ethanol alone, using 20–40 mice at each dose level. In the interaction experiments, 7c or diazepam was administered at several dose levels 30 min before administration of a threshold dose of ethanol (ED_5 = 5.6 g/kg; based on dose–response experiment). Immediately after ethanol administration, each mouse was placed in an individual cage on a rack, without food or water, and periodically evaluated for loss of righting reflex by attempting to place them on their backs. Mice that remained on their backs for 10 min or more were counted as positive for loss of righting reflex. A computer program was used to calculate effective dose (ED) levels with 95% confidence limits. In the interaction experiments, the ED_{50} represents the dose of test compound calculated to produce loss of righting reflex in half the mice when treated with an ED_5 dose of ethanol.

Acknowledgment. We thank the following members of our Physical Chemistry Department: Dr. F. Scheidl for elemental analysis, Dr. T. Williams for NMR spectra, Dr. W. Benz for mass spectra, and S. Traiman for IR spectra. We also especially thank W. May for technical assistance.

Registry No. 1a, 58582-22-2; 1b, 58583-07-6; 1c, 76049-20-2; 1d, 76049-73-5; 2b, 76049-76-8; 2c, 76049-78-0; 3a, 58582-16-4; 3b, 58582-30-2; 3c, 58582-31-3; 3d, 58582-72-2; 4b, 76049-79-1; 4c, 76049-80-4; 7b, 76988-59-5; 7c, 76988-39-1; 8b, 76988-60-8; 8c, 76988-65-3; 9a, 76988-24-4; 9b, 76988-25-5; 9c, 86712-00-7; 9d, 76988-45-9; 10, 76988-46-0; 11, 76988-40-4; 12, 76988-52-8; 13, 76988-50-6; 13 methanesulfonate, 86712-01-8; 14, 76988-72-2; 15a, 86712-02-9; 15b, 76988-22-2; 15c, 76988-41-5; 15d, 76988-37-9; 16, 76988-62-0; 17, 76988-53-9; 18, 76988-54-0; 19, 76988-58-4; 20, 76988-55-1; 21, 76988-56-2; 22, 76988-57-3; 23, 86712-03-0; 24, 86712-04-1; 25, 86712-05-2; 26, 86712-06-3; 27, 76988-47-1; 28, 76988-73-3; 29, 77000-35-2; 30, 77000-37-4; 31, 77000-36-3; $Me_2NCH(OMe)_2$, 4637-24-5; formamidine acetate, 64392-62-7; acetamidine hydrochloride, 124-42-5; isobutyramidine, 57536-10-4; thiourea, 62-56-6; guanidine, 113-00-8.

2-Benzazepines. 6.[1,2] Synthesis and Pharmacological Properties of the Metabolites of 9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine

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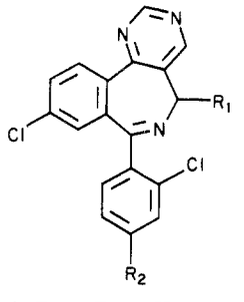
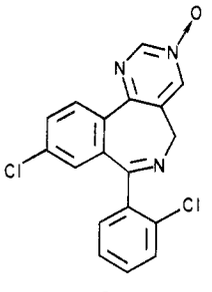
Research and Development Division, Hoffman-La Roche Inc., Nutley, New Jersey 07110. *Received February 17, 1983*

The 2-benzazepine 9-chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (1) has been selected for development as an anxiolytic agent. In support of this program, we have confirmed by chemical synthesis the structures of three in vitro (rat liver homogenate) metabolites of 1 and confirmed the structure of the major in vivo (dog and man) metabolite of 1, compound 2. Two of the metabolites, arising from hydroxylation of the pyrimidobenzazepine ring at the 5-position (2) and *N*-oxide formation at the 3-position of the pyrimidobenzazepine ring (3), were found to be as active as 1 in a series of pharmacological tests. The third metabolite, formed by hydroxylation of the 7-phenyl group in the 4-position (4), was found to be inactive in the same pharmacological screens.

The synthesis and biological activity of a series of pyrimido[5,4-*d*][2]benzazepine analogues was described in the preceding paper.[2] From this series of compounds, the dichloro derivative 1 was selected for further evaluation



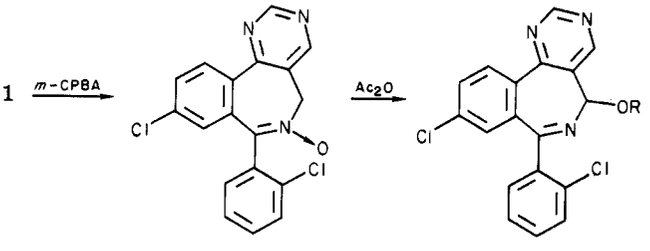
1, $R_1 = R_2 = H$
2, R_1 = OH; $R_2 = H$
4, $R_1 = H$; R_2 = OH



3

as an anxiolytic agent. The metabolism of 1 was studied[3] in vitro by using rat liver homogenate and resulted in the isolation of three metabolites. The structures of the metabolites were tentatively assigned formulas 2–4 on the basis of spectral data. The major in vivo metabolite of 1 in dogs and man was found to be compound 2, and the quantitative plasma levels of 1 and 2 in dogs (20-mg/kg dose) and man (5-mg/kg dose) have been described.[4] This report describes the syntheses of these compounds, confirming the assigned structures. The pharmacology of compounds 1–4 is also discussed.

