.5 mmol) of fumaric acid. This solution was concentrated to 10 mL and allowed to cool to ambient temperature. The tan crystals were collected by filtration, washed with ether and dried in a drying pistol over refluxing methanol at 10 mTorr: 1.13 g; mp 205−207 °C; ^1H NMR (300 MHz, CH_3OH-d_4) 1.03−1.07 (t, CH_3CH_2OH), 6.61 (s, 2H, CH=CH). Anal. ($C_{21}H_{25}N_3O_3S \cdot C_4H_4O_4 \cdot 0.33C_2H_5OH \cdot 0.5H_2O$) C,H,N.

11-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine Sulfoxide (26). A solution of 1.93 g (9.0 mmol) of sodium periodate in 15 mL of water was added dropwise over 20 min to 4.12 g (9.0 mmol) of the dihydrochloride of **23** in 20 mL of water which was cooled in an ice−water bath. The homogeneous solution was then stirred for 22 h. An aliquot treated with dilute sodium hydroxide and ethyl acetate on TLC analysis (20% methanol−ether) indicated two major components with R_f's 0.10 and 0.30 and a minute amount of starting material with R_f 0.47. The entire material was then treated with dilute sodium hydroxide and extracted with ethyl acetate which was washed with water, brine and dried ($MgSO_4$). Removal of solvent gave 2.70 g which was dissolved in toluene and refluxed for 2 h. TLC analysis (ibid) showed a major component with R_f 0.30 and minor components with R_f's 0.10 and 0.50. Toluene was removed invacuo and the major component was isolated by column chromatography using 20% methanol−ether to give 1.98 g of a glassy material. This material in 5 mL of ethanolic HCl was stirred for 10 min at which time a voluminous precipitate formed. After dilution with ether the solid was collected by filtation and dried in a dyring pistol at 66 °C and 5 mTorr: 2.15 g; mp 189−191 °C; *m/z* 400 $(M + H)^+$. Anal. ($C_{21}H_{25}N_3O_3S \cdot 1.85HCl \cdot 1.0H_2O$) C,H,N,Cl.

11-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine Sulfone (27). A solution of 3.0 g (11.57 mmol) of 10,11-dihydrodibenzo[*b,f*][1,4]thiazepin-11-one sulfone[35] and 0.5 mL of *N,N*-dimethylaniline in 30 mL of $POCl_3$ was refluxed for 18 h (method B, xylene). The imino chloride in 20 mL residual xylene was treated with 4.0 g of 1-[2-(2-hydroxyethoxy)ethyl]piperazine and refluxed overnight. The reaction mixture was partioned between ether and water and the ethereal extract was washed well with water and dried ($MgSO_4$). Removal of solvent in vacuo gave 2.5 g, homogeneous by TLC (5% $CH_3OH-CH_2Cl_2$), R_f 0.50: *m/z* 415.

A portion, 1.2 g, in ethanol was treated with ethanolic HCl and concentrated to 5 mL. Addition of ether resulted in the formation of a white solid which was collected by filtration and dried in a drying pistol at 65 °C and 10 mTorr: 1.5 g; mp 168−169 °C. Anal. ($C_{21}H_{25}N_3O_4S \cdot HCl \cdot H_2O$) C,H,N,Cl.

11-(4-[2-Hydroxyethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepine (28).[36] To the crude imino chloride prepared from 0.0088 mol of **39** (method B, as described for **23**) in 30 mL of xylene was added 2.98 g (0.023 mole) of 1-piperazinylethanol and the mixture stirred at reflux overnight. The mixture was added to 20 mL of water, basified to pH 12 with 10% sodium hydroxide and extracted with two 50-mL portions of ethyl ether. The combined extracts were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting gold-colored oil was chromatographed on silica gel (ethyl acetate), and the proper fractions combined to yield 2.85 g of an oil. Treatment of an etheral solution of the oil with ethereal HCl gave 2.04 g (56%) of white solid: mp 247−269 °C slow dec. Anal. ($C_{19}H_{21}N_3OS \cdot 2HCl$) C,H,N.

11-(4-[2-(2-[2-Hydroxyethoxy]ethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (29). To the crude imino chloride prepared from 0.0074 mol of **39** (method B, as described for **23**) in 20 mL of xylene was added 3.25 g (0.0149 mol) of 2-[2-[2-(1-piperazinyl)ethoxy]ethoxy]ethanol[37] and the mixture stirred at reflux overnight. The mixture was added to water, basified to pH 12 with 10% NaOH solution and extracted with three 50-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting yellow oil was chromatographed on silica gel (ethanol:hexane, 1:9), and the proper fractions combined to yield 1.18 g of an oil. Treatment of an ethereal solution with ethereal HCl gave 1.02 g (27%): mp 82 °C dec. Anal. ($C_{23}H_{29}N_3O_3S \cdot 2HCl \cdot H_2O$) C,H,N.

11-(4-[2-(1,3-Dimethoxy)propyl]piperazin-1-yl)dibenzo-[*b,f*][1,4]thiazepine (30). To the crude imino chloride prepared from 0.0048 mol of **39** (method B, as described for **23**) in 10 mL of toluene was added 1.81 g (0.0096 mol) of *N*-[2-(1,3-dimethoxy)propyl]piperazine[38] and the mixture stirred at reflux overnight. The mixture was treated with water, basified to pH 12 with 10% sodium hydroxide and extracted with three 50-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting brown oil was chromatographed on silica gel (hexane: chloroform, 1:4), and the proper fractions combined to yield 1.56 g of an oil. Treatment of an etheral solution of the oil with ethereal HCl gave 1.16 g (50%) of off-white solid: mp 130 °C dec. Anal. ($C_{22}H_{27}N_3O_2S \cdot 2HCl \cdot H_2O$) C,H,N.

11-(4-[2,3-Dimethoxypropyl]piperazin-1-yl)dibenzo-[*b,f*][1,4]thiazepine (31). To the imino chloride from 1.14 g (0.005 mol) of **39**, 5 drops of *N,N*-dimethylaniline and 16 mL of $POCl_3$ (method A, toluene) in 15 mL of xylene was added 1.88 g (0.010 mole) of 2,3-dimethoxypropylpiperazine (**49**) in 25 mL of xylene, the mixture refluxed for 8 h and then stirred at room temperature overnight. The solvent was removed in vacuo and the residue chromatographed on silica gel (ethanol: hexane 1:19). The product was converted to the dicitrate salt in ether and recrystallized from acetonitrile−ether: 1.71 g (44%); mp 68 °C dec. Anal. ($C_{22}H_{27}N_3O_2S \cdot 2C_6H_8O_7$) C,H,N.

