Dopamine Autoreceptor Agonists as Potential Antipsychotics. 3.[1] 6-Propyl-4,5,5a,6,7,8-hexahydrothiazolo[4,5-*f*]quinolin-2-amine

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A series of rigid tricyclic analogues of the dopamine (DA) agonist PD 118440 [4-(1,2,5,6-tetrahydro-1-propyl-3-pyridinyl)-2-thiazolamine] was synthesized and evaluated for dopaminergic activity and DA autoreceptor selectivity. (*R*)-(+)-6-Propyl-4,5,5a,6,7,8-hexahydrothiazolo[4,5-*f*]quinolin-2-amine ((+)-6) was identified as the most selective DA autoreceptor agonist from this group of compounds. It inhibited spontaneous locomotor activity (LMA) in rodents, reversed the γ-butyrolactone (GBL) induced accumulation of rat striatal DOPA and inhibited brain DA neuronal firing, all suggestive of direct DA autoreceptor agonist activity. However, (+)-6 is not completely free of postsynaptic DA activity, as evidenced by its stimulation of LMA in rats at high doses and its ability to produce stereotypy. On the other hand, (-)-6 appears to be a weak partial DA agonist with some effects on brain DA synthesis only at high doses. Like other DA autoreceptor agonists and DA antagonists, (+)-6 inhibited Sidman conditioned avoidance in squirrel monkeys, a test predictive of clinical antipsychotic activity. However, unlike classical antipsychotics, (+)-6 did not induce dystonias in haloperidol-sensitized squirrel monkeys, suggesting a minimal propensity toward extrapyramidal side effects (EPS).

Introduction

Presynaptic dopamine receptors (DA autoreceptors) serve an inhibitory feedback function on brain dopaminergic neurotransmission. Activation of DA autoreceptors inhibits DA neuronal firing as well as brain DA synthesis and release.[2] For this reason, recent years have witnessed the efforts of a large number of research groups seeking novel compounds that activate DA autoreceptors without appreciable activity at the more numerous postsynaptic DA receptors.[3] Since schizophrenia is generally believed to be associated with increased brain dopaminergic activity, these compounds are viewed as a promising therapeutic alternative to the classical DA antagonist antipsychotic drugs.[4] The postulate is that DA autoreceptor activation should produce a more subtle downregulation of brain dopaminergic activity than the complete blockade induced by DA antagonists. This should translate into a lack of the common side effects that are mechanistically associated with DA receptor blockade, such as extrapyramidal syndrome (EPS), tardive dyskinesia (TD), and hyperprolactinemia.[5]

We recently reported on PD 118440 (1),[6] an orally active DA agonist with marked central nervous system (CNS) effects. This compound activated central DA autoreceptors but showed little selectivity for pre- vs postsynaptic DA receptors. As seen with other nonselective DA agonists (i.e. apomorphine[7]), low doses of 1 stimulated DA autoreceptors selectively but high doses produced clear signs of postsynaptic DA stimulation. The separation between doses of 1 that produced effects mediated by pre- and postsynaptic DA receptor activation, respectively, was estimated to be in the 1-10-fold range, depending on the particular tests used. This report describes some of our efforts to modify the structure of 1 in order to increase DA autoreceptor selectivity while the good oral activity and CNS penetration of 1 is maintained.

The synthesis of 1 was the result of modeling studies that suggested that 1 possesses two energy minima with dihedral angles between the planes of both rings of 0° and 180°, respectively.[6] This is in agreement with the generally accepted view that the aromatic ring and amine nitrogen of DA agonists must be nearly coplanar.[8] In contrast to 1, a piperidine analogue lacking the stabilizing effect of the conjugation between the olefinic double bond and the aminothiazole ring was predicted to possess no energy

Table I. Effects of Target Compounds on DA Receptors

compd	DA receptor binding: IC_{50} (nM) ± SEM [or % inhibn] [^{3}H]SPIP[a,b]	[^{3}H]SCH-23390[b,c]	inhibn of LMA:[d,e] ED_{50} (mg/kg) ± SEM mouse, ip	rat, po
1	574 ± 10	~10 000	4.3 ± 1.4	3.1 ± 0.5
(±)-6	2197 ± 103	>10 000	9.4 ± 1.9	18.9 ± 2.6
(+)-6	860 ± 104	>10 000	3.7 ± 1.5	7.0 ± 0.8
(-)-6	2243 ± 11	>10 000	20.4 ± 3.8	>30
13	15 550 ± 1239	>10 000	9.3 ± 1.9	7.6 ± 3.3
17	1129 ± 86	>10 000	>30	NT[f]
18	3428 ± 244	~10 000	18.8 ± 1.7	NT
26	[14% at 10^{-5} M]	NT	>30	NT
27	[10% at 10^{-5} M]	NT	>30	NT
28	[16% at 10^{-5} M]	NT	>30	NT
29	1235 ± 92	>10 000	~7[g]	NT
35	[18% at 10^{-5} M]	NT	>20	>30
36	[10% at 10^{-5} M]	NT	>30	NT
apomorphine	24 ± 4	384 ± 8	6.9 ± 0.7	>30
(+)-3-PPP[h]	2280 ± 150	>10 000	NT	inactive[i]

[a] SPIP = spiperone; D_2 binding. [b] IC_{50} values were obtained from four or five concentrations, run in triplicate, by a nonlinear regression analysis. [c] D_1 binding. [d] ED_{50} values were generated from four to six doses; 5-12 animals were used per dose. [e] No ataxia was observed up to doses of 30 mg/kg. [f] NT = not tested. [g] A maximal 50% inhibition of activity was observed in the 3-10 mg/kg range, but the mice were greatly stimulated at 30 mg/kg. [h] 3-PPP: 3-(3-hydroxyphenyl)-1-propylpiperidine. [i] Maximal inhibition was 40% at 3 mg/kg sc. Higher doses produced stimulation.

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(1) For part 2 of this series, see: Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Pugsley, T. A.; Meltzer, L. T. Dopamine Autoreceptor Agonists as Potential Antipsychotics. 2. (Aminoalkoxy)-4*H*-1-benzopyran-4-ones. *J. Med. Chem.* **1991**, *34*, 248-256.
(2) (a) Carlsson, A. Receptor-Mediated Control of Dopamine Metabolism. In *Pre- and Postsynaptic Receptors*; Usdin, E., Bunney, W. E., Ed.; Marcel Dekker: New York, 1975; pp 49-65. (b) Roth, R. H. Dopamine Autoreceptors: Pharmacology, Function And Comparison With Postsynaptic Dopamine Receptors. *Commun. Psychopharmacol.* **1979**, *3*, 429-445.
(3) (a) New, J. S.; Takaki, S. Antipsychotic Agents. In *Annual Reports in Medicinal Chemistry*; Allen, R. C. Ed.; Academic Press: San Diego, 1988; Vol. 23, pp 2-4. (b) New, J. S.; Takaki, K. S. Antipsychotic Agents. In *Annual Reports in Medicinal Chemistry*; Allen, R. C. Ed.; Academic Press: San Diego, 1989; Vol. 24, pp 3-4. (c) Abou-Gharbia, M.; Moyer, J. A. Novel Antipsychotic Agents. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A. Ed.; Academic Press: San Diego, 1990; Vol. 25, pp 3-4.

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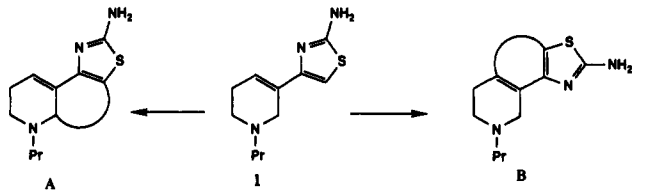
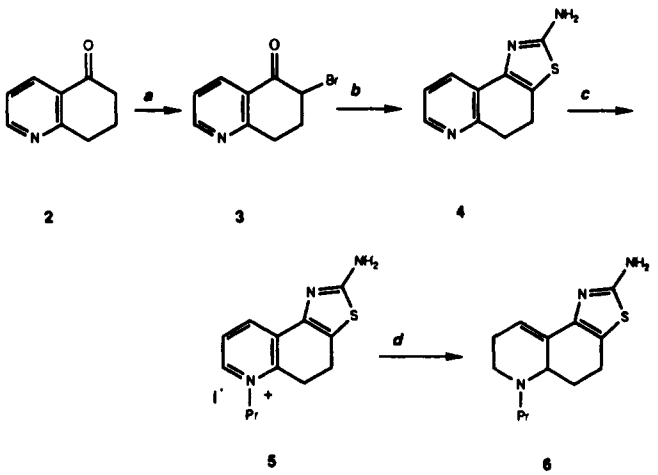


Figure 1. Rigid analogues of 1.

Scheme I[a]



[a](a) Br_2, 48% HBr, 25 °C; (b) H_2NCSNH_2, H_2O, 100 °C; (c) $ICH_2CH_2CH_3$, CH_3CN, reflux; (d) $NaBH_4$, $MeOH/H_2O$, 0 °C.

minimum close to the coplanar conformation. Subsequent experiments with this compound substantiated our prediction that it was not a good DA agonist.[6]

Conceptually, the compounds described in this report are the result of locking both coplanar conformations of 1 into rigid tricyclic structures represented by general

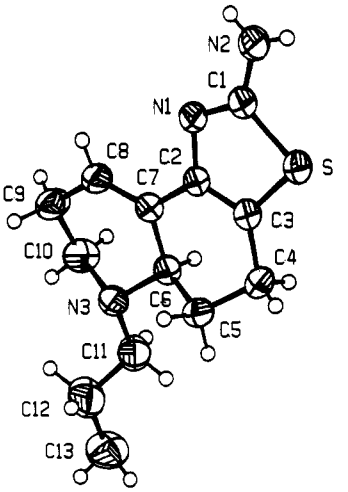


Figure 2. Computer-generated ORTEP drawing of (±)-6.

structures A and B in Figure 1. Our expectation was that these compounds would help identify which coplanar conformation of 1 is biologically significant. These rigid compounds might also be expected to possess improved DA autoreceptor selectivity, since incorporation of the (*m*-hydroxyphenyl)ethylamine DA pharmacophore into rigid tricyclic structures has produced relatively selective DA autoreceptor agonists.[9]

Chemistry

The synthesis of 6, a tricyclic structure of the general type A, is outlined in Scheme I. Dihydroquinolinone 2 was prepared according to the procedure of Rimek et al.[10] Reaction of 2 with bromine in 48% HBr gave the hydrobromide salt of 3[11] in 88% yield. An aqueous solution of 3 was treated with thiourea to produce tricyclic intermediate 4 in 63% yield. We have determined 4 to be extremely active in the Ames bacterial mutagenicity test and *it should be handled with extreme caution*![12] Reaction of 4 with a large excess of 1-iodopropane in refluxing acetonitrile or methanol produced the monoalkylated pyridinium quaternary salt 5[13] in 72% yield as the only

(4) (a) Corsini, G. U.; Pitzalis, G. F.; Bernardi, F.; Bocchetta, A.; Del Zompo, M. The Use of Dopamine Agonists in the Treatment of Schizophrenia. *Neuropharmacology* 1981, *20*, 1309–1313. (b) Wiedemann, K.; Benkert, O.; Holsboer, F. B-HT 920: A Novel Dopamine Autoreceptor Agonist in the Treatment of Patients with Schizophrenia. *Pharmacopsychiatry* 1990, *23*, 50–55.

(5) (a) Tamminga, C. Atypical Neuroleptics and Novel Antipsychotic Drugs. In *Neuroleptics: Neurochemical, Behavioral and Clinical Perspectives*; Coyle, J. T., Enna, S. J., Eds.; Raven: New York, 1983; pp 281–295. (b) Baldessarini, R. J.; Tarsy, D. Mechanisms Underlying Tardive Dyskinesia. In *The Basal Ganglia*; Yahr, M. D., Ed.; Raven: New York, 1976; pp 433–446.

(6) Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A. 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: A Novel Class of Compounds with Central Dopamine Agonist Properties. *J. Med. Chem.* 1990, *33*, 311–317.