Scheme I



5

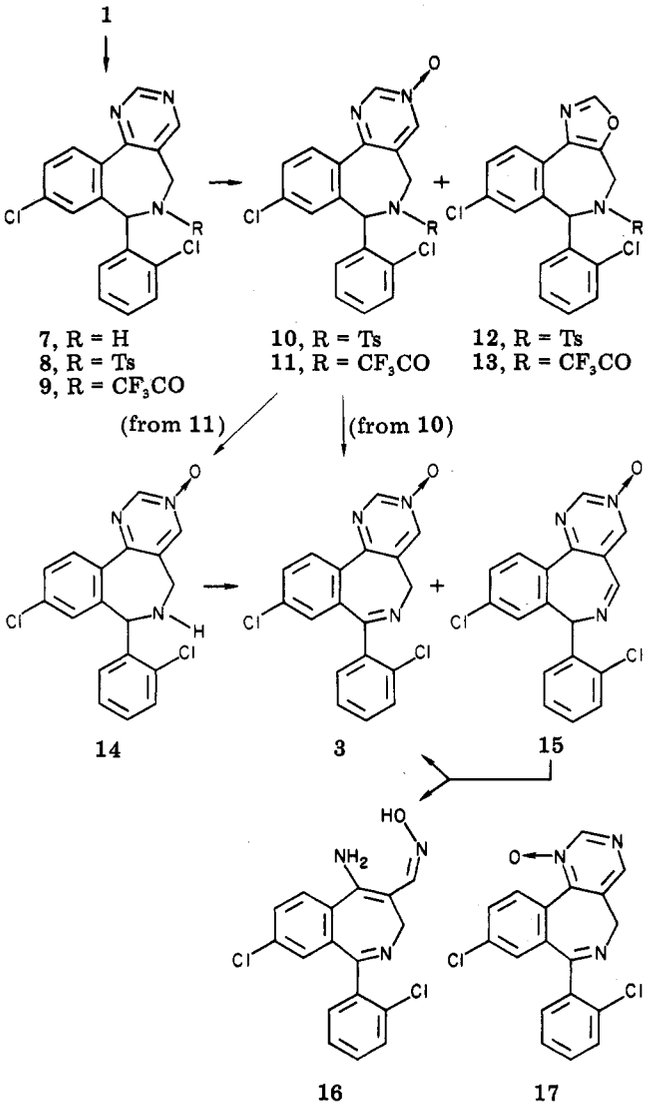
6, R = Ac
2, R = H

Chemistry. The initial structure assignments of the metabolites 2–4 were based on NMR and mass spectral data. The mass spectrum of metabolite A (compound 2) showed a molecular ion [*m/e* 355 (M^+)] that is 16 mass units greater than the molecular ion of compound 1 [*m/e* 339 (M^+)], indicating that an oxygen atom had been introduced in the metabolism of 1. The NMR spectrum of metabolite A showed the absence of the C-5 methylene protons (δ 4.51) of 1 and the appearance of a methine proton (δ 5.48). The mass spectrum of metabolite B (compound 3) showed a weak molecular ion [*m/e* 355 (M^+)] and a fragmentation pattern similar to compound

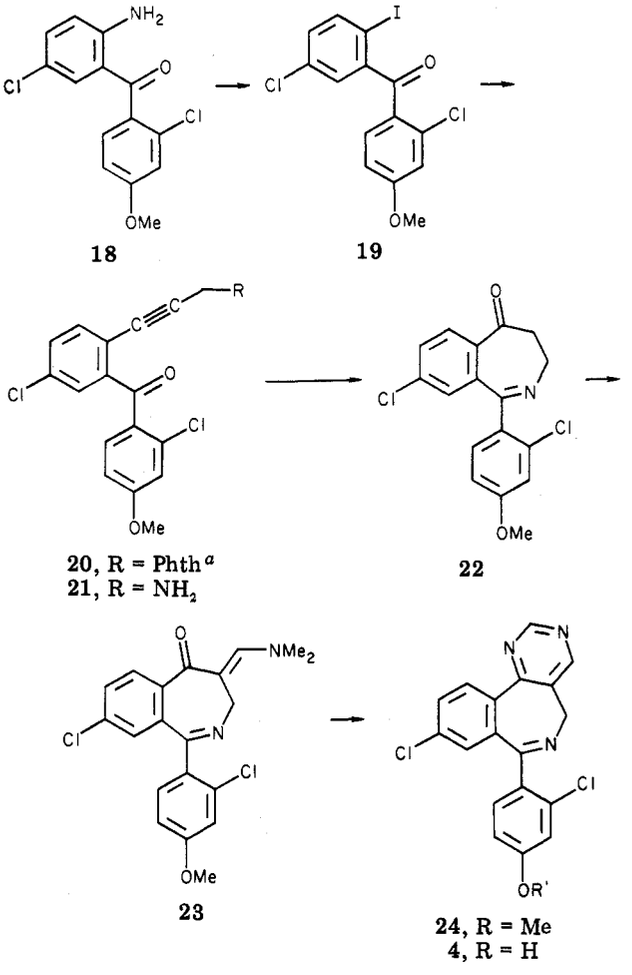
(1) Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.
(2) For paper 5 of this series, see Trybulski, E. J.; Benjamin, L. E.; Earley, J.; Fryer, R. I.; Gilman, N.; Reeder, E.; Walser, A.; Davidson, A. B.; Horst, W. D.; Sepinwall, J.; O'Brien, R.; Dairman, W. *J. Med. Chem.*, preceeding paper in this issue.
(3) The in vitro metabolism studies were performed under the direction of Dr. M. Schwartz, and the dog in vivo metabolism studies were conducted by Dr. F. Leinweber, both from our Department of Biochemistry and Drug Metabolism.
(4) Puglisi, C. V.; Ferrara, F. J.; de Silva, J. A. F. *J. Chromatogr. Biomed. Appl.*, in press.

0022-2623/83/1826-1596$01.50/0

Scheme II



Scheme III



[a] Phth = phthalimido.

1, which was suggestive of an *N*-oxide-type structure. The mass spectrum of metabolite C (compound **4**) showed a molecular ion [*m/e* 355 (M^+)] indicating the incorporation of an oxygen atom in the metabolism of compound **1**. The phenyl region in the NMR spectrum of metabolite C was suggestive of a phenolic group. Comparison of the NMR spectrum of metabolite C with the NMR spectrum of similar phenolic benzodiazepine metabolites[5] led to the tentative assignment of structure **4** to metabolite C.

The synthesis of the major in vivo and in vitro metabolite[4] of **1**, compound **2**, was readily accomplished with a Polonovski-type rearrangement[6] to introduce the oxygen atom at the 5-position (Scheme I). Oxidation of **1** with *m*-chloroperbenzoic acid gave preferentially the 6-*N*-oxide **5** without concomitant oxidation of the pyrimidine ring. Reaction of **5** with acetic anhydride at 100 °C led to the acetate **6**. Hydrolysis of **6** with 3 N sodium hydroxide gave **2**.

The selective oxidation of the 3-position nitrogen atom in the pyrimidobenzazepine **1** to produce metabolite **3** required the initial protection of the more readily oxidized imine nitrogen atom. Reaction of **1** with zinc and acetic acid in methylene chloride at −40 °C gave the amino compound **7** (Scheme II), which was subsequently derivatized with either tosyl chloride or trifluoroacetic anhydride to give the corresponding sulfonamide **8** or the trifluoroacetamide **9**. Oxidation of the pyrimidine ring in **8** (or **9**) with *m*-chloroperbenzoic acid gave a mixture of two products, the 3-*N*-oxide **10** (or **11**) and the oxazole **12** (or **13**). The metabolite **3** and only a trace of the double-bond isomer **15** was formed by treatment of **10** with sodium methoxide in methanol.

In a more circuitous manner, metabolite **3** was prepared from the trifluoroacetamide **11**. Hydrolysis of the trifluoroacetamido group with aqueous sodium hydroxide gave the secondary amino compound **14**, which when treated with bromine in methylene chloride buffered with aqueous potassium acetate gave almost exclusively **15** and only a trace of **3**. Equilibration of **15** with sodium methoxide in methanol gave **3** as the major product, together with a small amount of the ring-opened compound **16**.

