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Binding of 5*H*-Dibenzo[*a*,*d*]cycloheptene and Dibenz[*b*,*f*]oxepin Analogues of Clozapine to Dopamine and Serotonin Receptors[1]

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Series of 5,11-dicarbo- and 11-carbo-5-oxy-10-(1-alkyl-1,2,3,6-tetrahydro-4-pyridinyl) analogues and a 11-carbo-5-oxy-10-(1-methyl-4-piperidinyl) analogue of the atypical antipsychotic agent clozapine were prepared and tested for binding to the dopamine D-2L and D-4 and serotonin S-2A and S-2C receptors. Some of these analogues were found to have dopamine D-2L and D-4 and serotonin S-2A and S-2C receptor binding activities as high as or higher than those of clozapine, indicating that neither the diazepine structure nor the piperazine ring present in clozapine is essential for high antidopamine activity and or for high dopamine D-4 selectivity (K_i for the dopamine D-2L receptor/K_i for the dopamine D-4 receptor). Increasing in the effective size of the alkyl substituent at the tertiary amine nitrogen atom in the 1,2,3,6-tetrahydro-4-pyridinyl moiety in the 5*H*-dibenzo[*a*,*d*]cycloheptene series reduces the affinity for the dopamine D-4 receptor, but in the dibenz[*b*,*f*]oxepin series, no significant change in binding affinity to the dopamine D-4 receptor was observed. Equal or slightly higher affinity for the serotonin S-2A and S-2C receptors was observed for the 10-(1-ethyl-1,2,3,6-tetrahydro-4-pyridinyl) analogues in both series, but for the 10-[1,2,3,6-tetrahydro-1-(2-propenyl)-4-pyridinyl] analogues, any favorable steric factor is overshadowed by an unfavorable electronic effect as a result of change in the basicity of the tertiary amino group in the pyridinyl moiety. Replacement of three of the four nitrogen atoms in clozapine with three carbon or two carbon atoms and an oxygen atom and removal of the chlorine atoms gives 10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)dibenzo[*a*,*d*]cycloheptene and 10-(1-methyl-4-piperidinyl)dibenz[*b*,*f*]oxepin, each having twice the binding activity to the dopamine D-4 receptor as does clozapine and a dopamine D-4 selectivity equal to that of clozapine.

Over the past quarter century, it has become clear that dopamine is implicated in the etiology of schizophrenia and that endogenous levels of this neurotransmitter at various neuronal pathways of the brain can explain some of the clinical symptoms of the disease. However, it is not clear how an effective therapeutic dose of antipsychotic agents can alleviate those symptoms. The mechanism of action of antipsychotic agents, and in particular that of the atypical antipsychotic agent clozapine [8-chloro-11-(4-methylpiperazino)-5*H*-dibenzo-[*b*,*e*][1,4]diazepine, **1**, Table 1] is presently unknown,[2,3] clozapine being termed atypical in that it relieves the symptoms of schizophrenia but does not induce catalepsy in rats or extrapyramidal side effects in man.

Recent discovery, isolation, and cloning of dopamine receptors have confirmed that there are two distinct families of dopamine receptor subtypes: the dopamine D-1 family (D-1 and D-5 receptors) and the dopamine D-2 family (D-2L, D-2S, D-3, and D-4 receptors).[4] Similar studies of the serotonin receptors have also resulted in their classification into families of serotonin receptor subtypes: the serotonin S-1 (5-HT_1) family (S-1A, S-1B, S-1D, S-1E, and S-1F receptors), the serotonin S-2 (5-HT_2) family (S-2A, S-2B, and S-2C receptors), the serotonin S-3 (5-HT_3) family (S-3 receptor), and the S-6 (5-HT_6) family (S-6 receptor).[5]

Receptor binding studies with clozapine and other potential atypical antipsychotic agents have shown that these agents, in addition to blocking the dopamine D-2L receptor to varying degrees, also block other dopamine and serotonin receptors in human brain[6] and exert potent antagonist effects on the adrenergic, cholinergic, and histaminergic receptors.[7] In particular, the atypical antipsychotic profile of clozapine has been suggested to emanate from its preferential blockade of the dopamine D-1[8] or dopamine D-4 receptors.[6] In the case of blockade of the latter receptor, this preference is shown in Table 1 as a dopamine D-4 selectivity (K_i for the dopamine D-2L receptor/K_i for the dopamine D-4 receptor) for clozapine (**1**) of 10. Other atypical antipsychotic agents show dopamine D-4 selectivities substantially greater than one while typical antipsychotic agents show dopamine D-4 selectivities less than one.[9]

The atypical antipsychotic action of clozapine has also been linked to its more potent antagonist effect on the serotonin S-2A and S-6 receptors than on the dopamine D-2L receptor.[10] The serotonin S-2A selectivity (K_i for the dopamine D-2L receptor/K_i for the serotonin S-2A receptor) of clozapine (**1**) is 28 (Table 1), and it is suggested to be indicative of its atypical antipsychotic profile.[10]

Recently, we have evaluated the receptor binding profile of a series of 5,11-dicarbo and 5-oxy-11-carbo analogues of clozapine, each analogue incorporating the 4-methylpiperazino group of clozapine. Our objective

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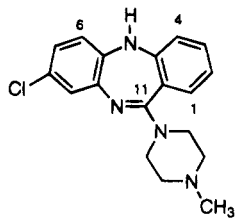
Table 1. Affinity and Clozapine and 5,11-Dicarbo Analogues of Clozapine for Dopamine and Serotonon Binding Sites



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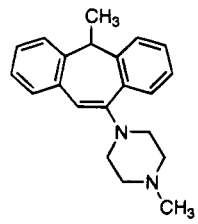

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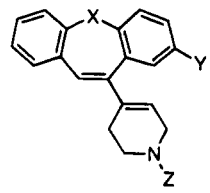
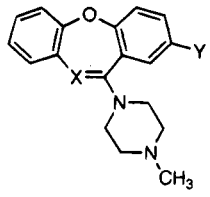


3

				inhibition constant, K_i, nM					
	substituents			dopamine			serotonin		
code	X	Y	Z	D-2L	D-4	D-2L/D-4[a]	S-2A	S-2C	D-2L/S-2A[b]
1[c]				220	21	10	8	8	28
2[c]				94	12	7.8	47	36	2.0
3a[c,d]	$CHCH_3$	H	CH_3	680	320	2.1	72	89	9.4
3b[c]	$C{=}C(CH_3)_2$	H	CH_3	570	270	2.1	1200	1500	0.48
3c[d]	CH_2	H	CH_3	89	12	7.4	6	14	15
3d	$C{=}C(CH_3)_2$	Cl	CH_3	440	100	4.4	760	1200	0.58
3e[d]	CH_2	H	CH_2CH_3	44	28	1.6	4.5	7.0	9.8
3f[d]	CH_2	H	$CH_2CH{=}CH_2$	83	60	1.4	20	46	4.2

[a] Dopamine D-4 selectivity. [b] Serotonin S-2A selectivity. [c] Testing data from ref 3. [d] Hydrochloride.

