Synthesis and Dopamine Agonist Properties of (±)-*trans*-3,4,4a,10b-Tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol and Its Enantiomers

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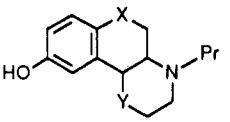
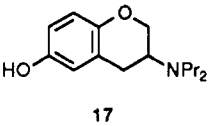
The dopamine agonist profile of (±)-*trans*-3,4,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (**16a**) and its enantiomers (**16b–c**) was examined. Racemic **16a** exhibited moderate affinity for the dopamine (DA) D_2 receptor labeled with the DA antagonist ligand [^{3}H]haloperidol and moderate in vivo activity; it attenuated γ-butyrolactone-stimulated DA synthesis, decreased DA neuronal firing of substantia nigra DA neurons, and inhibited exploratory locomotor activity in rats, a profile consistent with a DA autoreceptor agonist mechanism of action. The (+)-enantiomer **16b** possessed greater DA receptor affinity with the agonist ligand [^{3}H]-*N*-propylnorapomorphine than with the antagonist ligand. In rats it potently inhibited DA synthesis and neuronal firing and also inhibited exploratory locomotion. The (−)-enantiomer, on the other hand, did not have significant activity in any of these tests. This profile indicates that like many other rigid DA agonists, the dopaminergic activity resides in one enantiomer, in this case the (+)-enantiomer **16b**. On the basis of single-crystal X-ray analysis of a key intermediate, the absolute configuration of **16b** was found to be 4a*R*, 10b*R*.

While the ergolines such as lergotrile and bromocriptine are potent dopamine (DA) agonists, they are complex to synthesize and also possess serotonergic and adrenergic effects that tend to obscure their dopaminergic properties.[1] As part of an effort to develop simpler compounds with greater specificity for DA receptor sites, it was found that the *trans*-octahydrobenzo[*f*]quinolines which are obtained by replacing the indole portion of the ergolines with phenolic moieties retained their dopaminergic properties.[2] Such compounds can also be viewed as incorporating the structural elements of two central DA agonist structural types, the hydroxy-2-aminotetralins and 3-(1-propyl-3-piperidinyl)phenol (3-PPP). Wikstrom et al. reported that these compounds, e.g., *trans*-9-hydroxy-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**1**), did indeed possess selective DA agonist activity.[3] On the basis of data indicating that the synthetically less complex oxaergolines also possess good biological activity, the related series of *trans*-hydroxyhexahydronaphthoxazines were examined; the 4-propyl-9-hydroxy analogue, PHNO (**2**), was found to be a quite potent DA agonist.[4-6] More recently, **3** (CGS 15855A), a rigid *trans*-hexahydrobenzopyranopyridin-9-ol derived from the simpler 3-aminobenzopyran system, was reported to have DA agonist activity and also to possess some selectivity for autoreceptor sites.[7-9] As an extension to these compounds, we have synthesized and evaluated the dopaminergic properties of *trans*-3,4,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (PBPO, **16a**). We have also examined the (+)- and (−)-enantiomers of **16a**, **16b**, and **16c**, since the DA agonist activity of each of the previous compounds (**1–3**) has been demonstrated to reside in only one of the two enantiomers. While we were in the process of preparing this paper, Dijkstra and associates published a paper in which they reported that the racemic compound **16a** lacked DA agonist activity.[10] Since this is in contrast to our findings, we present our data on **16a** and also describe the activities of the enantiomers, **16b,c**.



1: X = Y = CH_2
2: X = CH_2, Y = O
3: X = O, Y = CH_2
16: X = Y = O



17

Chemistry

The synthesis of **16a–c** is outlined in Scheme I beginning from 4-methoxyphenol (**4**). Michael addition of **4** to acrylonitrile yielded 90% of cyanoethyl ether **5**, which in turn was hydrolyzed to acid **6** in 65% yield. Ring closure to benzopyran-4-one **7**[11] was achieved in 93% yield by treatment of **6** with thionyl chloride followed by trifluoromethanesulfonic acid. While several methods were explored to incorporate an amino group at the 3-position of the benzopyranone ring to facilitate formation of the oxazine ring, the interesting conversion of **7** to 3-aminobenzopyranone **9** in 82% overall yield by treatment of **7**

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(1) McPherson, G. A.; Beart, P. M. *Eur. J. Pharmacol.* **1983**, *91*, 363.
(2) Cannon, J. G.; Lee, T.; Iihan, M.; Koons, J.; Long, J. P. *J. Med. Chem.* **1979**, *22*, 341.
(3) Wikstrom, H.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Hacksell, U.; Johansson, A.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1982**, *25*, 925.
(4) Jones, H. J.; Anderson, P. S.; Baldwin, J. J.; Clineschmidt, B. V.; McClure, D. E.; Lundell, G. F.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirshfield, J. M.; Smith, G.; Lumma, P. K. *J. Med. Chem.* **1984**, *27*, 1607.
(5) Horn, A. S.; Dijkstra, D.; Hazelfoff, B.; DeVries, J. B.; Mulder, T. B. A.; Wijnberg, H.; Timmermans, B. B. M. W. M. *International Symposium on Medicinal Chemistry, Proceedings Vol. 1*; Swedish Pharmaceutical Press: Stockholm, 1984; p 466.
(6) Dijkstra, D.; Hazelfoff, B.; Mulder, T. B. A.; DeVries, J. B.; Wijnberg, H.; Norn, A. S. *Eur. J. Med. Chem.* **1985**, *20*, 247.
(7) Altar, C. A.; Boyar, W. C.; Wood, P. L. *Eur. J. Pharmacol.* **1987**, *134*, 303.
(8) Boyar, W. C.; Altar, C. A. *J. Neurochem.* **1987**, *48*, 824.
(9) Altar, C. A.; Boyar, W. C.; Oei, E.; W. C; Wood, P. L. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 115.
(10) Dijkstra, D.; Mulder, T. B. A.; Rollema, H.; Tepper, P. G.; Van der Weide, J.; Horn, A. S. *J. Med. Chem.* **1988**, *31*, 2178.
(11) Colonge, J.; Guyot, A. *Bull. Soc. Chim. Fr.* **1958**, 325.