In the synthesis of metabolite **3**, the peracid oxidation of the pyrimidine ring did not establish which of the two pyrimidine nitrogen atoms had been oxidized. Spectroscopically, there was insufficient evidence to distinguish between the two isomeric compounds **3** and **17**. The 3-*N*-oxide structure was confirmed by X-ray analysis as shown in Figure 1.

The structure of the novel oxazolobenzazepine byproduct **12** (and by comparison **13**) was determined by X-ray analysis as shown in Figure 2. The novel transformation of the pyrimidine **8** into the oxazole **12** will be the subject of a separate communication.

(5) Williams, T. H.; Sasso, G. J.; Ryan, J. J.; Schwartz, M. A. *J. Med. Chem.* **1979**, *22*, 436.
(6) Bell, S. C.; Gochman, C.; Childress, S. J. *J. Org. Chem.* **1963**, *28*, 3010.

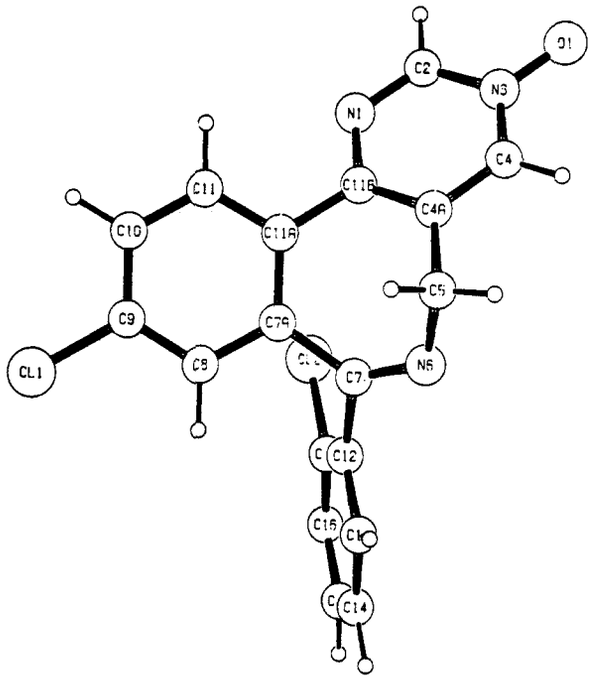


Figure 1. Structure of compound 3 as determined by X-ray analysis.

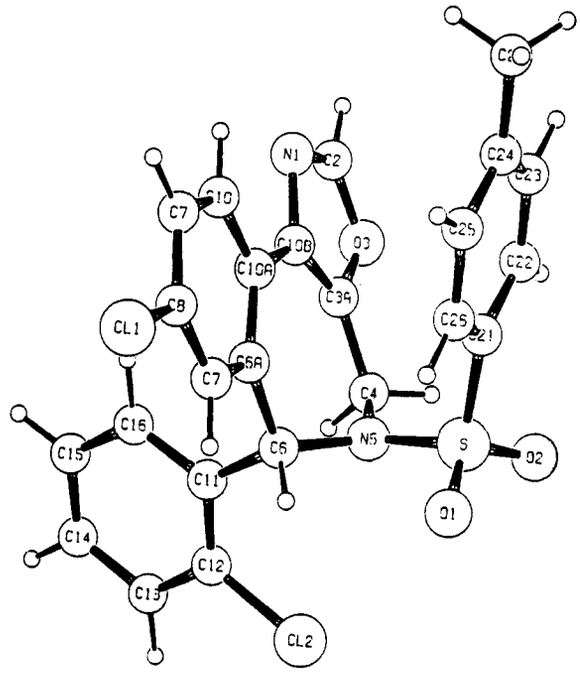


Figure 2. Structure of compound 12 as determined by X-ray analysis.

Metabolite 4 was prepared by utilizing the analogous reaction sequence used to prepare 1[2,8] (Scheme III) starting from the aminobenzophenone 18.[7] Diazotization of 18 with nitrosyl sulfate, followed by treatment of the diazonium salt with aqueous potassium iodide, gave compound 19. The palladium-catalyzed coupling of 19 with propargylphthalimide yielded the phthalimide 20.[7] Treatment of 20 with aqueous methylamine removed the phthaloyl group to give the amine 21. Hydration of the acetylene in 21 with cold concentrated sulfuric acid gave, after basification of the reaction medium, the 2-benzazepinone 22. Reaction of 22 with dimethylformamide dimethyl acetal gave 23, which was condensed with formamidine acetate in formamide to yield the pyrimidobenzazepine 24. Demethylation of the phenolic methyl group in 24 with boron tribromide in methylene chloride gave metabolite 4.

The synthetic compounds 2–4 prepared by the above schemes were compared by TLC, NMR, and mass spectroscopy with samples obtained from the metabolism study and were found to be identical.

Pharmacology. A pharmacological profile of metabolites 2–4 was determined by the [^{3}H]diazepam binding assay,[10] the anti-pentylenetetrazole test,[11] and the rotarod test,[10] and the results are listed in Table I. When compared to compound 1, metabolites 2 and 3 have a similar activity profile, whereas the 4′-hydroxy metabolite 4 was shown to be inactive in the tests. These results suggest

Table I. Pharmacology of 9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]-benzazepine (1) and Its Metabolites

compd	[^{3}H]diazepam binding assay:[a] IC_{50}, nM (rat)	anti-pentylene-tetrazole test:[b,c] ED_{50}, mg/kg (mice)	rotarod test:[c,d] ED_{50}, mg/kg (mice)
1	1.7	0.59	1.4
2	6.4	0.74	4.8
3	1.25	0.65	4.9
4	100	>100	>1000
diazepam	5.4	1.4	2.6

[a] The conditions of Mohler and Okada[10b] were used for this assay procedure. [b] The test was carried out on 50–54-day-old CF-1 male mice by a modification of the method of Everett and Richards.[11] The ED_{50} is calculated as the dose that would prevent convulsions in 50% of the mice tested after administration of 70 mg/kg of metrazole by the iv route. [c] Results are reported as 95% fiducial limits. [d] The conditions of Randall were used in this procedure.[12]

Table II. Summary of Crystal Data for Compounds 3 and 12

	3	12
formula	$C_{18}H_{11}Cl_2N_3O$	$C_{24}H_{18}Cl_2N_2O_3S\cdot CH_3OH$[a]
M_r	356.21	517.43
space group	$C2/c$	$P2_1/c$
a, Å	20.427 (3)	10.033 (3)
b, Å	8.281 (2)	12.512 (3)
c, Å	19.417 (3)	18.921 (4)
β, deg	104.96 (1)	94.04 (2)
z	8	4
d_{calcd}, g cm^{-3}	1.491	1.450 g cm^{-3}
μ(Cu Kα), cm^{-1}	37.7	35.6 cm^{-1}

[a] Reference 14.

