Aryl 1-But-3-ynyl-4-phenyl-1,2,3,6-tetrahydropyridines as Potential Antipsychotic Agents: Synthesis and Structure−Activity Relationships

Shelly A. Glase,* Hyacinth C. Akunne, Thomas G. Heffner, Juan C. Jaen, Robert G. MacKenzie, Leonard T. Meltzer, Thomas A. Pugsley, Sarah J. Smith, and Lawrence D. Wise

Departments of Chemistry and Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

Received September 29, 1995[⊗]

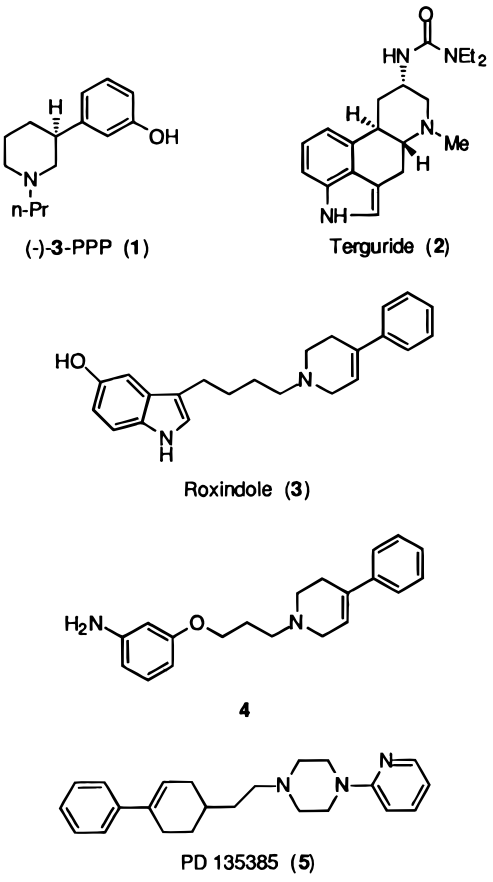
A novel series of aryl 1-but-3-ynyl-4-phenyl-1,2,3,6-tetrahydropyridines with dopaminergic activity is described. The structure−activity relationships of this series were studied by synthesis of analogs and evaluation of their affinities for the dopamine (DA) D_2 receptor and inhibition of locomotor activity (LMA) in rodents. The basic amine, alkyne chain length, and aryl groups were varied. Compounds having a 4-phenyl-1,2,3,6-tetrahydropyridine and an aryl group with hydrogen-bonding substituents separated by a butynyl chain were found to have the most potent dopaminergic activity. Several compounds that were found to have exceptional *in vivo* activity in LMA inhibition in rodents were evaluated for additional pharmacological activity including binding affinities for other DA receptor subtypes as well as effects on brain DA synthesis, DA neuronal firing, and conditioned avoidance responding in squirrel monkeys.

Introduction

Schizophrenia is generally believed to involve manifestations of an excessive dopaminergic neurotransmission in the brain.[1] Blockade of postsynaptic dopamine (DA) D_2 receptors is a characteristic common to all effective antipsychotics in clinical use today. Serious side effects of extrapyramidal syndrome, tardive dyskinesia, and hyperprolactinemia, which are associated with this class of drugs, have also been linked to their postsynaptic DA receptor blockade.[2] An alternative to the use of DA receptor antagonists would be to regulate DA neuronal function by activation of presynaptic DA receptors (DA autoreceptors). Their stimulation inhibits DA neuronal firing, synthesis, and release.[3] In order to be a viable antipsychotic agent, the DA agonist must selectively activate presynaptic DA receptors, since postsynaptic stimulation would tend to exacerbate psychotic symptoms.[4]

Traditional DA autoreceptor agonists can be classified as compounds derived from dopamine or the ergot skeleton. Notable examples are (−)-3-PPP (**1**)[5] and terguride (**2**)[6] which incorporate a dopaminergic pharmacophore into rigid structures. There are many more D_2 agonists that are linear, flexible compounds that do not easily fit the conventional models of the D_2 receptor. Some examples of this class are roxindole (**3**)[7] and the (aminoalkoxy)aniline **4**.[8] The flexibility of roxindole allows it to be superimposed over apomorphine with the indolic NH group acting as the *m*-hydroxy group of dopamine.[9] It is therefore reasonable to believe that the agonist activity of **4** could be explained in a similar manner.

Interestingly, the more rigid, linear compound PD 135385 (**5**)[10] was found to be a selective DA D_2 agonist. It is unlikely that the activity of this compound can be explained using the apomorphine backbone model. To determine whether other rigid, linear analogs would be equally potent and selective DA autoreceptor agonists, we prepared a series of compounds containing phenolic isosteres and a basic amine functional group separated by an alkynyl carbon chain (Figure 1). To understand the structure−activity relationship (SAR) of this new class of compounds, three structural features were investigated as follows: the aryl group, the alkyne chain length, and the basic amine ending.



Chemistry

The compounds found in Tables 1−3 were synthesized in one of four ways as shown in Scheme 1. Method A

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1996.

S0022-2623(95)00721-7 CCC: $12.00

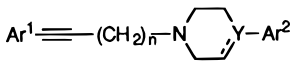


Figure 1.

provided a convenient means to vary the amine ending. An aryl halide was coupled to an alkynyl alcohol in 40−70% yield with bis(triphenylphosphine)palladium(II) chloride and copper iodide in refluxing dichloromethane with triethylamine.[11] The resulting arylalkynyl alcohol was converted to the mesylate under standard conditions followed by displacement with the desired amine in DMF in the presence of a base such as triethylamine or sodium bicarbonate. When $n = 1$ and 3, the yield from the alcohol to the final product was typically 40%, but when $n = 2$, elimination of the mesylate to the enyne was prevalent resulting in yields less than 20%.

The majority of the compounds were prepared by coupling **6** to an aryl halide with a palladium catalyst (method B). The butynylamine **6** was obtained by reacting 3-butynyl *p*-toluenesulfonate with 4-phenyl-1,2,3,6-tetrahydropyridine in DMF at 70 °C in the presence of sodium bicarbonate. The catalyst used in method B was palladium(II) acetate with triphenylphosphine in piperidine at 100 °C.[12]

Two additional palladium-coupling procedures are shown in methods C and D. In method C, **6** is reacted with an aryl halide in the presence of bis(triphenylphosphine)palladium(II) chloride with copper iodide in dichloromethane or acetonitrile. Method D uses tetrakis(triphenylphosphine)palladium(0) in refluxing butylamine to effect the coupling of **6** to the aryl halide.[13] The rate and yields of the various palladium-coupling reactions ranged from 25% to 81% depending on the functionality on the aryl halide. This reaction is facilitated by electron-withdrawing groups ortho or para to the halide.[14]

Results and Discussion

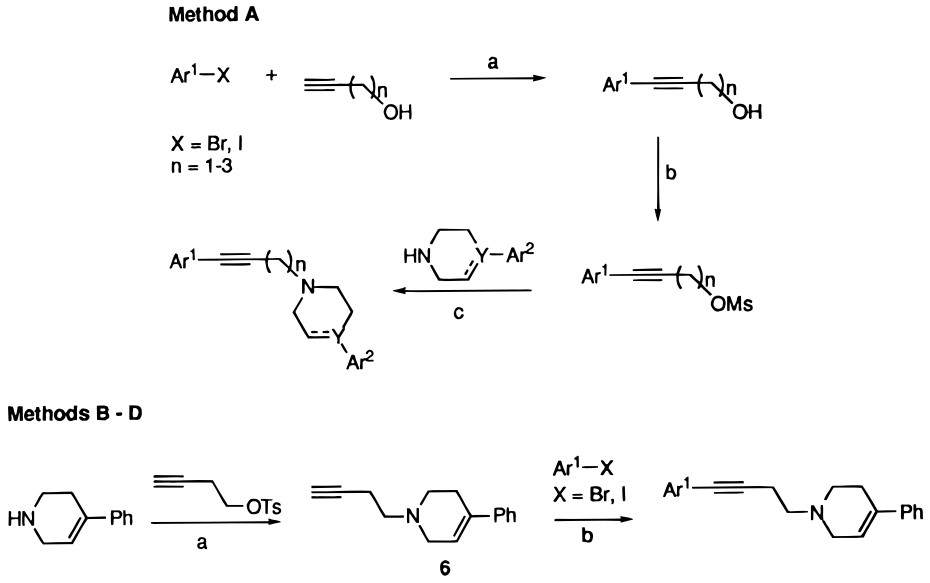
The first three tables summarize the results of the SAR studies including variation of the alkyne chain length (Table 1), basic amine ending (Table 2), and aryl group (Table 3). The compounds in these tables were evaluated for their affinity for the DA D_2 receptor in rat striatal membrane with the antagonist ligand [^{3}H]-spiperone[15] and for their ability to inhibit spontaneous locomotor activity (LMA) in mice (ip) and rats (po).[16] Several compounds that were particularly potent in these tests were then subjected to additional receptor binding and secondary pharmacological tests to determine their level of agonist activity and efficacy in a primate antipsychotic model (Tables 4 and 5).