Table 2. Affinity of Oxepin Analogues of Clozapine for Dopamine and Serotonin Binding Sites



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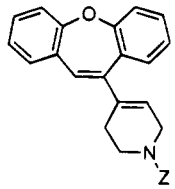

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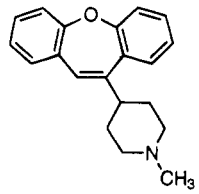


7

				inhibition constant, K_i, nM					
	substituents			dopamine			serotonin		
code	X	Y	Z	D-2L	D-4	D-2L/D-4[a]	S-2A	S-2C	D-2L/S-2A[b]
4a[c]	CH	H		21	2.0	11	4	6	5
4b[c,d]	N	Cl		21	4.9	4.3	*e*	*e*	
4c[c]	CH	Cl		2.5	0.54	4.6	3	3	0.8
5a			CH_3	230	29	7.9	6	20	38
5b[f]			CH_2CH_3	61	26	2.3	6.0	14	10
5c[f]			$CH_2CH{=}CH_2$	110	37	3.0	22	51	5.0
7[f]				82	9.5	8.6	3	8	30
19[g]				1.4	7.0	0.20	0.16		8.8

[a] Dopamine D-4 selectivity. [b] Serotonin S-2A selectivity. [c] Testing data from ref 3. [d] Loxapine. [e] Not reported. [f] Hydrochloride. [g] Risperidone. For structure, see text. Testing data from ref 11.

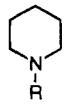
was the discovery of analogues of clozapine with lower propensity for side effects as the result of fewer heteroatoms than clozapine but with dopamine D-4 and serotonin S-2A selectivities similar to or greater than those of clozapine.[3] We have found that the 5,11-dicarbo analogue of clozapine, 5-methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**2**, Table 1), has 2-times the binding affinity for the dopamine D-2L and D-4 receptors as compared to clozapine and a dopamine D-4 selectivity of 8, essentially the same as that of clozapine. The binding affinities of **2** for the serotonin S-2A and S-2C receptors, however, were about 5 times less than those for clozapine and thus the serotonin S-2A selectivity for **2** is about 10 times less than that of clozapine.

For the corresponding 5-oxy-11-carbo analogue of **2**, 10-(4-methylpiperazino)-5*H*-dibenz[*b*,*f*]oxepin (**4a**, Table 2), the binding affinities for the D-2L and D-4 receptors were 10-times greater than those of clozapine (**1**). Thus **4a** binds more strongly to both the dopamine D-2L and D-4 receptors, but the dopamine D-4 selectivity of **4a** is the same as that of clozapine. Since the binding affinity of **4a** for both the serotonin S-2A and S-2C receptors is about the same as that of clozapine, the serotonin S-2A selectivity for **4a** is substantially lower than that of clozapine. It is to be noted that **4a** also has a somewhat higher binding affinity for the dopamine D-4 receptor than the typical antipsychotic agent loxapine (**4b**, Table 2) and thus a substantially higher dopamine D-4 selectivity.

Since the presence of the enamine moiety in 10-carbo analogues of clozapine such as **2** and **4a** leads to chemical instability,[3] we also investigated the binding to the dopamine D-2L and D-4 receptors and the serotonin S-2A and S-2C receptors of 5-methyl-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo-[*a*,*d*]cycloheptene (**3a**, Table 1) and 5-(2-isopropylidene)-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3b**, Table 1). For **3a** as

compared to **2**, the 1,2,3,6-tetrahydro-1-methyl-4-pyridinyl moiety decreases binding to the dopamine D-2L and D-4 and the serotonin S-2A and S-2C receptors and reduces its dopamine D-4 selectivity but increases its serotonin S-2A selectivity. For **3b**, binding to the dopaminergic receptors was about the same as that of **3a**, but binding to the serotonin S-2A and S-2C receptors was greatly reduced, indicating that binding to dopamine receptors without binding to serotonin receptors could possibly be achieved in clozapine analogues.

To achieve high dopamine D-4 selectivity without high serotonin S-2A selectivity, we have now prepared and tested (Tables 1 and 2) additional clozapine analogues each retaining the molecular topography of clozapine but with fewer heteroatoms than clozapine and each incorporating a 1,2,3,6-tetrahydro-1-methyl-4-pyridinyl moiety: 10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3c**), 2-chloro-5-(2-propylidene)-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3d**), and 10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)dibenz[*b*,*f*]oxepin (**5a**). On the basis of our previous results with **3a**,[3] we anticipated that the elimination of the C-5 methyl group (**3c**) and the presence of the 5-oxy group in **5a** would enhance binding to the dopamine and serotonin receptors. As also shown earlier,[3] the presence of a chlorine atom distal to the heterocyclic substituent in the 5,11-dicarbo series of clozapine analogues has an insignificant effect on binding to the dopamine D-2L and D-4 receptors; in the proximal position, however, affinities for both the dopamine D-2L and D-4 receptors are increased. Thus, we expected stronger binding to the dopamine D-2L and D-4 receptor without greatly increased binding to the serotonin S-2A and S-2C receptors for **3d** with its chlorine atom proximal to the 1-methyl-1,2,3,6-tetrahydro-4-pyridinyl moiety. Using *N*-methylpiperidine (**6a**), *N*-ethylpiperidine (**6b**), and *N*-(2-propenyl)piperidine (**6c**), with pK_a's of 9.94, 10.45, and 9.64,[12] respectively,