***S*-(+)-11-(4-[2,3-Dimethoxypropyl]piperazin-1-yl)-dibenzo[*b,f*][1,4]thiazepine (32).** A solution of 10.25 g (0.394 mol) of *S*-(−)-1-(2,3-dimethoxypropyl)-4-ethoxycarbonylpiperazine (**61**) and 10.7 g (0.19 mol) of potassium hydroxide in 60 mL of *n*-butanol was stirred at reflux for 18 h. The reaction flask was placed in an oil bath and the *n*-butanol removed in vacuo by distillation through a 4 in. Vigreaux column at aspirator pressure. Crude product was then collected to an oil bath temperature of 180 °C at vacuum pump pressure. Redistillation gave 6.56 g (88%) of *S*-(+)-*N*-2,3-dimethoxypropylpiperazine: bp 64−6 °C/0.1 mmHg; $[\alpha]_D^{27}$ +0.49° (*c* = 2, methanol).

To the crude imino chloride prepared from 0.005 mol of **39** (method A, toluene, as described for **31**) in 15 mL of toluene was added 1.88 g (0.010 mol) of *S*-(+)-*N*-2,3-dimethoxypropylpiperazine and the mixture stirred at reflux for 18 h. The solvent was removed in vacuo and the residue chromatographed on silica gel (ethyl acetate:chloroform, 1:2). The material was converted to the hydrochloride salt in ethereal HCl and recrystallized from acetonitrile−ether: 1.58 g (67%); mp 110 °C dec. Anal. ($C_{22}H_{27}N_3O_2S \cdot 2HCl \cdot H_2O$) C,H,N.

11-(4-[3,4-Dimethoxybutyl]piperazin-1-yl)dibenzo[*b,f*]-[1,4]thiazepine (33). A solution of the imino chloride from 1.11 g (0.005 mol) of **39** (method B, xylene, as described for **23**) in 10 mL xylene was treated with 1.98 g (0.0098 mol) of 1-(3,4-dimethoxybutyl)piperazine **64** and the mixture stirred at reflux for 24 h. The cooled mixture was added to 10 mL of water, basified to pH 12 with 10% NaOH. The organic layer was washed with saturated saline solution, dried ($MgSO_4$) and the solvent removed to yield a brown oil. Flash chromatography on silica gel with 5% methanol−chloroform gave 1.09 g (54%) of base. The material in ether was treated with ethereal HCl to yield a precipitate which was recrystallized from

ethanol−ethyl ether: 0.81 g; mp 68 °C dec. Anal. ($C_{23}H_{29}N_3O_2$·1.25HCl·0.5H_2O) H,N,Cl,C: calcd, 59.26; found, 59.75.

11-(4-[2-Methoxy-3-hydroxypropyl]piperazin-1-yl)-dibenzo[*b,f*][1,4]thiazepine (34). To the crude imino chloride prepared from 0.0065 mol of **39** (method B, as described for **23**) in 20 mL of toluene was added 2.29 g (0.013 mol) of 1-(2-methoxy-3-hydroxypropyl)piperazine (**66**) in 10 mL of toluene and the mixture was refluxed overnight. Water was added to the reaction mixture which was made basic by the addition of 15% sodium hydroxide solution and extracted with ethyl acetate. This extract was washed with three portions of 10% hydrochloric acid. The acidic aqueous phase was made basic with 15% sodium hydroxide and extracted with ethyl acetate and dried ($MgSO_4$). Removal of solvent in vacuo gave 2.34 g of crude product. Chromatography on silica gel (ethanol−hexane, 1:19) returned 1.81 g (72%) of pure product as a light green oil. The oil was converted to a citrate salt in ether. The salt was dissolved in 25 mL of distilled water, filtered and lyophilized: 2.29 g (52%); mp 75 °C dec. Anal. ($C_{21}H_{25}N_3O_2S$·1.5$C_6H_8O_7$) C,H,N.

11-(4-[1-Hydroxymethyl-2-methoxyethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (35). To the crude imino chloride prepared from 0.0040 mol of **39** (method B, as described for **23**) in 15 mL of xylene was added 0.70 g (0.004 mol) of *β*-methoxymethyl-1-piperazinylethanol[38] and 0.55 g (0.0040 mol) of potassium carbonate and the mixture stirred at reflux overnight. The mixture was filtered and the solvent removed in vacuo. The resulting gold-colored oil was chromatographed on silica gel (methanol:chloroform, 1:19) and the proper fractions combined to yield an oil which was treated with HCl in ethyl ether: 0.15 g; mp 116 °C dec. Anal. ($C_{21}H_{25}N_3O_2S$·1.5HCl·0.5H_2O) C,N,Cl,H: calcd, 6.20; found, 6.77.

11-(4-[*cis*-6-Hydroxymethyl-1,4-dioxan-2-ylmethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (36). To the crude imino chloride prepared from 0.010 mol of **39** (method A, toluene, as described for **31**) in 35 mL of toluene was added 4.33 g (0.020 mol) of *cis*-2-piperazinylmethyl-6-hydroxymethyl-1,4-dioxane (**67**) and the mixture stirred at reflux overnight. The mixture was treated with a little 10% sodium hydroxide, extracted with ethyl acetate, dried ($MgSO_4$), and the solvent removed in vacuo. The residue was chromatographed on silica gel (ethyl acetate), the proper fractions combined and the material converted to the hydrochloride salt with ethereal HCl. The white solid was recrystallized from methanol−ethyl ether and then methylene chloride−ethyl ethe: 4.05 g (81%); mp 195 °C dec. Anal. ($C_{23}H_{27}N_3O_3S$·2HCl) C,H,N.

11-(4-[1,4-Dioxan-2-ylmethyl]piperazin-1-yl)dibenzo-[*b,f*][1,4]thiazepine (37). To the crude imino chloride prepared from 0.0038 mol of **39** (method A, as described for **31**) in 16 mL of xylene was added 1.42 g (0.020 mol) of 2-piperazinylmethyl-1,4-dioxane **(69)** and the mixture stirred at reflux overnight. The mixture was treated with 25 mL of water, basified to pH 12 with 10% sodium hydroxide and the phases separated. The aqueous phase was extracted with two 50-mL portions of ethyl acetate, the combined extract dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting gold-colored oil was chromatographed on silica gel (ethyl acetate: chloroform, 1:2), and the proper fractions combined to yield 1.27 g of an oil. Trituration of the oil with hexane containing a little ethyl ether returned 0.89 g (59%): mp 118−121 °C. Anal. ($C_{22}H_{25}N_3O_2S$) C,H,N.

11-(4-[2-Tetrahydofuranylmethyl]piperazin-1-yl)-dibenzo[*b,f*][1,4]thiazepine (38). To the crude imino chloride prepared from 0.0053 mol of **39** (method B, as described for **23**) in 15 mL of xylene was added 1.80 g (0.0106 mol) of *N*-[2-tetrahydofuranylmethyl]piperazine[39] and the mixture stirred at reflux overnight. The mixture was poured onto excess 10% sodium hydroxide and extracted with two 50-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting gold-colored oil was chromatographed on silica gel (chloroform), and the proper fractions combined to yield an oil which was further converted to the dihydrochloride salt with HCl in ethyl ether. The dihydrochloride salt was recrystallized from methanol−ethyl ether: 0.88 g (37%); mp 260 °C dec. Anal. ($C_{22}H_{25}N_3OS$·2HCl) C,H,N.