(7) Mp 119–120 °C; prepared by reduction of the corresponding anthranil. The anthranil was prepared by adaptation of the method of David, R. B.; Pizzini, L. C. *J. Org. Chem.* **1960**, *25*, 1884.

(8) Trybulski, E. J.; Reeder, E.; Blount, J.; Walser, A.; Fryer, R. I. *J. Org. Chem.* **1982**, *47*, 2441.

(9) For analogous reactions, see (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Edo, K.; Yamanka, H.; Sakamoto, T. *Heterocycles* **1978**, *9*, 271. (c) Yoshihito, A.; Ohsawa, A.; Heihachiro, A.; Igeta, H. *Heterocycles* **1978**, *9*, 1397.

(10) (a) Squires, R. F.; Braestrup, C. *Nature (London)* **1977**, *266*, 732. (b) Mohler, H.; Okada, T. *Life Sci.* **1977**, *20*, 2101.

(11) Everett, G. M.; Richards, R. K. *J. Pharmacol. Exp. Ther.* **1944**, *81*, 402.

(12) Randall, L. O.; Kappell, B. "The Benzodiazepines"; Garattini, S.; Mussini, E.; Randall, L. O., Eds.; Raven Press: New York, 1973, pp 27–51.

Table III. Summary of Experimental Details for Crystallographic Analysis of Compounds 3 and 12

	3	12
crystal size, mm	0.06 × 0.15 × 0.55	0.12 × 0.15 × 0.7
maximum θ, deg	57	48
no. of reflections	2126	2221
absorption correction	yes	yes
least-squares refinement	full matrix	full matrix
heavier atoms	anisotropic	anisotropic
H atoms	isotropic	isotropic
final R	0.035	0.044
final wR	0.039	0.053
final difference map – largest peak, e Å^{-3}	<±0.2	±0.3

that the pharmacological profile of 1 should not be significantly altered by its metabolites.

Crystallography. All intensity data were measured on a Hilger–Watts diffractometer (Ni-filtered Cu $K\alpha$ radiation, θ–2θ scans, pulse height discrimination). The crystal data are given in Table II. A multiple solution procedure[13] was used to solve the two structures. Experimental details are summarized in Table III.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million downfield from internal Me_4Si. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC 110B instruments, respectively.

For column chromatography, Merck silica gel 60, mesh 70–230, was used. Anhydrous sodium sulfate was used for drying of organic solutions.