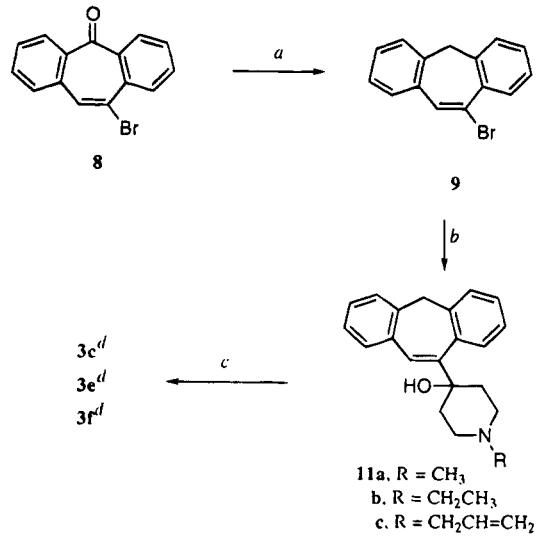
6a, R = CH_3
b, R = CH_2CH_3
c, R = $CH_2CH{=}CH_2$

as model compounds, we also prepared and tested the *N*-ethyl and *N*-(2-propenyl) analogues of **3c** and **5a** to investigate the effect of changes in the basicity of the tertiary amino group on receptor binding. In anticipation of higher dopamine D-2L and D-4 and serotonin S-2A and S-2C binding activity with greater dopamine D-4 and serotonin S-2A selectivities, we have also prepared a clozapine analogue with a completely reduced substituent at C-10, 10-(1-methyl-4-piperidinyl)-dibenz[*b*,*f*]oxepin (**7**, Table 2), a more similar structure to that of clozapine.

Results

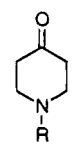
Synthesis. As shown in Scheme 1, the preparation of the 10-(1-alkyl-1,2,3,6-tetrahydro-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptenes **3c**, **3e**, and **3f** began with 10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one[13] (**8**). Reduction of **8** with lithium aluminum hydride–aluminum

Scheme 1

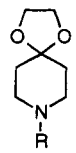


[a] –[c]Reagent (isolated yield): *a*, lithium aluminum hydride–aluminum chloride in ether–tetrahydrofuran (98%); *b*, *n*-butyllithium in hexane-ether and then 1-methyl-4-piperidone (**10a**) (62%), 1-ethyl-4-piperidone (**10b**) (67%) or 1-(2-propenyl)-4-piperidone (**10c**) (27%); *c*, concentrated hydrochloric acid in ethanol (56–73%).

chloride in ether–tetrahydrofuran[14] gave 10-bromo-5*H*-dibenzo[*a*,*d*]cycloheptene (**9**). Condensation of the lithium derivative of **9** with 1-methyl-4-piperidone (**10a**) gave 10-(4-hydroxy-1-methyl-4-piperidinyl)-5*H*-dibenzo[*a*,*d*]-cycloheptene (**11a**). In similar reactions, condensation of the lithium derivative of **9** with 1-ethyl-4-piperidone (**10b**) and 1-(2-propenyl)-4-piperidone (**10c**) gave 10-(1-ethyl-4-hydroxy-4-piperidinyl)- and 10-[4-hydroxy-1-(2-propenyl)-4-piperidinyl]-5*H*-dibenzo[*a*,*d*]cycloheptene (**11b** and **11c**). 1-(2-Propenyl)-4-piperidone (**10c**) was obtained by condensation of 3-bromopropene with 1,4-dioxa-8-azaspiro[4.5]decane[15] (**12a**) and subsequent hydrolysis of the resulting 8-(2-propenyl)-1,4-dioxa-8-azaspiro[4.5]decane (**12b**).[15]



10a, R = CH_3
b, R = CH_2CH_3
c, R = $CH_2CH{=}CH_2$

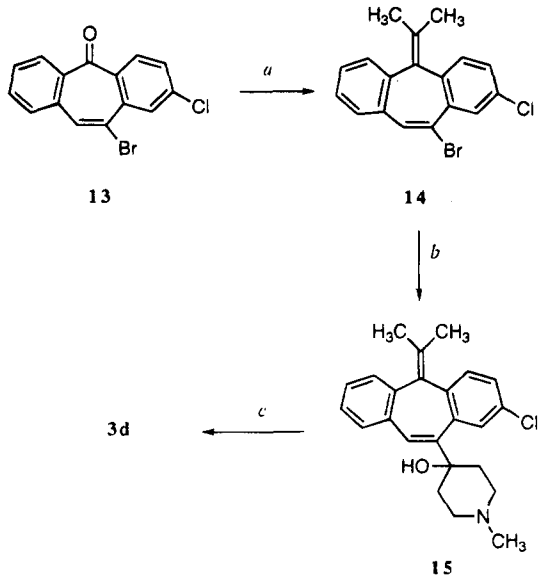


12a, R = H
b, R = $CH_2CH{=}CH_2$

Dehydration of **11a–11c** with hydrochloric acid in ethanol gave the 10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-, 10-(1-ethyl-1,2,3,6-tetrahydro-4-pyridinyl)-, and 10-[1,2,3,6-tetrahydro-1-(2-propenyl)-4-pyridinyl]-5*H*-dibenzo[*a*,*d*]cycloheptene (**3c**, **3e** and, **3f**), each isolated as its hydrochloride.

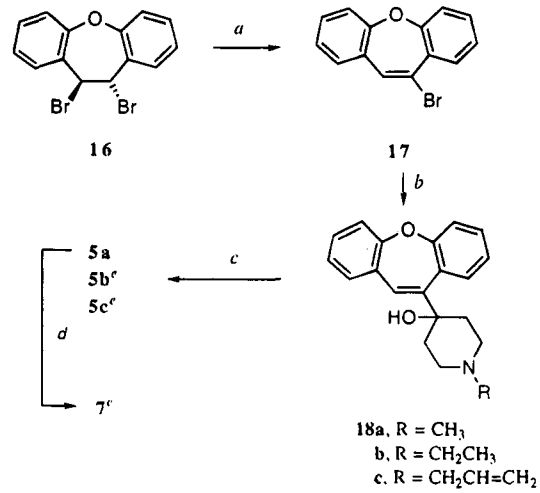
As outlined in Scheme 2, the key intermediate for the formation of 2-chloro-5-(2-propylidene)-11-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3d**) is 11-bromo-2-chloro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one[16] (**13**). The latter was prepared by way of a seven-step synthesis, the initial reaction being the condensation of phthalic anhydride with (*m*-chlorophenyl)acetic acid.[17] A Wittig reaction of **13** with the ylide prepared from isopropyltriphenylphosphonium iodide and *n*-butyllithium gave 11-bromo-2-chloro-5-(2-propylidene)-5*H*-dibenzo[*a*,*d*]cycloheptene (**14**).[18] Con-

Scheme 2



[a]-[c] Reagent (isolated yield): *a*, isopropyltriphenylphosphonium iodide and *n*-butyllithium in hexane–ether (68%); *b*, *n*-butyllithium in hexane–ether and then 1-methyl-4-piperidone (**10a**) (85%); *c*, concentrated hydrochloric acid in ethanol (73%).