10,11-Dihydrodibenzo[*b,f*][1,4]thiazepin-11-one (39). Prepared by the method of Schmutz et al.:[34] mp 256−257 °C (lit. mp 256 °C).

2-Methoxy-5,6-dihydro-11*H*-dibenz[*b,e*]azepin-6-one (40). To 2.85 g (13.36 mmol) of 2 amino-5-methoxydiphenylmethane[40] in 26 mL dioxane was added dropwise 0.80 mL (6.68 mmol) of trichloromethyl chloroformate and the mixture was heated at 54 °C (oil bath) for 3 h. Dioxane was removed in vacuo to give a residue of 3.21 g which was Kugelrohr distilled to give the isocyanate as an oil: 2.66 g (83% yield); bp 106−116 °C (air bath temperature) at 4−8 mTorr; TLC analysis (1:10 ether:hexane) indicated a single component at R_f 0.54; IR max (film) 2250(s) cm^{-1}.

A slurry of 1.48 g (11.08 mmol) of aluminum trichloride in 11 mL of *o*-dichlorobenzene was heated in an oil bath to 110 °C and a solution of 2.65 g (11.08 mmol) of the above isocyanate in 11 mL of *o*-dichlorobenzene was added dropwise. The temperature was raised to 150 °C and held for 3.5 h. Solvent was removed using a Kugelrohr (air bath temperature 120 °C) and water aspirator pressure. Treatment of the residue with ice gave a tan solid which was washed well with water and then with a little ether to give 2.62 g. This was dried in a drying pistol over refluxing methanol at 10 mTorr: 2.54 g; mp 228.5−231.5 °C; TLC (ether:hexane, 1:1) R_f 0.20; ^{1}H NMR (250 MHz, DMSO-d_6) 3.70 (3H, CH_3), 3.85 (2H, CH_2), 10.22 (1H, N*H*); IR max (Nujol) 3150(m), 1650(s) cm^{-1}; *m/z* 239.

2-Acetoxy-5,6-dihydro-11*H*-dibenz[*b,e*]azepin-6-one (41). Lactam **40**, 2.52 g (10.57 mmol), in 20 mL methylene chloride was cooled to −78 °C. Boron tribromide dimethyl sulfide, 11 mL (11 mmol), was added by syringe and the bath temperature was allowed to increase spontaneously. Since TLC analysis (5% CH_3OH−CH_2Cl_2) indicated that the demethylation was slow, additional amounts of the boron reagent were added: 15.9 mL (1.5 mmol) after 22 h and 11.1 mL (1 mmol) after a total of 28.5 h. Since starting material was still detected after 45 h, an additional 31 mL of a 1.0 M solution of boron tribromide in methylene chloride was added. After 3 h, no starting material was detected. The solvent was removed in vacuo, the residue was treated with ice and was made alkaline with dilute sodium bicarbonate. The tan solid which separated was collected by filtration and dried to give 2.38 g.

The above material, 2.36 g (10.48 mmol), and 2.92 mL (21 mmol) of triethylamine in 10 mL methylene chloride was cooled to 0 °C. Acetyl chloride, 0.09 g (11.53 mmol) in 15 mL methylene chloride was added dropwise. The solution was stirred at ambient temperature for 1.5 h and was then treated with water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give 2.87 g of the titled compound as a tan solid. TLC analysis (5% CH_3OH−CH_2Cl_2) showed a single component, R_f 0.34, and absence of starting material, R_f 0.23: IR (Nujol) 3150(m), 1750(s), 1638(s) cm^{-1}; *m/z* 267.

***N*-(*tert*-Butoxycarbonyl)-4-fluoro-2-thiophenylaniline (42).** A dry three-necked flask under nitrogen was charged with 1.61 g (7.62 mmol) of *N*-(*tert*-butoxycarbonyl)-4-fluoroaniline[41] and 75 mL of dry THF and cooled to −76 °C. By means of a syringe, 7.45 mL (16.76 mmol) of 2.25 M *tert*-butyllithium in hexane was added dropwise. After 15 min, the solution was allowed to warm to −22 °C, held for 1 h and cooled again to −76 °C. *S*-Phenyl benzenethiosulfonate, 2.29 g (9.14 mmol), was added in one portion. The solution was stirred overnight, allowing the bath temperature to rise spontaneously. After quenching with water, the THF was removed in vacuo and the residue was extracted with ether which was washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 2.44 g of an amber oil which by TLC (4% ether−hexane) was composed of a major component with R_f 0.40 and two minor impurities with lower R_f's. This material was purified by column chromatography, eluting with 4.5% ether−hexane: 1.57 g (65% yield) of a yellow oil; IR (film) 3358(m), 1740 (s) cm^{-1}; *m/z* 319; ^{1}H NMR (80 MHz, $CDCl_3$) 1.45 (s, 9H), 7.09−7.28 (m, 8H). Anal. ($C_{17}H_{18}FNO_2S$) C,H,N.

4-Fluoro-2-thiophenylaniline (43). The carbamate **42**, 2.90 g (9.08 mmol), in 9 mL of trifluoroacetic acid was stirred a ambient temperature for 30 min and the solvent was removed in vacuo. The residue was made alkaline with 10% sodium hydroxide, extracted with ether and dried ($MgSO_4$). Concentration in vacuo gave 1.89 g of a yellow oil, a single component by TLC (50% ether−hexane), R_f 0.68: IR max (film) 3448(m), 3355(m) cm^{-1}. This material was used without further purification.

4-Fluoro-2-(thiophenyl)phenyl Isocyanate (44). A solution of 1.88 g (8.57 mmol) of **43** in 15 mL of dioxane was treated dropwise with 0.85 g (4.28 mmol) of trichloromethyl chloroformate. The temperature was raised to 60 °C (oil bath) and held for 3.5 h. TLC analysis (20% ether−hexane) showed a major component with R_f 0.85 and a very minor impurity with R_f 0.34. Dioxane was removed in vacuo and the residue was Kugelrohr distilled: 1.83 g of a colorless oil; bp (air bath temperature) 97−109 °C at 20 mTorr; IR max (film) 2260(s) cm^{-1}. This material was used without further purification.