Compound **7** (Table 1), where $n = 1$, had no significant affinity for the DA D_2 receptor and was inactive in mouse LMA. The butynyl analogs **8** and **10**, however, demonstrated very good dopaminergic activity with K_i values of 30 and 37 nM for the DA D_2 receptor. Both compounds were quite potent *in vivo*. Compound **8** inhibited LMA with an ED_{50} value of 1.1 mg/kg in both mouse (ip) and rat (po), while **10** inhibited LMA in mouse and rat with ED_{50} values of 0.07 mg/kg ip and 1.4 mg/kg po. The pentynyl analogs **9** and **11** had slightly lower binding affinity and *in vivo* activity than their butynyl counterparts. Butyne was determined to be the optimal chain length and was used in subsequent SAR studies.

Since arylpiperazines and 4-aryl-1,2,3,6-tetrahydropyridines are common amine endings found in DA autoreceptor agonists (**3**−**5**),[7,8,10] the SAR of the butynyl series was explored further by substitution of a number of these amines (Table 2). Of the amine endings that were examined, the aryltetrahydropyridines **10** and **12** had the best dopaminergic activity. Compound **12** had only moderate binding affinity ($K_i = 255$ nM) but still possessed potent inhibition of LMA in mice with an ED_{50} value of 0.86 mg/kg ip. Of the arylpiperazines that were examined, **13** and **14** had weak binding affinity for the DA D_2 receptor ($K_i = 1673$ and 5388 nM) but retained significant inhibition of mouse LMA (ED_{50} values of 4.7 and 2.2 mg/kg ip). These results may be explained in a number of ways including activation of other receptors or formation of active metabolites. The pyrimidinylpiperazine **15** was inactive in DA D_2 binding and rodent LMA tests. Because of the high D_2 affinity and LMA potency of compound **10**, 4-phenyl-1,2,3,6-tetrahydropyridine was selected as the best amine ending to use in subsequent SAR studies.

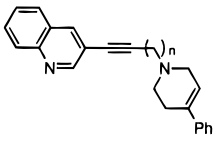
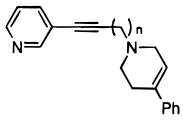
The 4-(3,6-dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butyne (**6**), having the optimal combination of alkyne chain length and amine ending, was used to prepare a variety of analogs (Table 3). The simple phenyl analog **16** had moderate DA D_2 affinity ($K_i = 284$ nM) and was weak in inhibiting LMA ($ED_{50} = 9.5$ mg/kg, mouse ip). Since classical dopamine agonist pharmacophores contain a hydrogen-bonding moiety like a catechol or phenol, compound **17** was prepared. The binding affinity for the DA D_2 receptor and the inhibition of LMA improved considerably ($K_i = 54$ nM and $ED_{50} = 1.5$ mg/kg, mouse ip) from the unsubstituted phenyl. As expected, **17** was not active orally ($ED_{50} > 30$ mg/kg, rat LMA po) since phenols are known to have poor oral bioavailability.[17] The phenol was replaced by an indole, which is a common bioisosteric replacement for phenol and catechol.[18] Even though compound **18** had only moderate DA D_2 binding affinity compared to the phenol analog **17** ($K_i = 193$ nM compared to 53 nM), **18** had equivalent activity to **17** in mouse LMA ip and oral activity in rat LMA with an ED_{50} value of 5.2 mg/kg po. Several additional nitrogen-containing heterocycles were prepared. The 4- and 3-pyridyl analogs **19** and **10** had very similar profiles, with DA D_2 affinities of 32 and 37 nM and ED_{50} values of 0.1 and 0.07 mg/kg in mouse LMA ip. It is interesting to note that the activity for the 2-pyridyl analog **20** dropped significantly. While the DA D_2 binding affinity for the quinoline **8** was essentially the same as for the corresponding pyridine **10** ($K_i = 30$ versus 37 nM), the binding affinity for the isoquinoline **21** was weaker ($K_i = 73$ nM). The three aniline analogs **22**−**24** show the same trends in dopaminergic activity as the pyridine series. The para- and meta-substituted compounds **22** and **23** had higher DA D_2 binding affinity ($K_i = 48$ and 87 nM versus 183 nM) and inhibition of rodent LMA than the ortho **24** (ED_{50} values of 0.36 and 0.68 mg/kg versus 1.6 mg/kg in mice ip). One might conclude from this, and the similar results for the pyridine series, that there is an important hydrogen-bonding interaction that can only be satisfied by substitution in the meta and para positions. The *in vitro* and *in vivo* activities of the two aminopyridine analogs **25** and **26** were also comparable to their pyridine (**19** and **10**) and aniline (**22** and **23**) counterparts. Ad-

Scheme 1[a]



[a] Method A: (a) $(PPh_3)_2PdCl_2$, CuI, Et_3N, CH_2Cl_2; (b) MsCl, iPr_2NH, CH_2Cl_2; (c) $NaHCO_3$ or Et_3N, DMF. Method B: (a) $NaHCO_3$, DMF; (b) $Pd(OAc)_2$, PPh_3, piperidine. Method C: (a) $NaHCO_3$, DMF; (b) $(PPh_3)_2PdCl_2$, CuI, Et_3N, CH_2Cl_2 or CH_3CN. Method D: (a) $NaHCO_3$, DMF; (b) $Pd(PPh_3)_4$, $BuNH_2$.

Table 1. Variation of Alkyne Chain Length

	compd no.	n	DA D_2 binding K_i (nM)[a]	inhibn of LMA ED_{50} (mg/kg)[b] mouse, ip	rat, po	synthetic method
	**7**	1	>10,000	>30	-[c]	A
	8	2	30	1.1	1.1	A
	9	3	40	3.6	18.6	A
	**10**	2	37	0.07	1.4	A,B
	11	3	56	0.72	4.3	A

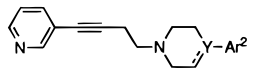
[a] [^{3}H]Spiperone in rat striatum; K_i values were obtained from four to six concentrations, run in triplicate, by a nonlinear regression analysis. [b] LMA = locomotor activity; ED_{50} values generated from three to six doses, n = 6−18 animals/dose. [c] Not tested.

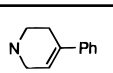
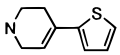
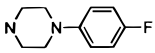
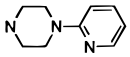
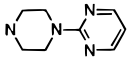
ditional oxygen-containing analogs **27**−**29** were also prepared but showed no improvement over the phenol **17**. The best aryl groups (Ar^1) were those containing nitrogen in the meta or para position. Because of their good DA D_2 binding affinity and high potency in inhibiting LMA in rodents, several of these aniline and pyridine analogs were selected to undergo additional receptor binding and pharmacological testing (Tables 4 and 5).

Table 4 summarizes the results of additional dopaminergic, serotonergic, and adrenergic binding for several of the best compounds selected from Table 3. None of the compounds had significant binding affinity for DA D_1 receptors[19] and very little binding affinity for DA D_4 receptors.[20] The binding to DA D_2 high-affinity sites was determined with the use of the DA agonist ligand [^{3}H]-*n*-propylnorapomorphine ([^{3}H]NPA).[21] These compounds, as expected of DA agonists, exhibited a greater affinity for DA agonist-labeled receptors than for DA antagonist-labeled sites (Table 3). They were also found to have high affinity for the DA D_3 receptor (0.36−24 nM), which may contribute to the observed inhibition of LMA[22] and decreased dopamine synthesis.[23] Only compound **26** showed even moderate affinity (69 nM) for 5-HT_{1a} receptors.[24] All of the compounds in Table 4, except **23**, had moderate (14.1−57.5 nM) affinity for α_1 receptors.[25]

The results of tests to determine autoreceptor agonist efficacy are shown in Table 5. *In vitro*, DA D_2 receptor activation stimulates [^{3}H]thymidine uptake in CHO p-5 cells.[20,26] When compared to the 100% maximal stimulation of mitogenesis by the full DA agonist quinpirole, the compounds described appear to be partial agonists with maximal stimulation of 49−85% and EC_{50} values of 0.5−1.7 nM. *In vivo*, DA autoreceptor agonist activity was evaluated by the ability of a compound to reverse the γ-butyrolactone (GBL)-induced increase in DA synthesis in rats, as measured by the rate of DOPA formation in rat striatum following decarboxylase inhibition.[27] The percent decrease of DOPA synthesis ranged from 42% to 79% at 10 mg/kg ip, suggestive of partial agonist activity at terminal DA autoreceptors.

Table 2. Variation of Amine Ending



	compd no.	DA D_2 binding K_i (nM)[a]	inhibn of LMA ED_{50} (mg/kg)[b] mouse, ip	rat, po	synthetic method
	**10**	37	0.07	1.4	A, B
	**12**	255	0.86	5.0	A
	**13**	1673	4.7	4.3	A
	**14**	5388	2.2	>30	A
	**15**	>10,000	>30	-[c]	A

[a–c] See footnotes for Table 1.

Autoreceptor agonist activity was also determined electrophysiologically by measuring the inhibition of DA neuronal firing in the substantia nigra of anesthetized rats.[28] In this test, all of the compounds listed in Table 5, except **25**, caused complete inhibition of DA neuronal firing at 2.5 mg/kg ip. Stimulation of LMA at higher doses (30 mg/kg ip in mice and 100 mg/kg po in rats), which is indicative of postsynaptic receptor activation, was not observed for the compounds described here. The apparent selectivity of some DA agonists for the autoreceptor may be due to the much larger receptor reserve of presynaptic versus postsynaptic DA D_2 receptors.[29,30] Consideration of the present results leads us to conclude that these compounds are partial DA agonists.