(7) Costall, B.; Lim, S. K.; Naylor, R. J. Characterization of the Mechanisms by Which Purported Dopamine Agonists Reduce Locomotor Activity of Mice. *Eur. J. Pharmacol.* 1981, *73*, 175–188.

(8) (a) Cannon, J. G. Dopamine Agonists: Structure–Activity Relationships. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag: Basel, 1985; Vol. 29, pp 306. (b) Liljefors, T.; Wikstrom, H. A Molecular Mechanics Approach to the Understanding of Presynaptic Selectivity for Centrally Acting Dopamine Receptor Agonists of the Phenylpiperidine Series. *J. Med. Chem.* 1986, *29*, 1896–1904. (c) Froimowitz, M.; Neumeyer, J. L.; Baldessarini, R. A Stereochemical Explanation of the Dopamine Agonist and Antagonist Activity of Stereoisomeric Pairs. *J. Med. Chem.* 1986, *29*, 1570–1573. (d) Johansson, A. H.; Karlen, A.; Grol, C. J.; Sundell, S.; Kenne, L.; Hacksell, U. Dopaminergic 2-Aminotetralins: Affinities for Dopamine D_2-Receptors, Molecular Structures, and Conformational Preferences. *Mol. Pharmacol.* 1986, *30*, 258–269.

(9) (a) Hjorth, S.; Svensson, K.; Carlsson, A.; Wikstrom, H.; Andersson, B. Central Dopaminergic Properties of HW-165 and its Enantiomers; *trans*-Octahydrobenzo(*f*)quinoline Congeners of 3-PPP. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1986, *333*, 205–218. (b) Altar, C. A.; Boyar, W. C.; Wood, P. L. Dopamine Autoreceptor Agonists Including CGS 15855A Decrease Dopamine Release and Metabolism in Mouse Brain. *Eur. J. Pharmacol.* 1987, *134*, 303–311.

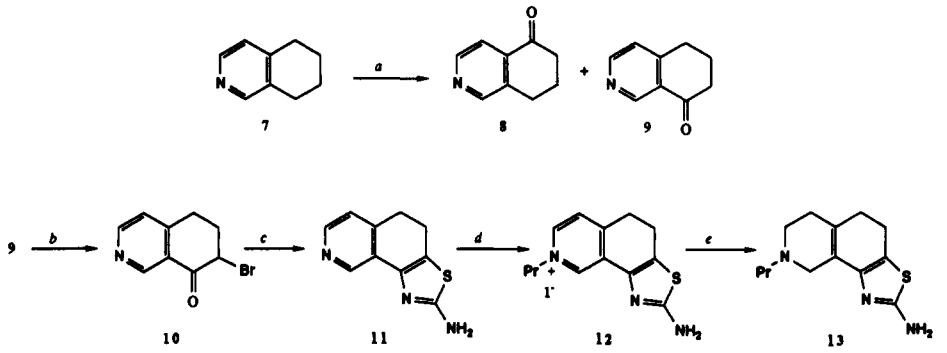
(10) Zymalkowski, F.; Rimek, H. J. *Arch. Pharm.* 1961, *294*, 759–765.

(11) Zymalkowski, F.; Rimek, H. J. *Arch. Pharm.* 1962, *295*, 217–223.

(12) A paper describing the mutagenicity of this and related compounds is in preparation. A preliminary account of this work has been presented: Kropko, M. L.; Jaen, J. C.; Wold, S. A.; Caprathe, B. W.; Wise, L. D.; Theiss, J. C. Bacterial Mutagenicity Assessment of Structurally-Related Quinoline Thiazolamine Compounds. 5th International Conference on Environmental Mutagens, Cleveland, Ohio, July 10–15, 1989. Abstract No. 307. *Environ. Mol. Mutagen.* 1989, *14* Suppl. 15, 107. See also footnote 13.

(13) Even though the mutagenic potential of these compounds has not been established experimentally, it is our opinion that they should be treated with extreme caution, given their structural similarity to 4 and to well-established mutagens such as IQ and MeIQ: (a) Kasai, H.; Yamaizumi, Z.; Shiomi, T.; Yokoyama, S.; Miyazawa, T.; Wakabayashi, K.; Nagao, M.; Sugimura, T.; Nishimura, S. Structure of a Potent Mutagen Isolated from Fried Beef. *Chem. Lett.* 1981, 485–488. (b) Sugimura, T.; Sato, S. Mutagens-Carcinogens in Foods. *Cancer Res.* 1983, *43* (*supl.*), 2415s–2421s.

Scheme II[a]



[a] (a) CrO_3, AcOH, H_2SO_4, 0 °C; (b) Br_2, 48% HBr, 25 °C; (c) H_2NCSNH_2, H_2O, 100 °C; (d) $ICH_2CH_2CH_3$, CH_3CN, reflux; (e) $NaBH_4$, $MeOH/H_2O$, 0 °C.

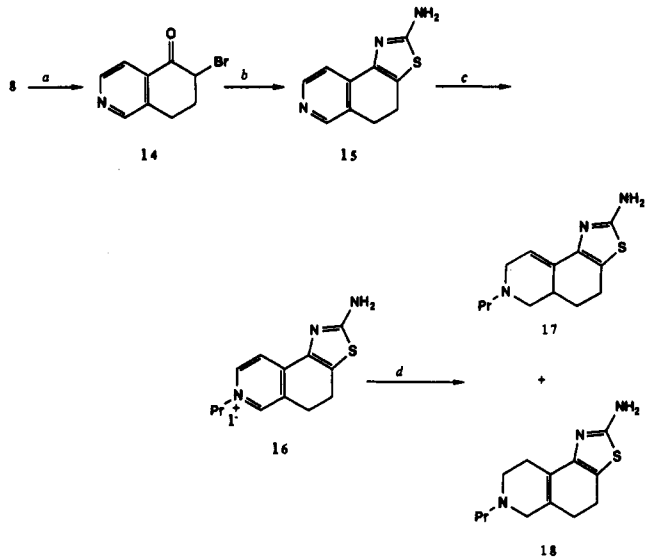
isolated product. Reduction of **5** with sodium borohydride in MeOH/water (1:1) at 0 °C produced **6** as the only detectable regioisomer in 35% yield. The structure of **6** was corroborated by single-crystal X-ray analysis; the computer-generated ORTEP drawing of **6** is presented in Figure 2. As required by our design rationale outlined above, the thiazole ring and the tetrahydropyridine nitrogen atom appear to be nearly coplanar.

Generic structure B (Figure 1) is exemplified by **13**, the synthesis of which is outlined in Scheme II. Tetrahydroisoquinoline **7** was prepared according to the method of Eliel[14] and oxidized with chromic acid by a slight modification of the procedure of Sugimoto et al.[15] to give isomeric ketones **8** and **9** in low yield. Ketone **9** was converted into **13** by a series of steps similar to those described above for the conversion of **2** into **6**.

Since ketone **8** was available as a byproduct of the synthesis of **9**, compounds **17** and **18**, which are structural isomers of **6** and **13**, were prepared by a sequence of reactions similar to the synthesis of **13** (Scheme III). In this particular case, reduction of quaternary salt **16** gave a mixture of regioisomers **17** and **18**.

The olefinic double bond of **1** is essential for inducing a coplanar orientation of both rings,[6] which is thought to be a requirement for dopaminergic activity. However, because tricyclic structures such as **6** lack free rotation around the bond that joins those two rings, the olefinic double bond may be superfluous. On the basis of this argument, compounds **28** and **29** were targeted for synthesis. As described in Scheme IV, hexahydroquinolinone **19** was reduced according to the procedure of Grob[16] to produce amino alcohol **20** as a mixture of three diastereomers which were protected as their *t*-BOC derivatives (**21**) in 96% yield. This mixture of protected amino alcohols was oxidized with PDC to give a mixture of *cis*- and *trans*-ketones **22**[17] (31%) and **23** (37%), respectively. These ketones were separated chromatographically and found to be fairly stable toward epimerization under the reaction conditions used for the next step. The kinetic enolate of **22** was formed with LDA at −78 °C and trapped

Scheme III[a]



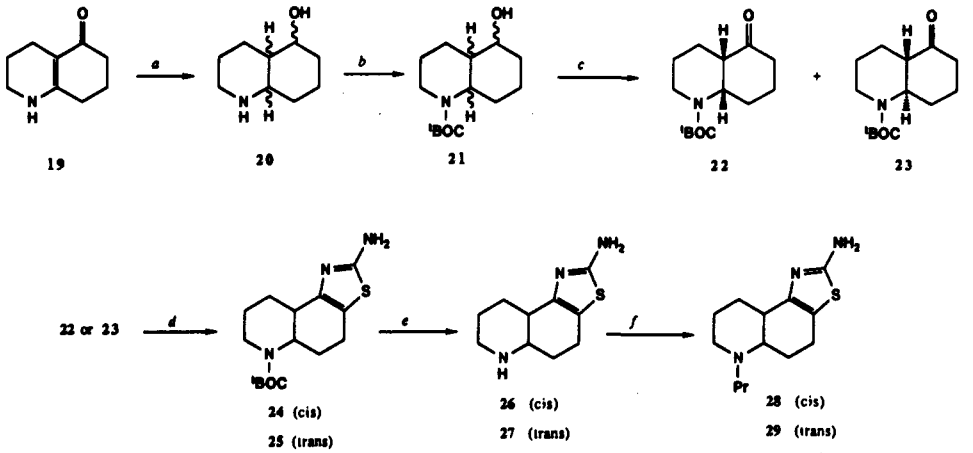
[a] (a) Br_2, 48% HBr, 25 °C; (b) H_2NCSNH_2, H_2O, 100 °C; (c) $ICH_2CH_2CH_3$, CH_3CN, reflux; (d) $NaBH_4$, $MeOH/H_2O$, 0 °C.

as its TMS enol ether, which was regioselectively brominated with NBS and treated with thiourea to give **24** in 53% overall yield. The *t*-BOC group was removed with HCl to give **26** in 98% yield. Reaction of **26** with 1-iodopropane in the presence of KOH gave the desired compound **28** in 81% yield. By a similar sequence of steps, *trans*-ketone **23** was transformed into *trans*-aminothiazole **29**.

As indicated below, dopaminergic activity seemed to reside in compounds of general structure A rather than B. The effect of changing the size of the central ring in structure A was explored by preparing compound **35**, the seven-member analogue of **6**. As depicted in Scheme V, chromic acid oxidation of **30**, following a procedure similar to the one used for the oxidation of **7**, produced ketone **31**[18] in 4.4% yield. The isomeric 9-ketone might have been formed in very small amounts but was never isolated. Bromination of **31** and reaction with thiourea produced tricyclic intermediate **33** in about 70% yield. Quaternary salt **34** was prepared and reduced to give the tetrahydro and hexahydro derivatives **35** (32%) and **36** (30%), respectively. The amount of overreduced product (**36**) obtained in this case was unexpected since similar results

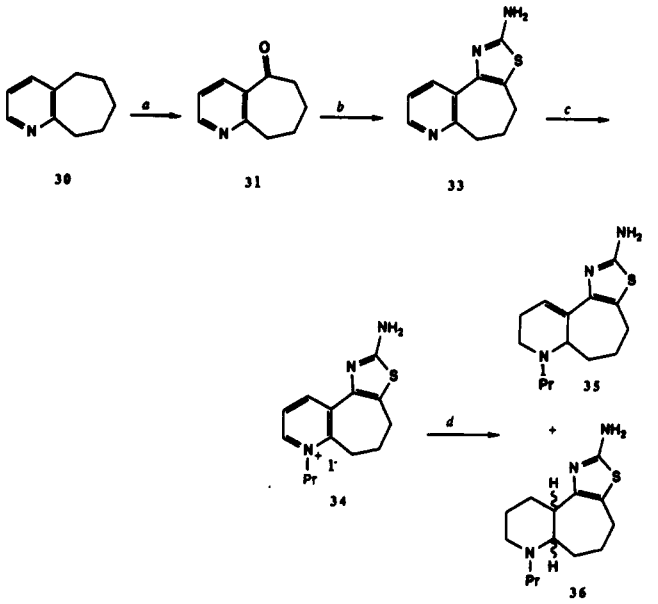
(14) Eliel, E. L.; Vierhapper, F. W. Selective Hydrogenation of Quinoline and its Homologs, Isoquinoline, and Phenyl-Substituted Pyridines in the Benzene Ring. *J. Org. Chem.* 1975, *40*, 2729–2734.
(15) Sugimoto, N.; Kugita, H.; Tanaka, T. Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. X. Oxidation of Alkylpyridines. *J. Pharm. Soc. Jpn.* 1956, *76*, 1308–1310.
(16) Grob, C. A.; Kiefer, H. R. *Helv. Chim. Acta* 1965, *48*, 799–808.
(17) LeBel, N. A.; Caprathe, B. W. Nitrones by Heterolytic Fragmentation of *N*-Hydroxyamino Sulfonates. Conversion of a Decahydroquinoline to a Perhydroazaazulene. *J. Org. Chem.* 1985, *50*, 3938–3940.
(18) Dammertz, W.; Reimann, E. Synthesis of 6,7,8,9-Tetrahydro-5H-cyclohepta[*b*]pyridine-5-one. *Arch. Pharm. (Weinheim, Ger.)* 1977, *310*, 172–174.

