[[(Arylpiperazinyl)alkyl]thio]thieno[2,3-*d*]pyrimidinone Derivatives as High-Affinity, Selective 5-HT$_{1A}$ Receptor Ligands†

Maria Modica,‡ Maria Santagati,*,‡ Filippo Russo,‡ Luca Parotti,§ Luca De Gioia,§ Carlo Selvaggini,§ Mario Salmona,§ and Tiziana Mennini§

Dipartimento di Scienze Farmaceutiche, Università di Catania, Viale A. Doria 6, 95125 Catania, Italy, and Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milano, Italy

Received November 28, 1995⊗

A series of 2-[[(4-aryl-1-piperazinyl)alkyl]thio]thieno[2,3-*d*]pyrimidin-4(1*H*)-one and 3-substituted 2-[[(4-aryl-1-piperazinyl)alkyl]thio]thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives was prepared and evaluated for *in vitro* 5-HT$_{1A}$ receptor affinity by radioligand binding assays; the selectivity for 5-HT$_{1A}$ receptors rather than α_1-adrenoceptors was also examined (ratio of the IC$_{50}$ α_1 to IC$_{50}$ 5-HT$_{1A}$). The binding tests gave indications about the best features of the [(arylpiperazinyl)alkyl]thio moiety and of the substituents on the thiophene and pyrimidinone rings for efficacious and selective 5-HT$_{1A}$ ligands. The most effective derivative for displacing [^{3}H]-8-OH-DPAT from rat hippocampal membranes was the 3-amino-2-[[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]thio]-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**70**) (IC$_{50}$ = 0.3 nM) with selectivity of 24 for the 5-HT$_{1A}$ over the α_1-adrenoceptor. Compound **73**, where the 2-methoxyphenyl on the N4 piperazine ring was replaced with a pyrimidine group, showed the best selectivity, with a ratio of 74, while its affinity IC$_{50}$ for 5-HT$_{1A}$ was 6.8 nM. These results, compared to those for compounds **46** (IC$_{50}$ 24 nM; selectivity 2) and **49** (IC$_{50}$ 226 nM; selectivity 5), N3 unsubstituted analogues of derivatives **70** and **73**, show the importance of an amino group in position 3 of the thienopyrimidine system for the interaction with 5-HT$_{1A}$ receptor binding sites, although this fragment can affect the affinity and selectivity only if linked to the (arylpiperazinyl)alkyl moiety. The better selectivity of piperidine **74** (IC$_{50}$ 0.8; selectivity 45) compared to the analogous piperazine **70** is also noteworthy. Twenty of the 30 molecules used for determining the binding affinity to 5-HT$_{1A}$ and α_1-adrenergic receptors were selected for QSAR analysis using a series of molecular descriptors and calculated with the TSAR software.

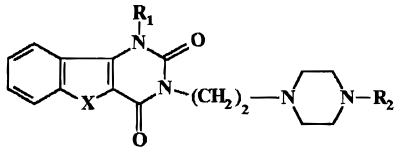
Introduction

The serotonin receptor subtype 5-HT$_{1A}$ is involved in physiological processes such as the regulation of mood, sleep, and sexual behavior[1] as well as in psychiatric disorders such as anxiety and depression.[2] Antianxiety and antidepressant compounds of the arylpiperazine class such as buspirone, gepirone, ipsapirone,[2−4] or NAN-190[5] show high affinity for 5-HT$_{1A}$ receptors, but poor selectivity.[5−7] Buspirone also acts on dopaminergic and α_1-adrenergic receptors,[8] and NAN-190 has similar affinity for 5-HT$_{1A}$ and α_1-adrenergic receptors.[9]

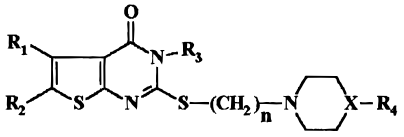
The specific aim of this work was to develop ligands with higher affinity and selectivity for the 5-HT$_{1A}$ receptor (5-HT$_{1A}$R) than for the α_1-adrenergic receptor (α_1AR). Selective 5-HT$_{1A}$R ligands might help clarify the role of 5-HT$_{1A}$R in anxiety and depression, and QSAR analysis of high-affinity selective compounds could improve our understanding of pharmacophoric models for these receptors.

Our group has already studied the affinity of some synthetic ligands for α_1AR and 5-HT$_{1A}$R which, in spite of their completely different pharmacology, show some common features in their binding sites.[10] We synthesized compounds of type A (Chart 1) and assessed the chemical features involved in affinity and selectivity for the two receptors.[10,11] In the present study we used type **B** compounds (Chart 1). These have an arylpiperazine moiety, which includes an aromatic nucleus coupled to a basic nitrogen atom at a suitable distance[12,13] (the basic pharmacophore for recognition of the ligands by the 5-HT$_{1A}$ binding site), connected by an alkyl chain to the thienopyrimidin-4-one system. This was chosen because type A derivatives, where the pyrimidine nucleus condensed with a heterocycle, showed a good interaction with 5-HT$_{1A}$R.[10,11]

Chart 1



A



B

The introduction of various substituents on the N4 piperazine, on the thiophene ring, and on pyrimidine and the synthesis of compounds **78**, **80**, **81**, and **83** (Tables 1 and 2) are justified by the intention to clarify

† Part of this work was presented at the "Januachem 92": 17th National Congress of The Italian Chemical Society, Genova, Italy, 25-30 October, 1992.

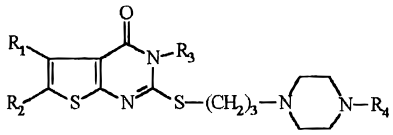
‡ Università di Catania.

§ Istituto di Ricerche Farmacologiche "Mario Negri".

⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1996.

S0022-2623(95)00866-1 CCC: $14.00

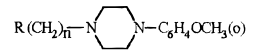
Table 1. Physical and Chemical Properties of Compounds **43**−**74**

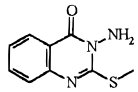
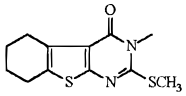
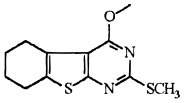
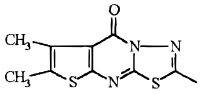


compd	R_1	R_2	R_3	R_4	mp, °C	recryst solv	% yield[a]	formula[b]
43	Me	Me	H	2-Cl-phenyl	165−166	EtOH	25	$C_{21}H_{25}ClN_4OS_2$
44	Me	Me	H	3-Cl-phenyl	188−190	EtOH	41	$C_{21}H_{25}ClN_4OS_2$
45	Me	Me	H	4-Cl-phenyl	224−226 dec	EtOH/dioxane	36	$C_{21}H_{25}ClN_4OS_2$
46	Me	Me	H	2-OMe-phenyl	163−164	EtOH	30	$C_{22}H_{28}N_4O_2S_2$
47	Me	Me	H	4-OMe-phenyl	193−194 dec	EtOH/dioxane	32	$C_{22}H_{28}N_4O_2S_2$
48	Me	Me	H	1-naphthyl	199−201	EtOH/dioxane	19	$C_{25}H_{28}N_4OS_2$
49	Me	Me	H	2-pyrimidinyl	225−226	EtOH/dioxane	81	$C_{19}H_{24}N_6OS_2$
50		$-(CH_2)_4-$	H	2-Cl-phenyl	179−180	EtOH	40	$C_{23}H_{27}ClN_4OS_2$
51		$-(CH_2)_4-$	H	3-Cl-phenyl	168−169	EtOH	48	$C_{23}H_{27}ClN_4OS_2$
52		$-(CH_2)_4-$	H	4-Cl-phenyl	226−227 dec	EtOH/dioxane	45	$C_{23}H_{27}ClN_4OS_2$
53		$-(CH_2)_4-$	H	2-OMe-phenyl	169−171	EtOH	51	$C_{24}H_{30}N_4O_2S_2$
54[c]		$-(CH_2)_4-$	H	2-OMe-phenyl	183−184	EtOH	25	$C_{23}H_{28}N_4O_2S_2$
55		$-(CH_2)_4-$	H	4-OMe-phenyl	205−206 dec	EtOH/dioxane	40	$C_{24}H_{30}N_4O_2S_2$
56		$-(CH_2)_4-$	H	1-naphthyl	209−210	EtOH/dioxane	18	$C_{27}H_{30}N_4OS_2$
57		$-(CH_2)_4-$	H	2-pyrimidinyl	175−176	EtOH	60	$C_{21}H_{26}N_6OS_2$
58	H	phenyl	H	2-Cl-phenyl	216−218	dioxane	46	$C_{25}H_{25}ClN_4OS_2$
59	H	phenyl	H	3-Cl-phenyl	208−210	EtOH/dioxane	30	$C_{25}H_{25}ClN_4OS_2$
60	H	phenyl	H	4-Cl-phenyl	239−241 dec	dioxane/DMF	30	$C_{25}H_{25}ClN_4OS_2$
61	H	phenyl	H	2-OMe-phenyhl	181−183	EtOH/dioxane	46	$C_{26}H_{28}N_4O_2S_2$
62	H	phenyl	H	4-OMe-phenyl	219−221 dec	EtOH/dioxane	40	$C_{26}H_{28}N_4O_2S_2$
63	H	phenyl	H	1-naphthyl	242−244	dioxane/DMF	19	$C_{29}H_{28}N_4OS_2$
64		$-(CH{=}CH)_2-$	H	2-OMe-phenyl	187−188	EtOH	25	$C_{24}H_{26}N_4O_2S_2$
65	H	H	NH_2	2-OMe-phenyl	100−102	ethyl acetate	18	$C_{20}H_{25}N_5O_2S_2$
66		$-(CH_2)_4-$	Me	2-OMe-phenyl	124−125	cyclohexane	30	$C_{25}H_{32}N_4O_2S_2$
67		$-(CH_2)_4-$	NH_2	2-OMe-phenyl	173−174	EtOH/dioxane	30	$C_{24}H_{31}N_5O_2S_2$
68	Me	Me	NH_2	phenyl	126−128	EtOH	41	$C_{21}H_{27}N_5OS_2$
69	Me	Me	Me	2-OMe-phenyl	111−112	EtOH	29	$C_{23}H_{30}N_4O_2S_2$
70	Me	Me	NH_2	2-OMe-phenyl	147−149	EtOH/dioxane	44	$C_{22}H_{29}N_5O_2S_2$
71	Me	Me	NHC_6H_5	2-OMe-phenyl	152−154	ethyl acetate	38	$C_{28}H_{33}N_5O_2S_2$
72	Me	Me	Me	2-pyrimidinyl	112−114	EtOH	45	$C_{20}H_{26}N_6OS_2$
73	Me	Me	NH_2	2-pyrimidinyl	204−206	EtOH/dioxane	22	$C_{19}H_{25}N_7OS_2$
74[d]	Me	Me	NH_2	2-OMe-phenyl	139−140	EtOH/dioxane	17	$C_{23}H_{30}N_4O_2S_2$

[a] All yields are nonoptimized. [b] All new compounds were analyzed for C, H, N and S, which were within 0.4% of the theoretical values. [c] Note: the alkyl chain in this case is two methylene groups long. [d] Note: the piperazine ring of **70** is replaced by a piperidine nucleus.