Scheme 3



[a]-[d] Reagent (isolated yield): *a*, potassium tert-butoxide in tert-butyl alcohol (92%); *b*, *n*-butyllithium in hexane-ether and then 1-methyl-4-piperidone (**10a**) (79%), 1-ethyl-4-piperidone (**10b**) (70%), or 1-(2-propenyl)-4-piperidone (**10c**) (36%); *c*, concentrated hydrochloric acid in ethanol (41-66%); *d*, hydrogen over platinum in 95% ethanol (10%). [e] Isolated as the hydrochloride.

densation of 1-methyl-4-piperidone (**10a**) with the lithium derivative of **14** formed 2-chloro-11-(4-hydroxy-1-methyl-4-piperidinyl)-5-(2-propylidene)-5*H*-dibenzo[*a*,*d*]cycloheptene (**15**) which on dehydration with hydrochloric acid gave **3d.**

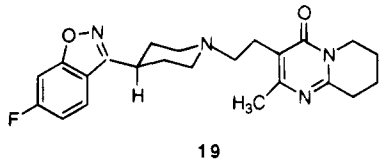
Scheme 3 shows the preparation of the dibenz[*b*,*f*]oxepins **5a**–**5c**, the important intermediate being 10-bromodibenz[*b*,*f*]oxepin[19] (**17**), prepared by dehydrobromination of *trans*-10,11-dibromo-10,11-dihydrodibenz[*b*,*f*]oxepin (**16**). The dibromide **16** was formed by bromination of dibenz[*b*,*f*]oxepin.[19] This latter intermediate is available by a reduction and rearrangement from 9*H*-xanthene-9-carboxylic acid.[20] Reaction of the lithium derivative of **17** with 1-methyl-, 1-ethyl-, and 1-(2-propenyl)-4-piperidone (**10a**–**10c**) gave, respectively, 10-[4-hydroxy-1-methyl-, 10-[1-ethyl-4-hydroxy-, and 10-[4-hydroxy-1-(2-propenyl)-4-piperidinyl]-dibenz[*b*,*f*]oxepin (**18a-18c**). Dehydration with hydrochloric acid in ethanol formed 10-[1-methyl-, 1-ethyl, and 1-(2-propenyl)-1,2,3,6-tetrahydro-4-pyridinyl]dibenz[*b*,*f*]oxepin (**5a**–**5c**). Reduction of **5a** with hydrogen in 95% ethanol over platinum gave 10-(1-methyl-4-piperidinyl)dibenz[*b*,*f*]oxepin (**7**).

Receptor Binding Studies. Affinities for dopamine D-2L and D-4 receptors are given in Tables 1 and 2 and were determined by inhibition of [^{3}H]spiperone ([^{3}H]-spiroperidol) binding in the presence of sodium chloride to membranes prepared from COS-7 cells transfected with a gene expressing the human dopamine D-2L and D-4 receptors, respectively, as previously reported.[9] Each inhibition constant[21] (K_i) was an average from two experiments, and the individual values from each of these experiments were consistently within 10% of each other.

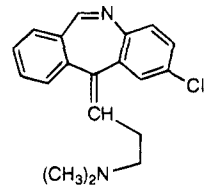
Affinities for the serotonin S-2A (5-HT$_{2A}$) and S-2C (5-HT$_{2C}$) receptors are also given in Tables 1 and 2 and were determined as previously reported[3] by inhibition of iodine-125-labeled lysergic acid diethylamide ([^{125}I]-LSD) binding to membranes prepared from NIH 3T3 cell line membranes containing the cloned rat serotonin S-2A receptor designated GF-6[22] and the cloned rat serotonin 2C receptor designated P$_o$,[22] respectively. The inhibition constants[21] (K_i) given in Tables 1 and 2 are mean values, rounded to no more that two significant figures, usually of three separate experiments, each done in triplicate. The standard errors of the mean are given in Table 1S in the supplementary material.

The data in Tables 1 and 2 indicate that a change in the effective size or nature of the substituent at C-5 in an analogue of clozapine can substantially effect the affinities for both the dopamine and serotonin receptors. The binding of 10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3c**) and 10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl]dibenz[*b*,*f*]oxepin (**5a**) to these receptors is substantially increased, as compared to 5-methyl-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3a**) and 5-(2-propylidene)-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3b**) analogues. The presence of a chlorine atom at C-2 in 2-chloro-5-(2-propylidene)-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3d**) increases binding, as compared to its dechloro analogue **3b**, to the dopamine D-2L and D-4 receptors and doubles the dopamine D-4 selectivity.

Of greater importance, however, are the observations that both the 5,11-dicarbo- and the 11-carbo-5-oxy-10-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl) analogues of clozapine, **3c** and **5a**, have virtually the same dopamine D-2L and D-4 and serotonin S-2A and S-2C receptor binding profiles and dopamine D-4 and serotonin S-2A binding selectivities as those of clozapine. Also the 11-carbo-5-oxy-10-(1-methyl-4-piperidinyl) analogue **7** has twice the binding affinity for the dopamine D-4 receptor as clozapine and a dopamine D-4 selectivity nearly as high as that of clozapine. Further, the serotonin selectivities of **3c**, **5a**, and **7** are substantially greater than that of the novel antipsychotic agent risperidone[11] (**19**, Table 2) currently in clinical trials, and the serotonin S-2A binding activities for these clozapine analogues are close to that of the atypical antipsychotic agent RMI-81,582 (**20**)[23] (K_i 2.5 nM[24]).