Scheme IV[a]



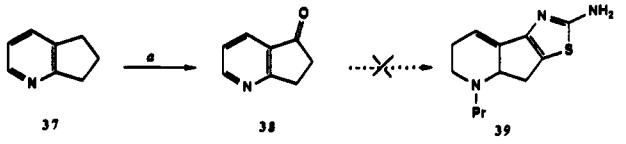
[a] (a) H_2, PtO_2, AcOH, 50 °C; (b) $(^tBuOCO)_2O$, 6 N NaOH, THF/H_2O, 25 °C; (c) PDC, CH_2Cl_2, 25 °C; (d) (i) LDA, THF, −78 °C, (ii) TMSCl, −78 °C, (iii) NBS, THF, 0 °C, (iv) H_2NCSNH_2, THF; (e) HCl, MeOH/$CHCl_3$; (f) $ICH_2CH_2CH_3$, KOH, EtOH, reflux.

Scheme V[a]



[a] (a) CrO_3, AcOH, H_2SO_4, 0 °C; (b) (i) Br_2, 48% HBr, 25 °C, (ii) H_2NCSNH_2, H_2O, 100 °C; (c) $ICH_2CH_2CH_3$, CH_3CN, reflux; (d) $NaBH_4$, MeOH/H_2O, 0 °C.

Scheme VI[a]



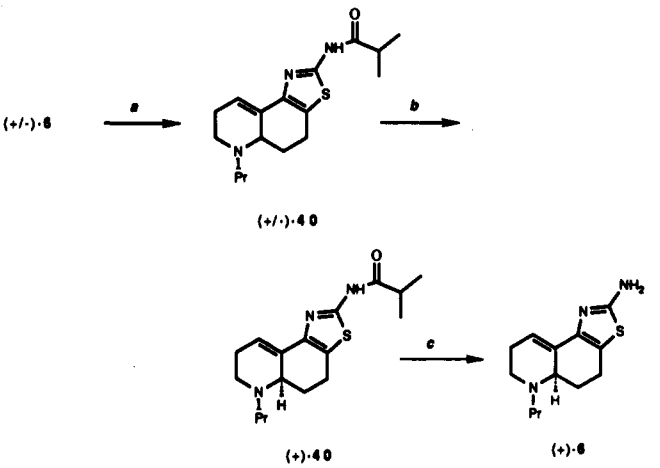
[a] (a) CrO_3, AcOH, H_2SO_4, 0 °C.

have never been observed in the preparation of **6**.

Compound **39**, the five-member analogue of **6**, was targeted for synthesis (Scheme VI) but could not be prepared due to the instability of the required ketone **38**.[19] Although **38** was prepared in about 10% yield by chromic acid oxidation of **37**, it could not be obtained analytically pure and seemed to decompose further when reactions were attempted on the crude material.

The resolution of **6** is outlined in Scheme VII. All attempts to resolve **6** directly by recrystallization of a

Scheme VII[a]



[a] (a) $[(CH_3)_2CHCO]_2O$, $(CH_3)_2CHCO_2Na$, reflux; (b) (−)-ditoluoyl-L-tartaric acid, EtOH; (c) 10% HCl, reflux.

number of crystalline diastereomeric salts failed to provide enriched material. Postulating that the two basic nitrogen atoms of the aminothiazole were competing with the N_6 nitrogen for complexation with the chiral acid, a small group of amides of **6** was prepared. Isobutyramide **40** was found to be suitable for our plans. Thus, two recrystallizations of the salt of **40** and either (−)- or (+)-ditoluoyltartaric acid routinely gave material with greater than 98% ee (determined by chiral HPLC: see the Experimental Section). Neutralization of the diastereomeric salts gave (+)-**40** and (−)-**40**, respectively. (+)-**40** and (−)-**40** were hydrolized with 10% HCl to give (*R*)-(+)-**6** and (*S*)-(−)-**6**, respectively. The absolute stereochemistry of (+)-**6** has been assigned as *R*, based on X-ray crystallography studies done on its *N*-methyl analogue. A full account of this work as well as the SAR of the *N*-alkyl group in structures related to **6** is in preparation.

Pharmacology

The affinity of compounds for DA D_2 receptors in rat striatal membranes was determined in vitro with the DA antagonist [^{3}H]spiperone ([^{3}H]SPIP)[20] and the DA agonist

(19) Ruangsiyanand, C.; Rimek, H. J.; Zymalkowski, F. *Chem. Ber.* **1970**, *103*, 2403–2410.

(20) Urwyler, S.; Markstein, R. Identification of Dopamine "D3" and "D4" Binding Sites, Labeled with [^{3}H]-2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene, as High Agonist Affinity States of the D1 and D2 Dopamine Receptors, Respectively. *J. Neurochem.* **1986**, *46*, 1058–1067.

Table II. Effects of Selected Compounds on Brain DA Synthesis and DA Neuronal Firing

compd	reversal of DOPA accumulation:[a] ED_{50} (95% CI) mg/kg ip	% inhibn of DA neuronal firing[b] ± SEM
1	1.3 (1.05–1.55)	100 ± 0
(±)-6	4.0 (3.10–5.30)	100 ± 0
(+)-6	1.3 (0.46–2.32)	91 ± 6
(−)-6	[14% at 10 mg/kg]	22 ± 8
13	[0% at 10 mg/kg]	NT[c]
29	[100% at 10 mg/kg]	94 ± 3
apomorphine	[57% at 0.3 mg/kg]	100 ± 0[d]
(+)-3-PPP	[58% at 10 mg/kg]	100 ± 0

[a] Shown are the ED_{50} values for the reversal of the increase in DOPA levels in the striatum of GBL-treated rats (n = 4 or 5 rats). Endogenous levels of DA were not affected by the test compounds. For compounds where an ED_{50} was not calculated, the percent reversal produced by a test dose is shown in brackets. [b] All compounds were administered at 2.5 mg/kg ip (n = 3–5 rats) unless otherwise noted. [c] NT = not tested. [d] At 0.25 mg/kg ip.

[^{3}H]-*N*-propylnorapomorphine ([^{3}H]NPA)[21] as ligands. Affinity for DA D_1 receptors was determined with the selective D_1 antagonist SCH23390.

Inhibition of exploratory locomotor activity (LMA) in mice and rats was used as a behavioral index of DA autoreceptor agonist activity.[22] Inhibition of the spontaneous firing of substantia nigra DA neurons in anesthetized rats[23] and reversal of the γ-butyrolactone (GBL) induced increase in the rate of L-dihydroxyphenylalanine (DOPA) synthesis[24] in rat corpus striatum were used as neurophysiological and neurochemical indices of DA autoreceptor agonist efficacy, respectively.

The relative selectivity of DA agonists for pre- vs postsynaptic DA receptors was assessed by studying their effects on rat spontaneous LMA over a wide dose range and comparing the doses of each compound that produced locomotor inhibition and stimulation, respectively,[7,25] and by evaluation of their ability to produce stereotypy in rats (postsynaptic DA receptor agonist effect).[26]

Finally, the most selective DA autoreceptor agonists from this series were evaluated in the Sidman avoidance test[27] in squirrel monkeys, a test which is considered to be predictive of clinical antipsychotic activity.[28] These compounds were also tested in haloperidol-sensitized squirrel monkeys,[29] a highly predictive test for antipsychotic-induced EPS.[28]

Results and Discussion

As shown in Tables I and II, 6 was found to be a DA autoreceptor agonist. Thus, 6 inhibited spontaneous LMA in rodents, reversed the GBL-induced accumulation of striatal DOPA and inhibited DA neuronal firing. On the other hand, even though 13 was able to inhibit LMA in rodents, it did not seem to possess a DA agonist mechanism of action since it was inactive in the GBL test. This suggests that of the two nearly coplanar conformations identified as energy minima for 1, conformation A, contained in 6, is likely to be the one responsible for DA agonist activity. This observation is further supported by the greater affinity of 6 vs 13 for D_2 receptors.

Interestingly, 29, the trans-saturated analogue of 6, also appears to be a DA agonist as indicated by its activity in the DA neuronal firing and GBL tests (Table II). Thus, as suggested above, the piperidine double bond that is essential for dopaminergic activity in 1 is no longer required when the relative orientation of the aminothiazole and piperidine rings is fixed as in 29. In fact, the pronounced stimulation observed in the mouse LMA test at doses greater than 10 mg/kg suggests that 29 activates both pre- and postsynaptic DA receptors (see footnote *g* in Table I). No such stimulation was ever observed in mice with 6.

In contrast, 28, the cis isomer of 29, possessed no dopaminergic activity. Also inactive were 26 and 27, the despropyl analogues of 28 and 29, respectively. The introduction of a seven-membered central ring in 35 and 36 was also detrimental to dopaminergic activity, probably by deforming the nearly coplanar arrangement of the tetrahydropyridine and thiazole rings found in 6.

Since 6 appeared to be the most selective DA autoreceptor agonist in the group, its enantiomers were evaluated (Tables I–III). While (+)-6 had affinity for DA receptors, decreased LMA in rodents, inhibited DA neuronal firing, and reversed GBL-induced striatal DOPA accumulation, all suggestive of a DA autoreceptor agonist mechanism of action, its enantiomer displayed quite a different profile. Thus, (−)-6 was weak in the rodent LMA and GBL tests. Its marginal activity in the GBL and neuronal firing test, together with its ability to increase DOPA accumulation in normal (not GBL treated) rats (Table III) suggests that (−)-6 may be a weak partial DA agonist.

Even though (±)-6 and (+)-6 inhibited LMA at low doses in rats, high doses of the compounds produced increasingly smaller effects. This suggests that these compounds do not possess complete selectivity for DA autoreceptors and that higher doses of compounds may activate

(21) Seeman, P.; Grigoriadis, D. Dopamine D_2 Receptor Dissociation Constant for Spiperone: Identical Values Using ^{3}H-Labeled Agonist or ^{3}H-Labeled Antagonist. *Biochem. Pharmacol.* **1985**, *34*, 4065–4066.

(22) (a) Strombom, U. Catecholamine Receptor Agonists. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1976**, *292*, 167–176. (b) Martin, G. E.; Bendesky, R. J. Mouse Locomotor Activity: an in-vivo Test for Dopamine Autoreceptor Activation. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 706–711.

(23) (a) Bunney, B. S.; Walters, J. R.; Roth, R. H.; Aghajanian, G. K. Dopaminergic Neurons: Effect of Antipsychotic Drugs and Amphetamine on Single Cell Activity. *J. Pharmacol. Exp. Ther.* **1973**, *185*, 560–571. (b) Bunney, B. S.; Aghajanian, G. K.; Roth, R. H. Comparison of Effects of L-Dopa, Amphetamine and Apomorphine on Firing Rate of Rat Dopaminergic Neurons. *Nature (London), New Biol.* **1973**, *245*, 123–125.