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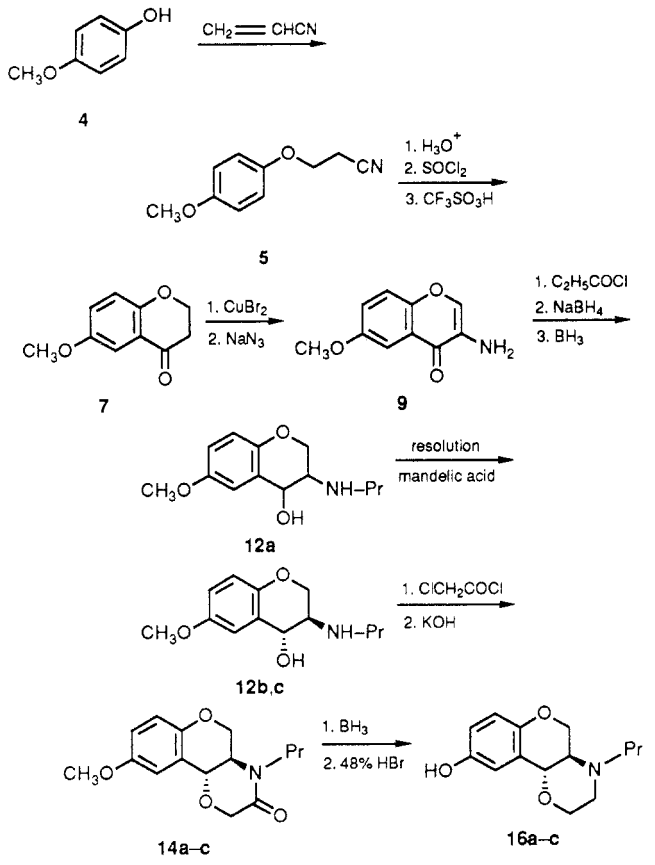
Scheme I



with cupric bromide followed by sodium azide provided the most efficient entry.[12] Compound **9** was converted to propionamide **10** with propionyl chloride in 68% yield. Attempts to reduce **10** to the desired amino alcohol **12a** with lithium aluminum hydride led to a mixture of products. However, treatment of **10** with sodium borohydride yielded 90% of the saturated alcohol **11**, which was further reduced with diborane to give only the *trans*-amino alcohol **12a** (71% yield). The high crystallinity of the mandelate salts of **12a** provided an excellent point in the synthesis to separate the enantiomers **12b,c** by fractional crystallization of the diastereomeric salts of **12a** with either (+)- or (−)-mandelic acid. The (+)-mandelic acid salt of **12b** was examined by single-crystal X-ray analysis, and the absolute configuration of **12b** was found to be 3*R*,4*R*.[13] The computer-generated ORTEP drawing of **12b** is presented in Figure 1. Reaction of **12a–c** with chloroacetyl chloride followed by ring closure with potassium hydroxide afforded oxazinones **14a–c** in about 80% yield. Subsequent reduction of **14a–c** with diborane yielded 85–90% of oxazines **15a–c**. Finally, hydrolysis of the 9-methoxy group with 48% hydrobromic acid or boron tribromide gave the target compounds, racemate **16a**, and the (+)- and (−)-enantiomers, **16b** and **16c**, respectively. The hydrobromide reaction was completed in 30 min. Longer reaction times led to decomposition. The enantiomeric purity of **16b** and **16c** was confirmed by chiral HPLC. On the basis of the X-ray analysis of **12b**, **16b** and **16c** were assigned the absolute configurations 4a*R*,10b*R* and 4a*S*,10b*S*, respectively.

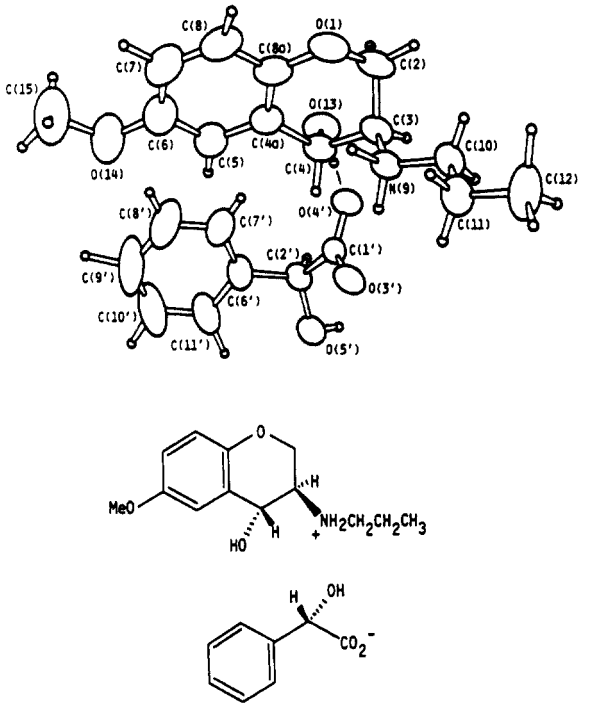


Figure 1. Computer-generated ORTEP drawing of the X-ray structure of the (+)-mandelic acid salt of **12b**.

Table I. Effects of **16a–c** and Reference Agents on DA Receptors

compd	[^{3}H]HPD[a,b] IC_{50}, nM	DOPA accumulation,[c] %: 30 mg/kg ip	DA neuronal firing,[d] %: 2.2 mg/kg ip	inhibn of LMA:[e] ED_{50}, mg/kg ip
16a	900	61.8 ± 9.9	99 ± 1	11.0
16b	409	88.4 ± 6.9	100 ± 0	5.4
16c	>100000	0	9 ± 3	>30
17[f]	800	100	100 ± 3	11.3
APO[i]	27	100[g]	100 ± 0[h]	0.3

[a] [^{3}H]Haloperidol. [b] IC_{50} values were determined by a nonlinear regression analysis from four or five concentrations run in triplicate. [c] Shown are percentages ± SEM for reversal of the γ-butyrolactone-stimulated increases in DOPA synthesis in rate striatum; N = 4–5. [d] Shown are the percentages ● SEM for decrease of the firing rate of rat substantia nigra DA neutrons; N = 3–4. [e] ED_{50} values for inhibition of locomotor activity (LMA) in mice were generated from four doses of at least three animals per dose. [f] Data taken from ref 19. [g] At 2.0 mg/kg ip. [h] At 0.25 mg/kg ip. [i] APO = apomorphine.

