pyridin-2-yl]methoxy]methyl]-4-hydroxy-3-(2-pyridylmethyl)pyrimidine (37). Compound **27** was reacted with 2-(chloromethyl)pyridine and the residue was crystallized from Et_2O to give title compound **37**: yield 102 mg (17%); mp 122–125 °C. Anal. ($C_{29}H_{29}Cl_2N_5O_6$) C, H, N.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-methoxypyrimidine (38). Trimethyloxonium tetrafluoroborate (0.85 g, 5.7 mmol) was added to a stirred suspension of **27** (1.00 g, 1.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C, and the mixture was stirred at room temperature for 24 h, washed with 5% aqueous Na_2CO_3 solution, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–1% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **38**: yield 80 mg (8%); mp 160–162 °C. Anal. ($C_{24}H_{26}Cl_2N_4O_6$) C, H, N.

Acknowledgment. We thank S. M. Denton and S. F. Tickner for their able technical assistance, A. J. Pettman and I. W. Sinclair for the large-scale synthesis of **12**, and A. G. Swanson for performing the NOE experiments on **33** and **37**. We are also grateful to P. J. Wadsworth and his staff for analytical and spectral data.

Substituted 5-Amino-4,5,6,7-Tetrahydroindazoles as Partial Ergoline Structures with Dopaminergic Activity

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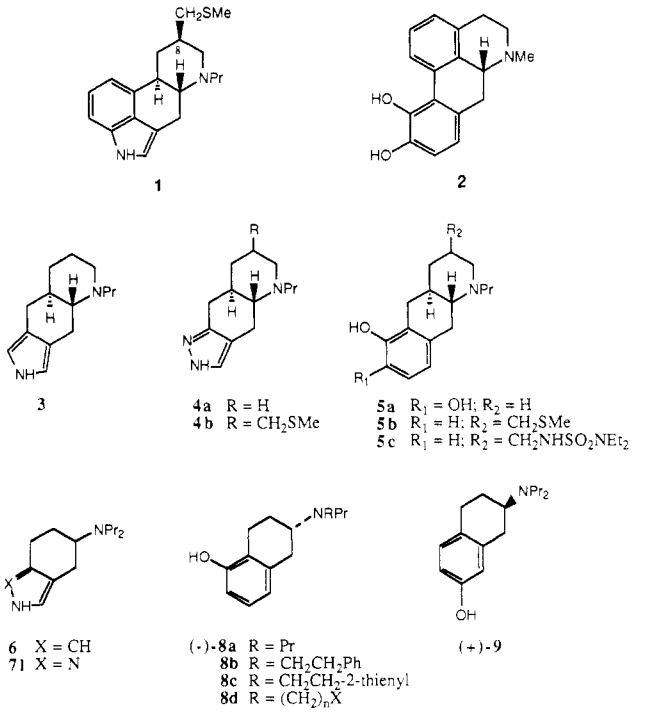
Two series of tetrahydroindazoles were synthesized and evaluated for dopaminergic activity. A number of these partial ergoline analogues possess substituents that could mimic the C-8 substituent of the dopaminergic ergolines. Of the unsymmetrically substituted amine series **7a–k**, the (monopropylamino)tetrahydroindazole **7b** was most interesting as it was found to selectively activate the dopamine (DA) autoreceptor at a dose of 5 mg/kg in rats. The disubstituted amines **7g–k** had significant DA postsynaptic activity as measured by increases of serum corticosterone levels in rats. The 6-substituted-5-aminotetrahydroindazoles **10a–d** were found to possess only marginal dopaminergic activity.

Classical neuroleptics are believed to exert their therapeutic effect by blocking the postsynaptic dopamine (DA) receptor.[1] This same pharmacological property is thought to be responsible for the development of undesirable extrapyramidal side effects and dyskinesias. A selective DA autoreceptor agonist which decreases synthesis and release of DA as well as the firing rate of DA neurons[2] might decrease dopaminergic function sufficiently to have antipsychotic activity without causing extrapyramidal side effects or tardive dyskinesias resulting from direct blockage of postsynaptic DA receptors. In this way, a new class of neuroleptic drugs devoid of extrapyramidal side effects might emerge.

Pergolide (**1**), a semisynthetic ergot alkaloid, preferentially activates the DA autoreceptor at low doses.[3] Martin and co-workers[4] found that pergolide showed the highest selectivity for the autoreceptor seen for the series of compounds tested. Therefore, we were interested in synthesizing partial pergolide analogues in an effort to increase selectivity for the presynaptic versus postsynaptic D_2 receptor.

A number of workers have synthesized a variety of partial ergoline compounds in order to determine the dopaminergic pharmacophore present in the ergoline skeleton. Originally,[5] it was thought that the phenethylamine portion was responsible for DA activity (Chart I, structure A). However, Nichols[6] noted that a comparison of the absolute configuration of the ergoline skeleton with that of the classical DA agonist, apomorphine (**2**), suggested that it was the rigid pyrroleethylamine moiety which was the DA pharmacophore (Chart I, structure B). Kornfeld[7] had also come to this conclusion and tested this hypothesis by synthesizing a number of partial ergoline structures. The octahydropyrrolo- and pyrazolo[3,4-*g*]quinolines **3** and



(1) Creese, I.; Burt, D. R.; Snyder, S. H. *Science* **1976**, *192*, 481.
(2) Aghajanian, G. K.; Bunney, B. S. *Arch. Pharmacol.* **1977**, *297*, 1. Tepper, J. M.; Nakamura, S.; Young, S.; Groves, P. M. *Brain Res.* **1984**, *309*, 317.
(3) Fuller, R. W.; Clemens, J. A.; Kornfeld, E. C.; Snoddy, H. D.; Smalstig, E. B.; Bach, N. J. *Life Sci.* **1979**, *24*, 375. Fuller, R. W.; Clemens, J. A.; Hynes, M. D., III *J. Clin. Psychopharmacol.* **1982**, *2*, 371.
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(7) (a) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481. (b) Titus, R. D.; Kornfeld, E. C.; Jones, N. D.; Clemens, J. A.; Smalstig, E. B.; Fuller, R. W.; Hahn, R. A.; Hynes, M. D.; Mason, N. R.; Wong, D. T.; Foreman, M. M. *J. Med. Chem.* **1983**, *26*, 1112.

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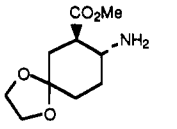
4a were found to be potent and selective D_2 agonists. The pyrazole analogue was resolved, and the absolute configuration of the active enantiomer, quinpirole [(−)-**4a**], correlates with that found in the ergolines and apomorphine.[7b] Dopaminergic activity has been shown also by the corresponding catechol derivative, (±)-1,2-dihydroxyoctahydrobenzo[*g*]quinoline (**5a**).[8] Nordmann and co-workers[9a] have remarked on the clear structural similarity between quinpirole and **5a**. This similarity further supports the hypothesis that the pyrrole and pyrazole ring systems can function as catechol bioisosteres.

The bicyclic analogues of **3**, **4a**, and **5a** have been synthesized and examined for their ability to mimic DA. Racemic pyrrole **6** and pyrazole **7l** showed modest dopaminergic activity.[7a] The case of the hydroxylated 2-aminotetralins is much more complex since DA activity is a function of both the position of the hydroxy group(s) and the absolute configuration of the 2-amine center. McDermed[10] has developed a model which is able to account for the fact that both (*S*)-(−)-5-OH-DPAT (**8a**) and (*R*)-(+)-7-OH-DPAT (**9**), but not their enantiomers, are DA agonists.

We chose the bicyclic pyrazole fragment as our starting point for further elaboration because it is the minimum dopaminergic pharmacophore suggested by the ergoline skeleton that combines metabolic and chemical stability. Incorporation of pergolide's C-8 (methylthio)methyl side chain led to the development of two different bicyclic pyrazoles, **7k** and **10a** (Scheme I). In addition to making the pergolide analogues, we were interested in expanding the SAR to include other substituents.



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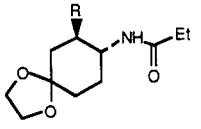
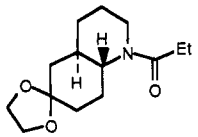


14a R = CO_2Me
14b R = CH_2OH
14c R = CHO
14d R = CH=CH-CO_2Me
14e R = $CH_2CH_2CO_2Me$
14f R = $CH_2CH_2CH_2OH$
14g R = $CH_2CH_2CH_2OMs$
14h R = $CH_2CH_2CH_2SMe$
14i R = $CH_2CH_2CH_2OMe$
14j R = CH=CH-CH_3
14k R = $CH_2CH_2CH_3$



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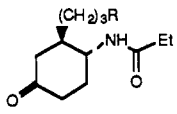
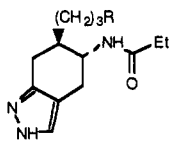
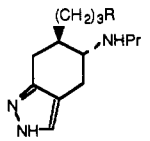


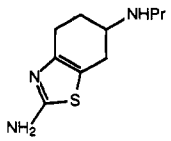
16a R = SMe
16b R = OMe
16c R = H
16d R = OH
16e R = OTHP