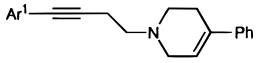
The compounds in Table 5 were also evaluated in the Sidman conditioned avoidance test in squirrel monkeys,[31] a primate test which has been correlated with antipsychotic efficacy in humans.[32] Compounds **22** and **25** had good activity at 2.8 and 3.8 mg/kg po; **26** was especially potent with an ED_{50} value of 0.43 mg/kg.

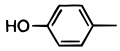
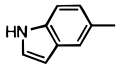
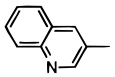
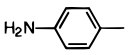
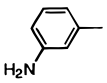
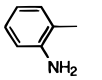
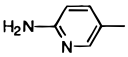
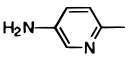
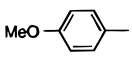
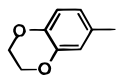
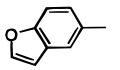
A comparison of roxindole (**3**) to **26** (Table 6) shows that **26** has weaker binding affinity for the D_2 family of receptors. Both compounds were equally effective in mouse LMA ip, but roxindole was less active orally in rats (12.8 mg/kg), suggesting differences in bioavailability. No stimulation of LMA was observed at high doses for either compound, indicating lack of significant postsynaptic stimulation. In tests to determine intrinsic activity (receptor mitogenesis, DOPA synthesis, and DA neuronal firing), **26** and roxindole appear to have similar agonist profiles. While **26** inhibited conditioned avoidance in the squirrel monkey at 0.43 mg/kg, roxindole was inactive. In clinical trials, roxindole was found to be ineffective and even exacerbated psychotic symptoms in some schizophrenic patients.[33]

Conclusion

This study has identified a novel series of aryl 1-but-3-ynyl-4-phenyl-1,2,3,6-tetrahydropyridines with DA receptor activity. Optimal activity is obtained when an aryl group, with meta or para H-bonding substituents, is attached to 4-phenyl-1,2,3,6-tetrahydropyridine through a 1-butynyl chain. A number of compounds in this series bind selectively to DA D_2 and D_3 receptors and have excellent *in vivo* activity in rodent LMA. These compounds stimulated mitogenesis in CHO p-5 cells transfected with the human D_{2L} receptor, reversed GBL-stimulated brain DA synthesis, and inhibited DA neuronal firing in rats, effects consistent with DA autoreceptor activation. In addition, compounds **22**, **25**, and **26** have good oral activity in a primate model of antipsychotic activity. This indicates that building rigidity into this type of chemical system does not diminish dopaminergic activity.

Table 3. Variation of Aryl Group



	compd no.	DA D_2 binding Ki (nM)[a]	inhibn of LMA ED_{50} (mg/kg)[b] mouse, ip	rat, po	synthetic method
	**16**	284	9.5	20.5	B
	**17**	54	1.5	>30	D
	**18**	193	1.2	5.2	D
	**19**	32	0.1	4.4	C
	**10**	37	0.07	1.4	A,B
	**20**	136	2.1	15.8	B
	**8**	30	1.1	1.1	A,B
	**21**	73	2.1	3.8	A
	**22**	48	0.36	2.7	C
	**23**	87	0.68	5.6	C
	**24**	183	1.6	23.9	C
	**25**	33	0.06	2.5	D
	**26**	63	0.15	1.7	C
	**27**	327	3.3	>30	D
	**28**	127	2.2	>30	D
	**29**	440	2.5	10.6	D

[a,b] See footnotes for Table 1.

Table 4. Evaluation of Selected Compounds in Receptor Binding

	receptor binding K_i (nM)					
compd no.	D_1[a]	D_2[b]	hD_3[c]	hD_4[c]	5-HT_{1a}[d]	α_1[e]
10	5004	3.3	20	681	555	14.1
19		4.1	6.5	570	593	25.8
22	>10 000	0.67	24	228	>10 000	34.5
23		18	0.36		1547	107
25	>10 000	19	7.0	278	632	55.8
26	>10 000	1.9	2.6	371	69	57.5

[a] [^{3}H]SCH 23390. [b] [^{3}H]NPA. [c] [^{3}H]Spiperone, human DA D_3 and D_4 receptors expressed in CHO K_1 cells. [d] [^{3}H]-8-OH-DPAT. [e] [^{3}H]Prazosin.

Experimental Section

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. ^{1}H NMR were determined for $CDCl_3$ or DMSO-d_6 solutions on Varian Gemini-200, XL-300, or 400 and Bruker AM 250 spectrometers. The peaks are described in ppm downfield from TMS (internal standard). IR spectra were recorded on a Nicolet MX-1 FT spectrophotometer. Mass spectra were obtained on a Finnigan 4500 or a VG analytical 7070E/HF mass spectrometer. Relative intensity values are listed in parentheses. Elemental analyses were performed by the Analytical Research Section at Parke-Davis, Ann Arbor, MI. 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).

Method A. 3-[3-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-propynyl]quinoline (7). To a degassed (N_2) solution of propargyl alcohol (17.5 mL, 0.30 mol), 3-bromoquinoline (27.1 mL, 0.20 mol), and triethylamine (83.6 mL, 0.60 mol) in CH_2Cl_2 (160 mL) were added copper(I) iodide (0.26 g, 1.4 mmol) and bis(triphenylphosphine)palladium(II) chloride (1.4 g, 2.0 mmol). The reaction mixture was heated at reflux under N_2 for 5 h, cooled, diluted with CH_2Cl_2 (200 mL), and washed with water (4 × 200 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave 3-(3-quinolinyl)-2-propyn-1-ol (19.3 g, 53%) as a white solid: mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 4.40 (br s, 1H), 4.58 (s, 2H), 7.56 (t, 1H, J = 6.9 Hz), 7.69−7.79 (m, 2H), 8.09 (d, 1H, J = 8.2 Hz), 8.22 (s, 1H), 9.04 (s, 1H); MS (EI) m/z 183 (100), 154 (85), 129 (40). Anal. ($C_{12}H_9NO\cdot0.13H_2O$) C, H, N, H_2O.

Methanesulfonyl chloride (1.9 mL, 25 mmol) was added dropwise to a cold (0 °C) solution of the above alcohol (3.5 g, 19 mmol) and diisopropylethylamine (6.7 mL, 38 mmol) in CH_2Cl_2 (70 mL), and the mixture was stirred for 1 h. The solvent was concentrated in vacuo without heating, and the resulting residue was taken up in DMF (40 mL). To this solution was added 4-phenyl-1,2,3,6-tetrahydropyridine (6.1 g, 38 mmol) and triethylamine (13.2 mL, 95 mmol). The reaction mixture was stirred overnight at 20 °C, concentrated in vacuo, diluted with CH_2Cl_2 (100 mL), and washed with water (100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 5 g of a dark yellow solid. This solid was recrystallized from heptane to give **7** (2.5 g, 40%) as a pale yellow solid: mp 100−101 °C; IR (KBr) 3413, 2904, 1489, 1324, 754, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 2H), 2.94 (t, 2H, J = 5.7 Hz), 3.41 (m, 2H), 3.75 (s, 2H), 6.12 (m, 1H), 7.21−7.43 (m, 5H), 7.55, (t, 1H, J = 7.2 Hz), 7.67−7.78 (m, 2H), 8.08 (d, 1H, J = 8.4 Hz), 8.33, (s, 1H), 8.92, (s, 1H); MS (EI) m/z 324 (62), 166 (100). Anal. ($C_{23}H_{20}N_2$) C, H, N.

3-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]-quinoline (8). 3-Bromoquinoline (20.4 mL, 0.15 mol) was coupled to 3-butyn-1-ol (17.0 mL, 0.225 mol) as described in the first step of the synthesis of **7** to give 4-(3-quinolinyl)-3-butyn-1-ol (13 g, 44%) as a light brown solid: mp 96−97 °C; IR (KBr) 3246, 2914, 2225, 1493, 1049, 785, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.70−2.79 (m, 3H), 3.90 (m, 2H), 7.51−7.57 (m, 1H), 7.66−7.74 (m, 2H), 8.06−8.14 (m, 2H), 8.88 (s, 1H); MS (EI) m/z 197 (90), 166 (100), 139 (41). Anal. ($C_{13}H_{11}NO$) C, H, N.

The above alcohol (4.0 g, 20 mmol) was reacted with 4-phenyl-1,2,3,6-tetrahydropyridine (6.45 g, 40 mmol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave **8** (0.78 g, 11%) as a yellow solid: mp 94−96 °C; IR (KBr) 3450, 2939, 1670, 1646, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.62 (m, 2H), 2.72−2.90 (m, 6H), 2.27−3.30 (m, 2H), 6.08 (m, 1H), 7.21−7.42 (m, 5H), 7.54 (t, 1H, J = 7.2 Hz), 7.65−7.76 (m, 2H), 8.07 (d, 1H, J = 8.4 Hz), 8.17 (s, 1H), 8.88 (s, 1H); MS (EI) m/z 338 (9.2), 172 (100). Anal. ($C_{24}H_{22}N_2\cdot0.09H_2O$) C, H, N, H_2O.