Results and Discussion

The in vitro affinity of the target compounds **16a–c** for DA D_2 receptors was determined by measuring their ability to displace [^{3}H]haloperidol from rat brain striatal membrane.[14] The DA autoreceptor agonist activity of these compounds was assessed neurochemically by measuring their ability to decrease DA synthesis in the corpus striatum in rats (i.e., inhibition of γ-butyrolactone-stimulated DOPA synthesis[15]) and electrophysiologically by measuring their inhibition of DA neuronal firing activity in the substantia nigra.[16] In addition, DA autoreceptor agonist activity was assessed behaviorally by examining their ef-

(12) (a) Szabo, V.; Nemeth, L. *Magy. Kem. Foly.* **1984**, *84*, 164; *Chem. Abstr.* **1978**, *89*(5), 43022*p*. (b) Rakosi, M.; Litkei, G.; Bognar, R.; Patonay, T. *Liebigs Ann. Chem.* **1979**, 162. (c) Litkei, G.; Mester, T.; Patonay, T.; Bognar, R. *Liebigs Ann. Chem.* **1979**, 174.

(13) A description of the single-crystal X-ray analysis and a table of crystallographic coordinates, bond lengths, and bond angles are available as supplementary material.

(14) Burt, D. R.; Creese, I.; Snyder, S. H. *Mol. Pharmacol.* **1976**, *12*, 800.

(15) Walters, J. R.; Roth, R. H. *Biochem. Pharmacol.* **1976**, *25*, 649.

(16) Bunney, B. S.; Walter, J. R.; Roth, R. H.; Aghajanian, G. K. *J. Pharmacol. Exp. Ther.* **1973**, *185*, 560.

fects on exploratory locomotor activity in mice.[17,18] The results with these compounds were compared to their simpler bicyclic analogue 6-hydroxy-3,4-dihydro-3-(dipropylamino)-2*H*-1-benzopyran (**17**)[19] and also to the dopamine agonist apomorphine (Table I).

The racemic compound **16a**, bound to the D_2 receptor with an IC_{50} of 900 nM, and in rats dosed intraperitoneally, decreased DOPA accumulation by 61.8% at 30 mg/kg and completely inhibited DA neuronal firing at 2.5 mg/kg, indicative of DA agonist activity. Compound **16a** also inhibited exploratory locomotor activity in mice (ED_{50} = 11.0 mg/kg ip). On the basis of this combined neurochemical, electrophysiological, and behavioral data, **16a** appears to have moderate DA autoreceptor agonist properties.

Dijkstra et al. reported that **16a** bound quite weakly to DA D_2 receptors as labeled by [^{3}H]DP-5,6-ADTN and [^{3}H]N-0437 (IC_{50}s of 3070 and 1600 nM, respectively) and did not significantly affect the concentrations of the DA metabolites, DOPAC and HVA, in rat striatum at 2.49 mg/kg ip.[10] Since **16a** is a DA agonist, it generally would have been expected to have a greater affinity for displacing the agonist ligands that they have utilized in their binding assay than for displacing the antagonist ligand that we used. However, their weaker binding data might be the result of differing experimental methodology. In addition, their lack of in vivo effects on DA metabolism may be due to a combination of the low dose of **16a** used in that study (2.49 mg/kg ip) and that changes in DA metabolite levels which reflect both pre- and postsynaptic effects may not be as sensitive a measure of DA agonist activity as are the effects on DA synthesis and neuronal firing activity. These latter tests only reflect effects on presynaptic DA receptors which are inherently more sensitive than postsynaptic DA receptors.[20]

Like earlier compounds of this structural type, i.e., **1–3**, the DA agonist activity apparently resides in one enantiomer, the (+)-isomer **16b**. This compound bound to dopamine D_2 receptors ([^{3}H]haloperidol) with an IC_{50} of 409 nM. In rats dosed ip, it reversed GBL-stimulated DOPA accumulation by 88.4% at 30 mg/kg and completely inhibited DA neuronal firing at 2.5 mg/kg, an effect which was reversed by the DA antagonist haloperidol. As with the racemic compound, **16b** inhibited exploratory locomotor activity in mice (ED_{50} = 5.4 mg/kg ip). The (−)-enantiomer, on the other hand, was essentially devoid of activity at the concentrations and doses tested; it did not have significant affinity for DA receptors or possess activity in the in vivo tests.

In accordance with a DA agonist mechanism of action, the active (+)-enantiomer, **16b**, possessed greater affinity for DA-agonist-labeled receptor sites ([^{3}H]-*N*-propylnorapomorphine as the ligand[21]) than for DA sites labeled by the antagonist ligand [^{3}H]haloperidol, 123 nM versus 409 nM, respectively (Table II). It potently decreased DOPA accumulation in rats pretreated with GBL (ED_{50} = 0.03 mg/kg sc). Interestingly, this result was confirmed in the behavioral test; **16b** also inhibited exploratory locomotor activity in rats with an ED_{50} of 0.03 mg/kg sc.

Table II. Pharmacological Profile of **16b**

test	16b	17[a]	APO[j]
[^{3}H]NPA,[b,c] IC_{50}, nM	123	13.3	2.60
[^{3}H]HPD,[c,d] IC_{50}, nM	409	800	27
DOPA accumulation,[e] ED_{50}, mg/kg sc	0.03	0.04[f]	0.06[g]
inhibn of LMA in rat,[h] ED_{50}, mg/kg sc	0.03	0.17	0.021
reversal of reserpine-induced depression in rat,[i] ED_{50}, mg/kg sc	6.25	13.4	0.096
DOPA accumulation,[e] 5 mg/kg po	100		
inhibn of LMA in rat,[h] ED_{50}, mg/kg po	5.8		

[a] See footnote *f*, Table I. [b] [^{3}H]-*N*-Propylnorapomorphine. [c] See footnote *b*, Table I. [d] See footnote *a*, Table I. [e] Shown are the doses of each compound giving half-maximal reversal of the γ-butyrolactone-stimulated increase in DOPA formation in rat striatum. [f] Administered ip. [g] Value taken from ref 27. [h] ED_{50} values for inhibition of locomotor activity (LMA) were generated from four doses; 5–12 rats were used per dose. [i] ED_{50} values were generated from three doses; 5–10 rats were used per dose. [j] APO = apomorphine.