Table 2. Physical and Chemical Properties of Compounds **78**, **80**, **81**, and **83**



Compd	R	n	mp,°C	recryst. solv. % yield[a]	formula[b]
78		3	138-140	EtOH 42	$C_{22}H_{27}N_5O_2S$
80		3	141-142	EtOH 18	$C_{25}H_{32}N_4O_2S_2$
81		3	153-154	EtOH 18	$C_{25}H_{32}N_4O_2S_2$
83		2	167-168	EtOH 39	$C_{22}H_{25}N_5O_2S_2$

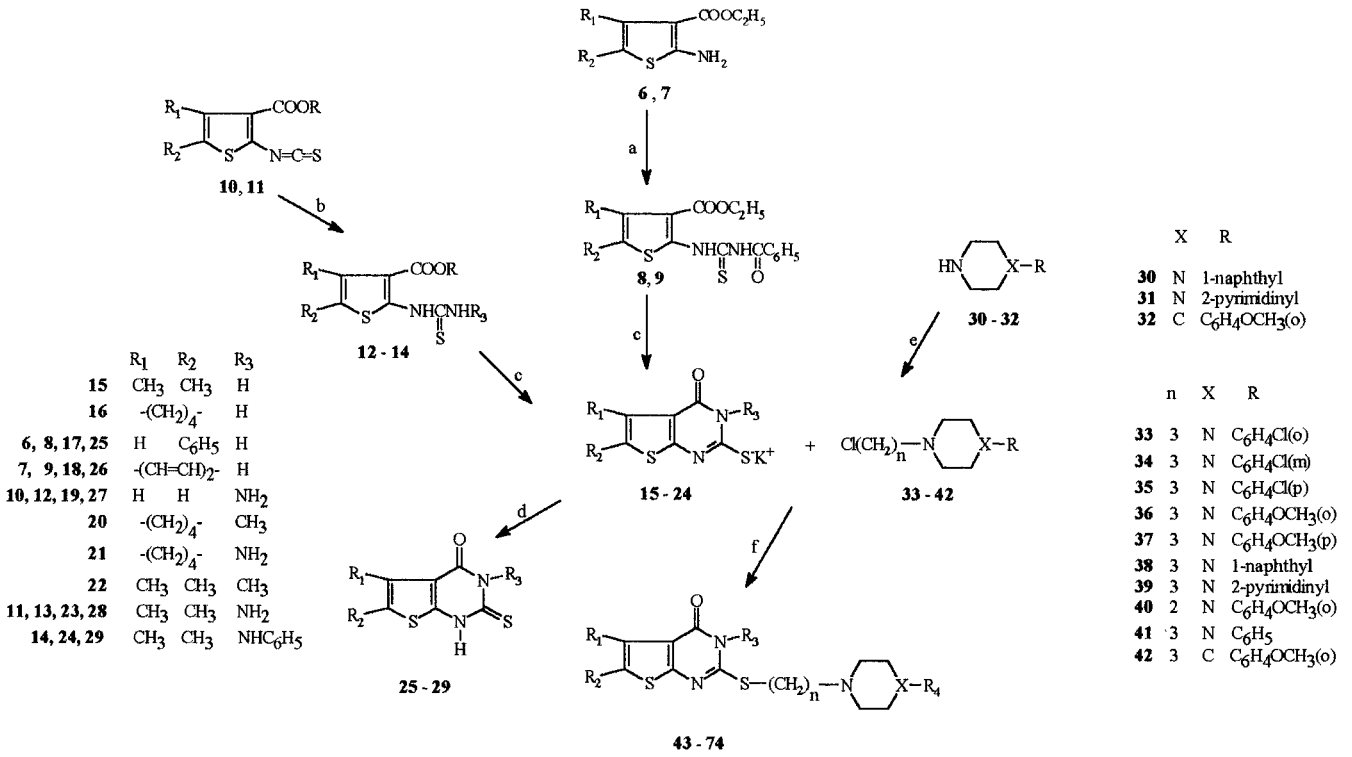
[a] All yields are nonoptimized. [b] All new compounds were analyzed for C, H, N, and S, which were within 0.4% of the theoretical values.

the structural requisites that distinguish the two receptor sites. Given the importance of the pharmacological data (see Results and Discussion), we carried out QSAR analysis on some compounds. The selection of compounds and results are fully explained in the Model section.

Chemistry

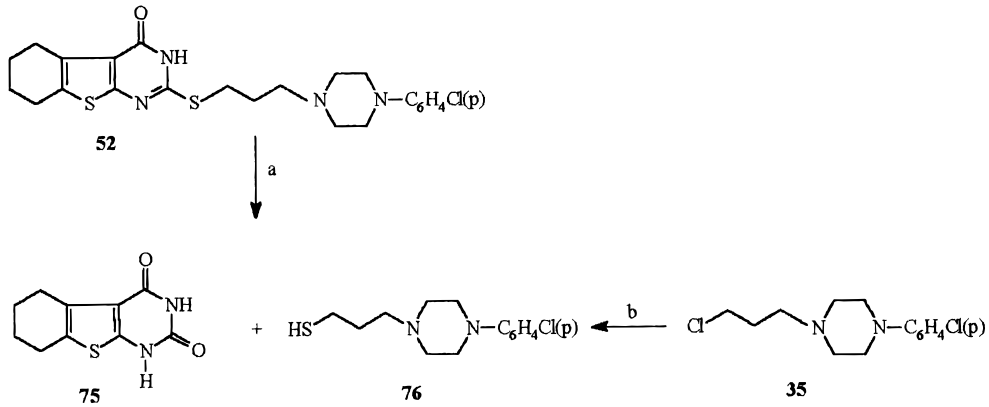
Compounds **8**−**74** were prepared according to Scheme 1. The potassium salts of the 2-thioxothieno[2,3-*d*]-pyrimidine derivatives **15**−**24** reacted at reflux in ethanol with the appropriate chloroalkyl compounds **33**−**42** to give the respective 2-[[(4-aryl-1-piperazinyl or -piperidinyl)alkyl]thio]thieno[2,3-*d*]pyrimidinones **43**−**74**. The new potassium salts **17** and **18** were synthesized from the amino esters **6** and **7** with ammonium thiocyanate and benzoyl chloride in acetone at reflux, with subsequent heating of the *N*-(3-carbethoxythien-2-yl)-*N*′-benzoylthioureas **8** and **9** with an ethanolic potassium hydroxide solution. The N3-substituted potassium salts **19**, **23**, and **24** were synthesized from the isothiocyanates **10** and **11** and hydrazine hydrate or phenylhydrazine in dichloromethane at room temperature, with subsequent heating of the (hydrazinothioxomethyl)amino derivatives **12**−**14** with an ethanolic potassium hydroxide solution. Acidification of an aqueous solution of the potassium salts **17**−**19**, **23**, and **24** gave the thioxo compounds **25**−**29**, whose structures were substantiated by elemental analysis and IR spectra. The unknown piperazines **38** and **39** and piperidine **42** were obtained by reaction of 1-(1-naphthyl)piperazine

Scheme 1[a]



[a] Reagents and conditions: (a) NH_4NCS, C_6H_5COCl, acetone, reflux; (b) NH_2NH_2 or $NH_2NHC_6H_5$, dichloromethane, room temperature; (c) KOH, absolute EtOH, reflux; (d) H_2O, HCl, room temperature; (e) $Cl(CH_2)_3Br$, NaOH 25%, acetone, room temperature, $Cl(CH_2)_3Br$, K_2CO_3, dimethylformamide, room temperature; (f) EtOH, reflux.

Scheme 2[a]



[a] Reagents and conditions: (a) HCl, EtOH, reflux; (b) NH_2CSNH_2, NaOH, reflux, HCl.

(**30**), 1-(2-pyrimidinyl)piperazine dihydrochloride (**31**), and 1-(2-methoxyphenyl)piperidine (**32**) with 1-bromo-3-chloropropane in acetone in the presence of sodium hydroxide for compounds **38** and **39** and in dimethylformamide in the presence of potassium carbonate for compound **42**.

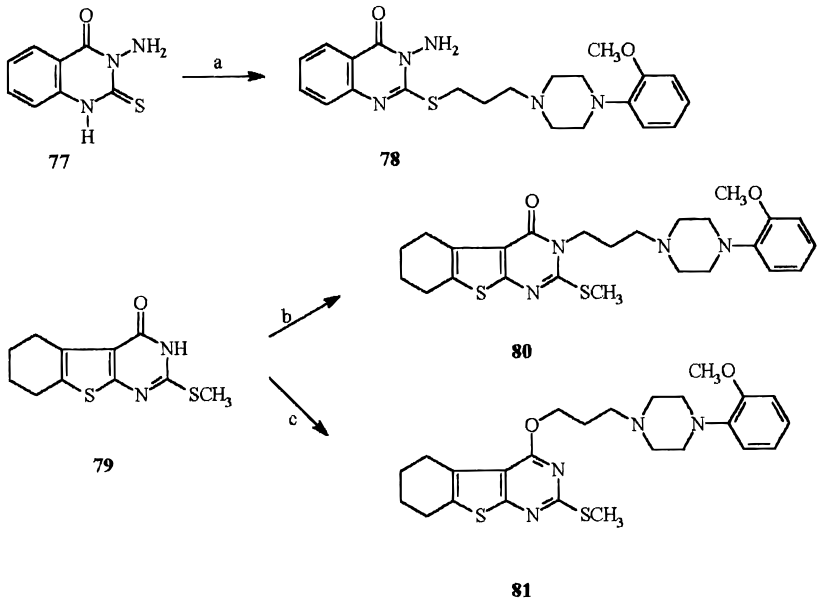
The structure of compounds **43**−**74** was supported by a chemical route (Scheme 2). From hydrolysis of compound **52** we obtained the octahydrobenzothienopyrimidindione **75**, identical to the known compound by mixed mp, analytical, and spectral data, and the (mercaptopropyl)(chlorophenyl)piperazine **76**, also prepared following the synthetic pathway shown in Scheme 2. This enabled us to confirm the assigned structures of **43**−**74**.