7-Fluoro-10,11-dihydrodibenzo[*b,f*][1,4]thiazepin-11-one (45). To a solution of 1.0 g (7.42 mmol) of aluminum chloride in 50 mL of *o*-dichlorobenzene at 100 °C was added a solution of 1.82 g of the crude **44** in 8 mL of the same solvent. The temperature was raised to 150 °C, held for 6.5 h and the solvent was removed using a Kugelrohr at 20 mmHg. The residue was treated with ice and triturated: 1.52 g of a tan solid; IR max (Nujol) 3150(m), 1660(s), 1645(s) cm^{-1}. This material was used without further purification.

4-Benzyloxy-2-bromonitrobenzene (46). A solution of 7.00 g (32.1 mmol) of 3-bromo-4-nitrophenol[42] in 20 mL of dimethylacetamide (DMAC) was added dropwise to a slurry of 0.78 g (32.1 mmol) of sodium hydride in 5 mL DMAC. The resulting homogeneous solution was warmed to 60 °C and a solution of 5.50 g (32.1 mmol) of benzyl bromide in 5 mL DMAC was added dropwise. After 6 h, the cooled contents were transferred with DMAC to a single-necked flask and the solvent was removed using a Kugelrohr at 75−100 °C (air bath temperature) and 20 mmHg. The residue was partitioned between ether and water and the ether extract was washed with water, brine and dried ($MgSO_4$). Removal of solvent in vacuo left 9.61 g which by TLC analysis (CH_2Cl_2) showed a major component at R_f 0.75 and some starting phenol at R_f 0.10. This material was chromatographed on silica gel with methylene chloride elution: 9.11 g; mp 76−78 °C; ^1H NMR (250 MHz, CH_3OH-d_4) 3.58 (s, 2H, CH_2), 5.40−5.44 (d, 1H, Ar), 5.75−5.76 (s, 1H, Ar), 5.84−5.87 (m, 5H, Ar), 6.40−6.44 (d, 1H, Ar); *m*/*z* 308 $(M + H)^+$. Anal. ($C_{13}H_{10}BrNO_3$) C,H,N.

4-Benzyloxy-2-(2′-carbomethoxy)thiophenylnitrobenzene (47). A solution of 4.62 g (30 mmol) of thiosalicylic acid in 20 mL DMAC was added dropwise to a slurry of 1.44 g (60 mmol) of sodium hydride in 10 mL DMAC. **46**, 8.30 g (27 mmol), was added as a solid and the heterogeneous solution was warmed in an oil bath to 80 °C for 1 h. TLC analysis (CH_2Cl_2) revealed the absence of the starting nitrobenzene. The cooled solution was treated with 5.6 mL (90 mmol) of iodomethane, the flask was stoppered and stirred at ambient temperature for 45 h (for convenience). TLC analysis (40% ether−petroleum ether) indicated a major component at R_f 0.35 and only two more mobile minor components. The content of the flask was partioned between water and ethyl acetate which was washed well with water, brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 11.36 g of a red oil which was heated in a Kugelrohr to give a distillate of 0.45 g, bp 130−135 °C (air bath temperature) at 5 mTorr, which was methyl 2-thiomethylbenzoate. The residual 10.58 g was chromatographed on 250 g of silica gel with methylene chloride elution: 9.60 g; mp 78−80 °C. The analytical specimen was obtained by drying an aliquot in a drying pistol at 5 mTorr at at ambient temperture: ^1H NMR (250 MHz, $CDCl_3$) 3.77 (s, 3H, CH_3), 4.87 (s, 2H, CH_2); *m*/*z* 396 $(M + H)^+$. Anal. ($C_{21}H_{17}NO_5S$) C,H,N.

4-Benzyloxy-2-(2′-carbomethoxy)thiophenylaniline (48). To 5.00 g (12.6 mmol) of **47** in 50 mL ethanol was added 14.26 g (63 mmol) of stannous chloride dihydrate[43] and the solution was refluxed for 40 min at which time TLC analysis (40% ether−petroleum ether) indicated the absence of the nitrobenzene. Ethanol was removed in vacuo. The residue was treated with ice, then water and portionwise with sodium bicarbonate until alkaline. Ethyl acetate was added and the mixture was filtered through Celite. The ethyl acetate extract was washed with water, brine and dried ($MgSO_4$). Concentration in vacuo gave a tan solid: 4.48 g; mp 105−107 °C; homogeneous by TLC (CH_2Cl_2), R_f 0.17. The analytical specimen was obtained by drying an aliquot in a drying pistol over refluxing methanol at 5 mTorr: *m*/*z* 366 $(M + H)^+$. Anal. ($C_{21}H_{19}NO_3S$) C,H,N.

7-Benzyloxy-10,11-diydrodibenzo[*b,f*][1,4]thiazepin-11-one (49). A dry three-necked flask equipped with a magnetic stirring bar and condenser with a nitrogen inlet was charged with 4.39 g (12.0 mmol) of **48**, 50 mL of dry methylene chloride and was cooled in an ice−salt bath to −10 °C. By syringe, 6.60 mL (13.2 mmol) of a 2 M solution of trimethylaluminum[44] in hexane was added. After 10 min the ice bath was removed and the solution was stirred at ambient temperature for 48 h. Cautiously, water was added dropwise (gasing), followed by 25 mL of 2 N HCl. The content of the flask was then partioned between 700 mL of water and 1500 mL of chloroform in order to get two homogeneous phases, and the chloroform extract was washed with brine and dried ($MgSO_4$). Concentration in vacuo gave a solid which was triturated with ether and air-dried: 3.66 g (91.7%) of a white solid; mp 240−243 °C; TLC (70% ether−petroleum ether), R_f 0.22. The analytical specimen was prepared by dissolving 57 mg in 25 mL of hot ethanol and concentrating to 9 mL where a solid began to separate. Filtration and drying in a drying pistol over refluxing methanol at 5 mTorr gave 43 mg: mp 240−242 °C; IR (Nujol) 3160(m), 1660(s) cm^{-1}; *m*/*z* 334 $(M + H)^+$. Anal. ($C_{20}H_{15}NO_2S$) C,H,N.

5-Fluoro-2-thiophenylaniline (50). A solution of 1.60 g (6.4 mmol) of 5-fluoro-2-thiophenylnitrobenzene[45] in 50 mL of ethanol was treated with 7.22 g (32.0 mmol) of stannous chloride dihydrate[43] and heated to reflux. TLC analysis (40% toluene−petroleum ether) after 15 min indicated a single major component with R_f 0.33 and the absence of the nitrobenzene (R_f 0.48). The solvent was removed in vacuo and the residue was triturated with ice. Sodium hydroxide solution (15%) was added in portions until a pH >7, followed by the addition of water and ethyl acetate. The resulting slurry was filtered through Celite and the ethyl acetate extract was washed with saline and dried ($MgSO_4$). Concentration in vacuo gave 1.23 g of an amber oil. TLC analysis (ibid) indicated, in addition to a major component at R_f 0.34, two minor impurities with R_fs 0.18 and 0.09. Kugelrohr distillation removed the former as forerun, the latter as residue, and gave 1.03 g of a pale yellow oil, bp 100−105 °C (air bath temperature) at 10 mTorr, which solidified on standing: mp 49−50 °C; *m*/*z* 220 $(M + H)^+$. Anal. ($C_{12}H_{10}FNS$) C,H,N.