9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine 6-Oxide (5). A solution of 6.8 g (20 mmol) of 1 and 6 g (30 mmol) of 85% *m*-chloroperbenzoic acid in 200 mL of CH_2Cl_2 was stirred at room temperature for 4 h. The mixture was washed with an excess of ice-cold dilute aqueous NaOH, dried, and filtered over Hy-flo. The filtrate was concentrated at reduced pressure to dryness. The residue was crystallized from a mixture of CH_2Cl_2 and ether to give 5.4 g (75%; mp 228–229 °C) of 5 as an off-white solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave 5 as off-white crystals: mp 216–217 °C (the reason for the higher melting point of the crude product was not investigated); NMR ($CDCl_3$) δ 5.08 (s, 2, C_5 H), 7.0–7.7 (m, 6, arom H), 8.25 (d, J = 8 Hz, 1, C_{11} H), 8.90 (s, 1, C_4 H), 9.36 (s, 1, C_2 H); mass spectrum, m/e 355 (M^+). Anal. ($C_{18}H_{11}Cl_2N_3O$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-5-ol Acetate (6). A mixture of 3 g (8 mmol) of 5 and 50 mL of acetic anhydride was heated on the steam bath for 22 h. The reaction mixture was concentrated at reduced pressure to dryness, and the residue was crystallized from a mixture of CH_2Cl_2 and ether to give 2.8 g (86%; mp 211–212 °C) of crude 6. Recrystallization from a mixture of CH_2Cl_2 and ether gave 6 as cream-colored prisms: mp 211–212 °C; IR ($CHCl_3$) 1753 (C=O), 1613 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 2.33 (s, 3, CH_3), 6.41 (s, 1, C_5 H), 7.2–7.6 (m, 5, arom H), 7.66 (dd, J = 2 and 9 Hz, 1, C_9 H), 8.28 (d, J = 9 Hz, 1, C_{11} H), 9.08 (s, 1, C_4 H), 9.32 (s, 1, C_2 H); mass spectrum, m/e 397 (M^+). Anal. ($C_{20}H_{13}Cl_2N_3O_2$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-5-ol (2). A solution of 4.8 g (12 mmol) of 6 in a mixture of 50 mL of THF, 50 mL of MeOH, and 4 mL of 3 N aqueous NaOH was stirred at room temperature for 30 min. The reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The organic layer was separated, dried, and concentrated at reduced pressure to dryness. The residue was crystallized from a mixture of CH_2Cl_2 and ether to give 4.1 g (95%; mp 105–117 °C) of 2 as an off-white solid. Recrystallization from a mixture of CH_2Cl_2 and acetone gave 2 as colorless prisms: mp 174–175 °C; NMR ($CDCl_3$) δ 5.16 (br d, J = 6 Hz, 1, OH), 5.42 (br d, J = 6 Hz, 1, C_5 H), 7.1–7.7 (m, 6, arom H), 8.22 (d, J = 8 Hz, 1, C_{11} H), 8.92 (s, 1, C_4 H), 9.23 (s, 1, C_2 H); mass spectrum, m/e 355 (M^+). Anal. ($C_{18}H_{11}Cl_2N_3O$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][2]benzazepine (7). A mixture of 68 g (0.2 mol) of 1, 27 g of zinc dust, and 250 mL of acetic acid in 600 mL of CH_2Cl_2 was stirred at −30 °C for 2 h. The mixture was filtered over Hy-flo into a stirred mixture of 600 mL of concentrated ammonium hydroxide and 500 mL of ice. The CH_2Cl_2 solution was separated, dried, and concentrated at reduced pressure. The residue crystallized from a mixture of CH_2Cl_2 and ether to give 5 g (75%) of 7 as a colorless solid. Recrystallization from a mixture of ether and CH_2Cl_2 gave 7 as colorless needles: mp 169–170 °C; IR ($CHCl_3$) 3330 (NH) and 1598, 1578 (arom) cm^{-1}; NMR ($CDCl_3$) δ 2.36 (br s, 1, NH), 3.58 (d, J = 14 Hz, 1) and 4.02 (d, J = 14 Hz, 1) (AB system, C_5 H), 5.13 (s, 1, C_6 H), 6.67 (d, J = 2 Hz, 1, arom H), 7.2–7.5 (m, 4, arom H), 7.8–8.0 (m, 2, arom H), 8.67 (s, 1, C_4 H), 9.33 (s, 1, C_2 H); mass spectrum, m/e 341 (M^+). Anal. ($C_{18}H_{13}Cl_2N_3$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-6-[(4-methylphenyl)sulfonyl]-5*H*-pyrimido[5,4-*d*][2]benzazepine (8). A solution of 6.1 g (18 mmol) of 7, 6.1 g (32 mmol) of TsCl, 10 mL of pyridine, and 0.1 g of 4-(dimethylamino)pyridine in 100 mL of CH_2Cl_2 was stirred at room temperature for 24 h. The mixture was washed with an excess of dilute ice-cold aqueous HCl and dilute aqueous NaOH. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. The residue crystallized from a mixture of CH_2Cl_2 and ether to give 6.9 g (78%; mp 200–201 °C) of 8 as a white solid. Recrystallization from a mixture of ether and CH_2Cl_2 gave 8 as colorless prisms: mp 200–201 °C; NMR ($CDCl_3$) δ 2.42 (s, 3, CH_3), 3.82 (d, J = 14 Hz, 1) and 4.92 (d, J = 14 Hz, 1) (AB system, C_5 H), 6.27 (s, 1, C_7 H), 6.8–7.5 (m, 8, arom H), 7.6–7.9 (m, 3, arom H), 8.77 (s, 1, C_4 H), 9.06 (s, 1, C_2 H); mass spectrum, m/e 495 (M^+). Anal. ($C_{25}H_{14}Cl_2N_3O_2S$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-6-(trifluoroacetyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (9). Trifluoroacetic anhydride (18 mL, 57 mmol) was added dropwise to a solution of 17.1 g (50 mmol) of 7 and 25 mL (32 mmol) of pyridine in 250 mL of CH_2Cl_2, which was cooled to 0 °C. After stirring for 1.5 h, the mixture was poured into ice-cold dilute aqueous HCl. The CH_2Cl_2 solution was separated, washed with saturated aqueous NaCl, dried, and concentrated at reduced pressure. The residue was crystallized from ether to give 17.2 g (50%) of 9 as pink crystals, mp 178–179 °C. Recrystallization from ether gave 9 as off-white crystals: mp 179–180 °C; IR ($CHCl_3$) 1690 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.48 (d, J = 16 Hz) and 4.83 (d, J = 16 Hz) (AB system C_5 H), 6.33 (m, 1 arom H), 6.7–7.7 (m, 5, arom H), 8.11 (d, J = 8 Hz, 1, arom H), 8.65 (s, 1, C_4 H), 9.18 (s, 1, C_2 H); mass spectrum, m/e 437 (M^+). Anal. ($C_{20}H_{12}Cl_2F_3N_3O$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-6-[(4-methylphenyl)sulfonyl]-5*H*-pyrimido[5,4-*d*][2]benzazepine 3-Oxide (10) and 8-Chloro-6-(2-chlorophenyl)-5,6-dihydro-5-[(4-methylphenyl)sulfonyl]-4*H*-oxazolo[5,4-*d*][2]benzazepine (12). A solution of 24.8 g (50 mmol) of 8 and 21 g (0.1 mol) of 85% *m*-chloroperbenzoic acid in 800 mL of CH_2Cl_2 was stirred at room temperature for 50 h. The CH_2Cl_2 solution was washed with ice-cold dilute aqueous NaOH, dried, and concentrated at reduced pressure to dryness. Purification by column chromatography (SiO_2, 100 g; eluents CH_2Cl_2, 10% ether in CH_2Cl_2, and then ethyl acetate) gave in the CH_2Cl_2 fractions 0.6 g (2%) of 12 as an off-white solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave 12 as long cream-colored prisms: mp 205–206 °C; NMR ($CDCl_3$) δ 2.24 (s, 3, CH_3), 3.74 (d, J = 20 Hz, 1) and 5.02 (d, J = 20 Hz, 1) (AB system, C_4 H), 6.49 (dd, J = 2 and 8 Hz, 1, arom H), 6.7–7.6 (m, 10, arom H), 7.64 (s, 1, C_2 H), 7.80 (d, J = 8 Hz, 1, C_{10} H); mass spectrum, m/e 484 (M^+). Anal. ($C_{24}H_{18}Cl_2N_2O_3S$) C, H, N.

The second band gave 5.3 g (21%) of starting material (8). The third fraction gave 6.8 g (26%) of 10 as colorless crystals. Recrystallization from a mixture of ether and CH_2Cl_2 gave 10 as colorless crystals: mp 243–244 °C; NMR ($CDCl_3$) δ 2.28 (s, 3, CH_3), 3.97 (d, J = 15 Hz, 1) and 4.58 (d, J = 15 Hz, 1) (AB system, C_5

(13) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

(14) Crystals of 12 suitable for X-ray analysis were obtained by recrystallization from methanol.

H), 6.37 (s, 1, C_7 H), 6.8–7.7 (m, 10, arom H), 7.72 (d, J = 8 Hz, 1, C_{11} H), 8.33 (d, J = 2 Hz, 1, C_4 H), 8.76 (d, J = 2 Hz, 1, C_2 H); mass spectrum, m/e 511 (M^+). Anal. ($C_{25}H_{19}Cl_2N_3O_3S$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-6-(trifluoroacetyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine 3-Oxide (11) and 8-Chloro-6-(2-chlorophenyl)-5-(trifluoroacetyl)-5,6-dihydro-4*H*-oxazolo[5,4-*d*][2]benzazepine (13). A solution of 13.1 g (30 mmol) of **9** and 9 g (44 mmol) of 85% *m*-chloroperbenzoic acid in 300 mL of CH_2Cl_2 was stirred at room temperature for 46 h. The mixture was washed with ice-cold dilute aqueous NaOH and brine. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. The residue (13.7 g) was purified by column chromatography (SiO_2, 100 g; eluents CH_2Cl_2, 20% ether in CH_2Cl_2, and then ethyl acetate). The first major band crystallized from a mixture of ether and petroleum ether to give 0.4 g (3%) of **13** as cream-colored prisms: mp 144–145 °C; IR ($CHCl_3$) 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.94 (d, J = 18 Hz, 1) and 5.06 (d, J = 18 Hz, 1) (AB system, C_4 H), 6.60 (dd, J = 2 and 8 Hz, 1, arom H), 6.8–7.6 (m, 6, arom H), 7.80 (s, 1, C_2 H), 8.26 (d, J = 8 Hz, 1, C_{10} H); mass spectrum, m/e 426 (M^+). Anal. ($C_{19}H_{11}Cl_2F_3N_2O$) C, H, N.