By reaction between piperazine **36** and the potassium salt of the 3-amino-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one (**77**), we synthesized the derivative **78**. Isomers **80** and **81** were prepared from the 5,6,7,8-tetrahydro-2-(methylthio)[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**79**) and compound **36** in acetonitrile in the presence of potassium carbonate for **80** and in dimethylformamide in the presence of sodium hydride for **81** (Scheme 3). Lastly, treatment of the potassium salt **23** with chloropropionyl chloride gave the (2-chloroethyl)thiadiazolothienopyrimidinone **82**, which reacted at 140 °C with 1-(2-methoxyphenyl)piperazine to give compound **83** (Scheme 4). The proposed structures of compounds **43**−**74**, **78**, **80**, **81**, and **83** were confirmed by elemental analysis (Tables 1 and 2) and by spectroscopic IR data and ^1H NMR spectra of some representative samples. (See the Experimental Section.)

Results and Discussion

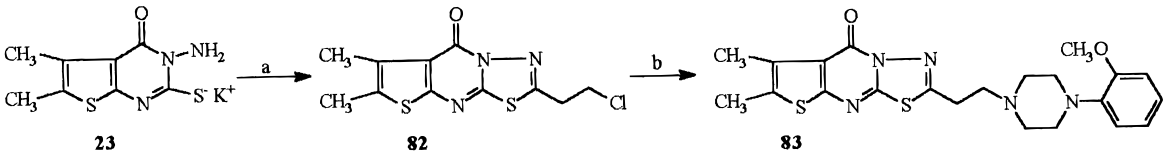
In Vitro SAR Study. The *in vitro* affinity for 5-HT_{1A} and α_1-adrenergic receptors was evaluated by radio-

Scheme 3[a]



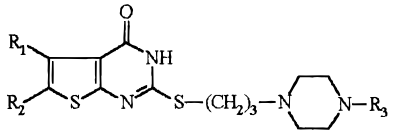
[a] Reagents and conditions: (a) KOH, EtOH, 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine, **36**, EtOH, reflux; (b) compound **36**, K_2CO_3, acetonitrile, reflux; (c) NaH, compound **36**, dimethylformamide, reflux.

Scheme 4[a]



[a] Reagents and conditions: (a) CH_3SO_3H, P_2O_5, chloropropionyl chloride; (b) 1-(2-methoxyphenyl)piperazine.

Table 3. Affinities of Compounds **43**−**50**, **53**, **54**, **56**, **57**, **61**, **63**, and **64**



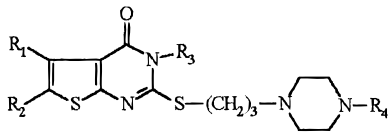
compd	R_1	R_2	R_3	IC_{50} (nM) (± SD)[a] 5-HT_{1A}[b]	IC_{50} (nM) (± SD)[a] α_1-A[c]	selectivity[a]
43	Me	Me	2-Cl-phenyl	460 ± 20	161 ± 34	0.35
44	Me	Me	3-Cl-phenyl	986 ± 83	299 ± 47	0.3
45	Me	Me	4-Cl-phenyl	NA[e]	NA[e]	
46	Me	Me	2-OMe-phenyl	24 ± 2	40 ± 5	2
47	Me	Me	4-OMe-phenyl	NA[e]	NA[e]	
48	Me	Me	1-naphthyl	355 ± 30	886 ± 17	2.5
49	Me	Me	2-pyrimidinyl	226 ± 104	1098 ± 154	5
50		$-(CH_2)_4-$	2-Cl-phenyl	943 ± 101	168 ± 38	0.2
53		$-(CH_2)_4-$	2-OMe-phenyl	59 ± 5	38 ± 9	0.6
54[f]		$-(CH_2)_4-$	2-OMe-phenyl	97 ± 6	20 ± 2	0.2
56		$-(CH_2)_4-$	1-naphthyl	371 ± 48	445 ± 19	1
57		$-(CH_2)_4-$	2-pyrimidinyl	505 ± 81	1814 ± 478	3.5
61	H	phenyl	2-OMe-phenyl	386 ± 30	224 ± 57	0.6
63	H	phenyl	1-naphthyl	2010 ± 1 × 10^{-6}	2454 ± 742	1
64		$-(CH{=}CH)_2-$	2-OMe-phenyl	46 ± 6	91 ± 18	2
serotonin				3 ± 0.5	NA[e]	
phentolamine				NA[e]	36 ± 7	

[a] IC values (nM) are followed by SD. [b] Affinity at [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT)-labeled 5-HT_{1A} sites. [c] Affinity at [^{3}H]prazosin-labeled α_1-adrenergic sites. [d] Selectivity for 5-HT_{1A} over α_1-adrenergic sites: calculated as IC (α_1)/IC (5-HT_{1A}). [e] <50% inhibition at 10^{-5} M. [f] Note: the alkyl chain in this case is two methylene groups long.

ligand binding assay. For the derivatives with notable affinity and selectivity toward 5-HT_{1A}R, we also evaluated the *in vitro* affinity for serotonin receptors 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 and for the dopaminergic receptors D_1 and D_2.

The results, shown in Table 3, lead to a series of considerations with regard to the structure−affinity relationship for the compounds of general structure **B** (Chart 1). By modification of the alkylpiperazine and thienopyrimidine moieties, we significantly improved

Table 4. Affinities of Compounds **65**−**74**



compd	R_1	R_2	R_3	R_4	IC_{50} (nM) (±SD) 5-HT_{1A}	IC_{50} (nM) (±SD) α_1-A	selectivity
65	H	H	NH_2	2-OMe-phenyl	1.2 ± 0.05	2.9 ± 0.5	2
66	−$(CH_2)_4$−		Me	2-OMe-phenyl	7 ± 1	64 ± 9	9
67	−$(CH_2)_4$−		NH_2	2-OMe-phenyl	1.3 ± 0.2	39 ± 2	30
68	Me	Me	NH_2	phenyl	3.3 ± 0.2	43 ± 7.8	13
69	Me	Me	Me	2-OMe-phenyl	3 ± 0.15	27 ± 5	9
70	Me	Me	NH_2	2-OMe-phenyl	0.3 ± 0.02	7.3 ± 1	24
71	Me	Me	NHC_6H_5	2-OMe-phenyl	497 ± 17	32 ± 5	0.06
72	Me	Me	Me	2-pyrimidinyl	65 ± 3	2030 ± 243	31
73	Me	Me	NH_2	2-pyrimidinyl	6.8 ± 0.5	506 ± 97	74
74[a]	Me	Me	NH_2	2-OMe-phenyl	0.8 ± 0.04	36 ± 11	45

[a] Note: the piperazine ring of **70** is replaced by a piperidine nucleus.

the 5-HT_{1A}R affinity and selectivity. For compounds **43**−**50**, **53**, **54**, **56**, **57**, **61**, **63**, and **64**, the results were as follows:

(i) The presence on the phenylpiperazine moiety of substituents in position 2 gives rise to derivatives with greater affinity than the 3- and 4-substituted analogue. The higher affinity of the 2-methoxy derivatives confirms the importance of this group and its position in the aromatic ring for serotonergic activity.[5,7,8] Replacement of the phenyl nucleus with the sterically more demanding naphthyl or with the pyrimidine nucleus notably reduces the affinity, so these groups do not appear suitable for replacing the 2-methoxyphenyl ring. However, dimethylthieno and tetrahydrobenzothieno N4 pyrimidine derivatives **49** and **57** have higher, though not exceptional, selectivity for 5-HT_{1A}R than α_1AR (**49** IC_{50} 226, selectivity 5, **57** IC_{50} 505, selectivity 3.5).

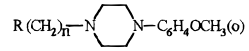
(ii) No significant difference is noted when a 5,6-dimethylthiophene (**46** IC_{50} 24, selectivity 2), tetrahydrobenzothiophene (**53** IC_{50} 59, selectivity 0.6), or benzothiophene (**64** IC_{50} 46, selectivity 2) is condensed with the pyrimidine ring. However, the phenyl substituent in position 6 of the thienopyrimidine ring does not interact favorably with 5-HT_{1A}R (**61** IC_{50} 386, selectivity 0.6), probably because of an unfavorable steric interaction between the phenyl group and the 5-HT_{1A} receptor.

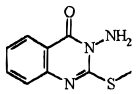
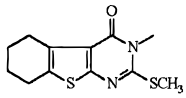
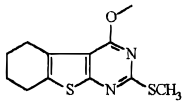
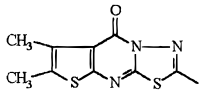
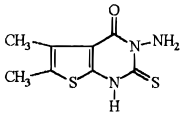
(iii) The shorter distance between the thienopyrimidine system and the piperazine ring in compound **54** scarcely affects the affinity for 5-HT_{1A}R and for α_1AR (IC_{50} 97 and 20, respectively) compared to that for the superior homologue **53** (IC_{50} 59 and 38, respectively). This point calls for further investigation.

The results with compounds **65**−**74** (Table 4) merit comment. We previously found[10,11] that the introduction of a methyl group on nitrogen in position 1 in the [(3-phenylpiperazinyl)alkyl]pyrimido[5,4-*b*]indole-2,4-diones improved the interaction of the ligand with 5-HT_{1A}R but not with the α_1AR. In our case, the amino group and, to a lesser extent, the methyl group on the nitrogen 3 of the thienopyrimidine system greatly improved both the affinity and selectivity, as shown by comparison of the results for N3 substituted compounds and the N3 unsubstituted analogues. Affinity for 5-HT_{1A}R was highest with the 3-amino-2-[[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]thio]-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**70**) (IC_{50} 0.3, selectivity 24) while selectivity was best with the 3-amino-2-[[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]thio]-5,6-dimethylthieno-[2,3-*d*]pyrimidin-4(3*H*)-one (**73**) (IC_{50} 6.8, selectivity 74). The methyl and, even more, the amino group appear to facilitate a specific interaction of the cyclic amide portion with the 5-HT_{1A} binding site, further stabilizing the ligand−receptor complex. The limited affinity of compound **71**, bearing an aniline group at position 3 of the thienopyrimidine system, for 5-HT_{1A}R (IC_{50} 497) but not for α_1AR (IC_{50} 32) confirms the more stringent steric requirement of ligands binding to the 5-HT_{1A}R.[10] The excellent result with derivative **74** (IC_{50} 0.8, selectivity 45), which has the bioisosteric piperidine nucleus instead of the piperazine (compound **70**), shows a improved selectivity which needs to be further investigated and confirms that N1 piperazine is involved in the principal ionic interaction with the 5-HT_{1A}R.[12,13] The results with compounds **65**, **68**, and **78** (Tables 4 and 5) compared to those with compound **70** show that the absence of substituents on thiophene or N4 phenyl and the substitution of isosteric benzene for thiophene reduce the selectivity (2, 13, and 8, respectively). The affinity of compound **78** toward 5-HT_{1A} is almost unaffected (IC_{50} 0.5), while that of compound **65** decreases (IC_{50} 1.2), like compound **68** (IC_{50} 3.3). The results in Table 5 for compounds **80** (IC_{50} 511, selectivity 0.2) and **81** (IC_{50} 1424, selectivity 0.05) illustrate that the link of the alkyl chain in position 3 or 4 of the pyrimidine ring significantly reduces the affinity to 5-HT_{1A}R. For compound **83**, where a portion of the thioalkyl chain and amine nitrogen is enveloped in the thiadiazole ring, the affinity and selectivity (IC_{50} 42, selectivity 3) are lower than those with compound **70**, confirming the importance of this chain and of the amino group. Finally, the lack of activity of compound **28** shows that the thienopyrimidine system influences affinity and selectivity only if it is linked to the (arylpiperazinyl)alkyl moiety.