8-Fluoro-10,11-dihydrodibenzo[*b,f*][1,4]thiazepin-11-one (51). A solution of 4.68 g (21.34 mmol) of 5-fluoro-2-thiophenylaniline (**50**) in 50 mL of dioxane was treated dropwise with 2.11 g (10.67 mmol) of trichloromethyl chloroformate. The temperature was raised to 60 °C (oil bath) and held for 2 h. TLC analysis (20% ether−hexane) showed a major component with R_f 0.84, the absence of starting aniline (R_f 0.48) and a very minor impurity with a lower R_f. Dioxane was removed in vacuo and the residue was Kugelrohr distilled to yield 3.93 g of 5-fluoro-2-(thiophenyl)phenyl isocyanate as a yellow oil: bp (air bath temperature) 88−101 °C at 20 mTorr; IR (film) 2260(s), 2210(s,sh) cm^{-1}. This material was used without further purification.

To a solution of 2.13 g (16.0 mmol) of aluminum chloride in 16 mL of *o*-dichlorobenzene at 100 °C was added a solution of 3.92 g of the crude 5-fluoro-2-(thiophenyl)phenyl isocyanate in 16 mL of the same solvent. The temperature was raised to 150 °C, held for 3.5 h and the solvent was removed using a Kugelrohr at 20 mmHg. The residue was treated with ice and triturated: 4.14 g of a tan solid; IR (Nujol) 3150(m), 1660(s), 1645(s) cm^{-1}. The analytical specimen was obtained by dissolving 726 mg in 60 mL of hot ethanol and concentration to

18 mL where a solid spontaneously formed. The resulting solid was dried in a drying pistol over refluxing methanol at 5 mTorr: 0.57 g; mp 241−242.5 °C; homogeneous by TLC (ether: hexane, 1:1) R_f 0.31; *m*/*z* 246 $(M + H)^+$. Anal. ($C_{13}H_8FNOS$) C,H,N.

5-Benzyloxy-2-(2′-carbomethoxy)thiophenylnitrobenzene (52). To a solution of 1.59 g (39.7 mmol) of NaOH in 30 mL of methanol was added 2.83 g (18.3 mmol) of thiosalicylic acid and after stirring for 15 min the solvent was removed in vacuo to give a nice solid. To this flask was added 4.83 g (18.3 mmol) of 5-benzyloxy-2-chloronitrobenzene,[46] followed by 30 mL of dry DMAC, and the solution was heated in an oil bath at 75 °C under nitrogen for 15 h. TLC analysis (CH_2Cl_2) showed only a minute amount of the starting nitrobenzene. The cooled solution was diluted with 20 mL of DMAC, 4.0 mL (64.2 mmol) of iodomethane was added, and the stoppered flask was stirred over the weekend (46 h). The content of the flask was then transferred to a single-necked flask with DMAC and the solvent was removed by Kugelrohr (80−100 °C at 20 mmHg). The residue was partioned between water and ethyl acetate which was washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo left a 7.23 g of a solid. This material was purified by chromatography eluting with methylene chloride to give 5.77 g (80.2% yield) which was homogeneous by TLC (CH_2Cl_2), R_f 0.68, and appeared to be light-sensitive: ^{1}H NMR (300 MHz, $CDCl_3$) 3.86 (s, 3H, CH_3), 5.11 (s, 2H, CH_2); *m*/*z* 396 $(M + H)^+$.

5-Benzyloxy-2-(2′-carbomethoxy)thiophenylaniline (53). To 5.00 g (12.6 mmol) of **52** suspended in 50 mL ethanol was added 14.26 g (63 mmol) of stannous chloride dihydrate[43] and solution was effected by heating to 90 °C (oil bath). After 55 min TLC analysis (40% ether−petroleum ether) indicated the absence of the nitrobenzene (R_f 0.50) and a major component with R_f 0.42. Ethanol was removed in vacuo. The residue was treated with ice, then water and portionwise with sodium bicarbonate until alkaline. Dilution with ethyl acetate resulted in a miky emulsion which was filtered through Celite. The ethyl acetate extract was washed with water, brine and dried ($MgSO_4$). Concentration in vacuo gave a brown oil, 4.60 g, homogeneous by TLC (CH_2Cl_2), R_f 0.40, which slowly solidified. The analytical specimen was obtained by drying 70 mg in a drying pistol over refluxing methanol at 5 mTorr: mp 94−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.95 (s, 3H, CH_3), 5.06 (s, 2H, CH_2); *m*/*z* 366 $(M + H)^+$. Anal. ($C_{21}H_{19}NO_3S$) C,H,N.

8-Benzyloxy-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepin-11-one (54). A dry three-necked flask equipped with a magnetic stirring bar and condenser with a nitrogen inlet was charged with 4.28 g (12.0 mmol) of **53**, 50 mL of dry methylene chloride and was cooled in an ice−salt bath to −10 °C. By syringe, 6.60 mL (13.2 mmol) of a 2 M solution of trimethylaluminum[44] in hexane was added. After 10 min the ice bath was removed and the solution was stirred at ambient temperature over the weekend. An aliquot was added to 1 N HCl and extracted with ethyl acetate. TLC analysis (CH_2Cl_2) indicated a major component with R_f 0.10 and some unreacted **53** with R_f 0.38. The solution was again cooled in an ice bath, 6 mL of 2 M trimethylaluminum in hexane was added and the solution was stirred at ambient temperature overnight. TLC analysis now indicated complete reaction. Cautiously, water was added dropwise (gasing), followed by 50 mL of 1 N HCl. The contents of the flask was then extracted with 500 mL of chloroform which was washed with brine and dried ($MgSO_4$). Concentration in vacuo gave a tan solid, 3.75 g. This was dissolved in 450 mL of hot ethanol, concentrated to 50 mL and left at ambient temperature. The resulting solid was collected by filtration and dried: 2.96 g; mp 206−208 °C; TLC (2.5% CH_3OH−CH_2Cl_2) R_f 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) 5.03 (s, 2H, CH_2), 8.84 (s, 1H, N*H*); *m*/*z* 334 $(M + H)^+$. Anal. ($C_{20}H_{15}NO_2S$) C,H,N.