This potent inhibition of locomotor activity suggested that **16b** might possess selectivity for brain DA autoreceptor sites. In order to obtain a better assessment of the relative potency at pre- and postsynaptic DA receptors, the effect of **16b** on locomotor activity was evaluated in reserpine-treated rats and compared to its effect on naive animals. While locomotor inhibition in normal rats is considered to be a measure of DA autoreceptor agonist effects,[18] reveral of locomotor inhibition in rats treated with reserpine is a sensitive indicator of postsynaptic DA agonist activity.[22] Compound **16b** inhibited locomotor activity in normal rats at a dose 200-fold lower than it reversed the locomotor inhibition of reserpine-treated animals. This is compared to a ratio of approximately 5 for apomorphine and 80 for the simpler benzopyran analogue **17** and suggests that **16b**, indeed, has selectivity for brain DA autoreceptor receptor sites.

Finally, **16b** caused a 100% reversal in DOPA accumulation (after GBL) at 5 mg/kg po. This oral activity was again confirmed behaviorally in rats; **16b** inhibited exploratory locomotor activity with an ED_{50} of 5.8 mg/kg po.

The stereochemistry of **16b** is analogous to that of the active enantiomers of the related ring systems, **1** and **2**.[4,23] These enantiomers as well as the active enantiomers of apomorphine, ergolines, and the aminotetralins all fit the model proposed by McDermed for DA receptor agonist activity.[24]

In summary, the present results indicate that **16a** does indeed possess DA agonist activity. Furthermore, this DA agonist activity, like that of other rigid DA agonists, resides in one enantiomer, isomer **16b**, which was assigned the 4a*R*,10b*R* configuration. Our biochemical, electrophysiological, and behavioral results indicate that **16b** is a quite potent DA agonist with selectivity for autoreceptor sites. Thus, it is possible to incorporate the ether linkages from both the hydroxyhexahydronaphthoxazine and the hexahydrobenzopyranopyridin-9-ol structures, **2** and **3**, re-

(17) Coughenour, L. L.; McLean, J. R.; Parker, R. B. *Pharmacol. Biochem. Behav.* **1977**, *12*, 800.
(18) (a) Martin, G. E.; Bendesky, R. J. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 706. (b) Svensson, L.; Ahlenius, S. *Eur. J. Pharmacol.* **1983**, *88*, 393. (c) Carlsson, A. *J. Neurol. Transm.* **1983**, *57*, 309. (d) Strombon, U. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1976**, *292*, 167.
(19) Wise, L. D.; DeWald, H. A.; Hawkins, E. S.; Reynolds, D. M.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A. *J. Med. Chem.* **1988** *31*, 688.
(20) Carlsson, A. *J. Neural. Transm.* **1983**, *57*, 309.
(21) Seeman, P.; Ulpian, C.; Grigoriadis, D.; Pri-Bar, I.; Buchman, O. *Biochem. Pharmacol.* **1985**, *34*, 151.
(22) Anden, N.-E.; Strombom, U.; Svensson, T. H. *Psychopharmacology (Berlin)* **1973**, *29*, 289.
(23) Wikstrom, H.; Sundell, S.; Lundmark, M. *Acta Pharm. Suec.* **1985**, *22*, 75.
(24) McDermed, J.; Freeman, H.; Ferris, R. *Catecholamines: Basic and Clinical Frontiers*; Usdin, E., Kopin, I., Barchas, J., Eds.; Pergamon: New York, 1979; p 568.
(25) Wise, L. D.; Butler, D. E.; DeWald, H. A.; Lustgarten, D.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. *J. Med. Chem.* **1986**, *29*, 1628.

spectively, into a single moiety, tetrahydropropylbenzopyranoxazinol **16**, and retain DA autoreceptor against activity.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and were uncorrected. The IR spectra were obtained on a Nicolet MX-1 FT spectrometer as KBr pellets or liquid film (LF). The proton NMR spectra were obtained on an IBM WP100SY NMR spectrometer (100 MHz) or a Varian XL200 NMR spectrometer (200 MHz). The peaks are described in ppm downfield from TMS (internal standard). The mass spectra were recorded on a Finnigan 4500 mass spectrometer or a VG Analytical 7070E/HF mass spectrometer; the spectra are described by the molecular peak (M) and its relative intensity as well as the base peak (100%). Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. Starting materials were obtained from Aldrich Chemial Co. and were used without purification. Chiral HPLC was performed on a LKB Enantiopac 100 mm × 4.0 mm i.d. column with 0.08 M NaH_2PO_4, 0.1 M NaCl, pH adjusted to 7.00 with NaOH/2-propanol (95:5).

4-Methoxyphenyl 2-Cyanoethyl Ether (5). A solution of 62 g (0.5 mol) of 4-methoxyphenol (**4**), 4 mL of Triton B, and 180 mL of acrylonitrile was refluxed for 20 h under nitrogen. The mixture was cooled to room temperature, diluted with 1 L of ether, and washed successively with 2 N sodium hydroxide, dilute hydrochloric acid, and water. The organic extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo to yield 80.0 g (90%) of an oil, which subsequently solidified. A sample was recrystallized from ether to give colorless needles, mp 63–66 °C. Anal. ($C_{10}H_{11}NO_2$) C, H, N. NMR ($CDCl_3$): δ 2.80 (2 H, t, J = 7 Hz), 3.80 (3 H, s), 4.20 (2 H, t, J = 7 Hz), 6.90 (4 H, s). MS: 177 (M, 70), 123 (100).

3-(4-Methoxyphenoxy)propionic Acid (6). A mixture of 65 g (0.37 mol) of **5** and 140 mL of concentrated hydrochloric acid was refluxed for 6 h. The solid was collected, washed well with water, and taken up into 400 mL of 1 N sodium hydroxide. The insolubles were removed by filtration; the filtrate was acidified with concentrated hydrochloric acid. The solid was collected, washed with water, and dried to afford 38.0 g (65%) of **6**, mp 110 °C. Anal. ($C_{10}H_{12}O_4$) C, H. NMR ($CDCl_3$): δ 2.80 (2 H, t, J = 7 Hz), 3.80 (3 H, s), 4.20 (2 H, t, J = 7 Hz), 6.85 (4 H, br s). MS: 196 (M, 70), 124 (100).