The results in Table 6 show the affinity of compounds **70**, **73**, and **74** for other 5-HT receptors and D_1 and D_2 receptors. These compounds have about 1000 times more selectivity for the 5-HT_{1A} receptor, with the exception of compound **73**, which has 10^{-8} M affinity for the 5-HT_3 receptor (10 times lower than its affinity for 5-HT_{1A}R), while compound **70** shows 10^{-8} M affinity for D_2 receptors (100 times lower than for 5-HT_{1A}R).

Table 5. Affinities of Compounds **78**, **80**, **81**, and **83**



Compd	R	n	IC_{50} (nM) (±SD) 5-HT_{1A}	α_1-A	selectivity
78		3	0.5 ±0.04	4 ±0.9	8
80		3	511 ±71	95 ±11	0.2
81		3	1424 ±160	75 ±12	0.05
83		2	42 ±6	125 ±41	3
28			NA[a]	NA[a]	

[a] <50% inhibition at 10^{-5} M.

Table 6. IC_{50} (nM) Values in Binding Tests of Compounds **70**, **73**, and **74** on 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 Receptors and on D_1 and D_2 Receptors

compd	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2C}	5-HT_3	D_1	D_2
70	0.3	700	300	600	800	400	60
73	6.8	NA[a]	1000	2000	20	600	2000
74	0.8	1400	300	1500	600	800	100

[a] <50% inhibition at 10^{-5} M. For the sake of clarity, SD are omitted since they were always less than 10%.

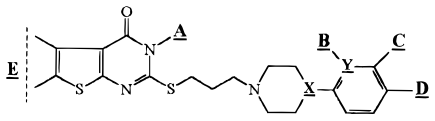


Figure 1. Two-dimensional structure of the molecular backbone common to 20 out of 30 molecules used in the QSAR analysis. Substituents and atoms to derive molecular descriptors are labeled. List of the molecular descriptors used in the QSAR study: total molecular volume of the molecule, total dipole of the molecule, molecular volume of substituents A, B, C, D and E, total dipole of substituent A, partial atomic charge of atoms X and Y, partial atomic charges of the atoms of substituents B and C directly bound to the molecular backbone.

QSAR Study. Among the 30 molecules used to determine the binding affinity toward 5-HT_{1A} and α_1-adrenergic receptors, 20 were considered suitable for QSAR analysis. These all had a common backbone structure with different substituents in positions A, B, C, D, and E (Figure 1). Molecules **28**, **64**, **78**, **80**, **81**, and **83** were not used because their molecular backbone was different from the one chosen as reference. Since the TSAR software cannot handle more than four substituents, the two substituents in position 1 and 2 of thiophene ring were considered together when the substituents were the same (i.e. the compound was locally symmetrical). Molecules **61** and **63** have different substituents on the thiophene ring and were discarded. Molecules **45** and **47** were discarded because their IC_{50} values were not calculated precisely.

Molecule **70**, which had the highest affinity for 5-HT_{1A}R, was considered as the lead compound for the QSAR study. The conformational space of this molecule was extensively investigated, as explained in Computations, and the conformation associated with the lowest energy value was considered as the most representative (Figure 2).

Many conformations with less than 5 kcal/mol energy difference were identified by the conformational search. This was expected in view of the extreme conformational freedom of the alkyl chain connecting the arylpiperazine and the thienopyrimidin-4-one system. The energy order of the different conformations of the molecule could change when bound to the receptor. However, the decision to use the lowest energy conformation obtained in vacuum seems logical when none or only very limited information is available about the receptor's three-dimensional structure. All the other molecules of the set used in the QSAR study were built using the structure of **70** as scaffold. This is an acceptable assumption for the comparison of molecules with the same atomic backbone but different substituents. It seems reasonable to assume that the backbone conformation is similar for all the molecules when bound to the receptor. When arranged on the scaffold conformation, none of the molecules showed bad steric clashing.

Different molecular properties of the molecules and their substituents were calculated for the QSAR study.

The preliminary structure−activity data reported for this set of compounds[14] and the variance properties associated with the calculated molecular descriptors prompted us to choose the following set of descriptors for this study: Total molecular volume of the molecule, total dipole of the molecule, molecular volume of substituents A, B, C, D and E, total dipole of substituent A, partial atomic charge of atoms X and Y, and partial atomic charge of the atoms of substituents B and C directly bound to the molecular backbone (Figure 1).

As a first step, the affinity data for the 5-HT_{1A} and α_1-adrenergic receptors were classified in two groups with IC_{50} values less than or more than 50 nM.

As a second step, a principal component analysis (PCA) was done on the 12 selected variables. The first three components explained more than 72% of the total variance. A graph was plotted showing the positions of the 20 molecules in the space defined by the first three PCs, and each point was colored according to the classification discussed above, for 5-HT_{1A} and α_1-adrenergic activity (data not shown). The points associated with molecules showing low or high affinity toward the 5-HT_{1A}R formed two distinct clusters in space, and the same was true for the α_1-adrenergic receptor (data not shown). The only clearly misclassified point with both the 5-HT_{1A} and the α_1-adrenergic data corresponded to molcule **71**. Interestingly, this is the only molecule of the set with an aniline group linked to the nitrogen at

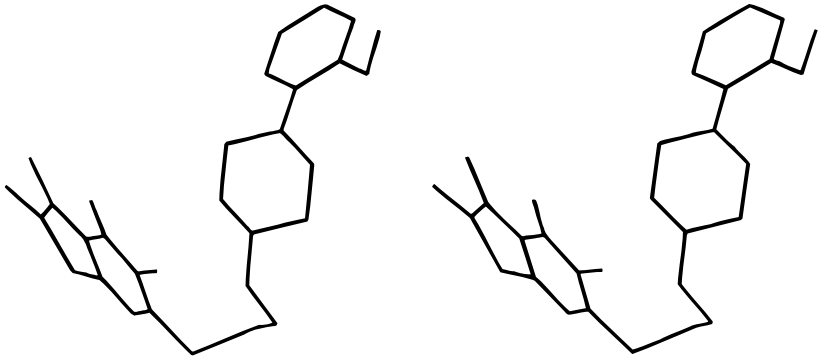


Figure 2. Stereopair picture of energy-minimized three-dimensional structure of molecule **70** (lead compound for the QSAR study).

Table 7. Discriminant Analysis for 5-HT_{1A} Receptors

step no.	variable entering	total fraction well-classified	well-classified fraction per class: class 1	well-classified fraction per class: class 2
1	PC2	0.706	0.70	0.714
2	PC1	1.0	1.0	1.0
cross-validation confidence estimates		0.882	0.90	0.857
number in class			10	8

Table 8. Discriminant Analysis for α_1-Adrenoceptors

step no.	variable entering	total fraction well classified	well-classified fraction per class: class 1	well-classified fraction per class: class 2
1	PC2	0.824	0.778	0.875
cross-validation confidence estimates		0.765	0.667	0.857
number in class			9	9

position 3 of the pyrimidine ring. Misclassification could be due to a wrong conformational and/or electronic description, which would falsify the molecular descriptors. Since this was the only molecule with that substituent, we eliminated **71** from the QSAR data set. A new PCA analysis was done with the remaining 19 molecules. The first three PCs explained more than 77% of the total variance and were used in discriminant and regression analysis. The coefficients for the first three PCs are reported in Tables 7 and 8. The only variable not well explained by the first three PCs was the partial atomic charge of atom X.

Discriminant analysis is a stepwise procedure which allows selection of the most significant variables for the molecules according to *a priori* activity classes defined by the criteria selected.[15] This approach was used to classify molecules and to obtain a predictive model for the data set. The data of the high- and low-affinity classes for 5-HT_{1A} and α_1-adrenergic receptors were used as dependent variables. The three PCs were used as independent variables for both activity data sets.

A very good model was obtained for 5-HT_{1A} with only PC 1 and 2 in it (Table 9). Confidence data were higher than 0.88, and all molecules were properly classified within this model. The α_1-adrenergic data were also satisfactory (Table 10). Only PC 2 entered the model and the confidence was higher than 0.79, indicating a good predictive model even if some molecules were misclassified. A cross-validation procedure was used to

Table 9. Regression Analysis for 5-HT_{1A} Receptors[a]

step	charge to model	partial F	overall F	overall s
initial			0.0	1.113
1	PC2 enters	21.36	21.36	0.738
2	PC1 enters	16.02	29.39	0.522
3	PC3 enters	5.442	27.63	0.454

[a] Multiple regression coefficient: $r = 0.930$; $r^2 = 0.864$. Cross-validation: $r(\mathrm{CV})^2 = 0.712$.

Table 10. Regression Analysis for α_1-Adrenoceptors[a]

step	charge to model	partial F	overall F	overall s
initial			0.0	0.762
1	PC2 enters	28.37	28.37	0.463

[a] Multiple regression coefficient: $r = 0.809$; $r^2 = 0.654$. Cross-validation: $r(\mathrm{CV})^2 = 0.593$.

assess the true predictive ability of the discriminant model. This provides a confidence estimate (equivalent to a cross-validation r^2 value) that should be a reliable guide to the predictive power of the final model. The confidence estimate must be compared with the probability of correctly classifying a molecule deliberately placed at random in the group and is therefore 1.0 for a perfect model.