***N*-(*tert*-Butoxycarbonyl)-3-fluoro-2-thiophenylaniline (55).** A dry three-necked flask equipped with a thermometer and nitrogen inlet was charged with 1.00 g (4.73 mmol) of *N*-(*tert*-butoxycarbonyl)-3-fluoroaniline[47] and 42 mL of THF and cooled to −76 °C. By means of a syringe, 4.63 mL (10.41 mmol) of 2.25 M *tert*-butyllithium in hexane was added dropwise. *S*-Phenyl benzenethiosulfonate, 1.43 g (5.68 mmol), was added in one portion. The solution was stirred overnight, allowing the bath temperature to rise spontaneously. After quenching with water, the THF was removed in vacuo and the aqueous residue was extracted with ether which was washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 1.53 g of an oil which slowly solidified. This material was column chromatographed, eluting with 5% ether−hexane: 0.84 g (56% yield) of an oil; homogeneous by TLC (20% ether−hexane), R_f 0.45; *m*/*z* 319; ^{1}H NMR (250 MHz, $CDCl_3$) 1.48 (s, 9H), 6.80−6.86 (t, 1H), 7.09−7.27 (m, 5H), 7.38−7.40 (q, 1H), 7.80 (s, 1H), 8.07−8.11 (d, 1H).

3-Fluoro-2-thiophenylaniline (56). 55, 0.83 g (2.60 mmol), in 3 mL of trifluoroacetic acid was stirred at ambient temperature for 30 min. The solvent was removed in vacuo. The residue was made alkaline with 10% sodium hydroxide, extracted with ether and dried ($MgSO_4$). Concentration in vacuo gave 0.54 g of a yellow oil which by TLC (30% ether−hexane) was essentially a single component, R_f 0.50: IR (film) 3450(m), 3368(m) cm^{-1}. This material was used without further purification.

3-Fluoro-2-(thiophenyl)phenyl Isocyanate (57). A solution of 0.53 g (2.42 mmol) of **56** in 5 mL of dioxane was treated dropwise with 0.24 g (1.21 mmol) of trichloromethyl chloroformate. The temperature was raised to 60 °C (oil bath) and held for 6 h. Dioxane was removed in vacuo and the residue was Kugelrohr distilled: 0.44 g of a colorless oil; bp (air bath temperature) 98−105 °C at 20 mTorr; IR (film) 2240(s,sh), 2210(s) cm^{-1}; TLC analysis (15% ether−hexane) showed a major component with R_f 0.70 and a very minor impurity with R_f 0.30. This material was used without further purification.

6-Fluoro-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepin-11-one (58). To a solution of 0.23 g (1.75 mmol) of aluminum chloride in 4 mL of *o*-dichlorobenzene at 100 °C was added a solution of 0.43 g (1.75 mmol) of **57** in 2 mL of the same solvent. The temperature was raised to 150 °C, held for 7 h and the solvent was removed using a Kugelrohr at 20 mmHg. The residue was treated with ice and triturated: 0.31 g of a light brown solid; IR (Nujol) 3165(w), 1660(s), 1650(s) cm^{-1}. This material was used without further purification.

1-(2,3-Dimethoxypropyl)piperazine (59). A mixture of 128.6 g (0.73 mol) of phenylmethylpiperazine, 100 g (0.80 mol) of 1-chloro-2-hydroxy-3-methoxypropane, 100.9 g (0.73 mol) of potassium bicarbonate and 1200 mL of toluene was stirred at reflux for 114 h and the hot solution was filtered. The salts were dissolved in water, extracted with toluene and ethyl ether, the organics dried ($MgSO_4$), filtered and added to the original toluene solution. The solvent was removed and the residue was distilled through a 4-in. Vigreaux column to yield 186.0 g (96%) of 1-(2-hydroxy-3-methoxypropyl)-4-phenylmethylpiperazine, bp 160−169 °C/0.2 mmHg, which was used in the next step without further purification.

To a stirred slurry of 33.6 g (0.7 mol) of 50% sodium hydride dispersion in mineral oil and 500 mL of dry toluene under nitrogen was added a solution of 186.0 g (0.70 mol) of 1-(2-hydroxy-3-methoxypropyl)-4-phenylmethylpiperazine in 500 mL of toluene over 45 min. The reaction was stirred at reflux for 1 h then cooled in an ice bath to 10 °C and 195 g (0.7 mol) of methyl iodide in 150 mL of toluene was added dropwise over 50 min. After stirring under nitrogen at room temperature overnight the mixture was treated with 250 mL of water and stirred until all the solid had dissolved. The layers were separated, the aqueous phase extracted twice with ethyl ether, the organics combined, dried ($MgSO_4$), filtered and the solvent removed in vacuo. The oil was decanted from a small amount of mineral oil and distilled through a 4-in. Vigreaux column to yield 43.1 g (22%) of 1-(2,3-dimethoxypropyl)-4-phenylmethylpiperazine, bp 154−7 °C/0.25 mmHg, which was used in the next step without further purification.

A mixture of 43.0 g (0.154 mol) of 1-(2,3-dimethoxypropyl)-4-phenylmethylpiperazine, 4.5 g of 10% Pd−C and 200 mL of absolute ethanol was hydrogenated in a Parr apparatus at 50 °C and 50 psi for 1.5 h with theoretical uptake of hydrogen.

The catalyst was filtered through a Celite pad, the solvent removed in vacuo and the residual oil distilled through a 4-in. Vigreaux column: 23.6 g; bp 83−94 °C/0.3 mmHg. Redistillation at 77−81 °C/0.4 mmHg returned 20.94 g (72%) of 1-(2,3-dimethoxypropyl)piperazine. Anal. ($C_9H_{20}N_2O_2$) C,N,H: calcd, 10.71; found, 9.92.

***S*-(+)-2,2-Dimethyl-4-[1-(4-ethoxycarbonylpiperazinyl)]methyl-1,3-dioxolane (60).** A mixture of 14.24 g (0.090 mol) of 1-ethoxycarbonylpiperazine, 25.00 g (0.0873 mol) of d-α,β-isopropylideneglycerol γ-tosylate, 12.06 g (0.0873 mol) of potassium carbonate and 100 mL of toluene was stirred at reflux for 54 h. The reaction was cooled, filtered and the saltcake was washed well with toluene. The toluene was removed under aspirator pressure and the residue distilled through a 4-in. Vigreaux column: 18.07 g (79%); bp 125−131 °C/0.05 mmHg. Redistillation gave 17.12 g (72%) of analytically pure material: bp 111−112 °C/0.1 mmHg; $[\alpha]^{25}_D$ +5.7° (*c* 3.9, methanol). Anal. ($C_{13}H_{24}N_2O_4$) C,H,N.

***S*-(−)-1-(2,3-Dimethoxypropyl)-4-ethoxycarbonylpiperazine (61).** A solution of 18.35 g (0.0674 mol) of **60** and 150 mL of absolute ethanol was treated with 100 mL of saturated etheral HCl, the mixture refluxed for 3 h and stirred at room temperature overnight. Since the cleavage was not complete ether was added and the mixed hydrochloride salts filtered off, dissolved in a small amount of methanol and treated with saturated etheral HCl to near the cloud point. The solution was stirred for 1 h, the solvent removed in vacuo and the residue was recrystallized from acetonitrile to yield 16.80 g (93%) of *S*-(−)-1-(2,3-dihydroxypropyl)-4-ethoxycarbonylpiperazine hydrochloride: mp 102−104 °C; $[\alpha]_D^{26}$ −24.9° (*c* 2.9, methanol).