(24) Walters, J. R.; Roth, R. H. Dopaminergic Neurons: Alteration in the Sensitivity of Tyrosine Hydroxylase to Inhibition by Endogenous Dopamine after Cessation of Impulse Flow. *Biochem. Pharmacol.* **1976**, *25*, 649–654.

(25) Carlsson, A. Dopamine Receptor Agonists: Intrinsic Activity vs State of Receptor. *J. Neural. Transm.* **1983**, *57*, 309–315.

(26) (a) Fray, P. J.; Sahakian, B. J.; Robbins, T. W.; Koob, G. F.; Iversen, S. D. An Observational Method for Quantifying the Behavioural Effects of Dopamine Agonists: Contrasting Effects of *d*-Amphetamine and Apomorphine. *Psychopharmacology* **1980**, *69*, 253–259. (b) Randup, A.; Munkvad, I. Stereotyped Activities Produced by Amphetamine in Several Animal Species and Man. *Psychopharmacologia* **1967**, *11*, 300–310.

(27) (a) Sidman, M. Two Temporal Parameters of the Maintenance of Avoidance Behavior by the White Rat. *J. Comp. Physiol. Psychol.* **1953**, *46*, 253–261. (b) Sidman, M. Avoidance Conditioning with Brief Shock and No Exteroceptive Warning Signal. *Science* **1953**, *118*, 157–158. (c) Heise, G.; Boff, E. Continuous Avoidance as a Base-Line for Measuring Behavioral Effects of Drugs. *Psychopharmacologia* **1962**, *3*, 264–282.

(28) Heffner, T. G.; Downs, D. A.; Meltzer, L. T.; Wiley, J. N.; Williams, A. E. CI-943, a Potential Antipsychotic Agent. I. Preclinical Behavioral Effects. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 105–112.

(29) Barany, S.; Ingvast, A.; Gunne, L. M. Development of Acute Dystonia and Tardive Dyskinesia in Cebus Monkeys. *Res. Commun. Chem. Pathol. Pharmacol.* **1979**, *25*, 269–279.

Table III. Additional Pharmacological Data for (±)-6 and Its Enantiomers

compd	[^{3}H]NPA[a] binding: IC_{50} (nM) ± SEM	effect on brain DOPA synthesis[b]: dose, mg/kg ip	effect on brain DOPA synthesis[b]: % control	inhibn of Sidman avoidance:[c] ED_{50}, mg/kg po (95% CL)	EPS[d] MED, mg/kg po
(±)-6	203.1 ± 15.6	5.0	63.0 ± 2.4*	11.2 (9.8; 12.7)	>10
(+)-6	138.4 ± 29.1	2.5	52.4 ± 2.6*	8.3 (7.5; 9.2)	>30
(−)-6	295.1 ± 20.9	20.0	153.2 ± 10.5*	>30	>30
thioridazine	NA[e]		NA[e]	3.9 (3.5; 4.3)	<2.5

[a] NPA = *N*-propylnorapomorphine. [b] Shown are the DOPA levels (percent of control) in the striatum of NSD 1015 (100 mg/kg ip) treated rates following administration of each compound (n = 4 rats). The control value for DOPA levels is 0.87 ± 0.09 μg/g. * $p < 0.05$ vs control group. [c] ED_{50} values were generated from three doses. Four animals were tested per dose. [d] MED = minimal effective dose; dose of test compound that induced EPS signs in at least one squirrel monkey (n = 3 animals per dose). [e] NA: not available.

Table IV. Selectivity of (±)-6 and Its Enantiomers for Pre- vs Postsynaptic DA Receptors in Rats

compd	ED_{50}, mg/kg sc: inhibn of locomotor activity[a]	ED_{50}, mg/kg sc: stimuln of locomotor activity[a,b]	ratio stimuln/inhibn
(±)-6	0.9	14.5	16.1
(+)-6	0.3	6.8	22.6
(−)-6	2.5	>30	>12
apomorphine	0.03	0.07	2.3
(+)-3-PPP	~3.0[c]	5.8	~2

[a] ED_{50} values were generated from four to six doses; 5–12 animals were used per dose. [b] Stimulation of LMA ED_{50} is defined as the dose of compound required to produce a 50% reversal of the maximal inhibition of LMA observed at lower doses of the same compound. [c] Very shallow dose–response curve.

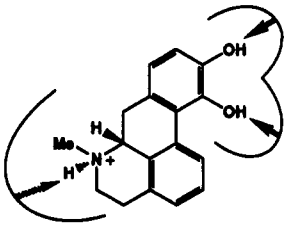
postsynaptic DA receptors. Table IV shows a comparison between the dose of each compound required to inhibit spontaneous rat LMA by 50% (inhibn ED_{50}) and the dose required for 50% reversal of the maximal inhibitory effect obtained with that compound (stimul ED_{50}). These doses are taken as indexes of the activation of pre- and postsynaptic DA receptors, respectively, and serve to estimate the degree of presynaptic selectivity of these compounds. In this analysis, (+)-6 and (±)-6 appear to be relatively selective DA agonists, with about a 20-fold separation between doses that activate pre- and postsynaptic receptors. Under the same conditions, apomorphine and (+)-3-PPP show only about a 2-fold separation.

In the case of the prototypical DA autoreceptor agonist 3-PPP [3-(3-hydroxyphenyl)-1-propylpiperidine] the weak partial agonist character of (−)-3-PPP blocks the postsynaptic activity of (+)-3-PPP in such a way as to make (±)-3-PPP appear to be a selective DA autoreceptor agonist.[30] By contrast, (−)-6 does not seem to contribute substantially to the profile of (±)-6. The autoreceptor selectivities of (±)-6 and (+)-6, reflected in their stimulation/inhibition ratios from Table IV, are not significantly different, and their potency in most tests is equivalent after correcting for the presence of the almost inactive (−)-6 in (±)-6.

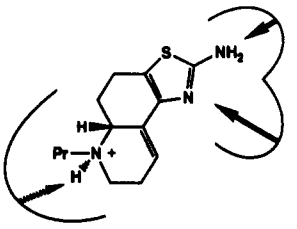
The postsynaptic DA agonist activity of (+)-6 was further evidenced by its ability to produce clear signs of stereotypy in rats, with an ED_{50} of 15.4 mg/kg po, a dose less than 3 times the ED_{50} for inhibition of LMA.

We have described a number of DA autoreceptor agonists that are efficacious inhibitors of Sidman conditioned avoidance in squirrel monkeys,[1,31] a test that is predictive of clinical antipsychotic activity.[28] As expected, both (±)-6 and (+)-6 were active in this test, with ED_{50} values of 11.2 and 8.3 mg/kg po, respectively (Table III). Compound (−)-6 was inactive in this test up to the highest dose tested of 30 mg/kg. Finally, administration of either (+)-6 or (−)-6 to haloperidol-sensitized squirrel monkeys, up to 30 mg/kg po, failed to induce the dystonic movements seen with DA antagonists such as thioridazine (Table III), which are predictive of EPS.[28]

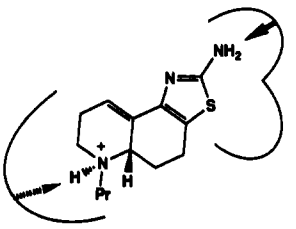
The stereochemical requirements for DA agonist activity are well understood. Shown in Figure 3, with the DA agonist (*R*)-(−)-apomorphine as a reference, are the likely orientations assumed by (−)-6 and (+)-6 in order to fit at the DA receptor. Key components of this fit are thought



R-(−)-Apomorphine



(+)-6



(−)-6

Figure 3. Schematic fit of (*R*)-(−)-apomorphine, (*R*)-(+)-6, and (*S*)-(−)-6 at the D_2 receptor.

(30) Wikstrom, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. Resolved 3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine and Its Analogues: Central Dopamine Receptor Activity. *J. Med. Chem.* 1984, *27*, 1030–1036.

(31) Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Pugsley, T. A.; Meltzer, L. T. Dopamine Autoreceptor Agonists as Potential Antipsychotics. 1. (Aminoalkoxy)anilines. *J. Med. Chem.* 1988, *31*, 1621–1625.

to be (i) the orientation of the N–H bond in the protonated N_6 atom, presumed to be involved in a key hydrogen bond with an aspartic residue at the DA receptor, (ii) the distance between N_6 and the thiazole ring, and (iii) the orientation of the aminothiazole ring (a bioisosteric replacement for the catechol ring) in such a way as to allow interaction with two serine residues in the DA receptor thought to be involved in hydrogen bonding with the catechol hydroxyl groups.[32] If the potential fit of these compounds into the DA receptor is analyzed vis a vis these criteria, (+)-6 seems to meet them all, as illustrated in Figure 3. Particularly interesting is the possibility that each nitrogen atom in the aminothiazole ring might be able to form a hydrogen bond with one of the serine residues mentioned above.

On the other hand, the orientation of (−)-6 within the same receptor model would be quite different, due primarily to the directional requirement that exists for the N_6–H bond. In this case, the NH_2 group might still be able to form a hydrogen bond at the "*p*-hydroxy site", but the molecule should be unable to interact efficiently with the site that would normally bind the catechol's *m*-hydroxy group, which has been shown to be the most important of the two for DA receptor binding.[33] This would account for the weak partial DA agonist activity of (−)-6. In addition to this orientation effect, unfavorable steric interactions between (−)-6 and the DA receptor could account in part for its weak activity.

Steric effects and the orientation of the *N*-alkyl substituent,[9,34] partial DA agonism (low intrinsic efficacy),[35] and D_2 selectivity (vs D_1)[36] have all been invoked in the literature as possible reasons for the apparent autoreceptor selectivity of a number of DA agonists. Any or all of these factors might be responsible for the relative DA autoreceptor selectivity of (+)-6.

Conclusions

The dopaminergic activity of (+)-6 supports the idea that the biologically relevant conformation of the DA agonist PD 118440 (1) exhibits a nearly coplanar arrangement of both ring systems, and it distinguishes between two such coplanar energy minima represented by 6 and 13, respectively. In addition, the increased rigidity of 6 compared to 1 leads to better DA autoreceptor selectivity, although a considerable amount of postsynaptic activity still exists.

Finally, all dopaminergic activity resides in (+)-6, while (−)-6 seems to be a weak partial DA agonist. The efficacy of (+)-6 in the Sidman avoidance test in squirrel monkeys and its lack of EPS liability in the same species qualify this compound as a potential antipsychotic with perhaps an improved profile over currently available agents.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were recorded on an IBM WP100SY NMR spectrometer (100 MHz) or a Varian XL200 NMR spectrometer (200 MHz) and were consistent with the proposed structures. The peaks are described in ppm downfield from TMS (internal standard). The mass spectra were obtained on a Finnigan 4500 mass spectrometer or a VG Analytical 7070E/HF mass spectrometer; the spectra are described by the molecular peak (M) and its relative intensity as well as the base peak (100%). Elemental analyses were performed by the Analytical Research Section at Parke-Davis, Ann Arbor, MI. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. GC analyses were performed with a 3% SE-30 (on 100/120 Supelcoport) column from Supelco Co. TLC was performed on 0.25 mm silica gel F254 (E. Merck) glass plates. Medium-pressure liquid chromatography (MPLC) was performed on silica gel (E. Merck, grade 60, 230–400 mesh, 60 Å) with a RB-SY pump (FMI).

7,8-Dihydro-5(6*H*)-quinolinone (2). The procedure of Rimek and Zymalkowski[10] was followed. Over a period of 1 h, 40.9 g (0.757 mol) of freshly distilled propiolaldehyde was added dropwise to a solution of 42.1 g (0.379 mol) of 3-amino-2-cyclohexenone in 1500 mL of DMF. The solution was stirred at room temperature for 12 h. The DMF was evaporated in vacuo. The resulting black tars were distilled in vacuo (bp 60–65 °C, 0.02–0.05 mm) to give 30.2 g (54%) of the title compound as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 2.14–2.24 (2 H, m), 2.65 (2 H, t, J = 6.6 Hz), 3.11 (2 H, t, J = 6.2 Hz), 7.28 (1 H, dd, J = 4.8 and 7.8 Hz), 8.18 (1 H, dd, J = 1.7 and 7.8 Hz), 8.65 (1 H, dd, J = 1.7 and 4.8 Hz). MS: m/e 148 (M + 1, 100). IR (LF): 1690 cm^{-1}. Anal. (C_9H_9NO): C, H, N.