3-[5-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-pentynyl]-quinoline (9). 3-Bromoquinoline (13.6 mL, 0.10 mol) was coupled to 4-pentyn-1-ol (11.1 mL, 0.12 mol) as described in the first step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave 5-(3-quinolinyl)-4-pentyn-1-ol (16.3 g, 78%) as a yellow solid: mp 55−56 °C; IR ($CHCl_3$ solution) 3437, 2928, 1805, 1490, 1466, 1025 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.72−1.83 (m, 2H), 2.59 (t, 2H, J = 7.2 Hz), 3.57−3.63 (m, 2H), 4.65 (t, 1H, J = 5.4 Hz), 7.62−7.68 (m, 1H), 7.76−7.82 (m, 1H), 7.96−8.06 (m, 2H), 8.45 (s, 1H), 8.87 (s, 1H); MS (EI) m/z 211 (100), 192 (48), 182 (46), 167 (56), 155 (45), 139 (31). Anal. ($C_{14}H_{13}NO$) C, H, N.

The above alcohol (2.0 g, 9 mmol), triphenylphosphine (2.98 g, 11 mmol), and imidazole (0.6 g, 9 mmol) were combined in CCl_4 (10 mL) and CH_3CN (10 mL), and the reaction mixture was stirred for 2 h at 20 °C. The reaction mixture was concentrated in vacuo and filtered through silica gel eluting with 50% EtOAc/hexanes. The chloride (1.7 g, 86%) was obtained as a yellow oil: IR ($CHCl_3$ solution) 3400, 3055, 2218, 1610, 1590, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04−2.16 (m, 2H), 2.69 (t, 2H, J = 6.8 Hz), 3.75 (t, 2H, J = 6.4 Hz), 7.50−7.56 (m, 1H), 7.66−7.76 (m, 2H), 8.07 (d, 1H, J = 8.3 Hz), 8.17 (s, 1H), 8.86 (s, 1H); MS (EI) m/z 229 (43), 194 (100), 166 (70), 139 (47); TLC (50% EtOAc/hexane) R_f = 0.35.

This chloride (1.5 g, 6.5 mmol), 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (1.53 g, 7.8 mmol), $NaHCO_3$ (1.65 g, 19.6 mmol), and NaI (0.05 g, 0.3 mmol) were combined in DMF (50 mL). The reaction mixture was stirred overnight at 80 °C, concentrated in vacuo, diluted with CH_2Cl_2 (100 mL), and washed with water (100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to give **9** (0.95 g, 41%) as a yellow oil. This oil was purified by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 and converted to the HCl salt: mp 191−192 °C; IR (KBr) 3455, 2574, 1566, 1488, 1446, 749 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (m, 2H), 2.67−2.79 (m, 3H), 2.82−3.15 (m, 1H), 3.24−3.40 (m, 3H), 3.65−3.90 (m, 2H), 4.01−4.15 (m, 1H), 6.21 (m, 1H), 7.21−7.50 (m, 5H), 7.72 (t, 1H, J = 7.3 Hz), 7.86 (t, 1H, J = 7.3 Hz), 8.02−8.12 (m, 2H), 8.85 (s, 1H), 9.02 (s, 1H); MS (EI) m/z 351 (55), 184 (71), 128 (85), 115 (100). Anal. ($C_{25}H_{24}N_2\cdot1.5HCl\cdot0.2H_2O$) C, H, N, Cl, H_2O.

3-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]-pyridine (10). 3-Bromopyridine (9.6 mL, 0.10 mol) was coupled to 3-butyn-1-ol (9.0 mL, 0.12 mol) as described in the first step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave the alcohol (7.36 g, 50%) as a gold oil: IR ($CHCl_3$ solution) 3373, 2955, 2205, 1566 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.71 (t, 2H, J = 6.2 Hz), 3.01 (t, 1H, J = 5.8 Hz), 3.80−3.88 (m, 2H), 7.19−7.24 (m, 1H), 7.67 (m, 1H), 8.48 (d, 1H, J = 4.9 Hz), 8.62 (s, 1H); MS (EI) m/z 147 (61), 117 (100), 89 (36), 63 (25); TLC (10% MeOH/CH_2Cl_2) R_f = 0.28.

The above alcohol (4.0 g, 27 mmol) was reacted with 4-phenyl-1,2,3,6-tetrahydropyridine (6.45 g, 40 mmol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave **10** (1.34 g, 17%) as a dark yellow solid: mp 74−75 °C; IR (KBr) 3288, 2932, 2359, 1565, 1494, 1477, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.54 (m, 2H), 2.60−2.67 (m, 2H), 2.72−2.79 (m, 4H), 3.18−3.21 (m, 2H), 6.01 (m, 1H), 7.11−7.34 (m, 6H), 7.61 (d, 1H, J = 7.9 Hz), 8.41 (d, 1H, J = 4.9 Hz), 8.57 (s, 1H); MS (EI) m/z 288 (6), 172 (100). Anal. ($C_{20}H_{20}N_2$) C, H, N.

3-[5-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-pentynyl]-pyridine (11). 3-Bromopyridine (9.6 mL, 0.10 mol) was

Table 5. Evaluation of Selected Compounds in Secondary *in Vivo* Tests

compd no.	DA D_2 receptor mitogenesis[a] maximal effect (%)[b]	DA D_2 receptor mitogenesis[a] EC_{50} (nM)[c]	decrease (%) of DOPA synthesis (10 mg/kg, ip)[d]	decrease (%) of DA neuronal firing (2.5 mg/kg, ip)[e]	inhibtn of conditioned avoidance ED_{50} (mg/kg, po)[f]
10	64	1.7 (0.54−5.6)	79 ± 3.1	100 ± 0	10.1 (6.8−13.4)
19	77	1.0 (0.45−2.6)	79 ± 6.6	93 ± 7	11.9 (8.8−16.0)
22	49	0.5 (0.24−1.2)	51 ± 5	81 ± 19	3.8 (2.4−6.0)
23	75	9.8 (2.7−35)	42 ± 4.4	98 ± 2.5	9.3 (4.3−20.1)
25	54	0.5 (0.13−1.9)	65 ± 6.7	63 ± 6	2.8 (2.3−3.4)
26	85	1.3 (0.32−5.3)	59 ± 4.2	100 ± 0	0.43 (0.25−0.73)

[a] Measurement of [^{3}H]thymidine incorporation in CHO p-5 cells expressing human D_{2L} receptors. [b] Percent maximal effect compared to that of the full DA agonist quinpirole (100%). [c] EC_{50} values (95% confidence intervals) were generated from 10 concentrations, $n = 4$. [d] Percent reversal of the increase on DOPA levels in the striatum of GBL-treated rats, $n = 4$. [e] Percent decrease of the firing rate of rat substantia nigra DA neurons, $n = 2$. [f] ED_{50} values (95% confidence intervals) were generated from three doses, 4 squirrel monkeys/dose.

Table 6. Comparison of Pharmacological Profiles

test	**26**	roxindole (**3**)
dopamine receptor binding (K_i, nM)[a]		
rat D_1 ([^{3}H]SCH 23390)	>10 000	>10 000
rat D_2 ([^{3}H]spiperone)	85	9.1
rat D_2 ([^{3}H]NPA)	1.9	
human D_3 ([^{3}H]spiperone)	2.8	0.4
human D_4 ([^{3}H]spiperone)	371	24
inhibition of LMA (ED_{50}, mg/kg)[b]		
in mouse ip	0.15	0.2
in rat po	1.7	12.8
DA D_2 receptor mitogenesis[c]		
maximal effect (%)	85	97
EC_{50} (nM)	1.3 (0.32−5.3)	0.37 (0.10−1.2)
decrease (%) of DOPA synthesis in rat[d] (10 mg/kg, ip)	59 ± 4.2	64 ± 2.2
decrease (%) of DA neuronal firing in rat[e] (2.5 mg/kg, ip)	100 ± 0	100 ± 0
inhibition of conditioned avoidance in squirrel monkey[f] ED_{50} (mg/kg, po)	0.43 (0.25−0.73)	>10

[a,b] See footnotes a and b in Table 1. [c] See footnotes a−c in Table 5. [d−f] See footnotes d−f in Table 5.

coupled to 4-pentyn-1-ol (13.9 mL, 0.15 mol) as described in the first step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave the alcohol (8.3 g, 52%) as a gold oil: IR ($CHCl_3$ solution) 3404, 2936, 2228, 1565, 1477, 1408, 1061, 807, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.82−1.92 (m, 2H), 2.57 (t, 2H, J = 7.0 Hz), 2.66 (br s, 1H), 3.79−3.84 (m, 2H), 7.19−7.24 (m, 1H), 7.64−7.69 (m, 1H), 8.47 (d, 1H, J = 4.9 Hz), 8.60 (s, 1H); MS (EI) m/z 161 (76), 142 (100), 132 (94), 117 (90); TLC (10% MeOH/CH_2Cl_2) R_f = 0.46.