Regression analysis looks at the relationship between a single dependent variable and more explanatory (independent) variables. To validate our results better we did a stepwise regression analysis using the pIC_{50} (nM) for 5-HT_{1A} and α_1-adrenergic receptors as dependent variables and the three PCs as independent variables. Regression equations are

$$y = 0.522\mathrm{PC1} - 0.853\mathrm{PC2} - 0.265\mathrm{PC3} + 1.636 \quad (\text{for 5-HT}_{1A})$$

$$y = -0.617\mathrm{PC2} + 2.170 \quad (\text{for } \alpha_1\text{-adrenergic})$$

All three PCs entered the regression equation for 5-HT_{1A}R, but only PC 2 for the α_1-adrenergic receptor. The cross-validation technique, used to estimate the true predictive value of regression models, confirmed the good predictive power of the model for 5-HT_{1A} and α_1-adrenergic receptors. (See Figure 3.) It is interesting to note that two or all three PCs entered the discriminant analysis and the regression model for the 5-HT_{1A}R, suggesting that all the variables explained by the first three PCs influence binding. However, only PC 2 entered the discriminant analysis and regression analysis for α_1-adrenergic receptors, suggesting that only these variables are important for interaction with the α_1-adrenergic receptor. However, results for the α_1-

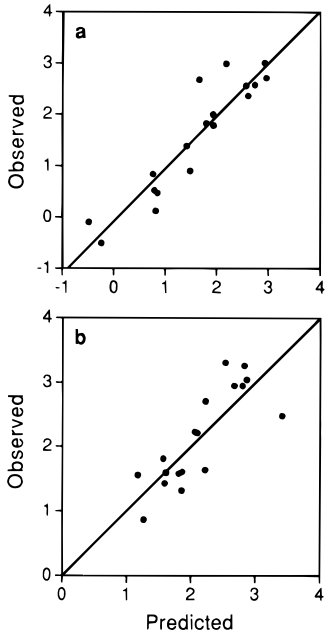


Figure 3. Plot of observed versus predicted log IC_{50} obtained in the regression analysis for (a) 5-HT_{1A} and (b) α_1-adrenergic receptors (see Tables 9 and 10 for statistics).

adrenergic receptor were somewhat less satisfactory, suggesting that factors not directly present in the molecular descriptors or not adequately explained by the first three PCs may play a significant role in binding affinity for this receptor. It is interesting to compare the IC_{50} values for compounds **70** and **74** toward 5-HT_{1A} and α_1-adrenergic receptors. These compounds differ only in the atom (N or C) in position 4 of the piperazine ring and show similar activity for 5-HT_{1A}R, whereas compound **74** has somewhat lower affinity for the α_1-adrenergic receptor. This suggests that the nitrogen in position 4 of the piperazine ring may play a role in the interaction with the α_1-adrenergic receptor. Unfortunately, the fact that only one compound had an atom different from N in that position excluded that variable from statistical analysis, as observed from the communality matrix.

Conclusions

The structure−activity relationships established with our compounds, which combine the 1-alkyl-4-arylpiperazine, a moiety known to be a good 5-HT_{1A} pharmacophore, and thienopyrimidinone, whose chemical modulations have led to powerful ligands with high affinity and excellent selectivity for 5-HT_{1A}R, underline the importance of the heterocycle structure bound to the alkylpiperazine moiety. The structural change that mainly affects selectivity and affinity toward the 5-HT_{1A}R is the introduction of substituents such as a methyl or amino group on the N3 pyrimidine nucleus.

We proposed a molecular model of the [(arylpiperazinyl)alkyl]thienopyrimidine system as a basis for a QSAR study, through a series of molecular descriptors calculated using the TSAR software. The results illustrate the relations between the steric and electronic properties of the molecules and their affinity toward 5-HT_{1A}R.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 281 spectrometer in KBr (potassium bromide) disks. Electron impact mass spectra (70 eV) were taken with a VG-2AB2SE instrument. ^{1}H NMR spectra were obtained at 250 MHz on a Bruker Model WP 250 spectrometer in DMSO-d_6 or $CDCl_3$ solution. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane as an internal standard; coupling constants (J) are in hertz. Elemental analyses were obtained on an EA1108 elemental analyzer Fisons-Carlo Erba instrument and were within 0.4% of the theoretical values. The purity of the compounds was checked by thin-layer chromatography (TLC) on Merck silica gel 60 F-254 plates. All commercial chemicals were used as received from Aldrich unless noted otherwise.

The following amino esters, isothiocyanates, potassium salts, and piperazines were synthesized by published procedures: ethyl 2-amino-5-phenylthiophene-3-carboxylate (**6**),[16] ethyl 2-aminobenzo[*b*]thiophene-3-carboxylate (**7**),[17] methyl 2-isothiocyanatothiophene-3-carboxylate (**10**),[18] ethyl 2-isothiocyanato-4,5-dimethylthiophene-3-carboxylate (**11**),[19] monopotassium salt of 2,3-dihydro-5,6-dimethyl-2-thioxothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**15**) and of 2,3,5,6,7,8-hexahydro-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**16**),[20] of 2,3,5,6,7,8-hexahydro-3-methyl-2-thioxo[1]benzothieno[2,3-*d*]-pyrimidin-4(1*H*)-one (**20**),[21a,b] of 3-amino-2,3-dihydro-2-thioxo-[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**21**),[22] of 2,3-dihydro-3,5,6-trimethyl-2-thioxothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**22**),[21a,b] 1-(3-chloropropyl)-4-(2-, 3-, or 4-chlorophenyl)piperazines (**33**−**35**),[23] 1-(3-chloropropyl)-4-(2- or 4-methoxyphenyl)piperazines (**36** and **37**),[24] 1-(2-chloroethyl)-4-(2-methoxyphenyl)piperazine **40**[25], 1-(3-chloropropyl)-4-phenyl-piperazine **41**[23].

***N*-(5-Phenyl-3-carbethoxythien-2-yl)-*N*′-benzoylthiourea (8) (Scheme 1).** To a solution of ammonium thiocyanate (2.6 g, 34 mmol) in anhydrous acetone (15 mL) was added benzoyl chloride (2.8 mL, 24 mmol). To the resulting suspension, after being refluxed for 5 min, was added a solution of amino ester **6** (5.93 g, 24 mmol) in anhydrous acetone (60 mL). The mixture was refluxed for another 5 min and filtered while hot. After cooling, the solid product was collected by filtration, poured into water, and filtered to give by recrystallization from benzene 4.92 g (50%) of **8** as yellow microcrystals: mp 220−221 °C; IR (KBr) 3290 (NH), 1695 and 1680 (C=O) cm^{-1}. Anal. ($C_{21}H_{18}N_2O_3S_2$) C, H, N, S.

***N*-(3-Carbethoxy[1]benzothien-2-yl)-*N*′-benzoylthiourea (9) (Scheme 1).** The thiourea **9** was obtained from amino ester **7** (5.3 g, 24 mmol) in the same manner as compound **8**, but the suspension was kept at reflux for 2 h and filtered while hot. The solvent was removed under reduced pressure, and the solid was collected with a small amount of ethanol and filtered. Recrystallization from ethanol/dioxane yielded 2.65 g (29%) of **9** as yellow microcrystals: mp 178−179 °C; IR (KBr) 3240 (NH), 1675 and 1670 (C=O) cm^{-1}. Anal. ($C_{19}H_{16}N_2O_3S_2$) C, H, N, S.

2-[(Hydrazinothioxomethyl)amino]thiophene-3-carboxylic Acid Ethyl Ester (12) (Scheme 1). A solution of isothiocyanate **10** (5.57 g, 28 mmol) in dichloromethane (70 mL) was added under stirring to a solution of hydrazine monohydrate (1.4 mL, 28 mmol) in dichloromethane (10 mL). The suspension obtained was stirred at room temperature for 1.30 h, and then the solid was collected by filtration and washed with dichloromethane and ethanol. Recrystallization from ethanol/dioxane gave 1.81 g (28%) of **12** as a yellow powder: mp 218−220 °C dec; IR (KBr) 3340 and 3140 (NH), 1680 (C=O) cm^{-1}. Anal. ($C_7H_9N_3O_2S_2$) C, H, N, S.

2-[(Hydrazinothioxomethyl)amino]-4,5-dimethylthiophene-3-carboxylic Acid Ethyl Ester (13) (Scheme 1). This product was prepared from isothiocyanate **11** in the same manner as compound **12**. Recrystallization from ethanol/dioxane gave 3.5 g (46%) of **13** as yellow microcrystals: mp 199−201 °C dec; IR (KBr) 3360, 3220 and 3140 (NH), 1660 (C=O) cm^{-1}. Anal. ($C_{10}H_{15}N_3O_2S_2$) C, H, N, S.

2-[[(Phenylhydrazino)thioxomethyl]amino]-4,5-dimethylthiophene-3-carboxylic Acid Ethyl Ester (14) (Scheme 1). A solution of isothiocyanate **11** (6.74 g, 28 mmol) in dichloromethane (70 mL) was added under stirring to a solution of an equimolar amount of phenylhydrazine in dichlo-

romethane (10 mL), and the mixture was stirred at room temperature for 1.30 h. The solvent was removed under reduced pressure and the solid collected with petroleum ether. Recrystallization from ethanol gave 2.96 g (30%) of **14** as yellow needles: mp 201−202 °C dec; IR (KBr) 3260 and 3160 (NH), 1670 (C=O) cm^{-1}. Anal. ($C_{16}H_{19}N_3O_2S_2$) C, H, N, S.

Preparation of the Potassium Salt of 2,3-Dihydro-6-phenyl-2-thioxothieno[2,3-*d*]pyrimidin-4(1*H*)-one (17) and Its 2-Thioxo Derivative 25 (Scheme 1). To a hot potassium hydroxide solution (0.6 g, 10.7 mmol) in absolute ethanol (30 mL) was added the thienylthiourea **8** (2.46 g, 6 mmol), and the mixture was refluxed under stirring for 1−2 h. The suspension was filtered while hot and the solid washed with hot absolute ethanol to give 1 g (56%) of **17**. The potassium salt **17** (0.24 g, 0.8 mmol) suspended in water (50 mL) was acidified with concentrated hydrochloric acid, and the mixture was stirred at room temperature for 30 min. The solid was collected by filtration and washed with water to give—recrystallized from ethanol/dioxane—0.12 g (58%) of the 2-thioxo derivative **25** as a pale yellow powder: mp >305 °C dec; IR (KBr) 3120 and 3080 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.33−7.71 (m, 6H, ArH), 12.52 (s, 1H, CONH), 13.54 (s, 1H, NH). Anal. ($C_{12}H_8N_2OS_2$) C, H, N, S.

In a similar manner the potassium salt **18** (0.93 g, 57%) and the 2-thioxo derivative **26** were obtained from compound **9**. Compound **26** was recrystallized from ethanol/dioxane to yield 0.11 g (59%) of a white powder: mp 285−287 °C; IR (KBr) 3160 and 3080 (NH), 1700 (C=O) cm^{-1}. Anal. ($C_{10}H_6N_2OS_2$) C, H, N, S.