6-Bromo-7,8-dihydro-5(6*H*)-quinolinone (3).[11] To a warm solution of 5.0 g (33.5 mmol) of 2 in 25 mL of 48% HBr was added dropwise 6.0 g (37.5 mmol) of bromine. The solution was stirred at room temperature for 1 h; then it was concentrated in vacuo. The solid residue was recrystallized from absolute ethanol to give 9.20 g (88.5%) of 3·HBr as a white solid. Mp: 187–189 °C dec (lit.[11] mp: 174–175 °C). *This compound is a skin irritant and should be handled with caution.* ^{1}H NMR (DMSO-d_6): δ 2.4–2.6 (2 H, m), 3.1–3.4 (2 H, m), 5.2 (1 H, dd, J = 3.6 and 6.3 Hz), 7.7 (1 H, dd, J = 4.9 and 7.9 Hz), 8.5 (1 H, d, J = 7.9 Hz), 8.9 (1 H, d, J = 4.9 Hz). MS: m/e 226/228 (M + 1, 5/5), 225/227 (M, 2/2), 91 (100). IR (KBr): 1700 cm^{-1}. Anal. (C_9H_8BrNO·HBr): C, H, N.

4,5-Dihydrothiazolo[4,5-*f*]quinolin-2-amine (4). A solution of 12.6 g (41.0 mmol) of 3 and 3.44 g (45.2 mmol) of thiourea in 100 mL of water was refluxed for 30 min. Upon basification of the cooled mixture with 5% NH_4OH, a solid formed. The solid was filtered, washed with water, and recrystallized from acetonitrile to afford 5.29 g (63.4%) of 4 as an orange-brown solid, mp 205–210 °C. **As indicated previously, this compound is a strong mutagen in the Ames assay and should be handled with extreme caution.**[12] ^{1}H NMR (DMSO-d_6): δ 2.87 (2 H, t, J = 7.7 Hz), 3.05 (2 H, t, J = 7.7 Hz), 7.04 (2 H, s), 7.19 (1 H, dd, J = 4.8 and 7.6 Hz), 7.73 (1 H, dd, J = 1.7 and 7.6 Hz), 8.22 (1 H, dd, J = 1.7 and 4.8 Hz). MS: m/e 203 (M, 100). Anal. ($C_{10}H_9N_3S$): C, H, N.

2-Amino-4,5-dihydro-6-propylthiazolo[4,5-*f*]quinolinium Iodide (5).[13] To a refluxing solution of 2.0 g (9.8 mmol) of 4 in 200 mL of acetonitrile was added 10.0 mL (102.5 mmol) of 1-

(32) The interaction of the hydroxyl groups of catecholamine neurotransmitters with receptor serine residues has been suggested: (a) Strader, C. D.; Sigal, I. S.; Dixon, R. A. F. Structural Basis of β-Adrenergic Receptor Function. *FASEB J.* **1989**, *3*, 1825–1832. (b) Strader, C. D.; Candelore, M. R.; Hill, W. S.; Sigal, I. S.; Dixon, R. A. F. Identification of Two Serine Residues Involved in Agonist Activation of the β-Adrenergic Receptor. *J. Biol. Chem.* **1989**, *264*, 13572–13578.

(33) McDermed, J. D.; Freeman, H.; Ferris, R. *Catecholamines: Basic and Clinical Frontiers*; Usdin, E., Kopin, I., Barchas, J., Eds.; Pergamon: New York, 1979; Vol. 1, pp 568–570.

(34) Wikstrom, H.; Andersson, B.; Elebring, T.; Svensson, K.; Carlsson, A.; Largent, B. N-Substituted 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines and 3-Phenylpiperidines: Effects on Central Dopamine and σ Receptors. *J. Med. Chem.* **1987**, *30*, 2169–2174.

(35) Arnt, J.; Hyttel, J. Dopamine D-2 Agonists with High and Low Efficacies: Differentiation by Behavioral Techniques. *J. Neural Transm.* **1990**, *80*, 33–50.

(36) (a) Hjorth, S.; Carlsson, A. Postsynaptic Dopamine (DA) Receptor Stimulator Properties of the Putative DA Autoreceptor-Selective Agonist B-HT 920 Uncovered by Co-treatment with the D-1 Agonist SK&F 38393. *Psychopharmacology* **1987**, *93*, 534–537. (b) Anden, N.-E.; Grabowska-Anden, M. Increased Motor Activity Following Combined Stimulation of B-HT 920-Sensitive and D-1 Dopamine Receptors. *Acta Physiol. Scand.* **1987**, *131*, 157–158. (c) Meltzer, L. T.; Wiley, J. N.; Williams, A. E.; Heffner, T. G. Evidence for Poststynaptic Dopamine Agonist Effects of B-HT 920 in the Presence of the Dopamine D-1 Agonist SKF 38393. *Psychopharmacology* **1988**, *95*, 329–332.

iodopropane. This mixture was refluxed for 12 h, during which time a precipitate formed and the color turned bright yellow. A fresh portion of 1-iodopropane (10.0 mL, 102.5 mmol) was added and the mixture was refluxed for another 12 h. The mixture was filtered hot; the bright yellow solid was washed with acetonitrile and dried to give 2.65 g (72.2%) of **5**. Mp: 256–260 °C dec. ^{1}H NMR (DMSO-d_6): δ 0.97 (3 H, t, J = 7.3 Hz), 1.84–1.93 (2 H, m), 3.09 (2 H, t, J = 7.9 Hz), 3.53 (2 H, t, J = 7.8 Hz), 4.58 (2 H, t, J = 7.6 Hz), 7.34 (2 H, br s, NH_2), 7.92 (1 H, br t, J = 7.0 Hz), 8.35 (1 H, d, J = 7.9 Hz), 8.72 (1 H, d, J = 6.1 Hz). MS: m/e 246 (M, 16), 245 (M − 1, 66), 244 (M − 2, 100). Anal. ($C_{13}H_{16}IN_3S$): C, H, N, S.

(±)-4,5,5a,6,7,8-Hexahydro-6-propylthiazolo[4,5-*f*]quinolin-2-amine (6). An ice-cold suspension of 2.55 g (6.8 mmol) of **5** in 100 mL of a MeOH/water (1:1) mixture was treated with 2.6 g (67.4 mmol) of sodium borohydride in small portions over a period of 30 min. The suspension was stirred at 0 °C for 3 h. The mixture was then acidified with 6 N HCl to pH 1 and concentrated in vacuo to remove the methanol. The residue was partitioned between 5% NH_4OH and CH_2Cl_2 and the organic phase was dried ($MgSO_4$). Evaporation of the solvent left a brown solid that was purified by MPLC on silica gel (2% NH_4OH in EtOAc) to give 0.60 g (35%) of **6** as a light tan solid. Mp: 146–149 °C. The dihydrochloride salt was prepared. Mp: 282–287 °C dec. ^{1}H NMR (D_2O): δ 1.02 (3 H, t, J = 7.4 Hz), 1.69–2.00 (3 H, m), 2.64–2.88 (5 H, m), 3.14–3.58 (3 H, m), 3.75–3.84 (1 H, m), 4.17 (1 H, br d, J = 12.8 Hz), 6.29 (1 H, br s). MS: m/e 249 (M, 25), 178 (100). Anal. ($C_{13}H_{19}N_3S$·2HCl·0.1H_2O): C, H, N, Cl, H_2O.

7,8-Dihydro-5(6*H*)-isoquinolinone (8) and 6,7-Dihydro-8-(5*H*)-isoquinolinone (9). A slight modification of the procedure of Sugimoto et al.[15] was used. An ice-cold solution of 100.0 g (0.75 mol) of 5,6,7,8-tetrahydroisoquinoline[14] (**7**) in 520 mL of glacial acetic acid and 110 mL of concentrated H_2SO_4 was treated dropwise with a solution of 106.4 g (1.06 mol) of chromium trioxide in 300 mL of acetic acid and 60 mL of water over a 2-h period. The resulting green solution was stirred at room temperature overnight. The mixture was cooled in an ice bath, carefully basified with NH_4OH to pH 11 and extracted with $CHCl_3$. The organic extract was dried over $MgSO_4$ and concentrated in vacuo leaving an oil with some solid particles. This residue was taken up into ether, filtered through Celite, and concentrated in vacuo to give 36.65 g of an oil that was determined by GC to be a mixture of **7** (85%), **8** (6%), and **9** (8%). This residue was distilled in vacuo (0.05 mm), and the following fractions were collected: 1, bp 42–62 °C, 24.83 g (**7**); 2, bp 67–80 °C, 7.92 g (mixture of **8** and **9**). This second fraction was chromatographed (MPLC; silica; EtOAc/hexane, 1:1) to yield 2.31 g of pure **8** (colorless oil), 2.71 g of pure **9** (colorless oil), and 2.32 g of a mixture of **8** and **9** (6.6% combined yield). The hydrochloride salts were prepared.

8·HCl. Mp: 235–238 °C (lit.[15] mp: 235–236 °C). ^{1}H NMR (DMSO-d_6): δ 2.07–2.16 (2 H, m), 2.74 (2 H, t, J = 6.5 Hz), 3.04 (2 H, t, J = 6.0 Hz), 8.02 (1 H, d, J = 5.6 Hz), 8.78 (1 H, d, J = 5.6 Hz), 9.00 (1 H, s). IR (KBr): 1707 cm^{-1}. MS: m/e 147 (M, 100), 119 (50). Anal. (C_9H_9NO·HCl): C, H, N.

9·HCl. Mp: 228–232 °C (lit.[15] mp: 227–228 °C). ^{1}H NMR (DMSO-d_6): δ 2.04–2.16 (2 H, m), 2.72 (2 H, t, J = 6.6 Hz), 3.15 (2 H, t, J = 6.0 Hz), 7.96 (1 H, d, J = 5.6 Hz), 8.87 (1 H, d, J = 6.0 Hz), 9.03 (1 H, s). IR (KBr): 1699 cm^{-1}. MS: m/e 147 (M, 100), 119 (97). Anal. (C_9H_9NO·HCl): C, H, N.

4,5-Dihydrothiazolo[5,4-*h*]isoquinolin-2-amine (11).[13] To a warm solution of 2.71 g (18.4 mmol) of **9** in 50 mL of 48% HBr was added a solution of 3.3 g (20.6 mmol) of bromine in 25 mL of 48% HBr. The mixture was stirred at room temperature for 1.5 h and concentrated in vacuo to give 5.8 g of crude bromo ketone **10**·HBr (mp 145–147 °C dec), which was carried on without further purification. A solution of 5.8 g of **10**·HBr in 50 mL of water was treated with 2.10 g (26.9 mmol) of thiourea. The solution was placed on a steam bath for 30 min, during which time the clear yellow solution became cloudy. The mixture was cooled in ice and basified with NH_4OH to pH 10, at which point a precipitate formed. This precipitate was filtered, washed with cold water and dried to give 3.48 g (93%) of **11**. Mp: 246–252 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.82 (2 H, t, J = 7.8 Hz), 2.97 (2 H, t, J = 7.8 Hz), 7.21 (2 H, br s), 7.22 (1 H, d, J = 4.8 Hz), 8.29 (1 H, d, J = 4.8 Hz), 8.62 (1 H, s). MS: m/e 203 (M, 100). Anal. ($C_{10}H_9N_3S$): C, H, N.