The above alcohol (5.0 g, 31 mmol), carbon tetrabromide (20.5 g, 62 mmol), and triphenylphosphine (16.3 g, 62 mmol) were combined with Et_2O (300 mL), and the reaction mixture was stirred at 20 °C for 1.5 h. The reaction mixture was concentrated in vacuo and filtered through silica gel eluting with 50% EtOAc/hexane. The bromide (4.5 g, 65%) was obtained as a yellow oil (2.2 g, 9.7 mmol) and was reacted with 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (2.28 g, 11.7 mmol) as described in the synthesis of **9**. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave **11** as a pale yellow solid: mp 63−64 °C; IR (KBr) 3463, 2931, 2897, 1477, 1405, 749, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83−1.94 (m, 2H), 2.49−2.64 (m, 6H), 2.71−2.75 (m, 2H), 3.18 (m, 2H), 6.07 (m, 1H), 7.17−7.41 (m, 6H), 7.64−7.69 (m, 1H), 8.46−8.49 (m, 1H), 8.63 (s, 1H); MS (EI) m/z 302 (89), 301 (100), 273 (98), 225 (89). Anal. ($C_{21}H_{22}N_2 \cdot 0.05H_2O$) C, H, N, H_2O.

3-[4-[3,6-Dihydro-4-(2-thienyl)-1(2*H*)-pyridinyl]-1-butynyl]pyridine (12). 4-Pyridin-3-ylbut-3-yn-1-ol (3.3 g, 22 mmol) from the synthesis of **10** was reacted with 4-(2-thienyl)-1,2,3,6-tetrahydropyridine (15.5 mL, 0.11 mol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2.5% MeOH/CH_2Cl_2 gave **12** (0.67 g, 10%) as a yellow solid: mp 77−78 °C; IR (KBr) 3417, 2951, 1407, 809, 709, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.60−2.84 (m, 8H), 3.24−3.25 (m, 2H), 6.09 (m, 1H), 6.96 (m, 2H), 7.11−7.14 (m, 1H), 7.21−7.28 (m, 1H), 7.68 (d, 1H, J = 8.0 Hz), 8.49 (d, 1H, J = 4.9 Hz), 8.63 (s, 1H); MS (EI) m/z 293 (8), 178 (100), 149 (17). Anal. ($C_{18}H_{18}N_2S \cdot 0.04H_2O$) H, N; C: calcd, 73.25; found, 72.27.

1-(4-Fluorophenyl)-4-[4-(3-pyridinyl)-3-butynyl]piperazine (13). 4-Pyridin-3-ylbut-3-yn-1-ol (4.0 g, 27 mmol) from the synthesis of **10** was reacted with 1-(*p*-fluorophenyl)-piperazine (9.8 g, 54 mmol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **13** (2.26 g, 27%) as a white solid: mp 97 °C; IR (KBr) 3433, 2822, 1512, 810, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.62−2.79 (m, 8H), 3.06−3.16 (m, 4H), 6.85−7.01 (m, 4H), 7.18−7.27 (m, 1H), 7.64−7.69 (m, 1H), 8.49 (d, 1H, J = 4.9 Hz), 8.63 (s, 1H); MS (EI) m/z 309 (24), 193 (100), 150 (85), 122 (87). Anal. ($C_{19}H_{20}N_3F$) C, H, N.

1-(2-Pyridinyl)-4-[4-(3-pyridinyl)-3-butynyl]piperazine (14). 4-Pyridin-3-ylbut-3-yn-1-ol (1.0 g, 6.8 mmol) from the synthesis of **10** was reacted with 1-(2-pyridyl)piperazine (1.66 g, 10 mmol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2.5% MeOH/CH_2Cl_2 gave **14** (0.40 g, 25%) as a yellow solid: mp 105−106 °C; IR (KBr) 3452, 2946, 1593, 1480, 1431, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.64−2.78 (m, 8H), 3.56−3.60 (m, 4H), 6.61−6.68 (m, 2H), 7.20−7.28 (m, 1H), 7.45−7.52 (m, 1H), 7.66−7.70 (m, 1H), 8.20 (d, 1H, J = 4.8 Hz), 8.50 (d, 1H, J = 4.9 Hz), 8.64 (s, 1H); MS (EI) m/z 292 (19), 198 (49), 176 (100), 121 (44). Anal. ($C_{18}H_{20}N_4 \cdot 0.08H_2O$) C, H, N, H_2O.

2-[4-[4-(3-Pyridinyl)-3-butynyl]-1-piperazinyl]pyrimidine (15). 4-Pyridin-3-ylbut-3-yn-1-ol (4.0 g, 27 mmol) from the synthesis of **10** was reacted with 4-(2-pyrimidyl)piperazine (8.9 g, 54 mmol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 2.5% MeOH/CH_2Cl_2 gave **15** (1.51 g, 19%) as a pale yellow solid: mp 96−97 °C; IR (KBr) 3412, 2942, 1583, 1559, 1480, 1451, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.57−2.86 (m, 8H), 3.41−3.88 (m, 4H), 6.48 (t, 1H, J = 4.8 Hz), 7.18−7.30 (m, 1H), 7.67 (d, 1H, J = 7.9 Hz), 8.30 (d, 2H, J = 4.8 Hz), 8.48 (d, 1H, J = 4.8 Hz), 8.63 (s, 1H); MS (EI) m/z 293 (3), 177 (100), 148 (83), 122 (46). Anal. ($C_{17}H_{19}N_5 \cdot 0.05H_2O$) C, H, N, H_2O.

4-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]-isoquinoline (21). 4-Bromoisoquinoline (31.2 g, 0.15 mol) was coupled to 3-butyn-1-ol (22.7 mL, 0.30 mol) as described in the first step of the synthesis of **7** to give 4-isoquinolin-4-ylbut-3-yn-1-ol (21.2 g, 72%) as a white solid: mp 65 °C; IR (KBr) 3252, 2275, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.38 (br s, 1H), 2.86 (t, 2H, J = 6.2 Hz), 3.95 (t, 2H, J = 6.3 Hz), 7.54−7.60 (m, 1H), 7.68−7.74 (m, 2H), 7.87 (d, 1H, J = 8.2 Hz), 8.16 (d, 2H, J = 8.3 Hz), 8.59 (s, 1H), 9.08 (s, 1H); MS (EI) m/z 197 (70), 166 (100), 139 (44). Anal. ($C_{13}H_{11}NO$) C, H, N.

The above alcohol (4.0 g, 20 mmol) was reacted with 4-phenyl-1,2,3,6-tetrahydropyridine (6.45 g, 40 mmol) as described in the second step of the synthesis of **7**. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **21** (1.04 g, 15%) as a yellow solid: mp 58−59 °C; IR (KBr) 3427, 2911, 1618, 1447, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.64 (m, 2H), 2.82−2.97 (m, 6H), 3.30−3.34 (m, 2H), 6.09−6.12 (m, 1H), 7.21−7.43 (m, 5H), 7.62 (t, 1H, J = 7.4 Hz), 7.74 (t, 1H, J = 8.1 Hz), 7.96 (d, 1H, J = 8.1 Hz), 8.27 (d, 1H, J = 8.3 Hz), 8.64 (s, 1H), 9.15 (s, 1H); MS (EI) m/z 338 (7), 172 (100), 166 (20). Anal. ($C_{24}H_{22}N_2 \cdot 0.09H_2O$) C, H, N, H_2O.

Method B. 4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butyne (6). 3-Butynyl *p*-toluenesulfonate (25 g, 0.11 mol), 4-phenyl-1,2,3,6-tetrahydropyridine (16.1 g, 0.10 mol), and $NaHCO_3$ (9.3 g, 0.11 mol) in DMF (150 mL) were heated to 70 °C for 5 h. The reaction mixture was concentrated in vacuo

and the resulting residue partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown oil. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave **6** (16 g, 76%) as a light yellow solid: mp 27 °C; IR (KBr) 3250, 2804, 748, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (t, 1H, J = 2.7 Hz), 2.43−250 (m, 2H), 2.57−2.59 (m, 2H), 2.65−2.78 (m, 4H), 3.19−3.23 (m, 2H), 6.03−6.06 (m, 1H), 7.20−7.40 (m, 5H); MS (EI) *m/z* 211 (22), 172 (100). Anal. ($C_{15}H_{17}N$) C, H, N.

1,2,3,6-Tetrahydro-4-phenyl-1-(4-phenyl-3-butynyl)pyridine (16). To a degassed (N_2) solution of **6** (3.0 g, 14 mmol) and iodobenzene (1.9 mL, 17 mmol) in piperidine (10 mL) were added palladium(II) acetate (31 mg, 0.14 mmol) and triphenylphosphine (74 mg, 0.28 mmol). The reaction mixture was heated to 80 °C under N_2 for 2 h, filtered, and concentrated in vacuo to give a brown oil. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **16** (1.0 g, 25%) as a white solid: mp 102−103 °C; IR (KBr) 2899, 1491, 1442, 1374, 833, 813, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61−2.81 (m, 8H), 3.27 (m, 2H), 6.07 (m, 1H), 7.23−7.43 (m, 10H); MS (EI) *m/z* 287 (9), 172 (100), 128 (17), 115 (19). Anal. ($C_{21}H_{21}N$) C, H, N.

1,2,3,6-Tetrahydro-4-phenyl-1-[4-(2-pyridinyl)-3-butynyl]pyridine (20). 2-Bromopyridine (0.99 mL, 10 mmol) was coupled to **6** (2.0 g, 9.5 mmol) as described in the synthesis of **16**. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave **20** (1.06 g, 39%) as a yellow solid: mp 88−89 °C; IR (KBr) 3433, 2954, 2223, 1581, 1465, 1427, 784, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (m, 2H), 2.69−2.90 (m, 6H), 3.24−3.28 (m, 2H), 6.06 (t, 1H, J = 1.7 Hz), 7.16−7.41 (m, 7H), 7.58−7.65 (m, 1H), 8.54 (d, 1H, J = 4.9 Hz); MS (EI) *m/z* 288 (9), 172 (100). Anal. ($C_{20}H_{20}N_2$) C, H, N.