6-Methoxy-2*H*-1-benzopyran-4-one (7).[11] To a solution of 67.0 g (0.34 mol) of **6** in 350 mL of toluene was added 60 mL of thionyl chloride. The solution was refluxed for 1.5 h and evaporated in vacuo. The residue was dissolved in 350 mL of chloroform, cooled to −65 °C, and treated dropwise with 51.0 g (0.34 mol) of trifluoromethanesulfonic acid. The cold bath was removed, and the mixture was allowed to equilibrate to room temperature. Water was added; the layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution. The organic extracts were dried over magnesium sulfate and evaporated to yield 56.0 g (93%) of **7** as an oil. An analytical sample of **7** was obtained by medium-pressure liquid chromatography (silica gel; hexane/ethyl acetate, 1:1) as an oil. Anal. ($C_{10}H_{10}O_3$) C, H. NMR ($CDCl_3$): δ 2.80 (2 H, t, J = 6 Hz), 3.80 (3 H, s), 4.50 (2 H, t, J = 6 Hz), 6.90 (1 H, d, J = 7.5 Hz), 7.10 (1 H, dd, J = 7.5 Hz, 2.5 Hz), 7.30 (1 H, d, J = 2.5 Hz). IR (LF): 1690 cm^{-1} (C=O). MS: 178 (M, 100).

3-Bromo-6-methoxy-2*H*-1-benzopyran-4-one (8). To a suspension of 25.0 g (0.11 mol) of cupric bromide in 125 mL of ethyl acetate was added at a fast drop rate a solution of 16.0 g (0.09 mol) of **7** in 125 mL of chloroform under nitrogen. The resulting mixture was refluxed for 1.5 h. The mixture was filtered through Celite; the filtrate was evaporated in vacuo to yield 20.5 g (89%) of a brown solid. Recrystallization of a sample from ether/petroleum ether afforded an analytical sample, mp 88–89 °C. Anal. ($C_{10}H_9BrO_3$) C, H. NMR ($CDCl_3$): δ 3.80 (3 H, s), 4.60–4.80 (3 H, m), 6.90–7.50 (3 H, m). MS: 256/258 (M, 40), 150 (100).

3-Amino-6-methoxy-4*H*-1-benzopyran-4-one (9).[12] To 5.2 g (0.02 mol) of **8** in 25 mL of DMF was added 1.8 g (0.027 mol) of sodium azide under nitrogen. The reaction temperature spontaneously rose to 45 °C. After the mixture was stirred for 2 h at 40–50 °C, it was poured into 300 mL of water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 3.5 (92%) of solid. A sample was recrystallized from ethyl acetate/petroleum ether, mp 98–100 °C. Anal. ($C_{10}H_9NO_3$) C, H, N. NMR ($CDCl_3$): δ 3.20 (2 H, br, NH_2), 3.90 (3 H, s), 7.15–7.45 (2 H, m), 7.60 (1 H, d, J = 2.5 Hz), 7.80 (1 H, s). IR (KBr): 1618 cm^{-1} (C=O). MS: 191 (M, 100).

***N*-(6-Methoxy-4-oxo-4*H*-1-benzopyran-3-yl)propionamide (10).** To a solution of 8.50 g (0.044 mol) of **9** and 8.0 mL of triethylamine in 150 mL of methylene chloride was added dropwise 5.0 g (0.05 mol) of propionyl chloride. The resulting mixture was stirred at room temperature for 20 h. A saturated sodium bicarbonate solution was added. The layers were separated, and the organic extract was dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was recrystallized from ether/petroleum ether. There were collected 6.8 g (68%) of **10**, mp 196–198 °C. Anal. ($C_{13}H_{13}NO_4$) C, H, N. NMR ($CDCl_3$): δ 1.25 (3 H, t, J = 7.5 Hz), 2.49 (2 H, q, J = 7.5 Hz), 3.90 (3 H, s), 7.29 (1 H, dd, J = 9 Hz, 3 Hz), 7.44 (1 H, d, J = 9 Hz), 7.55 (1 H, d, J = 3 Hz), 8.09 (1 H, br, NH), 9.41 (1 H, s). IR (KBr): 1606 cm^{-1} (C=O), 1681 cm^{-1} (C=O). MS: 247 (M, 30), 191 (100).

(±)-*trans*-*N*-(4-Hydroxy-6-methoxy-1-benzopyran-3-yl)-propionamide (11). To a solution fo 14.5 g (0.059 mol) of **10** in 600 mL of ethanol was added 24.0 g (0.6 mol) of sodium borohydride in small portions. The mixture was stirred for 20 h and concentrated in vacuo. The residue was taken up in 500 mL of dichloromethane and washed with 1 N sodium hydroxide. The organic extracts were dried over anhydrous magnesium sulfate and evaporated to yield 13.5 g (90%) of **11**, mp 150–155 °C. Anal. ($C_{13}H_{17}NO_4$) C, H, N. NMR ($CDCl_3$): δ 1.10 (3 H, t, J = 7.5 Hz), 2.16 (2 H, q, J = 7.5 Hz), 3.77 (3 H, s), 4.10–4.13 (1 H, m), 4.24–4.38 (2 H, m), 4.54 (1 H, br s), 5.84 (1 H, d, J = 7 Hz), 6.80–6.90 (3 H, m). MS: 251 (M, 6), 178 (100).

(±)-*trans*-3-(Propylamino)-6-methoxy-1-benzopyran-4-ol (12a). A solution of 12.0 g (0.05 mol) of **11** in 200 mL of THF was treated under nitrogen in small portions with 6.0 g (0.15 mol) of sodium borohydride followed by dropwise addition of 21.0 g (0.15 mol) of boron trifluoride etherate. The resulting mixture was stirred for 18 h at room temperature. Acetic acid (10 mL) was added cautiously, and the mixture was stirred for an additional 0.5 h. The mixture was diluted with 100 mL of dichloromethane and 100 mL of 3 N sodium hydroxide. The layers were separated, and the organic extracts were dried over magnesium sulfate. The solvent was evaporated, and the residue was treated with isopropanolic hydrogen chloride. There was deposited 4.9 g (71%) of **12a**, mp 175 °C. Anal. ($C_{13}H_{19}NO_3$·HCl) C, H, N. NMR ($CDCl_3$): δ 0.92 (3 H, t, J = 7.5 Hz), 1.50 (2 H, m), 2.70 (2 H, m), 3.80 (3 H, s), 4.00 (1 H, dd, J = 11.3 Hz, 4.6 Hz), 4.2–4.6 (3 H, m), 6.7–6.9 (3 H, m). MS: 237 (M, 30), 85 (100).