19



20

An increase in the effective size of the alkyl substituent at the tertiary nitrogen atom in the 1,2,3,6-tetrahydro-4-pyridinyl moiety at C-10 in the 5*H*-dibenzo[*a,d*]-cycloheptene series (**3c**, **3e**, and **3f**) reduced the affinity for the dopamine D-4 receptor, but in the dibenz[*b,f*]-oxepin series (**5a**–**c**), no significant change in binding to the dopamine D-4 receptor was observed. Equal or slightly higher binding to the serotonin S-2A and S-2C receptors was observed for the ethyl analogues (**3e** and **5b**) in both series, but for the 2-propenyl analogues, we speculate that any favorable steric effect was overshadowed by an unfavorable electronic effect as a result of a change in the basicity of the tertiary amino group in the pyridinyl group.[12]

Conclusions

Some of the compounds in the present series of 5,11-dicarbo and 11-carbo-5-oxy analogues of clozapine have receptor binding profiles similar to that of the atypical antipsychotic agent clozapine. In particular, the dibenzo[*a,d*]cycloheptene derivatives **2** and **3c** and the dibenz-[*b,f*]oxepin derivatives **5a** and **7** have affinities for the dopamine D-2L and D-4 receptors as high as or higher than those of clozapine and, for some, affinities for the serotonin S-2A and S-2C receptors also as high as or higher than those of clozapine. This indicates that neither the diazepine structure nor the piperazino group is essential for either high dopamine and serotonin receptor binding activity or dopamine D-4 and serotonin S-2A selectivities equal to those of clozapine. 10-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo-[*a,d*]cycloheptene (**3c**) and 10-(1-methyl-4-piperidinyl)-dibenz[*b,f*]oxepin (**7**) are the 5,11-dicarbo and 11-carbo-5-oxy analogues with the highest dopamine D-4 receptor activity, each being twice as active as clozapine in blocking the dopamine D-4 receptor. Since **3c** and **7** have only about one-twentieth the dopamine D-4 binding activity of 2-chloro-11-(4-methylpiperazino)dibenz-[*b,f*]oxepin (RMI 61140, **4c**), also evaluated for antipsychotic activity and extrapyramidal side effects in rats,[25] work is now in progress to increase the affinity for the dopamine D-4 receptor by preparation of the 1,2,3,6-tetrahydro-1-methyl-4-pyridinyl- and 1-methyl-4-piperidinyl-5,11-dicarbo and -11-carbo-5-oxo analogues of clozapine, each with a halogen atom proximal to the substituent group at C-10.

Experimental Section

Solvent evaporations were done at reduced pressure using a water pump. Melting points were taken in open capillary tubes and are corrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a JEOL FX-90Q or, as indicated, a Bruker AM-300 spectrometer operating at 90 and 300 MHz, respectively, and with tetramethylsilane as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield from the standard. Gas chromatography/mass spectra (GC/MS) were obtained with a Hewlett-Packard 5890 Series II gas chromatograph using a HP 1 cross-linked methylsilicone column (25 m × 0.20 mm) and a Hewlett-Packard 5971 Series mass spectrometer. In these spectra, only characteristic peaks are reported. Combustion analyses were done at Vanderbilt University (V) or by Galbraith Laboratories (G), Knoxville, TN, and agreed to within 0.4% of the calculated value or as otherwise noted.

10-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a,d*]cycloheptene Hydrochloride (3c·HCl). 10-(4-Hydroxy-1-methyl-4-piperidinyl)-5*H*-dibenzo[*a,d*]cycloheptene (**11a**; 1.00 g, 3.27 mmol) and concentrated hydrochloric acid (12 N, 6.5 mL, 78 mmol) in absolute ethanol (20 mL) were boiled for 17 h. Evaporation of the mixture left a white crystalline solid which on recrystallization from absolute ethanol gave **3c**·HCl (0.77 g, 73%): mp 257–262 °C dec; ^{1}H NMR (CD_3OD) δ 2.73 (m, 2, C-2 pyridinyl H), 2.99 (s, 3, NCH_3), 3.2–3.7 (m, 2, C-3 pyridinyl H), 3.70 (s, 2, C-5 H), 3.92 (m, 2, C-6 pyridinyl H), 5.98 (m, 1, C-5 pyridinyl H), and 7.1–7.5 ppm (m, 9, C-11 and aromatic H); GC/MS *m/e* (rel int) 287 (43, M^+), 109 (51), and 96 (100). Anal. (G) ($C_{21}H_{22}ClN$) C; H: calcd, 6.85; found: 7.26; N: calcd, 4.33; found, 3.43.

2-Chloro-5-(2-propylidene)-11-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-5*H*-dibenzo[*a,d*]cycloheptene (3d). 2-Chloro-11-(4-hydroxy-1-methyl-4-piperidinyl)-5-(2-propylidene)-5*H*-dibenzo[*a,d*]cycloheptene (**15**; 1.58 g, 4.16 mmol) was mixed with concentrated hydrochloric acid (12 N, 7.0 mL, 84 mmol) in absolute ethanol (25 mL), and the mixture was boiled for 18 h. Evaporation of the solvent left a yellow oil as residue. Water (20 mL) and ethyl acetate (20 mL) were added to the residue, and the mixture was made basic with 6 N sodium hydroxide. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 35 mL). The combined ethyl acetate solutions were dried (Na_2SO_4) and evaporated. Recrystallization of the solid residue from acetonitrile gave **3d** (1.10 g, 73%) as yellow prisms: mp 141–142 °C; 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.67 [s, 3, C=C(CH_3)CH_3], 1.69 [s, 3, C=C(CH_3)CH_3], 2.23 (m, 1, C-2 pyridinyl H), 2.41 (s, 3, NCH_3), 2.5–2.8 (m, 3, C-2 and C-3 pyridinyl H), 3.13 (m, 2, C-6 pyridinyl H), 5.88 (b, 1, C-5 pyridinyl H), 6.92 (s, 1, C-10 H), and 7.0–7.4 ppm (m, 7, aromatic H). Anal. (V) ($C_{24}H_{24}ClN$) C, H, N.

10-(1-Ethyl-1,2,3,6-tetrahydro-4-pyridinyl)-5*H*-dibenzo-[*a,d*]cycloheptene Hydrochloride (3e·HCl). As described for the preparation of **3c**·HCl from **11a**, 10-(1-ethyl-4-hydroxy-4-piperidinyl)-5*H*-dibenzo[*a,d*]cycloheptene (**11b**) was dehydrated with hydrochloric acid in ethanol. After removal of the reaction solvent, recrystallization from absolute ethanol gave **3e**·HCl (71%) as a pale yellow solid: mp >230 °C. Anal. (V) ($C_{22}H_{24}ClN$) C, H, N.