(±)-4,5,6,7,8,9-Hexahydro-8-propylthiazolo[5,4-*h*]isoquinolin-2-amine (13). A suspension of 3.48 g (17.1 mmol) of **11** in 500 mL of acetonitrile was refluxed under nitrogen for 2 h. The solution was filtered to remove a small amount of insoluble material. The filtrate was treated with 43.5 g (256 mmol) of 1-iodopropane and refluxed under nitrogen for 2 h. The mixture was filtered hot and the solid was washed with ether and dried to give 2.78 g of salt **12** as an orange solid. The hot acetonitrile filtrate was concentrated in vacuo to give an additional 2.52 g of **12**. Combined weight: 5.30 g (83% crude yield). Mp: 245–248 °C dec. ^{1}H NMR (DMSO-d_6): δ 0.88 (3 H, t, J = 7.3 Hz), 1.86–1.95 (2 H, m), 2.97 (2 H, d, J = 7.9 Hz), 3.27 (2 H, t, J = 7.9 Hz), 4.55 (2 H, t, J = 7.1 Hz), 7.24 (2 H, br s), 7.97 (1 H, d, J = 6.0 Hz), 8.77 (1 H, d, J = 6.0 Hz), 8.78 (1 H, s).

A suspension of 2.70 g (71.4 mmol) of $NaBH_4$ in 250 mL of methanol containing 5 mL of 6 N NaOH was cooled in an ice bath and treated with 5.2 g (13.9 mmol) of crude **12** in small portions. The addition required about 30 min and was exothermic. The mixture was stirred at room temperature for 3 h, cooled in an ice bath, and carefully acidified with 6 N HCl. The solution was concentrated in vacuo and the residue was partitioned between dilute NH_4OH and $CHCl_3$. The organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (silica; 2% NH_4OH in EtOAc) to give 3.85 g (90% for two steps) of **13** as a hygroscopic solid which was converted into its dihydrochloride salt. Mp: 258–260 °C dec. ^{1}H NMR (D_2O): δ 0.97–1.05 (3 H, t, J = 7.4 Hz), 1.77–1.88 (2 H, m), 2.47–2.63 (3 H, m), 2.63–2.82 (3 H, m), 3.23–3.37 (3 H, m), 3.63–3.73 (1 H, br d, J = 13 Hz), 3.86–3.94 (1 H, br d, J = 17 Hz), 4.16–4.24 (1 H, br d, J = 17 Hz). MS: m/e 249 (M, 39), 178 (100). Anal. ($C_{13}H_{19}N_3S$·2HCl·0.5H_2O): C, H, N, Cl.

4,5-Dihydrothiazolo[4,5-*f*]isoquinolin-2-amine (15).[13] A solution of 2.76 g (17.3 mmol) of bromine in 25 mL of 48% HBr was added dropwise to a warm solution of 2.31 g (15.7 mmol) of **8** in 50 mL of 48% HBr. The resulting solution was stirred at room temperature for 2 h and concentrated in vacuo to a yellow solid (**14**). This material was dissolved in 50 mL of water and treated with 1.80 g (23.7 mmol) of thiourea. The mixture was heated on a steam bath for 1 h, cooled in an ice bath, and basified with NH_4OH. The resulting green solid was collected, washed with water, and dried to give 3.47 g (>100% crude yield) of **15**, which was used in the next step without further purification.

(±)-4,5,5a,6,7,8-Hexahydro-7-propylthiazolo[4,5-*f*]isoquinolin-2-amine (17) and (±)-4,5,6,7,8,9-Hexahydro-7-propylthiazolo[4,5-*f*]isoquinolin-2-amine (18). A suspension of 3.25 g of crude **15** (16 mmol) in 600 mL of acetonitrile was refluxed under nitrogen for 2 h and filtered while still hot. The filtrate was treated with 40 g (0.235 mol) of 1-iodopropane and the mixture was refluxed overnight. Salt **16** was isolated as a yellow solid from the hot reaction mixture (2.03 g, 34%). The filtrate was later evaporated, and the brownish residue was combined with the first crop of **16** and carried on to the next step without further purification.

To a suspension of 2.2 g (58.1 mmol) of $NaBH_4$ in 250 mL of methanol containing 5 mL of 6 N NaOH was added in small portions salt **16** obtained above. The addition required about 15 min and was exothermic. The mixture was stirred at room temperature overnight. The solution was cooled in an ice bath, carefully quenched with 6 N HCl, and evaporated in vacuo. The residue was partitioned between dilute NH_4OH and $CHCl_3$. The organic extract was dried over $MgSO_4$ and concentrated to give 3.26 g of a green oil that was purified by MPLC (2% NH_4OH in EtOAc) to give 1.16 g of **17** and 0.74 g of **18**, both isolated as oils. The hydrochloride salts of these compounds were prepared by addition of the appropriate amount of a 1 N solution of HCl in ether to a solution of the compound in 2-propanol, followed by recrystallization of the resulting salts from ethanol.

17·2HCl. Mp: 262–264 °C dec. ^{1}H NMR (D_2O): δ 1.00 (3 H, t, J = 7.3 Hz), 1.43–1.70 (1 H, m), 1.80–1.88 (2 H, m), 2.08–2.16 (1 H, br d, J = 12.8 Hz), 2.76–3.10 (4 H, m), 3.15–3.40 (2 H, m), 3.70–3.88 (2 H, m), 4.06–4.23 (1 H, br d, J = ca. 17 Hz), 5.97 (1 H, br s). MS: m/e 249 (M, 82). Anal. ($C_{13}H_{19}N_3S$·2HCl): C, H, N.

18·2HCl. Mp: 242–245 °C dec. ^{1}H NMR (D_2O): δ 1.00 (3 H, t, J = 7.3 Hz), 1.75–1.89 (2 H, m), 2.37–2.49 (2 H, m), 2.70–2.84 (4 H, m), 3.19–3.32 (3 H, m), 3.71–4.15 (3 H, m). MS: m/e 249

(M, 100). Anal. ($C_{13}H_{19}N_3S$·0.45CH_3CN·2.2HCl·1.1H_2O): C, H, N.

Decahydro-5-quinolinol (20). The method of Grob et al.[16] was used. A solution of 66.7 g (0.441 mol) of 2,3,4,6,7,8-hexahydro-5(1*H*)-quinolinone (**19**) in 250 mL of glacial acetic acid containing 2 g of PtO_2 was hydrogenated at 450 psi and 50 °C for 75 h. Hydrogen uptake was only 57% of the theoretical. The sample was filtered and concentrated in vacuo. The residue was cooled in ice, basified with 6 N NaOH to pH 12, and extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to give 24.8 g (36%) of **20** as a light brown oily solid, which was a three-component isomeric mixture by GC analysis. This mixture was carried on to the next step without further purification.

Octahydro-5-hydroxy-1(2*H*)-quinolinecarboxylic Acid, 1,1-Dimethylethyl Ester (21). To a solution of 24.8 g (0.160 mol) of amino alcohol **20** in 1 L of a mixture of THF/water (1:1) was added 32 mL of 6 N NaOH (0.192 mol), followed by 41.8 g (0.192 mol) of di-*tert*-butyl dicarbonate in 250 mL of THF. The mixture was stirred at room temperature under nitrogen for 12 h and extracted with ether (4 × 500 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated in vacuo to give 82.83 g of a yellow viscous oil. The crude oil was purified by MPLC (isooctane/ether, 4:1) to give 39.14 g (96%) of **21** as a colorless liquid. GC analysis showed this product to be a mixture of three isomers that were carried on to the next step without attempting to separate them.

***cis*-Octahydro-5-oxo-1(2*H*)-quinolinecarboxylic Acid, 1,1-Dimethylethyl Ester (22), and *trans*-Octahydro-5-oxo-1(2*H*)-quinolinecarboxylic Acid, 1,1-Dimethylethyl Ester (23).** A suspension of 39.14 g (0.153 mol) of **21** and 346.0 g (0.920 mol) of pyridine dichromate in 1.5 L of CH_2Cl_2 was mechanically stirred for 72 h. The suspension was filtered through a pad of Celite, concentrated, suspended in 250 mL of ether, and again filtered through a pad of Celite. The filtrate was concentrated in vacuo to give 34.81 g of a brown oil. This residue was purified by MPLC (silica; isooctane/EtOAc 4:1) to give 12.16 g (31%) of **22**[17] as an oil and 14.38 g (37%) of **23** as a low-melting solid, mp 45–47 °C.

22. R_f 0.34 (silica, isooctane/EtOAc, 1:1). ^1H NMR ($CDCl_3$): δ 1.41–1.61 (1 H, m), 1.46 (9 H, s), 1.64–1.80 (5 H, m), 1.98–2.13 (2 H, m), 2.22–2.43 (2 H, m), 2.52–2.60 (1 H, dt, J = 9.5 and 6.3 Hz), 2.80–2.92 (1 H, dt, J = 13.3 and 2.5 Hz), 4.00–4.05 (1 H, br dd, J = 13.4 and 3.3 Hz), 4.32–4.40 (1 H, dt, J = 5.1 and 12.2 Hz). ^{13}C NMR ($CDCl_3$): δ 21.82, 22.87, 23.98, 24.50, 28.38, 37.39, 38.72, 51.99, 52.17, 79.79, 154.54, 212.22. MS: m/e 254 (M + 1, 96), 198 (100). IR (LF): 1695, 1709 cm^{-1}. Anal. ($C_{14}H_{23}NO_3$·0.4H_2O): C, H, N.

23. R_f 0.43 (silica, isooctane/EtOAc, 1:1). ^1H NMR ($CDCl_3$): δ 1.34–1.60 (2 H, m), 1.46 (9 H, s), 1.73–1.84 (1 H, m), 1.99–2.14 (3 H, m), 2.27–2.39 (3 H, m), 2.45–2.56 (1 H, dt, J = 3.2 and 12.3 Hz), 3.24–3.53 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 20.17, 22.35, 23.05, 28.39, 30.51, 41.12, 41.21, 50.62, 61.35, 79.60, 155.17, 200.94. MS: m/e 253 (M, 17), 57 (100). IR (KBr): 1704 cm^{-1} (br). Anal. ($C_{14}H_{23}NO_3$): C, H, N.

(±)-*cis*-2-Amino-5,5a,7,8,9,9a-hexahydrothiazolo[4,5-*f*]quinoline-6(4*H*)-carboxylic Acid, 1,1-Dimethylethyl Ester (24). A solution of 1.0 g (3.95 mmol) of **22** in 10 mL of THF was added dropwise via syringe to a solution of lithium diisopropylamide (LDA) (5.88 mmol) in 10 mL of THF, at −78 °C. The solution was stirred at this temperature for 3 h and a solution of 0.73 g (6.71 mmol) of chlorotrimethylsilane in 5 mL of THF was added dropwise. The resulting solution was stirred at −78 °C for 2 h and was allowed to warm up to room temperature. The solution was concentrated in vacuo and the oily residue was suspended in 25 mL of dry ether and filtered through Celite. The filtrate was concentrated to give 1.35 g of the TMS enol ether of **22** as a yellow oil.

A solution of 1.35 g (4.15 mmol) of the above silyl enol ether and 0.77 g (4.33 mmol) of *N*-bromosuccinimide in 25 mL of CCl_4 was refluxed under nitrogen for 1 h. The resulting suspension was filtered through Celite and concentrated to give 1.82 g of the corresponding crude α-bromo ketone as a yellow oil.

A solution of the above α-bromo ketone and 0.33 g (4.34 mmol) of thiourea in 50 mL of methanol was refluxed under nitrogen for 2 h. The solution was concentrated in vacuo, basified with saturated $NaHCO_3$ solution, and extracted into $CHCl_3$. The extract was dried over $MgSO_4$, filtered, and concentrated. The residue was triturated with ether, filtered, and dried to afford 0.65 g (53% from **22**) of **24** as a tan solid. Mp: 239–240 °C dec. ^1H NMR (DMSO-d_6): δ 1.28–1.63 (4 H, m), 1.40 (s, 9 H), 1.93–2.13 (2 H, m), 2.46–2.97 (4 H, m), 3.88 (1 H, br d, J = 12.6 Hz), 4.20 (1 H, br d, J = 11.4 Hz), 6.70 (2 H, br s). MS: m/e 309 (M, 17), 57 (100). Anal. ($C_{15}H_{23}N_3O_2S$·0.66H_2O): C, H, N.