Resolution of 12a. (−)-(3*R*,4*R*)-3-(Propylamino)-6-methoxy-1-benzopyran-4-ol (12b). A solution of 1.7 g (70 mmol) of **12a** (free base) in 5 mL of absolute ethanol was treated with 1 g (70 mmol) of (*S*)-(+)-mandelic acid in 7 mL of absolute ethanol. Ether was added until the solution begain to turn turbid (ca. 30 mL). The solution was allowed to stand 18 h at room temperature. The resulting solid was collected and recrystallized from ethanol/ether. There was obtained 1.05 g of salt, mp 157–160 °C. Treatment of the salt with 1 N sodium hydroxide regenerated the free base which was in turn converted to the hydrochloride salt. There was obtained 0.54 g of white crystalline **12b**, mp 203–205 °C. Anal. ($C_{13}H_{19}NO_3$·HCl) C, H, N, Cl. [α] = −79.9° (c = 2.06, H_2O). NMR (DMSO): δ 0.92 (3 H, t, J = 7.5 Hz), 1.64–1.77 (2 H, m), 3.00–3.07 (2 H, m, becomes dd after D_2O wash, J = 10 Hz, 6.5 Hz), 3.45 (1 H, br s), 3.72 (3 H, s), 4.30–4.32 (2 H, m), 4.88 (1 H, t, $J \simeq$ 5.3 Hz; becomes doublet after D_2O wash, J = 4.7 Hz), 6.27 (1 H, d, J = 6 Hz; disappears after D_2O wash, O*H*), 6.77–6.88 (2 H, m), 6.97 (1 H, d, J = 2.5 Hz). MS: 237 (M, 10), 56 (100).

Resolution of 12a. (+)-(3*S*,4*S*)-3-(propylamino)-6-methoxy-1-benzopyran-4-ol (12c). The combined filtrates from the resolution of **12b** were recovered and worked up as described for **12b** to yield 0.87 g of a mixture of **12b** and **12c**. This material was treated with 0.50 g (3.0 mmol) of (*R*)-(−)-mandelic acid in 6 mL of absolute ethanol as described for **12b**. There was obtained

1.0 g of salt, mp 154–157 °C. The free base was regenerated and converted to the hydrochloride salt. There was deposited 0.45 g of **12c** as white crystals, mp 203–205 °C. Anal. ($C_{13}H_{19}NO_3$·HCl) C, H, N, Cl. [α] = +79.9° (c = 2.07, H_2O). Spectral data for **12c** were identical with those described above for **12b**.

(±)-*trans*-3,4,4a,10b-Tetrahydro-9-methoxy-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-3-one (14a). To a mixture of 5.0 g (0.02 mol) of **12a** (hydrochloride) in 200 mL of dichloromethane and 5.0 g (0.125 mol) of sodium hydroxide in 40 mL of water was added dropwise 4.0 g (10.0 mol) of chloroacetyl chloride with stirring. After the mixture was stirred for an additional 2 h at room temperature, it was diluted with 100 mL of water. The layers were separated, and the organic layer was dried over magnesium sulfate. The solvent was evaporated, and residue was crystallized from ether. There was deposited 6.0 g (90%) of **13a**, mp 116–118 °C. Anal. ($C_{15}H_{20}ClNO_4$) C, H, N.

To a solution of 5.50 g (17.5 mmol) of **13a** in 200 mL of 2-propanol was added dropwise a solution of 1.0 g (17.8 mmol) of potassium hydroxide in 2 mL of water. The mixture was stirred at room temperature of 2 h and treated with 5 mL of 20% isopropranolic hydrogen chloride. The solvent was evaporated in vacuo. The residue was taken up in dichloromethane and washed with water and saturated sodium bicarbonate. The organic extracts were dried over anhydrous magnesium sulfate and evaporated to afford 4.8 g (93%) of **14a**. A sample was recrystallized from ethyl acetate/ether, mp 123–125 °C. Anal. ($C_{15}H_{19}NO_4$) C, H, N. All spectra data for **14a** were identical with those reported below for **14b**.

(−)-(4a*R*,10b*R*)-3,4,4a,10b-Tetrahydro-9-methoxy-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-3-one (14b). The procedure described above for the preparation of **14a** was followed for the transformation of **12b** into **14b**, mp 141–142 °C. Anal. ($C_{15}H_{19}NO_4$) C, H, N. [α] = −24.6° (c = 1.23, MeOH). NMR ($CDCl_3$): δ 0.95 (3 H, t, J = 7.4 Hz), 1.40–1.80 (2 H, m), 3.11–3.16 (1 H, m), 3.78 (3 H, s), 3.72–3.93 (2 H, m), 4.01 (1 H, t, J ≃ 10.5 Hz), 4.41–4.60 (3 H, m), 4.75 (1 H, d, J = 9 Hz), 6.75–6.85 (2 H, m), 6.95 (1 H, br s). IR (KBr): 1671 cm^{-1}. MS: 277 (M, 100).

(+)-(4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-9-methoxy-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-b]-1,4-oxazin-3-one (14c). The procedure described above for the preparation of **14a** was followed for the conversion of **12c** to **14c**, mp 140–141.5 °C. Anal. ($C_{15}H_{19}NO_4$) C, H, N. [α] = +25.8° (c = 1.39, MeOH). All spectral data for **14c** were identical with those described above for **14b**.

(±)-*trans*-3,4,4a,10b-Tetrahydro-9-methoxy-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazine (15a). To a solution of 3.0 g (0.01 mol) of **14a** in 75 mL of THF a 5–10 °C was added under nitrogen 1.6 g (0.04 mol) of sodium borohydride followed by dropwise addition of 5.6 g (0.04 mol) of boron trifluoride etherate. The reaction mixture was stirred for 18 h at room temperature. The mixture was treated with 5 mL of acetic acid and stirred with 75 mL of 3 N sodium hydroxide for 0.5 h. The product was extracted into dichloromethane; the organic extracts were dried over anhydrous magnesium sulfate and evaporated to yield 2.5 g (87%) of **15a**. A sample was treated with hydrogen chloride in 2-propanol to form the hydrochloride salt, mp 250–255 °C. Anal. ($C_{15}H_{21}NO_3$·HCl·0.5H_2O) C, H, N. All spectral data for **15a** were identical with those described below for **15c**.