A portion of **3e**·HCl was treated with 6 M sodium hydroxide, and the amine was extracted into ether (3×). The combined ether extracts were dried (Na_2SO_4). Evaporation of the ether gave **3e** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3, J = 7.2 Hz, CH_2CH_3), 2.3–2.8 (m, 6, C-2 and C-3 pyridinyl H and CH_2CH_3), 3.18 (m, 2, C-6 pyridinyl H), 3.66 (s, 2, C-5 H), 5.93 (m, 1, C-5 pyridinyl H), 7.08 (s, 1, C-11 H), and 7.0–7.5 ppm (m, 8, aromatic H); GC/MS *m/e* (rel int) 301 (55, M^+), 123 (47), and 110 (100).

10-[1,2,3,6-Tetrahydro-1-(2-propenyl)-4-pyridinyl]-5*H*-dibenzo[*a,d*]-cycloheptene Hydrochloride (3f·HCl). As described for the preparation of **3c**·HCl from **11a**, 10-[4-hydroxy-1-(2-propenyl)-4-piperidinyl]-5*H*-dibenzo[*a,d*]cycloheptene (**11c**) was dehydrated with hydrochloric acid in ethanol. After removal of the reaction solvent, recrystallization of the light brown residue from 2-propanol (3×) gave **3f**·HCl (56%) as white needles: mp 222–223 °C; ^{1}H NMR ($CDCl_3$) δ 2.74 (m, 2, C-2 pyridinyl H), 3.5–3.8 (m, 2, C-3 pyridinyl H), 3.68 (m, 2, C-5 H), 3.8–4.0 (m, 4, C-6 pyridinyl H and CH_2-CH=CH_2), 5.5–5.8 (m, 2, CH=CH_2), 5.9–6.3 (m, 2, CH=CH_2 and C-5 pyridinyl H), and 7.0–7.5 ppm (m, 9, C-11 and aromatic H). Anal. (V) ($C_{23}H_{24}ClN$) C, H, N.

10-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)dibenz-[*b,f*]oxepin (5a). As described for the preparation of **3c**·HCl from **11a**, 10-(4-hydroxy-1-methyl-4-piperidinyl)dibenz[*b,f*]-oxepin (**18a**) was dehydrated with hydrochloric acid in ethanol. After removal of the solvent, the white hydrochloride was dissolved in water, and the mixture was made basic with 6 N sodium hydroxide. The aqueous layer was extracted with

ether (3 × 40 mL), and the combined ether extracts were dried (Na_2SO_4). Evaporation of the ether and recrystallization of the residue from isopropyl ether gave **5a** (66%) as light yellow needles: mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3, NCH_3), 2.4–2.6 (m, 4, C-2 and C-3 pyridinyl H), 3.12 (m, 2, C-6 pyridinyl H), 5.91 (b, 1, C-5 pyridinyl H), 6.77 (s, 1, C-11 H), and 7.0–7.4 ppm (m, 8, aromatic H); GC/MS *m/e* 289 (100, M^+), 181 (82), and 96 (89). Anal. (V) ($C_{20}H_{19}NO$) C, H, N.

10-(1-Ethyl-1,2,3,6-tetrahydro-4-pyridinyl)dibenz[*b,f*]-oxepin Hydrochloride (5b·HCl). As described for the preparation of **3c**·HCl from **11a**, 10-(4-hydroxy-1-ethyl-4-piperidinyl)dibenz[*b,f*]oxepin (**18b**) was dehydrated with hydrochloric acid. After removal of the solvent, recrystallization of the solid residue from absolute ethanol gave **4b**·HCl (63%) as a pale yellow solid: mp >230 °C; ^{1}H NMR ($CDCl_3/D_2O$) δ 1.54 (t, 3, J = 9.0 Hz, CH_2CH_3), 2.6–3.0 (m, 2, C-2 pyridinyl H), 3.23 (q, 2, J = 9.0 Hz, CH_2CH_3), 3.35 (m, 2, C-3 pyridinyl H), 3.85 (b, 2, C-6 pyridinyl H), 5.90 (b, 1, C-5 pyridinyl H), 6.80 (s, 1, C-11 H), 7.0–7.4 ppm (m, 8, aromatic H). Anal. (V) ($C_{21}H_{22}ClNO$) C, H, N.

10-[1,2,3,6-Tetrahydro-1-(2-propenyl)-4-pyridinyl]dibenz[*b,f*]oxepin Hydrochloride (5c·HCl). As described for the preparation of **3c**·HCl from **11a**, 10-[4-hydroxy-1-(2-propenyl)-4-piperidinyl]dibenz[*b,f*]oxepin (**18c**) was dehydrated with hydrochloric acid in ethanol. After evaporation of the solvent, crystallization, and then recrystallization of the residue from 2-propanol gave **5c**·HCl (41%) as white needles: mp 211–213 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 2, C-2, pyridinyl H), 2.70 (m, 2, C-3 pyridinyl H), 3.0–3.3 (m, 4, C-6 pyridinyl H and $CH_2CH{=}CH_2$), 5.0–5.4 (m, 2, $CH{=}CH_2$), 5.6–6.2 (m, 2, C-5 pyridinyl H and $CH{=}CH_2$), 6.75 (s, 1, C-11 H) and 6.9–7.5 ppm (m, 8, aromatic H). Anal. (G) ($C_{22}H_{22}ClNO$) H, Cl, N; C: calcd, 75.09; found, 74.47.

10-(1-Methyl-4-piperidinyl)dibenz[*b,f*]oxepin Hydrochloride (7·HCl). 10-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)dibenz[*b,f*]oxepin (**5a**, 1.00 g, 0.346 mmol) in 95% ethanol (32 mL) and platinum oxide (0.25 g, 1.1 mmol) were reduced with hydrogen at room temperature with stirring overnight. The reaction mixture was filtered through Celite, and evaporation of the solvent left an oil as residue. The oil was dissolved in ether to which was added concentrated hydrochloric acid (0.25 mL), and evaporation of the ether left a white solid. Recrystallized from methanol and then from methanol-acetone (2×) gave **7**·HCl (0.110 g, 10%) as a white solid, which on the basis of its GC/MS was contaminated with 2% unreduced starting material **5a**·HCl and 2% of the 10,11-dihydro-10-(1-methyl-4-piperidinyl)dibenz[*b,f*]oxepin hydrochloride: mp >230 °C; 300-MHz ^{1}H NMR ($CDCl_3$) δ 2.18 (m, 2, piperidinyl H), 2.54 (m, 2, piperidinyl H), 2.84 (s, 3, NCH_3), 2.88 (m, 2, piperidinyl H), 3.39 (m, 1, C-4 piperidinyl H), 3.65 (m, 2, piperidinyl H), 6.78 (s, 1, C-11 H), and 7.1–7.8 ppm (m, 8, aromatic H); GC/MS *m/e* (rel int) 291 (12, M^+), 96 (18), and 70 (100). Anal. (V) ($C_{20}H_{22}ClNO$) C, H, N.