A solution of 15.05 g (0.056 mol) of *S*-(−)-1-(2,3-dihydroxypropyl)-4-ethoxycarbonylpiperazine and 23.58 g (0.168 mol) of methyl iodide in 65 mL of DMF was added dropwise under nitrogen to a stirred slurry of 8.88 g (0.185 mol) of 50% sodium hydride dispersion in mineral oil and 125 mL of THF, controlling the temperature at 50−60 °C by means of a water bath. The reaction mixture was stirred at 50−55 °C for 20 min, treated with several volumes of ether, stirred for 15 min and filtered. The saltcake was washed well with ether, the solvent removed in vacuo and the resulting oil was distilled through a 4-in. Vigreaux column: 11.60 g (80%); bp 125−134 °C/0.2 mmHg. Redistillation returned 9.58 g (66%): bp 115−22 °C/0.2 mmHg; >99.5% optical purity by NMR; $[\alpha]_D^{26}$ +2.2° (*c* 5.08, methanol). Anal. ($C_{12}H_{24}N_2O_4$) C,H,N.

4-(4-Ethoxycarbonylpiperazinylethyl)-2,2-dimethyl-(1,3)-dioxolane (62). To a stirred mixture of 80.0 g (0.35 mol) of 4-methylsulfonylmethyl-2,2-dimethyl-(1,3)-dioxolane,[48] 48.4 g (0.35 mol) of potassium carbonate and 400 mL of dry toluene, under nitrogen, was added dropwise 55.53 g (0.35 mol) 4-ethoxycarbonylpiperazine at ambient temperature. The mixture was refluxed for 17 h, cooled, filtered and the salt cake washed with three 150-mL portions of toluene. The solvent was removed and the brown oil distilled through a 4-in. Vigreaux column: 91.1 g of colorless product; bp 175−190 °C/0.1 mmHg. Redistillation through the same column returned 76.4 g (77%) of the titled compound: bp 130−140 °C/0.25 mmHg. Anal. ($C_{14}H_{26}N_2O_4$) H,C: calcd, 58.72; found, 57.81; N: calcd, 9.78; found, 9.35.

1-(3,4-Dimethoxybutyl)-4-ethoxycarbonylpiperazine (63). A solution of 76.43 g (0.27 mol) of **62** in 500 mL of methanol was treated with a 50-mL portion of saturated ethereal HCl. The mixture was heated at reflux for 1.5 h and the solvent removed in vacuo to yield a brown oil. The oil was dissolved in 100 mL of water and basified with 10% NaOH. Extraction with six 200-mL portions of methylene chloride and drying over $MgSO_4$ yielded a gold-colored oil which was chromatographed on silica gel (5% methanol in toluene) to yield 30.55 g (46%) of 1-(3,4-dihydroxybutyl)-4-ethoxycarbonylpiperazine which was used without further purification.

A solution of 14.00 g (0.057 mol) of 1-(3,4-dihydroxybutyl)-4-ethoxycarbonylpiperazine in 14 mL of dry THF was cautiously added dropwise, under a nitrogen atmosphere, to a stirred mixture of 6.00 g (0.125 mol) of 50% NaH/mineral oil, 75 mL of dry THF and 8.84 mL (0.14 mol) of iodomethane. The mixture was stirred at 40 °C for 20 min, cooled and cautiously treated dropwise with water until gas evolution subsided and all solids were in solution. The mixture was extracted with three 200-mL portions of ethyl ether, the combined extracts were washed with saturated saline, dried ($MgSO_4$), filtered and the solvent removed in vacuo to yield 12.28 g (79%) of a golden oil which was used without further purification. An analytical specimen was prepared as the oxalate salt in ethyl ether. Anal. ($C_{13}H_{26}N_2O_4 \cdot C_2H_2O_4$) C,H,N.

1-(3,4-Dimethoxybutyl)piperazine (64). To a solution of 12.28 g (0.045 mol) of **63** in 68 mL of *n*-butanol was added 12.2 g (0.22 mol) of KOH pellets and the mixture stirred at reflux overnight. The cooled reaction was filtered, the salts washed with ethyl ether and the solvent removed from the filtrate to yield an oil. Distillation through a 4-in. Vigreaux column yielded 5.50 g (64%) of as a colorless oil: bp 68−70 °C/0.15 mmHg. An analytical specimen was prepared as the hydrochloride salt in ethereal HCl. Anal. ($C_{10}H_{22}N_2O_2 \cdot 2HCl$) C,H,N.

1-Phenylmethyl-4-(2-methoxy-3-phenylmethoxypropyl)piperazine (65). A mixture of 74.88 g (0.424 mol) of phenylmethylpiperazine, 85.25 g (0.424 mol) of 1-chloro-2-hydroxy-3-phenylmethoxypropane,[49] 58.6 g (4.24 mol) of potassium carbonate and 700 mL of toluene was stirred at reflux for 40 h. After filtration the toluene was removed in vacuo and the residue was Kugelrohr distilled to yield crude 1-phenylmethyl-4-(2-hydroxy-3-phenylmethoxypropyl)piperazine: 129.3 g (90%); bp 225−230 °C/0.1 mmHg. This material was used without further purification

The above material in 300 mL of toluene was added over 25 min to a slurry of 17.6 g (0.366 mol) of 50% sodium hydride in mineral oil and 300 mL of toluene. The mixture heated slowly to reflux (vigorous evolution of hydrogen occurred at 70 °C) and held there for 90 min. The solution was cooled to 5 °C, a solution of 45 mL (0.366 mol) of methyl iodide in 75 mL of toluene was added dropwise and the mixture stirred at room temperature overnight. After the cautious addition of 300 mL of water and stirring for several hours the aqueous layer was separated and extracted twice with ethyl ether. The combined organic extract was dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude material was chromatographed on silica gel (ether:hexane, 1:1): 18.35 g (12%), as a yellow oil. Anal. ($C_{22}H_{30}N_2O_2$) H,N,C: calcd, 74.54; found, 74.04.

1-(2-Methoxy-3-hydroxypropyl)piperazine (66). A mixture of 16.9 g (0.48 mol) of **65**, 2 g of 10% Pd−C and 250 mL of ethanol was hydrogenated at 50 °C and 50 psi overnight. The catalyst was filtered off and the solvent was removed in vacuo. The residue distilled through a 4-in. Vigreaux column: 6.37 g (77%); bp 95−98 °C/0.2 mmHg. Anal. ($C_8H_{18}N_2O_2$) C,N,H: calcd, 10.41; found, 9.80.