17a R = SMe
17b R = OMe
17c R = H
17d R = OH
17e R = OTHP

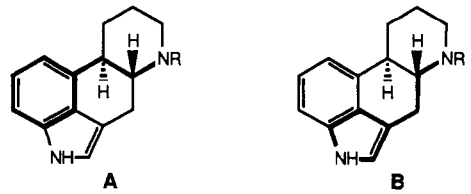


10a R = SMe
10b R = OMe
10c R = H
10d R = OH



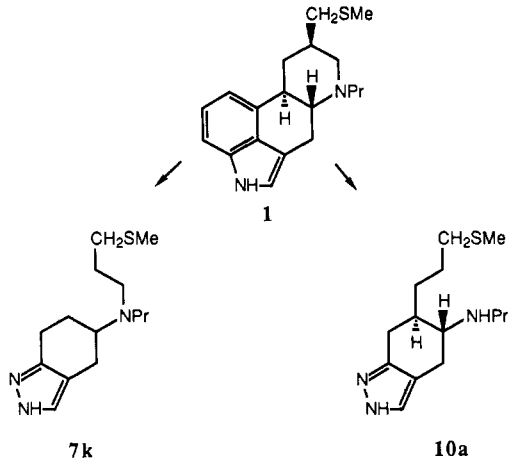
18

Chart I



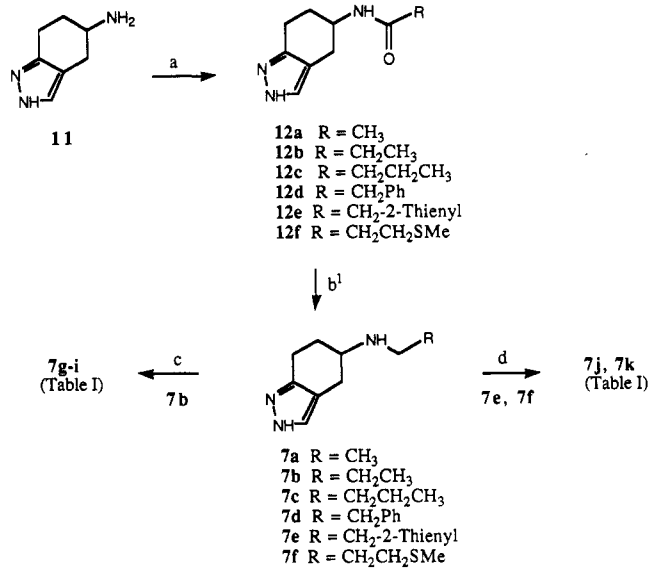
A **B**

Scheme I



1 **7k** **10a**

Scheme II[a]



11

12a R = CH_3
12b R = CH_2CH_3
12c R = $CH_2CH_2CH_3$
12d R = CH_2Ph
12e R = CH_2-2-Thienyl
12f R = CH_2CH_2SMe

7a R = CH_3
7b R = CH_2CH_3
7c R = $CH_2CH_2CH_3$
7d R = CH_2Ph
7e R = CH_2-2-Thienyl
7f R = CH_2CH_2SMe

[a] (a) RCOCl; (b) BH_3 (footnote 1: in the case of **7a**, $LiAlH_4$ was used); (c) RCHO, $NaBH_3CN$; (d) CH_3CH_2CHO, $NaBH_3CN$.

In the course of our work in this area, a number of publications appeared based on the strategy of adding ergoline-like side chains to known dopaminergic agonists. The (methylthio)methyl-substituted octahydropyrazolo-[3,4-*g*]quinoline 4b was already known and reported to be a potent dopaminergic agonist.[7a] Nordmann et al.[9] recently synthesized a number of substituted 1-hydroxyoctahydrobenzo[*g*]quinolines, including **5b** and **5c**, which also were excellent DA agonists. Horn et al.[11] reported the phenethyl (N-0434, **8b**) and 2-thienyl (N-0437, **8c**) derivatives of **8a**. Seiler and co-workers[12] further investigated the unsymmetrically substituted 5-hydroxy-2-amino-

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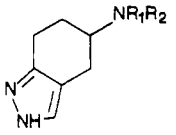
Table I. Binding and Serum Prolactin Results for **7a–k** and **18**



	R_1	R_2	binding,[a] IC_{50}, nM apo[d]	binding,[a] IC_{50}, nM spip[e]	prolactin inhibition[b,c] control, ng/mL	prolactin inhibition[b,c] treatment, ng/mL	prolactin inhibition[b,c] % inhibn
7a	H	Et	610	11600	16.8 ± 3.2	1.6 ± 0.2[f]	91
7b	H	Pr	65	15200	11.0 ± 2.0	2.4 ± 0.2[f]	78
7c	H	Bu	>10000	>10000	11.2 ± 2.3	13.4 ± 3.6	NS[g]
7d	H	CH_2CH_2Ph	15310	>10000	10.7 ± 3.1	6.0 ± 0.9	NS
7e	H	CH_2CH_2-2-thienyl	9160	>10000	8.0 ± 1.3	7.9 ± 0.9[h]	NS
7f	H	$CH_2CH_2CH_2SMe$	2030	>10000	8.6 ± 0.7	9.9 ± 1.4	NS
7g	Me	Pr	1233	8330	11.2 ± 2.3	2.0 ± 0.1[f]	82
7h	Bu	Pr	330	10000	11.2 ± 2.3	1.9 ± 0.1[f]	83
7i	Pr	CH_2CH_2Ph	140	1060	10.7 ± 3.1	1.4 ± 0.2[f]	87
7j	Pr	CH_2CH_2-2-thienyl	160	1410	10.7 ± 3.1	2.8 ± 0.5[f]	73
7k	Pr	$CH_2CH_2CH_2SMe$	310	3990	10.7 ± 3.1	1.1 ± 0.2[f]	90
18			280	>1000	16.5 ± 4.7	3.7 ± 0.2[f,h]	78
1	pergolide		1.6[i]	48[i]	16.7 ± 2.9	2.0 ± 0.3[f,j]	88

[a] For methodology, see ref 20. [b] For methodology, see ref 21; compounds were given at a dose of 5 mg/kg ip, except 1, which was given at a dose of 0.05 mg/kg ip. [c] Values are means plus or minus standard errors for 6–10 rats. [d] [^{3}H]Apomorphine, rat corpus striatum. [e] [^{3}H]-Spiperone, calf corpus striatum. [f] Significant difference from control group ($P < 0.05$). [g] Not significant. [h] Dose was 1 mg/kg ip. [i] Data taken from ref 7b. [j] The dose was 0.05 mg/kg ip.

tetralins, **8d**. They found that substitution of one of the *N*-propyl groups of **8a** with various groups similar to those found effective for the ergolines [e.g., **8d**, X = CH_2CN, CH_2SMe, $CH_2NHSO_2N(Et)_2$] did not significantly improve dopaminergic activity.

Results and Discussion

Chemistry. The bicyclic pyrazoles **7a–k** were prepared as shown in Scheme II. The secondary amines **7a–f** were prepared by acylation of **11**,[5a] followed by reduction with diborane, except in the case of **7a**, where $LiAlH_4$ was used. The tertiary amines were synthesized by either of two routes depending on the availability of the corresponding acid chlorides or aldehydes. In the case of **7g–i**, amine **7b** was reductively aminated with the appropriate aldehyde to give the desired products. Alternatively, the corresponding secondary amines, **7e** and **7f**, were reductively aminated with propional to give tertiary amines **7j** and **7k**.

The bicyclic pyrazoles **10a–d** were prepared in the following manner. Amine **13**[13] was acylated and reduced to give alcohol **14b**. Swern[14] oxidation to **14c** followed by a Wadsworth–Emmons[15] reaction gave unsaturated ester **14d**. The conversion of **14d** to **14f** required two stepwise reductions: hydrogenation of the double bond and $LiBH_4$ reduction of the ester. Conversion of alcohol **14f** to the corresponding mesylate **14g** and displacement of the mesylate with methanethiol gave **14h**. An attempted displacement with methoxide resulted in cyclization to give amide **15**. However, the desired methyl ether **14i** could be obtained by treatment of **14f** with silver oxide in methyl iodide. Aldehyde **14c** was treated with the ethylidene Wittig reagent to give **14j** as a mixture of cis and trans isomers, which upon hydrogenation gave **14k**.

The pyrazole ring was constructed by using standard techniques. The regiochemistry of the annelation sequence was the same as seen by Kornfeld and co-workers.[7a] Ketals **14h**, **14i**, and **14k** were hydrolyzed in hydrochloric acid to the corresponding ketones **16a–c**. The ketones were treated with tris(dimethylamino)methane followed by hydrazine to give pyrazoles **17a–c**. Reduction of the amide side chain with borane resulted in the desired α-substituted pyrazoles **10a–c**. In the case of **10d**, it was necessary to protect the primary alcohol as its THP ether before formation of the pyrazole ring. Therefore, alcohol **14f** was hydrolyzed to ketone **16d** and protected as its THP ether **16e**. Treatment of ketone **16e** as above resulted in pyrazole **17e**. Hydrolysis of the THP protecting group and diborane reduction gave pyrazole **10d**. We also prepared aminothiazole **18**. Since the completion of this work, a report[16] has appeared describing a synthesis of **18** identical with that employed in our laboratory.

Pharmacology. The unsymmetrically substituted pyrazole series **7a–k** were evaluated for their ability to displace [^{3}H]apomorphine and [^{3}H]spiperone from rat striatal membranes and their effects on serum prolactin levels (Table I). In addition, these compounds were evaluated for their effects on DA turnover (Table II) and serum corticosterone levels (Table III). One striking result is that the secondary amines with a substituent greater than propyl are neither active in the binding assays nor are they effective at lowering prolactin levels. There has been a considerable discussion in the DA literature suggesting the importance of a "*N*-propyl" binding site for D_2 activation.[17] Our results support this conclusion as the *N*-ethyl and *N*-propyl secondary amines **7a** and **7b** are active, while the *N*-butylamine **7c** and secondary amines containing bulkier substitutions are inactive. Similar results were found in the 2-aminotetralin series.[17]

The surprising result was that the monopropyl pyrazole **7b** was the most potent compound at displacing [^{3}H]-apomorphine. Moreover, **7b** possessed the largest separation of affinity for the [^{3}H]apomorphine site as compared to the [^{3}H]spiperone site. It significantly lowered serum