Preparation of the Potassium Salt of 3-Amino-2,3-dihydro-2-thioxothieno[2,3-*d*]pyrimidin-4(1*H*)-one (19) and Its 2-Thioxo Derivative 27 (Scheme 1). Compound **12** (2 g, 8.6 mmol) was added to a solution of potassium hydroxide (0.48 g, 8.6 mmol) in absolute ethanol (35 mL), and the mixture was refluxed under stirring for 1−3 h. The suspension was filtered hot, and the solid was washed with hot absolute ethanol to give 1.82 g (89%) of compound **19**. The potassium salt **19** (0.59 g, 2.5 mmol) suspended in water (50 mL) was acidified with concentrated hydrochloric acid, and the mixture was stirred at room temperature for 30 min. The solid was then collected by filtration and washed with water. Recrystallization from ethanol/dioxane gave 0.1 g (20%) of the 2-thioxo derivative **27** as a light brown powder: mp >310 °C; IR (KBr) 3220 and 3120 (NH), 1660 (C=O) cm^{-1}. Anal. ($C_6H_5N_3OS_2$) C, H, N, S.

In a similar manner the following compounds were obtained.

Potassium Salt 23 (1.95 g, 86%) and the 2-Thioxo Derivative 28. Recrystallization from ethanol/dioxane gave 0.13 g (23%) of a pale yellow powder: mp 268−269 °C dec; IR (KBr) 3295, 3240 and 3160 (NH), 1675 (C=O) cm^{-1}. MS *m/e* 227 (M^+). Anal. ($C_8H_9N_3OS_2$) C, H, N, S. These analytical and spectral data were similar to those of the compound synthesized with another procedure.[26]

Potassium Salt 24 (1 g, 34%) and the 2-Thioxo Derivative 29. Recrystallization from ethanol gave 0.12 g (16%) of a yellow powder: mp 284−285 °C dec; IR (KBr) 3280 and 3140 (NH), 1700 (C=O) cm^{-1}. Anal. ($C_{14}H_{13}N_3OS_2$) C, H, N, S.

1-(3-Chloropropyl)-4-(1-naphthyl)piperazine (38) (Scheme 1). To a solution of 1-(1-naphthyl)piperazine[27] (**30**) (1.23 g, 5.8 mmol) in acetone (5 mL) were added a solution of sodium hydroxide (0.3 g, 7.5 mmol) in water (2.2 mL) and 1-bromo-3-chloropropane (0.57 mL, 5.8 mmol). The mixture was kept under stirring at room temperature for 8 h. The organic layer was separated, extracted with petroleum ether, and washed with water. The combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield 1 g (60%) of **38** as a dark oil, which was immediately used without further purification for the final step.

1-(3-Chloropropyl)-4-(2-pyrimidinyl)piperazine (39) (Scheme 1). To a mixture of 1-(2-pyrimidinyl)piperazine dihydrochloride **31** (3 g, 12.6 mmol) in acetone (15 mL) were added a solution of sodium hydroxide (1.5 g, 37.5 mmol) in water (6 mL) and 1-bromo-3-chloropropane (1.38 mL, 14 mmol). The mixture was stirred at room temperature for 8 h. The organic layer was separated, extracted with diethyl ether, and washed with water. The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield 1.6 g (53%) of **39** as a semisolid product. An analytical sample of the free base was obtained as the hydrochloride salt with HCl-saturated ethanol, which was recrystallized from absolute ethanol to give 0.9 g (49%) of a white powder: mp 251−253 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.24 (m, 2H, $CH_2CH_2CH_2$), 2.99−3.56 (m, 10H, CH_2N, piperazine H), 3.75 (t, J = 6.3 Hz, 2H, CH_2Cl), 6.74 (t, J = 4.8 Hz, 1H, H pyrimid), 8.43 (d, J = 4.8 Hz, 2H, H pyrimid), 11.56 (br s, 1H, NH^+). Anal. ($C_{11}H_{17}ClN_4$·HCl) C, H, N.

1-(3-Chloropropyl)-4-(2-methoxyphenyl)piperidine (42) (Scheme 1). A mixture of 1-(2-methoxyphenyl)piperidine[28] (**32**) (1.67 g, 8.7 mmol), 1-bromo-3-chloropropane (1.03 mL, 10 mmol), and potassium carbonate (1.45 g, 10.5 mmol) was stirred at room temperature for 20 h in dimethylformamide (10 mL). The residue was removed by filtration and the solvent evaporated under reduced pressure. The brown oil was extracted with diethyl ether and washed with water. The organic extracts were separated, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to yield 0.5 g (21%) of a yellow oil, which was immediately used without further purification for the final step.

2-[[3-[4-(2-Chlorophenyl)-1-piperazinyl]propyl]thio]-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-one (43) (Scheme 1). To a suspension of the potassium salt **15** (1.08 g, 4.61 mmol) in ethanol (15 mL) was added 1-(3-chloropropyl)-4-(2-chlorophenyl)piperazine (**33**) (1.26 g, 4.63 mmol), and the mixture was stirred at reflux for 6 h. After cooling, the solid was collected by filtration, washed with ethanol and water, and recrystallized (Table 1).

Compounds **44**−**57** and **59**−**63** were prepared in like manner, except that 6 mmol of the appropriate piperazines **38** and **39** were used for products **48**, **49**, **56**, **57**, and **63**. Compound **58** was prepared in the same manner as **43**, but after the suspension was cooled, the solvent was removed under reduced pressure and the sticky residue was collected with warm cyclohexane, filtered, washed with water, and recrystallized. In the case of compound **64**, after cooling and filtration, the solution, by evaporation of a small amount of solvent, gave the desired product (Table 1).

2-[[3-[4-(2-Chlorophenyl)-1-piperazinyl]propyl]thio]-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-one (43): IR (KBr) 1680 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 2H, $CH_2CH_2CH_2$), 2.30 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.44 (t, J = 6.7 Hz, 2H, CH_2N), 2.50 (m, 4H, piperazine H), 2.97 (m, 4H, piperazine H), 3.17 (t, J = 7.5 Hz, 2H, SCH_2), 6.98−7.40 (m, 4H, ArH).

2-[[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propyl]thio]-3-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (66) (Scheme 1). To a suspension of the potassium salt **20** (0.87 g, 3 mmol) in ethanol (15 mL) was added 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine **36** (0.96 g, 3.6 mmol), and the mixture was stirred at reflux for 6 h. After cooling, the solid product was collected by filtration, washed with ethanol and water, and recrystallized (Table 1).

Compounds **65** and **67**−**73** were prepared in the same manner as **66**, except that for **65**, after the mixture was cooled, the solvent was removed under reduced pressure and the sticky residue was collected with warm ethyl acetate, filtered, washed with water, and recrystallized, while for products **67** and **69**, after the mixture was cooled, the residue was removed by filtration, the solvent evaporated, and the solid product collected with warm ethanol and water, filtered, and recrystallized. In the preparation of compound **67** the solvent used was dioxane (20 mL).

In the case of compound **72**, after the mixture was cooled, the residue was removed by filtration and the desired product crystallized from the solution. Piperidine derivative **74** was prepared from compound **42** in the same manner as **66**, but after the mixture was cooled, the solvent was removed under reduced pressure and the residue was collected with a small amount of ethanol, washed with water, and recrystallized (Table 1).

2-[[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propyl]thio]-3-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (66): IR (KBr) 1675 (C=O) cm^{-1}; ^{1}H NMR

(DMSO-d_6) δ 1.84 (m, 6H, $CH_2CH_2CH_2$, H-6,7), 2.50 (m, 6H, CH_2N, piperazine H), 2.70 (m, 2H, H-5), 2.84 (m, 2H, H-8), 3.13 (m, 6H, piperazine H), 3.26 (t, J = 7.2 Hz, 2H, SCH_2), 3.44 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 6.86−6.92 (m, 4H, ArH).

Hydrolysis of 2-[[3-[4-(4-Chlorophenyl)-1-piperazinyl]-propyl]thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]-pyrimidin-4(1*H*)-one (52) (Scheme 2). To a suspension of compound **52** (0.7 g, 1.5 mmol) in ethanol (15 mL) was added hydrochloric acid 6 N (20 mL), and the mixture was refluxed for 6 h. After cooling, the solid was collected by filtration; recrystallization from acetic acid gave 0.139 g (42%) of compound **75** as white crystals: mp 315 °C; IR (KBr) 3160 and 3100 (NH), 1700 and 1650 (C=O) cm^{-1}. Anal. ($C_{10}H_{10}N_2O_2S$) C, H, N, S.

These analytical and spectral data were like those of known compound.[29] From the filtrate, concentrated and neutralized with 10% NaOH, was obtained a solid that, twice recrystallized from ethanol, yielded 10 mg of **76** as a white powder: mp 107−109 °C; MS *m/e* 270 (M^+). Anal. ($C_{13}H_{19}ClN_2S$) C, H, N, S. The analytical and spectral data were similar to those of the compound synthesized with the following procedure.

1-(3-Mercaptopropyl)-4-(4-chlorophenyl)piperazine (76) (Scheme 2). A mixture of 1-(3-chloropropyl)-4-(4-chlorophenyl)piperazine (**35**) (0.65 g, 2.4 mmol) and thiourea (0.19 g, 2.5 mmol) was refluxed in ethanol (4 mL) for 4 h. A solution of sodium hydroxide (1.05 g, 26 mmol) in 80% ethanol (6 mL) was added, and the reaction mixture was refluxed for another 40 h. To the cooled reaction mixture was added 4 N hydrochloric acid (5 mL), and the mixture was heated for 30 min. The solution, neutralized with 10% NaOH, gave, by recrystallization from ethanol, 50 mg of the desired product **76** as a white powder: mp 107−109 °C; ^{1}H NMR (DMSO-d_6) δ 1.82 (m, 2H, $CH_2CH_2CH_2$), 2.42 (t, J = 7 Hz, 2H, CH_2N), 2.49 (t, J = 5.1 Hz, 4H, piperazine H), 2.78 (t, J = 7 Hz, 2H, CH_2SH), 3.10 (t, J = 5.1 Hz, 4H, piperazine H), 6.86−7.20 (m, 4H, ArH). Anal. ($C_{13}H_{19}ClN_2S$) C, H, N, S.