Method C. 4-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]pyridine (19). To a degassed (N_2) solution of **6** (3.0 g, 14 mmol), 4-bromopyridine hydrochloride (2.7 g, 14 mmol), and triethylamine (5.9 mL, 42 mmol) in CH_2Cl_2 (50 mL) were added copper(I) iodide (18 mg, 0.096 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.10 g, 0.14 mmol). The reaction mixture was heated at reflux under N_2 overnight, cooled, diluted with CH_2Cl_2 (20 mL), and washed with water (4 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown solid. Purification by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 gave **19** (1.79 g, 45%) as a tan solid: mp 112−113 °C; IR (KBr) 3415, 2922, 1592, 821, 756, 546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60−2.86 (m, 8H), 3.25−3.28 (m, 2H), 6.06−6.09 (m, 1H), 7.18−7.38 (m, 7H), 8.53 (d, 2H, J = 5.6 Hz); MS (EI) *m/z* 288 (8), 172 (100). Anal. ($C_{20}H_{20}N_2$) C, H, N.

4-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]benzenamine (22). 1-Bromo-4-nitrobenzene (2.1 g, 10.4 mmol) was coupled to **6** (2.0 g, 9.46 mmol) as described in the synthesis of **19**. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave 1,2,3,6-tetrahydro-1-[4-(4-nitrophenyl)-3-butynyl]-4-phenylpyridine (2.0 g, 66%) as a gold solid: mp 148−149 °C; IR (KBr) 3443, 2813, 1591, 1511, 1338, 854, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (m, 2H), 2.70−2.87 (m, 6H), 3.26 (m, 2H), 6.08 (m, 1H), 7.21−7.41 (m, 5H), 7.53 (d, 2H, J = 8.9 Hz), 8.15 (d, 2H, J = 9.0 Hz); MS (EI) *m/z* 332 (5), 172 (100). Anal. ($C_{21}H_{20}N_2O_2$) C, H, N.

The above nitro compound (1.6 g, 4.8 mmol) was suspended in 95% EtOH (25 mL) and heated to 80 °C. To this suspension were added concentrated HCl (0.08 mL) and reduced iron (2.5 g). The reaction mixture was stirred at 80 °C for 0.5 h, filtered through Celite, and concentrated in vacuo to give 1.52 g of a gold solid. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave **22** (1.0 g, 70%) as a gold solid: mp 88−89 °C; IR (KBr) 3372, 2906, 1625, 1606, 1514, 828, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60−2.70 (m, 4H), 2.77−2.83 (m, 4H), 3.24−3.26 (m, 2H), 3.74 (br s, 2H), 6.07 (m, 1H), 6.58 (d, 2H, J = 8.4 Hz), 7.19−7.41 (m, 7H); MS (EI) *m/z* 302 (19), 172 (100), 130 (28). Anal. ($C_{21}H_{22}N_2 \cdot 0.08H_2O$) C, H, N, H_2O.

3-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]benzenamine (23). 1-Iodo-3-nitrobenzene (5.0 g, 20 mmol) was coupled to **6** (4.24 g, 20 mmol) as described in the synthesis of **19**. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave 1,2,3,6-tetrahydro-1-[4-(3-nitrophenyl)-3-butynyl]-4-phenylpyridine (5.76 g, 87%) as a yellow solid: mp 93−95 °C; IR (KBr) 2970, 2375, 1534, 1347 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (m, 2H), 2.70−2.77 (m, 2H), 2.80−2.87 (m, 4H), 3.28 (m, 2H), 6.08 (m, 1H), 7.21−7.51 (m, 6H), 7.73 (d, 1H, J = 8.9 Hz), 8.15 (d, 1H, J = 9.0 Hz), 8.25 (s, 1H); MS (EI) *m/z* 332 (11), 172 (100). Anal. ($C_{21}H_{20}N_2O_2$) C, H, N.

The nitro intermediate was reduced as described in **22**. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave **23** (1.62 g, 40%) as a pale yellow solid: mp 117−118 °C; IR (KBr) 3476, 2918, 1614, 1597, 1578, 1490, 752, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62−2.73 (m, 4H), 2.80−2.91 (m, 4H), 3.28−3.32 (m, 2H), 3.57 (br s, 2H), 6.06 (m, 1H), 6.60 (d, 1H, J = 7.9 Hz), 6.73 (s, 1H), 6.81 (d, 1H, J = 7.7 Hz), 7.07 (t, 1H, J = 7.8 Hz), 7.21−7.41 (m, 5H); MS (CI) *m/e* 303 (MH^+, 4), 172 (100). Anal. ($C_{21}H_{22}N_2$) C, H, N.

2-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]benzenamine (24). 1-Bromo-2-nitrobenzene (4.06 g, 20 mmol) was coupled to **6** (4.24 g, 20 mmol) as described in the synthesis of **19**. Purification by MPLC on silica gel eluting with 10% EtOAc/hexane gave 1,2,3,6-tetrahydro-1-[4-(2-nitrophenyl)-3-butynyl]-4-phenylpyridine (2.43 g, 36%) as a gold solid: mp 187−188 °C; IR (KBr) 1524, 1342, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (m, 2H), 2.70−2.90 (m, 6H), 3.28 (m, 2H), 6.08 (m, 1H), 7.21−7.44 (m, 6H), 7.53−7.63 (m, 2H), 7.96 (d, 1H, J = 9.0 Hz); MS (CI) *m/e* 333 (MH^+, 23), 172 (100). Anal. ($C_{21}H_{20}N_2O_2 \cdot 0.90HCl \cdot 0.11H_2O$) H, N; C: calcd, 68.69; found, 67.72.

The nitro intermediate was reduced as described in **22**. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **24** (1.5 g, 68%) as a light brown solid: mp 133−134 °C; IR (KBr) 3428, 2923, 1637, 1493, 750, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61−2.71 (m, 2H), 2.75−2.84 (m, 6H), 3.26−3.29 (m, 2H), 4.37 (br s, 2H), 6.08 (m, 1H), 6.60 (m, 2H), 7.03−7.09 (m, 1H), 7.19−7.39 (m, 6H); MS (CI) *m/e* 303 (MH^+, 25), 172 (100). Anal. ($C_{21}H_{22}N_2 \cdot 0.05H_2O$) C, H, N, H_2O.

6-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]-3-pyridinamine (26). 2-Bromo-5-nitropyridine (4.23 g, 21 mmol) was coupled to **6** (4.0 g, 19 mmol) as described in the synthesis of **19**. Purification by MPLC on silica gel eluting with 0.5% MeOH/CH_2Cl_2 gave 5-nitro-2-[4-(4-phenyl-3,6-dihydro-2*H*-pyridin-1-yl)but-1-ynyl]pyridine (3.3 g, 52%) as a gold solid: mp 133−134 °C; IR (KBr) 3437, 2924, 2222, 1589, 1571, 1516, 1370, 856, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (m, 2H), 2.75−2.92 (m, 6H), 3.25−3.28 (m, 2H), 6.07 (m, 1H), 7.21−7.56 (m, 6H), 8.42 (d, 1H, J = 8.6 Hz), 9.37 (s, 1H); MS (EI) *m/z* 333 (5), 172 (100). Anal. ($C_{20}H_{19}N_3O_2 \cdot 0.1H_2O$) C, H, N, H_2O.

The nitro intermediate was reduced as described in **22**. Purification by MPLC on silica gel eluting with 5% MeOH/CH_2Cl_2 gave **26** (1.34 g, 74%) as a gold solid: mp 136−137 °C; IR (KBr) 3382, 2924, 1633, 1589, 1561, 1476, 748, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59−2.86 (m, 8H), 3.25 (m, 2H), 3.78 (br s, 2H), 6.06 (m, 1H), 6.88 (d, 1H, J = 8.5 Hz), 7.16−7.40 (m, 6H), 8.02 (s, 1H); MS (CI) *m/e* 303 (MH^+, 4), 172 (100). Anal. ($C_{20}H_{21}N_3 \cdot 0.05H_2O$) C, H, N, H_2O.

Method D. 4-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]phenol (17). To a degassed (N_2) solution of **6** (0.50 g, 2.4 mmol), 4-iodophenol (0.52 mL, 2.4 mmol), and butylamine (20 mL) was added tetrakis(triphenylphosphine)-palladium(0) (0.17 mg, 0.15 mmol). The reaction mixture was heated to reflux under N_2 overnight, cooled, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to give a brown solid. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **17** (0.16 g, 22%) as a tan solid: mp 135−136 °C; IR (KBr) 3400, 2930, 1606, 1510, 1267, 832, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62−2.71 (m, 4H), 2.81−2.87 (m, 4H), 3.30−3.31 (m, 2H), 6.07 (m, 1H), 6.76 (d, 2H, J = 8.5 Hz), 7.21−7.42 (m, 7H); MS (EI) *m/z* 303 (11), 172 (100). Anal. ($C_{21}H_{21}NO$) C, H, N.