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Table II. Effects on Dopamine and Metabolite Levels[a] in Whole Brain for **7a–k** and **18**[b,c]

	dopamine			DOPAC[d]			HVA[e]		
	nmol/g		% change	nmol/g		% change	nmol/g		% charge
no.	control	treatment	from control	control	treatment	from control	control	treatment	from control
7a	5.40 ± 0.10	6.39 ± 0.08[f]	+18	0.58 ± 0.02	0.55 ± 0.01	NS	0.44 ± 0.01	0.40 ± 0.0u	NS
7b	4.05 ± 0.13	4.86 ± 0.18[f]	+20	0.57 ± 0.02	0.51 ± 0.02	NS	0.49 ± 0.01	0.51 ± 0.02	NS
7c	4.48 ± 0.11	3.90 ± 0.15[f]	−13	0.50 ± 0.02	0.53 ± 0.01	NS	0.36 ± 0.02	0.36 ± 0.01	NS
7d	4.48 ± 0.11	3.65 ± 0.11[f]	−19	0.50 ± 0.02	0.51 ± 0.03	NS	0.36 ± 0.02	0.34 ± 0.01	NS
7e	4.48 ± 0.11	3.47 ± 0.05[f]	−23	0.50 ± 0.02	0.49 ± 0.02	NS	0.36 ± 0.02	0.38 ± 0.0u	NS
7f	4.61 ± 0.11	3.91 ± 0.15[f]	−15	0.46 ± 0.02	0.49 ± 0.01	NS	0.24 ± 0.01	0.27 ± 0.02	NS
7g	4.48 ± 0.11	5.16 ± 0.20[f]	+15	0.50 ± 0.02	0.43 ± 0.02[f]	−14	0.36 ± 0.02	0.22 ± 0.02[f]	−39
7h	4.48 ± 0.11	4.94 ± 0.12[f]	+10	0.50 ± 0.02	0.39 ± 0.02[f]	−22	0.36 ± 0.02	0.20 ± 0.01[f]	−44
7i	4.48 ± 0.11	4.41 ± 0.10	NS	0.50 ± 0.02	0.40 ± 0.02[f]	−20	0.36 ± 0.02	0.23 ± 0.01[f]	−36
7j	4.48 ± 0.11	4.78 ± 0.21	NS	0.50 ± 0.02	0.43 ± 0.02[f]	−14	0.36 ± 0.0i	0.24 ± 0.02[f]	−33
7k	4.61 ± 0.11	4.92 ± 0.10	NS	0.46 ± 0.02	0.28 ± 0.01[f]	−39	0.24 ± 0.01	0.16 ± 0.01[f]	−33
18	4.61 ± 0.11	5.08 ± 0.07[f]	+10	0.46 ± 0.02	0.35 ± 0.01[f]	−24	0.24 ± 0.01	0.15 ± 0.01[f]	−38
1[g]	5.54 ± 0.16	6.42 ± 0.09[f]	+16	0.64 ± 0.0	0.53 ± 0.01[f]	−17	0.44 ± 0.02	0.32 ± 0.01[f]	−27

[a] For methodology, see ref 23. [b] Compounds were given at a dose of 10 mg/kg ip. [c] Values are mean plus or minus standard errors for five rats per group. [d] 3,4-Dihydroxyphenylacetic acid. [e] Homovanillic acid. [f] Significant difference from control group ($P < 0.05$). [g] Dose was 0.3 mg/kg ip.

Table III. Effects on Serum Corticosterone Levels[a] in Whole Brain for **7a–k** and **18**[b,c]

	serum corticosterone μg/100 mL		% change
no.	vehicle	treatment	from control
7a	6.2 ± 0.5	16.6 ± 7.9	NS
7b	9.4 ± 2.2	31.7 ± 7.4[d]	+337
7c	5.5 ± 0.5	5.8 ± 0.7	NS
7d	5.5 ± 0.5	7.7 ± 1.5	NS
7e	5.5 ± 0.5	5.5 ± 0.3	NS
7f	3.6 ± 0.4	3.8 ± 0.6	NS
7g	5.5 ± 0.5	41.0 ± 2.1[d]	+745
7d	5.5 ± 0.5	38.6 ± 3.0[d]	+702
7i	5.5 ± 0.5	17.5 ± 6.6	(+318)[e]
7j	5.5 ± 0.5	17.3 ± 4.9[d]	+314
7k	3.6 ± 0.4	48.0 ± 1.7[d]	+1333
18	3.6 ± 0.4	54.0 ± 2.8[d]	+1500
1[f]	7.5 ± 1.1	54.0 ± 5.2[d]	+720

[a] For methodology, see ref 24. [b] Compounds were given at a dose of 10 mg/kg ip. [c] Values are mean plus or minus standard errors for five rats per group. [d] Significant difference from control group ($P < 0.05$). [e] Increase not significant due to large standard error. [f] Dose was 0.3 mg/kg ip.

Table IV. Effects of **7b** on Dopa Accumulation in GBL-Treated Rats[a]

pretreatment with **7b**, mg/kg	striatal dopa,[b] nmol/g	pretreatment with **7b**, mg/kg	striatal dopa,[b] nmol/g
none	24.8 ± 0.8	3.0	16.9 ± 1.0[c]
0.3	25.2 ± 2.0	10.0	12.1 ± 0.8[c]
1.0	23.1 ± 0.9	none (no GBL)	9.7 ± 0.4[c]

[a] For methodology, see ref 25. [b] Values are means plus or minus standard errors for five rats per group. [c] Significant difference from top group ($P < 0.01$).

prolactin at 5 mg/kg both ip and po. When tested in the 6-OH-DA-lesioned rat, **7b** had marginal activity with only one in five rats turning (60 turns for 30 min). Although **7b** was not found to significantly alter steady-state levels of DOPAC and HVA at doses up to 10 mg/kg in whole rat brain, in the GBL model of DA autoreceptor activity, **7b** completely antagonized dopa accumulation in a dose-dependent manner (Table IV). Using in vivo dialysis techniques, a decrease in extracellular HVA was observed, indicating autoreceptor activation (Figure 1). However, **7b** was found to raise serum corticosterone levels (Table III). In addition, doses slightly higher than 10 mg/kg ip in rats and doses of 5 mg/kg ip in pigeons caused stereotyped behavior indicative of postsynaptic dopaminergic activity which precluded further interest in **7b**.

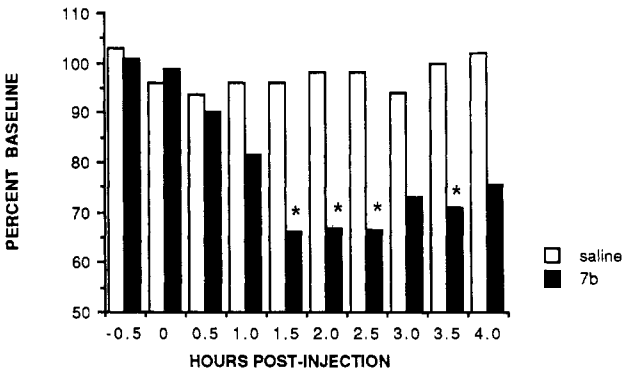


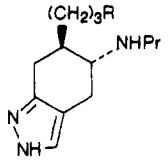
Figure 1. Changes in extracellular HVA vs hours postinjection following 5 mg/kg **7b** or saline, ip. For methodology, see Experimental Section. Asterisk (*) denotes significant difference from saline control ($P < 0.01$).

Our initial results with **7b** had led us to make the aminothiazole derivative **18**. We found **18** to be slightly more potent than the pyrazole analogue at a dose of 10 mg/kg ip, with significant effects on DA turnover in whole rat brain in addition to raising serum corticosterone levels 15 times over control levels. On the basis of the corticosterone data, we concluded that **18** may have postsynaptic DA agonist activity, although Schneider et al.[16] have suggested that **18** possesses a pronounced selectivity for the DA autoreceptor on the basis of its inability to elicit stereotyped behavior in mice at doses up to 40 mg/kg.

The tertiary amines **7g–l** all showed similar activity. The two arylethyl derivatives **7i** and **7j** were slightly less active in vivo although they were more potent in the binding assays. The pergolide analogue **7k** was the most potent of the series by a slight margin as shown by its effects on serum corticosterone levels. In addition, stereotyped behavior was noted at doses of 5 mg/kg ip. Therefore, the pergolide analogue **7k** does not appear to be particularly selective for the DA autoreceptor. The methyl propyl analogue **7g** was only slightly less potent that those analogues (e.g., **7i**, **7j**, and **7k**) with side chains designed to occupy the ergoline 8-substituent binding site. This lack of increased activity in the tertiary amine series runs parallel to the findings for the 2-aminotetralin series as discussed previously.

The testing results obtained for the bicyclic pyrazole series **10a–d** indicated only marginal dopaminergic activity (Table V). We therefore concluded that the presence of a nonrigid side chain at C-5 of the bicyclic pyrazole structure interferes with efficient binding at both the high-

Table V. Binding and Serum Prolactin Results for **10a–d**



no.	R	binding,[a] % disp (1000 nM)[d] apo[e]	spip[f]	prolactin inhibition[b,c] control, ng/mL	treatment, ng/mL	% inhibn
10a	SMe	45	10	8.2 ± 0.7	7.8 ± 7.8	NS[g]
10b	OMe	50	12	8.2 ± 0.7	4.6 ± 0.2[h]	44
10c	H	41	9	8.2 ± 0.7	5.1 ± 0.2[h]	38
10d	OH	45	10	8.2 ± 0.7	4.4 ± 0.4[h]	46

[a] For methodology, see ref 20. [b] For methodology, see ref 21; compounds were given at a dose of 5 mg/kg ip. [c] Values are means plus or minus standard errors for 6–10 rats. [d] Percent displacement at 1000 nm. [e] [^{3}H]Apomorphine, rat corpus striatum. [f] [^{3}H]-Spiperone, calf corpus striatum. [g] Not significant. [h] Significant difference from control group ($P < 0.05$).

and low-affinity D_2 receptor.

In summary, incorporation of the (methylthio)methyl side chain of pergolide, as well as various other side chains, onto the BC bicyclic pyrazole fragment of the ergoline skeleton, via two different substitution patterns, did not significantly increase DA activity. The most interesting compound was the monopropyl pyrazole **7b**, which showed a slight preference for the DA autoreceptor at a dose of 5 mg/kg in rats.

Experimental Section

Synthetic Methodology. All melting points were taken with a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined with a Nicolet DX-10 FTIR spectrometer. ^{1}H NMR were obtained on a GE QE 300 spectrometer. Chemical shift values are reported in ppm (δ) downfield from Me_4Si or DSS. Mass spectra were recorded on a Consolidated Electrodynamics Corp. 21-110 for EI spectra, on a Varian Mat 731 for FD spectra, or on a Zab 3F-VG Analytical for FAB spectra for determination of exact mass. Elemental analyses were done either on a Perkin-Elmer 240 elemental analyzer or on a Control Equipment Corp. 240-XA and are within 0.4% of the theoretical values. Preparative HPLC was done on a Waters Prep 500 system. All new, chiral compounds are racemic.