(±)-*cis*-4,5,5a,6,7,8,9,9a-Octahydrothiazolo[4,5-*f*]quinolin-2-amine (26). To a solution of 1.0 g (3.2 mmol) of **24** in 50 mL of a mixture of MeOH/$CHCl_3$ (1:1) was added 12 mL (12 mmol) of 1 N HCl solution in ether. The solution was stirred at room temperature under nitrogen for 12 h. A fresh portion of 10 mL of ethereal hydrogen chloride was added and the mixture was stirred at room temperature for another 12 h. The mixture was concentrated in vacuo and the solid residue was washed with ether, filtered, and dried to give 0.89 g (98%) of the dihydrochloride salt of **26**. Mp: 268–271 °C dec. ^1H NMR (D_2O): δ 1.55–1.80 (2 H, m), 1.80–2.10 (3 H, m), 2.15–2.35 (1 H, m), 2.50–2.75 (2 H, m), 3.00–3.20 (3 H, m), 3.70–3.80 (1 H, m). MS: m/e 209 (M, 100). Anal. ($C_{10}H_{15}N_3S$·2HCl·0.4H_2O): H, N, Cl. C: calcd 41.50, found 41.92.

(±)-*cis*-4,5,5a,6,7,8,9,9a-Octahydro-6-propylthiazolo[4,5-*f*]quinolin-2-amine (28). A solution of 0.16 g (5.5 mmol) of **26** in 100 mL of absolute EtOH was treated with 1.12 g (20 mmol) of finely ground potassium hydroxide and 8.50 g (50 mmol) of 1-iodopropane. The mixture was heated at reflux under nitrogen for 20 h. The mixture was concentrated in vacuo and the residue was partitioned between CH_2Cl_2 and 5% $NaHCO_3$. The organic phase was dried over $MgSO_4$ and evaporated in vacuo, leaving 1.13 g (81.8%) of **28** as an oil which was converted to its dihydrochloride salt. Mp: 230–232 °C dec. ^1H NMR (D_2O): δ 1.00 (3 H, t, J = 7.4 Hz), 1.71–2.32 (7 H, m), 2.32–2.84 (3 H, m), 3.08–3.50 (5 H, m), 3.89–3.96 (1 H, m). MS: m/e 251 (M, 98), 222 (100). Anal. ($C_{13}H_{21}N_3S$·2HCl·0.25H_2O): C, H, N, Cl.

(±)-*trans*-2-Amino-5,5a,7,8,9,9a-hexahydrothiazolo[4,5-*f*]quinoline-6(4*H*)-carboxylic Acid, 1,1-Dimethylethyl Ester (25). The procedure described above for the synthesis of **24** was followed for the conversion of 19.46 g (76.8 mmol) of **23** into **25** (9.82 g, 41%). Mp: 231–233 °C dec. ^1H NMR ($CDCl_3$): δ 1.1–1.5 (1 H, m), 1.4 (9 H, s), 1.5–1.9 (2 H, m), 2.0–2.8 (6 H, m), 2.8–3.2 (2 H, m), 3.8–4.2 (1 H, dt, J = 5.0 and 14.2 Hz), 4.9 (2 H, br s). MS: m/e 309 (M, 2), 57 (100). Anal. ($C_{15}H_{23}N_3O_2S$): C, H, N.

(±)-*trans*-4,5,5a,6,7,8,9,9a-Octahydrothiazolo[4,5-*f*]quinolin-2-amine (27). The procedure described above for the synthesis of **26** was followed for the conversion of 1.68 g (5.4 mmol) of **25** into **27** (1.04 g, 90%). Mp: 191–199 °C; ^1H NMR (DMSO-d_6): δ 0.96–1.20 (1 H, m), 1.36–1.70 (3 H, m), 1.75–1.85 (1 H, br d), 2.00–2.15 (1 H, br t), 2.20–2.40 (2 H, m), 2.40–2.55 (3 H, m), 2.93 (1 H, br d, J = 10.5 Hz), 3.32 (1 H, br s, N*H*), 6.63 (2 H, s, NH_2). MS: m/e 209 (M, 100). Anal. ($C_{10}H_{15}N_3S$): C, H, N.

(±)-*trans*-4,5,5a,6,7,8,9,9a-Octahydro-6-propylthiazolo-[4,5-*f*]quinolin-2-amine (29). The procedure described above for the synthesis of **28** was repeated for the conversion of 1.46 g (7.0 mmol) of **27** into **29** (0.47 g, 27%). Mp: 180–188 °C. ^1H NMR (DMSO-d_6): δ 0.82 (3 H, t, J = 7.2 Hz), 0.95–1.15 (1 H, m), 1.35–1.75 (6 H, m), 2.00–2.70 (8 H, m), 2.90 (1 H, br d, J = 11 Hz), 6.63 (2 H, s, NH_2). MS: m/e 251 (M, 35), 222 (100). Anal. ($C_{13}H_{21}N_3S$·0.5H_2O): C, H, N.

6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-5-one (31).[18] The preparation of this compound was similar to the synthesis of **9** above. [2,3]Cycloheptenopyridine (**30**; 99.4 g, 0.675 mol) was obtained from Aldrich Chemical Co. The crude reaction mixture was purified by MPLC (EtOAc/hexane, 1:1) to give 13.2 g of unreacted **30** and 4.77 g of **31** (4.4%) as a yellow oil. A small amount (ca. 0.5%) of another component, perhaps the isomeric 5,6,7,8-tetrahydro-9*H*-cyclohepta[*b*]pyridin-9-one was detected but could not be obtained pure. A small portion of **31** was converted to its hydrochloride salt, a colorless solid. Mp: 155–159 °C. ^1H NMR (DMSO-d_6): δ 1.76–2.03 (4 H, m), 2.84–2.90 (2 H, m), 3.51 (2 H, t, J = 6.1 Hz), 7.97 (1 H, dd, J = 5.6 and 7.9 Hz), 8.58 (1 H, dd, J = 1.6 and 7.9 Hz), 8.92 (1 H, dd, J = 1.6 and 5.6

Hz). ^{13}C NMR (DMSO-d_6): δ 20.2, 23.0, 30.0, 40.7, 124.9, 136.0, 143.8, 144.5, 157.2, 200.5. IR (KBr): 1690 cm^{-1}. MS: *m/e* 161 (M, 74), 133 (100). Anal. ($C_{10}H_{11}NO$·HCl): C, H, N.

5,6-Dihydro-4*H*-thiazolo[4′,5′:3,4]cyclohepta[1,2-*b*]pyridin-2-amine (33). To a warm solution of 4.61 g (28.6 mmol) of **31** in 50 mL of 48% HBr was added dropwise a solution of 5.0 g (31.3 mmol) of bromine in 10 mL of 48% HBr over a period of about 20 min. The red solution was stirred at room temperature for 2 h and then evaporated in vacuo (bath temperature, 50 °C) to give a red oil. This oil was triturated with 50 mL of ethanol. The white solid that formed was filtered and washed with ether to give 6.93 g (75%) of bromo ketone **32**·HBr. Mp: 193–195 °C: ^1H NMR ($CDCl_3$): 1.83–1.97 (1 H, m), 2.09–2.29 (2 H, m), 2.46–2.59 (1 H, m), 3.18–3.41 (2 H, m), 5.38 (2 H, dd, *J* = 8.2 and 4.6 Hz), 7.75 (1 H, dd, *J* = 5.5 and 7.6 Hz), 8.31 (1 H, d, *J* = 7.6 Hz), 8.83 (1 H, d, *J* = 5.5 Hz). MS: *m/e* 241/239 (M + 1, 6) 86/84 (100). Anal. ($C_{10}H_{10}BrNO$·HBr·0.15H_2O): C, H, N, Br.

A solution of 6.78 g (21.1 mmol) of crude **32**·HBr in 100 mL of water was treated with 1.93 g (25.3 mmol) of thiourea and the solution was heated on a steam bath for 2 h. The hot mixture was filtered through Celite; the filtrate was cooled in an ice bath and made basic with concentrated NH_4OH. The solid formed was filtered and dried to give 4.26 g (93%) of **33** as an off-white solid. Mp: 220–222 °C dec. ^1H NMR (DMSO-d_6): δ 1.94–2.05 (2 H, m), 2.89 (2 H, t, *J* = 6.7 Hz), 3.00–3.04 (2 H, m), 6.90 (2 H, s), 7.25 (1 H, dd, *J* = 4.9 and 7.7 Hz), 8.24–8.29 (2 H, m). ^{13}C NMR (DMSO-d_6): δ 24.9, 27.3, 37.9, 121.4, 123.0, 129.4, 136.1, 141.1, 146.2, 158.8, 164.9. MS: *m/e* 217 (M, 100). Anal. ($C_{11}H_{11}N_3S$·0.1H_2O): C, H, N.

(±)-5,6,6a,7,8,9-Hexahydro-7-propyl-4*H*-thiazolo[4′,5′:3,4]cyclohepta[1,2-*b*]pyridin-2-amine (35) and (±)-5,6,6a,7,8,9,10,10a-Octahydro-7-propyl-4*H*-thiazolo[4′,5′:3,4]cyclohepta[1,2-*b*]pyridin-2-amine (36). A solution of 3.95 g (18.2 mmol) of **33** in 500 mL of acetonitrile was treated with 31.4 g (0.184 mol) of 1-iodopropane and the mixture was refluxed under nitrogen for 96 h. The solvent was evaporated in vacuo, and the residue was filtered and washed with ether to give 8.0 g of **34** as a bright yellow solid that was used directly without further purification.

An ice-cold solution of **34** obtained above in 500 mL of MeOH/H_2O (1:1) was treated dropwise with a solution of 3.9 g (0.103 mol) of $NaBH_4$ in 500 mL of methanol containing 10 mL of 6 N NaOH. The mixture was stirred at room temperature for an additional 2 h and carefully acidified by addition of 6 N HCl. The mixture was concentrated in vacuo, the residue was partitioned between dilute NH_4OH and $CHCl_3$, and the organic extract was dried over $MgSO_4$. The solvent was evaporated in vacuo, leaving 4.90 g of a red oil which was purified by MPLC (2% NH_4OH in EtOAc) to give 1.72 g (32%) of **35** as a brown oil and 1.62 g (30%) of **36** (mixture of cis and trans) as a yellow oil. Both compounds were converted into the respective hydrochloride salts.

35·2HCl. Mp: 281–282 °C dec. ^1H NMR (DMSO-d_6): δ 0.91 (3 H, t, *J* = 7 Hz), 1.60–2.20 (6 H, m), 2.50–2.90 (4 H, m), 2.95–3.15 (2 H, m), 3.20–3.50 (2 H, m), 4.05–4.25 (1 H, m), 6.40 (1 H, br s), 9.05 (2 H, br), 11.20 (1 H, br s). MS: *m/e* 263 (M, 100). Anal. ($C_{14}H_{21}N_3S$·2HCl): C, H, N, Cl.

36·2HCl. Mp: 237–242 °C dec. ^1H NMR (DMSO-d_6): δ 0.92 (3 H, m), 1.50–2.10 (10 H, m), 2.40–2.80 (2 H, m), 2.90–3.10 (2 H, m), 3.10–3.25 (1 H, m), 3.50–3.90 (3 H, m), 9.20 (2 H, m), 11.10 (1 H, br s). MS: *m/e* 265 (M, 69), 236 (100). Anal. ($C_{14}H_{23}N_3S$·2HCl·0.5H_2O): C, H, N, Cl.

6,7-Dihydro-5*H*-cyclopenta[*b*]pyridin-5-one (38).[19] The procedure described above for the synthesis of **31** was used for the oxidation of [2,3]cyclopentenopyridine (Aldrich Chemical Co.). MPLC (hexanes/EtOAc; 3:1) of the reaction mixture yielded a 10% yield of **38** as an unstable purple solid that could not be obtained analytically pure and was only characterized spectroscopically. ^1H NMR ($CDCl_3$): δ 2.6–2.8 (2 H, m), 3.1–3.3 (2 H, m), 7.2 (1 H, dd, *J* = 9, 6 Hz), 7.9 (1 H, dd, *J* = 9, 2 Hz), 8.7 (1 H, dd, *J* = 6, 2 Hz).