The second major band gave 3.5 g (26%) of starting material (**9**). The third band, which crystallized from a mixture of CH_2Cl_2 and ether, gave 2.9 g (21%; mp 108–109 °C) of **11** as an off-white solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave **11** as colorless prisms: mp 209–211 °C; IR ($CHCl_3$) 1704 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.59 (s, 2, C_5 H), 6.50 (dd, J = 2 and 8 Hz, 1, arom H), 7.1–7.8 (m, 6, arom H), 8.20 (d, J = 8 Hz, 1, C_{11} H), 8.25 (d, J = 2 Hz, 1, C_4 H), 8.92 (d, J = 2 Hz, 1, C_2 H); mass spectrum, m/e (M^+). Anal. ($C_{20}H_{12}Cl_2F_3N_3O_2$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine 3-Oxide (3). A mixture of 2.0 g (3.9 mmol) of **10** and 8 mL of a 4 M MeOH solution of sodium methoxide in a mixture of 130 mL of THF and 180 mL of MeOH was stirred at room temperature for 19 h. The mixture was poured into ice-cold aqueous NaCl and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous NaCl, dried, and concentrated at reduced pressure. The residue was purified by column chromatography (SiO_2, 20 g; eluents 20% ether in CH_2Cl_2 and then 10% MeOH in CH_2Cl_2) to give 0.3 g (20%) of **3** in the 10% MeOH in CH_2Cl_2 eluent as a white solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave **3** as long colorless prisms: mp 189–190 °C; IR ($CHCl_3$) 1620 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 4.46 (br s, 2, C_4 H), 7.1–7.7 (m, 6, arom H), 8.16 (d, J = 8 Hz, 1, C_{11} H), 8.47 (d, J = 2 Hz, 1, C_4 H), 9.02 (d, J = 2 Hz, 1, C_2 H); mass spectrum, m/e 355 (M^+). Anal. ($C_{18}H_{11}Cl_2N_3O$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][2]benzazepine 3-Oxide (14). A mixture of 4.9 g (11 mmol) of **11** in 50 mL of 3 N aqueous NaOH, 100 mL of EtOH, and 100 mL of THF was stirred at room temperature for 30 min. The mixture was concentrated at reduced pressure to a small volume. The resulting precipitate was collected by filtration to give 3.6 g (91%; mp 259–260 °C) of **14** as a colorless solid. Recrystallization from THF gave **14** as colorless crystals: mp 263–264 °C; IR ($CHCl_3$) 3325 (NH) cm^{-1}; NMR (Me_2SO-d_6) δ 3.0–4.0 (m, 3, C_5 H, NH), 5.06 (s, 1, C_7 H), 6.44 (d, J = 2 Hz, 1, arom H), 7.3–7.6 (m, 4, arom H), 6.72 (d, J = 8 Hz, 1, C_{11} H), 7.99 (br d, J = 6 Hz, 1, arom H), 8.54 (d, J = 2 Hz, 1, C_4 H), 9.00 (d, J = 2 Hz, 1, C_2 H); mass spectrum, m/e 357 (M^+). Anal. ($C_{18}H_{13}Cl_2N_3O$) C, H, N.

9-Chloro-7-(2-chlorophenyl)-7*H*-pyrimido[5,4-*d*][2]benzazepine 3-Oxide (15). A mixture of 2.1 g (5.9 mmol) of **14** and 8 mL (7.2 mmol) of a 5% (v/v) CH_2Cl_2 solution of Br_2 in 500 mL of CH_2Cl_2 and 2.0 g (20 mmol) of potassium acetate in 20 mL of H_2O was stirred at room temperature. After 3 h, 4 mL (29 mmol) of triethylamine was added, followed by continued stirring for 15 min. The mixture was washed with brine and H_2O. The CH_2Cl_2 solution was dried and concentrated at reduced pressure. The residue was purified by column chromatography (SiO_2, 20 g; eluent, 1:1 mixture of CH_2Cl_2 and ethyl acetate) to give 1.2 g (56%; mp 242–244 °C) of **15** as colorless needles: IR ($CHCl_3$) 1630 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 5.28 (d, J = 2 Hz, 1, C_7 H), 6.51 (d, J = 2 Hz, arom H), 7.4–7.7 (m, 4, arom H), 8.03 (d, J = 8 Hz, 1, C_{11} H), 8.38 (d, J = 7 Hz, 1, arom H), 8.61 (d, J = 2 Hz, 1, C_5 H), 9.01 (d, J = 2 Hz, 1, C_4 H), 9.21 (d, J = 1 Hz, 1, C_2 H); mass spectrum, m/e 355 (M^+). Anal. ($C_{18}H_{11}Cl_2N_3O$) C, H, N.

Isomerization of 15 into 3. A mixture of 2.4 g (6.7 mmol) of **15**, 125 mL of THF, 250 mL of MeOH, and 10 mL of a 4.3 M MeOH solution of sodium methoxide was stirred at room temperature for 24 h. The mixture was partitioned between aqueous NaCl and CH_2Cl_2. The organic layer was dried and concentrated at reduced pressure to dryness. The residue (2.7 g) was purified by column chromatography (SiO_2, 50 g; eluent, 40% THF in CH_2Cl_2) to give as the first product band 0.6 g of **16** (25%; mp 184–186 °C) as a colorless solid. Recyrstallization from ether gave **16** as colorless needles: mp 192–193 °C dec; IR (KBr) 3470 (NH), 3280, 3160 (OH) and 1630, 1595 (C=N) cm^{-1}; NMR (Me_2SO-d_6) δ 4.96 (d, J = 2 Hz, 1, C_1 H), 6.38 (d, J = 2 Hz, 1, arom H), 7.3–7.8 (m, 5, arom H), 7.89 (d, J = 2 Hz, 1, C_2 H), 8.11 (br s, 2, NH_2), 8.16 (s, 1, CH), 8.35 (br d, J = 7 Hz, 1, arom H), 10.82 (s, 1, OH); mass spectrum, m/e 345 (M^+). Anal. ($C_{17}H_{13}Cl_2N_3O$) C, H, N.

The second product band gave 0.7 g (29%) of **3** as colorless crystals, mp 187–189 °C.