(±)-5-Propanamido-4,5,6,7-tetrahydroindazole (12b). Amide **12b** was prepared in 73% yield in an analogous manner to that described for amide **12a**,[7a] except the free base was purified by flash chromatography (0–10% MeOH/$CHCl_3$ with 0.5% NH_4OH) followed by recrystallization from EtOAc/hexane: mp 178–179 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.00 (t, 3 H), 1.64 (m, 1 H), 1.88 (m, 1 H), 2.07 (m, 3 H), 2.30 (dd, 1 H), 2.64–2.80 (m, 3 H), 3.90 (m, 1 H), 7.27 (br s, 1 H), 7.77 (br d, 1 H); MS, m/e 194 (M + 1); IR (KBr) 3329, 3142, 3100, 3075, 2980, 2947, 2932, 1640, 1539, 1340, 1265, 971 cm^{-1}. An analytical sample was prepared by conversion to the dihydrochloride salt which was recrystallized (MeOH/Et_2O). Anal. ($C_{10}H_{17}N_3OCl_2$) C, H, N, Cl.

(±)-5-Butanamido-4,5,6,7-tetrahydroindazole (12c). To a solution of amine **11**[7a] (3.5 g, 16.7 mmol) and NaOH (2.0 g, 50 mmol) in 250 mL of a 1:1 mixture of THF/H_2O at 0 °C was added butyryl chloride (2.1 mL, 20 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h. Additional NaOH (0.4 g, 10 mmol) and butyryl chloride (0.5 mL, 3.34 mmol) were added, and the reaction mixture was stirred for an additional 7 h before removal of the THF under reduced pressure. The aqueous solution was made basic and was extracted with 20% MeOH/$CHCl_3$. The organic portions were dried, filtered, and evaporated to yield the crude amide which was purified by preparative HPLC (10% EtOH/$CHCl_3$) followed by recrystallization from EtOAc/hexane to give 1.85 g (54%) of butyryl amide: mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.52 (m, 2 H), 1.67 (m, 1 H), 1.96 (m, 1 H), 2.06 (t, 2 H), 2.32 (dd, 1 H), 2.48–2.82 (m, 3 H), 3.93 (m, 1 H), 7.27 (br s, 1 H), 7.83 (d, 1 H), 12.33 (br s, 1 H); MS, m/e 208 (M + 1); IR ($CHCl_3$) 3464, 3437, 3020, 3005, 2967, 2935, 2876, 1661, 1509, 1216 cm^{-1}. Anal. ($C_{11}H_{17}N_3O$) C, H, N.

(±)-5-(Phenylethanamido)-4,5,6,7-tetrahydroindazole (12d). In a manner similar to that used to obtain amide **12c**, amine **11** was treated with phenylacetyl chloride to give amide **12d** as an oil in 62% yield: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 1 H), 1.98 (m, 1 H), 2.32 (dd, 1 H), 2.68 (m, 2 H), 2.87 (dd, 1 H), 3.56 (s, 2 H), 4.26 (m, 1 H), 5.43 (br d, 1 H), 7.28 (m, 6 H); MS, m/e 255 (M); IR ($CHCl_3$) 3466, 3019, 3007, 2973, 2938, 1661, 1512, 1496, 1225, 1207 cm^{-1}. Anal. ($C_{15}H_{17}N_3O$) C, H, N.

(±)-5-(2-Thienylethanamido)-4,5,6,7-tetrahydroindazole (12e). In a manner similar to that used to obtain amide **12c**, amine **11** was treated with 2-thienylacetyl chloride to yield amide **12e** as an oil in 45% yield: ^{1}H ($CDCl_3$) δ 1.84 (m, 1 H), 2.00 (m, 1 H), 2.36 (dd, 1 H), 2.72 (m, 2 H), 2.88 (dd, 1 H), 3.76 (s, 2 H), 4.28 (m, 1 H), 5.6 (br d, 1 H), 6.08–7.04 (m, 2 H), 7.25 (m, 2 H); MS, m/e 261 (M); IR ($CHCl_3$) 3466, 3409, 3019, 3009, 2970, 2938, 1667, 1514, 1237, 1215 cm^{-1}. Anal. ($C_{13}H_{15}N_3OS$) C, H, N, S.

(±)-5-(Ethylamino)-4,5,6,7-tetrahydroindazole (7a) Dihydrochloride. To a solution of **12a**[7a] (2.7 g, 15 mmol) in 250 mL of anhydrous THF under a nitrogen atmosphere, $LiAlH_4$ (0.96 g, 25.3 mmol) was added as a solid. The reaction mixture was refluxed for 16 h and worked up according to the procedure of Steinhardt.[18] The crude product mixture was purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$ with 0.5% NH_4OH) to yield 1.08 g (43%) of the free base. The HCl salt was formed in HCl/MeOH and was recrystallized from MeOH/Et_2O to give 400 mg (11%) of **7a**: mp 240–247 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (t, 3 H), 1.92 (m, 1 H), 2.30 (m, 1 H), 2.60–3.20 (m, 7 H), 3.42 (br s, 1 H), 7.86 (s, 1 H); IR (KBr) 3425, 2796, 1586, 1471, 1433 cm^{-1}. Anal. ($C_9H_{17}N_3Cl_2$) C, H, N, Cl.

(±)-5-(1-Propylamino)-4,5,6,7-tetrahydroindazole (7b) Dihydrochloride. To a suspension of amide **12b** (7.0 g, 36.2 mmol) in 80 mL of THF was added 145 mL (145 mmol) of a 1 M solution of borane in THF. The reaction mixture was refluxed for 3 h and then stirred at room temperature for 16 h. Excess 3 N HCl was added and the THF removed by distillation. The mixture was heated on a steam bath for an additional 3 h and left at room temperature for 14 h. The reaction mixture was made basic with concentrated NH_4OH and was extracted with 20% MeOH/$CHCl_3$. The combined organic portions were dried, filtered, and evaporated to yield the free base as a cloudy oil. The HCl salt was formed in HCl/MeOH and was recrystallized from MeOH/Et_2O to give 7.5 g (82%) of **7b**, as a white solid: mp 215–218 °C; ^{1}H NMR (D_2O) δ 1.07 (t, 3 H), 1.80 (m, 2 H), 3.45 (m, 1 H), 3.75 (dd, 1 H), 3.84–4.08 (m, 2 H), 4.15–4.20 (t, 2 H), 4.25 (dd, 1 H), 4.65 (m, 1 H), 7.82 (s, 1 H); MS, m/e 179 (M); IR (KBr) 2963, 2783, 2721, 2510, 2435, 1553, 1460, 1327, 1190 cm^{-1}. Anal. ($C_{10}H_{19}N_3Cl_2$) C, H, N, Cl.

(±)-5-(1-Butylamino)-4,5,6,7-tetrahydroindazole (7c) Dihydrochloride. Amine **7c** was obtained in 32% yield by borane reduction of **12c** as described for **7b**: mp 206–208 °C; ^{1}H NMR (D_2O) δ 0.88 (t, 3 H), 1.37 (m, 2 H), 1.66 (m, 2 H), 2.03 (m, 1 H), 2.40 (m, 1 H), 2.72 (dd, 1 H), 2.82–3.08 (m, 2 H), 3.08–3.30 (m, 3 H), 3.62 (m, 1 H), 7.94 (s, 1 H); MS, m/e 193 (M); IR (KBr) 3080, 2952, 2859, 2760, 2645, 2550, 2482, 1600, 1578, 1438, 1340, 1092, 800 cm^{-1}. Anal. ($C_{11}H_{21}N_3Cl_2$) C, H, N, Cl.

(±)-5-(Phenethylamino)-4,5,6,7-tetrahydroindazole (7d) Dihydrochloride. Amine **7d** was obtained in 55% yield by borane reduction of **12d** as described for **7b**: mp 221–232 °C; ^{1}H NMR (DMSO-d_6) δ 1.96 (m, 1 H), 2.37 (dd, 1 H), 2.96–3.32 (m, 5 H), 3.50 (br s, 1 H), 6.88 (br s, 1 H), 7.30 (m, 5 H), 7.84 (s, 1 H), 9.64 (br d, 1 H); MS, m/e 241 (M); IR (KBr) 3370, 3000, 2730, 2630, 1583, 1493, 1450, 765 cm^{-1}. Anal. ($C_{15}H_{21}N_3Cl_2$) C, H, N, Cl.

(±)-5-[[2-(2-Thienyl)ethyl]amino]-4,5,6,7-tetrahydroindazole (7e) Dihydrochloride. Amine **7e** was obtained in 67% yield by borane reduction of **12e** as described for **7b**: mp 242–250 °C; ^{1}H NMR (DMSO-d_6) δ 1.95 (m, 1 H), 2.34 (m, 1 H), 2.70 (m, 2 H), 2.88 (m, 1 H), 3.10 (dd, 1 H), 3.28 (s, 4 H), 3.48 (m, 1 H),

(18) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1967; Vol. 1, p 584.

6.96 (br s, 1 H), 7.00 (m, 2 H), 7.42 (m, 1 H), 7.80 (s, 1 H), 9.66 (br d, 1 H); MS, *m/e* 248 (M + 1); IR (KBr) 3060, 2960, 2699, 2638, 2482, 1585, 1440, 815, 725 cm^{-1}; high-resolution MS 248.1198 (M + H) $C_{13}H_{17}N_3S$.