3-Amino-2[[3[4(2-methoxyphenyl)-1-piperazinyl]-propyl]thio]-quinazolin-4(3*H*)-one (78) (Scheme 3). The 3-amino-2,3-dihydro-2-thioxo-quinazolin-4(1*H*)-one (**77**)[30] (0.45 g, 2.3 mmol) was refluxed with a solution of potassium hydroxide (0.32 g, 5.7 mmol) in absolute ethanol (23 mL) for 1 h. The suspension was filtered while hot to obtain the corresponding potassium salt (0.5 g, 2.1 mmol) that was condensed rapidly with an equimolar amount of piperazine **36**. The suspension was refluxed under stirring in ethanol (15 mL) for 6 h; after cooling, the solid was collected and recrystallized (Table 2): IR (KBr) 3300 and 3130 (NH), 1665 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.88 (m, 2H, $CH_2CH_2CH_2$), 2.48 (t, J = 7 Hz, 2H, CH_2N), 2.54 (m, 4H, piperazine H), 2.98 (m, 4H, piperazine H), 3.11 (t, J = 7 Hz, 2H, SCH_2), 3.76 (s, 3H, OCH_3), 5.75 (s, 2H, NH_2), 6.83−6.91 (m, 4H, ArH), 7.42 (t, J = 7.7 Hz, 1H, H-7), 7.52 (d, J = 7.7 Hz, 1H, H-5), 7.77 (t, J = 7.7 Hz, 1H, H-6), 8.08 (d, J = 7.7 Hz, 1H, H-8).

Preparation of 5,6,7,8-Tetrahydro-2-(methylthio)-3-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl][1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (80) and of O-Substituted Isomer 81 (Scheme 3). 5,6,7,8-Tetrahydro-2-(methylthio)[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**79**)[31] (0.53 g, 2.1 mmol), anhydrous potassium carbonate (0.29 g, 2.1 mmol), and 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine (**36**) (0.67 g, 2.5 mmol) were heated at reflux in acetonitrile (20 mL) for 6 h. After the mixture was cooled, the solid product was filtered and recrystallized to give a mixture of compounds **80** and **81**. The pure compound **80** crystallized from the filtrate (Table 2). To a solution of compound **79** (0.9 g, 3.6 mmol) in DMF (30 mL) was added sodium hydride (0.20 g, 8.7 mmol 60% suspension in a mineral oil). The suspension was stirred for 30 min, piperazine **36** was added, and the reaction mixture was refluxed under stirring for 5 h. The suspension was filtered and the filtrate was concentrated under reduced pressure to give, by two recrystallizations, the desired compound **81** (Table 2).

Compound **80**: IR (KBr) 1675 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.83 (m, 6H, $CH_2CH_2CH_2$, H-6,7), 2.48 (m, 6H, CH_2N, piperazine H), 2.58 (s, 3H, SCH_3), 2.69 (m, 2H, H-5), 2.89 (m, 6H, H-8, piperazine H), 3.76 (s, 3H, OCH_3), 4.10 (t, J = 7.5 Hz, 2H, $CONCH_2$), 6.80−6.90 (m, 4H, ArH).

Compound **81**: ^{1}H NMR (DMSO-d_6) δ 1.83 (m, 4H, H-6,7), 1.96 (m, 2H, $CH_2CH_2CH_2$), 2.51 (m, 6H, CH_2N, piperazine H), 2.55 (s, 3H, SCH_3), 2.76 (m, 2H, H-5), 2.87 (m, 2H, H-8), 2.96 (m, 4H, piperazine H), 3.77 (s, 3H, OCH_3), 4.54 (t, J = 6.3 Hz, 2H, OCH_2), 6.85−6.90 (m, 4H, ArH).

2-(2-Chloroethyl)-6,7-dimethyl-8*H*-[1,3,4]thiadiazolo-[3,2-*a*]thieno[2,3-*d*]pyrimidin-8-one (82) (Scheme 4). To a mixture of potassium salt **23** (0.9 g, 3.4 mmol), P_2O_5 (0.48 g, 3.4 mmol), and CH_3SO_3H (2.20 mL, 38 mmol) was added 3-chloropropionyl chloride (0.33 mL, 3.4 mmol), and the mixture was stirred for 4 h at 80−90 °C. The cooled reaction mixture was poured into cold water and neutralized with 10% NaOH. The solid product was filtered and washed with water. Recrystallization from ethanol/dioxane gave 0.43 g (42%) of **82** as a light brown powder: mp 216−218 °C dec; IR (KBr) 1680 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.47 (t, J = 6.3 Hz, 2H, CH_2), 3.92 (t, J = 6.3 Hz, 2H, CH_2Cl). Anal. ($C_{11}H_{10}ClN_3OS_2$) C, H, N, S.

2-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-6,7-dimethyl-8*H*-[1,3,4]thiadiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-8-one (83) (Scheme 4). A mixture of the thiadiazolo derivative **82** (0.48 g, 1.6 mmol) and 1-(2-methoxyphenyl)-piperazine (1.6 g, 8.3 mmol) was heated at 140 °C on an oil bath for 2 h. After the mixture was cooled, the melted residue was collected with warm ethanol and recrystallized (Table 2): IR (KBr) 1660 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.69 (m, 6H, CH_2N, piperazine H), 3.03 (m, 4H, piperazine H), 3.20 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 6.92 (m, 4H, ArH).

Pharmacology. Binding Assays. Male CRL:CD(SD)BR-COBS rats weighing about 150 g were killed by decapitation, and their brains were rapidly dissected (hippocampus for 5-HT_{1A}; striatum for 5-HT_{1B}, D_1 and D_2; cortex for 5-HT_{2A}, 5-HT_3 and α_1 adrenergic receptors), frozen, and stored at −80 °C until the day of assay. Pig brains were obtained from a local slaughterhouse, and the cortex (for 5-HT_{2C}) was rapidly removed and stored at −80 °C until assay.

Tissue was homogenized in about 50 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4) (or 50 mM Hepes-HCl (pH 7.5) for 5-HT_3 receptors) using an Ultra Turrax TP-1810 (2 × 20 s) and centrifuged at 50000*g* for 10 min (Beckman model J-21B refrigerated centrifuge). The pellet was resuspended in the same volume of fresh buffer, incubated at 37 °C for 10 min, and centrifuged again at 50000*g* for 10 min. The pellet was then washed once by resuspension in fresh buffer and centrifuged as before. The pellet was then resuspended in the appropriate incubation buffer (50 mM Tris-HCl (pH 7.7) for 5-HT_{2A} receptors, with the addition of 10 μM pargyline for the other receptors containing 4 mM $CaCl_2$ for 5-HT_{1A} receptors, 0.1% ascorbic acid for α_1 adrenergic receptors, 4 mM $CaCl_2$ and 0.1% ascorbic acid for 5-HT_{1B} and 5-HT_{2C} receptors; 50 mM Hepes-HCl pH 7.4 containing 10 μM pargyline for 5-HT_3 receptors, 50 mM Tris-HCl pH 7.1 containing 10 μM pargyline, 120 mM NaCl, 5 mM Kcl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% ascorbic acid for D_1 and D_2 receptors) just before the binding assay.

Binding assays were done as previously described.[32] Briefly, the following incubation conditions were used. 5-HT_{1A}: [^{3}H]-8-OH-DPAT (sp act. 157 Ci/mmol, NEN) final concentration 1 nM, 30 min, 25 °C (nonspecific binding: 5-HT 10 μM). 5-HT_{1B}: [^{3}H]-5-HT (sp act. 14.6 Ci/mmol, NEN) final concentration 2 nM, 30 min, 25 °C (nonspecific binding: 5-HT 10 μM). 5-HT_{2A}: [^{3}H]ketanserin (sp act. 60.0 Ci/mmol, Amersham) final concentration 0.7 nM, 15 min, 37 °C (nonspecific binding: methysergide 1 mM). 5-HT_{2C}: [^{3}H]mesulergine (sp act. 73.0 Ci/mmol, NEN) final concentration 1 nM, 30 min, 37 °C (nonspecific binding: mesulergine 10 mM). 5-HT_3: [^{3}H]-BRL43694 (sp act. 84.8 Ci/mmol, NEN) final concentration 1 nM, 30 min, 25 °C (nonspecific binding: GR38032 10 μM). D_1: [^{3}H]SCH23390 (sp act. 71.1 Ci/mmol, NEN) final concentration 0.4 nM, 15 min, 37 °C (nonspecific binding: (−)-*cis*-flupentixol 10 μM). D_2: [^{3}H]spiperone (sp act. 19.0 Ci/mmol, NEN) final concentration 0.2 nM, 15 min, 37 °C (nonspecific binding: (−)-sulpiride 100 μM). α_1-Adrenergic: [^{3}H]prazosin (sp act. 71.8

Ci/mmol, NEN) final concentration 0.2 nM, 30 min, 25 °C (nonspecific binding: phentolamine 3 μM).

Incubations were stopped by rapid filtration under vacuum through GF/B filters which were then washed with 12 mL (4 × 3 times) of ice-cold 50 mM Tris-HCl (pH 7.4) or 50 mM Hepes-HCl (pH 7.5) using a Brandel M-48R apparatus and counted in 4 mL of Filter Count (Packard) in a LKB 1214 RACKBETA liquid scintillation spectrometer with counting efficiency about 60%. Dose inhibition curves were analyzed by the "Allfit" program to obtain the concentration of unlabeled drugs that inhibited ligand binding by 50%.

Computations. Theoretical studies were run on a Silicon Graphics Indigo R3000 workstation. The energetically favorable conformation of the lead compound (molecule **70**) was sought using Cobra (Oxford Molecular Ltd., Oxford, U.K.), a software package based on the Wizard system,[33] which processes from the input of a two-dimensional representation of the molecule (in which atom types, connectivity and stereochemistry are defined) and generates acceptable conformations, which were classified according to their potential energy. All of the other molecules used in the study were built using the preferred conformation of molecule **70** as scaffold.

Partial atomic charges were calculated using AMPAC AM-1 semiempirical calculations[34] on the lowest energy conformation obtained with COBRA. Total dipole moments for whole molecules and substituents (in Debye units) were calculated using the center of charge gravity as an origin with the following equation

$$\vec{\mu} = e\sum_i \vec{r}_i q_i$$

where r_i = distance of an atom i from the origin and q_i = charge of atom i. Molecular volumes of molecules and substituents were calculated using standard van der Waals radii for each element. The other molecular descriptors were calculated with methods implemented in TSAR. Descriptors showing little variance were not used.

The interactive investigation of QSAR was done using TSAR, a three-dimensional integrated analysis sofware (Oxford Molecular Ltd., Oxford, U.K.). Principal component analysis (PCA) was used to extract a meaningful QSAR interpretation from a multivariate data table with many columns.[15] In all of the PCA in this study, only the first three PCs were considered for further evaluation. Molecules were depicted in the three principal component axes, using three-dimensional graphics, to establish the most important details about ligands. To avoid the results being dominated by properties with the largest numerical range, PCA was performed after standardization of data by mean and standard deviation.