2′,5-Dichloro-2-iodo-4′-methoxybenzophenone (19). A mixture of 7 g (0.1 mol) of $NaNO_2$ and 45 mL of H_2SO_4 was heated on a steam bath to ca. 80 °C until complete solution was achieved. The solution was cooled to 30 °C, and 29.6 g (0.1 mol) of **18**[7] was added in portions, keeping the temperature between 30 and 40 °C. The mixture was stirred for 1 h and then slowly poured into 200 g of ice. The solution was filtered through Hy-flo, and to the stirred filtrate was added slowly a solution of 40 g (0.18 mol) of sodium tetrafluoroborate in 80 mL of H_2O. The resulting precipitate was collected by filtration and washed with a small amount of H_2O. The moist precipitate was slurried in a mixture of 240 mL of H_2O and 100 mL of ether. A solution of 40 g (0.24 mol) of KI in 100 mL of H_2O was added dropwise. The mixture was stirred at room temperature for 30 min and filtered over a bed of Hy-flo. The ether layer of the filtrate was separated, dried, and concentrated in vacuo to dryness. The residue crystallized from ether to give 10 g (24%; mp 115–117 °C) of **19** as a yellow solid. Recrystallization from ether gave **19** as slightly yellow prisms: mp 119–120 °C; IR ($CHCl_3$) 1671 (C=O), 1598 (arom) cm^{-1}; NMR ($CDCl_3$) δ 3.86 (s, 3, CH_3), 6.8–7.3 (m, 4, arom H), 7.50 (d, J = 9 Hz, 1, arom H), 7.80 (d, J = 8 Hz, 1, arom H); mass spectrum, m/e 406 (M^+). Anal. ($C_{14}H_{19}Cl_2IO_2$) C, H.

1-[4-Chloro-2-(2-chloro-4-methoxybenzoyl)phenyl]-3-phthalimidopropyne (20). A mixture of 20 mL of 98% diethylamine, 40 mL of CH_2Cl_2, 0.3 g (0.4 mmol) of $[(C_6H_5)_3P]_2PdCl_2$, 80 mg (0.4 mmol) of CuI, 8.1 g (20 mmol) of **19**, and 4.2 g (23 mmol) of *N*-propargylphthalimide was stirred at room temperature under argon for 18 h. The mixture was concentrated at reduced pressure to dryness. The residue was diluted with 20 mL of *i*-PrOH, and 6.9 g (75%; mp 184–185 °C) of crude **20** was collected by filtration. Recrystallization from acetone gave **20** as cream-colored prisms: mp 190–192 °C; IR ($CHCl_3$) 1785, 1730 (imide C=O), 1676 (ketone C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.83 (s, 3, CH_3), 4.36 (s, 2, CH_2), 6.6–6.8 (m, 2, arom H), 7.2–7.6 (m, 4, arom H), 7.8 (m, 4, arom H); mass spectrum, m/e 463 (M^+). Anal. ($C_{25}H_{15}Cl_2NO_4$) C, H, N.

3-Amino-1-[4-chloro-2-(2-chloro-4-methoxybenzoyl)-phenyl]propyne (21). A mixture of 23 g (50 mmol) of **20**, 200 mL of CH_2Cl_2, and 25 mL of 40% aqueous methylamine was stirred at room temperature for 2.5 h. The reaction mixture was poured into ice–H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. The residue was crystallized from ether to give 8.5 g (50%) of **21** as cream-colored prisms: mp 69–70 °C; IR ($CHCl_3$) 3390 (NH_2), 1665 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.14 (s, 2, NH_2), 3.34 (s, 2, CH_2), 3.86 (s, 3, CH_3), 6.85 (dd, J = 3 and 8 Hz, arom H), 6.96 (d, J = 3 Hz, 1, arom H), 7.4–7.6 (m, 4, arom H); mass spectrum, m/e 333 (M^+). Anal. ($C_{17}H_{13}Cl_2NO_2$) C, H, N.

The HCl salt of **21** was prepared by dissolving **21** in an excess of 6% methanolic HCl and precipitating the product by adding ether. Recrystallization from a mixture of MeOH and ether gave the salt of **21** as colorless needles: mp 213–214 °C dec; IR (KBr) 2890, 2840 (NH_3), 1658 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.67 (s, 2, CH_2), 3.89 (s, 3, CH_3), 6.9–7.1 (m, 2, arom H), 7.4–7.7 (m, 4, arom H), 8.73 (br s, 3, NH_3). Anal. ($C_{17}H_{14}Cl_2$·HCl) C, H, N.

8-Chloro-1-(2-chloro-4-methoxyphenyl)-3,4-dihydro-5*H*-2-benzazepin-5-one (22). A solution of 15.8 g (47 mmol) of **21** in 20 mL of CH_2Cl_2 was added dropwise with stirring to 40 mL

of concentrated H_2SO_4 at 0–10 °C. The mixture was stirred at 0–15 °C for 4 h, poured over ice, made alkaline with an excess of NH_4OH, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. Purification of the residue (13 g) by column chromatography (SiO_2, 55 g; eluent, CH_2Cl_2 and then ether) gave, on concentration of the ether fraction, 4.6 g (29%) of **22** as a crystalline solid: mp 116–117 °C; IR ($CHCl_3$) 1685 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.06 (m, 2) and 3.91 (m, 2) (A_2B_2 system, CH_2CH_2), 3.82 (s, 3, CH_3), 6.8–7.1 (m, 2, arom H), 7.4–7.6 (m, 2, arom H), 7.82 (d, J = 8 Hz, 1, C_{11} H); mass spectrum, m/e 333 (M^+). Anal. ($C_{17}H_{13}Cl_2NO_2$) C, H, N.

8-Chloro-1-(2-chloro-4-methoxyphenyl)-3,4-dihydro-4-[(dimethylamino)methylene]-5*H*-2-benzazepinone (23). A mixture of 6.4 g (19 mmol) of **22**, 12 mL of DMF, and 6 mL of dimethylformamide dimethyl acetal was heated on a steam bath for 1 h. The reaction mixture was concentrated at reduced pressure to dryness, and the residue was crystallized from a mixture of CH_2Cl_2 and ether to give 5.8 g (77%, mp 144–145 °C) of **23** as a yellow solid. Recrystallization from a mixture of ether and CH_2Cl_2 gave **23** as yellow needles: mp 145–147 °C; IR ($CHCl_3$) 1648 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.26 (s, 6, CH_3), 3.60 (d, J = 13 Hz, 1) and 4.85 (d, J = 13 Hz, 1) (AB system, C_3 H), 6.8–7.0 (m, 2, arom H), 7.4–7.6 (m, 2, arom H), 7.76 (s, 1, =CH), 8.00 (d, J = 8 Hz, 1, C_{11} H); mass spectrum, m/e 388 (M^+). Anal. ($C_{20}H_{18}Cl_2N_2O_2$) C, H, N.