(±)-5-[[3-(Methylthio)propyl]amino]-4,5,6,7-tetrahydroindazole (7f) Dihydrochloride. 3-(Mercaptomethyl)propionyl chloride was made from the corresponding methyl ester[19] by saponification with KOH followed by treatment with thionyl chloride. In an analogous manner to that used to obtain amide **12c**, amide **12f** was obtained in 54% yield from amine **11** and 3-(mercaptomethyl)propionyl chloride: mp 162–164 °C; ^1H NMR (DMSO-d_6) δ 1.69 (m, 1 H), 1.89 (m, 1 H), 2.05 (s, 3 H), 2.26–2.42 (m, 3 H), 2.48–2.80 (m, 5 H), 3.92 (m, 1 H), 7.28 (s, 1 H), 7.95 (d, 1 H), 12.30 (br s, 1 H); MS, *m/e* 240 (M + 1); IR (KBr) 3307, 3135, 3058, 2932, 2914, 1634, 1541, 1204, 1158, 1048 cm^{-1}.

Amine **7f** was obtained in 64% yield by borane reduction of **12f** as described for **7b**: mp 200–207 °C; ^1H NMR (D_2O) δ 2.02 (m, 3 H), 2.08 (s, 3 H), 2.40 (m, 1 H), 2.62 (t, 2 H), 2.74 (dd, 1 H), 2.84–3.10 (m, 2 H), 3.16–3.32 (m, 3 H), 3.66 (m, 1 H), 7.92 (s, 1 H); MS, *m/e* 225 (M); IR (KBr) 3370, 2955, 2802, 2734, 2637, 2480, 1587, 1435 cm^{-1}. Anal. ($C_{11}H_{21}N_3SCl_2$) C, H, N, Cl, S.

(±)-5-(*N*-Methyl-*N*-propylamino)-4,5,6,7-tetrahydroindazole (7g) Dihydrochloride. To a solution of **7b** (3.5 g, 13.9 mmol) and NaOAc (1.95 g, 23.8 mmol) in 250 mL of MeOH was added 37% aqueous formaldehyde (7.0 mL, 81.6 mmol) followed by $NaBH_3CN$ (1.5 g, 23.8 mmol). The reaction mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure to give a residue, which was partitioned between 1 N HCl and Et_2O. The aqueous layer was basified with concentrated NH_4OH and extracted with 20% MeOH/$CHCl_3$. The combined organic portions were dried, filtered, and evaporated to give 4.0 g of an oil, which was purified by flash chromatography (0–8% MeOH/$CHCl_3$). A portion of the free base was converted to the dihydrochloride salt and recrystallized from MeOH/Et_2O to give 348 mg (9%) of **7g**: mp 125–129 °C; ^1H NMR (D_2O) δ 1.00, (t, 3 H), 1.80 (m, 2 H), 2.14 (m, 1 H), 2.22 (m, 1 H), 2.80–3.38 (m, 5 H), 3.82 (m, 1 H), 7.93 (s, 1 H); MS, *m/e* 193 (M); IR (KBr) 3400, 2919, 2880, 2635, 2516, 1574, 1460, 1203, 1040 cm^{-1}. Anal. ($C_{11}H_{21}N_3Cl_2$) C, H, N, Cl.

(±)-5-(*N*-Propyl-*N*-butylamino)-4,5,6,7-tetrahydroindazole (7h) Dihydrochloride. To a solution of **7b** (3.5 g, 12.4 mmol) and NaOAc (1.95 g, 23.8 mmol) in 250 mL of MeOH was added butyraldehyde (10.5 mL, 124 mmol) followed by $NaBH_3CN$ (1.5 g, 23.8 mmol). The reaction mixture was treated as described above for amine **7g** to give 3.1 g (72%) of amine **7h** as the dihydrochloride salt: mp 122–124 °C; ^1H NMR (D_2O) δ 0.95 (m, 6 H), 1.20 (m, 2 H), 1.70 (m, 4 H), 2.15 (m, 1 H), 2.23 (m, 1 H), 2.74 (m, 2 H), 3.06–3.38 (m, 6 H), 3.86 (m, 1 H), 7.94 (s, 1 H); MS, *m/e* 235 (M); IR (KBr) 3390, 3145, 2875, 2634, 2531, 1575, 1455, 1200, 1085, 925 cm^{-1}; high-resolution MS 236.21356 (M + H) ($C_{14}H_{25}N_3$).

(±)-5-(*N*-Propyl-*N*-phenethylamino)-4,5,6,7-tetrahydroindazole (7i) Dihydrochloride. To a solution of the dihydrochloride salt of **7b** (4.0 g, 15.9 mmol) and NaOAc (2.6 g, 31.7 mmol) in 250 mL of MeOH was added phenylacetaldehyde (11.2 mL, 96 mmol) followed by $NaBH_3CN$ (1.45 g, 23 mmol). The reaction mixture was treated as described above for amine **7g** to give 3.0 g (53%) of amine **7i** as the dihydrochloride salt. The salt was titrurated with Et_2O to give 404 mg (7%) of a hygroscopic foam, **7i**: mp 123.5–126 °C; ^1H NMR (DMSO-d_6) δ 0.95 (t, 3 H), 1.83 (m, 2 H), 1.98 (m, 1 H), 2.40 (m, 1 H), 3.02–3.52 (m, 6 H), 3.91 (m, 2 H), 7.23–7.57 (m, 5 H), 7.62 (s, 1 H), 10.65 (br s, 1 H); high-resolution MS 284.212 (M + H) $C_{18}H_{25}N_3$. Anal. ($C_{18}H_{27}N_3Cl_2$) C, H, N, Cl.

(±)-5-[*N*-Propyl-*N*-[2-(2-thienyl)ethyl]amino]-4,5,6,7-tetrahydroindazole (7j) Dihydrochloride. Amine **7j** was prepared in 59% yield by reductive amination of **7e** with propionaldehyde as described above for amine **7h**: mp 119–132 °C; ^1H NMR (DMSO-d_6) δ 0.94 (t, 3 H), 1.82 (m, 2 H), 1.96 (m, 1 H), 2.42 (m, 1 H), 2.80 (m, 3 H), 3.15 (m, 3 H), 3.42 (m, 4 H), 3.72 (m, 1 H), 7.00 (m, 1 H), 7.04 (s, 1 H), 7.42 (d, 1 H), 7.64 (s, 1 H), 10.86 (br s, 1 H); high-resolution MS 290.1675 (M + H) $C_{16}H_{23}N_3S$. Anal. ($C_{16}H_{25}N_3Cl_2S$) C, H, N, Cl, S.

(±)-5-[*N*-Propyl-*N*-[3-(methylthio)propyl]amino]-4,5,6,7-tetrahydroindazole (7k) Dihydrochloride. Amine **7k** was prepared in 94% yield by reductive amination of **7f** with propionaldehyde as described above for amine **7h**. The dihydrochloride salt of **7k** was isolated as a hygroscopic foam: ^1H NMR (D_2O) δ 0.76 (t, 3 H), 1.58 (m, 2 H), 1.90 (s, 3 H), 1.78–2.03 (m, 3 H), 2.22 (m, 1 H), 2.42 (t, 2 H), 2.72 (m, 2 H), 2.84–3.30 (m, 6 H), 3.67 (m, 1 H), 7.74 (s, 1 H); IR (KBr) 2965, 2620, 2532, 1580, 1562, 1460, 1440 cm^{-1}; MS, *m/e* 267 (M); high-resolution MS 268.1838 (M + H) $C_{14}H_{25}N_3S$.

(±)-*trans*-Methyl 8-Propanamido-1,4-dioxaspiro[4.5]decane-7-carboxylate (14a). To a solution of primary amine **13**[13] (0.5 g, 2.3 mmol) and pyridine (0.19 mL, 2.3 mmol) in 25 mL of methylene chloride at 0 °C was added propionyl chloride (0.25 mL, 2.9 mmol). The reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction mixture was poured onto ice, and the phases were separated. The aqueous phase was extracted with chloroform. The combined organic layers were dried, filtered, and evaporated to yield the crude product which was purified by flash chromatography on silica gel (25–50% THF/hexane) to give 280 mg (44%) of amide **14a**: ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H), 1.43 (m, 1 H), 1.75 (m, 2 H), 1.94 (m, 2 H), 2.06 (m, 1 H), 2.17 (q, 2 H), 2.64 (m, 1 H), 3.67 (s, 3 H), 3.95 (s, 4 H), 4.10 (m, 1 H), 5.61 (br d, 1 H); MS, *m/e* 271 (M + 1); IR ($CHCl_3$) 3020, 1733, 1670, 1512, 1269, 1215, 1156, 1093, 1048, 1037 cm^{-1}. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 118–120 °C. Anal. ($C_{13}H_{21}NO_5$) C, H, N.

(±)-*trans*-*N*-[7-(Hydroxymethyl)-1,4-dioxaspiro[4.5]dec-8-yl]propanamide (14b). To a suspension of lithium borohydride (0.88 g, 40.4 mmol) in THF was added ester **14a** (4.5 g, 16.6 mmol) in portions. The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. An additional 0.37 g (16.6 mmol) of lithium borohydride was added, and the mixture was stirred for 48 h. The solvent was evaporated and the residue taken up in H_2O. The pH was adjusted to 7 with 1 N HCl and stirred for 1 h. The aqueous layer was extracted with $CHCl_3$, and the combined extracts were dried, filtered, and evaporated. The crude product obtained was purified by recrystallization from THF/hexane to give 2.56 g (64%) of alcohol **14b**: mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H), 1.52 (br t, 1 H), 1.59–1.76 (m, 3 H), 1.76–1.93 (m, 3 H), 2.27 (q, 2 H), 3.27 (br t, 1 H), 3.62 (dt, 1 H), 3.74 (m, 1 H), 3.95 (m, 4 H), 4.06 (dd, 1 H), 6.08 (br d, 1 H); MS, *m/e* 244 (M + 1); IR ($CHCl_3$) 3433, 3019, 2952, 2886, 1653, 1516, 1215, 1157, 1097, 977 cm^{-1}. Anal. ($C_{12}H_{21}NO_4$) C, H, N.