5-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]-1*H*-indole (18). 5-Bromoindole (0.93 g, 4.7 mmol) was coupled to **6** (1.0 g, 4.7 mmol) as described in the synthesis of **17**. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave **18** (0.42 g, 28%) as a yellow solid: mp 173−174

°C; IR (KBr) 2917, 2818, 1495, 1446, 809, 744, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (m, 2H), 2.59−2.65 (m, 2H), 2.72−2.81 (m, 4H), 3.21 (m, 2H), 6.01 (m, 1H), 6.37 (m, 1H), 7.09−7.34 (m, 8H), 7.61 (s, 1H), 9.98 (br s, 1H); MS (EI) *m/z* 326 (15), 172 (100). Anal. ($C_{23}H_{22}N_2 \cdot 0.05H_2O$) C, H, N, H_2O.

5-[4-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-1-butynyl]-2-pyridinamine (25). 2-Amino-5-bromopyridine (1.0 g, 5.8 mmol) was coupled to **6** (0.50 g, 2.4 mmol) as described in the synthesis of **17**. Purification by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 gave **25** (0.58 g, 33%) as a yellow solid: mp 180−181 °C; IR (KBr) 3411, 2924, 1611, 1497, 1389, 825, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60−2.70 (m, 4H), 2.78−2.83 (m, 4H), 3.25 (d, 2H, J = 3.2 Hz), 4.53 (br s, 2H), 6.07 (m, 1H), 6.41 (d, 1H, J = 8.5 Hz), 7.21−7.46 (m, 6H), 8.14 (s, 1H); MS (EI) *m/z* 303 (11), 172 (100). Anal. ($C_{20}H_{21}N_3 \cdot 0.10H_2O$) C, H, N, H_2O.

1,2,3,6-Tetrahydro-1-[4-(4-methoxyphenyl)-3-butynyl]-4-phenylpyridine (27). *p*-Iodoanisole (1.1 g, 4.7 mmol) was coupled to **6** (1.0 g, 4.7 mmol) as described in the synthesis of **17**. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **27** (0.54 g, 36%) as a white solid: mp 148−149 °C; IR (KBr) 2934, 1605, 1508, 1376, 837, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61−2.72 (m, 4H), 2.80−2.86 (m, 4H), 3.26−3.30 (m, 2H), 3.79 (s, 3H), 6.07 (m, 1H), 6.81 (d, 2H, J = 8.8 Hz), 7.20−7.41 (m, 7H); MS (EI) *m/z* 317 (12), 172 (100). Anal. ($C_{22}H_{23}NO \cdot 0.05H_2O$) C, H, N, H_2O.

1-[4-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)but-3-ynyl]-4-phenyl-1,2,3,6-tetrahydropyridine (28). 3,4-(Ethylenedioxy)-bromobenzene (1.02 g, 4.7 mmol) was coupled to **6** (1.0 g, 4.7 mmol) as described in the synthesis of **17**. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **28** (0.68 g, 42%) as a yellow solid: mp 105−107 °C; IR (KBr) 2958, 1573, 1499, 896, 809, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59−2.75 (m, 4H), 2.77−2.82 (m, 4H), 3.24−3.26 (m, 2H), 4.23 (s, 4H), 6.06 (m, 1H), 6.76 (d, 1H, J = 8.0 Hz), 6.86−6.92 (m, 2H), 7.22−7.40 (m, 5H); MS (CI) *m/e* 346 (MH^+, 49), 216 (52), 172 (100). Anal. ($C_{23}H_{23}NO_2$) C, H, N.

1-[4-(5-Benzofuranyl)-3-butynyl]-1,2,3,6-tetrahydro-4-phenylpyridine (29). 5-Bromobenzofuran[34] (1.00 g, 5.1 mmol) was coupled to **6** (1.25 g, 5.1 mmol) as described in the synthesis of **17**. Purification by MPLC on silica gel eluting with 25% EtOAc/hexane gave **29** (0.43 g, 26%) as a yellow solid: mp 127−130 °C; IR (KBr) 3429, 2897, 2822, 2771, 2361, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60−2.64 (m, 2H), 2.70−2.73 (m, 2H), 2.83−2.89 (m, 4H), 3.29 (m, 2H), 6.07 (m, 1H), 6.72 (m, 1H), 7.21−7.42 (m, 7H), 7.61 (s, 1H), 7.66 (s, 1H); MS (EI) *m/z* 327 (11), 198 (26), 172 (100). Anal. ($C_{23}H_{21}NO \cdot 0.05H_2O$) C, H, N, H_2O.

Pharmacological Methods. Cell Cultures. CHO K_1 cells (donated by Dr. J. Granneman, Wayne State University, Detroit, MI) expressing either human D_3, human D_{2L}, or human $D_{4.2}$ receptors[20] were grown in F-12 medium (GIBCO Laboratories, Grand Island, NY) supplemented with 10% fetal bovine serum (Hyclone Laboratories, Logan, UT) in T-150 culture flasks in a humidified atmosphere of 5% CO_2 and 95% air.

Receptor Binding Assays. The inhibition of binding of [^{3}H]ligand to each receptor (final concentration), brain area, nonspecific agent (final concentration), and method were carried out as follows: DA D_2, [^{3}H]spiperone (0.2 nM), rat striatum, and (+)-butaclamol (1.0 μM) according to the method of Grigoriadis and Seeman;[15] human D_3, [^{3}H]spiperone (0.5 nM), CHO K_1 cells, and haloperidol (1.0 μM);[20] human $D_{4.2}$, [^{3}H]spiperone (0.2 nM), CHO K_1 cells, and haloperidol (1.0 μM);[20] 5-HT_{1A}, [^{3}H]-8-OH-DPAT (0.4 nM), rat hippocampus, and 8-OH-DPAT (1 μM) by the method of Peroutka;[24] α_1-adrenergic, [^{3}H]prazosin (0.1 nM), rat cortex, and phentolamine (10 μM) by the method of Morrow and Creese.[25]

Inhibition of Spontaneous Locomotor Activity.[16] Mice were treated with compounds administered ip followed immediately by a 1 h test. Rats were treated orally or subcutaneously with compounds 1 h or immediately prior to a 30 min test, respectively. Locomotor activity was measured in darkened cylindrical photobeam chambers. Data are expressed as percent inhibition of LMA relative to vehicle-treated animals, and an ED_{50} was calculated from increasing doses by regression analysis.

Mitogenesis Assay.[20] The effects of test compounds on [^{3}H]thymidine uptake were carried out essentially as described by Chio *et al.*[26] CHO p-5 cells transfected with human D_{2L} cDNA were seeded into 96-well plates at a density of about 5000 cells/well and grown at 37 °C in a minimum essential medium (αMEM; Gibco) with 10% calf serum for 2 days. The wells were then rinsed three times with serum-free media. Fresh media (90 μL) were added along with 10 μL of test compound in water or vehicle alone. Eight wells of each plate received 100 μL of αMEM with 10% fetal calf serum. After culture for 16−17 h, [^{3}H]thymidine (1 μCi/well) was added for 4 h. The cells were trypsinized and harvested onto filter mats with a 96-well Brandel cell harvester. The filters were counted in a Beta-Plate scintillation counter.

Inhibition of GBL-Stimulated DA Synthesis.[27] Compounds were administered to male Long-Evans rats (Blue Spruce Farms, Altamont, NY) 1 h and GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) 30 min before sacrifice. Brain striatal levels of DOPA were analyzed by HPLC with electrochemical detection.[35] DOPA concentrations were 1.03 ± 0.04 and 3.76 ± 0.28 mg/g ± SEM for control and GBL-treated animals, respectively (n = 10).

Effects on the Firing Rate of Substantia Nigra DA Neurons.[28] 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 wave form and firing pattern, and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Base-line firing rate was calculated by averaging the rate over 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.

Conditioned Avoidance in Squirrel Monkeys. This procedure was carried out according to methods described previously.[31] Inhibition of conditioned avoidance was measured for 6 h after oral administration of compound. Drug effects were expressed as percentage inhibition of avoidance responding relative to control performance during the 4 h of peak effect.

Acknowledgment. We would like to thank C. L. Christoffersen, A. E. Corbin, S. DeMattos, L. Georgic, D. J. Johnston, F. W. Ninteman, K. A. Serpa, Y.-H. Shih, S. Z. Whetzel, J. Wiley, and K. Zoski for biological testing.

References

(1) Haracz, J. L. The Dopamine Hypothesis: An Overview of Studies With Schizophrenic Patients. *Schizophr. Bull.* **1982**, *8*, 438−469.

(2) (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. (c) Boyd, A. E.; Reichlin, S. Neural Control of Prolactin Sectetion in Man. *Psychoneuroendocrinology* **1978**, *3*, 113−130.

(3) (a) Carlsson, A. In *Pre- and Postsynaptic Receptors*; Usdin, E., Bunney, W. E., Eds.; Marcel Dekker: New York, 1975; p 49. (b) Roth, R. H. Dopamine Autoreceptors: Pharmacology, Function and Comparison with Postsynaptic Dopamine Receptors. *Commun. Psychopharmacol.* **1979**, *3*, 429−445.