(+)-(4a*R*,10b*R*)-3,4,4a,10b-Tetrahydro-9-methoxy-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazine (15b). The procedure described above for the synthesis of **15a** was followed for the synthesis of **15b** from **14b**, a sample of which was characterized as the HCl salt, mp 251–252 °C. Anal. ($C_{15}H_{21}NO_3$·HCl) C, H, N, Cl. [α] = +56.9° (c = 1.24, MeOH). The (−)-isomer **14b** gives the (+)-isomer **15b**. All spectral data for **15b** were identical with those described below for **15c**.

(−)-(4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-9-methoxy-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazine (15c). The procedure described above for the preparation of **15a** was followed for the synthesis of **15c** from **14c**; a sample of which was characterized as the HCl salt, mp 250–252 °C. Anal. ($C_{15}H_{21}NO_3$·HCl) C, H, N; Cl; calcd, 11.65; found, 12.20. [α] = −62.1° (c = 1.20, MeOH). NMR (DMSO): δ 0.94 (3 H, t, J = 7.3 Hz), 1.60–1.85 (2 H, m), 3.00 (1 H, br), 3.10–3.45 (3 H, m, includes NH), 3.45–3.75 (2 H, m), 3.70 (3 H, s), 4.20–4.31 (3 H, m), 4.84 (1 H, dd, J = 11 Hz, 3.4 Hz), 5.21 (1 H, d, J = 9.1 Hz), 6.79–6.87 (3 H, m). MS: 263 (M, 50), 161 (100).

(±)-*trans*-3,4,4a,10b-Tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (16a). To a solution of 4.0 g (0.015 mol) of **15a** in 300 mL of dichloromethane under nitrogen was added dropwise 8.0 g (0.03 mol) of boron tribromide at 5 °C. The resulting mixture was stirred at 0 °C for 1 h and at room temperature of an additional 3 h. The mixture was cooled in an ice bath and treated with 80 mL of 6 N sodium hydroxide. The layers were separated; the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was taken up in 70 mL of 1 N sodium hydroxide, treated with DARCO, and filtered. The filtrate was acidified to pH 6.5 with concentrated hydrochloric acid, adjusted to pH 9 with concentrated ammonium hydroxide, and extracted with dichloromethane. The organic extracts were evaporated, and the residue was treated with 2-propanolic hydrogen chloride. There was deposited 0.23 g of **16a**, mp 225–230 °C. Anal. ($C_{14}H_{19}NO_3$·HCl·0.5H_2O) C, H, N. The spectral data for **16a** were identical with those described below for **16c**.

(+)-(4a*R*,10b*R*)-3,4,4a,10b-Tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (16b). A solution of **15b** (5.1 g, 19.3 mmol) in 175 mL of 48% hydrobromic acid was refluxed, under a nitrogen atmosphere, for exactly 30 min. After the reaction flask was cooled in an ice water bath, the mixture was diluted with 200 mL of water and treated with small portions of concentrated ammonium hydroxide until basic. Following extraction with dichloromethane (3 × 250 mL), the organic phase was washed with water and dried over magnesium sulfate. Following filtration of the drying agent, 20 mL of ethereal hydrogen chloride was added to the solution. The solvent was evaporated in vacuo, leaving a dark solid (5.5 g, 100%), which was recrystallized from absolute ethanol to yield an off-white solid, mp 265–271 °C dec. Anal. ($C_{14}H_{19}NO_3$·HCl) C, H, N. [α] = +62.7° (c = 1.07, H_2O). All spectral data for this compound were identical with those described below for **16c**.

(−)-(4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (16c). The procedure described above for the synthesis of **16b** was followed for the synthesis of **16c**, mp 259–264 °C dec. Anal. ($C_{14}H_{19}NO_3$·HCl) C, H, N, Cl. [α] = −63.0 °C (c = 1.11, H_2O). NMR (DMSO): δ 0.94 (3 H, t, J = 7.4 Hz), 1.60–1.83 (2 H, m), 2.90–3.10 (1 H, br), 3.10–3.75 (5 H, m, includes NH), 4.12–4.23 (3 H, m), 4.79 (1 H, dd, J = 11 Hz, 3.5 Hz), 5.10 (1 H, d, J = 9.9 Hz), 6.61–6.76 (3 H, m), 11.90 (1 H, br O*H*). MS: 249 (M, 50), 147 (100).

Pharmacological Methods. Dopamine Receptor Binding Assays. The affinities of compounds for rat brain striatal DA D_2 receptors labeled with [^{3}H]haloperidol and [^{3}H]NPA were measured by the methods described by Burt et al.[14] and Seeman et al.,[21] respectively.

Effects on Dopamine Synthesis.[15] Tests compounds were administered to male Long-Evans rats (Blue Spruce Farms, Altamont, NY) 30 min prior to injection of GBL (750 mg/kg ip) and the dopa decarboxylase inhibitor NSD 1015 (100 mg/kg ip), and after 30 min the animals were sacrificed. Striatal DOPA levels were measured by HPLC electrochemical detection.[26] Data are expressed as percentage reversal of DA synthesis (as indicated by DOPA levles) relative to GBL/NSD 1015 treated animals (vehicle and GBL control levels of DOPA: 0.76 ± 0.06 and 2.01 ± 0.10 μg/g ± SEM, respectively); N = 4–5.

Effects on Firing Rate of Substantia Nigra Dopamine Neurons.[16] The firing rates of zona compacta DA cells were recorded in chloral hydrate anesthetized rats. DA cells were identified by waveform and firing pattern. The recording site was verified by histology. Drugs were administered ip via an indwelling catheter. Base-line firing rate was calculated by averaging the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal inhibition; N = 3–4 cells.

Inhibition of spontaneous locomotor activity[17] was carried out according to the methods described in a previous paper.[25]

(26) Pugsley, T. A.; Myers, S. M.; Shih, Y. H. *J. Cardiovasc. Pharmacol.* In press.
(27) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlson, A.; Wilkstrom, H.; Lindgerg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469.