(±)-*trans*-Methyl 3-(8-Propanamido-1,4-dioxaspiro[4.5]-dec-7-yl)-2-propenoate (14d). To a solution of oxalyl chloride (0.39 mL, 4.5 mmol) in 30 mL of methylene chloride at −78 °C was added a solution of dimethyl sulfoxide (0.64 mL, 9.0 mmol) in 10 mL of methylene chloride. After addition was complete, the mixture was stirred for 3 min before the addition of a solution of alcohol **14b** (1.0 g, 4.1 mmol) in 10 mL of dichloromethane. After 40 min, triethylamine (2.9 mL, 20.6 mmol) was added. The mixture was stirred for 10 min and then allowed to warm to room temperature. After 1 h, the reaction mixture was partitioned between H_2O and methylene chloride. The organic layer was dried, filtered, and evaporated to give 970 mg (98%) of aldehyde **14c**: mp 123–125 °C; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H), 1.58–2.12 (m, 6 H), 2.20 (q, 2 H), 2.52 (m, 1 H), 3.96 (s, 4 H), 4.20 (m, 1 H), 5.97 (br d, 1 H), 9.54 (d, 1 H); MS, *m/e* 242 (M + 1); IR ($CHCl_3$) 3023, 3019, 3013, 2957, 1725, 1669, 1508, 1215, 1156, 1101 cm^{-1}.

To a rapidly stirring suspension of freshly washed sodium hydride (1.2 g, 29.9 mmol, of a 60% dispersion in mineral oil) in 150 mL of DME under a nitrogen atmosphere was added a solution of trimethyl phosphonoacetate (4.84 mL, 29.9 mmol) in 20 mL of DME. The reaction mixture was stirred at room temperature for 1 h before the addition of a solution of aldehyde **14c** (7.2 g, 29.9 mmol) in 50 mL of DME. After stirring 1 h at room temperature, the reaction mixture was refluxed for 45 min. The reaction mixture was poured into 600 mL of ice water and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and evaporated. The crude product was recrystallized from EtOAc/hexane to give 6.2 g (70%) of ester **14d**: mp 135–137 °C; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3 H), 1.48–2.12 (m, 6 H), 2.16 (q, 2 H), 2.46 (m, 1 H), 3.72 (s, 3 H), 3.84 (m, 1 H), 3.96 (s, 4 H), 5.60

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(br d, 1 H), 5.84 (d, 1 H), 6.80 (dd, 1 H); MS, *m/e* 297 (M); IR ($CHCl_3$) 3019, 2954, 1718, 1661, 1510, 1487, 1288, 1239, 1215, 1146 cm^{-1}. Anal. ($C_{15}H_{23}NO_5$) C, H, N.

(±)-*trans*-Methyl 3-(8-Propanamido-1,4-dioxaspiro[4.5]-dec-7-yl)propanoate (14e). A solution of ester **14d** (1.0 g, 3.34 mmol) in 200 mL of EtOAc was hydrogenated over 10% Pd/C (180 mg) at an initial pressure of 40 psi for 3 h at room temperature. The catalyst was removed by filtration and the filtrate concentrated to obtain 1.0 g (100%) of ester **14e**: ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H), 1.30–2.04 (m, 10 H), 2.25 (q, 2 H), 2.40 (m, 1 H), 3.55–3.73 (m, 1 H), 3.67 (s, 3 H), 3.93 (s, 4 H), 5.71 (br d, 1 H); MS, *m/e* 299 (M); IR ($CHCl_3$) 3019, 2950, 1730, 1665, 1505, 1215, 1210, 1138, 1095, 1068 cm^{-1}. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 111–113 °C; Anal. ($C_{15}H_{25}NO_5$) C, H, N.

(±)-*trans*-*N*-[7-(3-Hydroxypropyl)-1,4-dioxaspiro[4.5]-dec-8-yl]propanamide (14f). To a rapidly stirring suspension of lithium borohydride (2.8 g, 128 mmol) in 400 mL of THF was added a solution of ester **14e** in 100 mL of THF. The reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was suspended in water, and 100 mL of 1 N HCl was added. After 1 h the resulting aqueous solution was extracted with $CHCl_3$. The combined organic layers were dried, filtered, and evaporated. The crude product was purified by flash chromatography (5% MeOH/$CHCl_3$) on silica gel to afford 10 g (90%) of alcohol **14f**: mp 85–86 °C; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H), 1.20–1.98 (m, 11 H), 2.21 (q, 2 H), 2.70 (br s, 1 H), 3.62 (m, 3 H), 3.94 (s, 4 H), 5.80 (br d, 1 H); MS, *m/e* 272 (M + 1); IR ($CHCl_3$) 3440, 3020, 2945, 2880, 1665, 1515, 1230, 1215, 1145, 1060, 930 cm^{-1}. Anal. ($C_{14}H_{25}NO_4$) C, H, N.

(±)-*trans*-*N*-[7-[3-(Methylthio)propyl]-1,4-dioxaspiro-[4.5]dec-8-yl]propanamide (14h). To a solution of alcohol **14f** (5.0 g, 18.4 mmol) in 300 mL of pyridine at 0 °C was added methanesulfonyl chloride (1.57 mL, 20.3 mmol). The reaction mixture was stirred an addition 10 min at 0 °C and then for 2 h at room temperature. The reaction mixture was poured onto ice water saturated with $NaHCO_3$. The aqueous mixture was extracted with chloroform, and the combined organic layers were dried, filtered, and evaporated to give 6.1 g of mesylate **14g** in 95% yield. The mesylate was taken on without further purification.

A stock solution of 5.2 M methanethiol (25 g) in 100 mL of DMF was prepared. A portion of the stock solution (6.6 mL, 34.4 mmol) was added to 125 mL of DMF and cooled to 0 °C. To the cooled solution was added sodium hydride (1.38 g of a 60% mineral oil dispersion, 33.5 mmol), and the reaction mixture was warmed to room temperature. A solution of mesylate **14g** (6.0 g, 17.2 mmol) in 125 mL of DMF was added, and the reaction mixture was stirred for 2 h. The reaction was quenched by pouring onto ice water and then was extracted with chloroform. The combined organic layers were dried, filtered, and evaporated to give the crude product, which was purified by flash chromatography (EtOAc) on silica gel to give 3.27 g (63%) of thiol **14h**: mp 75 °C; ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H), 1.21–1.79 (m, 9 H), 1.89 (qt, 2 H), 2.08 (s, 3 H), 2.22 (q, 2 H), 2.46 (t, 2 H), 3.66 (qd, 1 H), 3.94 (s, 4 H), 5.44 (br d, 1 H); MS, *m/e* 302 (M + 1); IR ($CHCl_3$) 3220, 3010, 2950, 1655, 1512, 1215, 1140 cm^{-1}. Anal. ($C_{15}H_{27}NO_3S$) C, H, N, S.

(±)-*trans*-*N*-[7-(3-Methoxypropyl)-1,4-dioxaspiro[4.5]-dec-8-yl]propanamide (14i). To a solution of alcohol **14f** (3.53 g, 13.0 mmol) in methyl iodide (70 mL, 1.12 mmol) was added silver oxide (19.8 g, 85.4 mmol) in portions. The reaction mixture was stirred in a sealed flask at room temperature for 3 days. The reaction mixture was diluted with methylene chloride and filtered through Celite. The filtrate was evaporated and the residue purified by flash chromatography (1:1 THF/hexane) on silica gel to afford 2.75 g (79%) of methyl ether **14i**: mp 94–95 °C; ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H), 1.29–1.78 (m, 9 H), 1.90 (m, 2 H), 2.21 (q, 2 H), 3.30 (s, 3 H), 3.33 (m, 2 H), 3.64 (m, 1 H), 3.94 (s, 4 H), 5.43 (br d, 1 H); MS, *m/e* 286 (M + 1); IR ($CHCl_3$) 3438, 3010, 2945, 2880, 1662, 1512, 1235, 1215, 1145, 1110, 1070, 930 cm^{-1}. Anal. ($C_{15}H_{27}NO_4$) C, H, N.

(±)-*trans*-*N*-(7-Propyl-1,4-dioxaspiro[4.5]dec-8-yl)-propanamide (14k). To a suspension of ethyltriphenylphosphonium bromide (17 g, 45.8 mmol) in 400 mL of THF was added 28.6 mL of a 1.6 M solution of *n*-BuLi (45.8 mmol) in hexane. The solution was stirred for 2 h at room temperature before the addition of 1.5 mL of 1.6 M solution of *n*-BuLi (2.40 mmol) in hexane. After 30 min, a solution of aldehyde **14c** (9.6 g, 39.8 mmol) in 100 mL of THF was added and the reaction mixture stirred for 18 h. A precipitate had formed and was removed by filtration through Celite. The filtrate was evaporated to give the crude product, which was purified by flash chromatography (1:1 THF/hexane) on silica gel to afford 5.3 g of olefin **14j** in a 53% yield as a mixture of *E* and *Z* isomers. The mixture was taken on to the next step.

A solution of olefin **14j** (5.3 g, 20.9 mmol) in 200 mL of ethanol was hydrogenated over 1.6 g of 5% Pd/C at an initial hydrogen pressure of 40 psi. After 30 h, an additional 2.1 g of catalyst was added and the hydrogenation continued for another 30 h. The catalyst was removed by filtration and the filtrate evaporated. The crude product was purified by flash chromatography (1:1 THF/hexane) on silica gel to give 3.15 g (59%) of alkane **14k**: mp 134–136 °C; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.15 (t, m, 4 H), 1.25–1.97 (m, 10 H), 2.22 (q, 2 H), 3.64 (qd, 1 H), 3.93 (s, 4 H), 5.42 (br d, 1 H); MS, *m/e* 256 (M + 1); IR ($CHCl_3$) 3445, 3010, 2960, 2940, 2870, 1660, 1510, 1210, 1158, 1125 cm^{-1}. Anal. ($C_{14}H_{25}NO_3$) C, H, N.

(±)-*trans*-3-[3-(Methylthio)propyl]-4-propanamidocyclohexanone (16a). To a solution of ketal **14h** (3.2 g, 10.6 mmol) in 50 mL of methanol was added 60 mL of 2 N HCl. The mixture was stirred at room temperature for 2 h and then poured onto an ice water mixture. The resulting solution was made basic with NH_4OH and extracted with 20% *i*-PrOH/$CHCl_3$. The combined organic layers were dried, filtered, and evaporated to give 2.7 g (99%) of ketone **16a**: mp 80 °C; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H), 1.22–1.86 (m, 6 H), 2.08 (s, 3 H), 2.12–2.56 (m, 9 H), 4.07 (m, 1 H), 5.82 (br d, 1 H); MS, *m/e* 258 (M + 1); IR ($CHCl_3$) 3440, 3020, 3005, 2940, 2908, 2870, 1712, 1765, 1508, 1455, 1425, 1215 cm^{-1}. Anal. ($C_{13}H_{23}NO_2S$) C, H, N, S.