(4) (a) Carlsson, A. In *Receptors and Ligands in Psychiatry*; Sen, A. K., Lee, T., Eds.; Cambridge University Press: Cambridge, 1988; pp 1−10. (b) Arnt, J.; Christensen, A. V.; Hyttel, J.; Larsen, J.-J.; Svendsen, O. Effects of Putative Dopamine Autoreceptor Agonists in Pharmacological Models Related to Dopaminergic and Neuroleptic Activity. *Eur. J. Pharmacol.* **1983**, *86*, 185−198. (c) Corzini, G. U.; Pitzalis, G. F.; Bernardi, R.; Bocchetta, A.; Del Zompo, M. The Use of Dopamine Agonists in the Treatment of Schizophrenia. *Neuropharmacology* **1981**, *20*, 1309−1313. (d) Meltzer, H. Y.; Kolakowska, T.; Robertson, A.; Tricou, B. J. Effect of Low-Dose Bromocriptine in Treatment of Psychosis: The Dopamine Autoreceptor-Stimulation Strategy. *Psychopharmacology* **1983**, *81*, 37−41.

(5) (a) Wikström, 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. (b) Hjorth, S.; Carlsson, A.; Clark, D.; Svensson, K.; Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arviddson, L.-E.; Johansson, A.; Nilsson, J. L. G. Central Dopamine Receptor Agonist and Antagonist Actions of the Enantiomers of 3-PPP. *Psychopharmacology* **1983**, *81*, 89−99.

(6) Kehr, W. Transdihydrolisuride, a Partial Dopamine Receptor Antagonist: Effects on Monoamine Metabolism. *Eur. J. Pharmacol.* **1984**, *97*, 111−119.

(7) Seyfried, C. A.; Greiner, H. E.; Haase, A. F. Biochemical and Functional studies on EMD 49980: A Potent, Selectively Presynaptic D_2 Dopamine Agonist with Actions on Serotonin Systems. *Eur. J. Pharmacol.* **1989**, *160*, 31−41.

(8) 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.

(9) Böttcher, H.; Barnickel, G.; Hausberg, H.-H.; Haase, A. F.; Seyfried, C. A.; Eiermann, V. Synthesis and Dopaminergic Activity of Some 3-(1,2,3,6-Tetrahydro-1-pyridylalkyl) indoles. A Novel Conformational Model to Explain Structure-Activity Relationships. *J. Med. Chem.* **1992**, *35*, 4020−4026.

(10) Jaen, J. C.; Caprathe, B. W.; Wise, L. D.; Meltzer, L. T.; Pugsley, T. A.; Heffner, T. G. Synthesis and Pharmacological Evaluation of the Enantiomers of the Dopamine Autoreceptor Agonist PD 135385. *Biol. Med. Chem. Lett.* **1993**, *3*, 639−644.

(11) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarene, and Bromopyridines. *Tetrahedron Lett.* **1975**, *50*, 4467−4470.

(12) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985; pp 299−306.

(13) Just, G.; Singh, R. The Synthesis of 11−13-Membered Diacetylenic and 18-Membered Tetraacetylenic Ring Systems. *Tetrahedron Lett.* **1987**, *48*, 5981−5984.

(14) (a) Cassar, L. Synthesis of Aryl- and Vinyl-Substituted Acetylene Derivatives by the Use of Nickel and Palladium Complexes. *J. Organometal. Chem.* **1975**, *93*, 253−257. (b) Dieck, H. A.; Heck, R. F. Palladium Catalyzed Synthesis of Aryl, Hererocyclic and Vinylic Acetylene Derivatives. *Organometal. Chem.* **1975**, *93*, 259−263.

(15) Grigoriadis, D.; Seeman, P. Complete Conversion of Brain D_2 Dopamine Receptors from the High- to the Low-Affinity State for Dopamine Agonists, using Sodium Ions and Guanine Nucleotide. *J. Neurochem.* **1985**, *44*, 1925−1935.

(16) (a) Strömbom, U. Catecholamine Receptor Agonists. Effects on Motor Activity and Rate of Tyrosine Hydroxylation in Mouse Brain. *Nauyn-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.

(17) Swart, P. J.; Jansman, F. G. A.; Drenth, B. F. H.; de Zeeuw, R. A.; Dijkstra, D.; Horn, A. S. Impact of Structural Differences on the *In vitro* Glucuronidation Kinetics of Potentially Dopaminergic Hydroxy-2-Aminotetralins and Naphthoxazines Using Rat and Human Liver Microsomes. *Pharmacol. Toxicol.* **1991**, *68*, 215−219.

(18) (a) Cannon, J. G.; Demopoulos, B. J.; Long, J. P.; Flynn, J. R.; Sharabi, F. M. Proposed Dopaminergic Pharmacophore of Lergotrile, Pergolide, and Related Ergot Alkaloid Derivatives. *J. Med. Chem.* **1981**, *24*, 238−240. (b) Asselin, A. A.; Humber, L. G.; Voith, K.; Metcalf, G. Drug Design via Pharmacophore Identification. Dopaminergic Activity of 3H-Benz[e]indol-8-amines and Their Mode of Interaction with the Dopamine Receptor. *J. Med. Chem.* **1986**, *29*, 648−654. (c) Seiler, M. P.; Hagenbach, A.; Wüthrich, H.-J.; Markstein, R. *trans*-Hexahydroindolo[4,3-*ab*]phenanthridines ("Benzergolines"), the First Structural Class of Potent and Selective Dopamine D_1 Receptor Agonists Lacking a Catechol Group. *J. Med. Chem.* **1991**, *34*, 303−307.

(19) Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L. C.; Barnett, A. Characterization of the Binding of [^{3}H]SCH 23390, a Selective D_1 Receptor Antagonist Ligand, in Rat Striatum. *Life Sci.* **1984**, *35*, 1885−1893.

(20) Pugsley, T. A.; Davis, M. D.; Akunne, H. C.; MacKenzie, R. G.; Shih, Y. H.; Damsma, G.; Wikström, H.; Whetzel, S. Z.; Georgic, L. M.; Cooke, L. W.; DeMattos, S. B.; Corbin, A. E.; Glase, S. A.; Wise, L. D.; Dijkstra, D.; Heffner, T. G. Neurochemical and Functional Characterization of the Preferentially Selective Dopamine D_3 Agonist PD 128907. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1355−1366.

(21) Seeman, P.; Grigoriadis, D. Dopamine Receptors in Brain and Periphery. *Neurochem. Int.* **1987**, *10*, 1−25.

(22) (a) Damsma, G.; Bottema, T.; Westerink, B.; Tepper, P.; Dijkstra, D.; Pugsley, T. A.; MacKenzie, R. G.; Heffner, T. G.; Wikström, H. Pharmacological Aspects of R-(+)-7-OH-DPAT, a Putative Dopamine D_3 Receptor Ligand. *Eur. J. Pharmacol.* **1993**, *249*, R9−R10. (b) Daly, S.; Waddington, J. L. Behavioural Effects of the Putative D-3 Dopamine Receptor Agonist 7-OH-DPAT in Relation to Other "D-2-like" Agonists. *Neuropharmacology* **1993**, *32*, 509−510. (c) Svensson, K.; Carlsson, A.; Waters, N. Locomotor Inhibition by the D_3 Ligand R-(+)-7-OH-DPAT is Independent of Changes in Dopamine Release. *J. Neural Transm.: Gen. Sect.* **1994**, *95*, 71−74. (d) Mierau, J.; Schneider, F. J.; Ensinger, H. A.; Chio, C. L.; Lajiness, J. E.; Huff, R. M. Pramipexole Binding and Activation of Cloned and Expressed Dopamine D_2, D_3 and D_4 Receptors. *Eur. J. Pharmacol.-Mol. Pharmacol.* **1995**, *290*, 29−36.

(23) Meller, E.; Bohmaker, K.; Goldstein, M.; Basham, D. A. Evidence That Striatal Synthesis-inhibiting Autoreceptors are Dopamine D_3 Receptors. *Eur. J. Pharmacol.* **1993**, *249*, R5−R6.

(24) Peroutka, S. J. Selective labeling of 5-HT_{1A} and 5-HT_{1B} binding sites in bovine brain. *Brain Res.* **1985**, *344*, 167−171.

(25) Morrow, A. L.; Creese, I. Characterization of α_1 adrenergic receptor, subtypes in rat brain: a reevaluation of [^{3}H]WB 4101 and [^{3}H]prazosin binding. *Mol. Pharmacol.* **1986**, *29*, 321−330.

(26) Chio, C. L.; Lajiness, J. E.; Huff, R. M. Activation of Heterologously expressed D_3 dopamine receptors: Comparison with D_2 dopamine receptors. *Mol. Pharmacol.* **1994**, *45*, 51−60.

(27) 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.

(28) (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. (c) 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.

(29) Ruffalo, R. R. Important Concepts of Receptor Theory. *J. Auton. Pharmacol.* **1982**, *2*, 277−295.

(30) Meller, E.; Bohmaker, K.; Namba, Y.; Friedhoff, A. J.; Goldstein, M. Relationship Between Receptor Occupancy and Response at Striatal Dopamine Autoreceptors. *Mol. Pharmacol.* **1987**, *31*, 592−598.

(31) (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.

(32) 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.

(33) Wetzel, H.; Benkert, O. Dopamine Autoreceptor Agonists in the Treatment of Schizophrenic Disorders. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1993**, *17*, 525−540.

(34) Humphrey, G. R.; Madar, A. M.; Thompson, A. S. Intermediates for Substituted Azetidinones Useful as Anti-Inflammatory and Antidegenerative Agents. U.S. Patent 5,149,838, 1992.

(35) (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. M.; 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.

JM950721M