Effects on Spontaneous Locomotion in Reserpine-Treated Rats.[22] Drugs were administered sc to rats treated with 5 mg/kg of reserpine 24 h prior to testing. The effect on locomotor activity was measured immediately after as described above.

Registry No. **5**, 63815-39-4; **6**, 20811-60-3; **7**, 5802-17-5; **8**, 66125-08-4; **9**, 67064-55-5; **10**, 123594-58-1; **11**, 123594-59-2; **12a**, 123594-60-5; **12a**·HCl, 123621-20-5; **12b**, 123671-94-3; **12b**·(*S*)-PhCH(OH)CO_2H, 123671-95-4; **12b**·HCl, 123671-96-5; **12c**, 123805-43-6; **12c**·(*R*)-PhCH(OH)CO_2H, 123877-16-7; **12c**·HCl, 123877-17-8; **13a**, 123594-61-6; **14a**, 123594-62-7; **14b**, 123671-97-6; **14c**, 123671-98-7; **15a**, 123594-63-8; **15a**·HCl, 123594-65-0; **15b**, 123748-66-3; **15b**·HCl, 123671-99-8; **15c**, 123748-67-4; **15c**·HCl, 123672-00-4; **16a**, 123594-64-9; **16b**, 123671-92-1; **16c**, 123671-93-2; H_2C=CHCN, 107-13-1; *p*-$MeOC_6H_4OH$, 150-76-5.

Supplementary Material Available: Tables listing fractional atomic coordinates and temperature factor parameters, bond lengths and angles, hydrogen bonding parameters, and general displacement parameter expressions (13 pages); a table of observed and calculated structure amplitudes (12 pages). Ordering information is given on any current masthead page.

Cholecystokinin-A Receptor Ligands Based on the κ-Opioid Agonist Tifluadom

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Tifluadom, a κ-opioid agonist and cholecystokinin-A (CCK-A) receptor antagonist, was utilized as a model to prepare a series of 2-(aminomethyl)- and 3-(aminomethyl)-1,4-benzodiazepines. These compounds were tested in vitro as inhibitors of the binding of [^{125}I]CCK to rat pancreas and guinea pig brain receptors. All compounds with IC_{50}'s less than 100 μM proved to have greater affinity for the CCK-A receptor, with the most potent analogue, **6e**, having an IC_{50} of 0.16 μM. The benzodiazepines described in this study are simultaneously CCK-A and opioid receptor ligands. The ramification of this dichotomy on current concepts of peptide hormone action are discussed. These results further demonstrate the versatility of the benzodiazepine core structure for designing nonpeptide ligands for peptide receptors and the ability to fine-tune the receptor interactions of these benzodiazepines by appropriate structure modifications.

The elucidation of the physiologic role of the gastrointestinal hormone cholecystokinin (CCK) has been pursued in recent years with increased vigor. This mounting interest derives, in part, from the present availability of several nonpeptidal antagonists, some of which bind to the CCK receptor as avidly as the natural ligand CCK-8.[1-5] Among these, the prototypical agent is the highly selective and orally effective CCK-A antagonist (3*S*)-(−)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide, **1** (MK-329, formerly L-364,718)[6] (Chart I).

The reasoning which formed the basis of the design process which led to the potent CCK-A antagonist MK-329 (**1**) was predicated on the benzodiazepine ring in the natural product CCK antagonist asperlicin and its role as a structural mimic for fragments of the CCK peptide chain.[1] In the incipient phase of the development of **1**, it was recognized that the benzodiazepine core structure was the key feature which linked asperlicin with 1,4-benzodiazepine progenitors of **1**. Prudence thus dictated that analogous ring systems be examined for CCK receptor binding affinity.[3,7,8] Indeed, after completion of these studies, several reports appeared which demonstrated that a number of anxiolytic 1,4-benzodiazepines (e.g. diazepam, lorazepam, chlordiazepoxide) antagonize the effects of CCK both in the periphery[9-11] and in the central nervous system.[12,13] However, the observed effects are weak. The benzodiazepine κ-opioid agonist tifluadom (**2**, Chart I) was assayed in these laboratories and determined to be a moderately potent, CCK-A-selective receptor antagonist.[14] This finding prompted the preparation of analogues of tifluadom in an attempt to gain insight into the structural prerequisites necessary for CCK receptor binding affinity and selectivity. Herein we detail this study, which includes the synthesis and pharmacological evaluation of the series of (2-aminoethyl)- and 3-(aminomethyl)-1,4-benzodiazepines, the physiochemical properties of which are summarized in Tables I and II, derived from the tifluadom core structure.

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(1) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918.
(2) Makovec, F.; Chiste, R.; Bani, M.; Revel, L.; Setnikar, I.; Rovati, A. L. *Eur. J. Med. Chem.* **1986**, *21*, 9.
(3) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M.; Chang, R. S. L.; Lotti, V. J. *J. Med. Chem.* **1988**, *31*, 176.
(4) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235.
(5) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1989**, *32*, 13.
(6) Chang, R. S. L.; Lotti, V. J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4923.
(7) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Freidinger, R. M.; Chang, R. S. L.; Lotti, V. J. *J. Med. Chem.* **1988**, *31*, 264.
(8) Parsons, W. H.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Holloway, M. K.; Smith, G. M.; Davidson, J. L. *J. Med. Chem.* **1989**, *32*, 1681.
(9) Kubota, K.; Sugaya, K.; Sunagane, N.; Matsuda, I.; Uruno, T. *Eur. J. Pharmacol.* **1985**, *110*, 225.
(10) Kubota, K.; Sugaya, K.; Matsuda, I.; Matsuoka, Y.; Terawaki, Y. *Jpn. J. Pharmacol.* **1985**, *37*, 101.
(11) Meldrum, L. A.; Bojarski, J. D.; Calam, J. *Eur. J. Pharmacol.* **1986**, *123*, 427.
(12) Bradwejn, J.; deMontigny, C. *Nature (London)* **1984**, *312*, 363.
(13) Bradwejn, J.; deMontigny, C. *Ann. N.Y. Acad. Sci.* **1985**, *448*, 575.
(14) Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Keegan, M. E. *Neurosci. Lett.* **1986**, *72*, 211.

0022-2623/90/1833-0450$02.50/0