(±)-*trans*-3-(3-Methoxypropyl)-4-propanamidocyclohexanone (16b). Cyclohexanone **16b** was prepared from ketal **14i** in 100% yield in a similar manner to that described for **16a**: ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H), 1.22–1.85 m, 6 H), 2.13–2.56 (m, 7 H), 3.30 (s, 3 H), 3.36 (m, 2 H), 4.05 (qd, 1 H), 5.91 (br d, 1 H); MS, *m/e* 242 (M + 1); IR ($CHCl_3$) 3440, 3010, 2935, 2870, 1712, 1665, 1508, 1225, 1115 cm^{-1}. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 89–91 °C. Anal. ($C_{13}H_{23}NO_3$) C, H, N.

(±)-*trans*-3-Propyl-4-propanamidocyclohexanone (16c). Cyclohexanone **16c** was prepared from ketal **14k** in 100% yield in a similar manner to that described for **16a**: ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.18 (t, 3 H), 1.10–1.83 (m, 6 H), 2.12–2.54 (m, 7 H), 4.06 (qd, 1 H), 5.91 (br d, 1 H); MS, *m/e* 212 (M + 1); IR ($CHCl_3$) 3440, 3010, 2960, 2940, 1712, 1765, 1510, 1235, 1215 cm^{-1}. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 110–112 °C. Anal. ($C_{12}H_{21}NO_2$) C, H, N.

(±)-3-(3-Hydroxypropyl)-4-propanamidocyclohexanone (16d). Cyclohexanone **16d** was prepared from ketal **14f** in 88% yield in a similar manner to that described for **16a**: ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H), 1.38 (m, 2), 1.66 (m, 3 H), 1.83 (m, 1 H), 2.27 (m, 4 H), 1.46 (m, 3 H), 3.11 (s, 1 H), 3.60 (m, 2 H), 4.05 (m, 1 H), 6.28 (br d, 1 H); MS, *m/e* 228 (M + 1); IR 3432, 3008, 2975, 2942, 1715, 1665, 1512, 1233, 1220, 1216, 1211, 1050 cm^{-1}. An analytical sample was prepared by recrystallization from EtOAc: mp 85–87 °C. Anal. ($C_{12}H_{21}NO_3$) C, H, N.

(±)-*trans*-6-[3-(Methylthio)propyl]-5-(1-propylamino)-4,5,6,7-tetrahydroindazole (10a) Dihydrochloride. To a solution of ketone **16a** (500 mg, 1.95 mmol) in 15 mL of benzene was added tris(dimethylamino)methane (490 μL, 3.1 mmol). The reaction mixture was refluxed for 2 h. Additional tris(dimethylamino)methane (310 μL, 2.0 mmol) was added and the reaction mixture refluxed for 2 h. After cooling to room temperature, the solvent was evaporated and the residue dissolved in 20 mL of methanol. Hydrazine (600 μL, 19 mmol) was added and the solution stirred for 18 h. The solvent was evaporated and the crude product purified by flash chromatography (4% MeOH/$CHCl_3$ with 0.5% concentrated NH_4OH) on silica gel to give 354 mg of pyrazole **17a** as a foam in 65% yield: ^1H NMR ($CDCl_3$) δ 1.14 (t, 3 H), 1.30 (m, 1 H), 1.52–1.76 (m, 3 H), 2.02 (m, 1 H), 2.08 (s, 3 H), 2.21 (m, 3 H), 2.48 (m, 4 H), 2.86 (m, 2

H), 4.18 (m, 1 H), 5.94 (br d, 1 H), 7.28 (s, 1 H); MS, *m/e* 282 (M + 1); IR ($CHCl_3$) 3470, 3010, 2940, 1665, 1510, 1215 cm^{-1}.

To a solution of amide **17a** (1.44 g, 5.13 mmol) in 50 mL of THF was added 25.7 mL of 1 M borane (25.7 mmol) in THF. The resulting mixture was refluxed to 4 h and then cooled to room temperature before addition of 100 mL of 1 N HCl. The mixture was heated on a steam bath for 10 h and allowed to cool to room temperature. The mixture was made basic with NH_4OH and extracted with 20% *i*-PrOH/$CHCl_3$. The combined extracts were dried, filtered, and evaporated to give crude product which was purified by flash chromatography (10% MeOH/$CHCl_3$ with 0.5% NH_4OH) on silica gel to afford 452 mg (26%) of amine **10a**. The free base was converted to the dihydrochloride salt as a hygroscopic foam: ^1H NMR (D_2O) δ 1.00 (t, 3 H), 1.37–1.86 (m, 6 H), 2.11 (s, 3 H), 2.48–2.61 (m, 3 H), 2.83–3.19 (m, 6 H), 3.72 (m, 1 H), 7.89 (s, 1 H); MS, *m/e* 267 (M). Anal. ($C_{14}H_{27}N_3SCl_2$) C, H, N, S, Cl.

(±)-*trans*-6-(3-Methoxypropyl)-5-(1-propylamino)-4,5,6,7-tetrahydroindazole (10b) Dihydrochloride. Pyrazole **17b** was prepared in 64% yield from ketone **16b** and isolated as a foam in a similar manner to that described for **17a**: ^1H NMR (DMSO-d_6) δ 1.02 (t, 3 H), 1.17 (m, 1 H), 1.54 (m, 3 H), 1.81 (m, 1 H), 2.11 (q, 2 H), 2.33 (m, 2 H), 2.59 (m, 1 H), 2.67 (dd, 1 H), 2.83 (dd, 1 H), 3.20 (s, 3 H), 3.29 (t, 2 H), 3.81 (m, 1 H), 7.26 (s, 1 H), 7.72 (br d, 1 H); MS, *m/e* 266 (M + 1); IR ($CHCl_3$) 3470, 3440, 3010, 2950, 2870, 1663, 1508, 1215, 1112 cm^{-1}.

To a solution of amide **17b** (1.20 g, 4.49 mmol) in 50 mL of THF was added 22.5 mL of a 1 M borane (22.5 mmol) solution in THF. The reaction mixture was refluxed for 4 h and then stirred at room temperature for 16 h. The borane complex was hydrolyzed by heating with 90 mL of 4 N HCl for 5 h. The acidic solution was cooled to 0 °C and made basic with NH_4OH. The aqueous mixture was extracted with 20% *i*-PrOH/$CHCl_3$, and the combined organic layers were dried, filtered, and evaporated. The crude product was purified by flash chromatography (10% MeOH/$CHCl_3$ with 0.5% NH_4OH) on silica gel, and the resulting free base was converted to the dihydrochloride salt to afford 863 mg (59%) of **10b** as a hygroscopic foam: ^1H NMR (D_2O) δ 0.99 (t, 3 H), 1.32–1.81 (m, 6 H), 2.51 (m, 1 H), 2.83–3.18 (m, 6 H), 3.34 (s, 3 H), 3.50 (t, 2 H), 3.72 (m, 1 H), 7.84 (s, 1 H); MS, *m/e* 251 (M); high-resolution MS 252.2071 (M + H) $C_{14}H_{26}N_3O$.

(±)-*trans*-6-Propyl-5-(1-propylamino)-4,5,6,7-tetrahydroindazole (10c) Dihydrochloride. Pyrazole **17c** was prepared from ketone **16c** in 79% yield and isolated as a foam in a similar manner to that described for **17a**: ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.06–1.56 (m, 8 H), 2.02 (m, 1 H), 2.20 (q, 2 H), 2.46 (td, 2 H), 2.86 (td, 2 H), 4.18 (br m, 1 H), 5.88 (br d, 1 H), 7.28 (s, 1 H); MS, *m/e* 236 (M + 1); IR ($CHCl_3$) 3465, 3440, 3010, 2960, 2935, 1660, 1508, 1215 cm^{-1}.

Amine **10c** was prepared in 28% yield by borane reduction of amide **17c** in a manner similar to that described for amine **10b**. The dihydrochloride salt of **10c** was isolated as a hygroscopic foam: ^1H NMR (D_2O) δ 0.92 (t, 3 H), 0.98 (t, 3 H), 1.32–1.54 (m, 4 H), 1.63–1.78 (m, 2 H), 2.50 (m, 1 H), 2.78–3.02 (m, 3 H), 3.02–3.18 (m, 3 H), 3.70 (m, 1 H), 7.84 (s, 1 H); MS, *m/e* 221 (M); high-resolution MS 222.1965 (M + H) $C_{13}H_{23}N_3$.

(±)-*trans*-6-(3-Hydroxypropyl)-5-propanamido-4,5,6,7-tetrahydroindazole (17d). To a solution of alcohol **16d** (6.3 g, 27.8 mmol) in 200 mL of CH_2Cl_2 at 0 °C was added dihydropyran (10.3 mL, 113 mmol) followed by *p*-toluenesulfonic acid monohydrate (43 mg, 0.23 mmol). After 15 min the reaction mixture was warmed to room temperature for 2 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution and the organic layer dried, filtered, and evaporated to give 8.7 g (100%) of protected alcohol **16e** as a foam: ^1H NMR ($CDCl_3$) δ 1.11 (t, 3 H), 1.21–2.57 (m, 19 H), 3.17–4.13 (m, 5 H), 4.40 (br m, 1 H), 5.49 (dd, 1 H).

Pyrazole **17e** was prepared from ketone **16e** in a similar manner to that described for **17a** and isolated as a foam: ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H), 1.20–3.00 (m, 18 H), 3.12–4.20 (m, 5 H), 4.40 (br m, 1 H), 6.32 (br d, 1 H), 7.09 (s, 1 H).