(±)-*N*-(4,5,5a,6,7,8-Hexahydro-6-propylthiazolo[4,5-*f*]quinolin-2-yl)-2-methylpropanamide (40). A suspension of 6.9 g (28 mmol) of **6** and 10.0 g (90 mmol) of sodium isobutyrate in 150 mL of isobutyric anhydride was heated at 100 °C under nitrogen for 4 h. The solution was cooled to room temperature and quenched by addition of 100 mL of 15% hydrochloric acid. The mixture was extracted with ethyl acetate. The aqueous phase was made basic with ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by MPLC (2% NH_4OH in EtOAc) to give 8.95 g (100%) of **40** as an off-white solid. Mp: 162–165 °C. ^1H NMR ($CDCl_3$): δ 0.95 (3 H, t, *J* = 7.3 Hz), 1.24 (6 H, m), 1.52–1.76 (3 H, m), 2.13–2.91 (9 H, m), 3.07–3.15 (2 H, m), 6.32 (1 H, br s). MS: *m/e* 319 (M, 48), 178 (100). Anal. ($C_{17}H_{25}N_3OS$): C, H, N.

(*R*)-(+)-*N*-(4,5,5a,6,7,8-Hexahydro-6-propylthiazolo[4,5-*f*]quinolin-2-yl)-2-methylpropanamide ((+)-40). A solution of 26.6 g (83.3 mmol) of (±)-**40** in 250 mL of 95% EtOH was combined with a solution of 23.5 g (58.3 mmol) of (−)-ditoluoyl-L-tartaric acid hydrate in 100 mL of EtOH. The volume was reduced to 325 mL on a steam bath. Repeated scratching of the flask walls with a glass rod and several cycles of warming/cooling induced crystallization of a white salt (35.5 g). This salt was recrystallized from 185 mL of 95% EtOH. (The flask was kept at 60–65 °C for the first hour of the crystallization, then at room temperature for 2 h, and finally at 4 °C overnight.) The crystalline white salt was filtered, washed with 50 mL of ether, and air-dried to give 15.7 g (53.6%) of (+)-**40**·(−)-ditoluoyl-L-tartrate. Mp: 174–175 °C. This salt was partitioned between ethyl acetate and dilute ammonium hydroxide. The organic phase was dried over $MgSO_4$ and evaporated to give 6.5 g of (+)-**40** as an off-white solid. Mp: 148–149 °C. $[\alpha]_D$: +83.3° (*c* = 1.5, MeOH). ^1H NMR ($CDCl_3$): δ 0.94 (3 H, t, *J* = 7.3 Hz), 1.09 (3 H, d, *J* = 6.9 Hz), 1.16 (3 H, d, *J* = 6.8 Hz), 1.48–1.71 (3 H, m), 2.11 (1 H, br d), 2.27–2.57 (5 H, m), 2.76–2.86 (3 H, m), 2.93–3.11 (2 H, m), 6.33 (1 H, br s), 12.05 (1 H, s). MS: *m/e* 319 (M, 72), 178 (100). Anal. ($C_{17}H_{25}N_3OS$): C, H, N.

(*S*)-(−)-*N*-(4,5,5a,6,7,8-Hexahydro-6-propylthiazolo[4,5-*f*]quinolin-2-yl)-2-methylpropanamide ((−)-40). This compound was prepared in a manner analogous to that of (+)-**40** using (+)-ditoluoyl-D-tartaric acid as the resolving agent. Mp: 146–147 °C. $[\alpha]_D$: −81.8° (*c* = 1.12, MeOH). Anal. ($C_{17}H_{25}N_3OS$·0.5H_2O): C, H, N.

(*R*)-(+)-4,5,5a,6,7,8-Hexahydro-6-propylthiazolo[4,5-*f*]quinolin-2-amine ((+)-6). A solution of 6.5 g (20.3 mmol) of (+)-**40** in 500 mL of 10% hydrochloric acid was refluxed under nitrogen for 2 h. The mixture was cooled in an ice bath and made basic with ammonium hydroxide. The product was extracted into CH_2Cl_2. The organic extract was dried over $MgSO_4$ and the filtered solution was treated with 50 mL of 1 N HCl in ether. The mixture was evaporated in vacuo, and the residue was recrystallized from MeOH/EtOAc to give 4.40 g (69%) of (+)-**6**·2HCl. Mp: 266–268 °C dec. $[\alpha]_D$: +146.5° (*c* = 1.14, H_2O). Anal. ($C_{13}H_{19}N_3S$·2HCl): C, H, N, Cl. A second crop (1.80 g) of (+)-**6**·2HCl was obtained (mp 265–268 °C dec), bringing the yield up to 96%. The optical purity of (+)-**6** was determined to be >99% by chiral HPLC (LKB Enantiopac 100 mm × 4.0 mm i.d. column; 0.08 M NaH_2PO_4, 0.1 M NaCl, pH adjusted to 7.00 with NaOH/2-propanol (95:5) as the mobile phase).

(*S*)-(−)-4,5,5a,6,7,8-Hexahydro-6-propylthiazolo[4,5-*f*]quinolin-2-amine ((−)-6). The method described above for the synthesis of (+)-**6** was followed for conversion of (−)-**40** into (−)-**6**·2HCl. Mp: 272–274 °C (dec). $[\alpha]_D$: −140.6° (*c* = 1.05, H_2O). Anal. ($C_{13}H_{19}N_3S$·2HCl·0.25H_2O) C, H, N. This compound was found to be >99% optically pure by chiral HPLC (see above).

Pharmacological Methods. [^{3}H]Spiperone, [^{3}H]-*N*-Propylnorapomorphine, and [^{3}H]SCH23390 Receptor Binding Assays. The affinity of compounds for brain DA receptors was determined by standard receptor binding assays,[37] according to methods described previously.[28]

Inhibition of spontaneous locomotor activity and motor coordination[22a,b,38] were carried out according to methods described previously.[28]

(37) Burt, D. R.; Creese, I.; Snyder, S. H. Properties of [^{3}H]-Haloperidol and [^{3}H]Dopamine Binding Association with Dopamine Receptors in Calf Brain Membranes. *Mol. Pharmacol.* 1976, *12*, 800–812.

(38) Svensson, L.; Ahlenius, S. Suppression of Exploratory Locomotor Activity in the Rat by the Local Application of 3-PPP Enantiomers into the Nucleus Accumbens. *Eur. J. Pharmacol.* 1983, *88*, 393–397.

Effects on the Firing Rate of Substantia Nigra DA Neurons.[23] The action potential of zona compacta DA cells was recorded in chloral-anesthetized rats by using standard extracellular recording techniques. DA cells were identified by waveform and firing pattern, and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Baseline firing rate was calculated by averaging the rate over the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Inhibition of GBL-Stimulated DA Synthesis.[24] Compounds were administered to male Long-Evans rats (Blue Spruce Farms, Altamont, NY) 1 h before sacrifice, and GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 and 25 min, respectively, before sacrifice. Brain striatal levels of dihydroxyphenylalanine (DOPA) were analyzed by HPLC with electrochemical detection.[39]

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Supplementary Material Available: Tables listing fractional atomic coordinates and temperature factor parameters, bond lengths and angles, hydrogen bonding parameters, general displacement parameter expressions (13 pages); a table of observed and calculated structure amplitudes (23 pages). Ordering information is given on any current masthead page.

(39) (a) Myers, S.; Pugsley, T. A. Decrease in Rat Striatal Dopamine Synthesis and Metabolism in vivo by Metabolically Stable Adenosine Receptor Agonists. *Brain Res.* **1986**, *375*, 193-197. (b) Pugsley, T. A.; Myers, S.; Shih, Y. S. Effects of CI-926 (3-[4-[4-(3-Methylphenyl)-1-piperazinyl]butyl]-2,4-imidazolidinedione), an Antihypertensive Agent, on Rat Brain Catecholamine and Serotonin Turnover. *J. Cardiovas. Pharmacol.* **1989**, *13*, 455-464.

Folate Analogues. 35. Synthesis and Biological Evaluation of 1-Deaza, 3-Deaza, and Bridge-Elongated Analogues of N^{10}-Propargyl-5,8-dideazafolic Acid[1]

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Structural modifications at the pyrimidine ring and at the C^9,N^{10}-bridge region of the thymidylate synthase (TS) inhibitors N^{10}-propargyl-5,8-dideazafolate (1; PDDF; CB 3717), 2-desamino-N^{10}-propargyl-5,8-dideazafolate (2, DPDDF), and 2-desamino-2-methyl-N^{10}-propargyl-5,8-dideazafolate (3, DMPDDF) have been carried out. Methods for the synthesis of 2-desamino-N^{10}-propargyl-1,5,8-trideazafolate (4), 2-desamino-2-methyl-N^{10}-propargyl-3,5,8-trideazafolate (5a), and 2-desamino-2-methyl-N^{10}-propargyl-5,8-dideaza-1,2-dihydrofolate (6) have been developed. The bridge-extended analogues isohomo-PDDF (7) and isohomo-DMPDDF (8) contain an additional methylene group interposed between N^{10} and the phenyl ring of 1 and 3, respectively. All new compounds were evaluated as inhibitors of TS and the growth of tumor cells in culture. Selected analogues were tested as substrates of folylpolyglutamate synthetase (FPGS) and striking differences in substrate activity were observed among these compounds, indicating that structural modifications at the pyrimidine ring of classical antifolates profoundly influence their polyglutamylation. Enzyme inhibition data established that both N^1 and N^3-H of the pyrimidine ring are essential for efficient binding of quinazoline-type antifolates to human TS.

The recent discovery of a number of very specific and powerful quinazoline antifolates that inhibit thymidylate synthase[2-4] (TS, EC 2.1.1.45) has stimulated the search for related compounds possessing more desirable therapeutic indices.[4,5] Striking biological results were obtained when the 2-amino group of the potent TS inhibitor N^{10}-propargyl-5,8-dideazafolate (PDDF; CB3717) was replaced with a methyl group.[3,4] The 2-desamino-2-methyl analogue 3 exhibited approximately the same substrate activity as 1 toward folylpolyglutamate synthetase (FPGS), indicating that polyglutamylation was not significantly affected by this structural change (Chart I). But the transport characteristics of 3 in H35 hepatoma cells were dramatically different from those of 1.[4] While 1 had no effect on MTX transport in H35 hepatoma cells, 3 inhibited MTX and (6*R*,6*S*)-5-formyltetrahydrofolate (folinic acid) influx into these cells efficiently. H35 R cells that were resistant to MTX by virtue of a transport defect were cross resistant to 3 but not to 1. Although 3 was a weaker inhibitor of TS compared to 1, it was 40-60 times more active as a growth inhibitor of Manca human lymphoma and H35 hepatoma cells. These results taken together indicated that further structural changes of 1 at the pyrimidine portion of the quinazoline ring might lead to the devel-

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(1) Previous paper: Abraham, A.; McGuire, J. J.; Galivan, J.; Nimec, Z.; Kisliuk, R. L.; Gaumont, Y.; Nair, M. G. *J. Med. Chem.* **1991**, *34*, 222.
(2) Jones, T. R.; Calvert, A. H.; Jackman, A. L.; Brown, S. J.; Jones, M.; Harrap, K. R. *Eur. J. Cancer* **1981**, *17*, 11.
(3) Hughes, L. R.; Marsham, P. R.; Oldfield, J.; Jones, T. R.; O'Connor, B. M.; Bishop, J. A. M.; Calvert, A. H.; Jackman, A. L. *Proc. Am. Assoc. Cancer Res.* **1988**, *29*, 286.
(4) Patil, S. D.; Jones, C.; Nair, M. G.; Galivan, J.; Maley, F.; Kisliuk, R. L.; Gaumont, Y.; Duch, D.; Ferone, R. *J. Med. Chem.* **1989**, *32*, 1284.
(5) Jones, T. R.; Varney, M. D.; Webber, S. E.; Welsh, K. M.; Webber, S.; Matthews, D. A.; Appelt, K.; Smith, W. S.; Janson, C.; Bacquet, R.; Lewis, K. K.; Marzoni, G. P.; Katherdekar, V.; Howland, E.; Booth, C.; Herrmann, S.; Ward, R.; Sharp, J.; Mooman, E.; Bartlett, C.; Morse, C. *Proc. Am. Assoc. Cancer Res.* **1990**, *31*, 340.

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