10-Bromo-5*H*-dibenzo[*a,d*]cycloheptene (9). Aluminum chloride (10.2 g, 76.5 mmol) in ether (100 mL) was added dropwise to a slurry of lithium aluminum hydride (2.9 g, 76 mmol) in ether (100 mL). After stirring for 10 min, 10-bromo-5*H*-dibenzo[*a,d*]cyclohepten-5-one[13] (**8**; 19.4 g, 68.0 mmol) in tetrahydrofuran (70 mL) was added, and the mixture was boiled overnight. The mixture was cooled with ice, and water (100 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with water (3 × 70 mL) and dried ($MgSO_4$). Evaporation of the ether gave **9** (18.1 g, 98%) as a light yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, **2**, C-5 H), and 7.1–7.4 (m, 7, aromatic H), 7.67 (s, 1, C-11 H), and 7.78 ppm (dd, 1, C-9 H); GC/MS *m/e* (rel int) 270/272 (53, M^+) and 191 (100, $[M - Br]^+$).

10-(4-Hydroxy-1-methyl-4-piperidinyl)-5*H*-dibenzo[*a,d*]-cycloheptene (11a). Under nitrogen, *n*-butyllithium (1.6 M in hexane, 38 mL, 61 mmol) was added dropwise with stirring to 10-bromo-5*H*-dibenzo[*a,d*]cycloheptene (**9**; 15.0 g, 55.3 mmol) in ether (350 mL) at −78 °C. The solution was stirred at −78 °C for 1.5 h, and 1-methyl-4-piperidone (**10a**; 18.8 g, 0.166 mol) in ether (60 mL) was added dropwise at −78 °C. The mixture was stirred for an additional 5 h, allowed to warm gradually to room temperature, and then stirred overnight. Addition of water (150 mL) caused the formation of a white precipitate which dissolved on the addition of ethyl acetate (250 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The ethyl acetate solutions were combined and dried ($MgSO_4$). Evaporation of the solvent gave a light yellow oil (16.0 g) as a residue, which on crystallization from ethyl acetate gave **11a** (10.4 g, 62%) as a white solid: mp 185–186 °C; ^{1}H NMR ($CDCl_3$) δ 1.7–2.8 (m, 9, OH and piperidinyl H), 2.32 (s, 3, NCH_3), 3.43 (d, 1, J = 12.5 Hz, C-5 H), 3.67 (d, 1, J = 12.5 Hz, C-5 H), 7.0–7.4 (m, 8, C-11 and aromatic H), and 8.00 ppm (dd, 1, C-9 H); GC/MS *m/e* (rel int) 305 (67, M^+), 287 (15, $[M - 18]^+$), 96 (58), and 70 (100). Anal. (V) ($C_{21}H_{23}NO$) C, H, N.

10-(1-Ethyl-4-hydroxy-4-piperidinyl)-5*H*-dibenzo[*a,d*]-cycloheptene (11b). As described for the preparation of **11a** by the addition of **10a** to the lithium derivative of **9**, **11b** was prepared by the addition of 1-ethyl-4-piperidone (**10b**) to the lithium derivative of 10-bromo-5*H*-dibenzo[*a,d*]cycloheptene (**9**). Crystallization of the crude product from ethyl acetate (2×) gave **11b** (67%): mp 144–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3, J = 13.0 Hz, CH_2CH_3), 1.8–2.8 (m, 9, OH and piperidinyl H), 2.52 (q, 2, J = 13.0 Hz, CH_2CH_3), 3.45 (d, 1, J = 13.0 Hz, C-5 H), 3.70 (d, 1, J = 13.0 Hz, C-5 H), 7.0–7.3 (m, 8, C-11 and aromatic H), and 8.03 ppm (dd, 1, C-9 H). Anal. (V) ($C_{22}H_{25}NO$) H, N; C: calcd, 82.72; found, 83.15.

10-[4-Hydroxy-1-(2-propenyl)-4-piperidinyl]-5*H*-dibenzo[*a,d*]cycloheptene (11c). As described for the preparation of **11a** by the addition of **10a** to the lithium derivative of **9**, **10c** was prepared by the addition of 1-(2-propenyl)-4-piperidone (**10c**) to the lithium derivative of 10-bromo-5*H*-dibenzo[*a,d*]cycloheptene (**9**). Crystallization of the crude product from hexane gave **11c** (27%) as a white solid: mp 120–121 °C; ^{1}H NMR ($CDCl_3$) δ 1.7–2.8 (m, 9, OH and piperidinyl H), 3.02 (d, 2, J = 7.2 Hz, $CH_2CH{=}CH_2$), 3.55 (d, 1, J = 11.6 Hz, C-5 H), 3.66 (d, 1, J = 11.6 Hz, C-5 H), 5.0–5.3 (m, 2, $CH{=}CH_2$), 5.6–6.2 (m, 1, $CH{=}CH_2$), 7.0–7.4 (m, 8, C-11 and aromatic H), and 8.02 ppm (dd, 1, C-9 H). Anal. (V) ($C_{23}H_{25}NO$) C, H, N.

11-Bromo-2-chloro-5-(2-propylidene)-5*H*-dibenzo[*a,d*]-cycloheptene (14). Under nitrogen, *n*-butyllithium (1.6 M in hexane, 3.8 mL, 6.1 mmol) was added dropwise to a stirred solution of isopropyltriphenylphosphonium iodide (2.41 g, 5.58 mmol) in ether (42 mL). The mixture was boiled for 3.5 h and then was cooled to room temperature. 11-Bromo-2-chloro-5*H*-dibenzo[*a,d*]cyclohepten-5-one[16] (**13**; 1.70 g, 5.32 mmol) in tetrahydrofuran (20 mL) was added dropwise, and the mixture was stirred overnight. The cooled reaction mixture was added to water (20 mL), and the layers were separated. The organic layer was dried ($MgSO_4$), and the organic solvent was evaporated. The residue was dissolved in a minimum amount of methylene chloride and added to a column of silica gel. Elution with hexane and evaporation of the hexane gave **14** (1.25 g, 68%) as a colorless oil: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.67 [s, 3, $C{=}C(CH_3)CH_3$], 1.69 [s, 3, $C{=}C(CH_3)CH_3$], 7.0–7.5 (m, 6, aromatic H), 7.54 (s, 1, C-10 H), and 7.81 ppm (d, 1, J = 2.1 Hz, C-1 H).