To a solution of **17e** (6.4 g, 20.6 mmol) in 200 mL of methanol was added *p*-toluenesulfonic acid monohydrate (8.18 g, 43 mmol) in 30 mL of methanol. The resulting solution was stirred for 4 h, and then the solvent was evaporated. The residue was made basic with aqueous NH_4OH and extracted into 3:1 $CHCl_3$/*i*-PrOH. The combined organic layers were dried, filtered, and evaporated to give crude product which was purified by flash chromatography (4–8% MeOH/$CHCl_3$) on silica gel to give 4.0 g (60%) of pyrazole **17d** from ketone **16d**: ^1H NMR (CD_3OD) δ 1.15 (t, 3 H), 1.30 (m, 1 H), 1.53 (m, 1 H), 1.69 (m, 2 H), 1.93 (m, 1 H), 2.23 (q, 2 H), 2.43 (dd, 2 H), 2.85 (m, 1 H), 2.93 (dd, 1 H), 3.57 (t, 2 H), 3.98 (m, 1 H), 4.90 (s, 3 H), 7.30 (br s, 1 H); MS, *m/e* 252 (M + 1); IR (KBr) 3268, 3185, 3116, 3055, 2978, 2910, 1648, 1551, 1432, 1055, 950 cm^{-1}. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 178–180 °C. Anal. ($C_{13}H_{21}N_3O_2$) C, H, N.

(±)-*trans*-6-(3-Hydroxypropyl)-5-(1-propylamino)-4,5,6,7-tetrahydroindazole (10d) Dihydrochloride. Amine **10d** was prepared in 32% yield by borane reduction of amide **17d** in a manner similar to that described for amine **10b**: mp 173–177 °C; ^1H NMR (D_2O) δ 0.94 (t, 3 H), 1.28–1.76 (m, 6 H), 2.52 (m, 1 H), 2.82–3.16 (m, 6 H), 3.58 (t, 2 H), 3.72 (d, 1 H), 7.96 (s, 1 H); MS, *m/e* 237 (M); IR (KBr) 3215, 3080, 2940, 2880, 2717, 2630, 2570, 1580, 1460, 1060 cm^{-1}. Anal. ($C_{13}H_{25}N_3OCl_2$) C, H, N, Cl.

Pharmacological Methodology. DA receptor binding affinities were determined according to standard preparations and methodology.[20] Prolactin levels were measured in nonreserpinized male rats according to the method of Clemens et al.[21] Contralateral rotational behavior of unilateral 6-hydroxydopamine nigrostriatal-lesioned rats was assessed by using the method of Ungerstedt and Arbuthnott.[22] The DA metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were measured in brain by liquid chromatography with electrochemical detection.[23] Corticosterone concentration in serum was determined spectrofluorometrically by the method of Solem and Brinck-Johnsen.[24]

Effects on the DA autoreceptor in striatum were assessed in the experimental paradigm of Roth.[25] DA turnover was measured by the accumulation of L-dopa after decarboxylase inhibition in rats treated with γ-butyrolactone to interrupt impulse flow in DA neurons. All rats receive the decarboxylase inhibitor (*m*-hydroxybenzyl)hydrazine dihydrochloride (NSD 1015) at a dose of 100 mg/kg ip 40 min before they were killed. γ-butyrolactone was injected ip at 500 mg/kg 5 min before NSD 1015 and 10 min after the DA agonist was injected ip. Dopa concentration was measured by liquid chromatography with electrochemical detection.

The in vivo dialysis experiments were carried out as follows. Male Sprague-Dawley rats weighing between 300 and 400 g were anesthetized with metofane (methoxyfluorane) and placed in a stereotaxic apparatus. Through a hole drilled in the skull, a miniature dialysis probe[26] was lowered slowly into the corpus striatum. The stereotaxic coordinates were taken from the atlas of Pelligrino et al.[27] and were as follows: anterior 1.5 mm from bregma, lateral 3 mm from the midsagital suture, and ventral 5.6 mm from dura. Once the probe had been inserted into the striatum, it was cemented in place with dental acrylic. The rats were allowed at least 2 days to recover from surgery before striatal dialysate samples were collected. On the day samples were to be collected, rats were placed in a circular chamber and the input of the dialysate probe was connected to a syringe pump which pumped saline through the probe at a rate of 1 mL/min. The dialysate exiting the probe was collected at 30-min intervals and

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assayed for HVA levels by HPLC. Amine **7b** or its saline vehicle was administered to the rat ip. Dialysate samples were collected for 4 h following the injection. Each rat received both saline vehicle and **7b** injections on separate days. Average, preinjection dialysate HVA levels were assigned the value of "100% base line", and changes in dialysate HVA levels following injection were compared to these levels.

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Registry No. (±)-**7a**, 121867-66-1; (±)-**7a** (free base), 121867-55-8; (±)-**7b**, 121867-67-2; (±)-**7b** (free base), 121867-56-9; (±)-**7c**, 121867-68-3; (±)-**7c** (free base), 121867-57-0; (±)-**7d**, 121867-69-4; (±)-**7d** (free base), 121867-58-1; (±)-**7e**, 121867-70-7; (±)-**7e** (free base), 121867-59-2; (±)-**7f**, 121867-71-8; (±)-**7f** (free base), 121867-60-5; (±)-**7g**, 121867-72-9; (±)-**7g** (free base), 121867-61-6; (±)-**7h**, 121867-73-0; (±)-**7h** (free base), 121867-62-7; (±)-**7i**, 121867-74-1; (±)-**7i** (free base), 121867-63-8; (±)-**7j**, 121867-75-2; (±)-**7j** (free base), 121867-64-9; (±)-**7k**, 121867-76-3; (±)-**7k** (free base), 121867-65-0; (±)-**10a**, 121868-03-9; (±)-**10a** (free base), 121867-98-9; (±)-**10b**, 121868-04-0; (±)-**10b** (free base), 121867-99-0; (±)-**10c**, 121868-05-1; (±)-**10c** (free base), 121868-00-6; (±)-**10d**, 121868-06-2; (±)-**10d** (free base), 121868-02-8; (±)-**11**, 74197-16-3; (±)-**12a**, 74197-10-7; (±)-**12b**, 121867-51-4; (±)-**12b**·2HCl, 121867-77-4; (±)-**12c**, 121867-52-5; (±)-**12d**, 121867-53-6; (±)-**12e**, 121867-54-7; (±)-**13**, 121867-78-5; (±)-**14a**, 121867-79-6; (±)-**14b**, 121867-80-9; (±)-**14c**, 121867-81-0; (±)-**14d**, 121867-82-1; (±)-**14e**, 121867-83-2; (±)-**14f**, 121867-84-3; (±)-**14g**, 121867-85-4; (±)-**14h**, 121867-86-5; (±)-**14i**, 121867-87-6; (±)-(*E*)-**14j**, 121867-88-7; (±)-(*Z*)-**14j**, 121958-22-3; (±)-**14k**, 121867-89-8; (±)-**16a**, 121867-90-1; (±)-**16b**, 121886-90-6; (±)-**16c**, 121867-91-2; (±)-**16d**, 121867-92-3; (±)-**16e**, 121867-96-7; (±)-**17a**, 121867-93-4; (±)-**17b**, 121867-94-5; (±)-**17c**, 121867-95-6; (±)-**17d**, 121868-01-7; (±)-**17e**, 121867-97-8; butyryl chloride, 141-75-3; phenylacetyl chloride, 103-80-0; 2-thienylacetyl chloride, 39098-97-0; 3-(mercaptomethyl)propionyl chloride, 7031-23-4; butyraldehyde, 123-72-8; phenylacetaldehyde, 122-78-1; propionaldehyde, 123-38-6; propionyl chloride, 79-03-8.

Quantitative Structure–Activity Relationships in Dihydropteroate Synthase Inhibition by Multisubstituted Sulfones. Design and Synthesis of Some New Derivatives with Improved Potency†

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On the bases of the linear correlation existing for a training set of homomultisubstituted 4-aminodiphenyl sulfones between the computed (INDO) electronic net charges of the SO_2 group and the enzymic inhibition data on dihydropteroate synthase from *Escherichia coli*, seven new heteromultisubstituted derivatives were designed, synthesized, and tested for their inhibition potencies. These compounds were found to be from 5–11 times more effective than 4,4′-diaminodiphenyl sulfone. The implications of the results in the drug design and in the model for the enzyme–inhibitors interaction are discussed.

The diaryl sulfone derivatives (SO), like sulfanilamides (SA), exert their biological action by inhibiting the enzyme dihydropteroate synthase (DHPS) competitively with respect to the substrate 4-aminobenzoate.[1] The important role of these compounds as antibacterial,[1] antimalarial,[2] and antileprotic[3] agents is well-recognized. Moreover, the urgent need for potent antimalarials,[2] the increased incidence of the so-called atypical mycobacterial infections,[3] and the representative role assumed by SO and SA in the development of some aspects of quantitative structure–activity relationship (QSAR) methodologies[1] have led to a renewed interest in this class of drugs.

On the basis of QSAR analysis of a large series of SO using both empirical and quantum chemical descriptors of the molecular structure, we concluded[4,5] that, like in the case of SA, the electronic structure of the common moiety 4-$NH_2C_6H_4SO_2$, modulated by the substituents, is the determining factor connected with inhibitory potency. In particular, the more electron-rich the common moiety is, the more active the compounds are. This situation is at its best realized by the design and synthesis of multisubstituted SO bearing electron-donor substituents, the most efficient one being the hydroxy group, which can dissociate, giving the hydroxylate anion.

In the present work, the inhibitory effect exerted by some newly synthesized 2′,4′- and 2′,4′,6′-substituted SO on the enzymic activity has been studied and correlated with theoretical electronic features of the SO_2 group. The 2′-CH_3, 4′-OH; 2′,6′-$(CH_3)_2$, 4′-OH; and 2′-Cl, 4′-OH derivatives are about 1 order of magnitude more effective than the 4,4′-diaminodiphenyl sulfone (DDS). The equations found allow us, on a simple basis, to design multisubstituted SO and predict their biological activity prior to synthesis.

Results and Discussion

Table I reports the measured ap_E values, giving the inhibitory effect on DHPS from *E. coli* of 11 new SO derivatives (compounds **14–24**), together with the previously

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