Discriminant analysis was carried out using the calculated PC variables generated by PCA on selected molecular descriptors. A cross-validation procedure was used to assess the true predictive ability of the discriminant model.

The first three PCs were also used as independent variables in a stepwise regression analysis in our calculation for 5-HT_{1A} and α_1-adrenergic activity. The technique of cross-validation was used to estimate the true predictive power of the regression models.

Acknowledgment. The authors thank Mrs. Judy Baggott for revision of the text.

Supporting Information Available: Supporting information available: Spectral data for compounds **45**, **47**−**50**, **53**, **57**, **59**, **61**, **67**, **68**, and **70**−**74** (IR and ^{1}H NMR) (3 pages). Ordering information is given on any current masthead page.

References

(1) Hillver, S.; Bjork, L.; Li, Y.; Svensson, B.; Ross, S.; Andèn, N.; Hacksell, U. (S)-5-Fluoro-8-hydroxy-2-(dipropylamino)tetralin: a putative 5-HT_{1A}-receptor antagonist. *J. Med. Chem.* **1990**, *33*, 1541−1544 and references therein.

(2) Reviews: (a) Glennon, R. A. *Neurosci. Biohehav. Rev.* **1990**, *14*, 35. (b) Kostowski, W.; Plaznik, A.; Archer, T. Possible implications of 5-HT_{1A} function for the etiology and treatment of depression. *New Trends Exp. Clin. Psychiatry* **1989**, *5*, 91−116. (c) Soubrie, P. 5-HT_{1A} receptors: A bridge between anxiety and depression. In *Behavioral Pharmacology of 5-HT*; Bevan, P., Cools, A., Archer, T., Eds.; Lawrance Erlbaum Assoc.: Hilldale, NJ, 1989; pp 337−352. (d) Traber, J.; Glaser, T. 5-HT receptor-related anxiolytics. *Trends Pharmacol. Sci.* **1987**, *8*, 432−437.

(3) Fuller, R. W.; Robertson, D. W. Progress in antidepressant drugs. *Annu. Rep. Med. Chem.* **1991**, *26*, 23−32.

(4) Romero, A. G.; McCall, R. B. Advances in central serotoninergics. *Annu. Rep. Med. Chem.* **1992**, *27*, 21−30.

(5) Glennon, R. A.; Naiman, N. A.; Lyon, R. A.; Titeler, M. Arylpiperazine derivatives as high-affinity 5-HT_{1A} serotonin ligands. *J. Med. Chem.* **1988**, *31*, 1968−1971.

(6) Glennon, R. A.; Westkaemper, R. B.; Bartyzel, P. Medicinal Chemistry of Serotonergic Agents. *Serotonin Receptor Subtypes: Basic and Clinical Aspects*; Peroutka, S. J., Eds.; Wiley-Liss, Inc.: New York, 1991; Vol. 15, pp 19−64.

(7) Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Titeler, M.; Lyon, R. A.; Weisberg, E. NAN-190: an arylpiperazine analog that antagonizes the stimulus effects of the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). *Eur. J. Pharmacol.* **1988**, *154*, 339−34.

(8) Hibert, M. F.; Mir, A. K.; Fozard, J. R. Serotonin (5-HT) Receptors. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Eds.; Pergamon Press, Inc.: New York, 1990; Vol. 3, pp 567−600.

(9) Raghupathi, R. K.; Rydelek-Fitzgerald, L.; Teitler, M.; Glennon, R. A. Analogues of the 5-HT_{1A} serotonin antagonist 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine with reduced α_1-adrenergic affinity. *J. Med. Chem.* **1991**, *34*, 2633−2638.

(10) Romeo, G.; Ambrosini, G.; Guccione, S.; De Blasi, A.; Russo, F. Pyrimido[5,4-*b*]benzofuran and pyrimido[5,4-*b*]benzothiophene derivatives. Ligands for α_1 and 5-HT_{1A} receptors. *Eur. J. Med. Chem.* **1993**, *28*, 499−504.

(11) Russo, F.; Romeo, G.; Guccione, S.; De Blasi, A. Pyrimido[5,4-*b*]indole derivatives. 1. A new class of potent and selective α_1-adrenoceptor ligands. *J. Med. Chem.* **1991**, *34*, 1850−1854.

(12) Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. Graphic computer-aided receptor mapping as a predictive tool for drug design: development of potent, selective, and stereospecific ligands for the 5-HT_{1A} receptor. *J. Med. Chem.* **1988**, *31*, 1087−1093.

(13) Hibert, M. F.; McDermott, I.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. Radioligand binding study of a series of 5-HT_{1A} receptor agonists and definition of a steric model of this site. *Eur. J. Med. Chem.* **1989**, *24*, 31−37.

(14) Modica, M.; Synthesis of thieno[2,3-*d*]pyrimidine derivatives. Ligands for 5-HT_{1A} receptors. Dottorato di Ricerca, Italian Ph.D., 1994.

(15) Chatfield, C.; Collins, A. J. *Introduction to multivariate analysis*; Chapman and Hall: London, 1980.

(16) Gewald, K.; Schinke, E.; Boettcher, H. Heterocycles from CH-acidic nitriles. VIII. 2-Aminothiophenes from methylene-active nitriles, carbonyl compounds, and sulfur. *Chem. Ber.* **1966**, *99*, 94−100.

(17) Gewald, K.; Neumann, G. Heterocycles from CH-acid nitriles. XIV. 2-Aminothionaphthene. *Chem. Ber.* **1968**, *101*, 1933−1939.

(18) Sugiyama, M.; Sakamoto, T.; Tabata, K.; Endo, K.; Ito, K.; Kobayashi, M.; Fukumi, H. Condensed thienopyrimidines. II. II. Synthesis and gastric antisecretory activity of thiazole and polymethylene condensed thienopyrimidine derivatives. *Chem. Pharm. Bull.* **1989**, *37*, 2122−2131.

(19) Kienzle, F.; Kaiser, A.; Minder, R. E. Synthesis of 2,3,4,5-1*H*-tetrahydroimidazo[2,1-*b*]quinazoline-2,5-diones and analogous 2,3,4,5-1*H*-tetrahydroimidazo[1,2-*a*]thieno[2,3-*d*] (or [3,2-*d*])-pyrimidine-2,5-diones. *Helv. Chim. Acta* **1983**, *66*, 148−157.

(20) Dobosh, A. A.; Khipak, S. M.; Smolanka, I. V. Ciclization of substituted 2-(N-acylthioureido)-3-carbethoxythiophenes. *Khim. Geterotsikl. Sodim.* **1974**, *4*, 486−488.

(21) (a) Devani, M. B.; Shishoo, C. J.; Pathak, U. S.; Parikh, S. H.; Shah, G. F.; Padhya, A. C. Synthesis of 3-substituted thieno-[2,3-*d*]pyrimidin-4(3*H*)-one-2-mercaptoacetic acid and their ethyl esters for pharmacological screening. *J. Pharm. Sci.* **1976**, *65*, 660−664. (b) The unknown potassium salts were obtained from the respective 2-thioxo derivative and a solution of an equimolar amount of KOH in absolute ethanol at reflux.

(22) Santagati, A.; Santagati, M.; Modica, M. Synthesis of 2,3,5,6,7,8-hexahydro-3-amino-2-thioxo[1]benzothieno[2,3-*d*]-pyrimidin-4(1*H*)-one and derivatives of the new heterocyclic system 7,8,9,10-tetrahydro-3*H*,11*H*-[1]benzothieno[2′,3′:4,5]pyrimido[2,1-*b*][1,3,4]thiadiazin-11-one. *Heterocycles* **1993**, *36*, 1315−1321.

(23) Pollard, C. B.; Lauter, W. M.; Nuessle, N. O. Derivatives of piperazine. XXXIV. Some reactions of trimethylene chlorobromide with 1-arylpiperazines. *J. Org. Chem.* **1959**, *24*, 764−767.

(24) Bourdais, J. Alkylation of piperazines in N,N-dimethylformamide. *Bull. Soc. Chim. Fr.* **1968**, *8*, 3246−3249.
(25) Bermann, M. C.; Bonte, J. P.; Lesieur-Demarquilly, I.; Debaert, M.; Lesieur, D.; Leinot, M.; Benoit, J.; Labrid, C. Pharmacomodulation of the benzoxazolinone model by arylpiperazine structure. *Eur. J. Med. Chem.—Chim. Ther.* **1982**, *17*, 85−88.
(26) Santagati, A.; Modica, M.; Santagati, M.; Cutuli, V.; Amore, D.; Caruso, A. Synthesis and pharmacological properties of thieno-[2′,3′:4,5]pyrimido[2,1-*b*][1,3,4]thiadiazine derivatives. *Il Farmaco* **1995**, *50*, 605−609.
(27) Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Titeler, M.; McKenney, J. D. 5-HT_1 and 5-HT_2 Binding characteristics of some quipazine analogues. *J. Med. Chem.* **1986**, *29*, 2375−2380.
(28) Parcell, R. F. 4-(o-Substituted-phenyl)-1-hydroxyalkylpiperidines. U.S. Patent 2,891,066, 1959; *Chem. Abstr.* **1960**, *54*, 4627d.
(29) Wamhoff, H.; Mumtaz, E. Heterocyclic β-enamino esters; 35. Heteroannulated uracils by means of chlorosulfonyl isocyanate an sulfonyl analogs of uracil. *Synthesis* **1985**, *2*, 190−194.
(30) Cherbuliez, E.; Willhalm, B.; Jaccard, S.; Rabinowitz, J. Formation and rearrangement of esters. LXXVIII. Reaction of o-methoxycarbonylphenyl isothiocyanate with diamines and hydrazine, and cyclization of some N-phenyl-N′-hydroxyalkylthioureas. *Helv. Chim. Acta* **1967**, *50*, 2563−2568.
(31) Sauter, F.; Deinhammer, W. Synthesis of 2-mercaptothieno[2,3-*d*]pyrimidin-4(3*H*)-ones. *Monatsh. Chem.* **1973**, *104*, 1593−1598.
(32) Caccia, S.; Confalonieri, S.; Guiso, G.; Bernasconi, P.; Cagnotto, A.; Skorupska, M.; Mennini, T. Brain uptake and distribution of the potential memory enhancer CL 275,838 and its main metabolites in rats: relationship between brain concentrations and in vitro potencies on neurotrasmitter mechanisms. *Psychopharmacology* **1994**, *115*, 502−508.
(33) Leach, A. R.; Prout, K.; Dolata, D. P. Automated conformational analysis: Algorithms for the efficient construction of low energy conformations. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 271−282.
(34) Dewan, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. Development and use of quantum mechanical molecular models. 76. AM1: a new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

JM950866T