***cis*-2-Piperazinylmethyl-6-hydroxymethyl-1,4-dioxane (67).** A mixture of 67.4 g (0.382 mol) of phenylmethylpiperazine, 80.7 g (0.382 mol) of 2-hydroxymethyl-6-bromomethyl-1,4-dioxane,[50] and 52.8 g of potassium carbonate in 700 mL of toluene was stirred at reflux overnight. The salts were filtered off, dissolved in water, the solution extracted with toluene and the extracts combined with the toluene filtrate. The toluene was removed in vacuo and the residual oil was Kugelrohr distilled to yield 100.0 g (85%) of 1-phenylmethyl-4-(6-hydroxymethyl-1,4-dioxan-2-ylmethyl)piperazine as a pale yellow viscous oil that was used without further purification.

A mixture of 99.5 g (0.325 mol) of 1-phenylmethyl-4-(6-hydroxymethyl-1,4-dioxan-2-ylmethyl)piperazine, 7.5 g of 10% Pd−C and 400 mL of absolute ethanol was hydrogenated in a Parr apparatus at 50 °C and 50 psi for 7 h. The catalyst was filtered through Celite and the solvent was removed in vacuo to yield an oil with solidified. This solid was recrystallized from a toluene−hexane−ethyl ether mixture to yield 48.9 g (70%) of a white solid, mp 103−110 °C. The recrystallization liquor was concentrated in vacuo and the residue was distilled through a 4-in. Vigreaux column: 16.3 g (23%) of a viscous yellow oil; bp 150−160 °C/0.2 Torr. ^{13}C NMR confirmed that the solid was essentially one isomer while the oil consisted of

the same isomer contaminated with 30−40% of the other isomer. Recrystallization of the solid twice from ethyl acetate returned a single isomer (^{13}C NMR and TLC 20% aqueous ammonia in methanol): mp 111−114 °C. The assignment of the 2,6-*cis*-configuration was made on the basis of COSY NMR (J_{H2H3} and $J_{H2H3'}$ = 10.0 and 11.3 Hz; J_{H6H5} and $J_{H6H5'}$ = 10.9 and 11.9 Hz) and on the existence of a NOE between H2 and H6. Anal. ($C_{10}H_{20}N_2O_3$) C,H,N.

1-Phenylmethyl-4-(dioxan-2-ylmethyl)piperazine (68). A mixture of 11.62 g (0.066 mol) of phenylmethylpiperazine, 15.03 g (0.066 mol) of 2-iodomethyl-1,4-dioxane,[51] and 9.11 g (0.066 mol) of potassium carbonate in 200 mL of toluene was stirred at reflux overnight. The salts were filtered off, the toluene was removed in vacuo and the residual brown oil was chromatographed on silica gel (methanol−toluene 1:19) to yield 16.67 g (91%) of a white solid that was used without further purification. Recrystallization of a sample from toluene yielded an analytical sample: mp 66−68 °C. Anal. ($C_{16}H_{24}N_2O_2$) C,H,N.

2-Piperazinylmethyl-1,4-dioxane (69). A mixture of 13.45 g (0.049 mol) of **68**, 1 g of 10% Pd−C and 200 mL of absolute ethanol was hydrogenated in a Parr apparatus at 50 °C and 50 psi for 20 h. An additional 2 g of 10% Pd−C was added and the mixture hydrogenated under the same condition for an additional 10 h. The catalyst was removed by filteration through Celite and the solvent was removed in vacuo to yield a yellow oil. Kugelrohr distillation gave 6.59 g which solidified: mp 44−49 °C. Anal. ($C_9H_{18}N_2O_2$) H,N,C: calcd, 58.04; found, 57.26.

Antagonism of Apomorphine-Induced Climbing and Apomorphine-Induced Disruption of Swimming (apomorphine swimming "normalization" test). Female Swiss-Webster mice weighing approximately 20 g were deprived of food for approximately 24 h and then dosed intraperitoneally (ip), orally (po) or subcutaneously (sc) with various doses of vehicle or a compound to be tested over a range of doses (N = 20 mice/treatment group). Thirty minutes later they were administered apomorphine HC1 at 1.25 mg/kg sc and placed into climbing cages. These cages were 9 cm wide, 15 cm deep and 30 cm high. One wall had 27 horizontal rungs spaced 1 cm apart. Thirteen minutes after apomorphine each mouse was observed continuously for 1 min and the highest and lowest rung reached by its front paws was recorded. The mean of these two scores was used as the score for that mouse. (The highest and lowest potential scores were 27 and 0, respectively.)

Immediately after the 1-min climbing observation period each mouse was placed into a circular swimming tank for 2 min and the number of "swims" was counted. The height of the tank was 15 cm and the diameter was 28 cm. A circular obstacle, 10.5 cm in diameter and 17 cm high, was placed in the center of the tank creating a circular swimming channel 8.75 cm wide. The water level was 5.5 cm and the water was kept at room temperature. Marks were placed on the floor and side of the tank 180° apart. A "swim" was scored each time a mouse swam from one mark to the other and the median number of swims for all the mice was used as the score for that treatment. The mice were observed through overhead mirrors, and the number of 180° swims was recorded for each mouse. The mice were observed at all times for side effects of the drugs being tested, such as salivation, tremor, stimulation, piloerection, etc.

Dykinesias in Haloperidol-Sensitized Cebus Monkeys. Adult female and male Cebus monkeys served as subjects. They were dosed with 1 mg/kg of haloperidol orally, once per week, until dyskinetic reactions occurred. These dyskinetic reactions consisted of any one or more of the following buccooral movements: repetitive tongue protrusions, repetitive biting or licking of the bars of the cage; and the following choreoathetoid-like movements: various twisting and/or jerking movements of the arms or legs; twisting of the torso or neck. When these reactions occurred reliably over a period of weeks the monkeys were considered to be "sensitized" and could be used to test for the occurrence of dyskinetic reactions to other drugs. The interval between drug treatments was at least 2 weeks. Drug were administered orally (2 mL/kg). After dosing, the monkey was immediately returned to its home cage. Two observers working in 1−3-h shifts then observed each monkey continuously for dyskinetic reactions for 6−7 h after drug administration. Every 30 min the observer recorded the type of reaction that had occurred and its severity (weak, weak-to-medium, medium, medium-to-strong, or strong), and for repetitive reactions such as tongue protrusions or licking or biting the bars, the observer recorded the number of such movements in 1-min time samples. Many agents were administered over a range of doses.

Drug Treatments. All drugs were administered using the vehicle hydroxypropylmethylcellulose (0.5% w/w), Tween 80 (0.1% w/w) in distilled water.

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Supporting Information Available: Elemental analyses for compounds **2**, **4**−**38**, **42**, **46**−**51**, **53**, **54**, and **59**−**69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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