9-Chloro-7-(2-chloro-4-methoxyphenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (24). A mixture of 8 g (20 mmol) of **23**, 9 g (86 mmol) of formamidine acetate, and 90 mL of formamide was heated on a steam bath for 16 h. The mixture was poured into ice–water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. The residue crystallized from ether to give 5.7 g (77%; mp 104–108 °C) of **24** as a yellow solid. Recrystallization from ether gave **24** as yellow prisms: mp 108–112 °C; NMR ($CDCl_3$) δ 3.81 (s, 3, CH_3), 4.0–5.0 (br s, 2, C_5 H), 6.8–7.0 (m, 2, arom H), 7.2–7.7 (m, 3, arom H), 8.27 (d, J = 8 Hz, 1, C_{11} H), 8.81 (s, 1, C_4 H), 9.29 (s, 1, C_2 H); mass spectrum, m/e 369 (M^+). Anal. ($C_{19}H_{13}Cl_2N_3O$) C, H, N.

3-Chloro-4-(9-chloro-5*H*-pyrimido[5,4-*d*][2]benzazepin-7-yl)phenol Hydrochloride Hydrate (4). A solution of 0.9 g (2.4 mmol) of **24** in 50 mL of CH_2Cl_2 was added slowly to a stirred solution of 3 g (12 mmol) of boron tribromide in 25 mL of CH_2Cl_2. The mixture was refluxed with stirring for 23 h, poured into a small amount of ice, and concentrated at reduced pressure to a small volume. The residue was dissolved in THF and diluted with an excess of dilute aqueous NaOH. The solution was stirred at room temperature for 10 min, diluted with H_2O, and extracted with ether. The ether layer which contained starting material was separated and discarded. The aqueous solution was neutralized with acetic acid and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. The residue (0.5 g) was dissolved in an excess of methanolic HCl and diluted with ether, and the resulting precipitate was collected by filtration to give 0.3 g (29%; mp 247–250 °C dec) of **4** as a yellow solid. Recrystallization from a mixture of MeOH and ether gave **4** as yellow needles: mp 249–251 °C dec; IR (KBr) 3400 (OH) and 2660, 2020, 1900 (C=NH) cm^{-1}; NMR (Me_2SO-d_6) δ 4.80 (br s, 2, C_5 H), 7.0–7.2 (m, 2, arom H), 7.4–8.2 (m, 5, arom H), 8.39 (d, J = 8 Hz, 1, C_{11} H), 9.12 (s, 1, C_4 H), 9.40 (s, 1, C_2 H). Anal. ($C_{18}H_{11}ClN_3O$·HCl) C, H, N.

The free base of **4** was prepared by dissolving the HCl salt in dilute aqueous NaOH, neutralizing the solution with acetic acid, and extracting the base into CH_2Cl_2. The CH_2Cl_2 solution was dried and concentrated at reduced pressure to dryness. The residue crystallized from a mixture of CH_2Cl_2 and ether and gave the free base of **4** as cream-colored prisms: mp 208–210 °C; IR (KBr) 2760, 2660 (OH), 1595, 1570 (arom) cm^{-1}; NMR (Me_2SO-d_6) δ 4.0–5.5 (vbr s, 2, C_5 H), 6.7–6.9 (m, 2, arom H), 7.15 (d, J = 2 Hz, 1, arom H), 7.38 (d, J = 9 Hz, 1, arom H), 7.73 (dd, J = 2 and 8 Hz, 1, C_{10} H), 8.20 (d, J = 8 Hz, C_{11} H), 8.93 (s, 1, C_4 H), 9.22 (s, 1, C_2 H), 10.10 (br s, 1, OH); mass spectrum, m/e 355 (M^+). Anal. ($C_{18}H_{11}Cl_2N_3O$) C, H, N.

Metabolite A (compound **2**): NMR (CD_3OD) δ 5.47 (s, 1, C_5 H), 7.18 (d, J = 2 Hz, 1, arom H), 7.2–7.8 (m, 5, arom H), 8.27 (d, J = 8 Hz, 1, C_{10} H), 9.14 (s, 1, arom H), 9.22 (s, 1, arom H); mass spectrum, m/e 355 (M^+).

Metabolite B (compound **3**): NMR (CD_3OD) δ 4.51 (br s, 2, C_5 H), 7.18 (d, J = 2 Hz, 1, arom H), 7.2–7.8 (m, 5, arom H), 8.26 (d, J = 8 Hz, 1, C_{10} H), 8.85 (d, J = 2 Hz, 1, arom H), 9.16 (d, J = 2 Hz, 1, arom H).

Metabolite C (compound **4**): NMR ($CDCl_3/CD_3OD$, 5:1) δ 4.08 (br s, 1) and 4.77 (br s, 1) (AB system, C_5 H), 6.78 (s, 1, arom H), 6.82 (d, J = 2 Hz, 1, arom H), 7.25 (d, J = 2 Hz, 1, arom H), 7.3–7.5 (m, 1, arom H), 7.66 (dd, J = 2 and 8 Hz, C_9 H), 8.22 (d, J = 8 Hz, 1, C_{10} H), 8.83 (s, 1, C_4 H), 9.25 (s, 1, C_2 H); mass spectrum, m/e 355 (M^+).

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Registry No. **1**, 76988-39-1; **2**, 76988-67-5; **3**, 76988-77-7; **4**, 86709-89-9; **4** (free base), 86709-90-2; **5**, 76988-65-3; **6**, 76988-66-4; **7**, 76988-73-3; **8**, 86709-91-3; **9**, 76988-75-5; **10**, 76988-76-6; **11**, 76988-78-8; **12**, 86709-92-4; **13**, 86709-93-5; **14**, 76988-79-9; **15**, 86709-94-6; **16**, 86709-95-7; **18**, 86709-96-8; **19**, 86709-97-9; **20**, 86709-98-0; **21**, 86709-99-1; **21**·HCl, 86710-00-1; **22**, 86710-01-2; **23**, 86710-02-3; **24**, 86710-03-4; *N*-propargylphthalimide, 7223-50-9; formamidine acetate, 3473-63-0; dimethylfurmamide dimethyl acetal, 4637-24-5.

Supplementary Material Available: Tables IV and V, the bond lengths and angles in compound **3**; Tables VI and VII, the final atomic and anisotropic thermal parameters for compound **3**; Tables VIII and IX, the bond lengths and angles in compound **12**; and Tables X and XI, the final atomic and anisotropic thermal parameters for **12** (9 pages). Ordering information is given on any current masthead page.

C_4-Substituted 1-β-D-Ribofuranosylpyrazolo[3,4-*d*]pyrimidines as Adenosine Agonist Analogues

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The synthesis of four novel C_4-substituted 1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidines is reported, and the compounds were examined as adenosine receptor agonist analogues. Neither receptor affinity nor biological activity was as potent as the purine counterparts. Adenosine agonists appear to be sensitive to modification of the purine base, with a nitrogen atom in the 7 position necessary for efficacy.

In recent years, several investigators have proposed adenosine to be a neurotransmitter or neuromodulator acting on a variety of physiological systems. Receptor classifications have been defined by several investigators

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