2-Chloro-11-(4-hydroxy-1-methyl-4-piperidinyl)-5-(2-propylidene)-5*H*-dibenzo[*a,d*]cycloheptene (15). Under nitrogen, *n*-butyllithium (1.6 M in hexane, 3.8 mL, 6.1 mmol) was added dropwise to a stirred solution of 11-bromo-2-chloro-5-(2-propylidene)-5*H*-dibenzo[*a,d*]cycloheptene (**14**; 1.90 g, 5.50 mmol) in ether (20 mL) at −78 °C. The solution was stirred at −78 °C for an additional 2 h, and 1-methyl-4-piperidone (**10a**; 2.06 g, 18.2 mmol) in ether (12 mL) was added at −78 °C. The solution was stirred at −78 °C for 5 h, allowed to warm to room temperature, and stirred overnight at room temperature. Water (25 mL) and ether (25 mL) were added, and the layers were separated. The aqueous layer was extracted with ether (2 × 25 mL), and the ether layer and ethereal extracts were each washed with water (4 × 25 mL) and the combined ether extracts were dried ($MgSO_4$). Evaporation of the ether and recrystallization of the residue from ethyl acetate gave **15** (1.78 g, 85%): 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 3, $C{=}C(CH_3)CH_3$], 1.68 [s, 3, $C{=}C(CH_3)CH_3$], 1.8–2.7

(m, 8 piperidinyl H), 2.19 (s, 3, NCH_3), 3.48 (b, 1, OH), 7.0–7.3 (m, 7, C-10 and aromatic H), and 8.26 ppm (d, 1, J = 1.8 Hz, C-1 H).

Addition of concentrated hydrochloric acid to an ethereal solution of a small portion of **15** and recrystallization of the resulting precipitate from absolute ethanol gave **15**·HCl as white plates: mp >230 °C. Anal. (V) ($C_{24}H_{27}Cl_2NO$): C, H, N.

10-Bromodibenz[*b,f*]oxepin (17). *trans*-10,11-Dibromo-10,11-dihydrodibenz[*b,f*]oxepin[19] (**16**; 6.00 g, 16.9 mmol) and potassium *tert*-butoxide (2.47 g, 22.0 mmol) were mixed in *tert*-butyl alcohol (127 mL), and the mixture was boiled for 1 h. The solution was poured onto ice, and the *tert*-butyl alcohol was removed by evaporation. The resulting aqueous slurry was extracted with ether (3 x 50 mL), and the combined organic layers were washed with 5% aqueous sodium bisulfite (100 mL) and dried (Na_2SO_4). Evaporation of the ether gave **17** (4.26 g, 92%) as a yellow oil (lit.[19] mp <0 °C); ^{1}H NMR ($CDCl_3$) δ 6.9–7.5 (m, 7, aromatic H), 7.31 (s, 1, C-11 H), and 7.72 ppm (dd, 1, C-9 H); GS/MS *m/e* (rel int) 272/274 (98, M^+) and 165 (100).

10-(4-Hydroxy-1-methyl-4-piperidinyl)dibenz[*b,f*]oxepin (18a). As described for the preparation of **11a** by the addition of **10a** to the lithium derivative of **9**, **18a** was prepared by the addition of 1-methyl-4-piperidone (**10a**) to the lithium derivative of 10-bromodibenz[*b,f*]oxepin (**17**). Recrystallization of the crude product from ethyl acetate gave **18a** (79%) as white prisms: mp 182–183 °C; ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 1, OH), 1.9–2.8 (m, 8, piperidinyl H), 2.29 (s, 3, NCH_3), 7.03 (s, 1, C-11 H), 7.0–7.4 (m, 7, aromatic H), and 8.01 ppm (dd, 1, C-9 H); GC/MS *m/e* (rel int) 307 (41, M^+), 289 (100, $[M - 18]^+$), 181 (65), 96 (52), and 70 (30). Anal. (V) ($C_{20}H_{21}NO_2$) C, H, N.

10-(1-Ethyl-4-hydroxy-4-piperidinyl)dibenz[*b,f*]oxepin (18b). As described for the preparation of **11a** by the addition of **10a** to the lithium derivative of **9**, **18b** was prepared by the addition of 1-ethyl-4-piperidone (**10b**) to the lithium derivative of 10-bromodibenz[*b,f*]oxepin (**17**). Recrystallization of the crude product from ethyl acetate (2×) gave **18b** (70%) as a white solid: mp 152–154 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3, J = 9.0 Hz, CH_2CH_3), 1.7–2.9 (m, 11, piperidinyl, CH_2CH_3, and OH), 7.02 (s , 1, C-11 H), 7.1–7.3 (m, 7, aromatic H), and 8.05 ppm (dd, 1, C-9 H). Anal. (V) ($C_{21}H_{23}NO_2$) C, H, N.

10-[4-Hydroxy-1-(2-propenyl)-4-piperidinyl]dibenz[*b,f*]oxepin (18c). As described for the preparation of **11a** by the addition of **10a** to the lithium derivative of **9**, **18c** was prepared by the addition of 1-(2-propenyl)-4-piperidone (**10c**) to the lithium derivative of 10-bromodibenz[*b,f*]oxepin (**17**). Recrystallization of the crude product from hexane gave **18c** (36%) as light yellow prisms: mp 128–129 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 1, OH), 1.9-2.9 (m, 8, piperidinyl H), 3.04 (d, 2, CH_2-$CH{=}CH_2$), 5.0–5.3 (m, 2, $CH_2CH{=}CH_2$), 5.6–6.2 (m, 1, $CH{=}CH_2$), 7.04 (s, 1, C-11 H), 7.1–7.4 (m, 7, aromatic H), and 8.03 ppm (dd, 1, C-9 H). Anal. (V) ($C_{22}H_{23}NO_2$) C, H, N.

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Supplementary Material Available: A table of the binding affinities of the 5,11-dicarbo analogues **3c–3f** and oxepin analogues **5a–5c** and **7** to serotonin S-2A and S-2C binding sites, showing the mean K_i's, the number of separate experiments, and the standard errors of the mean (1 page). Ordering information is given on any current masthead page.

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